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Edited by Hany A. El-Shemy

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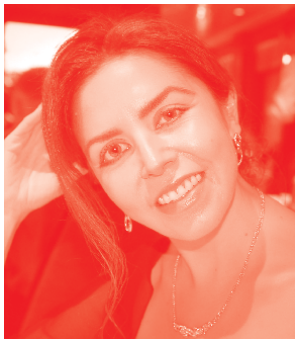

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Meet the editor

Prof. Hany A. El-Shemy received a Ph.D. in Biochemistry from the University of Cairo, Egypt, and a Ph.D. in Genetic Engineering from the University of Hiroshima, Japan. He holds two patents and has written thirteen international books. He has also published more than 100 SCI journal papers and 55 conference presentations. Dr. El-Shemy was a technique committee member as well as chair of many international conferences. He has also served as editor for journals including *PLOS ONE*, *BMC Genomics*, and *Current Issues in Molecular Biology.* He has received several awards, including state prizes from the Academy of Science, Egypt (2004, 2012, and 2018), the Young Arab Researcher prize from the Shuman Foundation, Jordan (2005), and Cairo University Prizes (2007, 2010, and 2014). He served as an expert for the African Regional Center of Technology, Dakar, Senegal, as well as a visiting professor at Pan African University, African Union. He served as vice president of the Academy of Science and Technology, Egypt, from 2013 to 2014. Since 2014 he has been the dean of the Faculty of Agriculture, Cairo University. In 2018, he was elected a fellow of the African Academy of Science.

Contents

Preface

Natural drugs from plants can be used to treat several diseases. As such, this book describes the important plants used by individuals and drug manufacturers worldwide for treating illness and developing novel medications. It consists of sixteen chapters that review plant extracts, their active ingredients (e.g., alkaloids), side effects, and how they compare to synthetic medicines for treating disease.

The book is a useful resource for researchers and students in medicine and pharmacology.

It is also recommended for readers to take a look at a related book, *Natural Medicinal Plants.*

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Chapter 1

Gamma-Aminobutyric Acid (GABA) and the Endocannabinoids: Understanding the Risks and Opportunities

Steven P. James and Dena Bondugji

Abstract

The Gamma-aminobutyric acid (GABA) system is the main inhibitory neurotransmitter system in the central nervous system (CNS) of vertebrates and is involved in critical cellular communication and brain function. The endocannabinoid system (ECS) was only recenty discovered and quickly recognized to be abundantly expressed in GABA-rich areas of the brain. The strong relationship between the GABA system and ECS is supported both by studies of the neuraoanatomy of mammalian nervous systems and the chemical messaging between neurons. The ECS is currently known to consist of two endocannabinoids, Anandamide (AEA) and 2-Arachidonyl Glycerol (2-AG), that function as chemical messengers between neurons, at least two cannabinoid receptors (CB_1 and CB_2), and complex synthetic and degradative metabolic systems. The ECS differs from the GABA system and other neurotransmitter systems in multiple ways including retrograde communication from the activated post-synaptic neuron to the presynaptic cell. Together, this molecular conversation between the ECS and GABA systems regulate the homeostasis and the chemical messaging essential for higher cortical functions such as learning and memory and may play a role in several human pathologies. Phytocannabinoids are synthesized in the plant *Cannabis sativa* (*C. sativa*). Within the family of phytocannabinoids at least 100 different cannabinoid molecules or derivatives have been identified and share the properties of binding to the endogenous cannabinoid receptors CB_1 and CB_2. The well-known psychoactive phytocannabinoid Δ^9-tetrahydrocannabinol (THC) and the non-psychoactive cannabidiol (CBD) are just two of the many substances synthesized within *C. sativa* that act on the body. Although the phytocannabinoids THC and CBD bind to these endogenous receptors in the mammalian CNS, these plant derived molecules have little in common with the endocannabinoids in structure, distribution and metabolism. This overlap in receptor binding is likely coincidental since phytocannabinoids evolved within the plant kingdom and the ECS including the endocannabinoids developed within animals. The GABA and ECS networks communicate through carefully orchestrated activities at localized synaptic level. When phytocannabinoids become available, the receptor affinities for CB_1 and CB_2 may compete with the naturally occurring endocannabinoid ligands and influence the GABA-ECS communication. In some instances this addition of phytocannabinoids may provide some therapeutic benefit while in other circumstances the presence of these plant derived ligands for the CB_1 and CB_2 receptors binding site may lead to disruption of important

functions within the CNS. The regulatory approval of several THC products for nausea and vomiting and anorexia and CBD for rare pediatric seizure disorders are examples of some of the benefits of phytocannabinoids. Concerns regarding cannabis exposure in utero and in the child and adolescence are shrill warnings of the hazards associated with disrupting the normal maturation of the developing CNS.

Keywords: endocannabinoids, GABA, phytocannabinoids, homeostasis

1. Introduction to the GABA system

Gamma-aminobutyric acid (GABA), an amino acid, is the primary inhibitory neurotransmitter in the vertebrate central nervous system (CNS). Although it was first identified in plants in the late nineteenth century, only in 1950 was it first identified in fresh extracts of animal brain including reptiles, avian, mammals and man [1]. It is now accepted that GABA is present almost exclusively within the brain and retina of vertebrates and only in extremely limited amounts in the peripheral nervous system and other organs of the body. It has been estimated that within the CNS, GABA is the neurotransmitter for as many as one-third of the neurons with the majority of these cells as interneurons that modulate the activity of neural networks. GABA neurons are widely expressed throughout the CNS including the cerebral cortex, hippocampus, striatum, substantia nigra, globus pallidus, cerebellum and olfactory bulbs. Within the structures, GABA receptors are found not only on the cell membranes of neurons but on supporting glial tissue and astrocytes [2].

As an amino acid, GABA serves other biological roles in addition to that of a neurotransmitter. It also functions as a precursor for the assembly of proteins and as metabolic intermediary. Despite these multiple functions, GABA is also responsible for regulation of neuronal excitability and is the primary inhibitory messenger in the CNS. GABA is highly concentrated in the CNS and present in millimoles per gram in the brain compared to nanomoles per gram of the more more commonly recognized neurotransmitters including dopamine, 5-hydroxytryptamine (serotonin) and norepinephrine [3].

GABA is known to have affinity for two distinct families of receptors similar to the excitatory amino acid Glutamate. The first and most prevalent of the two in the brain is the ionotropic $GABA_A$ receptor, a large glycoprotein of ~275 kDa and consists of a pentameric transmembrane receptor typically including two α subunits, two β subunits and one γ. Variations frequently occur and may even include δ subunit substituted for γ that encircle a central, chloride-permeable pore. The $GABA_A$ is found on both presynaptic and postsynaptic neuronal cell membranes. Upon the binding of two GABA molecules to the extracellular site, the pore opens and allows the flow of chloride ions into the cell with hyperpolarization of the cell membrane and inhibition of action potentials [4].

The $GABA_A$ receptor was cloned in 1987 and multiple subunits have subsequently been identified and grouped within seven functionally unique families. These multiple isoforms result in a highly complex system of receptors with functions dependent upon the expression of subunits.

Two binding sites for GABA sit on the $GABA_A$ receptor along with other sites that include a benzodiazepine receptor, a barbiturate receptor, and alcohol. In every instance, these binding sites function independently of each other. As a result, each receptor does not compete with activation of other receptors and the overall effect is synergestic rather than competitive [5].

The $GABA_B$ receptor is a second type of receptor and is a metabotropic site that belongs to the G-Protein Coupled Receptor (GPCR) superfamily. Pretreatment

of isolated tissue from rodent atria and vas deferens with the $GABA_A$ antagonist bicucullin in 1979 first eslablished that two populations of receptors existed when the expected response to GABA was not found [6]. Twenty years passed before the $GABA_B$ receptor was finally cloned. As a GPCR, this receptor is broadly distributed throughout the CNS and mediates slow and prolonged inhibitory messaging through $G_{ai/o}$-type proteins. As a GPCR, $GABA_B$ contains seven transmembrane domains with an extracellular N-terminus tail and acts through a second messenger system by inhibition of adenylate cyclase and cAMP formation inactivating voltage-gated Ca^{2+} channels and K^+ channels [5].

Three receptor subunits are associated with $GABA_B$ site. A long, extracellular N-terminal called the Venus fly-trap (VFT) domain includes an orthosteric binding site, a seven transmembrane domain and the C-terminus tail within the cell comprise the $GABA_B$ receptor. Ligands to the $GABA_B$ receptor have been identified and include the selective $GABA_B$ agonist Baclofen, various investigational antagonists that poorly penetrate the blood- brain barrier (BB) and several allosteric modulators under study [7].

Because of the ubiquity of GABA in the CNS It is not surprising that disordered GABA signaling has been implicated in several human neurological and psychiatric diseases. Anxiety, sleep, seizure, Alzheimer's, Parkinson's and substance abuse are some of several disorders suspected to be linked to the GABA system. Already several medication classes that have affinity for the GABA receptor, including benzodiazepines, muscle relaxants, sedative-hypnotics and anticonvulsants, are now routinely used in clinical medicine.

The production, release and degradation of GABA is mediated through multiple processes. The main precursor of GABA is glutamic acid, an excitatory neurotransmitter itself. GABA is synthesized by the irreversible single-step α-decarboxylation of glutamic acid by the enzyme glutamic acid decarboxylase (GAD), found initially in bacteria and plants and then later in the mammalian CNS and retina. There are two isoforms of the decarboxylase GAD (GAD_{65} and GAD_{67}) that are involved in the synthesis of GABA with GAD_{65} closely associated with the presynaptic vesicles. This relationship strongly suggests that a coupled process is involved in the the conversion of cytosol glutamate to storage of intravesicular GABA. There are also vesicular transports systems termed VGAT for the sequestration of the neurotransmitter into the vesicle. VGAT is also the same vesicular transport for another inhibitory amino acid transmitter glycine in the spinal cord [8].

Similar to most decarboxylases, pyridoxine is required as a co-factor [1]. The localization of GAD in the brain generally correlates closely with the distribution of GABA. After synthesis, GABA is stored in vesicles in the presynaptic terminals in cells classified as "GABAergic" cells. When GABAergic cells receive a depolarizing stimulus, vesicular fusion and exocytosis occurs and GABA is released into the synaptic cleft. GABA signaling is primarily terminated by its reuptake into both neuronal and glial cells through membrane transporter systems. Through this uptake system the presynaptic cytosol and vesicles can reuse GABA. Astrocytes also express membrane transporters systems for GABA and play a significant role in GABA metabolism. When reuptake occurs in these non-neuronal cells or non-GABAergic cells, the availability of GABA as a neurotransmitter is reduced [8].

In addition to uptake through membrane transporters, GABA may also be broken down by the enzyme GABA Transaminase (GABA-T). GABA-T is, unlike GAD, widely expressed in both central and peripheral systems and possibly helps limit exogenous GABA from influencing CNS activities. In the CNS, this primary enzyzme is associated with GABA breakdown and is found both in GABA-ergic neurons and astrocytes. One product of GABA-T is glutamate which may be involved in the recycling of glutamate to form new GABA. GABA is also

metabolized extracellularly by GABA-transaminase (GABA-T) into succinate semialdehyde, which then enters the krebs cycle for further metabolism [9].

2. Introduction to the endocannabinoid system (ECS)

The identification of Δ^9-tetrahydrocannabinol (THC) as the psychoactive constituent of cannabis opened a door to unexpected discoveries in neuroscience. Cannabis is the generic name for *C. sativa* (*C. sativa*) or hemp and belongs to the botanical group *Cannabaceae* that also contains hop. Cannabis was found to contain numerous molecular structures similar to THC, including cannabidiol (CBD) and cannabinol (CBN) and others. These new structures were initially referred to as cannabinoids and led to the obvious question of how, and why these botanical compounds worked in animals.

It was initially believed that these plant-based cannabinoids like THC, now referred to as phytocannabinoids, probably influenced animal physiology through a nonspecific mechanism to alter cellular membranes. Soon after establishing the laboratory synthesis of THC, modifications of the structure were created and tested in the laboratory. The availability of these synthetic analogs of THC led to the unexpected finding that the psychoactive effect of THC was stereospecific and occurred through binding to an unknown endogenous receptor [10, 11]. Evidence of an endogenous receptor was discovered in 1988 that revealed affinity for the THC molecule in rodent brain [12]. This previously unknown receptor was named CB_1 and found to be a G-Protein Coupled Receptor (GPCR) with seven transmembrane helices. Within a few years, a second peripheral receptor was cloned and named CB_2. Both receptors in humans were found to have 44% of the amino acid residues identical and in the transmembrane crossings 68% were the same. Although CB_1 was the first receptor identified in the brain and was considered a central receptor, it is now known that it is widely distributed outside the CNS but at lower expression, including the respiratory, cardiovascular, skin, ophthalmic systems, and the adrenal glands. CB_2, originally discovered in the spleen and thought to be a peripheral receptor, was later found to be present in limited amounts within the CNS and widely available in immune tissue and skin [13].

Although only recently discovered in the late 20th century, it is now recognized that the CB_1 and CB_2 receptors are the most plentiful G-protein coupled receptors (GPCR) in the body. CB_1 is especially abundant in the brain and is more plentiful than all other receptors including GABA.

The presence of these two endogenous cannabinoid receptors led to the expectation that endogenous ligands must lay ahead. Several years earlier the opiate receptors had been discovered in the brain that had affinity for compounds obtained from the opium plant. This led to the isolation of a class of endogenous ligands termed the enkephalins that were bioactive neuropeptides.

Soon after the identification of the cannabinoid receptors, the endogenous ligand arachidonylethanolamine was isolated in 1993 and found to have agonist properties for CB_1. This ligand was found in rodent brain and was composed of elements from arachidonic acid and ethanolamine. This unexpected ligand was soon christened Anandamide (AEA), a Sanskrit word for 'bliss' [14].

Arachidonic acid is a polyunsaturated fatty acid found in membrane phospholipids in several body organs including the brain [15–17]. In addition to being a precursor for AEA, arachidonic acid is also an important precursor for eicosanoids including prostaglandins. Shortly after the discovery of AEA, a second bioactive lipid that also included arachidonic acid, 2-arachidonylglycerol (2-AG), was found with binding affinity for both cannabinoid receptors. Unlike AEA, 2-AG had been

known for over fifty years as an intermediary in metabolic pathways of triglycerides and other glyceride molecules and is far more available than AEA. 2-AG was found to be a full agonist of CB_1 and CB_2 and abundantly available throughout the body [18, 19]. In contrast, anandamide is a partial agonist of CB_1 and CB_2 and belongs to the family of N-acylethanolamines (NAE). NAEs consist of saturated and monounsaturated fatty acids that include palmitic and oleic acids and these other NAEs are more abundant than AEA but do not bind to cannabinoid receptors [20]. Although only recently discovered in the late 20th century, it is now established that the CB_1 and CB_2 receptors are the most plentiful G-protein coupled receptors (GPCR) in the body. CB_1 is especially abundant in the brain and is more plentiful than all other receptors including GABA. The observation that the ECS is so highly expressed within the brain and the finding that the system is highly conserved in the evolution of animals illustrate the importance of the system in the healthy function of man.

Together AEA and 2-AG are referred to as endocannabinoids. These two endogenous ligands are produced in multiple body systems and activate cannabinoid receptors. These endocannabinoid chemical structures are long-chain, polyunsaturated fatty acid chains and differ significantly from the ring structured phytocannabinoids present in cannabis, with different binding affinities to the cannabinoid receptors. The endogenous 2-AG, for example, is a full agonist to the CB_1 and CB_2 receptors while the plant-derived THC is only a partial agonist. In addition, another important phytocannabinoid, CBD, has even less affinity with only very limited binding to cannabinoid receptors. As endogenous lipids, although both bind to the cannabinoid receptors, the NAE molecule AEA and the monoacylglycerol (MAG 2-AG as) belong to two distinct families with different synthetic and degradative pathways. Both AEA and 2-AG appear unique among their separate families as they are the only molecules that bind to the cannabinoid receptors CB_1 and CB_2.although they share affinities with the several similar lipids for non-cannabinoid receptors. In addition, both endocannabinoids and other bioactive lipids have redundant pathways in the synthesis and breakdown of the lipid molecules. This diversity in metabolism and binding to multiple receptor families by the NAEs and MAG lead to a highly complex system that regulates many important functions [21].

Collectively, the cannabinoid receptors CB_1 and CB_2, the two endocannabinoid messengers AEA and 2-AG, and the associated and separate enzymatic systems are called the endocannabinoid system (ECS). The ECS is a major system in human and the CB_1 and CB_2 receptors are expressed within the CNS and several peripheral organs including heart, liver, fat, skin, eye and the intestines [22].

As details about the ECS emerged during the 1990s and into this century, it has become apparent that endocannabinoids interact with several neurotransmitter systems and play an important role in regulating physiological functions. Autoradiographic localization of cannabinoid receptors in the rat established the rich co-localization of cannabinoid receptors with GABA-containing neurons [23, 24]. It has been reported that GABA is produced and released by inhibitory interneurons comprising between 20–60% of neurons in some areas of the brain [25]. The CB_1 and CB_2 receptors have been found to be highly expressed in areas rich with GABA neurons including the cortex, basal ganglia, substantia nigra and cerebellum. Compared to classic neurotransmitters including GABA and Glutamate [24, 26], the ECS is far more abundant and widely distributed compared to these systems. Thus, activation of the CB_1 receptor (the most abundant GPCR in the CNS) interacts with adjacent neurons including GABA and regulates neurotransmitter function to express their central effects.

The ECS is also one of the most pleiotropic systems in mammals and differs from other neurotransmitter systems in several ways. Importantly, most intercellular transmission proceeds anterograde with the release of neurotransmitters

from presynaptic neurons that bind to receptors on the postsynaptic membranes. Neurotransmitters, stored in vesicles within the presynaptic cytosol, are released as chemical messengers upon activation of the presynaptic neuron. After release into the synapse, the chemical messengers are subsequently broken down in the synaptic cleft or taken up by transport systems into the neuron or adjacent supporting cells [27].

Endocannabinoids act in the opposite direction from a postsynaptic neuron to presynaptic neuron. This retrograde direction allows the ECS to neuromodulate the forward direction of chemical communication. Because of their highly lipophilic properties, endocannabinoids are not stored in vesicles but are synthesized from membrane lipids only when required. Once released, the endocannabinoid diffuses to its' receptor target on the presynaptic neuron and helps regulate overall neurotransmission. In the brain, the presynaptic receptor is predominantly CB_1 with limited CB_2 found in microglia and other tissue. Eventually the endocannabinoid is released by the receptor and taken up by either the pre- or postsynaptic neuron for final degradation [17].

The endocannabinoids are synthesized in the post-synaptic membrane only after the cell is activated and then rapidly degraded after binding to the presynaptic cannabinoid receptor, the effect of stimulation is localized and limited in duration similar to GABA and other neurotransmitters. In addition, although these actions occur binding of AEA and 2-AG primarily to the CB_1 receptor in the brain, other non-cannabinoid receptors have also been identified that directly bind and are activated by endocannabinoids [28].

3. The discovery of anandamide (AEA)

Anandamide (AEA) was isolated from pig brain in 1992 and found to be a derivative of the fatty acid arachidonic acid. As the first endocannabinoid to be discovered, the molecule was named anandamide after the Sanskrit word Ananda that means bliss [29]. As a member of the N-acylethanolamines, it was established that AEA shared multiple synthetic pathways with other glycophospholipids [17].

Typical of other neurotransmitters, AEA functions as a chemical messenger between neurons. However, there are significant differences between endocannabinoids and neurotransmitters including GABA. Soon after its discovery, the uniqueness of AEA was established with the observation that the messenger was synthesized only on demand and diffuse across the synaptic cleft in a retrograde direction to the presynaptic neuron [17].

Following the inflow of calcium^{2+} into the postsynaptic cell, AEA is synthesized from the precursor membrane lipid N-arachidonyl-phosphatidylethanolamine (NAPE). NAPE is present in brain only in small amounts and cannot sustain prolonged synthesis of AEA. As with 2-AG, AEA contains arachidonic acid and combines this membrane constituent with phosphatidylethanolamine (PE), utilizing a calcium^{2+} dependent enzyme N-acyltransferase (NAT). The primary pathway for synthesis of anandamide is conversion of NAPE to anandamide through the action of a NAPE-specific phospholipase D (PLD), although several other pathways are known to exist. Similar to other synthesis in the NAE family, the NAPE pathway is not exclusive for AEA. Although the importance of other pathways have yet to be established, it is known that in genetically modified mice without NAPE-PLD, no reduction of the production of AEA is found [30].

Since multiple pathways may be associated with the synthesis of AEA, the abundance of choices has been suggested to enhance the number of stimuli that may initiate the production of AEA. Lipopolysaccharide (LPS), for example, is an

endotoxin in the outer membrane of gram-negative bacteria that plays a critical role in the protection of the microbe. Exposure to macrophages activates LPS to defend the bacteria and numerous lipid mediators including AEA are released. The synthesis and release of AEA and the other bioactive lipids is not believed to occur through the intermediate NAPE but rather through the secondary pathways that lead to AEA [20].

The breakdown of AEA results in the release of arachidonic acid and ethanolamine. Within the post-synaptic cell, an intracellular serine amidase named fatty acid amide hydrolase (FAAH) cleaves the long-chain fatty acid of AEA although other available hydrolytic enzyme systems in the cytosol appear to have little effect on AEA. Numerous studies have used disruption of this serine hydrolase through genetic or pharmacological manipulation to increase AEA activity. Manipulation of the FAAH system has already become the target of new drug development in an attempt to increase AEA in the treatment of human pathology [31, 32].

Other non-hydrolytic enzymes also break down AEA including lipoxygenases and cyclooxygenases. These non-FAAH systems are very active at non-cannabinoid receptors although their importance in deactivation of AEA at cannabinoid receptors has yet to be determined [20].

AEA is not the only ethanolamide that can bind to cannabinoid receptors. Other bioactive lipids in this class include numerous compounds including palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) bind to the CB_1 receptor. Each of these ligands has distinctive physiological effects associated with them. PEA is associated with several indications including use as an anti-inflammatory or analgesic, while OEA appears useful as an appetite suppressant to reduce body weight [33, 34].

Both PEA and OEA are polyunsaturated fatty acids with multiple double bonds within the long chain. Other polyunsaturated fatty acids have also been reported to have agonist activity for the cannabinoid receptors. Only AEA, among the saturated and monounsaturated fatty acids, has been found to have affinity for the cannabinoid receptors.

4. 2-Arachidonylglycerol (2-AG): the second endocannabinoid

2-arachidonylglycerol (2-AG) is a monoacylglycerol that incorporates arachidonic acid at the 2 position of the glycerol backbone. This molecule serves the dual function of a lipid intermediary while also functioning as a chemical messenger within the ECS. Although this endocannabinoid was discovered later than AEA, 2-AG is several hundred fold more common in the CNS compared to AEA and is a full agonist to both the CB_1 and CB_2 receptors.

There are two major pathways for the synthesis of 2-AG. Similar to AEA, initiation of the process to manufacture 2-AG requires an inflow of calcium^{2+} into the neuron. The primary pathway for synthesis involves a precursor, phosphatidylinositol, converted by phospholipaseβ or phospholipaseγ, to the intermediary lipid 1,2-diacylglycerol (1,2-DAG). The 1,2-DAG is then hydrolyzed by a DAG lipase to form the endocannabinoid 2-AG.

There is a secondary pathway also available that involves the production of the intermediary 2-arachidonyl lysophospholipid. Once 2-arachidonyl lysophospholipid is available, this lysophospholipid in the presence of the enzyme lysophospholipase-C (LYSOPLC) is rapidly converted to 2-AG.

The breakdown of 2-AG also occurs through a primary pathway but several minor alternatives are also present. Hydrolysis of 2-AG by monoacylglycerol lipase (MAGL) is the most common pathway and involves the cleavage of the ester bond within the 2-AG structure to form arachidonic acid and glycerol. There are at least

two forms of MAGL that have been found in rodent and rabbit models. In comparison to the small amounts of AEA and its associated degradative enzymes, 2-AG is widely distributed throughout the CNS along with its synthetic and degradative enzymes. Perhaps because of the breadth of distribution of 2-AG in the CNS, some overlap with AEA occurs. However, a more important distinction is that MAGL is found only in the presynaptic neuron and degradation of 2-AG occurs after release from the presynaptic cannabinoid receptor. AEA, in comparison, after its release from the presynaptic cannabinoid receptor must traverse the synaptic cleft and enter the postsynaptic neuron where it is broken down by the NAE degrading enzyme FAAH [17, 35, 36].

The development of genetically modified mice deficient in MAGL along with the synthesis of MAGL inhibitors have provided useful tools to study the properties of 2-AG. Use of these ligands that block the synthesis of MAGL have revealed elevations of this endocannabinoid, especially in the brain and to a lesser extent multiple organs in the body including the heart, liver, kidney, and brown adipose tissue. Although 2-AG is the major endocannabinoid that binds to the cannabinoid receptors in brain, it clearly also serves an important role in the the regulation of chemical signaling in other organ systems. When the breakdown of 2-AG appears is impaired due to these receptor anatagonists or genetic manipulations, arachidonic acid is significantly reduced in the brain. This suggests that the production of 2-AG serves an important role not just in the formation of an endocannabinoid but also in the in the production of proinflammatory molecules [37].

Other alternative routes for 2-AG degradation are also available. Cycloxygenase-2 (COX-2) and lipoxygenases are secondary enzyme systems that also reduce 2-AG. COX-2 serves an important role in the inflammatory process and converts arachidonic acid to prostaglandins. Lipoxygenases oxidizes polyunsaturated fatty acids and these are non-heme, iron-containing enzymes that are found in a broad range of eukaryotes. They are known to be involved in the metabolism of the eicosanoids including the prostaglandins [37].

5. Endocannabinoid-GABA regulation of chemical messaging

In the 1990s, the phenomenon of "depolarization-induced suppression of inhibition" (DSI) was first reported in the purkinje cells of the cerebellum [38] and later in hippocampal pyramidal cells [39]. DSI occurs through the activation of the CB_1 receptor and is considered the classic example how endocannabinoids regulate neuronal behavior through retrograde signaling and suppression of GABA release. The CB_1 receptor is densely expressed on the GABA presynaptic neurons that are abundantly found in the cerebral cortex, hippocampus and amygdala and are essential for higher cortical functions including learning and memory. Small interneurons release GABA and communicate with the larger purkinje cells and pyramidal neurons. This interaction moderated by the release of GABA results in hyperpolarization of the larger post-synaptic cell and subsequent inactivation. Activation of the CB_1 receptor located on the presynaptic interneuron inhibits the release of GABA and thus suppresses the inhibition of the larger cells. It is now well established that this inhibition of GABA release from the interneuron is the result of retrograde communication from the activated postsynaptic cell to the presynaptic GABA-containing interneurons through the release of endocannabinoids that facilitate an increase of intracellular calcium^{2+} and the initiation of the DSI. Other cannabinoid agonists in addition to endocannabinoids are also known to block interneuron release of GABA through depolarization-induced suppression of inhibition. Presynaptic CB_1 antagonists, such as rimonabant, have also been reported

to block the effect of CB_1 receptor activation further establishing the critical role of retrograde modulation of chemical signaling through the ECS [22]. Thus, inhibition of GABA release is governed through depolarization of the presynaptic neuron by endocannabinoid binding to the presynaptic CB_1 receptor [40, 41].

A few years after the discovery of DSI, presynaptic stimulation of CB_1 through retrograde transmission of endocannabinoids was found to also occur with excitatory neurons and the phenomenon was termed "depolarization induced suppression of excitation"(DSE). Unlike DSI and the inhibition of GABA release, DSE inhibits the release of excitatory neurotransmitters including glutamate through a similar retrograde release of endocannabinoids. Although initially discovered the inactivation of Purkinje cells, DSE has also been observed in other regions of the brain although the role of endocannabinoids in these areas is less well established [42].

Dependent upon the presynaptic neurotransmitter, stimulation of presynaptic CB_1 receptor through retrograde release of endocannabinoids moderates the communication between cells. This changing effect of the endocannabinoids on GABA and glutamate release and the shaping of synapses occrs through a process called synaptic plasticity. Activation of a single synapse is usually insufficient to activate the post-synaptic cell and multiple synapses must fire simultaneously. The coordination and magnitude of the synaptic communication determines the change of voltage in the post-synaptic cell and the strength of the signal. Reductions in the number of presynaptic cells or incoordination of firing results in weakening of the signal.

The strengthening of synapses over time is termed long term potentiation and requires coordination of firing of the pre and post synaptic cells within a window of 20 msec. Cellular firing outside the temporal window weakens the synapse and reduces the voltage difference over time and is referred to as long term depression.

There is a balance in the regulation of excitation and inhibition that allows the brain to physically adapt for learning and memory [43]. Generally these changes are incremental and occur continuously at the synaptic level through a process termed synaptic plasticity [44].

Although glutamate has received a great deal of attention in the process of neuroplasticity, GABA also plays an important, or perhaps equal, role in the adaptation of the nervous system. Changes in neuronal activity and excitation by glutamate release may initiate off-setting activation of inhibitory inputs through GABA interneurons. In both activation and inhibition of the synaptic signal, retrograde release of endocannabinoids through DSI and DSE likely mediates synaptic depression [43].

6. GABA and the tale of two cannabinoids

The endocannabinoid system maintains homeostatsis in the CNS primarily through activation of the CB_1 receptor. This receptor is also responsible for the well-known behavioral and physiological effects of the phytocannabinoids. The mechanism of how this modulation of the CNS occurs is by retrograde signaling through activation of the CB_1 receptor. As noted earlier, the ECS and GABA neurons are collocated in many areas of the brain and this close proximity may explain how CB_1 binding influences the GABA system. The cortex, hippocampus, hypothalamus and cerebellum are areas in the brain where this overlap of the ECS and GABA is especially prominent.

There are several preclinical studies that have examined the inhibition of GABA release in the presence of cannabinoid agonists. One early *in vitro* study employing

an investigational synthetic cannabinoid agonist (WIN 55,212–2) on hippocampal interneurons found a diminuition of GABA release from the neurons after exposure. In another *in vitro* study the same investigational agent plus a second experimental cannabinoid agonist (CP-55940) were evaluated in rodent corpus striatum and found a dose-dependent reduction in GABA release.

Acute administration of the phytocannabinoid THC has also been studied. In an *in vivo* electrophysiological project after treatment, extracellular GABA in the prefrontal cortex was found to be significantly reduced compared to baseline. Different areas of the rodent brain were studied including the corpus striatum, and prefrontal cortex. One study reported different findings that THC and a synthetic cannabinoid failed to have effects on GABA synthesis and uptake in the globus pallidus in substantia nigrae of the rodent brain [45, 46].

Two other studies also evaluated the effect of THC on GABA release in rodent models. One evaluated THC alone and reported a dose-dependent reduction in GABA uptake in the rat globus pallidus [47, 48].

The abundance of CB_1 receptors on presynaptic neurons and their relationship to the strength of inhibition was assessed in a study of cholecystokinin (CCK) expressing GABA interneurons in the hippocampus. Earlier studies had demonstrated that the number of ion-channel-forming AMPA receptors could predict the magnitude of the postsynaptic response [49, 50] and that more GABA receptors were associated with greater inhibition. However, CB_1 receptors are GPCR and operate through different mechanisms including modulation of voltage-gated Ca^{2+} and K^+ channels and second messenger systems. Using the CB_1 receptor antagonist AM251, the effect of activation was measured in basket cells and dendritic-layer innervating (DLI) cells. Basket cells have a significant higher expression of CB_1 receptors and DLI have significantly less receptor density. The CB_1 receptor antagonist AM251 increased the action-potential inflow of Ca^2 by 54% in basket cells but not in DLI. However, this increase was significantly reduced from the expected effect of the large number of receptors. A CB_1 agonist decreased Ca^{2+} independent from the CB1 receptor expression. Collectively this suggests that only a subpopulation of CB_1 receptors in close proximity to the Ca^{2+} channel participate in the endocannabinoid modulation of GABA release [51].

Another study evaluated the effect of exposure to cannabinoids in adolescent rats. Using electrophysiological and immunohistochemical techniques, early-, mid- and late adolescent rats were treated with a CB_1 agonist (WIN). Early and middle adolescent rats were found to exhibit significant disinhibition of prefrontal cortex (PFC) behaviors at the later adult stage. This result was reversed when the adolescent rat was infused with the positive allosteric modulator GABAA agonist Indiplon. This response suggests that at certain stages of development exposure to cannabinoid agonists may be critical in the downregulation of GABA in the PFC and expressed in the adult stage of maturation [52].

A recent review summarized the literature on the interaction of endocannabinoids and neurotransmitters [22] although only a few have been reported for GABA. Administration orally or intravenously of the endogenous cannabinoid agonists including the endocannabinoids is technically difficult and their interpretation limited. On the other hand, phytocannabinoids can be smoked, ingested or applied as a topical with significant absorption and physiological effects mediated through cannabinoid receptors. In one report of adolescents, thirteen habitual users of cannabis were compared to sixteen non-canabis normal controls in a study using standard ^1H MRS techniques performed on a MAGNETOM trio whole body MRI/MRS system to determine GABA metabolism in the anterior cingulate cortex (ACC) [53]. reported reduced levels of GABA in the anterior cingulate cortex (ACC) of adolescents that were habitual users of marijuana when compared to match controls. The ACC

surrounds the anterior area of the corpus callosum and communicates with the prefrontal cortex and parietal lobe in addition to deeper limbic structures including the amygdala, nucleus accumbens and hippocampus. It is well established that GABA plays an important role in the maturation of these area in the adolescent brain and disruption of this process may result in neuropsychiatric and substance abuse issues later in life.

Results of the MRS scans revealed significantly lower levels of ACC GABA activity in adolescents that habitually used cannabis. Reduced ACC glutamate levels in adolescents that habitually used cannabis had been reported in an earlier study [54] with MRS imaging and in this follow-up report these findings paralleled the reduction in glutamate with a similar reduction of GABA.

Enhancement of GABA activity has been proposed as a therapeutic approach to the treatment of cannabis use. In one randomized clinical trial (RCT) fifty patients with cannabis dependency were treated with Gabapentin 1200 mg/day or placebo for twelve weeks. Compared to placebo, the study reported significant reduced use of cannabis measured by several assessments including urine drug screens. Gabapentin is a structural analog of GABA and was initially thought to act on the GABA system. Later studies demonstrated that Gabapentin does not alter GABA activity or receptors although it may increase GABA synthesis and non-synaptic GABA release [55].

In the first of two studies, the GABA reuptake inhibitor Tiagabine (Gabitril), was assessed in eight cannabis users and compared when combined with oral THC. THC was dosed at 30 mg p.o. and tiagabine at 6 and 12 mg p.o.. Subjects were trained to use established drug-discriminationprocedures to identify placebo and drug conditions, blinded to the study condition and were informed they would receive placebo, THC and tiagabine, alone or in combination during the study. Tiagabine was found to enhance the discriminative-stimulus, self-report and performance results when given with THC and to produce similar outcomes when administered alone [56].

In a subsequent study the investigators replaced tiagabine with baclofen and repeated the trial. In contrast to tiagabine, baclofen is a selective $GABA_B$ agonist but has not effect on the $GABA_A$. Results of both studies were similar suggesting that $GABA_B$ receptors are involved at least in part with the effect of elevated GABA on cannabinoid-related behaviors [57].

The authors commented that although $GABA_B$ enhanced the effects of THC, they could not rule out that accentuation of GABA at $GABA_A$ receptors could also contribute to the outcome.

In addition to evaluation of the ECS and GABA through pharmacological enhancement of GABA, an interesting clinical study reporting that pharmacological-induced deficiency of GABA increased the effects of THC in several psychiatric assessments. Using normal subjects, this double-blind, placebo-controlled study evaluated flumazenil, an antagonist and partial inverse agonist of the $GABA_a$ receptor, against intravenous THC or placebo. Blocking the $GABA_a$ receptor with flumazenil accentuated the psychological effects of THC including psychoses and anxiety and a decrease in the THC-induced P300 amplitude [58].

Through imaging studies of the ECS, manipulation of the synthesis and degradation of endocannabinoids, and pharmacological interventions much has been learned about the cannabinoids since the initial discovery of of the first cannabinoid receptor CB_1 in 1988 [59]. The ECS plays a major role in the maturation and homeostatsis of the CNS and activation of the CB_1 receptor is the primary initiating event. Modulation of other neurotransmitter systems including GABA can then occur through retrograde transmission [60].

Ligands other than the endocannabinoids also bind to CB_1 and CB_2 receptors and much can be learned through observation of the effects of these non-endocannabinoids. Although phytocannabinoids, evolved through time in the plant kingdom and differ significantly from endocannabinoids, the overlap in affinity for cannabinoid receptors offer additional means to study the modulation by the ECS and neurotransmitter systems.

Phytocannabinoids are produced in the plant *C. sativa* (cannabis) and are C_{21} terpenophenolic molecular ring structures grouped into eleven classes. Currently about 120 different phytocannabinoids have been identified in cannabis and comprise approximately 24% of the weight of the plant. The first class of phytocannabinoids is the most common (approximately 17%) and contains the psychoactive THC. Variations in the growth of the plant *C. sativa* including growing conditions and sunlight, geography, processing and storage, and plant variety can all significantly alter the proportion of each chemical class. For this reason, cannabis is constantly in change and this variation can influence the pharmacological properties of different cannabis extracts [61].

There are several large epidemiological studies of phytocannabinoid effects on the ECS. Although banned in many areas, Cannabis is the most used illicit drug globally with an estimated 3.8% (182.5 million) of the global population exposed to cannabis [62, 63]. Within the United States, the estimated exposure is even higher with 8.4% (22.2 million) of the population reported to have used cannabis in one year. With relaxation of laws and greater duration of use combined with the change in composition and potency of cannabis, real world studies can provide us important information in understanding the function of the ECS system and the effects of disruption of normal processes.

Among the most important epidemiological studies are reports of exposure to cannabis of pregnant women and the effects on their offspring. In a recent study it was estimated that 5.2% (115,000) of pregnant women are exposed during their preganancy. Some of these women likely use cannabis unaware of their pregnancy and inadvertently expose the first trimester fetus to THC when the nervous system is first initiated. Others may choose to use THC later in pregnancy believing it is a safe remedy for pregnancy-associated nausea and vomiting while neurotransmitter systems are evolving. Others may just believe that cannabis use is safe and be unaware of the potential hazard to the unborn [64].

As with many drugs, however, cannabinoids carry significant safety concerns for pregnant women and as a lipophilic molecule easily traverse the placenta into the fetal bloodstream. Animal studies have shown a clear association between cannabinoids and lower birth weight. In humans, several large, well-conducted studies have explored the short- and long-term effects on fetal, child and adolescents and possible teratogenicity of prenatal cannabis exposure on fetal development (Hurd et al. 2005).

The Ottawa Prenatal Prospective Study (OPPS) was a large, epidemiological study of 291 expectant, middle class Canadian women. Within this group of expectant mothers, 20% used cannabis sometime during their pregnancy. All subjects were evaluated during their pregnancy and for the first six years using standardiazed neuropsychological tools.

At birth, there were observations made of increased startle reflex in children exposed in utero to cannabis, but no significant change in weight or increased presence of congenital malformations. By age four, however, behavioral changes including decreased visual performance, attention, and memory were apparent. In older children, impaired executive function was reported [65, 66].

In 1991 a second longitudinal study named the Maternal Health Practices and Child Development Study (MHPCD) was reported on 519 expectant mothers

and live born infants. Unlike the earlier study in Ottawa, expectant mothers were largely lower class economically with poorer prenatal care. Expectant mothers were evaluated at 4 and 7-month gestation offspring evaluated until young adulthood. Growth parameters including birth weight, head or chest circumference, and gestational age were analyzed at birth with no statistical differences noted between newborns with non-exposure in utero and in newborns with maternal use of cannabis. There was a small effect on decreased birth length in exposure the first two months and a positive effect on body weight with usage in the third trimester [67]. In a follow-up of the offspring in this study up to two decades later, prenatal maternal exposure to cannabis was found to result in a greater risk of cannabis use in their children at adolescence (38% before age 15). By age 22 in-utero cannabis-exposed children were more apt to not complete high school (54.4% vs. 37.2% in controls), be unemployed (67.6% vs. 52.1%) and more likely to have been arrested (56% vs. 27.3%) [68].

The Dunedin study was a third, and more controversial, project conducted in New Zealand on 1037 individuals followed from birth to 38 years. One measurement obtained over the course of the study was the evaluation of the association between cannabis use and neuropsychological outcomes. Neuropsychological assessments were obtained before the age when cannabis use occurred and changes studied. Cannabis use was obtained at age 13 and then at age 38 after a pattern of consistent use. It was found that there was an associated decline in IQ related to the frequency and length of exposure to cannabis. The greatest vulnerability appeared to occur with adolescent exposure. The authors found that persistent cannabis use was associated with neuropsychological decline broadly across domains of functioning, most significantly in the domains of executive functioning and processing speed. Study participants with more persistent cannabis dependence also showed greater IQ decline over the years, along with greater overall cognitive decline. Greater cognitive impairment was observed in those who began cannabis use in adolescence. The investigators also pointed out that cessation of cannabis use did not fully restore neuropsychological functioning in these adolescence-onset users [69, 70].

Another recent large, retrospective, cohort study of 661,617 pregnant women study conducted over six years in Ontario, Canada examined the association between self-reported cannabis use in pregnancy and any adverse maternal or perinatal outcomes. The investigators accounted for known confounding factors, such as tobacco use, in one of two cohorts by the use of a matched design analysis. The results showed that preterm birth rate, at less than 37 weeks' gestation, for both the matched and unmatched cohorts were significantly higher in the women who reported cannabis use. The rate of preterm birth rate in the unmatched cohort was 12.0% in cannabis users, compared to 6.1% in nonusers. In the matched cohort, the rate of preterm birth was 10.2% in cannabis users versus 7.2% in nonusers. A continuous increase in relative risk of preterm birth from cannabis exposure was observed between 34 to 36 6/7 weeks' and 28 to 31 6/7 weeks' gestation, respectively. Because this type of increase was not observed for very preterm birth at less than 28 weeks' gestation, it was conjectured that cannabis exposure may be more strongly associated with early and moderate preterm births versus very preterm births. Cannabis use in the subjects was also significantly associated with the following secondary outcomes: small for gestational age, placental abruption, transfer to neonatal intensive care, and 5-minute Apgar score of less than 4 [71].

Both the OPPS and MHPCD studies were consistent in demonstrating behavioral and cognitive impairment years after exposure to cannabis in-utero. The Dunedin study also reported decline in IQ related to cannabis exposure beginning in adolescence. Collectively, all three studies report important deficits that

emerge over time in child and adolescent maturation. A limitation of these studies, however, is the continuing social acceptance of cannabis use and increasing potency of THC.

To provide more current information, an NIH-initiative, the Adolescent Brain Cognitive Development (ABCD) Study is ongoing. This is a national, multisite, longitudinal cohort study that is prospectively following subjects from childhood through adolescence to explore the effects of substance use such as cannabinoids, among other experiences, on neurocognitive development. There are, of course, many challenges associated with long epidemiologic studies. Aside from participant loss and difficulty maintaining controls, the constant flux in the content of cannabinoid products over the years, namely the significant increases in the ratio of THC to CBD, presents significant inconsistency in comparing these long studies or predicting current risk.

7. Final comments

GABA is an amino acid concentrated within the CNS and is recognized as the major inhibitory neurotransmitter in the brain [1]. With the exception of a second, excitatory amino acid neurotransmitter glutamate, GABA is present in millimoles/gm in brain tissue compared to nanomolar/gm concentrations of the other classic neurotransmitters [72].

The physiological effects of GABA do not occur in isolation. The functional relationship beween the two systems begins after the release of GABA from an activated presynaptic neuron and stimulation of the postsynaptic cell. Endocannabinoids are then manufactured on-demand and released to bind to cannabinoid receptors on the presynaptic membrane terminating the release of GABA.

The CB_1 receptor is highly expressed in several regions of the brain including the forebrain, amygdala, hippocampus, substantia nigra and cerebellum. This receptor is frequently in GABA containing neurons and this overlap allows for close coordination and interaction between the two systems. As a result, the ECS provides an important feedback to the GABA system and participates in the maturation of the CNS and the function of the adult brain [72, 73].

The GABA system and the ECS, similar to all neurotransmitters, are limited to brief synaptic activity at discrete locations and are quickly terminated through either enzymatic breakdown or reuptake mechanisms. GABA is stored in presynaptic vesicles and released after excitation by an action potential into the synapse to stimulate the postsynaptic cell. The endocannabinoids, in contrast, are synthesized in the postsynaptic membrane on demand only after the cell is stimulated. Upon release, the endocannabinoid moves in a retrograde direction across the synapse and binds to the CB_1 receptor on the presynaptic neuron. Once the endocannabinoid is bound to the CB_1 receptor, the release of neurotransmitters from the presynaptic neuron is terminated.

How endocannabinoids work in moderating GABA is introduced in the discussion of depolarization induced suppression of inhibition (DSI). This is a critical concept on how the chemical signal with GABA release is moderated by the activation of the CB_1 receptor. Although less established, activation of this cannabinoid receptor may also activate another amino acid transmitter glutamate through a similar mechanism termed depolarization induced suppression of excitation (DSE).

Several preclinical studies of ECS and GABA in this chapter followed the initial papers on DSI and DSE and the concept of CB_1 receptor activation influencing the release of GABA (and potentially glutamate). Although for technical reasons it has not been possible to study the effect of AEA and 2-AG directly, these studies chose

to utilize several laboratory-created CB_1 agonists under investigation or the phytocannabinoid THC. No matter the source of the agonist, the findings consistently found that stimulation of the CB_1 receptor reduced the release of GABA.

From these studies it is apparent that activation of the CB_1 receptor is not exclusive to endocannabinoids. As discussed earlier, the plant *C. sativa* produces phytocannabinoids including THC that also are agonists and partially bind to the CB_1 receptor [74]. These molecules evolved in the plant kingdom for evolutionary imperatives that are incongruent with the evolution of the ECS in animals. Although they differ significantly from the endocannabinoids in chemical structure, synthesis, degradation, phytocannabinoids including THC and CBD are of great interest since they have CB_1 receptor activity and similarly influence the release of GABA. This affinity is likely coincidential yet provides additional information on the interplay between the physiological functions regulated by GABA and activation of CB_1.

Earlier in this chapter several large epidemiological studies were reviewed reporting the effects of cannabis on the development of the nervous system in utero to maturity. These studies are informative because they describe the effects of cannabinoids on the developing nervous system and adult where GABA plays an important role. From these reports it is likely that early maternal exposure to phytocannabinoids results in impairment in the offspring through disruption of the development of the nervous system with behavioral abnormalities appearing later in life [65, 68, 75, 76].

There are obvious limitations in large scale studies since In normal circumstances ECS and GABA collaborate in limited and localized coordination in development. Phytocannabinoids act systemically throughout the body and are not limited to discrete synapses. In addition, since phytocannabinoids are lipid soluble, sequestered in fat tissue, and broken down by hepatic enzymes, the location and duration of exposure to phytocannabinoids differs from the brief, focused synaptic interaction between GABA and the endocannabinoids. Nevertheless, these large studies of cannabis use provide important information on how phytocannabinoids may disrupt GABA function that may be reflected in the abnormalities reported in these larg scale studies. Cannabis is regarded by many as relatively 'safe' and is becoming 'legal' in many areas. However, other 'safe' and 'legal' drugs including nicotine and alcohol are associated with serious public health concerns. These studies give us insight into the possible risks associated with using phytocannabinoids and influencing the communication between GABA and the endocannabinoids.

The interaction of GABA and the ECS is important for normal physiological function. As our knowledge of this modulation of the CNS advances, additional knowledge and treatments will likely emerge that will provide unexpected benefits to patients. However, epidemiological studies of exposure to cannabis also provide important information they reveal the disadvantages and risks of disruption of the GABA-ECS systems. As increased access and duration of usage evolve, we will learn more of the benefits, and risks, of cannabiods.

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Chapter 2

Phytocosmetics and Phytopharmaceuticals from African Medicinal Plants

Aliyu Ahmad Warra

Abstract

Africa contains some of the richest biodiversity in the world, blessed with bountiful plants of economic importance and plants of medicinal importance which when developed would reduce our expenditure on imported drugs to meet our health needs. Plants are source of phytochemicals that possess emollients, humectants and medicinal properties. A complex mixture derived from plant sources are also used as a medicine or drug (phytomedicine, or phytopharmaceuticals). The demand for phytocosmetics and phytopharmaceuticals is increasing. Due to growing global market demand for phytocosmetics such as skin care, toiletries, perfumes and other cosmetics, there are greater opportunities through participation of local community in processing the plant resources to extract the products at subsistence level for industrial needs especially now that Africa needs local source of raw materials for the development of local industries for contribution to continental and interbational development. However, little or no research was conducted on the cosmetic potential of such plant resources. Plant-based cosmetics have an important role in modern society, natural based cosmetics, fragrances, and personal care products have increasingly become the greener alternative to nonherbal preparations. In this chapter, African perspective of phytocosmetics and phytopharmaceuticals are covered. Aspects of phytochemistry, botanicals for cosmetic use and formulation, the importance of phytocosmetic in traditional medicine, efficacy, safety research and patent among other areas are discussed in details. Applications of nanobiomaterials in phytocosmetics and phytopharmaceuticals, functional herbal cosmetics, emerging technologies in phytocosmetics phytopharmaceuticals development, and pharmaceutical phytocosmetics were explicated. Entrepreneurial platform for phytocosmetics is captured using the selected African medicinal plants.

Keywords: Medicinal plants, phytocosmetics, phytopharmaceuticals, phytochemistry, nanotechnology, entrepreneurship

1. Introduction

Plants are complex organisms that produce different metabolites responding to the environment they live in. In relation to the skin, its well-being and appearance is affected by phytomolecules interacting with skin cells. Using ethnobotanical studies on the one hand and physico-chemical analyses on the other, a rich inventory of

plants with potential to enrich modern cosmetic products have been pictured [1]. Examples of plants used for personal care which are investigated with new scientific advances was reported [2]. Mutations of viruses and microbes and the emergence of distinct types of diseases along with numerous patients with specific cases that continuous to develop push the industrial and biopharmaceutical sectors to collaborate with each other to innovate and develop new biodrug to face this dilemma and serve the interest of all mankind healthcares [3]. In this regard Biopharmaceutical researchers are pursuing many innovative scientific approaches that are driving therapeutic advances. They are working on new medicines for many diseases, including: cancers, heart dierese and stroke, HIV, asthma and allergy, skin diseases, mental disorders, rare diseases and neurological disorders [4]. A number of advantages including rapid production and scalability, the ability to produce unique glycoforms, and the intrinsic safety of food crops has enable plants to be used in the production of useful recombinant proteins. The expression methods used to produce target proteins are divided into stable and transient systems depending on applications that use whole plants or minimally processed forms [5]. A review has addressed the demand for recombinant biopharmaceuticals in the COVID-19 era [6]. A recent trend in what is seen as an emerging technology for phytocosmetic science development, where new technology updates consumer demand, the phytocosmetics enterprise requires that industries have the technical know- how to develop new technologies with lower costs and time to launch, which demands expertise that often small and medium scale industries do not have, requiring a process of transferring knowledge and technology [7].

1.1 Phytocosmetic development

Formulatation of a polyherbal cosmetic cream comprising plant extracts such as *Glycyrrhiza glabra* root, *Piper betle* leaves and *Azadirachta indica* leaves and to check their antimicrobial potential which can be used in the treatment of infectious skin diseases was reported [8]. Herbs are used in pharmaceutical and cosmetic industry for extracting active ingredients. Medicinal plants whose oils, extracts and tinctures contain active basic principles of plant protection preparations and resources used in obtaining pharmaceuticals and cosmetics products was reported [9, 10]. **Table 1** and **Figure 1(a–h)** showed some plants used in cosmetics and their potential.

1.1.1 Innovation using Plant stem cells

Current development has made it possible to prepare extract from the plant stem cells for the production of both common or professional care cosmetics. The impact of the plant stem cell extract, common apple tree type (Uttwiler Sp‰tlauber) to human skin as one of the first plant sorts, which are used in cosmetology and esthetic dermatology was described [11]. An emerging innovation of using cosmetic ingredients containing plant stem cells and their extracts has made its way into the industry. To create safe and effective organic topical skin care, plant stem cells could hold an interesting role if we can harness these benefits in cosmetics. A recent research interest has focus on the unique properties of plant stem cells which have been both in developing new cosmetics and studying how these extracts/ phytohormones will influence animal skin. A report has dwell into current hand- on experiments in plant stem cell-based cosmetics and has deeply highlighted on the challenges that we need to overcome in order to see meaningful changes in human skin using topical cosmetics derived from plant stem cells [12].

Plants	Potential
Aloe (*Aloe vera*_L)	Depigmentation, moisturizing
Lemon grasss (*Cymbopogon citratus*)	Anti-dandruff, fragrance
Rose (*Rosa centifolia*, L.)	Perfuming effect
Coconut (*Cocos nucifera* L.)	Preventing hair damage
Thuja (*Thuja Occidentalis*`	Counter irritant
Fenugreek (*Trigonella foenum graecum* L).	Wash for skin inflammations and eczema
Garlic (*Allium sativum*)	Antiseptic, bacteriostatic, antiviral
Ginger(*Zingiber officinale*, Roscoe)	Antiseptic, fragrance

Mohd-Nasir and Mohd-Setapar [10].

Table 1.
Some plants used in cosmetics and their potential.

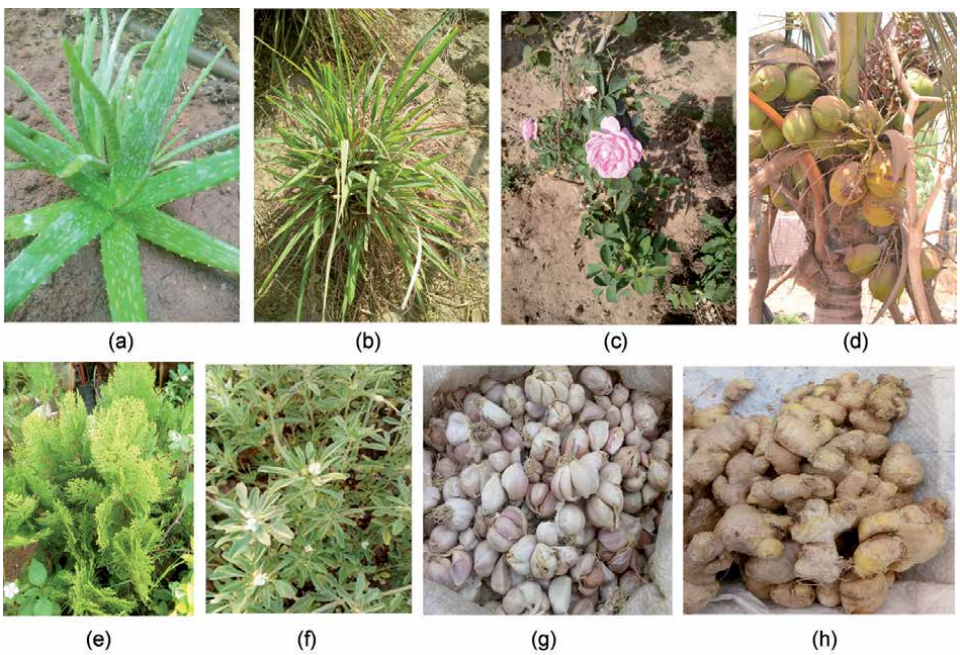

Figure 1.
(a-h) Some plants used in cosmetic preparations. (a) Aloe (Aloe vera_L) (b) Lemon grasss (Cymbopogon citratus) (c) Rose (Rosa centifolia, L.) (d) Coconut (Cocos nucifera L.) (e) Thuja (Thuja Occidentalis) (f) Fenugreek (Trigonella foenum-graecum L.) (g) Garlic (Allium sativum L.) (h) Ginger (Zingiber officinale).

1.1.2 Potential of plant extracts in herbal cosmetics

Plant oils and leaves have played a significant role in improving the quality of human life for thousands of years and have served as valuable raw materials for phycosmetics [13, 14]. Lipids from plants are used in their natural form as emollients and humectants, they provide a rich, non-greasy skin-feel with low odor and color to cosmetic and personal care formulations. In addition to the use of extracted seed oil for cooking, seed oils are also used for soaps, detergents, perfumes and related products. Inedible oil from seeds can be used to reduce the over use of the edible ones [15]. Common seed oils in most areas, especially rural

areas are mostly underutilized coupled with low productions due to a lack of good markets. To achieve national and entrepreneurial development, we need to design and develop strategy in order to explore and utilize full benefits of these seed oils [16]. Various methods of extraction are employed for the extraction of plant oils, leaves, stems and root extracts ranging from traditional to laboratory methods. Hot water floatation is the most common for traditional extraction; mechanical means is used for cold pressing while for researches in the laboratory different suitable solvents are used to achieve the desired results [17]. Herbal extracts are primarily added to the cosmetic formulations due to several associated properties such as antioxidant, antiinflammatory, antiseptic and antimicrobial properties. Even today, people in rural and urban areas depend upon herbs for traditional cosmetics [18].

1.2 Biopharmaceutical development

Plant-made pharmaceuticals have economic potential in the manufacture of biologic pharmaceuticals [19]. In recent years, there is paradigm shift in the use of transgenic plants for the production of therapeutic compounds from being an laboratory- base with potent capacity to be commercialized in order to deliver products useful in animal and human therapies. Productions have been made possible not only in more traditional areas of therapeutic development (e.g., the identification and isolation of bioactive secondary metabolites), but also with efforts in relatively unexploited areas such as the production of novel bioactive peptides therapy, and edible oral vaccines [20].

1.2.1 Transgenic plants platform

Due to their easy transformation, plants have considerable potential for the production of biopharmaceutical proteins and peptides and provide a cheap source of protein. Several biotechnology companies are now actively developing, field testing, and patenting plant expression systems, while clinical trials are proceeding on the first biopharmaceuticals derived from them. Product purification being a an expensive process has now made it an urgent need to develop new methods are to overcome this problem, including oleosin-fusion technology, which allows extraction with oil bodies. In some cases direct ingestion of the genetically modified plant which is a method of a biopharmaceutical product delivery potentially removes the need for purification. Such biopharmaceuticals and edible vaccines have the tendency of making immunization programs in developing countries cheaper and potentially easier to administer by storing and distribution as seeds, tubers, or fruits Some of the most expensive biopharmaceuticals of restricted availability, such as glucocerebrosidase, could become much cheaper and more plentiful through production in transgenic plant [21]. For the production of extraordinary high amounts of recombinant proteins, it has been demonstrated that transgenic plants can be developed facilitating the rational production of therapeutics [22]. Considering the nearly 500 biotechnology products approved or in development globally, and with production capacity limitation, it is very clear the need for efficient means of therapeutic protein production. Through recombinant DNA technology, plants can now be used to produce pharmacologically active proteins, including mammalian antibodies, blood product substitutes, vaccines, hormones, cytokines, and a variety of other therapeutic agents. In view of a decision as to whether a food crop or a non-food crop is more appropriate, efficient biopharmaceutical production in plants involves the proper selection of host plant and gene expression system [23].

1.3 Herbal cosmeceuticals

Herbal cosmeceuticals are a new type of plant product representing a hybrid between pharmaceuticals for skin diseases and cosmetic products. Considering the valuable scientific contributions welcomed by the scientific community on the field of cosmeceuticals, research should be further expanded as one can tap into a wealth of discovery and development of important cosmeceuticals from natural resources to address consumer and patients demand [24]. As an alternative to prevent adverse effect from chemical or artificial compounds usage natural ingredients from plants in cosmetics are incorporated. The active compounds in natural ingredients offer valuable bioactivities such as antioxidant, Various plants along with their active phytochemicals like alkaloids, flavonoids, saponins, sterols, triterpenes, tannins, etc. are responsible for activities like antioxidant, anti-inflammatory, sunlight protection, skin regeneration, de-pigmentation, anti-dandruff, anti-hair fall, anti-lice, etc. [25]. Herbal manufacturers are engaged in the production of cosmeceutical products such as body lotion, face packs, skin cleansers, fairness creams etc. There has been tremendous improvement in the cosmeceutical industry with natural products being more in demand than their synthetic counterparts; due to shift in consumer preference from synthetic cosmetics to natural ones this has been possible [26]. Novel drug delivery systems are nowadays used in herbal cosmetics the advantage of which includes; enhanced efficacy, improved stability and decrease allergic potential of some herbal substances, hence, choosing an appropriate drug delivery system for a herbal cosmetic is able to provide increased efficacy, stability and enhanced safety of the final product. Besides these advantages above mentioned, the complex nature of herbal cosmetics have made them more complicated in the fulfillment of quality requirements either during production or after packaging and during shelf life the critical nature that need to fulfill long-term stability and dermatological safety. Interestingly, critical parameters that affect the final quality and stability of herbal cosmetics are the specifications of herbal inputs, structure of formulation and manufacturing process [27].

1.4 African perspective

Apart from other herbal pharmacopeia, the use of phytocosmetics in the African culture is perhaps the oldest and most diverse. Rural Africa is especially blessed with affordable phytocosmetics prescribed by traditional healers accessible to the local community and sometimes the only option left for skincare in such remote areas. In fact, there remains insufficient updated favorable compendium of phytocosmetics from the African herbal pharmacopeia. In an attempt to provide a key scientific databases which have been screened to probe trends of the rapidly increasing amount of scientific publications on phytocosmetics from the African herbal pharmacopeia, updated general review of a few plants which are among the most popular and promising phytocosmetics from the African pharmacopeia are presented. This will also help to create important impact of phytocosmetics of African origin with different aspects, such as phytochemical profile, botanical aspects, biological properties, traditional uses, taxonomy, and clinical studies as well as future trials regarding the usage of these plants [28]. Since developing African countries face health problems that they struggle to solve. The major causes of which are high therapeutic and logistical costs, this made Plant-made therapeutics easy to produce due to the lack of the safety considerations associated with traditional fermenter-based expression platforms, such as mammalian cells. The easy nature of plant biosystems to scale up and being inexpensive and do not require refrigeration or a sophisticated medical infrastructure made it advantageous

to provide an opportunity for plant-made pharmaceuticals to counteract diseases for which medicines were previously inaccessible to people in countries with few resources [29]. Plants have the potential to rapidly produce recombinant proteins on a large scale at a relatively low cost compared to other production systems, provided concerns about biosafety, human health (allergenic response to plant-specific glycans), and other factors are adequately addressed and the right candidate genes, a strong commercial need, and a good production system are build as bridge between basic research on Plant Molecular Farming and its commercial application. They are able to produce a number of therapeutic proteins, some of which have been through pre-clinical or clinical trials and are close to commercialization. They have the potential to mass-produce pharmaceutical products with less cost than traditional methods. For combating the Ebola outbreak in Africa, tobacco-derived antibodies have been tested and used [30]. Herbal-based and plant-derived products can be exploited with sustainable comparative and competitive advantage. Some indigenous African plants with chemotherapeutic properties and possible ways of developing them into potent pharmacological agents using biotechnological approaches were reviewed. Examples of the selected plants and their active compounds are, *Garcinia kola* Kolaviron, Palm Oil Carotenoids, Alchornea laxiflora (Benth) alkaloids, cadiac glycosides saponins and phenolic compounds, Vernonia amygdalina (compositae) vernodaline, vernolide, vernomygdine and edotides, Mallotus oppositifolius (Euphorbiaceae) alkaloids, phenols, flavonoids, anthraquinones and cardenolides, *Hibiscus sabdariffa* L gossypetin, glucoside, bibiscin, hibiscus anthocyanin and Hibiscus protocatechuic acid [31]. The importance of the traditional medicine in the preparation of natural phytocosmetics was highlighted in north-eastern Algeria, the study was able to record the available information the importance of phytocosmetic in traditional medicine [32]. Explorative survey was conducted to document the natural resources (plant and non-plant materials) used for folk cosmeceuticals by rural communities in Vhembe district municipality, Limpopo province, South Africa. Documentation of the high number of natural resources in Vhembe district which is rich in ethnopharmacological knowledge is an indication that scientific investigation of the efficacies and safety of these natural resources is highly recommended as a drive aimed at innovations with benefits to the rural communities who are the custodians of this valuable knowledge [33]. A study was able to record the remaining available information on phytocosmetics in traditional medicine orally passed down through generations in South West Nigeria [34]. A study explored the indigenous knowledge of traditional cosmetic plants used by the Xhosa women of the Eastern Cape Province of South Africa. The local cosmetic applications of the plants included uses for changing skin complexion, sunlight protection, treating pimples and body rashes, removing spots, making skin soft, treating sunburns, making skin smooth and maintaining a healthy skin [35]. International companies with their marketing potential are been attracted by the development of cosmetics from Africa, from seed oils and their component. The African phytocosmetic enterprise is expected to double in the next decade with the rate of sales increasing up to a rate of 5–10% of beauty care products. In Africa the per capita spending on cosmetics ranges from 10 to 20 times lower than in developed market, but Africans a resurgence of phytocosmetic products when look forward can provide increase of marketers who are interested in their future growth [36]. A study was conducted to assess the knowledge of the. The pharmacognostic review of traditional herbal cosmetics in Gbaya ethnic group in the Eastern Cameroon showed that these plants all contain diverse phytochemicals like enzymes, minerals, vitamins, alkaloids, phenolic compounds, steroids, saponins, glycosides, carbohydrates, coumarins, lecithin, and essential oils that are all active cosmetic ingredients. The Gbaya people use various recipes for their tooth hygiene,

skin and hair care. Thus, promoting their sustainable use and the equitable sharing of benefits which is a pathway for harnessing the conservation of these plants and the local development [37]. Medicinal plant extracts are widely used as active ingredients in cosmetics. Plant material can come from a variety of sources, including commercial production horticulture and wild harvest in developing countries. Sustainably produced plant material does not threaten biodiversity, release pollution, compete with the food supply, or exploit local people [38].

2. Conclusion

With recent development in phytocosmetis and biopharmaceuticals especially in Africa, it is imperative to establish a cluster between academia and industry to ensure smooth development of emerging cosmetic products. In fact, efforts in making greener cosmetics shows promising progress worldwide and it is expected to keep expanding to meet growing consumer demand.

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Chapter 3

Mass Spectrometry and Its Importance for the Analysis and Discovery of Active Molecules in Natural Products

Paco Noriega, Gabriela Gortaire and Edison Osorio

Abstract

Mass spectrometry is one of the best techniques for analyzing the structure of a molecule. It usually provides information about the molecular weight of a substance, and it can present atomic mass units and up to ten thousandths of atomic mass units depending on the accuracy of the mass analyzer. In addition, it provides information on the positive ions formed in the ionization process, which is linked to the chemical structure of the molecule and the nature of the bonds. This technique is widely used for analyzing compounds from natural products. The development of the technique combined with the use of software and databases has been remarkable in recent years, improving the ionization processes and the ion analysis. Since natural products generally constitute a mixture of a complex quantity of components, mechanisms have been developed for coupling to chromatographic techniques of various kinds. This review aims to show how mass spectrometry has contributed to the qualitative quality control in natural products, as well as in the finding of new metabolites of industrial interest.

Keywords: Mass spectrometry, Natural Products, GC/MS, HPLC/MS, new metabolites

1. Introduction

Mass spectrometry is an analytical technique whose purpose is discovering new molecules, determining quantities of known components and determining structural and chemical properties of a molecule.

The detection capability in mass spectrometry is very small, of about 10^{-12} grams and its application field is multifaceted, being used in industries such as: chemical, pharmaceutical, biotechnology, food, among others. It is frequently used in environmental and medical sciences, and in molecular biology.

Some of its most common uses are related to:

Performing doping tests in athletes [1].
Locating petroleum reservoirs through the use of precursors in the rocks [2].
Controlling fermentation of products in biotechnology processes [3].
Determining genetic damages [4].

Determining the presence of contaminants in food [5].
Identifying the structure of biomolecules, such as nucleic acids [4].
Analyzing the biodegradation of medications [6].
Establishing the age of geochemical and archeological samples [7].

The origin of mass spectrometry goes back to the experiments by J. J. Thompson, which evidenced, on one side, the presence of electrons, and on the other side, the presence of positive radiation, when energy falls into a vacuum tube to which a difference in electric potential was applied [8]. Thompson remarked the importance that this new technique might have in the field of chemical analysis and described it in his book "Rays of Positive Electricity and Their Application to Chemical Analysis" [9]; however, despite this interesting possibility of use, mass spectrometry was relegated to the field of experiments in physics. It was not until the 1940s, that the first analytical mass spectrometers started to be developed.

At present, Mass Spectrometry and Nuclear Magnetic Resonance, are the most complete and widespread techniques in educational and research labs around the world, regarding the study and discovery of organic molecules. In the field of natural products many of the studies about secondary metabolites have been validated in a mass spectrometer, since it is a very complete technique for the identification and control of this type of substances.

2. Mass spectrometry, fundamentals and instrumentation

A mass spectrometer is an instrument with the capability of measuring the mass of a molecule after it has been ionized. Due to the extremely small mass of a molecule expressed in grams or kilograms, it is more convenient to measure its molecular mass, expressed as mols; for example, the mass of a hydrogen atom is 1.66×10^{-24} grams, but its mol is approximately 1 gram, or if it is desired in Daltons, considering that this unit is equivalent to 1/12 of the mass of an isotope carbon-12.

The spectrometry does not directly measure the mass of an isotope, but rather its mass-to-charge ratio of the ions that are formed (m/z), where z is the charge, most of the ions formed in the mass spectrometry have a value of charge of z = 1.

The mass spectrometers are constituted by various components, namely: 1) system for introducing the sample, 2) ionization source, 3) mass analyzer, 4) detection system and 5) data analysis system. Components 2, 3 and 4 should be necessarily subject to a vacuum system; a summarized scheme of the instrument may be seen in **Figure 1**.

The parts that diversify and create the different instrumentation variants are the ionization source and the mass analyzer.

A classic system requires the formation of ions in gaseous phase; however, the latest instrumentation advances have generated methodologies that enable introducing molecules in liquid phase or even in solid phase. The process for generating the mass spectrum is:

1. Production of ions and fragmentation

2. Separation of the ions according to their mass-to-charge ratio

3. Detection

The ion production, also known as ionization, occurs in different manners. The classic one is by means of the interaction of an electric current (electronic

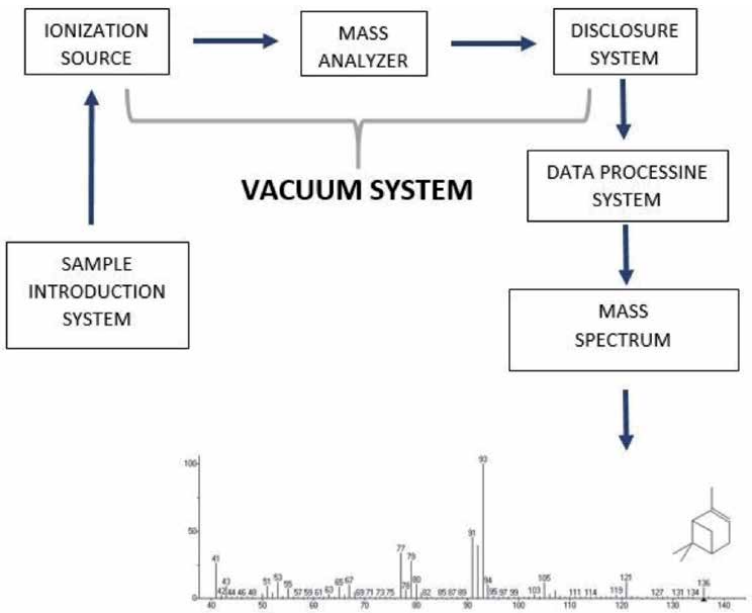

Figure 1.
Scheme of a mass spectrometer.

ionization) with a substance in vapor phase. The energy is considered as high and has been standardized at 70 eV, which is greater than the energy of the bonds of any molecule.

Another method is chemical ionization (Cl) where the rupture is produced due to the incidence of a gaseous substance with an extra proton, for example CH_5^+, on substances in vapor phase. Chemical ionization is less energetic than electronic ionization and produces less fragmentation.

Other types of ionization of recent development are:

(Fast Atom Bombardment, FAB): impact of atoms at high velocity on a sample dissolved in a liquid matrix.

(Secondary Ion Mass Spectrometry, SIMS): impact of ions at high velocity on a thin film of sample deposited on a metal substrate, or dissolved in a liquid matrix (Liquid SIMS).

(Plasma Desorption, PD): impact of fragments of nuclear fission, for example, of the ^{252}Cf on a solid sample deposited on a metal foil.

(Matrix Assisted Laser Desorption Ionization, MALDI): impact of high energy photons on a sample enclosed in an organic solid matrix.

(Field Desorption, FD): imposition of a strong electric field on a sample deposited on a special metal probe.

(Electrospray Ionization, ESI): formation of charged liquid particles which are emitted by desorption or desolvation.

The purpose of the mass analyzers is to separate the ions according to their mass-to-charge ratio. The mass analyzers have different features, namely:

Magnetic sector mass spectrometry. They deviate the trajectory of the ions in circular trajectories that depend on the momentum/charge ratio.

Quadrupole. Consists of 4 poles or bars arranged parallelly, the separation of the ions is the result of the application of a combination of continuous (DC) and alternating at a radiofrequency (RF) electric fields.

Ion trap. The ion trap operates similarly to the quadrupole, with the difference that it may hold and store the ions inside the trap.

Fourier transform ion cyclotron resonance mass spectrometry (FT-ICR). The ions are trapped electrostatically in a cubic cell inside a constant magnetic field.

Time off flight (TOF). They separate ions according to the time employed to travel a particular distance; an ion of smaller mass will have a larger velocity, based on equation $Ec = mv^2/2$ that relates kinetic energy with mass and velocity.

Figure 2 shows the ionization sources, as well as the diverse analyzers which will finally determine the types of instruments that are found in the market.

In most mass spectrometry analyzers, with the exception of the FT-ICR, ions are detected after the separation, transforming the collision energy of the ions on the detector, in order to produce in it further emission of electron and photon ions that are opportunely measured in charge or light detectors.

A mass spectrometer of recent development is the orbitrap, which is a modification of the ionic trap; in this the ions are injected tangentially in an electric field, and they remain turning around a central electrode, highlighting a high mass resolution of them [10].

2.1 The mass spectrum

A mass spectrum consists of a diagram of ionic abundance as a function of its mass-to-charge ratio. The mass spectra are reported as simple histograms, such as the one seen in **Figure 3**.

In this example all the ions are positively charged; it is observed the molecular ion at a value m/z of 32, a majority ion at m/z 31 due to the loss of the H from the OH group, and an ion at m/z 15 which is due to the loss of the hydroxyl (OH).

Depending on the ionization source and the energy employed, spectra will be available with more or less positive fragments aside from the information about the molecular weight of the molecule.

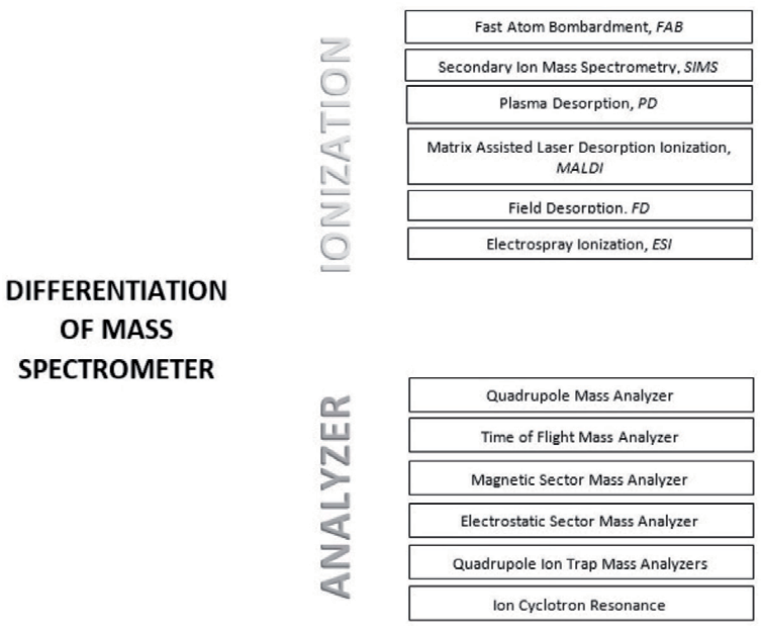

Figure 2.
Ionization sources and analyzers in mass spectrometry.

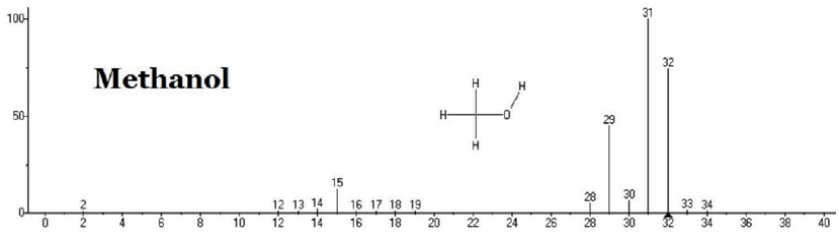

Figure 3.
Mass spectrum of the methanol.

2.2 Introducing the sample in the mass spectrometer

High purity solid samples may be directly placed in a probe inside the instrument, in which it occurs the evaporation of the sample that has been introduced in the vacuum system. Gaseous or liquid samples require special systems for feeding the regulated flow.

When the sample to be analyzed is a complex mixture of compounds, chromatography equipment may be coupled to the mass spectrometer, such as gas chromatography (GC) or high-performance liquid chromatography (HPLC). The GC/MS systems were developed in the 60s, because the samples that enter to chromatographic column are already in gaseous phase and this facilitates its introduction in the mass spectrometer; an instrument of this type is observed in **Figure 4**. The coupling with liquid chromatography did not occur until the 80s, due to difficulty of producing an operational vacuum system.

At present, the development of GC/MS and LC/MS systems provide a great variety of instruments that facilitate the separation and analysis work, both for quantifying as well as for discovering new structures, with the field of natural products being one of the most benefited from these latest advances.

2.3 MS-MS analysis

The coupling of two MS–MS mass analysis states is useful for analyzing compounds in complex mixtures and for determining the structure of unknown molecules.

Figure 4.
Gas chromatography equipment coupled to mass spectrometer. Life Sciences Laboratory, Salesian Polytechnic University.

The MS–MS evaluation offers the possibility of analyzing the ions formed in a further fragmentation of those ions formed in the first test.

If the first ionization technique offers the possibility of having various fragments in a highly purified sample, the second ionization offers the possibility of acquiring valuable structural information, and through it achieve a high possibility of determining the structure of a new molecule.

3. Mass spectrometry and natural products

The high development achieved in the last hundred years by mass spectrometry with a great variability of techniques and instruments, makes possible that basically all molecules that are part of natural products may be analyzed, both qualitatively and quantitatively [11, 12], **Figure 5** shows various spectra of natural substances obtained by electronic ionization. The extracts coming from biological matrices with natural products are generally a mixture of various compounds, and thus it is very common the use of GC or LC coupled systems [13, 14].

New techniques such as Electrospray Ionization, have increased the number of possible biomolecules to be analyzed, including those of high molecular weights [15]. Similarly, the use of powerful mass analyzers makes it possible to analyze molecular ions or fractionated ions with an extremely efficient resolution [16].

3.1 Essential oils

Essential oils are metabolites of volatile nature; therefore, studies of chemical composition are relatively simple, generally achieving percentages above 90% when investigating the molecules that compose these natural products [17, 18].

The combination of evaluations of mass spectra and retention indices provide information that may be verified in specific databases for this type of compounds [19].

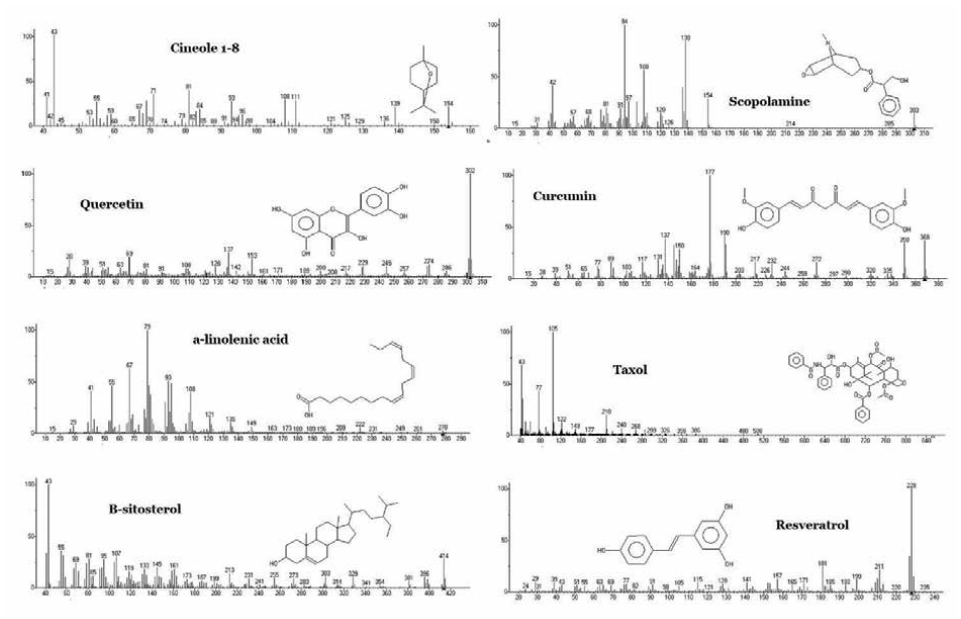

Figure 5.
Spectra of natural molecules obtained by electronic ionization.

Further studies of GC/MS in molecules separated in TLC, may reveal specific biological properties such as antibacterial or antioxidant [20].

3.2 Fatty acids

Various plant species contain saturated and unsaturated fatty acids, studies are generally carried out by GC/MS, although the compounds of high molecular weight are non-volatile, this is solved employing chemical derivatization methodologies, forming methyl or ethyl esters [21, 22]. Numerous species of nutritional and pharmaceutical interest such as *Plukenetia volubilis* [23], *Borrago officinalis* [24], and fish oil [25], are analyzed using this methodology.

3.3 Aromas and flavors

The aromas and flavors in fruits and vegetables are fundamental for distinguishing their taste features, given their volatility the GC/MS equipment is the ideal for understanding the chemistry of this group of substances. Many of these molecules are very volatile and therefore are not removable in vapor stream, for introducing them in the chromatographic system they are previously extracted with non-polar solvents [26] or may be directly injected with head space introduction systems [27, 28].

3.4 Phenols and polyphenols

Few phenolic compounds may be directly analyzed in an GC/MS system, generally those structures of low molecular weight [29].

Most of the phenolic and polyphenolic compounds are non-volatile and have two analytic paths for their structures to be determined, the first is through chemical derivatization, using the mechanism of sylitation, which make them volatile [30–31].

The second is through instruments that couple HPLC to mass spectrometry, which has made that a large part of the tests are carried out directly, after their separation in one column. The advantage of the electrospray ionization technique is the possibility of ionizing molecules that lack of volatility [32, 33].

The use of mass analyzers of resolution greater than the quadrupole, such as the TOF or the orbitrap, has resulted in values of m/z that reach more precise levels, which has resulted in greater confidence in the identification of a substance [34–36].

3.5 Alkaloids

The alkaloids are active ingredients whose structural feature is to have nitrogen in their structure, many of these molecules have a significant biological activity. Some alkaloids may be directly analyzed in GC/MS equipment, such as nicotine and other present in tobacco [37], caffeine and xanthine alkaloids [38, 39], and others whose volatility enables its separation in gas chromatography such as tropane alkaloids [40].

The most frequently used method in the test of these metabolites is the LC/MS in its diverse variants, such as the LC/MS [41], LC/MS–MS [42], some with a greater mass resolution such as the HPLC-TOF-MS [43]. The use of powerful mass analyzers such as Orbitrap, may lead to the discovery of new structures of this nature [44].

3.6 Cannabinols

The cannabinols constitute a family of natural products of about 70 compounds, of which the most important are the THC and the CBD [45]. The discovery of the endocannabinoid 1 and endocannabinoid 2 systems, 4 decades ago, awakened the medicinal interest of these substances [46]. These compounds have a high solubility in non-polar solvents and are volatile at the injection temperatures in a gas chromatography equipment, consequently a qualification and quantification of them occur in a very good manner in GC/MS systems [47, 48]. The LC/MS is also useful in the analysis of these substances [49–50].

4. Conclusions

Practically all the natural products may be analyzed by means of mass spectrometry, its high sensitivity and detailed structural information, make it an essential tool in research and product development labs.

Equipment with analyzers that have high resolutions can provide us with extremely exact values of molecular ions, and thus being able to differentiate the nature of the molecules.

At present there is a great variety of equipment coupled to LC or GC separation systems, which is ideal for the natural extracts that are generally a mixture of substances of diverse nature. Similarly, the combination of ionization and analyzer techniques, has been able to provide an instrumental variability that currently convert it in a technique highly appreciated for the discovery of new natural structures.

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Chapter 4

Ethnomedicinal Uses of Some Common Malaysian Medicinal Plants

Idris Adewale Ahmed

Abstract

Historically, natural products have always been a rich source of novel pharmacological leads, thus, making the ethnobotanical and ethnopharmacological knowledge an important and major asset of the medicinal plant-based drug discovery in providing hints for effective and safe chemotherapeutic compounds. Such knowledge, however, requires a thorough review and documentation of the ethnomedicinal and indigenous uses of local plants of every part of the world. Malaysia is a global hub for natural products which contributes to its GDP. Malaysia is also one of the 12 most diverse Megabiodiversity countries. Its rainforest is ranked 4th on the list of biodiversity hotspots in Asia after India, China, and Indonesia and is also acknowledged as the world's oldest rainforest. Natural products are relevant to both Malaysian health care and agriculture which are parts of the national key economic areas (NKEA) under the Government's Economic Transformation Plan as well as parts of the United Nations' 17 Sustainable Development Goals (SDGs). Though the quality, efficacy, and safety of herbal products require global and international standardization, herbal products should be made accessible to low-income and rural communities across the globe. The proper documentation of the ethnopharmacological important plants in addition to their preservation and cultivation would enhance the sustainable use of the various indigenous plants. This work is unique in the sense that it is meant to review some of the most important high-value herbal products in Malaysia. Though it covers only a few representatives of Malaysian medicinal plants.

Keywords: *Boesenbergia rotunda*, *Orthosiphon aristatus*, *Morinda citrifolia*, *Polyalthia bullata*, *Hylocereus polyrhizus*, *H. undatus*, *Vitex trifolia*

1. Introduction

The Malaysian rainforest is not only acknowledged as the world's oldest rainforest but also ranked 12th in the world as well as 4th on the list of biodiversity hotspots in Asia after India, China, and Indonesia. Malaysia has an estimated 12,500 species of seed plants with about 1200 species of medicinal plants [1]. Malaysia is also endowed with more than 3000 species of medicinal plants among its over 15,000 flowering plants [2, 3]. The Malaysian herbal industry, which is fully supported by the government, is also enjoying rapid development in line with the growing global herbal industry owing to the increasing demand for healthy

functional food, herbal supplements, herbs-based energy drinks, and cosmetics. Malaysia, in addition to its vast biodiversity, is also endowed with multi-ethnic cultures offering a unique combination of folk and traditional medication such as Ayurveda, the Traditional Chinese Medicine (TCM), Kampo, and Jamu for the development of the herbal industry [4]. Despite the advancement in synthetic chemistry, the use of Complementary and alternative methods (CAM) to support medical treatment, reinforce the immunity system, prevent relapses in cancer, reduce disease symptoms, and maintain health is also increasingly becoming more popular worldwide with almost 80% (about two thirds) of the population in developing countries still depending on herbal supplement products to meet their healthcare needs, according to the World Health Organization [5]. On the other hand, most of the conventional pharmaceutical drugs under development and those already in the market today owe their origins to natural products, though the products derived from virtually all-natural sources do not necessarily represent the final form of the active ingredients [6]. Similarly, about 84% of approved drugs for the treatment of CNS diseases, for instance, are either natural products or natural products inspired by over 400 clinically approved CNS drugs traceable to 20 natural product scaffolds [7].

Furthermore, the cost and adverse reactions of pharmacotherapy have lent immense support for the adoption of safe alternatives using various herbal formulations. The World Health Organization (WHO) defines herbal products or herbal preparations as herbal medicines containing active ingredients derived from the plants' parts or other plant materials, or their combinations. Breastfeeding mothers, especially, prefer herbal products to manage post-natal depressive symptoms. According to the literature, the percentages of women using at least one herbal product during the breastfeeding period in the US, China, Australia, and Italy are 16%, 20%–45%, 59.9%, and 97%, respectively. Herbal products are known to enhance milk supply and are thus commonly used as a traditional prophylactic during insufficient milk production to meet the child's nutritional needs. Herbal products, as a general health supplement, also offer self-empowerment, self-reassurance, and other psychological benefits during lactation, in addition to other general ailments such as colds, constipation, coughs, headaches, and depressive symptoms [5, 8]. Admittedly, the lack of standardization and heterogeneity of regulatory standards for herbal products between, and within countries and regions have made it quite difficult to generalize about the quality, efficacy, and safety of herbal products [1, 8]. Nevertheless, this study is aimed to review some of the most important high-value herbal products in Malaysia. Admittedly, the work covers only a few representatives of Malaysian medicinal plants. The taxonomic classifications of the few plants discussed in this study are itemized in **Table 1**.

1.1 Agarwood (gaharu)

Agarwood otherwise known as gaharu (**Figure 1**) is a highly valuable fragrant heartwood and resinous wood mainly produced through changes in the chemical and physiological compounds of woods through natural or artificial damage like injury, cutting wound, insect disturbance, microorganism (fungi), and other non-pathological processes from *Aquilaria* or *Gyrinops* species (family Thymelaeaceae). It is also one of the most valuable non-timber forest products throughout the world. It is a protected tropical tree species used as incense for perfumery, religious ceremonies, and traditional medicine through the ages globally [9–11]. Though natural agarwood is very precious owing to its extreme rarity, nevertheless, it is very popularly used in medicines, high-grade perfumes, and several other products [12].

Categories	Names	Names	Names	Names	Names	Names	Names
Kingdom	Plantae	Plantae	Plantae	Plantae	Plantae	Plantae	Plantae
Subkingdom	Viridiplantae	Viridiplantae	Viridiplantae	Viridiplantae	Viridiplantae	Viridiplantae	Viridiplantae
Infrakingdom	Streptophyta	Streptophyta	Streptophyta	Streptophyta	Streptophyta	Streptophyta	Streptophyta
Superdivision	Embryophyta	Embryophyta	Embryophyta	Embryophyta	Embryophyta	Embryophyta	Embryophyta
Division	Spermatophyta	Spermatophyta	Spermatophyta	Spermatophyta	Tracheophyta	Tracheophyta	Tracheophyta
Subdivision	Angiospermae	Angiospermae	Angiospermae	Angiospermae	Spermatophytina	Spermatophytina	Spermatophytina
Class	Dicotyledonae	Monocotyledonae	Monocotyledonae	Magnoliopsida	Magnoliopsida	Magnoliopsida	Magnoliopsida
Superorder		Commelinids	Eudicots	Asteranae	Liliane	Eudicots	Asteranae
Order	Thymelaeales	Bromeliales	Caryophyllales	Lamiales	Zingiberales	Lamiales	Gentianales
Family	Thymelaeaceae	Bromeliaceae	Cactaceae	Lamiaceae	Zingiberaceae	Lamiaceae	Rubiaceae
Genus	*Aquilaria*	*Ananas*	*Hylocereus*	*Vitex L. – chastetree*	*Boesenbergia*	*Orthosiphon*	*Morinda*
Species	*A. malaccensis*	*A. comosus*	*H. undatus*	*Vitex agnus-castus L. – chaste tree*	*B. rotunda*	*O. aristatus*	*M. citrifolia*
Common name	Agarwood	Pineapple	Dragon fruit	Vitex	Fingerroot	Cat's whiskers	Indian mulberry

Table 1.
Taxonomic classification of the reviewed plants.

Figure 1.
Agarwood (gaharu). Source: https://yxinenergy.com/wp-content/uploads/2020/12/agarwood_v4.png

Agarwood is mainly obtained from tree trunk as well as other parts of the tree such as tree branches and collected in the wood form and then traded as wood dust or powder, wood chips, and Agar-oil [13]. According to Wyn and Anak [14], About 19 plant species that are native to Malaysia are thought to produce agarwood (Peninsula: 13 spp., Sabah: 11 spp., Sarawak: 13 spp. The five most common types of oleoresin-producing *Aquilaria* in Peninsular Malaysia are *A. beccariana, A. hirta, A. malaccensis, A. microcarpa*, and *A. rostrata* [15]. However, *Aquilaria crassna, A. malaccensis*, and *A. sinensis* are the most popular plantation species. Agarwood leaves are also characterized with beneficial pharmacological properties like acetylcholinesterase (AChE) inhibitory, analgesic, antidiabetic, antioxidant, antibacterial, anti-inflammatory, anticancer, anti-arthritic, antitumor, antidepressant, antifungal, antihistaminic, cytotoxic, hepatoprotective, laxative, and lipid-lowering owing to their various bioactive constituents such as 2-(2-phenylethyl) chromones, benzophenones, fatty acids, flavonoids, phenolic acids, steroids, xanthonoids, terpenoids, and alkanes [16–18]. According to the literature [12], over 130 2-(2-phenylethyl) chromone derivatives have been identified from different kinds of agarwood. Hagaru as well as derivative products are common in traditional medicine practices throughout the Southeast Asian communities, such as the Ayurvedic, Chinese, Japanese, Malaysian, Tibetan, and Unani medicines. Its essential oil has also been reported to possess anticancer and anti-inflammatory activities [17, 19, 20].

1.2 Pineapple (*Ananas comosus*)

Pineapple (*Ananas comosus* [L.] Merr.) is the third most important tropical succulent fruit, after banana and citrus. It is seasonal and highly perishable [21, 22] and majorly produced in Latin America and Southeast Asia. It has several health benefits due to the high contents of bioactive compounds including carbohydrates, glycosides, organic acids, proteins, polyphenols, vitamins, and other compounds [23–25]. It is an herbaceous perennial monocotyledonous plant belonging to the family Bromeliaceae (Annonaceae) and subfamily Bromelioideae with about 2000 species and an annual global production of over 14 million tons. The aroma, color, flavor, juiciness, texture, sweetness, and overall appearance of the pineapple flesh are among the most important contributing factors to its acceptance by consumers [22]. Pineapple is very rich in bioactive and volatile compounds, phenolic compounds, dietary fiber, minerals (such as calcium, potassium), nutrients, and vitamins (such as vitamin C, and vitamin A), thus, offering several health benefits such as antioxidant and anti-inflammatory activities, anti-obesity and dyslipidemia functions, monitoring of nervous system function as well as healing of bowel movement [26]. The pineapple fruit and the other various parts of the plant

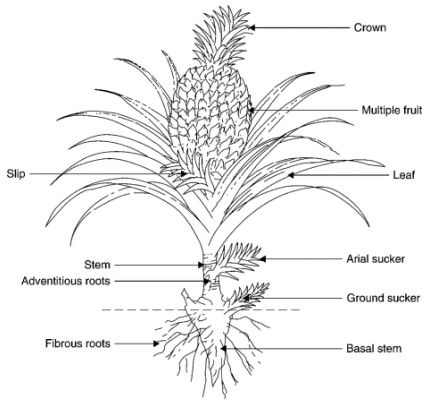

Figure 2.
*Various parts of Pineapple (*Ananas comosus *[L.] Merr.).Source: https://ars.els-cdn.com/content/image/3-s2.0-B978085709090450010X-f10-01-9780857090904.gif*

(**Figure 2**) such as the leaf, skin, rhizome, root, stem, and latex have been used in various native cultures as medicine [27, 28]. Both the stem and the fruit extracts, for instance, are rich sources of cysteine proteases (bromelain). *A. comosus* extract is very rich in both proteolytic enzymes (such as bromelain) and nonproteolytic enzymes [28, 29] which are considered a phytotherapeutic drug owing to their characteristics anti-edematous, anti-inflammatory, fibrinolytic, and anti-thrombotic activities [30]. The inedible pineapple peel is also a rich in polyphenols [24]. Its crude extract possesses various medicinal qualities in addition to being a rich source of bioactive compounds and nutrients such as proteins, lipids, minerals, vitamin C, carotenoids, and flavonoids [27]. Pineapple leaves are also used for many applications in folk medicines such as anti-diabetic, antidyslipidemic, emmenagogue, anti-oxidant, vermicide, wound healing, and antimicrobial activity [28]. The leaf extract has inhibitory effects on protein denaturation and proteinase activity in addition to its remarkable anti-inflammatory activity through controlled secretion of tumor necrosis factor-α, interleukin-1β, and prostaglandins in a carrageenan-induced inflammatory rat model [25].

1.3 Pitaya (dragon fruit)

Hylocereus undatus (white pitaya) is an economically-important antioxidant-rich fruit. The fruit (**Figure 3**) is also rich in fiber and vitamins [31]. It belongs to the Cactaceae family and originated in the Americas [32]. Similarly, red-purple pitaya (*Hylocereus polyrhizus*) is also very rich in red-violet pigments known as betacyanins which offer health-promoting effects and protective benefits against degenerative diseases, such as cardiovascular diseases, cancer, diabetes, heart diseases, and obesity [33]. The white-flesh of *H. undatus* fruits with its red peel have characteristics sensorial properties as well as huge economic importance. Both the pulps and peels of *H. undatus* are very rich in antioxidants, fiber, vitamins, free from toxic and thus safe for consumption as well other medicinal uses for the treatment of degenerative diseases such as arteriosclerosis, arthritis, brain dysfunction, cancer, diabetes, inflammation, and heart diseases [31]. The seed oil of *H. undatus* and *H. polyrhizus* are also rich in linoleic, oleic, and palmitic acids, in addition to other phytosterol compounds (such as campesterol, cholesterol, stigmasterol, and β-sitosterol) and phenolic acid compounds (such as caffeic, gallic, protocatechuic, p-coumaric, p-hydroxybenzoic, syringic and vanillic acids) [34]. The remarkable antibacterial activity of both *H. undatus* and *H. polyrhizus* is attributed to their

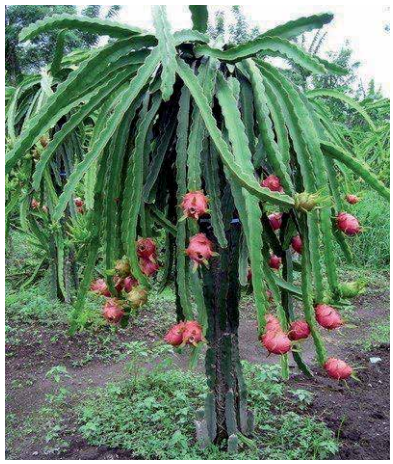

Figure 3.
*Dragon fruit (*Hylocereus undatus*). Source: https://i.pinimg.com/originals/f5/0e/29/f50e2953a7a249b1baf6a11a96c6c2a7.jpg*

presence of various antioxidant compounds and essential fatty acids such as linoleic and linolenic acids [35]. The essential oils of *H. undatus* fruits have outstanding antifungal activity [32].

1.4 *Vitex* spp.

The *Vitex* spp., with over 270 species globally, is the largest genus in the family Lamiaceae (Verbenaceae) and consists of deciduous shrubs and trees which are majorly distributed in the tropics and subtropics. About 12 species of Vitex are found in India, 14 species in China, and 30 species in the Malesian region. They are used as ornamental plants, in addition to their unique ethnobotanical, medicinal, and pharmacological uses for the treatment of many health problems, such as dermatitis, herpes, itching, malaria, and menstruation control [36–38]. The genus *Vitex* is a small deciduous shrub, about 3–6 m high and commonly found on the banks of channels, ponds, and rivers. Its fruits are used traditionally for the treatment of cold, nervous headache, migraine, rheumatism, and wind-heat while the leaves reportedly exhibit antitubercular, cytotoxic, and trypanocidal activities. Other common uses of the plant include amenorrhea, memory enhancement, pain relief, removal of a bad taste in the mouth, fever cure, hair loss treatment, antibacterial anti-cancerous, anti-diabetes, anti-inflammation, as well as treatment of dysentery, mouth infections, respiratory infections, and premenstrual problems [39, 40]. The hepatoprotective activity of the genus *Vitex* has also been reported and attributed to its rich iridoids contents [41]. Other major classes of compounds that have been isolated from the genus *Vitex* are flavonoids, steroids, and terpenes. More p-hydroxybenzoic acid and agnuside were, however, obtained in the leaves' extracts than bark samples [42]. Furthermore, several diterpenoids such as abietane, clerodane, labdane, halimane, and norlabdane have also been isolated from the *Vitex* genus [40].

1.5 Temu kunci (*Boesenbergia rotunda*)

Temu kunci (*Boesenbergia rotunda*) otherwise referred to as fingerroot belongs to the Zingiberaceae family. It is one of the most prominent ginger and medicinal plants in South East Asia [43]. The vernacular names of temu kunci are shown in

Table 2 [44] while its other common botanical names are *Boesenbergia rotunda* Linn. Mansft, *Curcuma rotunda* L., *Gastrochilus panduratum* RIDL., *Kaempferia pandurata* Roxb., *Boesenbergia cochinchinensis*, *Boesenbergia pandurata*, *Curcuma rotunda*, *Gastrochilus panduratus*, *Gastrochilus rotundus*, *Kaempferia cochinchinensis*, and *Kaempferia ovate* [45]. The genus *Boesenbergia* comprises about fifty genera and over 1000 species distributed throughout tropical and subtropical regions [44, 46].

The ginger family (Zingiberaceae) contains about 1500 species and 50 genera globally. Several species of Zingiberaceae consisting mainly of herbaceous perennial plants are used in food (as spices), as well as ornamental plants, in cosmetics, and dyes. The rhizomes and leaves (**Figure 4**) are characterized by the presence of essential oils, flavones, flavonoids, and cyclohexenyl chalcone derivatives [47, 48]. The rhizome is traditionally used, in Indonesia, for the treatment of several diseases in folk medicine owing to its diverse pharmacological and biological activities such as antibacterial, antifungal, antioxidant, anti-inflammatory, and anti-cancer [46].

The essential oils of *B. rotunda* are directly used in the preparation of Ayurvedic drugs, cosmetics, perfumery, and spices in India [49]. Similarly, in Thailand's primary health care system, *B. rotunda* rhizome is recommended for the treatment of abscesses, leukoplakia, leukorrhea, and stomachache [50]. It is also used as a flavoring agent or eaten as a vegetable, in Thai cuisine, owing to its rich bioactive compounds such as boesenbergin, cardamonin, pinocembrin, pinostrobin, panduratin A, and 4-hydroxypanduratin A [51]. *B. rotunda* essential oils usuallu contain both oxygenated and non-oxygenated monoterpenes such as γ-terpinene, β-ocimene, 1,8-cineole, myrcene, borneol, camphene, camphor, methyl cinnamate, citral, terpineol, geranial, geraniol, neral, nerolidol, limonene, and 11-dodecen-1-ol [46].

B. rotunda is commonly and locally consumed in many Asian countries such as China, Indonesia, India, Malaysia, and Thailand. It is mostly cultivated as small home ranches and used as a food condiment due to its aromatic flavor [45]. The aphrodisiac activity of *B. rotunda* has also been greatly explored due to its richness in boesenbergin, krachaizin, pinostrobin, and panduratin [44].

Names	**Origin**
Chun jiang, Soh Shi	Chinese
Temoe koentji	Dutch
Petits doigts	French
Fingerwurz, Runde Gewurzlilie	German
Chekkur	India
Temu kunci	Indonesian
Gajutu	Japanese
Khchiey	Khmer
Neng kieng	Lao
Temu kunci	Malay
Kae-aen, Kra Chai, Wan-phraa-thit	Thai
Ngai num kho, Bong nga truat, Cu ngai	Vietnamese

Table 2.
The vernacular names of B. rotunda.

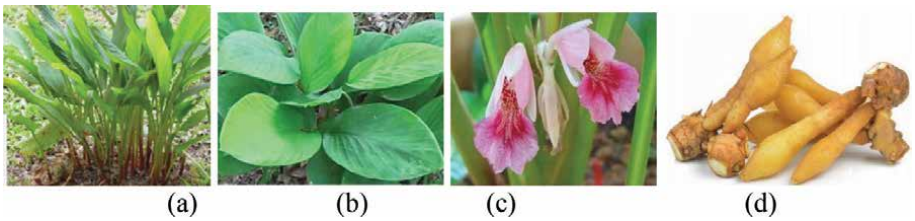

Figure 4.
(a) B. rotunda *plant, (b)* B. rotunda *leaf, (c)* B. rotunda *flower, and (d)* B. rotunda *rhizome.*

Traditionally, *B. rotunda* is used to treat several disorders such as colic disorder, dental caries, diarrhea, dry cough, fungal infection, mouth irritation, leukorrhea, stomach discomfort, rheumatism. It is also commonly used an antiseptic for wounds, anti-insecticidal, anti-mutagenic, anti-tumor, and anti-inflammatory. Both its extracts and compounds, especially panduratin derivatives, have reportedly shown several interesting biological activities such as antibacterial, antioxidant, anti-inflammatory, anti-cancer; antiviral; anti-aging; anti-obesity; skin hydration, barrier function [46, 52]. *B. rotunda* ethanolic extract and its panduratin A has also been reported to remarkably inhibit SARS-CoV-2 infection at both pre-entry and post-infection phases. Panduratin A also suppresses viral infectivity in the human airway epithelial cells [53].

1.6 Misai Kucing (*Orthosiphon aristatus*)

Misai kucing (*Orthosiphon aristatus*) (Blume) Miq. locally called "Kumis Kucing (Java tea)" and "Misai kucing", "cat's whiskers" in Indonesia and Malaysia, respectively belongs to the family Lamiaceae [2, 3, 54].

O. aristatus leaves are commonly used as a tea (java tea) in the Southeast Asia and Europe regions [55]. It is also a well-known medicinal plant in Southeast Asia and mostly cultivated both in Indonesia and Malaysia. Its leaves (**Figure 5**) have been used traditionally in Malaysia for the treatment of many infectious and chronic diseases such as angiogenesis-related diseases like eruptive fever, edema, inflammation, urinary lithiasis, influenza, hepatitis, jaundice, rheumatism, diabetes, and hypertension (owing to its richness in flavonoids, hexoses, saponins, organic acids, terpenoids, chromene, myo-inositol and polyphenols [54, 56, 57]. *Orthosiphon* tea is also commonly used as a diuretic for the removal of uric acid stones from the kidney as well as for abdominal pain, urinary disorders, edema, gout, menstrual disorders,

Figure 5.
*Misai kucing (*Orthosiphon aristatus*). Source: https://4.bp.blogspot.com/_-exY1vxyY6M/SsZ8dV-GfGI/AAAAAAAAB1s/lj94bMIzk9U/s400/Floridian_1020275561_207.jpg*

and tonsillitis, in addition to other pharmacological properties such as antioxidant, antibacterial, anti-inflammatory, cytotoxic, hepatoprotective, and vasodilative [55]. Some of the compounds contained in the leaves of *O. aristatus* include acetovanillochromene, caffeic acid derivatives, flavonol glycosides, lipophilic flavones, oleanolic acid, orthochromene A, orthosiphol A, orthosiphol B, orthosiphononeA, orthosiphonone B, neoorthosiphols A, neoorthosiphols B, and ursolic acid [58]. Misai kucing is one of the most important and high-value herbal prodcuts in Malaysia. Others are tongkat Ali, kacip Fatimah, bumi, dukung anak, mengkudu, roselle, ginger, mas cotek, belalai, gajah, and pegaga [59].

1.7 Mengkudu (*Morinda citrifolia* L.)

Mengkudu (*Morinda citrifolia* L.) (Noni) is one of the most important traditional Polynesian herbal and medicinal plants as well as foodstuffs for over 2000 years which is grown widely throughout the pacific. It is locally called 'mengkudu' in Malaysia. It belongs to the family Rubiaceae (coffee family) as well as the subfamily Rubioideae. It plays contains several electrolytes, phytochemicals, and vitamins, thus, playing an essential role in daily dietary intakes. The constituents of mengkudu have several biological activities such as antibacterial, antiviral, anti-tumor, and antifungal, thus playing a great role in the immune system [60, 61]. The various parts of the plant including the fruit, flower, leaves (**Figure 6**), bark, and root are used in many traditional medicine preparations [62–64]. *M. citrifolia* fruit has remarkable hepatotoxicity effects owing to the presence of anthraquinones in the seeds and skin which had potent quinone reductase inducer activity [64]. It is also used to treat various other ailments such as respiratory-tract and skin infections [62]. *M. citrifolia* has broad healing properties and thus used for the treatment of anxiety, cancer, colds, flu, diabetes, blood pressure, and depression owing to the fruit's richness in phenolic compounds such as caffeine, chlorogenic acid, ellagic acid, gallic acid, quercetin, rutin, and rosmarinic acid [61]. *M. citrolia* leaf is rich in campesterol, oxalic acid, stigmasterol, β-sitosterol, (+)-catechin, (−)-epicatechin, rutin, quercetin, scopoletin, and kaempferol and commonly consumed by many cultural groups, in addition to the treatment of allergy, helminthic infections, hyperlipidemia, oxidative stress, and open wounds [65].

Figure 6.
*Mengkudu (*Morinda citrifolia *L.) fruit, flower, leaves. Source: https://www.makanabis.com/bima-content/2020/01/02/l-morinda-buah7e76d7f51fd414b6bbd998cf8fa74e77202001021439 38-bimacms.jpg*

2. Conclusion

Malaysia is a global hub for natural products which contributes to its GDP. Malaysia is also one of the 12 most diverse Megabiodiversity countries. Natural products are relevant to both health care and agriculture which are parts of the national key economic areas (NKEA) under the Government's Economic Transformation Plan as well as parts of the United Nations' 17 Sustainable Development Goals (SDGs). It is worthy of note that the quality, efficacy, and safety of herbal products require standardization. Herbal products should also be made easy and accessible to low-income and rural communities across the globe. The proper documentation of the ethnopharmacological important plants in addition to their preservation and cultivation would enhance the sustainable use of the various indigenous plants.

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Chapter 5

A Traditional and Pharmacological Approach of Medicinal Plants in Mizoram, India

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Abstract

Traditional medicine is the sole method of treatment in rural India even today. Several communities practice their traditional method of treatment and are not affected by the advances in modern medicine. The tribal communities prefer to use and consult their own traditional practitioners since these are easily available, accessible and cheap. It is also believed that these are free of side effects and very effective. The Mizos of the north-eastern state of India (Mizoram), use several plants to treat various ailments. Their practices are unique and are usually carried out by elderly persons of the community or traditional healers. Several plants used in their traditional medicine have been scientifically validated for their efficacy and toxicity studies. However, a large number still awaits identification and efficacy validations. This manuscript describes both the studied and untouched medicinal plants used in the traditional medicine system of the Mizos of Mizoram. Although, several other remedies are yet to be discovered, this study has described most of them in current use.

Keywords: medicinal plants, Mizoram, traditional medicines, traditional practices

1. Introduction

Medicinal plants serve as the mainstay of various traditional disease management strategies since time immemorial [1]. These practices are passed onto many generations and some have even led to great discoveries providing instant cure and eradication of various diseases. Despite the growth in the pharmaceutical industry, modern health care system and drugs are still impractical and inaccessible for the less privileged communities [2]. According to World Health Organization (WHO), about 90% of the people in developing countries still use traditional medicines as their primary health care system, while in some parts in combination with modern drugs [3]. Due to high reliance on traditional medicines, WHO has laid down strategies for the improvement of health care system in developing countries particularly for the economically deprived communities. The strategies aim to frame policy, enhance safety, efficacy, quality, ensure access and to promote balanced use of traditional medicines. Through these strategies, traditional medicines are projected to be integrated into disease management programs in Primary Health Centers (PHC), thereby increasing recognition and support from the Government [4]. International organizations and policy makers believe that primary health care system PHCs are

still the best to meet the needs of the people in villages and are assumed to be the universal solution for improving human health [5].

The practice of traditional healing in Indian culture has been assumed to be as old as civilization. Traditional healing by various medicinal plants has been trusted and has gained much acceptance among many cultures as the proportion of cure is believed to be high and significant [6]. This may perhaps be related to the rich biodiversity where plants having medicinal values can be obtained from the forest at any disposal. Poor economy background of deprived communities may as well play an important role in the high reliance on forest resources for medicinal purpose and nutraceuticals [7].

Mizoram, one of the 7 sister states of Northeast India is inhabited mainly by the Mizo tribe (**Figure 1**). It shares an international boundary with Bangladesh in the south western part and with Myanmar in the south eastern side. It also shares the national boundary with the state of Assam in the north; Manipur in the north east and Tripura in the west. It is located between 21°56′N to 24°31′N, and 92°16′E

Figure 1.
A traditional Mizo couple.

to 93°26′E. The climate of Mizoram is relatively mild. It is never too hot nor too cold during summer and winter [8]. The state lies in the Indo-Myanmar sub-tropical forest region and is a biodiversity hot-spot with many endemic species. The rich biodiversity provides immense treasure and sustainable supply of medicinal plants and hence leads to frequent use of plants as medicine [9]. The knowledge and practices are passed down the generations which are still in practice while some are kept in secrecy by villagers [10]. Medicinal plants are the immediate rescue for various ailments especially in remote areas where modern medical facilities are far from being attained [11]. The practices are quite similar in most parts of the state but the parts of the plant, type of preparation and consumption vary slightly from place to place. In most cases, decoction of the different parts of the plants is consumed orally without meticulous proper dosage [12]. Consumption of decoction of leaves is the most common form of use other than raw, aqueous

Figure 2.
A traditional healer preparing medicine.

extract, powdered, crushed, drooping or homogenized in water. The parts of the plant mainly used as medicine are leaves, roots, seeds and stem bark, among which leaves constitute the highest percentage. Besides, various ingredients such as sugar, oil, water, honey, and citrus juice are added to enhance the taste, aid consumption and to conceal the smell [13]. These medicines are usually prepared at home (**Figure 2**). The medicinal plant parts are also usually processed at home (**Figure 3**).

Traditional knowledge and practices serve as the basic framework for scientific studies including chemical analysis and biological activity studies. Different varieties of plants have been used as medicine among which some of them are still in use today (**Table 1**). The various plants used for treatment of various common diseases are discussed in this study.

Figure 3.
Turmeric being dried for use as medicine.

Sl. No	Ailment	Medicinal plant
1	Parasite infections	*Euphoria longan, Morus alba, Punica granatum, Schima wallichi*, *Eupatorium odoratum, Annona squamosa, Artemisia nilagirika, Lagerstroemia speciosa, Benincasa hispida, Carica papaya, Dioscorea bulbifera, Michelia champaca, Piper longum, Trichosanthes anguina, Chenopodium ambrosioides, Gossypium* sp., *Dalbergia pinnata, Ziziphus oenoplia, Acacia oxyphylla, Milletia pachycarpa, Millettia taiwaniana, Imperata cylindrica, Ilex khasiana, Acmella oleracea, Callicarpa arborea*
2	Diarrhea	*Catunaregam spinosa, Chrysophyllum lanceolatum*, *Aegle marmelos*, *Ziziphus mauritiana*, *Tamarindus indica, Spondias pinnata, Rhus semialata, Garcinia morella, Garcinia cowa, Ficus racemose, Emblica officinalis, Dillenia indica, Bruinsmia polysperma, Artocarpus chama, Parkia roxburghii, Mikania micrantha*, *Melastoma malabathricum, Rourea minor, Rhododendron arboretum, Quercus serrata, Quercus oblongata, Punica granatum, Psidium guajava, Pogostemon cablin, Picrasma javanica, Phyllodium pulchellum, Osbeckia chinensis, Acer oblongum, Actinida chinensis*, *Careya arborea*, *Mussaenda macrophylla, Stereospermum tetragonum, Clerodendrum colebrookianum, Blumea lanceolaria*
3	Skin	*Achyranthes aspera, Albizia chinensis, Artocarpus lakiicha, Jatropa curcus, Arisaema tortuosum, Artemisia indica*, *Chenopodium ambrosioides*, *Chenopodium viscosum, Elsholtzia blanda, Buddleja asiatica, Centella asiatica*, *Lantana camara, Actinida chinensis, Eryngium foetidum, Mimosa pudica, Polygonum plebeium*, *Prunus cerasoides, Buddleia asiatica, Erythrina stricta, Tinospora cordifolia, Psychotria calocarpa, Mimosa pudica, Oroxylum indicum, Nigella sativa*
4	Diabetes	*Dillenia pentagyna, Casearia tomentosa, Abrus precatorius, Averrhoa carambola, Lagerstroemia speciosa, Phyllanthus fraternus, Tinospora cordifolia, Aloe barbadensis*, *Artocarpus heterophyllus*, *Curcuma longa, Emblica officinalis, Mimosa indica, Mimosa pudica, Albizia procera, Aegle marmelos, Allium cepa*, *Alstonia scholaris, Allium sativum, Clerodendrum colebrookianum, Plantago major, Physalis angulate, Passiflora quadrangularis, Scurrula parasitica, Mallotus roxburghianus*
5	Cancer	*Aglaia edulis, Prunus domestica, Ficus hirta, Dillenia pentagyna, Ageratum conyzoides, Blumea lanceolaria*, *Aloe barbadensis*, *Artocarpus heterophyllus, Azadirachta indica*, *Carica papaya*, *Clerodendrum colebrookianum*, *Curcuma longa*, *Emblica officinalis*, *Mimosa indica, Momordica charantia, Ageratum conizoides*, *Gynura conyza, Dillenia indica, Scurrula parasitica, Rhynchotechum ellipticum, Aegle marmelos, Allium hookeri*, *Eryngium foetidium*, *Mikania micrantha, Alpinia galanga, Ageratum conyzoides, Solanum khasianum, Lonicera macrantha, Senecio scandens*, *Croton caudatus*, *Mussaenda macrophylla, Callicarpa arborea, Byttneria aspera, Rhus javanica*
6	Malaria	*Acacia concina*, *Andrographis paniculata, Adhatoda vasica, Alstonia scholaris, Artemisia nilagirika*, *Clerodendrum serratum*, *Acacia concinna*, *Acer oblongum, Alstonia scholaris, Anogeissus acuminata, Artemisia vulgaris, Begonia inflata, Borginia ciliate, Canna indica, Cassia fistula, Chickrassia tabularis, Dichroa febrifuga, Eryngium foetidum, Kyllinga monocephala, Lantana camara, Mikania micrantha, Musa paradisiaca*, *Sylvestris* sp., *Passiflora nepalensis, Phyllanthus fraternus, Picrasma javantica, Piper betle, Piper longum, Prunus cerasoides, Rotheca serrate, Spathodea stipulata*, *Stereosrermum personatum, Vitex peduncularis, Garcinia cowa, Plantago major, Pittosporum napaulense*
7	Fungal infections	*Ficus auriculata, Gelsemium elegans, Chickrassia tabularis, Spathodea stipulate, Asparagus racemosus, Homalomena aromatica, Curcuma longa, Trachyspermum ammi, Callicarpa macrophylla, Bidens pilosa*
8	Measles	*Securinega virosa*, *Adhatoda vasica, Azadirachta indica, Amomum subulatum, Cucurma caesia, Anacolosa crassipes, Securinega virosa, Phyllanthus airy-shawii, Homalomena aromatica, Anogeissus acuminata, Lantana camara, Rhus javanica*
9	Chickenpox	*Securinega virosa, Adhatoda vasica, Rhus semialata, Embelia nagushia, Anogeissus acuminata, Averrhoa carambola, Embelia vestita*

Sl. No	Ailment	Medicinal plant
10	Jaundice	*Chonemorpha fragrans, Emblica officinalis*, *Oroxylum indicum*, *Terminalia chebula*, *Dillenia pentagyna, Clerodendrum colebrookianum*, *Catharanthus roseus*, *Cassia fistula*, *Carica papaya, Capsicum frutescens*, *Aeschynanthus sikkimensis*, *Adhatoda zeylanica, Adhatoda vasica, Homalomena aromatica, Passiflora* sp., *Acacia concina, Amomum subulatum, Gynura conyza, Lagerstroemia speciosa, Laportea crenulate, Momordica charantia, Musa superba, Alocasia indica, Cucurma caesia, Passiflora edulis, Andrographis paniculate, Ardisia paniculate, Averrhoa* sp., *Dendrocnide sinuate, Dillenia indica, Hibiscus rosa-sinensis, Lagerstroemia speciosa, Mallotus roxburghianus, Phyllanthus fraternus, Ficus semicordata, Hedyotes scandens, Mimosa pudica, Bridelia monoica, Benicasia hisipida Curcuma longa, Dendrocnida sinuate, Euphorbia royleana, Saccharum officinarum, Garcinia cowa, Vitex peduncularis, Rubus rosifolius, Punica granatum*
11	Stomach issues	*Aloe barbadensis, Aporosa octandra*, *Erythrina stricta*, *Lagerstroemia speciosa*, *Artemisia indica, Baccaurea ramniflora, Berberis nepalensis*, *Dillenia pentagyna*, *Elaegnus caudate*, *Erythrina alba, Callicarpa arborea, Blumea lanceolaria, Carica papaya, Citrus aurantifolia, Curcuma longa, Curcumorpha longiflora, Helicia robusta*, *Mallotus philippensis, Lobelia angulate, Mentha arvensis, Musa* sp., *Osbeckia sikkimensis, Tinospora cordifolia, Zanonia indica, Smilax glabra, Senecio scandens, Scoparia dulcis, Saprosma ternatum, Prismatomeris tetrandra, Picria felterrae*, *Picrasma quassiooides, Picrasma javanica, Acer oblongum, Aganope thyrsiflora*
12	Food poisoning	*Zingiber officinale, Parkia roxburghii, Carica papaya, Trachyspermum roxburghianum, Phyllanthus emblica, Parkia timoriana, Acer oblongum*
13	Respiratory ailments	*Occimum tenuiflorum, Zingiber officinale, Drymaria cordata, Terminalia crenulate, Sonchus arvensis, Solanum tuberosum, Senna occidentalis, Pueraria tuberosa, Achyranthes aspera, Uncaria sessilifructus, Tithonia diversifolia, Syzygium cumini, Sonerila maculate, Sapindus mukorossi, Zingiber officinale, Occimum tenuiflorum, Terminalia chebula*
14	Typhoid	*Vitex peduncularis*, *Occimum tenuiflorum, Adina cordifolia*
15	Tonsilitis	*Uncaria sessilifructus, Aeschynanthus sikkimensis, Costus speciosus, Sterculia villosa, Smilax glabra, Sarcococca pruniformis, Sapindus mukorossi, Abelmoschus manihot*
16	Blood pressure	*Amomum dealbatum*, *Aporosa octandra, Semecarpus anacardium, Catharanthus roseus, Trachycarpus martianus, Terminalia arjuna, Solanum incanum, Senna occidentalis, Senecio scandens, Rauvolfia serpentine, Picrasma quassiooides, Picrasma javanica, Passiflora quadrangularis*
17	Vomiting	*Annona squamosa, Pratia begonifolia, Trichosanthes anguina, Trachyspermum roxburghianum, Pogostemon cablin, Alangium chinense*
18	Snake bite	*Antidesma bunius, Phyllanthus acidus, Benicasia hisipida, Wrightia arborea, Pogostemon cablin, Tagetes erecta, Solanum anguivi, Rauvolfia serpentine, Acacia pennata, Pothos scandens*
19	Toothache	*Paedaria foetida, Centella asiatica, Solanum incanum, Lepidagathis rigida, Millettia pachycarpa, Cynodon dactylon, Acmella paniculate, Tabernaemontana divaricate, Solanum viarum, Psidium guajava, Physalis angulate, Osbeckia stellate, Osbeckia crinite*
20	Kidney ailments	*Solanum nigrum, Scoparia dulcis, Saraca asoca, Citrus sinensis, Saccharum arundinaceum, Osbeckia sikkimensis, Achyranthes bidentata, Smilax ovalifolia, Costus speciosus, Jasminum nervosum, Hedychium spicatum, Rotula aquatic, Begonia inflata, Desmos chinensis, Ardisia macrocarpa, Myrica esculenta, Ageratina adenophora, Stevia rebaudiana, Actephila excelsa, Oryza sativa, Vitex peduncularis, Solanum nigrum, Centella asiatica, Occimum tenuiflorum, Phyllanthus fraternus, Ricinus communis, Sida acuta, Hedyotes scandens, Helicia robusta, Mimosa pudica, Plantago asiatica, Xanthium strumarium, Tagetes erecta, Syzygium cumini, Stevia rebaudiana, Siegesbeckia orientalis, Sida acuta, Pseudognaphalium luteoalbum, Actephila excelsa*

Table 1.
Commonly used medicinal plant by the Mizos of Mizoram.

2. Medicinal plants used in the traditional medicine system

2.1 Parasitic infections

Different varieties of plants have been used traditionally for the treatment and elimination of parasites in human and livestock. In Mizoram, the fruits of *Euphoria longan* (Lour.) Steud (theifeihmung), bark of *Morus alba* L. (thingtheihmu), and the juice of the fruit and bark of *Punica granatum* L. (theibuhfai) have been reported to have antiparasitic activities [14]. The bark extract of *Schima wallichi* (khiang), crushed leaves of *Eupatorium odoratum* Linn. (tlangsam) [15], juice of *Annona squamosa* L. leaves (theiarbawm), decoction of the leaves of *Artemisia nilagirika* Clarke (sai), root mixed with powdered fruits of *Lagerstroemia speciosa* ZL. (chawnpui), seeds of *Benincasa hispida* (maipawl), seeds of *Carica papaya* L. (thingfanghma), decoction of the tubers of *Dioscorea bulbifera* L. (ram-bahra), leaf juice of *Michelia champaca* L. (ngiau) mixed with honey, decoction of *Piper longum* L. (voko-hrui), and the fruits of *Trichosanthes anguina* L. (berul) have also been reported to be used frequently for the elimination of parasites [13]. Also, *Chenopodium ambrosioides* L., *Gossypium* (la) species and *Dalbergia pinnata* (Lour.) (Hruitengtere) have been reported to possess anthelmintic efficacy [16, 17]. In addition, the roots of *Ziziphus oenoplia* (L.) Mill. (muvanlai hling) are also consumed as an anthelminthic [18].

Acacia oxyphylla, locally known as Khang-ngo has been reported for its use as a deworming agent. Its alcohol extract has exhibited significant nematocidal activity at 5, 10 & 20 mg/ml concentrations against the fowl nematode *Ascaridia galli* [19] and anticestodal activity against the fowl cestode *Raillietina echinobothrida* [20]. The root peels of *Milletia pachycarpa,* locally known as Ru-lei showed a concentration dependent activity against *R. echinobothrida* and *A. galli* [21, 22]. Also, the extract of *Acacia caesia* stem bark (20 mg/ml) has been found to possess distinct anthelmintic activity against the tapeworm *Raillietina tetragona* [23]. The methanol extract of *Millettia taiwaniana* roots are also known to possess significant anthelmintic activity at 20 mg/ml against intestinal tapeworms *Taenia tetragona* and *Raillietina galli* [24, 25]. Likewise, the chloroform extract of *Imperata cylindrica* roots have exhibited anthelmintic activity against *R. tetragona* and *A. galli* [26]. *Ilex khasiana,* locally known as KZ thing also showed activities in which the methanol extract of leaves exhibited a concentration dependent increase in anthelmintic activity against *R. tetragona* [27]. The hexane, chloroform and methanol extracts of *Acmella oleracea,* locally known as ansapui or ankasa in Mizo, showed distinct anthelmintic activity against *R. echinobothrida* and *A. galli* [28, 29]. Likewise, the alcohol extract of *Callicarpa arborea,* locally known as hnahkiah is known to possess anticestodal activity against *R. echinobothrida* [30].

2.2 Diarrhea

Certain plants from Mizoram have been reported for their capacity to ameliorate diarrhea. The juice of the fruits of *Catunaregam spinosa* (Thunb.) (Sazukthei), bark of *Chrysophyllum lanceolatum* Casar. (Theipabuan), *Aegle marmelos* (Correa) Linn. (Belthei), *Ziziphus mauritiana* Lam. (Borai/Kawrsunhlu), *Tamarindus indica* L. (Tengtere), decoction of the bark of *Spondias pinnata* (L.f.) Kurz. (Tawitaw), fruits of *Rhus semialata* Murray (Khawmhma), fruits of *Garcinia morella* (Gaertn.) Desr. (Kawrvawmba), boiled leaves of *Garcinia cowa* Roxb. ex Choisy. (Chengkek), fruits of *Ficus racemosa* L. (Thei-chek/Chho), crushed bark juice of *Emblica officinalis* Gaertn. (Sunhlu), decoction of the bark of *Dillenia indica* L. (Kawrthindeng), fruits of *Bruinsmia polysperma* (C. B. Clarke) Steenis. (Theipaling/Kawh/Theirelchhin/

Theichhinkhup), and the inner coat of the bark of *Artocarpus chama* Buch. Ham. (Tatkawng) were described to be effective against diarrhea [14]. The fruits or young shoots of *Parkia roxburghii* G. Don (zawngtah), boiled leaves of *Mikania micrantha* (Japan hlo), and *Melastoma malabathricum* Linn. (Builukham) are often used for the treatment of diarrhea [15]. Also, the infusion of the leaves of *Rourea minor* (Gaertn.) Alston (chingpirinu thei/pho arh) and the flowers of *Rhododendron arboretum* Sm. (chhawkhleiparsen) are used for treating diarrhea and dysentery. Galls produced from the tree of *Quercus serrata* (sasua/sasaw thing), fruits of *Quercus oblongata* D. Don (then), young fruits of *P. granatum* Linn. (theibuhfai/ Darjeeling/manding), bark and young leaves of *Psidium guajava* Linn. (kawlthei/ kawiam/charthei), *Pogostemon cablin* (Blanco) Benth. (Patchouli), and the infusion of the bitter bark of *Picrasma javanica* Blume (thing damdawi/khawsik damdawi thing) are also known to be used to treat dysentery. In addition, the decoction of the bark, leaves and roots of *Phyllodium pulchellum* (L.) Desv., decoction of the roots of *Osbeckia chinensis* Linn. (builukham), and a decoction of bark and leaves of *Acer oblongum* Wall. Ex DC. (thing phingphihlip) are also used for treating diarrhea [18].

The activities of certain traditionally acclaimed antidiarrheal plants on different microorganisms have been evaluated. The methanol extracts of 12 plants namely, *Albizia lebbeck, Bombax ceiba, Abroma augusta, Actinida chinensis, Careya arborea, Chonemorpha fragrans, Clerodendrum colebrookianum, Costus speciosus, D. indica, Gynura conyza, Hibiscus sabdariffa, and Momordica charantia* showed distinct inhibition zones against gram positive bacteria (*Staphylococcus aureus*), gram negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*), and yeast (*Candida albicans*) with Minimum Inhibitory Concentration (MIC) ranging from 1.635 to 7.972 mg/ml [31]. Likewise, *A. chinensis*, *C. arborea*, *Mussaenda macrophylla* and *Stereospermum tetragonum* extracts were also reported to have inhibition activity against 4 microorganisms namely *Fusarium graminarum*, *S. aureus*, *Escherichia coli* and *Fusarium oxysoporum f. sp. ciceri* [32]. The alcohol extracts of *C. colebrookianum* Walp., exhibited antimicrobial activity against bacteria such as *E. coli* (MTCC DH5α), *Serratia marcescens* (MTCC 7103) and *S. aureus* (MTCC 4301) [33]. The alcohol extracts of *Blumea lanceolaria* root, stem and leaf showed antibacterial activity against three bacteria namely *E. coli*, *S. aureus* and *Pseudomonas aeruginosa* [34].

2.3 Skin diseases

For the treatment of various skin diseases, the crushed leaves of *Achyranthes aspera* L. (buchhawl) and *Albizia chinensis* (Osb.) Merr. (vang), juice of the crushed bark of *Artocarpus lakiicha* Roxb. (theitat) and *Jatropa curcus* L. (thingthau), pounded poultice of *Arisaema tortuosum* (Wall.) Schott. (mithi vaimim), crushed leaf juice of *Artemisia indica* Willd. (sai), *Chenopodium ambrosioides* (buarchhimtir), *C. viscosum* Vent. (phuihnamchhia) and *Elsholtzia blanda* Benth. (nauhri), powdered flower pastes of *Buddleja asiatica* Lour. (serial), infusion of *Centella asiatica* (L.) Urban (lambak), and *Lantana camara* var. aculeate (L.) Mold. (hling pangpar) have been reported to be effective against various skin diseases [35]. The bark infusion of *A. chinensis* Merr. (vang) was also found to be effective against skin disorders [13]. Plants such as *Eryngium foetidum* L. (bahkhawr/bachikhawm), *Mimosa pudica* L. (hlo nuar/hlo zak), *Polygonum plebeium*, and *Prunus cerasoides* D. Don are often used for the treatment of various diseases of the skin [36]. *Buddleia asiatica* Lour (Se rial/Sial rial), paste of bark of *Erythrina stricta* Roxb. (Fartuahpui), and the root paste of *Tinospora cordifolia* (DC.) Miers. ex. Hook. (Theisawntlung) have also been reported for their healing properties of skin diseases [17, 37]. The juice of the stem, bark and leaves of *Psychotria calocarpa* Kurz (kawr pelh), and an

infusion of the bark of *A. chinensis* (Osb) Merr. (Vang) is commonly used as a lotion for scabies and various skin diseases [18].

The ethanolic extract of *M. pudica* (hlo nuar) was found to heal wound in a concentration dependent manner [38]. The ethanolic extract gel of *Oroxylum indicum* (archangkawm) (10%) was found to enhance wound contraction which led to reduction of mean healing time in mice [39]. The dried seed extract of *Nigella sativa* has been known to accelerate collagen synthesis thereby reducing wound healing time [40].

2.4 Diabetes

Antidiabetic properties of certain plants have been reported from different parts of Mizoram. Decoction of the bark of *Dillenia pentagyna* Roxb. (Kaihzawl), decoction of the roots of *Casearia tomentosa* Roxb. (Vakithei) [14], juice of *Abrus precatorius* L. (sentet) leaves mixed with milk [13], fruits of *Averrhoa carambola* L. (theiherawt), bark of *Lagerstroemia speciosa* (L.) Pers. (thla do/chawnpui), decoction of the aerial parts of *Phyllanthus fraternus* Webster. (Mithi sunhlu) and decoction of the stem of *Tinospora cordifolia* (DC.) Miers. ex. (hrui vankai/hrui vankai hnah mam) are commonly used to treat diabetes [37]. Antidiabetic activity of plants such as *Aloe barbadensis* (L.) Burm.f. (awle lei), *Artocarpus heterophyllus* (Lam.) (lamkhuang/la ui), *Curcuma longa* (L.) (aieng), *E. officinalis* (L.) (sunhlu), *M. indica* (L.) (theihai), and *M. pudica* (L.) (hlo nuar) have also been reported [31]. *Albizia procera* Roxb. (kang tek), *A. marmelos* (L). Corr (bel thei), *Allium cepa* Linn. (purun sen), *Alstonia scholaris* (thuamriat), *Allium sativum* Linn, (Linn.) R. Br (purun var), and *C. colebrookianum* Walp. (phuihnam) are frequently used for the treatment of diabetes [41, 42]. A decoction of the whole plant of *Plantago major* Linn. (kel ba an), fruits, stem and leaves of *Physalis angulata* L. Var. *angulata* L. (Kelasawirawphit/chalpang puak), tea made from leaves of *Passiflora quadrangularis* L. (sapthei lian chi) and fruits of *A. marmelos* (L.) Correa (bel thei) have been reported for their use as an antidiabetic remedy [18].

The ethanolic extract of *Scurrula parasitica* (thlilthli ek bawm) at concentrations of 100 and 200 mg/kg has been known to possess significant hypolopidemic and antihyperglycemic activity in albino rats [43]. The methanolic extract of *Mallotus roxburghianus* (zawngte nawhlung) leaves have shown to possess antidiabetic properties on streptozocin induced diabetic models of experimental animals. However, the activity may not be dose dependent, as the two different doses of extract (200 mg/kg and 400 mg/kg) did not show any significant variation in the results [44].

2.5 Cancer

Increase in cancer cases in recent years has led to the exploration of certain anticancer plants for immediate remedy. The juice of *Aglaia edulis* (Roxb.) Wallich (raithei) fruits, crushed fruits of *Prunus domestica* L. (Japan theite), fruits of *Ficus hirta* Vahl. (sazutheipui) and the decoction of the bark of *D. pentagyna* Roxb. (kaihzawl) are known to be effective against certain types of cancer [14]. The anticancer activity of the roots of *Ageratum conyzoides* (Linn.,) (vaihlenhlo), leaves of *B. lanceolaria* Linn. (buar ze), stem and bark of *D. pentagyna* Roxb. (kaihzawl), *Aloe barbadensis* (L.) (awle lei), *Artocarpus heterophyllus* (Lam.) (lamkhuang), *Azadirachta indica* (A. Juss) (nim thing), *C. papaya* (L.) (thing fanghma), *C. colebrookianum* (Walp.) (phuihnam), *C. longa* (L.) (aieng), *E. officinalis* (L.) (sunhlu), *Mimosa indica* (L.) (hlo nuar) and *M. charantia* (L.) (changkha/changkha rek) have also been reported [31]. Roots of *Ageratum conizoides* Linn. (vaihlenhlo), leaves of *B. lanceolaria* Linn. (buar ze) and *G. conyza* sp., stem bark of *D. pentagyna* Roxb

(kaihzawl), and *D. indica* Linn. (kawrthindeng) were also found to possess anticancer property [45]. The decoction of the whole plant of *Scurrula parasitica* L. (thlikthliekbawm) and the decoction of the leaves of *Rhynchotechum ellipticum* (Wall. Ex D. Dietr.) A. DC. (tiarrep) are recommended for the treatment of cancer [18].

A study also suggested that *D. pentagyna* (kaihzawl) used in the traditional medicine of the Mizos, has antitumor activity against murine ascites Dalton's lymphoma [46]. In another study, the ethanolic extract of *A. marmelos* (L.) Correa (bel thei) showed protection against cardiotoxicity [47]. *Allium hookeri* (mizo purun), *Eryngium foetidium* (bahkhawr/bachikhawm), *Mikania micrantha* (japan hlo), and *Alpinia galanga* (ai chal) were found to exhibit cytotoxicity against HeLa cells in a dose dependent manner. The IC_{50} were found to be 138.5, 199.7, 49.02, and 209.4 μg/mL, respectively [48]. The root extract of *A. conyzoides* (vaihlenhlo), stem bark of *D. pentagyna* (kaihzawl), fruit of *Solanum khasianum* and leaves of *Lonicera macrantha* (leihruisen), *Senecio scandens* (saiek hlo), *Croton caudatus* (ran lung damdawi/kam sa hulh/vawkze), *Mussaenda macrophylla* (vakep) and *B. lanceolaria* (buarze) were found to have anticancer activity against cancer cells such as MCF-7, HeLa, and Dalton's lymphoma cells. Out of these, extracts of *D. pentagyna* and *S. khasianum* were found to be a potent source of anticancer compound [49]. The methanolic extracts of the leaves of *Callicarpa arborea* Roxb. (hnahkiah) and *Byttneria aspera* Colebr. (zawng luang hrui/zawng hnuang hrui) were found to have anticancer activity against human cancer cell lines such as colon cancer cell lines (HT-29), breast cancer cell line (MCF-7), cervical cancer cell line (HeLa), leukemia cell line (MOLT-4) and ovarian cancer cell line (OVCAR-3) [50]. The aqueous extract of *C. caudatus* Geisel (ran lung damdawi/kam sa hulh/vawkze) was found to have in vivo anticancer activity against Dalton's lymphoma (% increase in life span 92.5%) and an in vitro anticancer activity with IC_{50} of 28.36 μg/ml [49]. The chloroform extract of *C. arborea* (hnahkiah) showed promising anti-proliferative and cytotoxic activity against A549, Type II human adenocarcinoma cell line [51]. The leaf, bark and fruit extract of *Rhus javanica* L., were also found to possess anticancer activity against HeLa cell line [52].

2.6 Malaria

Different varieties of plants are used for treating malaria based on traditional practices. The leaf infusion of *Acacia concina* DC (khangthur), *Andrographis paniculata* Nees. (hnahkhapui), decoction of the leaves and roots of *Adhatoda vasica* Nees. (kawldawi), decoction of the bark of *Alstonia scholaris* R.Br. (thuamriat), and decoction of the leaves of *Artemisia nilagirika* Clarke (sai) have been reported for their use as an antimalarial agent [13]. Also, *Clerodendrum serratum* (L.) Moon (Ram phuihnam) [17], *Acacia concinna* (Willd.) DC. (Khang-thur), *Acer oblongum* Wall. ex DC. (Thing-phing-phi-hlip), crushed juice or decoction of the stem bark of *Alstonia scholaris* L. R. Br. (thuamriat), decoction of the aerial parts of *A. paniculata* (Burm. f.) Wall. ex Nees (hnah-kha-pui), decoction of the bark of *Anogeissus acuminata* Roxb. ex DC. Guill. (zai-rum), decoction of the roots or leaves of *Artemisia vulgaris* L. (sai), decoction of the rhizome of *Begonia inflata* C.B. Clarke (se-khup-thur), decoction of the leaves of *Borginia ciliate* (Haw.) Sternb. (kham- dam-dawi), infusion of the leaves or powdered roots of *Canna indica* L. (kung-pui-mu-thi), decoction of the roots of *Cassia fistula* L. (ngai-ngaw/phung-ril), decoction of the leaves and bark of *Chickrassia tabularis* Andr. Juss. (zawngtei), decoction of leaves or roots of *Dichroa febrifuga* Lour. (khaw-sik-dam-dawi or ui-te-pangang-hlo), leaf juice of *Eryngium foetidum* L. (bahkhawr), decoction of the roots of *Kyllinga monocephala* Rottb. (artelubawk), decoction of the leaves of *Lantana camara* L. (Shilong tlang-sam or til-duh-par), juice of the leaves of *Mikania micrantha*

H.B.K. (Japan-hlo), decoction of the leaves of *Musa paradisiaca* L. var., *Sylvestris* sp. (changel), decoction of the roots of *Passiflora nepalensis* Wall. (nau-awi-mu-hrui), decoction of the whole plant of *Phyllanthus fraternus* Web. (mitthi-sun-hlu), decoction of the bark of *Picrasma javantica* Bl. (thing-dam-dawi or khaw-sik- dam-dawi-thing), leaf juice of *Piper betle* L. (panruang), decoction of the fruits of *Piper longum* L. (vako-hrui), decoction of the leaves, seed and roots of *P. major* L. (kelba-an), decoction of the bark of *Prunus cerasoides* D. Don. (tlaizawng), decoction of the roots, stem and leaves of *Rotheca serrate* L. Steane & Mabb. (lei-dam-suak), decoction of the flower, leaves and bark of *Spathodea stipulata* Wall. (zih-haw), *Stereosrermum personatum* (Hassk.) De. Chatt. (zihnghal), and a decoction of the young stem, bark and leaves of *Vitex peduncularis* Wall. (thing-khawi-lu-pa) [53] are used to treat malaria. In addition, the roots of *Garcinia cowa* (dang kha) [54], the decoction of the whole plant of *P. major* Linn. (kel ba an), bark of *Pittosporum napaulense* (DC.) Rehder & Wilson (thing pho arh) and the decoction of the roots of *Passiflora nepalensis* Wallich (Nauawimu hrui) are commonly used for the treatment of malaria [18].

2.7 Fungal infections

The juice of the fruits of *Ficus auriculata* Lour. (theibal), root of *Gelsemium elegans* Benth. (hnamtur), and *Alocasia indica* (saidawl/vandaw) have been reported for their use in the traditional medicine of the Mizos as an antifungal agent [14, 46, 55]. The leaf extract of *Chickrassia tabularis* Andr. Juss. (zawngtei), *P. betle* L. (panruang) and the paste of the leaves and bark of *Spathodea stipulata* Wall. (zih-haw) are well known antifungal agents [53]. The decoction of the roots of *Asparagus racemosus* Willd. (arkebawk) is often consumed for treating fungal infection [16].

The essential oil of *Homalomena aromatica* (anchiri) was found to be effective against three pathogenic fungi namely, *Epidermophyton floccosum*, *Microsporum gypseum*, and *Trichophyton rubrum* with Minimum Cidal Concentration (MCC) between 1.2 to 1.8 μl/ml [56]. The essential oil of *C. longa* (aieng) was found to exhibit antifungal activity against pathogenic fungi *Trichophyton rubrum* and *T. mentagrophytes* with Minimum Inhibitory Concentration (MIC) of 2.1 mg/ml and 1.9 mg/ml respectively [57]. The essential oil extracted from the mature seeds of *Trachyspermum ammi* L. showed inhibition against *Candida albicans* and *Aspergillus flavus* with MIC of 0.086 mg/ml and 0.202 mg/ml respectively [58]. The ethanol and aqueous extracts of *Callicarpa macrophylla* Vahl. stem was found to have antifungal activity against six pathogenic fungi namely, *Rhizopus oligosporus*, *Gibberella fujikoroi*, *C. albicans*, *Myrothecium verrucaria*, *Cryptococcus neoformans*, *A. niger*, and *Neurospora crassa* [59]. Also, the methanol extract of the leaves of *Bidens pilosa* was also found to have inhibition activity against *C. albicans* at concentration of 10 mg/ml with 9.1 mm zone of growth inhibition [60].

2.8 Measles

The boiled leaves of *Securinega virosa* Roxb. (saisiak), *Adhatoda vasica* Nees. (kawldai) and the decoction of the leaves of *Azadirachta indica* used in the Mizo traditional medicine are reported to be effective against measles [61]. The decoction of the rhizome of *Amomum subulatum* Roxb. (ailaidum) [13] and *Cucurma caesia* (ailaidum) are often used for the treatment of measles [55]. The boiled leaves of *Anacolosa crassipes* Kurz (lushai nautur) and *S. virosa* (Roxb. ex Willd.) Baill. are used while bathing while the leaf juice of *Phyllanthus airy-shawii* Brunel & J.P.Roux. (mawsai) are applied on the infected skin [16]. Also, the fresh juice of *Homalomena aromatica* (anchiri) roots [35], paste of the leaves of *Anogeissus acuminata* Roxb. ex

DC. Guill. (zairum), leaves of *Lantana camara* L. (shillong tlangsam) [53] and the decoction of the leaves of *Rhus javanica* L. (khawmhma) have been reported for their efficacy against measles [52].

2.9 Chicken pox

The boiled leaves of *Securinega virosa* Roxb. (saisiak) is often used while bathing to cure chicken pox, while the boiled leaves of *Adhatoda vasica* Nees. (kawldawi) and the raw fruits of *Rhus semialata* (khawmhma) are consumed for the treatment of chicken pox [61]. A decoction of the leaves of *Embelia nagushia* D. Don (thing) [13], paste of the leaves of *Anogeissus acuminata* Roxb. ex DC. Guill. (zairum), paste of the leaves of *A. carambola* L. (theiherawt) [53] and a decoction of the leaves of *Embelia vestita* Roxb. (tling) are also often used [14].

2.10 Jaundice

The fruit, leaves and roots of *Chonemorpha fragrans* (Moon.) (phungtheikelki) are taken raw or boiled to treat jaundice [61]. Also, the fruit juice of *E. officinalis* Gaertn. (sunhlu) [15], *Jatropha curcas* L. (kang damdawi/thing thau), *M. charantia* L. (changkha/vhangkha rek), *O. indicum* vent. (archangkawm), *Terminalia chebula* (re raw), *Zingiber officinale* Roscoe (sawhthing), *D. pentagyna* Roxb. (kaihzawl), *C. colebrookianum* Walp. (phuihnam), *Catharanthus roseus* L. (kumtluang), *Cassia fistula* L. (ngaingaw/phungril), *Carica papaya* L. (thingfanghma), *Capsicum frutescens* L. (hmarcha pui), *Aeschynanthus sikkimensis* Stapf, *Adhatoda zeylanica* Nees and *Adhatoda vasica* Nees (kawldawi) are used commonly for the treatment of jaundice [62]. The roots of *Homalomena aromatica* (anchiri) [56], the inner portion of the fruit of *Passiflora spp* (sapthei), infusion of the leaves of *Acacia concina* DC. (khangthur), decoction of the leaves of *Amomum subulatum* Roxb. (ailaidum), decoction of the leaves of *G. conyza* Cass. (buarze), root decoction of *Lagerstroemia speciosa* ŽL. Pers. (chawn-pui or thlado), root decoction of *Laportea crenulata* Gaud. (thakpui), juice of the leaves of *M. charantia* L. (changkha), and the stem juice of *Musa superba* Roxb. (tumbu or changel) have been reported to be effective against jaundice [13]. Also, *Alocasia indica* (Saidawl/Vandawl), *C. papaya* (thingfanghma), *Cucurma caesia* (ailaidum) and *Passiflora edulis* (sapthei) are frequently used for the treatment of jaundice [55]. The use of the whole plant of *Andrographis paniculata* (Burm.f.) Wall. ex. Nees (hnahkhapui), boiled juice of *Ardisia paniculata* Roxb. (naunuar), fruits of *Averrhoa sp*. (theiherawt), boiled roots of *Dendrocnide sinuata* (Blume) Chew (thakpui), boiled fruit juice of *D. indica* L. (kawrthindeng), fruit of *Hibiscus rosa-sinensis* L. (midum pangpar/bangla par), crushed leaves of *Inula cappa* (Buch.-Ham. ex D. Don) DC. (buarthau), and the aerial parts and roots of *Lagerstroemia speciosa* (L.) Pers. (chawnpui/ thlado) have also been reported to possess efficacy against jaundice [16]. In addition, the twigs of *Mallotus roxburghianus* Muell. (zawngtenawhlung), juice of the whole plant of *Phyllanthus fraternus* Webster. (mithisunhlu) [63], decoction of the leaves of *Ficus semicordata* var. conglomerate (Roxb.) Kurz. (theipui), *Hedyotes scandens* D. Don, (kelhnamtur/laikingtuibur), and a decoction of the whole plant of *Phyllanthus fraternus* Webs (mithisunhlu) have been described to be effective against jaundice [35]. The leaves of *M. pudica* (hlonuar) [38], boiled roots of *Bridelia monoica* (Lour.) Merr. (phaktel), decoction of the leaves of *Ficus semicordata* Buch. Ham. ex Sm. (theipui) [14], crushed leaves of *Benicasia hisipida* (Thumb.) Cogn. (maipawl), decoction of the troot stock of *C. longa* L. (aieng), decoction of the roots of *Dendrocnida sinuate* (Blume) (thanpui), decoction of the leaves of *Euphorbia royleana* Boiss. (chawng), juice of the tender shoot of *Musa sp*.

(changel) and juice of the stem of *Saccharum officinarum* L. (fu) are also used for the treatment of jaundice [37]. Also, the leaves of *Garcinia cowa* (dang kha), decoction of the whole plant of *M. pudica* L. (hlonuar), infusion of the bark and leaves of *V. peduncularis* wall. Ex Schauer are used to treat jaundice [54, 64]. The decoction of the stem, leaves and roots of *Rubus rosifolius* Sm. Ex Baker (hmubel-bing/chultheihmu) and the young fruits of *P. granatum* Linn. (theibuhfai/ Darjeeling/manding) are also commonly used to cure jaundice [18].

2.11 Gastritis/stomach problem/ulcer

Certain medicinal plants are recommended and used for the treatment and alleviation of gastric problems. Aerial raw parts of *Aloe barbadensis* var. chinensis Haw. (*Aloe vera*), decoction of the bark of *Aporosa octandra* (Buch. Ham. ex D. Don) (chhawntual), *Erythrina stricta* Roxb. (fartuahpui), *Lagerstroemia speciosa* (L.) Pers. (thlado/chawnpui), decoction of the leaves of *Artemisia indica* Willd. (sai), and the bark of *Baccaurea ramniflora* Lour. (pangkai) are consumed half an hour before food to treat gastritis. The decoction of the bark of *Berberis nepalensis* (DC.) Spreng. (pualleng), *D. pentagyna* Roxb. (kaihzawl), *Elaegnus caudate* Schlecht. ex Momiyama (kel), *Erythrina alba* Cogn. & Marchal (fartuah par var) and *Callicarpa arborea* Roxb. (hnahkiah), raw leaves of *B. lanceolaria* Roxb. (buarze), juice of the pounded leaves of *C. papaya* L. (thingfanghma), and the juice of *Citrus aurantifolia* Christm. (nimbu) fruits are consumed in the morning, whereas, a decoction of the root stock of *C. longa* L. (aieng), root stocks of slices of *Curcumorpha longiflora* Wall. (ailaidum), decoction of the bark and leaves of *Helicia robusta* (Roxb.) R. Br. Ex Blume (pasaltakaza), *Mallotus philippensis* (Lam.) Muell. Arg. (thingkhei), crushed leaves of *Lobelia angulate* Forst. (choakthi), aerial parts of *Mentha arvensis* L. (pudina), juice of tender shoots of *Musa sp*. (changel), decoction of the roots of *Osbeckia sikkimensis* Craib. (builukham pa), decoction of the stem of *Tinospora cordifolia* (DC.) Miers. ex. Hook. (theisawntlung), and water poured into the fruit cavity of *Zanonia indica* L. (lalruanga dawi bur) are commonly used for treating gastric problems and ulcer [37]. The pounded tuberous roots of *Smilax glabra* Roxb. (tluangngil) is used for stomachache and the decoction of the leaves of *Senecio scandens* Buch.-Ham ex D. Don (saiekhlo), juice of the pounded leaves, roots and stem of *Scoparia dulcis* L. (perhpawng chaw/thlum dem dem) and the leaves of *Saprosma ternatum* (Wall.) Hook.f. (pelhvawm/thinglawhleng) are used for pain relief. The juice of the leaves of *Prismatomeris tetrandra* (Roxb.) K. Schum. (telenga mai suak), decoction of the whole plant of *Picria felterrae* Lour. (khatual), and a decoction of the bark and leaves of *Picrasma quassiooides* (thing damdawi/khawsik damdawi thing/thingpil kha) are consumed for treating stomach ulcer. Powdered adry fruits of *Picrasma javanica* Blume (thing damdawi/khawsik damdawi thing) is commonly used to treat stomach ache and the decoction of the bark and leaves of *Acer oblongum* Wall. Ex DC. (thing phingphihlip) and a decoction of the fruits of *Aganope thyrsiflora* (Benth.) (hulhu) are commonly used for various stomach problems [18].

2.12 Food poisoning/allergy

For food poisoning and allergies, different parts of plants such as roasted root stock of *Zingiber officinale* Rosc. (sawhthing) and the bark of *Parkia roxburghii* Roxb. (zawngtah) are chewed while the juice of the leaves of *C. papaya* L. (thing-fanghma) is used to treat meat allergy [37]. Also, the leaves of *Trachyspermum roxburghianum* (DC) H Wolff (pardi) are consumed as a remedy for food allergy and the pounded fruits of *Phyllanthus emblica* L. (sunhlu), young leaves and seeds

of *Parkia timoriana* (DC.) Merr. (zawngtah), and a decoction of the bark and leaves of *Acer oblongum* Wall. Ex DC. (thing phingphihlip) are used to treat food poisoning and allergies [18].

2.13 Cough

A decoction of the bark of *Occimum tenuiflorum* Linn. (keifang) and roasted root stock of *Zingiber officinale* Rosc. (sawhthing) are consumed to treat cough [37]. The whole plant of *Drymaria cordata* (L.) Willd. (changkalrit) is boiled and the steam is inhaled to treat sinusitis and cough [16]. Likewise, the bark of *Terminalia crenulate* Roth (tuairam), the roots of *Sonchus arvensis* L. (khuanglawi), and the leaves of *Solanum tuberosum* Linn. (alu) are used to treat chronic cough. Similarly, *Senna occidentalis* (L.) Link (rengan), tubers of *Pueraria tuberosa* (Willd.) DC. (zawng tur/thingba/bul ei) and juice of the pounded leaves of *Achyranthes aspera* Linn. (bu chhawl/ui hlo) are used to treat cough [18].

2.14 Sore throat

A decoction of the young leaves or root bark of *Uncaria sessilifructus* Roxb. (ralsamkuai), whole plant of *Tithonia diversifolia* (Hemsl.) A. Gray (bawngpupar), seed of *Syzygium cumini* (L.) Skeels (hmuipui/lenhmui), juice of *Sonerila maculata* Roxb. (thaksenhlo), and an infusion of the fruit pulp of *Sapindus mukorossi* Gaertn. (hlingsi) are consumed to treat sore throat [18]. Also, the roasted root stock of *Zingiber officinale* Rosc. (sawhthing), decoction of the bark of *O. tenuiflorum* Linn. (keifang) [37] and the fruit of *Terminalia chebula* Retz. (reraw) are consumed to get relief from cough [63].

2.15 Typhoid

The decoction of the leaves of *V. peduncularis* Wall. ex. Schauer. (thingkhawilu), *O. tenuiflorum* Linn. (tulsi) and *Adina cordifolia* Roxb. (lungkhup) are used as medication for typhoid [37].

2.16 Tonsilitis

The tender leaves of *Uncaria sessilifructus* Roxb. (ralsamkuai) are chewed in case of infection of the tonsils [37]. Also, an infusion of the flowers of *Aeschynanthus sikkimensis* (C.B. Clarke) Stapf. (bawltehlantai) and water from the boiled leaves of *Costus speciosus* (Koeing) Smith. (sumbul) is consumed for relief from tonsilitis [63]. In addition, a decoction of the bark of *Sterculia villosa* Roxb. (khaupui) and decoction of the leaves of *Smilax glabra* Roxb. (tluangngil) are also used. The decoction of the leaves of *Sarcococca pruniformis* Lindl. (pawhrual), infusion of the fruit pulp of *Sapindus mukorossi* Gaertn. (hlingsi) and the seeds of *Abelmoschus manihot* (L.) Medik. Var. *pungens* (uichhu me/uichhu hlo) are commonly eaten as a remedy [18].

2.17 Blood pressure

The fruits of *Amomum dealbatum* Roxb. (aidu), *Aporosa octandra* (Buch. Ham. ex D. Don) (Chhawntual) and juice of the leaf stalk of *Semecarpus anacardium* Linn. F. (vawmbal-pui) are consumed to control and lower blood pressure [14]. Also, the raw leaves of *Catharanthus roseus* Linn. (kumtluang) are often used as a remedy for high blood pressure (63). The flower bud of *Trachycarpus martianus*

(Wall. Ex. Mart.) H. Wendl. (buarpui), bark and leaves of *Terminalia arjuna* (Roxb. Ex. DC) (changkurmam), the fruits of *Solanum incanum* Linn. (samtawk), *Senna occidentalis* (L.) Link (rengan), leaves of *Senecio scandens* Buch.-Ham ex D. Don (saiekhlo), roots of *Rauvolfia serpentine* (L.) Benth. Ex Kurz (thisensang damdawi/thingzungkha), decoction of the bark and leaves of *Picrasma quassiooides* (thing damdawi/khawsik damdawi thing/thingpil kha), infusion of the bitter bark of *P. javanica* Blume (thing damdawi/khawsik damdawi thing) and tea made from leaves of *Passiflora quadrangularis* L. (sapthei lian chi) are also commonly consumed to lower high blood pressure [18].

2.18 Antiemetic

The fruits of *Annona squamosa* L. (Theiarbawm) [14] and the crushed leaf juice of *Pratia begonifolia* Lindl. (choak thi) are used as a remedy for vomiting [63]. The fruit and leaves of *Trichosanthes anguina* L. (berul), seeds of *Trachyspermum roxburghianum* (DC) H Wolff (pardi), *Pogostemon cablin* (Blanco) Benth. (Patchouli) and the roots and stem of *Alangium chinense* (Lour.) Harms (arsa rim nam) are often consumed as medication to prevent vomiting [18].

2.19 Antivenin

For venomous snake bites, mature leaves of *Antidesma bunius* (L.) Spreng. (tuaitit) and the crushed roots of *Phyllanthus acidus* (L.) Skeels. (kawlsunhlu) are frequently used [14]. *T. indica* L. (tengtere) seeds are attached to the biting area, while crushed juice of the leaves of *Benicasia hisipida* (Thumb.) Cogn. (maipawl) and juice of the tender shoots of *Musa sp.* (changel) are applied on the bitten area [37]. Also, the bark of stem and roots of *Wrightia arborea* (Dennst) Mabb. (hleng) and the stem of *Pogostemon cablin* (Blanco) Benth. (Patchouli) are given as an antidote to snake bite. In addition, a decoction of the root, stem and leaves of *Tinospora crispa* (L.) Hook. F. & Thomson (hruivankai), flowers of *Tagetes erecta* L. (derhken), fruits of *Solanum incanum* Linn. (samtawk), crushed fruits of *Solanum anguivi* Lam. (samtawkte), juice of the leaves of *S. dulcis* L. (perhpawng chaw/thlum dem dem), roots of *Rauvolfia serpentine* (L.) Benth. Ex Kurz (thisensang damdawi/thingzungkha), stems of *Pothos scandens* Linn. (laiking tai rua), decoction of the tender leaves of *Acacia pennata* (L.) Willd. (khanghu) and leaves of *A. pruinescens* Kurz (khangpawl) have also been reported to be effective upon external application [18].

2.20 Toothache

For instant relief from toothache, certain plant parts and their fumes are used. *Solanum* sp. (bawngek hling) fruits are smoked, whereas, the stem of *Paedaria foetida* L. (vawihuihhrui), aerial parts of *Centella asiatica* (L.) Urb. (lambak) and the flower of *Dendrobium sp.* (nauban) are chewed to treat toothache [37]. Also, the whole plant of *Solanum incanum* Linn. (samtawk/bawkbawnkha) [18], leaves of *Lepidagathis rigida* Dalz. (vangvat tur) and infusion of the roots of *Millettia pachycarpa* Benth. (rulei) are used to treat tooth decay while the whole plant of *Cynodon dactylon* (Linn.) Pers. (phaitual) is inhaled [63]. Likewise, the leaves and flowers of *Acmella paniculata* (ankasate) are eaten raw to cure toothache [64]. The root bark of *Tabernaemontana divaricate* (L) R. Br. Ex Roem. & Schult. (pararsi/kelte bengbeh), seeds of *Solanum viarum* Dunal (at hlo hling/rulpuk), fruit of *Solanum incanum* Linn. (samtawk), juice of pounded leaves, roots and stem of *S. dulcis* L. (perhpawng chaw/thlum dem dem), paste of the bark of *Psidium guajava* Linn.

(kawlthei/kawiam/charthei) are applied on the area of toothache. Also, warm water of the cooked leaves of *P. major* Linn. (kel ba an/tuikuk antam) is retained in the mouth to cure toothache. The fruit, stem and leaves of *Physalis angulata* L. var. *angulata* L. (kelasawirawphit/chalpang puak), decoction of the leaves of *Osbeckia stellate* Buch.-Ham.ex Ker Gawl. (builukham pa), decoction of the roots of *Osbeckia crinite* Benth. Ex C.B. Clarke (builukham) and the whole plant or flower head of *A. oleracea* (ansapui/ankasa kir) are chewed to cure toothache [18].

2.21 Kidney problems

A decoction of the aerial parts of *Solanum nigrum* L. (anhling), *S. dulcis* L. (perh-pawngchaw), decoction of the bark of *Saraca asoca* Roxb. (mualhawih), leaves of *Citrus sinensis* (L.) Osbeck (serthlum), roots of *Saccharum arundinaceum* Retz. (rairu-ang) and *Achyranthes bidentata* Blume (vangvat tur/vangvat hlo) are used as a diuretic and to ease urination. A decoction of the roots of *O. sikkimensis* Craib. (builukham pa), aerial parts of *Hedychium spicatum* Koenig (kelhnamtur), *Jasminum nervosum* Lour., (maufimhlo), roots of *Oryza sativa* L. (buh) and roots of *Smilax ovalifolia* Roxb. Ex. D. Don (kaihapui) are used to treat urinary complaints and urinary tract infections. For the removal of kidney stones, a decoction of the aerial parts of *Costus speciosus* (Koenig) J.E. Sm (sumbul), infusion of the bark and leaves of *V. peduncularis* wall. Ex Schauer (thingkhawilu pa), water from boiled leaves of *Solanum nigrum* Linn. (anhling), and the juice of the pounded leaves, roots and stem of *S. dulcis* L. (perhpawng chaw/ thlum dem dem) are commonly used. The root of *Rotula aquatic* Lour. (tuipuisuthlah/ tuipuisuthlah) is also used for the removal of bladder stones [37, 18]. An infusion of the whole plant of *Begonia inflata* Cl. (sekhupthur hmul), decoction of the root and leaf of *Desmos chinensis* (Lour.) (zunin damdawi) and decoction of the root of *O. crinite* Benth. Ex C.B. Clarke (builukham) are used to treat painful urination [63].

Similarly, *Ardisia macrocarpa* Wall. (vahrit thei), bark of *Myrica esculenta* Buch. Ham. ex D. Don. (keifang), decoction of the leaves of *Embelia vestita* Roxb. (tling), fruits of *Ardisia macrocarpa* Wall. (vahrit thei) [14], raw aerial parts of *C. asiatica* (L.) Urb. (lambak), decoction of the bark of *O. tenuiflorum* Linn. (keifang) [37], steamed root extract of *O. sikkimensis* Craib. (builukham pa), infusion of the whole plant of *Phyllanthus fraternus* Webster. (mithi sunhlu), crushed leaves of *Ricinus communis* Linn. (mutih), crushed root of *Sida acuta* Burm. F. (khingkhih), decoction of the roots, stem and leaves of *Cissus discolor* Blume (sangharhmai), boiled whole plant of *Hedyotes scandens* Roxb. (laiking tuibur) [63], decoction of the whole plant of *M. pudica* L. (hlonuar), decoction of the bark of *H. robusta* (Roxb.) R. Br. Ex Blume. (pasaltakaza), decoction of the whole plant of *Plantago asiatica* L. (kelbaan) [63], decoction of the roots of *Xanthium strumarium* L (chabet), leaves of *Tagetes erecta* L. (derhken), seeds of *Syzygium cumini* (L.) Skeels (hmuipui/ lenhmui), leaves of *Stevia rebaudiana* (Bertoni) Hemsl. (hnahthlum), *Siegesbeckia orientalis* Linn. (ansapui suak), roots of *S. acuta* Burm.f. (khingkhih/valatha), leaves of *Pseudognaphalium luteoalbum* (L.) (kawhte mei bu), fruits of *Actephila excelsa* (Dolz) Mull.-Arg. (Telenga mai/pem hlek damdawi), and the leaves of *Ageratina adenophora* (Spreng.) R. M. King & H. Rob. (Bihar hlo/Nepal tlangsam/ tlangsam suak/aieng rim nam) are consumed to cure various kidney and urinary troubles such as urinary insufficiency, and diseases of the urethra [18].

3. Conclusions

Traditional medicine practices continue to thrive in rural India, particularly in the tribal dominant states. Studies that have evaluated their efficacy have revealed

positive results, indicating that the traditionally used medicinal plants are capable of healing several ailments. Documenting these traditional practices is the first step towards scientifically evaluating both their efficacy and toxicity. Several medicinal plants that continue to be used in traditional medicine still await their scientific validation. Hence, similar studies to document these practices needs to be executed which will not only prevent an age-old tradition from becoming extinct but could also lead to the discovery of new drugs.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 6

A Review on the Ethnobotanical Uses, Phytochemistry and Pharmacological Effect of *Luffa cylindrinca*

Kazeeem Akinyinka Akinwumi, Oluwole Olusoji Eleyowo and Omolara Omowunmi Oladipo

Abstract

Luffa cylindrica, popularly known as sponge gourd is a tropic and sub-tropical fibrous plant with fruits containing black seeds. The fruit is consumed by humans as a vegetable in many parts of Asia, while different parts of the plant are used for cosmetics and as medicine in many parts of the globe. The plant has been used in the treatment of many ailments including nose cancer, snake venom, wound healing, edema, enterobiasis, filaria, whooping cough, stomach upset, stomach pain and malaria. Many health-promoting compounds such as flavonoids (apigenin-7-glucuronide luteolin-7-O-*β*-D-glucuronide methyl ester, -O-feruloyl-*β*-D-glucose, luteolin-7-O-*β*-D-glucuronide methyl ester), phenolics acids (p-Coumaric, gallic, caffeic, chlorogenic), triterpenoids (oleanolic acid and echinocystic acid), saponins (Lucyoside A-M), tannins (catechin), ribosome-inactivating proteins (α- luffin), carotenoids (9 -cis neoxanthin, all-trans-lutein, all-trans-β-carotene), chlorophylls (chlorophyll a and b, pheophytin), cucurbitacin B and gypsogenin have been detected or isolated from different parts of the plants. Extracts of the plant and isolated compounds have wide spectrum pharmacological activities and have been shown to possess antiemetic, antidiabetic, antiviral, wound healing, anticancer, antipyretic, anti-inflammatory, antifungal, anti-bacteria, anthelmintic, hypoglycemic and antihyperglycemic, anti-inflammatory, antioxidant activity, and hepatoprotective effects in animal models. However, further information is needed on its safety and mechanisms of action. The present article is an updated review of the ethnobotanical uses, pharmacological actions, phytochemistry, safety, and future application of *Luffa cylindrica* in translational medicine.

Keywords: *Luffa cylindrica*, medicinal plants, phytochemicals,antioxidant

1. Introduction

Luffa cylindrica is an important edible and medicinal plant that belong to the Cucurbitaceae family. It has many common names including smooth luffa, sponge luffa, vegetable sponge gourd, climbing okra, dishcloth gourd, and Chinese okra [1]. Locally in Nigeria, it is commonly referred to as kankan or kankan oyibo in Yoruba, while the Hausas call it soosoo. The Igbos named it Asisa. The plant is a

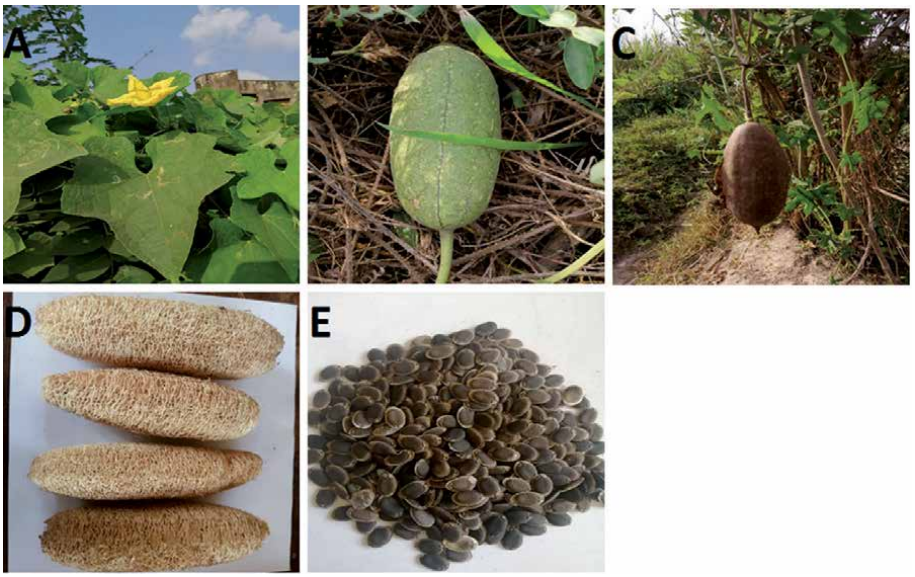

Figure 1.
Different parts of Luffa cylindrica *(A) leaves with flower (B) matured fruits (C) dried fruits (D) Luffa sponge (E) seeds.*

sub-tropical crop which when planted in northern latitudes warrants hot and humid climates as well as prolonged chilly planting conditions. Also, a vast abseiling shrub with such a greenish, scrumptious vine that is slender but very stiff, extending to a length of 30 feet is *Luffa cylindrica.* It has a fleshy egg –shaped dehiscent fruit with a green papillary dermis, transversely characterized with black crevasses which generally range from 10 to 15 in total. A taut piny filament is discovered under each one of these protrusions [2]. Its leaves are 7–20 cm across and have three lobes. Flowers are bright yellow in color. The fruits which grow to about 60 cm in length are oval-shaped, smooth and, are made up of many seeds. The fruit is brown when matured and dries on the vine to resemble an inedible sponge-like structure. The picture of different parts of the plant is shown in **Figure 1.**

2. Distribution

Luffa cylindrica is commonly found in the humid tropics and Asia. Although the plant is of medieval or primitive origin, it is difficult to decide if Africa or Asia is the ancestral home. In West Africa, the plant grows naturally, but this is also presumed to be a consequence of evasion from planting since the crop is known in many cultures in the area as 'white people's sponge.' Proof of Asian ancestry is however scarce. It is also not clear how well the vine has dispersed over the vast coastal area. Many dispute that rising temperatures are a detonation factor, but the likely cause of the extensive distribution of *Luffa cylindrica* is most often human dispersal. It is documented to have evolved from India but it extensively grows as a weed in Nigeria and many other African countries.

3. Traditional and medicinal uses

Luffa cylindrica has diverse ethnomedicinal uses especially in Africa and Asia. The thawed fiber is used in Ghana for the filtration of water and palm wine [3]. Leaf

formulations are used topically for oedemas and for treating malaria in Togo. The fruit is used on tumor and inflammation in Guinea, while the pulp of the fruit is used as a desiccant in Guinea and Nigeria. There are culinary conifers cultivated in Guinea and Côte d'Ivoire. Zulu people in South Africa take a leaf decoction to treat stomach pain. The root formulation and leaf syrup were documented to be ingested in Tanzania to decrease the probability of pregnancy termination. The leaves are used for the stimulation of wound healing and abscess cognitive development. The leaves are grounded with water and the juice is used for stomach upset medication in Rwanda. Leaf decoctions are used to make childbearing smoother in Uganda. Pulverized leaves are anally inserted for enterobiasis therapy in the Central African Republic. Decoction of the leaves is fully viable against filaria and a colloidal solution of fresh leaves is used to combat whooping cough in Congo-Brazaville. Root formulation is used in Gabon as medicine for nose cancer. A root and leaf aqueous extract is documented to be consumed and used as an aborticide in an enema in the Democratic Republic of the Congo. The seed is used in Egypt for managing diabetes. The pulp of the whole crop is often used as a remedy for acid reflux in African

Country	Local name	Medicinal value	Plant part used	Preparation/application
Togo	Bassarii-Bindumpo, Gudscha, Tem	Oedema and malaria treatment[a]	Leaf	Formulation/ oral
Guinea	Manding-Mandinka	Treatment of tumor, inflammation and as an emollient[a]	Fruit Fruit pulp	
Nigeria	Kan-kan oyibo (Yoruba), Ihion-osa (Edo), sooso (Hausa), asisa (Igbo)	Use as an emollient.[a]	Fruit pulp	
South Africa		Treatment of Stomach pain[a]	Leaf	Decoction/oral
Uganda		Aiding child birth[a]	Leaf	Decoction/oral
Rwanda		Treatment of stomach upset and wounds[a]	Leaf	Decoction/oral Decoction/topical
Tanzania		Anti-abortion[a]	Leaves/root	Formulation/oral
Central African Republic		Enteriobiasis therapy[a]	Leaves	Pulverization/Rectal insertion
Congo-Brazaville		Filaria and whooping cough treatment[a]	Leaves	Decoction/oral
Gabon		Treatment of nose cancer[a]	Root	Formulation/oral
DR Congo		Aborticide[a]	Leaf	Formulation/oral
Egypt		Managing diabetes	Seed	

[a] *Available at https://uses.plantnet-project.org.*

Table 1.
Local names and medicinal uses of L.cylindrica *in Africa.*

indigenous medication. The traditional uses of *Luffa cylindrica* in different parts of Africa are summarized in **Table 1**.

Production of edible forms has taken place in India and the Philippines where the crop is mainly bred. A brand of curry which is produced from the fruit is stripped, chopped and, fried in China and India. The fruit is consumed fresh or diced and processed in Japan for later consumption. The fruit is also employed as a therapy for the treatment of cynocy-tous and flu in Asia. Traditional medicine practitioners in China use the seed and sponge of the old fruits of the plant as stomachic, antipyretic and anthelmintic medicine. In addition, dried fruit is used as therapy for abdominal, chest, muscle, and joint pains [4]. Moreover, the fruits are employed in the treatment of rheumatism, dyspnea, cough and skin inflammation in Chinese folk medicine [5]. The fruit reduces breast swellings and it is combined with other Chinese herbs as a remedy against cancer. The fibrovascular bundle of *Luffa cylindrica* dried fruit is officially listed as a treatment for paralytic diseases in Chinese pharmacopeia. In Korea, *Luffa cylindrica* fruit pulp is used to treat fever, induce hemostasis, stimulate menstrual flow, strengthen the network vessels, invigorate blood and clear phlegm [6]. In Japan, the water extract of the vascular bundle of the plant, 'Hechimasui' is used as diuretic, antitussive and skin lotion [7]. In Java-Indonesia, the leaf juice is used for amenorrhea, while it is used for treating snake bites and dysentery in India [8]. The Santals people of Indian, use the plant in treating cramps, convulsion, tetanus, leprosy and syphilis [9]. Oil extracted from the seed is used for treating skin infection, while the fruit or its tincture is used as a therapy against intestinal and biliary colitis, jaundice, hepatomegaly, splenomegaly, dropsy, nephritis, bronchitis, tuberculosis and ascites in Indian herbal medicine practice [9]. The Filipinos used the leaves for orchitis and skin diseases [8].

4. Other ethnomedicinal uses

Raw or prepared as a vegetable, the new fruit can be consumed, but it must be selected before entrenching the spongy cotyledons and before generating the extinguishing substances. The leaves are also consumed as a vegetable, while the charred seeds contain edible oil that is safe for consumption. The gritty and hazardous seed cake is not ideal for livestock feed but could be used as a compost since the plant is rich in nitrogen and phosphorus [3]. The plant is used for treating bowel and bladder hemorrhage, hemorrhoids, toothache, scarlet fever and smallpox [8]. *Luffa cylindrica* seeds are used for treating fever and respiratory disorders including sinusitis, bronchitis and asthma [10, 11]. The seed oil is used as a lubricant and atopically applied to the skin in the treatment of leprosy, shingles, boils and other skin diseases. The oil also found application in several cosmetic products including sunscreens, anti-aging creams, moisturizers, sunless tanners, facial cleansers and sunscreens. The oil is used in sunscreens because of its toxicity to skin cancer cells.

Goats feed on the fruits and leaves [3], while bees prey on their flowers. The root formulations are also used to relieve of stomach pain and as a muscle relaxant. The leaves are used for stimulation of wound repair and echogenic cognitive development. The fruit sag is consumed as a powerful prophylactic, while the seeds are consumed for their anti-parasitic and relaxing properties. The fruit is also used in the treatment of piles and hematuria [12]. Additionally, the fresh fruit is demulcent, cooling and beneficial to the intestine, stomach and genital organs [8]. The flower of *Luffa cylindrica* is used as a therapy against migraine [13].

5. Pharmacological activities

5.1 Antioxidant activity

The methanol and chloroform *Luffa cylindrica* leaves extract exhibited antioxidant property via enhanced scavenging of DPPH and superoxide radicals in a dose-dependent fashion [14]. Similarly, its methanol extract displayed free radical scavenging ability against hydrogen peroxide, hydroxyl and nitric oxide radicals. Ethanol extract of the fruit of *Luffa cylindrica* was earlier reported to possess strong antioxidant activity against DPPH radical [15]. Methanol extract of *Luffa cylindrica* vegetable thermally processed by different methods was recently found to show varying degrees of antioxidant properties as measured by thiobarbituric acid, DPPH, ferric thiocyanate and ferric reducing antioxidant power radicals scavenging assays [16]. Similarly, Bulbul *et al.* [17] using DPPH scavaging assay obtained IC_{50} values of 50.32, 56.27 and 61.24 μg/m for ethyl acetate, n-hexane and chloroform extracts of the leaves of *Luffa cylindrica* respectively as compared to an IC_{50} value of 43.22 μg/ml obtained for ascorbic acid, which was used as a standard. *In vivo*, antioxidant capacity of the fruit extract of *L.cylindrica* was recently demonstrated in a rat model of cataract. The extract delayed the initiation and inhibit the progression of H_2O_2- induced cataract by inhibiting lipid peroxidation and modulating cellular antioxidants and antioxidant enzyme activity [18].

5.2 Anti-inflammatory activity

Anti-inflammatory activity was exhibited by chloroform extract of *Luffa cylindrica* whole plant through marked reduction of carrageenan-induced rat paw edema in experimental animals that received 50 mg/kg body weight of the extract [19]. Ethyl acetate and ethanol extracts of *Luffa cylindrica* peel and pulp displayed anti-inflammatory action against LPS-induced inflammation in RAW 264.7 cells by modulating NO, IL-6, PGE2, iNOS, pIκβα and p-ERK expression [20]. Moreover, two fractions from the petroleum ether and benzene extracts of the seed exhibited anti-inflammatory activity in the same experimental animal model [9]. Lucyoside B, a triterpenoid saponin extracted from the fruit of *Luffa cylindrica* also exhibited anti-inflammatory effects through subdual of proinflammatory mediators such as iNOS, IL-6 and MCP-1 at the transcriptional and translational levels coupled with the production of NO [21].

5.3 Anticancer activity

The aqueous-ethanol extract of *Luffa cylindrica* leaves displayed anticancer effects against MCF-7, BT-474, and MDA-MB-231 cell lines which epitomize three sub-types of breast cancer: luminal A, luminal B, and triple-negative [22]. The observed effect was attributed to the presence of phytochemicals such as apigenin and luteolin. The hot water extract of *Luffa cylindrica* whole plant also exhibited anticancer activity against circulating tumor cells of hepatocellular carcinoma especially the cells subpopulation CD133+ /CD44+ with little effect among CD133+ /CD44- subpopulation [23]. Aqueous-ethanol extract of *Luffa cylindrica* leaves showed anticancer activity on three different subtypes of breast cancer including luminal A, luminal B and Her2/neu enriched through reduction of total cell viability, CD44+/24- and total CD24+ cell sub-populations percentages after treatment with the extract [24]. More recently, the anti-cancer activity of hydro-ethanol extract of *Luffa cylindrica* against CD34+/CD38+ and CD34+/CD38+ leukemic stem cells obtained from patients with acute lymphoblastic leukemia was investigated

by Yehia *et al.* [25]. The extract effectively induced cell cycle arrest and apoptosis in both populations of cells as well as exert inhibitory effects against proliferation and colonogenicity of leukemic cells. Aqueous extract of the whole plant displayed cytotoxicity against blood-derived cancer stem cells [23, 24]. The cytotoxic activity of the whole plant ethanol extract to the HT-29 and HCT-15 cell lines has also been documented [26]. The anti-tumor activity of *L. cylindrica* seeds was linked to its luffin content [27].

5.4 Anti-viral effects

The *L. cylindrica* vine demonstrated 66.7–80% protection against Japanese B encephalitis virus when given has pre-treatment to mice before viral infection, while the protection diminished when given 210 minutes post-infection to the virus [28]. Luffin P1, a ribosome-inactivating peptide isolated from *Luffa cylindrica* seeds displayed anti-HIV-1 activity in infected C8166 T-cell lines by binding HIV reverse response element and possibly via charge complementation with cellular or viral proteins [29, 30]. Recently, *in silico* analysis revealed that four saponins namely lucyoside H, lucyoside F, 3-O-β-D-glucopyranosyl-oleanolic acid and 3-O-β-D-glucopyranosyl-spinasterol from air-dried fruits of *L. cylindrica* showed strong affinity for the substrate-binding pocket of SARS-CoV-2 Mpro with docking energy scores of–7.54, 7.47, −7.29 and − 7.13 kcal/mol, respectively as compared with the binding ability equivalent of N3 protease inhibitor (−7.51 kcal/mol), which is an established inhibitor [31]. Therefore, suggesting that *L. cylindrica* and these aforementioned compounds could find application in the prevention and treatment of SARS-CoV-2.

5.5 Antifungal activity

The ethyl acetate extract of *Luffa cylindrica* leaves displayed antifungal activity against *Candida albicans*, *Candida tropicalis*, *Trichophyton rubrum* together with four clinical isolates of *C. albicans, C. tropicalis, Microsporum canis* and *Epidermophyton flocossum* [32]. Some compounds isolated from the benzene and petroleum ether of *Luffa cylindrica* seeds also displayed anti-fungal properties against *Candida albicans* [9]. The petroleum ether crude extract of *Luffa cylindrica* fruits exhibited anti-fungal property against *Candida albicans* and *Aspergillus niger* [33]. The butanol extract displayed profound antifungal action against *Trichophyton longifusus* and *Fusarium solani,* while the ethyl acetate fraction of the crude methanol extract markedly inhibited the growth of *Microsporum canis* [34]. *In vivo* antifungal activity was also exhibited by crude ethyl acetate extract of *Luffa cylindrica* leaves in laboratory animals by promoting plodding healing of the infected skin of experimental animals [32].

5.6 Antibacterial activity

The petroleum ether extract obtained from *Luffa cylindrica* fruit showed potent antibacterial activity against bacteria *Bacillus cereus, Bacillus megaterium, Bacillus subtilis, Staphylococcus aureus, Sarcina lutea, Escherichia coli, Salmonella typhi, Pseudomonas aeruginosa, Salmonella paratyphi, Shigella dysenteriae, Vibrio mimicus,* and *Vibrio parahemolyticus* [33]. Crude methanol and n-hexane fraction of *Luffa cylindrica* also exhibited antibacterial activity against *Bacillus subtilis*, while the butanol fraction exhibited relative activity against *S. flexenari* [34]. The chloroform and n-hexane extract of *Luffa cylindrica* leaves showed potent antibacterial activity against gram-positive and gram-negative bacteria [17].

5.7 Anthelmintic activity

Both crude ethanol and methanol extracts of *Luffa cylindrica* leaves displayed anthelminthic activity against *Pheretima posthuma* [1, 14]. In fact, the anthelminthic activity of the ethanol extract was comparable to the standard drug mebendazole [14].

5.8 Anti-pyretic activity

Methanol extract of *Luffa cylindrica* leaves displayed antipyretic activity by decreasing the rectal temperature of experimental animals at the studied doses and also impeding the compression of abdominal walls in experimental animals, which were induced with agony sensation depending on the dose [35].

5.9 Hypoglycemic and anti-diabetic activity

Methanol extract of *Luffa cylindrica* fruit exhibited excellent hypoglycemic properties in alloxan-induced rat models by decreasing blood glucose level [36]. A significant reduction in blood sugar of glucose-loaded mice after administration of methanol extract of *Luffa cylindrica* fruit further demonstrated the antihyperglycemic activity of *Luffa cylindrica* fruit [37]. Moreover, hydro and ethanol extracts of the fruits exhibited comparable β-cells renegeration with glibenclamide in the alloxan model of diabetes in rats [38]. El-Fiky *et al.* [39] also investigated the effect of oral administration of ethanol seed extract of *Luffa cylindrica* on a streptozotocin rat model of diabetes. The results showed the extract drastically reduced blood glucose level in diabetic rats within three hours of treatment and the efficacy of the extract in reducing blood glucose was similar to a standard anti-diabetic drug, metformin. Tryptic and alcalase protein hydrolysates from the seed have strong inhibitory action against angiotensin-converting enzymes, α-amylase and α-glucosidase [40]. The authors therefore opined that plant holds strong potential in the treatment of hypertension and diabetes.

5.10 Hepatoprotective activity

Methanol extract of *L.cylindrica* leaves displayed hepatoprotective effects through the reduction of serum liver enzymes in a paracetamol model of hepatic injury [41]. The hydroalcoholic extract of *Luffa cylindrica* leaves also exhibited a similar hepatoprotective property in the erythromycin estolate-induced model of liver damage [42]. Increased serum liver enzyme levels in paracetamol-induced rats reduced drastically on treatment with alcohol and aqueous extracts of *Luffa cylindrica* fruits coupled with conservation of the structural integrity of liver membrane [43].

5.11 Sedative and anti-epileptic effects

The sedative, anti-epileptic and anti-convulsant activities of alcohol extract of *L cylindrica* fruits were investigated in rats by Sunil *et al.* [44]. The results showed that the extract at 400 mg/kg body weight lessened the sleep induction time and prolonged the sleeping time in rats exposed to diazepam. At the same dose, the extract lengthened the latency time, but reduced the time of seizure in the pentylenetetrazole-induced model of convulsion, while it decreased total seizure time as well as clonic tonic time in the maximal electroshock model of convulsion. These effects were however lower than that of standard drugs, diazepam and phenytoin.

5.12 Skin protection

Umehara *et al.* [7] investigated the effect of *L.cylindrica* fruit extract on UVB-irradiation-induced mice model of dry skin and demonstrated that the extract and isolated phenylpropanoids inhibited trans-dermal water loss in hairless mice. The extract and p-coumaric acid isolated from the extract stimulated dome formation by MDCK I cells. Additionally, p-coumaric acid increased mRNA expression of water permeability and reabsorption protein, AQP3. The authors, therefore, concluded that p-coumaric was responsible for *L. cylindrica* related water permeability and that *L. cylindrica* could contribute to the treatment of disease relating to the inability to retain moisture including dry syndrome. Furthermore, an extract obtained from the fruit pulp prevented the development of atopic dermatitis-like skin lesions in mice exposed to *Dermatophagoides farinae* [6].

5.13 Anti- emetic activity

The ethanol extract of the fruit peel of *L.cylindrica* showed significant anti-emetic activity in young chicks at a dose of 150 mg/kg body weight [45]. The ethanol and hexane extracts of leaves and male flowers of *L. cylindrica* exhibited anti-emetic effect against chick emesis facsimilia. The anti-emetic effects of hexane extract of male *L. cylindrica* flowers and leaves were at 71.5% and 43.5% inhibition of reteches respectively, whereas the ethanol extract of leaves and male flowers of *L. cylindrica* was at 68.66% and 68.46% inhibition of reteches respectively [46].

5.14 Wound healing activity

Different parts of *L. cylindrica* have been reported to possess wound healing capacity. Chloroform extract of the whole plant showed wound healing activity in a rat model by reducing the wound area and time of epithelization [19]. Diethyl ether, n-hexane, chloroform, ethyl acetate, butanol and methanol seed extract also promoted wound healing in rats [47]. Diethyl ether extract showed the highest wound healing activity, while the weakest activity was displayed by chloroform extract [47].

5.15 Effects on hematological parameters

Raw and thermally processed *Luffa cylindrica* seed meal fed to albino rats had no adverse effects on the hematological indices of the experimental animals [48].

However, administration of methanol extract of *L.cylindrica* leaves to rats produced an elevation in the hematological parameters in experimental animals [49].

5.16 Oxytocic activity

Aqueous extract of *L.cylindrica* leaves increased uterine motility in an isolated rat uterus [50]. Thus suggesting that *L.cylindrica* is oxytocic and giving credence for its use in Uganda to facilitate labour and treat postpartum issues.

6. Chemical composition

L.cylindrica is rich in nutrients and phytochemicals. Several recent studies have revealed that *L. cylindrica* leaves, fruits, and seeds are a rich source of

carbohydrates, protein, fiber, fats, amino acids and minerals [48, 51]. The mineral found in the seeds of *Luffa cylindrica* plant include sodium, iron, phosphorus, calcium, zinc, potassium, manganese, copper, chromium, magnesium [51]. Moderate amounts of K (13.86 mg/100 g) and Na (8.18 mg/100 g) were found in the seed, but the concentration of Cr (0.25 mg/100 g) was low [50]. *L.cylindrica* fruit is an excellent source of Vitamins A, B5, B6, C, and dietary fiber.

According to the preliminary phytochemical screening test carried out on different extracts of *L.cylindrica* leaf and seed extracts, all the extracts were found to contain saponin, alkaloids and cardiac glycosides [52]. Only the seed extracts contained the steroidal rings, while anthraquinones, tannins and phlobatinnins were not detected in any of the extract [52]. Reducing carbohydrates, flavonoids, tannins, saponins and glycosides were also detected in the plant extract [2]. The phytochemical screening carried out on the methanol and ethyl acetate extract of the leaves of *L.cylindrica* indicated that the extracts of leaves of *L.cylindrica* contain carbohydrates, sterols, saponins, flavonoids, alkaloid and phenols, while resins, tannins, terpenes, balsams and anthraquinones were not found [32]. Another preliminary phytochemical screening of aqueous methanol extract of *L.cylindrica* leaves revealed the presence of sugar molecules including glucose, fructose and galactose as well as the presence of amino acids such as phenylalanine, glycine and tyrosine [53]. Moreover, phytate and oxalate were found in the methanol extract of flowers and leaves of *L. cylindrica* [54]. The *L. cylindrica* seeds contain high amount of saponins, alkaloids and phlobotannins. The butanol extract of *Luffa cylindrica* seeds contains alkaloids and deoxy sugars, while the diethyl ether extract contains deoxy sugars, cardiac glycosides, alkaloids and carbohydrates [47]. The chloroform extract contains deoxy sugars and cardiac glycosides [47]. Quantitative analysis of the sponge revealed that it contains 1.2, 0.5, 17.94 and 20.74 mg/g of ascorbic acid, total anthocyanins, flavonoids and phenolics respectively [55]. The total flavonoid and phenol in the aqueous and ethanol extracts of Luffa pulp and peels were reported to range from 0.94–14.02 mg/g GAE and 0.33–18.09 mg/g QE respectively, while olenolic acid, carotenoids, and chlorophylls were in the range 0.01–25.79,0.01–14.87 and 0.04–37.29 mg/g extract respectively [20].

A penotacyclic triterpenoid saponin, lucyoside O was isolated from the leaves of *L.cylindrica*. Lucyin A, lucyosides G, N, O, Q, P, R, ginsenosides Re and Rg1, 21β- hydroxyoleanoic acid and 3-O-β-D-glucopyranosyl- maslinic acid, were also identified in the leaves of *Luffa cylindrica* [22]. In addition, Lucyoside K was isolated from the hydro-ethanol extract of the leaf extract, while Lucyoside A-M were identified in the fruit extract of the plant [22]. A peptide with luffacyclin that possessed antifungal activity was also isolated from *L. cylindrica* seeds. Sapogenins (I & II) were isolated from ethanol extract of the seeds and were both found to exhibit immunomodulatory effects [56]. Some triterpenoids and fibrinolytic saponins were isolated from seeds and fruits of the plant [47]. Moreover 22, 23-dihydroxy spinasterol and 3-hydroxy-1-methylene-2,3,4,4-tetrahydroxynapthalene-2-carbaldehyde were separated from the petroleum ether extract of the fruit [57]. Very recently [31] isolated lucyoside F, lucyoside H, 3-O-β-D-glucopyranosyl-spinasterol and 3-O-β-D-glucopyranosyl-oleanolic acid from the dried fruits.

L. cylindrica is very rich in polyphenols. Aqueous ethanol extract of *L. cylindrica* leaves contains phenolics such as apigenin 7 glucuronide, eriodictyol –7 glucoside, kaemferide, luteolin-O-diglucoside, neodiosmin, diosmin and kaempferol 3 - [2″‘,3″‘,4″‘-triacetyl - α - L -arabinopyranosyl -(1–6) -glucoside] or its isomer kaempferol 3 -[2″‘,3″‘,5″‘- triacetyl - α - L -arabinofuranosyl -(1–6) –glucoside [22].

Similarly, Sunnil *et al.* [44] recently used LC-ESI-MS/MS to identified several flavonoids and polyphenol including hyperoside, kaempferol-3,7-O-bis-α-L-rhamnoside, quercetrin, tliroside, acacetin, datiscin, fortunellin, linarin, luteolin, bobin, vitexin, vitexin-2"-O-rhamnoside, saponarin from the alcohol extract of the whole fruit of *L. cylindrica.* In addition, Yadav *et al* [16] also identified the following phenolics and flavonoids: gallic acid (0–26.8 μg/ml), caffeic acid (0.23–18.4 μg/ml), cinnamic acid (1.52–8.6 μg/ml), ferulic acid (9.31–49.6 μg/ml), ellagic acid (0–78.8 μg/ml), rutin (0–79.3 μg/ml), quercetin (45.18–55.42), myrecetin (20.95–35.79 μg/ml), catechin (66.24–77.87 μg/ml) from methanol extract of *L. cylindrica* fruits thermally processed by different methods. Furthermore, Hlel *et al* (2017) using HPLC/TOF-MS identified chlorogenic acid, gentisic acid, gallic acid, vanillic acid, salicylic acid, ferulic acid, 4-hydroxy benzoic acid, p-coumaric acid, naringenin, catechol and rutin in *L. cylindrica* fruits at different stages of maturation. The amount of quercetin, luteolin and myrictin in the sprout extract of *L. cylindrica* was quantified using UPLC-MS/MS as 32.5, 12.5 and 32.4 μg/g respectively. Meanwhile, five derivatives of cinnamic acid including 1-O-p-coumaroyl--D-glucose, 1-O-feruloyl-,-D-glucose, 1-O-caffeoyl--D-glucose and p-coumaric acid well as three flavonoids glycosides namely: apigenin-7-O-,-D-glucuronide methyl ester, diosmetin-7-O--D-glucuronide methyl ester, and luteolin 7-O--D-glucuronide methyl ester) were earlier identified in *Luffa cylindrica* [15]. A phenylpropanoid glucoside, 4-O-feruloyl-glucose was isolated from a natural source for the first time in *L. cylindrica* fruit [7]. Other phenylpropanoid glucosides that were isolated from the edible part of *Luffa cylindrica* are 4-O-caffeoyl-glucose, 1-O-caffeoyl-β-glucose, 6-O-caffeoyl-glucose, 4-O-p-coumaroyl-glucose, 1-O-p-coumaroyl-β-glucose, 6-O-p-coumaroyl-glucose, 4-O-feruloyl-glucose, 1-O-feruloyl-β-glucose, 6-O-feruloyl-glucose [58].

Other compounds there were recently isolated from the dried fruits of L.*cylindrica* includes: 3,5-dihydroxy-δ-valerolactone, phenanthrene,1,2-naphthoquinone, cinnamic acid, (S)-dehydrovomifoliol, 2,6-dimethyl-1,4-benzenediol, litchiol B, pinoresinol phthalic acid, 4-(hydroxymethyl)benzene-1,2-diol, tridecan-7-one, apigenin and henicosan-11-one [31]. Similarly, fifty-three volatile compounds including aromatics (10.1%), acids (15.1%), ketones (38.2%), alcohols (51.6%) and aldehydes/furans (66.2%) were recently identified by [59] in young and matured fruits of *Luffa cylindrica* using headspace SPME-GS-MS and UPLC-MS. Hydrocarbons including noctacosane, n-heptacosan, n-hexacosane n-tetracosane, n-tricosane, tetraeicosane-6-ol, nanodecane-6-ol, dieicosane-6-ol and eicosane-6-ol have earlier been identified in the fruit of *L. cylindrica* [12]. The diverse types of phytochemicals found in *L. cylindrica* have various biological effects (**Table 2**) and could account for its wide pharmacological activities.

6.1 Acute toxicity studies

Etim *et al* [49] administered methanol leave extract of *L. cylindrica* to Swiss albino mice at doses up to 4000 mg/kg body weight. Treated animals did not die nor display signs of toxicity. In addition, there was no mortality in animals exposed to *L. cylindrica* fruit extracts at doses between 100 and 2,000 mg/kg body weight [145]. Similarly, Oyeyemi *et* al. [146] reported that administration of 5000 mg/kg of both hydro-methanol and aqueous extracts of *L. cylindrica* leaves did not induce acute toxicity in mice. However, the extracts given at doses between 200 and 1600 mg/kg increased bone marrow micronucleated polychromatic erythrocytes formation, but of a lower degree to the positive control, methyl methanesulfonate (Oyeyemi *et* al, 2015). An LD50 of 450 mg/kg body weight was reported for crude petroleum ether extract of the fruit [123].

Phyto chemicals	Compounds	Pharmacological action	Ref.
Flavonoids	Apigenin 7 glucuronide,	Anti-oxidant, anti-complement, anti-inflammatory, and aldose reductase inhibitory activities	[60]
	Kaempferol 3 - [2″‘,3″‘,4″‘- triacetyl - α - L -arabinopyranosyl -(1–6) -glucoside],	NRPA	
	Kaempferide,	Anticancer, cardioprotective and Osteo-protective, anti-oxidant, anti-inflammatory, anti-bacterial anti-viral	[61, 62].
	Diosmin,	Anti-ulcer, anti-inflammation, anti-oxidation, anti-diabetes, anti-cancer, anti-microbial, hepato- protective, neuroprotective cardio-protective, nephroprotective, and retinal protection.	[63, 64]
	Neodiosmin, Eriodictyol –7 glucoside,	NRPA Antioxidant, anti-inflammatory, anti-cancer	[65]
	Quercetin	Antioxidant, anti-inflammatory, anticancer, cardio-protective, neuroprotective, pneumo-proective, hepatoprotective	[66, 67]
	Myrecetin	Antioxidant, antitumor, anti-inflammatory, neuroprotective, immunomodulatory, antimicrobial, antiviral, hepatoprotective, anti-obesity, cardiovascular protection	[68, 69]
	Rutin	Antioxidant, anti-inflammatory neuroprotective, antitumor, sedative, anti-convulsant, anti-Alzheimer, anti-cholesteremic, anti-asthmatic, antiosteoporotic, anticataract, immunostimulatory, antimicrobial, antiviral, antihypertensive	[70]
	Catechin	Anticardiovascular, antioxidant, neuroprotection, hepatoprotection, anti-infectious, anti-diabetic	[71]
	Luteolin	Antioxidant, anti-inflammatory, antitumor, antiapoptotic, anti-allergy,	[72]
	Hyperoside	Anticancer, anti-inflammatory, Anti-oxidant, antiparasite, anti-cholesterolemic, cardioprotection, antidepressant, anti-aging.	[73–75]
	Kaempferitrin	antioxidant, anti-inflammatory, antitumor, anti-angiogenic	[76]
	Quercetrin	Antioxidant, antitumor,	[77]
	Tiliroside	Antioxidant, antidiabetic, anti-obesity, anti-inflammatory, hepatoprotective, anti-allergy, anti-thrombotic, neuroprotective osteogenic, antiobesity, antimicrobial, antiviral, antiprotozoal, antihypertensive antiaging	[78, 79]
	Acacetin	antioxidant, anti-inflammatory, anti-depressant, antinociceptive antitumor, neuroprotective	[80–82]
	Datiscin Fortunellin	NRPA Antioxidant, anti-inflammatory, antidiabetic, cardioprotective	[83]
	Linarin	Antioxidant, anti-inflammatory, osteogenic, anti-cholinesterase neuroprotection, analgesic cardioprotective,	[84, 85]
	Robinin	NRPA	
	Vitexin	Antioxidant, neuroprotective anti-inflammatory,antidiabetic, anti-tumor, hepatoprotection, cardio-protective, amtiviral, antibacteria	[86, 87]
	Vitexin-2”-O-rhamnoside	Antioxidant	[88]
	Saponarin	Hepatoprotective, antioxidant anti-lipid peroxidation	[82, 89]

Phyto chemicals	Compounds	Pharmacological action	Ref.
Phenols	p- coumaric acid,	Antioxidant, antiviral, anti-inflammatory, anti-cancer, anti-lipidemic, anti-gout, antimicrobial, immunomodulatory, antiplatelet aggregation, anti-diabetic, anxiolytic, anti-arthritis, antipyretic, analgesic.	[90, 91]
	1-O-feruloyl-β-D-glucose,	Anti-adipogenic	[92]
	1-O-(4- hydroxyl benzoyl) glucose.	NRPA	
	Gallic acid,	Antioxidant, antiobesity, antihyperglycaemic, antidiabetic, anti-lipid peroxidative, wound healing, anti-inflammatory, 10.1016/j.phrs.2018.08.002 neuroprotective, cardioprotective, antimicrobial, gastroprotective	[93]
	Gentisic acid	Antioxidant, anti-inflammatory, neuroprotective, antigenotoxic, hepatoprotective, antimicrobial, anticancer, analgesic, skin-lightening, muscle relaxation, cardioprotective	[94]
	Chlorogenic acid	Antioxidant, cardioprotective, neuroprotective, renoprotective, antidiabetic, antitumour, Gasto-intestinal protection, antitumour	[95]
	4 -hydroxy benzoic acid Vanillic acid,	NRPA Anti-obseity, anti-inflammatory, antioxidant, neuroprotective cardioprotective	[96–98]
	Salicylic acid,	Anti-inflammatory, analgesic	[99]
	Naringenin,	Antioxidant, antibacterial, antitumor, anti-inflammatory, cardioprotective, antiadipogenic immunomodulatory, antiviral	[100]
	Catechol	Antioxidant, anticancer	[101]
	Caffeic acid	Antioxidant, anticancer, antiviral, antimicrobial, anti-inflammatory, Antidiabetic, cardioprotective, immunostimulatory,	[102]
	Ferulic acid	Antioxidant anti-inflammatory, anticancer, antidiabetic, antimicrobial, antithrombotic, anti-arrhythmic, antidiabetic, immunostimulatory, anti-aging, neuroprotective, photoprotective	[103]
	Cinnamic acid	Antioxidant, antidiabetic, antimicrobial, anti-melanogenesis, UV-protective	[104, 105]
	Ellagic acid	Antioxidant, hepatoprotective antitumor, antiangiogenic, antimetastatic, anti-inflammatory ,neuroprotective, antidiabetic, anti-atherogenic	[106, 107]
Triterpenoids	Oleanolic acid	Antioxidant immunomodulatory, antiviral, antimicrobial, hepatoprotective, cardioprotective anti-inflammatory, analgesic antihypertensive, anticancer, immunostimulatory	[108, 109]
	Echinocystic acid	Antioxidant, anti-inflammatory, antibacterial, antiapoptotic, antiviral, antitumor antioxidant, Immunostimulatory	[110, 111]
	Gypsogenin 3-O-*β*-D-glucopyranosyl-maslinic acid,	Antitumour Immunostimulatory	[112]
	Dehydrovomifoliol	Anticancer, anticholinesterase	[113, 114]

Phyto chemicals	Compounds	Pharmacological action	Ref.
Saponin	Lucyoside K, Lucyoside O,	NRPA	
	Lucyoside B	Anti-inflammatory	[21, 115];
	Lucyosides N &P Lucyosides A,C-M,R Ginsenosides Re	Fibrinolytic activity NRPA Anti-arrhythmic, modulation of insulin resistance [116–118]	[119]
	Ginsenosides Rg1	Neuroprotective, anti-depressant, anti-inflammatory, anti-sepsis	[27, 120–122]
	21*β*-hydroxyoleanoic acid	NRPA	
Cucurbitacins	Cucurbitacin B	Anticancer	[123]
	Cucurbitacin E	Immunomodulatory, anti-inflammatory, neuroprotective anti-tumorigenic,	[124].
Peptides	Luffacyclin	Antifungal	[125]
	Luffin –a Luffin -b	Abotificient, Antitumour, Abotificient, Antitumour	[27, 125] [27, 125]
	Luffins P1,	Anti-HIV, antitumour, antifungal	[29, 30, 125]
	Luffin B	Antitumor, Antiviral	[8]
	Luffins S,	Antitumor, Antiviral	[29, 30, 125]
	Luffin –α	Antitumor	[27]
	Bryonolic acid	Inhibits passive cutaneous anaphylaxis and delayed hypersensitivity	[126]
Phenyl propanoid glucosides	1-O-feruloyl-β-D-glucose, 1-O-caffeoyl-β-D-glucose 4-O-caffeoyl-glucose.	Antioxidant NRPA	[15, 127]
	6-O-caffeoyl-glucose 4-O-p-coumaroyl-glucose 1-O-p-coumaroyl-β-glucose	Antiradical and antioxidant NRPA NRPA	[128]
	6-O-p-coumaroyl-glucose 6-O-feruloyl-glucose 1-O-feruloyl-β-glucose 4-O-feruloyl-glucose	NRPA Antioxidant NRPA	[129]

Phyto chemicals	Compounds	Pharmacological action	Ref.
Volatiles and other compounds	3-hydroxy1-methylene-tetrahydroxy-napthalene-2-carbaldehyde	Antimicrobial	[57]
	22, 23-dihydroxy spinasterol	Antimicrobial	[57]
	Phenanthrene	Antimicrobial, spasmolytic, anti-inflammatory, antiplatelet aggregation, antiallergic activities and phytotoxic effects	[130, 131]
	Litchiol B	Antioxidant,anti-bacteria	[132]
	Pinoresinol	Anti-proliferative, antioxidant	[133]
	Pentanoic acid	NRPA	
	Nonanoic acid	Bioherbicides	[134]
	1-Octen-3-ol	Pesticides	[135]
	β-linalool	Antioxidant, antibacterial	[136]
	α-terpineol Nonanal	Antioxidant, insecticidal, anticancer, anti-nociceptive, anticonvulsant, antihypertensive, antiulcer Antifungal, antidiarrheal	[137, 138]
	Nonadienal	Anti-bacteria	[59]
	Decanal	Antimicrobial	[139]
	Eugenol	Mosquito repellant, antifungal, antibacterial, antiinflamatory antioxidant	[140]
	Limonene	Antitumour, anti-inflammatory, antioxidant, antiviral,antibacterial	[141]
	Trihydroxy-octadecadienoic acid	Antifungal *a*nd bacteria	[141, 142]
	Trihydroxy-octadecenoic acid	Antiviral	[143]
	Octadecadienoic acid	Antidiabetic	[144]

NRPA = no reported pharmacological action

Table 2.
Some phytochemicals in Luffa cylindrica *and their pharmacological action*.

7. Conclusion and future perspective

The review provides an up-to-date and comprehensive summary of the traditional uses, pharmacology and phytochemical composition of *Luffa cylindrica*. *Luffa cylindrica* has been eaten as food and used in folk medicine for several years especially in Africa and Asia for the treatment of many diseases including malaria, stomach disorders, whooping cough, oedemas, wounds, tumor, filarial, rheumatism, dyspnea, inflammation, leprosy, syphilis, bronchitis, tuberculosis, dysentery and amenorrhea. In the last few decades, the plant has attracted attention due to its potential pharmacological actions including anti-inflammatory, anticancer antioxidant, anti-viral, antimicrobial, anti-diabetic, hepatoprotective, sedative, anthelmintic, anti-pyretic, anti-epileptic, hypoglycemic, skin protection. Anti-emetic and wound healing. The repertoire of beneficial and health-promoting phytochemicals that are present in *Luffa cylindrica* could be responsible for diverse

ethnomedicinal uses and pharmacological activity recorded for the plant. However, like many other medicinal plants, efforts should be made to standardize its usage in different disease models through activity-guided bioassays and isolation of active principle(s). Formulated standardization of *Luffa cylindrica* extract is needed to have reproducible results that can be integrated into translation medicine. In addition, more mechanistic and comprehensive safety studies on *Luffa cylindrica* are needed to enhance its pharmaceutical potentials and know the long-term effects of consumption of *L. cylindrica* as medicine since most of the studies found in literature only addressed its acute toxicity. Moreover, more clinical studies are warranted to confirm the pharmacological activities of *Luffa cylindrica* extracts and its constituents in order to translate results obtained from animal studies into human.

Taken together, *Luffa cylindrica* holds great potential as a repository of beneficial phytochemicals that can be leveraged on for the betterment of human health. Research efforts should therefore be directed at optimizing the bioactive extracts and/or phytochemicals for health promotion and improving the quality of life.

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Chapter 7

The Importance of *Sceletium tortuosum* (L.) N.E. Brown and Its Viability as a Traditional African Medicinal Plant

Richard James Faber, Charles Petrus Laubscher and Muhali Olaide Jimoh

Abstract

Sceletium tortuosum is a succulent plant that belongs to the family Mesembryanthemaceae (Aizoaceae). It is indigenous to South Africa, where it is well known by the indigenous people, especially in Namaqualand where the plant is utilized regularly for its medicinal and psycho-active properties. The main alkaloids responsible for these properties are mesembrine, mesembrenine (mesembrenone), and mesembrenol. The potential of the plant to be an alternative supplement in the promotion of health and treating a variety of psychological and psychiatric disorders such as depression and anxiety has stimulated interest in its pharmacological property and possibility of its commercialization. The economic value of indigenous medicinal plants in South Africa is approximately US$60 000 000 or R4 000 000 000 annually. Thus, interest in the knowledge and use of Traditional African Medicinal Plants (TAMP) as well as meeting pharmacological and economic needs of ever-increasing human population has led to the commercialization of traditional African medicines at a fast rate. It was found that *S. tortuosum* has clear pharmaceutical and economical importance and is one of the only known plants to contain the alkaloids mesembrenone and mesembrine which can be utilized for the promotion of health and/or treating a variety of psychological disorders such as anxiety and depression.

Keywords: African medicine, Aizoaceae, alkaloids, hydroponics, mesembrine, mesembrenine, mesembrenol, mesembryanthemaceae

1. Introduction

Sceletium tortuosum (L.) N.E. Br. and *Sceletium expansum* L. Bolus (formerly known as *Mesembryanthemum tortuosum* L. and *Mesembryanthemum expansum* L.) forms part of the succulent group of plants within the Mesembryanthemaceae family (**Figure 1**). The common names given to *Sceletium* are kanna and kougoed. However, some may argue that the name kougoed refers to the finished traditional preparation made by drying and fermenting the harvested plant material, which

Figure 1.
Sceletium *plant and its "skeletonised appearance" of the dried leaves [1].*

increases its stimulating effect. The plant is native to South Africa, where it is well known by the indigenous people, especially in Namaqualand, where the plant is utilized regularly for its medicinal and anti-depressant properties [2].

According to Schultes [3] and Harvey *et al*. [4] the main substances responsible for these properties are the alkaloids mesembrine, mesembrenine (mesembrenone), and mesembrenol. Interest in *S. tortuosum* has been growing for its potential to be an alternative supplement in the promotion of health and treating a variety of psychological and psychiatric disorders such as depression and anxiety [5]. Studies on the chemistry and biological activity on Traditional African Medicinal Plants (TAMP) have only recently (1997–2008) been published, despite TAMP having been reported as one of the oldest medicinal systems in various ethnobotanical reports [6, 7].

Soilless culture systems (SCS's) in controlled greenhouse environments have proven to be the most effective strategy for agricultural production by providing flexibility as well as control. Crops can be produced in and out of season, while water and soilless media can easily be monitored for its total nutrient status. For these reasons SCS's within a greenhouse environment provide for high quality products and high yields, even in places where environmental conditions would not usually permit [8].

Relevant natural compounds, mainly secondary metabolite concentration and composition, determine the quality of medicinal plants. However, water availability, light intensity and temperature are examples of various environmental conditions which affect the quality and quantity of such secondary metabolites [9]. Hence, investigating the effect of different soilless growing media and fertigation regimes on the vegetative growth and alkaloid concentration of *S. tortuosum* will contribute to developing optimal growing protocols for cultivating high quality medicinal plants in hydroponics for the ethno-pharmaceutical industry. The aim of this chapter was therefore, to highlight pharmaceutical and economic viability of *S. tortuosum* and relate the medicinal value of the plant with respect to the bioactive compound found in it and suggest ways of cultivating the plant in a soilless systems.

2. Mesembryanthemaceae FENZL: a sub family of Aizoaceae

Within the family Aizoaceae Martinov. there are currently four sub-families, namely Sesuvioideae, Aizooideae, Ruschioideae, and Mesembryanthemoideae [10, 11]. Succulent plants within the Aizoaceae family are popularly termed "Mesembs", and sometimes placed in their own family, the Mesembryanthemaceae [2]. Common terms used to describe this group of succulent plants are vygies, fig-marigolds, flowering-stones, ice plants and, midday flowers, among others. These plants fascinate many plant enthusiasts and have become popular collector's items due to their remarkable variation in leaf architecture, flower color and form, and fruit structure (**Figure 2**). Different genera within the family grow in various habitats, and examples can thus be found growing in rocky crevices, silty flats and in saline wastelands. Mesembs occur mainly in south-western Africa, including Angola, South Africa, Zimbabwe, Botswana and Namibia [2, 12] (**Figure 3**).

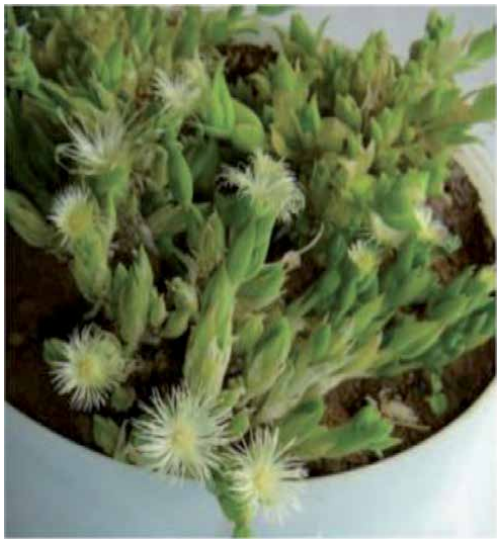

Figure 2.
Sceletium tortuosum *plant surrounded by its white flowers [13].*

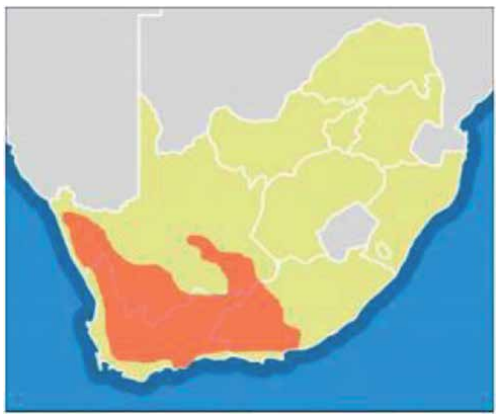

Figure 3.
Geographical map indicating the distribution of Sceletium *in South Africa (redrawn by Gerike & Viljoen [1]).*

This family has received a large amount of attention in the present century both in herbaria collections and in the field. There are several reasons why the family is important in the ecosystems where they occur: they stabilize soil, which prevents erosion; various insects are catered for year-round by their blossoms, while some leaves serve as fodder for livestock. Apart from its ecological importance, this group of plants also has ethnobotanical value, and is used in making soap, poultices, preserves and also in some cases can serve as a type of psycho-active stimulant [2] (**Figure 2**).

3. The genus *Sceletium* (L.) N.E. BR.

S. tortuosum (L.) N.E. Br. and *S. expansum* L. Bolus (formerly known as *Mesembryanthemum tortuosum* L. and *Mesembryanthemum expansum* L.) forms part of the succulent group of plants within the Mesembryanthemaceae family. The name *Sceletium* is derived from the Latin word sceletus, or skeleton in English, due to the noticeable leaf veins resembling skeleton-like structures within dried leaves of the plants. *Sceletium* spp. are easily identified by this skeletonised structure of the leaves [2, 10]. The common names given to *Sceletium* are kanna and kougoed. However some may argue that the name kougoed refers to the finished traditional preparation made by drying and fermenting the harvested plant material, which increases its psychoactive effect [2, 14] (**Figure 4**).

Strong evidence suggest that the indigenous people of southern Africa used one or both *Sceletium* species as a vision-inducing narcotic. However, the hallucinogenic effect of kanna/kougoed could have been confused with other intoxicating plants such as *Cannabis* spp. or *Sclerocarya* spp. as the narcotic use of the plant was never observed directly. Despite this, alkaloids possessing sedative, cocaine-like effects have been found within both of these species of *Sceletium* [3]. Other known species of *Sceletium* include the following: *S. crassicaule* L. Bolus, *S. exalatum* Gerbaulet, *S. expansum* L. Bolus, *S. rigidum* L. Bolus, *S. strictum* L. Bolus, and *S. varians* (Haw.) Gerbaulet [2, 10].

Figure 4.
A commercial product by medico herbs containing dried S. tortuosum *in capsules (https://medicoherbs.com/products/kanna-capsules-60).*

Figure 5.
A commercial product by Phyto force containing tinctured S. tortuousm *(https://www.phyto-force.co.za/product/*Sceletium*/).*

S. tortuosum is now considered a medicinal crop plant and is classified as mind-altering, sedative, euphoric, and not hallucinogenic [14, 15]. The alkaloids responsible for these psychoactive properties are mesembrine and mesembrenone. However, the concentration of alkaloids within individual plants may vary depending on their chemotype. Uses of the plant include the treatment of anxiety, stress, nervous tension, alcohol addiction, colic in infants and for suppressing hunger and thirst (**Figure 5**). With clear ethno-pharmaceutical value it is also worthy to mention that the use of *S. tortuosum* develops no physical or psychological dependency [15].

4. Relevance of traditional African medicinal plants

Interest in the knowledge and use of Traditional African Medicinal Plants (TAMP) as well as an ever-increasing human population has led to the commercialization of traditional African medicines at a fast rate [16]. As stated in Keirungi and Fabricius [17], the economic value of indigenous medicinal plants in South Africa is approximately US$60 000 000 or R4 000 000 000 annually. The number of people in South Africa that depend on TAMP to aid their medical needs is estimated at 27 million [18]. The majority of plants used for traditional medicine are harvested from the wild except for some which are selected and cultivated by traditional healers [19].

In 1998 it was estimated that 20 000 tonnes of plant material were being traded in South African markets [20]. Seven hundred thousand tonnes of plant material have been extracted from the wild for this market which mostly consist of people with disadvantaged socio-economic situations or backgrounds [21]. As stated in Makunga et al. [21], US$ 50–100 million in the form of approximately 1000 plant species are being exchanged in this informal sector.

5. Secondary metabolites and alkaloids

Plant secondary metabolites are divided into three categories, namely terpenoids, flavonoids, and alkaloids. Consisting of multiple chemical structures and biological activities, secondary metabolites are an extremely wealthy source of compounds and are utilized in pharmaceutical, nutraceutical, cosmetic and fine chemical industries. Examples of familiar natural plant products that are used as drugs and/or dietary supplements are: artemisinin, paclitaxel, ginsenoside, lycopene, and resveratrol [22]. Secondary metabolites play a major role in plants' adaptation to their environment and are thought to be responsible for antimicrobial and anti-viral activities exhibited by plants [23, 24]. Apart from protecting plants against leaf damage instigated by the incident light intensity via ultra-violet trapping mechanisms, they cause allelopathy, antipathogens and antifeeding mechanisms in plants [25–27].

Alkaloids are potent secondary metabolites that consist of one or several nitrogen (N) atoms in their molecular structure. There are approximately 20 000 alkaloid structures that have been described and are classified according to their molecular ring (heterocyclic) structure. There are different types of mesembrine alkaloids in Sceletium species. Among these are; (3aS,7aS)-3a-(3,4-dimethoxyphenyl)-1-methylhexahydro-1H-indol-6(2H)-one; (3aR,7aS)-3a-(3,4-dimethoxyphenyl)-1-methyl-3,3a,7,7a-tetrahydro-1H-indol-6(2H)-one; (3aS,6 R,7aS) – 3a-(3,4-dimethoxyphenyl) – 1-methyloctahydro-1H-indol-6-ol; and (3aR,6S,7aS)-3a-(3,4-dimethoxyphenyl)-1-methyl-2,3,3a,6,7,7a-hexahydro-1H-indol-6-ol [28, 29]. These groups are indole, isoquinoline, quinolone, tropane, pyrrolizidine and quinolizidine alkaloids. Some alkaloids are neurotoxins and/or mind-altering substances. Most have pharmacological or toxicological relevance, and many isolated alkaloids serve as therapeutic agents in medicine [16]. Alkaloids confer several biological effects on plants such as stimulants (caffeine and ephedrine), antitussive (codeine), pain killer (morphine), anti-malarial (quinine), aphrodisiac (yohimbine), phosphodiesterase inhibitor (papaverine), antiarrhythmic (ajmaline), anti-gouty arthritis (colchicines), anti-rheumatic pains (capsaicin), antiglaucoma (pilocarpine) and anti-psoriasis berberine [30–32].

Like section Ganymedes (*Narcissus pallidulus* and *Narcissus triandrus*) within Amaryllidaceae family, *Sceletium* is one of the few plant genera containing mesembrine alkaloids [33, 34]. According to Krstenansky [29], not all *Sceletium* species have been reported to contain mesembrine alkaloids. While species like *S. tortuosum, S. anatomicum, S. crassicaule, S. expansum, S. namaquense* and *S. strictum* have been reported to contain mesembrinated, the status of *S. archeri, S. emarcidum, S. exalatum, S. joubertii, S. rigidum, S. varians* and *S. subvelutinum* in terms of mesembrine alkaloids is not yet confirmed [29, 35].

6. Soilless culture

Soilless culture, also known as hydroponics and/or hydroculture is the term that is used when methods of growing plants without soil is utilized. Artificial or soilless substrate may or may not be used to provide structural support for the plants depending on the grower and method used [36].

Ecological imbalances such as extreme temperatures, chemical toxicity and oxidative stress are threatening conventional agricultural practices. With an annual rise in population and consumers becoming more aware of the quality, quantity and nutritious value of products consumed, challenges within agricultural systems to keep up with demands and standards are becoming more complex. The need for more efficient and controlled cultivation methods have risen dramatically. Soilless

culture systems have been proved to be one of the most efficient and effective cultivation method in the agriculture industry of today [8].

7. Electrical conductivity and nutrients

Serving as indicators for soil fertility, nutrient concentrations within soil have been of interest for decades. Nutrients can be organic or inorganic. Availability, utilization, translocation and absorption of nutrients by crop plants for growth and development are referred to as mineral nutrition. Plants require a variety of nutrients in order to successfully grow and develop to their full potential. The most important mineral nutrients are the macro nutrients, namely nitrogen, phosphorous and potassium, although plants also require micro-nutrients in smaller amounts which can be argued to be equally important [37].

Plants require nitrogen (N) in the largest quantities compared to other elements. N serves as a constituent for many plant cell components such as, amino acids, proteins and nucleic acids. When there is a lack of N availability to a plant, the plants growth will be inhibited rapidly, followed by the common characteristic symptom, chlorosis in older leaves [38, 39]. Phosphorous (P) serves as an integral component of valuable compounds found in plant cells. These include phospholipids as well as sugar-phosphate intermediates of respiration and photosynthesis. Necrotic spots, dark-green colouration of leaves, which could also become malformed, as well as rapid malfunctioning of photosynthetic apparatus and stunted growth are common characteristic symptoms of P deficiency [39, 40].

Furthermore, various enzymes that are important in respiration and photosynthesis are activated by potassium (K). The osmotic potential of plant cells are also partly regulated by K. Marginal chlorosis of leaves, which further develops into necrosis of leaf tips or margins and in between veins is the most common symptom of K deficiency in plants [39, 41]. Likewise, cell wall synthesis and mitotic cell division depend on the availability of calcium (Ca) ions. Normal functioning of plant membranes and various plant responses to environmental and hormonal signals require Ca. Necrosis of young meristematic regions where cell division and cell wall formation is most prominent is a characteristic symptom of Ca deficiency [39, 42]. Also, cystine, cysteine, and methionine are amino acids in which sulfur (S) is found. Sulfur is also a constituent of a number of co-enzymes and vitamins, namely coenzyme A, S-adenosylmethionine, biotin, Vitamin B1 and pantothenic acid, which are all essential for optimal metabolism in plant cells [39, 43].

Electrical conductivity (EC) is the measurement used to indicate the total concentration of nutrients within an aqueous solution. High EC indicates a high concentration of nutrients within the solution, while a low EC indicates a low concentration of nutrients [44]. When plants are supplied with a high EC nutrient solution, the nutrient concentration within the leaves will not necessarily be higher than in plants supplied with a low EC nutrient solution [45], suggesting that the nutrient uptake in plants is not necessarily based on the amount of nutrients available.

8. Water amounts

Production of plants in the modern sense requires advancements in technology that will allow the optimization of cultivating high quality plant material while minimizing the use of natural resources, such as water [46]. This is also true for the growing of medicinal and aromatic plants, as well as plant production in general [47].

South African agriculture faces increasing pressure to use water more efficiently, as the industry must oblige to demonstrate efficient and effective water use due to

limited valuable natural resources [48]. The role of irrigated farming in the livelihood of a nation cannot be underscored. In South Africa in particular, agricultural sector uses the highest volume of water compared to other sectors. To increase the amount of water needed in other critical sector of the economy, there is the need to improve on water use efficiency during irrigation through reduced water consumption without compromising yield. Regrettably, the concept of irrigation efficiency is often misinterpreted leading to the general belief that water just evaporates with minimal irrigation efficiencies and re-emerges with significant progress in agricultural productivity [49]. This necessitated the emergence of the South African water management framework which oversees holistically, the water source, the irrigation farm, bulk conveyance system and the irrigation scheme to ensure water balance across all sectors [49].

It has been observed that a considerably higher concentration of secondary metabolites are produced in medicinal or spice plants grown under water deficient conditions, compared to identical plants of the same species grown with ample amounts of water [50]. Although changes in the synthesis of desired natural compounds is clear when drought stress is applied to plants, the overall effect of applying drought stress for optimizing specific secondary metabolites in plants remains complex. The amount of water also influences other relevant factors such as plant biomass yield and rate of growth. Depending on the plant and the growers' desired outcome with regards to quality, quantity, and rate of growth, the amount of water applied should be carefully considered as there is no prevalent recommendation that can be made for all plants. By deliberately applying drought-stress without first thoroughly investigating how different plants react to different amounts of water and the method of applying it could yield undesirable results [51].

9. Conclusion

Sceletium tortuosum is indigenous to South Africa. It is one of the very few plants known to contain highly sought after mesembrine alkaloids. Its potential as an alternative supplement in the promotion of health and treating a variety of psychological and psychiatric disorders such as depression and anxiety has stimulated interest in its pharmacological property and possibility of its commercialization. Therefore, meeting pharmacological and economic needs of ever-increasing human population necessitates the use of efficient systems such as hydroponics which require minimum use of land and environmental factors can be maximally controlled to cultivate the plant for optimal yield.

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Chapter 8

Phytochemistry and Ethnopharmacology of *Vebris nobilis* Delile (Rutaceae)

Francis Omujal

Abstract

Vepris nobilis Mziray (formerly *Teclea noblis* Delile) is an ever-green plant in the tropical climate. The different parts (leaves, stem bark, roots and fruits) of this plant are popular for treatment of various diseases including; malaria, rheumatism, arthritis, pneumonia, cough, fever, measles, asthma, common cold, headache, join and chest pains and as antithelmintic. Several phytochemical compounds including quinoline and furoquinoline alkaloids, terpenoids and flavonoids have been isolated from the different plant. Pharmacological investigations on the different crude extracts and isolated compounds covering antipyretic, analgesic, anti-inflammatory, antimicrobial, antimalarial, antileishmanial and ant-trypanosomal have been conducted.

Keywords: *Vepris nobilis*, Teclea noblis, Phytochemistry, Ethnopharmacology

1. Introduction

The genus Teclea Delile subsumed into Vepris Mziray (Rutaceae-Toddalieae) were merged because of their similarity in morphological characteristics [1]. Currently, there are about 86 species in the genus vepris comprising of evergreen shrubs and trees, predominantly of tropical lowland evergreen forest, but with some species extending into submontane forests and some into drier forests and woodland distributed in Africa, Saudi Arabia and India. In Africa, the species in the genus vepris are widely distributed in countries like Ethiopia, Sudan, Somalia, Cameroon, South Africa, Kenya, Uganda and Tanzania [2].

Vepris nobilis Mziray, formerly *Teclea noblis* Delile (family Rutaceae) is about 2-12 m high but can be much taller in rain forests. Its bark is smooth and gray and has branchlets glabrous. The leaves are trifoliolate, occasionally 2-or 1 foliolate; petiole 1.5–6 cm long, sometimes slightly grooved at the apex usually glabrous. The leaflets are subsessile or with a petiolulate up to 10 mm long, oblong-elliptic, 5–15 cm long, 1.5–4 cm broad, acute to acuminate at the apex, narrowly cuneate at the base, glabrous, but sometimes puberulous on the midrib; lateral nerves numerous. The inflorescence of terminal and axillary panicles 4–15 cm long, glabrous. The flowers are polygamous with four Sepals united into a cupuliform calyx 0.6–0.8 mm long; lobes small, ovate, ciliate., narrowly elliptic, 3.5–4 mm long, 1.5–1.7 mm broad. The male flowers are with 4–5 stamens 3–5.5 mm long; anthers basifixed; rudimentary ovary slender and glabrous while the female flower are with 4 or 5

staminodes 0.5–1.2 mm long. The ovary are subglobose, 1–1.4 mm in diameter, glabrous unilocular, 2-ovulate; style up to 0.5 mm long. The stigma are disk-shaped and peltate, 1 mm in diameter, red, glabrous, barely foveolate, wrinkled when dry and one seeded. Its fruit are yellow, orange or red in color, round or ellipsoid becoming wrinkled 6–8 x 5–6 mm. The seed are ovoid 5.5–6.0 mm long. *Vepris nobilis* is native to Uganda, Kenya, Tanzania and Ethiopia [3].

2. Ethnomedicinal uses

Vepris nobilis is used in folk or traditional medicine to treat several diseases or illnesses. A decoction of the arial parts of the plant has been reported to treat malaria [4]; stem bark as a remedy for gonorrhea and pain; a mixture of the bark and leaves as analgesics and antipyretic [5, 6]; leaves as a cure for fever [2, 7], pneumonia [3] and malaria [8]; roots for treating rheumatism, arthritis, pneumonia [9, 10], as an anthelminthic [11], weight loss and chronic cough [12]. A decoction of stem bark and root in treating asthma, common cold, headache, join and chest pains [11, 13]. Steam inhalation of the leaves was reported to cures fever [3] and stem bark as a chewing stick for brushing teeth [14].

3. Chemistry

3.1 Extraction yield

The percentage extraction yield of the leaves of *V. nobilis* with methanol, hexane, dichloromethane and ethyl acetate was found to be 10.95, 2.73, 2.48 and 1.57%, respectively [15]. However, extraction yields for roots with methanol, and a mixture of dichloromethane (DCM) and methanol in the ratio of 1: 1 was found to be 2.12 and 2.36% [16]. Hydro distillation of the leaves of *V. nobilis* resulted in 0.23% essential oil yield [7].

3.2 Phytochemicals

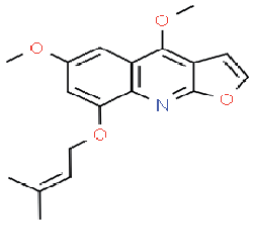
Phytochemical analyses of the leaves, fruits, roots and stem bark have indicated presence of several phytochemicals. For instance, ethanol extract *V. nobilis* root bark and the leaves were found to contain tannins, reducing compounds, alkaloids, steroid glycosides, polyuronides, glucides, starch, coumarin derivatives and flavonoids [16, 17]. The fractionation of the different plant part extract has resulted in the identification of several quinoline and furoquinoline alkaloids, terpenoids and flavonoids.

3.2.1 Alkaloids

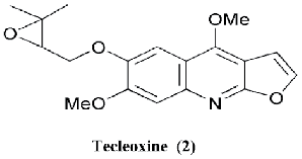
Alkaloids are organic heterocyclic nitrogen compounds that are weak bases. They form a bicyclic system in which benzene and a pyridine ring are fused together. There are several quinoline, furoquinoline and acridone alkaloids identified in the different plant parts. For instance, furoquinoline alkaloids; tecleabine [18], tecleoxine [7], isotecleoxine [19], methylnkolbisine [5], chlorodesnkolbisine [20], pteleine [21], isohaplopine-3,3-dimethylallylether [22], nobiline [23] haplopine-3,3-dimethylallylether [24] anhydroevoxine [9], kokusaginine [12] and

8-methoxyflindersine [25]; and acridone alkaloid, arborinine [26] were isolated from the aerial parts of *V. nobilis* [4, 5].

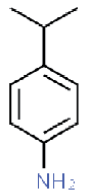
Similarly, furoquinoline alkaloids including nobiline [23], montrifoline [8], skimmiamine [4], flindersiamine [6] and maculine [11] were isolated from the leaves; and isoplatydesmine [2], ribalinine [27] and edilinine [1] isolated from both the leaves and fruits [8]. The fruits of *V nobilis* fruit were found to contain furoquinoline alkaloids; acetylmontrifoline [10], montrifoline [8], maculine [11], kokusaginine [12] and skimmiamine [4, 8]. The stem bark was found to contain furoquinoline alkaloids, Nkolbisine [28] while the root contained tecleabine [18], N -methylflindersine [29], flindersiamine [6], skimmianine [4] and desloratadine [13, 17].



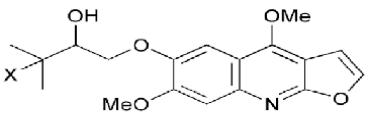
Tecleabine (1)



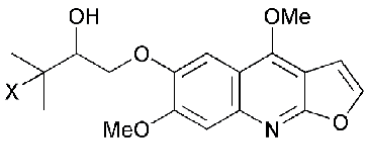
Tecleoxine (2)



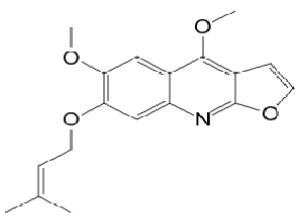
Iso-tecleoxin (3)



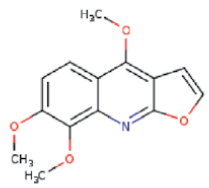
Methylnkolbisine (4), X=OMe



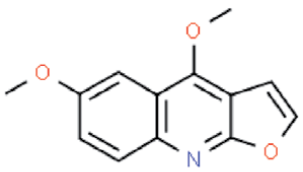
chlorodesnkolbisine (5) , X=Cl



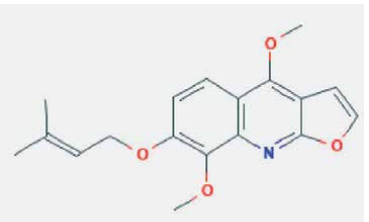
Pteleine (6)



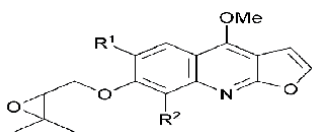
isohaplopine-3,3-dimethylallylether (7),



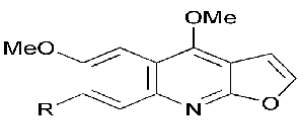
Nobiline (8)



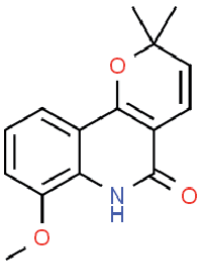
haplopine-3,3-dimethylallylether (9)



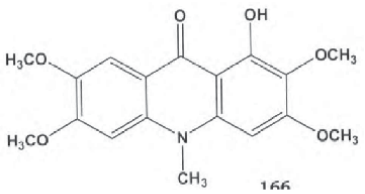
Anhydroevoxine R^1=H, R^2=OMe (10)



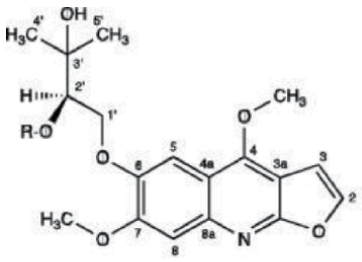
kokusaginine R= OMe (11)



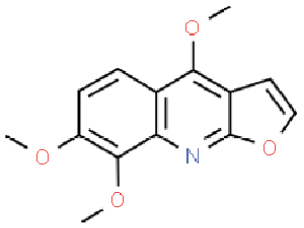
8-methoxyflindersine (12)



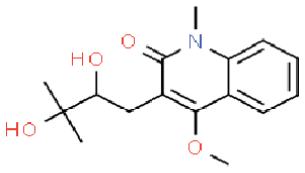
Arborinine (13)



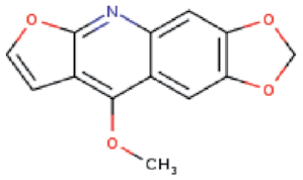
Montrifoline (R=H) (14)



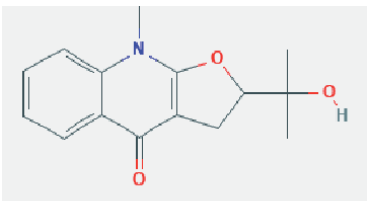
Skimmianine (15)



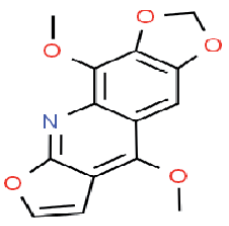
Flindersiamine (16)



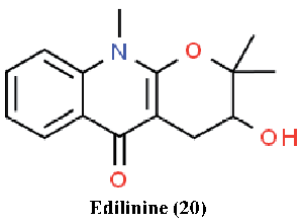
Maculine (17)



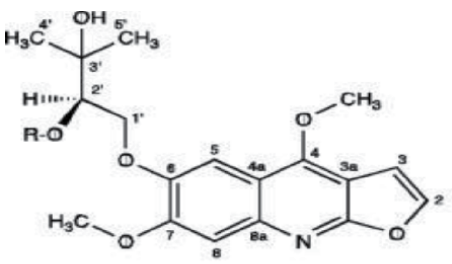
isoplatydesmine (18)



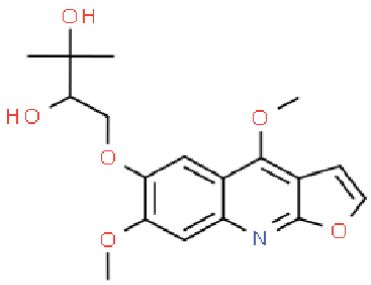
Ribalinine (19)



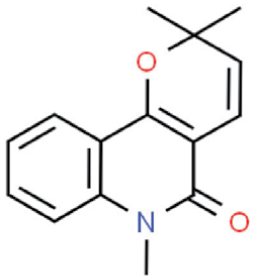
Edilinine (20)



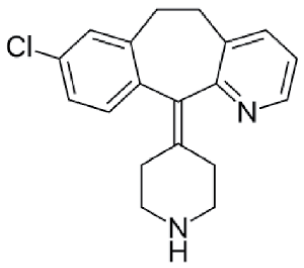
Acetylmontrifoline R= CH3-CO-(21)



Nkolbisine (22)



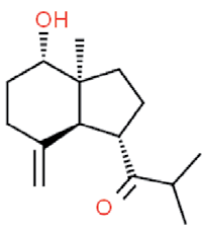
N -methylflindersine (23)



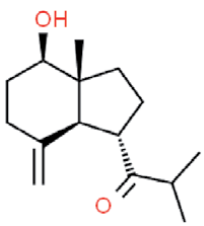
Desloratadine (24)

3.2.2 Terpenoids

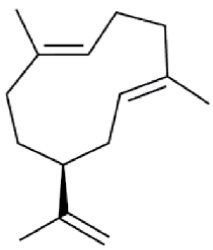
Terpenes form the largest group of natural compounds and they are usually identified on the basis of the number of isoprene units they possess. For instance, terpenes with one, two and three isoprene unit are called hemiterpene, monoterpenes and sesquiterpene, respectively. Essential oils mainly comprise of monoterpenes or/and sesquiterpenes. Ocheng et al. [14] and Al-Rehaily [7] evaluated essential oil profile of the roots and leaves respectively. In both studies, Germacrene-D [14] and Ocimene [17] were the major sesquiterpene and monoterpene hydrocarbon (**Table 1**). A study by Al-Rehaily et al., [19] also isolated sesquiterpenes, teclenone A [30] and teclenone B [31] from the aerial parts while a study by Al-Rehaily et al., [5] isolated lupeol from the leaves of V. nobilis. β-sitosterol was one of the setroids isolated from the aerial parts of *V. nobilis* [15, 19].



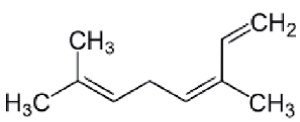
Teclenone A (25)



Teclenone B (26)



Garmacrene D (27)



Ocimene (28)

Compound	% Area	
	Root [29]	Leaves [7]
trans-β-Ocimene	8.5	
Ocimene isomer		22.3
Epoxyocimene		0.2
α-Copaene-11-ol		0.7
δ-Cadinene	7.3	1.9
γ-Elemene	2.4	
Elemol		2.9
Spathulenol		0.2
Guaiol		3.9
Bulnesol		2.5
Benzyl benzoate		0.3
Elemene		1.5
Germacrene D	54.4	19.0
α-Gurjunene	4.9	
α-Cardinol	9.1	
Tau-Cardinol	2.0	
Nerolidol	1.9	
Muurolol	3.4	
Phytol	1.2	
Methyl isoeugenol	1.7	
Palmitic acid	2.1	
β-Myrcene		0.1
Linalool		1.6
Dihydroedulan II		1.0
Dihydroedulan I		0.5
α-Copaene		0.6
β-Bourbonene		0.4
Cyperene		0.2
Methyl-N-methyl		0.3
β-Caryophyllene		0.9
α-Humulene		1.3
Other compounds less than 1% in the oil.	1.1	

Table 1.
Essential oils from the leaves and roots of V. nobilis.

3.2.3 Flavonoids

Flavonoids are a class of polyphenol phytochemicals made up of a skeleton of 15-carbon atoms which consists of two benzene rings (ring A and B) linked via a heterocyclic pyrane ring [26]. Depending on the chemical structures, flavonoids are divided into clases like anthocyanins, flavones, flavonols, flavanones,

dihydroflavonols, chalcones, aurones, flavonons, flavan and proanthocyanidins, isoflavonoids, isoflavones, isoflavonones, isoflavons, isoflavene, biflavonoids, neoflavonoids and flavonoid alkaloids. A study conducted by Al-Rehaily et al. [5] isolated flavanone 4,5-dihydroxy-7- prenyloxyflavanone from aerial parts of *V. nobilis* [5]. Phytochemical quantification of flavonoids in the roots resulted in 33.5 and 20.6 mg/g. Quercetin Equivalent while quantification of phenolic compounds resulted in 168.4 mg/g Garlic Acid Equivalent.

4. Pharmacological activity

Vepris nobilis has been reported to poses analgesic, antipyretic, anti-malarial, anti-plasmodial, antimicrobial, anti-inflammatory, anti-caseinolytic, anti-leishmanial and anti-trypanosomal activities.

4.1 Antipyretic and analgesic activities

Pyrexia or fever is the increase in body temperature above normal physiological range, which may result due to physiological stress such as during microbial infections as natural defense system of the body is activated [32]. Usually, at the elevated body temperature, there is increased production of proinflammatory mediators' cytokines such as interleukin 1β, β, α and TNF-α which enhance the formation of prostaglandin E2 (PGE2) near the peptic hypothalamus area and the prostaglandin in turn act on the hypothalamus. To lower the elevated body temperature, antipyretic drugs administered usually inhibit COX-2 expression thereby inhibiting prostaglandin synthesis.

Since *V. nobilis* is used to treat fevers, a study on the antipyretic and analgesic activity of ethyl acetate fraction from the residue of the 85% ethanol extract of *V. nobilis* was found to exhibit a significant antipyretic effect in hyperthermic rats and rabbits [32]. Similarly, essential oils of the leaves of *V nobilis* showed significant analgesic and antipyretic activity recorded in both writhing and tail flick test in mice [7]. Analgesic and antipyretic activity in this study was attributed to Central nervous system depression as observed in the behavioral studies on the animals.

A study conducted by Mascolo et al. [2] by intravenous administration of 50 mg/kg of dried leaf extract of *V. nobilis* resulted in antipyretic and analgesic activity, and thereby causing decrease in body temperature, with the effect being equipotent to acetylsalicylic acid. The same extract also demonstrated antinociceptive activity as judged by its ability to increase the thermal response latencies of mice kept on heated surface with IC_{25} of 26.1 mg/kg compared to acetylsalicylic acid with IC_{25} of 32.5 mg/kg. In a study conducted on antipyretic and analgesic activities of ethanolic extract of *V. nobilis*, a compound 4,6-dimethoxy-7-((3-methylbuta-1,3-dien-1-yl) oxy)furo [2,3-b]quinolone was found as a good lead compound to be developed into a drug for managing pain.

4.2 Anti inflammatory activity

Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents with the aim to inactivate or destroy the invading organism, remove irritants and set the stage for tissue repair. In the process, proinflammatory cytokines like TNF-α, IL-6, and IL-1β are produced in large quantities by macrophages and monocytes that stimulate the cellular responses via increasing prostaglandins (PGs) and reactive oxygen species [33]***. In laboratory animal experiments, inflammatory pain can be induced by acetic acid

due it is ability to induce capillary permeability and liberating endogenous substances that excite pain nerve endings [34].

A study conducted on ethanol extract dose-related effect of *V. nobilis* extract on carrageenin-induced oedema at high doses of 200-300 mg/kg significantly modified carageenin oedema with IC_{25} of 157.5 mg/kg compared to acetylsalicylic acid with 22.5 mg/kg [2]. This biological effect was attributed to phytochemicals present in the extract because of their potential to inhibit the cyclooxygenase enzyme in peripheral tissues and interfere with the transduction mechanism of primary afferent nociceptors.

A similar study conducted by Omujal et al. [17] found that 400 and 600 mg ethanolic root bark extract / kg of body weight on formalin induced paw oedema in mice was inhibited much better than by 25 mg of Diclofenac sodium /kg body weight, and indicated that compounds including, *N*-methylflindersine, Skimmianine, Germacrene-D, α-Cubebene, α-Cardinol and lupeol could be responsible for the anti-inflammatory activity.

4.3 Antimicrobial activity

Microbial infection is the process of invasion of infectious agents into the organism. These infectious agents mainly include bacteria, virus, parasite and fungi naturally occurring in the environment [24]. Antimicrobial activity can be defined as a collective term for all active principles (agents) that inhibit the growth of bacteria, viruses and fungi. Although antibiotics play an essential role in treating microbial infections, extracts of plants have also been attributed to contribute significantly to antibiotic activity. Currently, some of the antimicrobial drugs on the market have been isolated from natural sources.

Studies on the antimicrobial activity of the leaves; stem bark and roots of *V. nobilis* on gram-negative bacteria (like *Escherichia coli*), gram-positive bacteria (e.g., *Staphylococcus aureus* and *Bacillus subtilis*) and fungi (e.g. *Candida albican*) has been conducted. For instance, the inhibition zones (in mm) of DCM, hexane, ethyl acetate and methanol crude extracts of the air-dried leaf extracts of *V. nobilis* showed activity against *S. aureus* with DCM exhibiting the highest activity among the solvent, though its activity was lower than that of ampicilin or gentamycin. In these solvents, DCM and methanol also registered some activity against *S. pneumoniae* and *B. subtilis.*

A study conducted by Kisangau et al. [12] also determined the antimicrobial activity of petroleum ether extract of the leaves of *V. nobilis* and found activity against *B. subtilis* and *E. coli*, though there activities were lower than ampicillin and gentamicin, respectively. Furthermore, antimicrobial activity against *S. typhi* and *E. coli* were only realized in DCM and methanol extract. A similar study conducted by Nuru et al. [16] found that methanol root extract of *V. nobilis* showed promising activity against *S. aureus* and *P.aeruginosa,* but not for *Klebsiella pneumania* and *E. coli.* When an extract of a mixture of solvents (DCM and methanol in the ratio of 1:1) on the same microorganism was evaluated, the results were contrary. In another study conducted on fractionated furoquinoline alkaloids e.g. maculine and benzoylbetulin isolated from its roots showed antimicrobial activity against *S. aureus* and *P. aeruginosa* [16].

Although Onyacha et al. [15] and Kuete et al. [25] found that kokusaginine, dictamine, 8-Dimethoxy-7-(3-methyl-but-2-enyloxy)-furo [2, 3-*b*] quinoline, and β-Sitosterol isolated from *V. nobilis* showed activity towards *S. aureus* and *S. pneumonia,* Michael [27] had indicated earlier that kokusaginine and dictamine had not exhibited antimicrobial activity towards a range of microorganisms at concentrations even up to 100 g/mL But a study by Kuete et al. [25] also found that that

kokusaginine, kolbisine, maculine and lupeol had promising antimicrobial activity on bacteria and fungi. A similar study by Adamska-Szewczyk et al. [18] indicated that dictamine alkaloid possed anti-fungal properties while that of Onyancha et al. [13] indicated that skimmianine alkaloid showed antimicrobial sensitivity to *B. subtilis*, *B. cereus*, *S. aureus*, *S. epidermidis*, *S. pyogenes*, *Enterobacter aerogenes*, *Enterococcus* spp., *E.coli*, *Klebsiella pneumonia*, *P. aeruginosa*, *E. cloacae*, *Shigella sonnei*, *Salmonella typhimurium*, *Burkholderia cepacia*, *Morganella morganii* and *Candida albicans*, *C. tropicali*, *C. krusei*, *C. parapslosis*, *Sacharomyces cerevisae*, *Cryptococcus neoformans* and *C. gatti* [15].

Although a study by Al-Rehaily [7] indicated no microbiological potential of the essential oil from the leaves against a number of micro-organism, a study by Ocheng et al. [29] reported that essential oils from the root possessed antimicrobial sensitivity to periodontopathic and cariogenic bacteria clinically present in the dental plaque including A*ggregatibacter. Actinomycetemcomitans (*HK 1519) and *Porphyromonas gingivalis* (ATCC 33277), *Bacillus megaterium* (BM11), *Streptococcus mutans* but not to *Lactobacillus acidophilus* (NCTC 1723) at concentrations of 0.01%, 0.1 and 1%. An invitro antibacterial study of teclenone A (**1**) and teclenone B conducted against *S. aureus, P. aeruginosa*, *C. albicans* and *Cryptococcus neoformans* were found to be inactive [19].

4.4 Anti-malarial and antiplasmodial activity

Malaria is one of the major parasitic infection in many tropical and subtropical regions that has contributed the largest burden on public health of most developing countries with global estimates of 600 million new infections annually and at least 1 million of these infections being fatal [35]. *Vepris nobilis* is one of the medicinal plants used in traditional medicine to treat malaria in rural areas where malaria is the major cause of death. A study conducted by Lacroix et al. [8] on the antiplasmodial activity of ethyl acetate extracts of the fruits and leaves showed that leaves had more activity than the fruits with 98% instead of 55% growth inhibition of *Plasmodium falciparum* FcB1 strain at 10 mg/ml, respectively [8]. In another study conducted on the stem bark extract of *V. nobilis* against *P. falciparum* FcB1 strain (10 μg/mL), 54.7% inhibition was obtained compared to chloroquine with 98.1% Inhibition, and this showed a promising anti-plasmodial activity against *P. falciparum.* In terms of toxicity on two cell lines, the stem bark extract showed low cyto-toxicity of 36.0% and 22.0% with inhibition of KB cells (10 μg/mL) and MRC5 cells (10 μg/ml), respectively [4].

Further investigation of anti-plasmodial activity of skimmianine alkaloid from the arial parts and leaves of *V. nobilis* show a weak activity against *P. falciparum* with cytotoxicity being exhibited towards L-6 cells [18]. A study on the antimalarial activity of kokusaginine and maculine against chloroquine sensitive (CQS) strain of *P. falciparum* NF54 *in vitro* with concentrations ranging from 2 to 8 μM showed partial suppression of parasitic growth with significantly different from untreated control group after four days. Montrifoline alkaloid from the fruits of *V. nobilis* also showed a weak activity against chloroquine- resistant FcB1/Colombia strain of *P. falciparum* with IC_{50} of 56 mg/ml compared to chloroquine 0.1 mg/ml, and its cytotoxicity was found to be weak with IC_{50} with greater than 50 mg/ml. Arborinine alkaloid isolated from arial parts of *V. nobilis* was found to have moderate antimalarial activity against CQS D10 strain of *P.falciparum* with IC_{50} values of 12.3 and 24.5 mM respectively [6].

In another study by Waffo et al. [36] there was antimalarial activity of 12.3 μM of arborinine alkaloid against a Nigerian CQS strain. Similarly, Mwangi et al. [29]

found anti-plasmodial activities of arborinine and skimmianine alkaloids from *Teclea trichocarpa* against chloroquine-resistance strain K1 to be mild with IC_{50} of 1.61 and 5.60, respectively compared to chloroquine with IC_{50} of 0.0665 μg/ml.

However, furaquinoline alkaloids including teclealbine, −tecleoxine, isotecleoxine, methylnkolbisine, chlorodesnkolbisine, anhydroevoxine and pteleine were reported to be ineffective in antimalarial tests [4]. Similarly, in vitro antimalarial activity of teclenone A and teclenone B against *P. falciparum* D6 and W2 clones registered no activity [19].

4.5 Anti-leishmanial and anti-trypanosomal activity

Leishmaniasis is a disease caused by a protozoa parasite from over *20* Leishmania *species*. Over 90 sandfly species are known to transmit Leishmania *parasite*s through the bites of infected female phlebotomine sandflies which feed on blood to produce eggs [37]. Globally, leishmaniasis disease affects over 350 million people. Although chemotherapeutic therapies including pentavalent antimonials, miltefosine, stibogluconate, amphotericin B and paromomycin are used against leishmaniasis, medicinal plants are also potential sources of lead compounds. A study conducted by Lacroix et al. [4] on the anti-leishmanial activity of montrifoline alkaloid from the leaves of *V. nobilis* found moderate activity against *Leishmania donovani* with EC_{50} of 31.2 mg/ml and no activity against *Trypanosoma brucei* when compared with pentamidine with EC_{50} of 3.1 mg/ml. Even Adamska-Szewczyk et al. [18] indicated anti-leishmanial activity of skimmianine activity. Most alkaloids extracted from the fruits and leaves were found not to show *Trypanosoma brucei* activity with their EC_{50} being ≥125 mg/ml when compared with that of pentamidine with EC_{50} of 1.8 mg/ml [4]. *N*-methyl-8-methoxyflindersin, isolated from the leaves of *Raputia heptaphylla* was found to show antiparasitic activity against *Leishmania* promastigotes and amastigotes [38].

4.6 Anti-caseinolytic activity

Snakebite envenomations continue to be a threat to public health in some parts of the world. At least 1,841,000 snakebites resulting in about 94,000 deaths are recorded annually. Venomous snakebites have been traditionally treated with medicinal plants. Pharmacological invitro evaluation of aqueous methanol crude plant extract of *V. nobilis* demonstrated significant abilities to inhibit the caseinolytic effect of crude *Bitis arietans* venom and this was related to the higher composition of flavonoids, flavonols and phenolics [20]. Caseinolytic activity is the ratio of the absorbance of casein relative to the absorbance of the venom-casein mixture.

4.6.1 Anthelmintic activity

Helminth infections cause major morbidity and mortality in both human and animals. In developing countries, helminth infections pose a major threat to public health and contribute to the prevalence of malnutrition, anemia, eosinophilia and pneumonia [21]. Anthelmintics can be defined as drugs that either kill or expel infesting helminths or their larvae from the gastrointestinal tract or that live in tissue. Natural products have been found as potential sources for new, effective and safe anthelmintic drug. Although *V. nobilis* is ethnomedicinally reported to be anthelmintic, a study by Muema et al. [2] on lupeol terpenoid isolated from *V. nobiis* was found not to show anthelmintic activity.

4.7 Anti-depression activity

Depression is an illness which involves not only mood or emotion disorder but also the physical body and thought process disorder including loss of interest, reduced energy and concentration. This disease is estimated to affect about 21% of the world population. Although there are existing drugs for treatment of depression, they are associated with side effects like dry mouth, fatigue, gastrointestinal or respiratory problems, anxiety, agitation, drowsiness, and cardiac arrhythmias. There are several phytochemicals with antidepressant activity. Adamska-Szewczyk et al. [18] has indicated that alkaloids like kokusaginine and skimmianine in *V. nobilis* inhibit 5-HT2 receptor activity, thus suggesting their significance in the treatment of various diseases related to serotonin neurotransmission including depression [18].

4.8 Toxicity of *V. nobilis*

Assessing the safety of medicinal plants has been regarded to be essential even if it has been used for decades. A study by Mailu et al., [11] on toxicity of dichloromethane and ethanol extracts of aerial parts of *V. nobilis* found mild toxicity and no toxicity to brine shrimp as showed by their LC_{50} of 75.5 μg/mL and 156.6 μg/mL respectively [10]. In another study using brine shrimp lethality tests conducted on various solvent leaf extracts of *V. nobilis* including hexane, dichromethane, ethyl acetate and methanol against *Artemia salina* found LD_{50} of 235, 165, 557 and 268 respectively [15]. It was concluded that *V. nobilis* leaf extracts were non-toxic. Brine shrimp results of $LC_{50} < 1.0$, 10–30, 30–100 and > 100 μg/mL are regarded highly toxic, toxic, moderately toxic, mildly toxic and none toxic respectively [10]. Even an alkaloid, 6-dimethoxy-7-((3-methylbuta-1,3-dien-1-yl) oxy) furo[2,3- b] quinolone isolated from *V. nobilis* was predicted with median lethal dose (LD_{50}) of 1600 mg/kg, suggesting its toxicity to be of class 4, which has LD_{50} between 300 and 2000.

5. Conclusion

Vepris noblis is a rich source of furoquinoline alkaloids, terpenoids and flavonoids. The extracts and phytochemical compounds extracted from the different parts have shown promising pharmacological antimalarial, analgesic, anti-inflammatory and antipyretic activities. Toxicity studies also indicate that *V. nobilis* is generally safe.

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Chapter 9

Total Phenolic Content and Polyphenolic Profile of Tunisian Rosemary (*Rosmarinus officinalis* L.) Residues

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Abstract

Plants, especially herbs and spices, have always been the major sources of numerous natural compounds with antioxidant activity and other beneficial properties and, specifically, Rosemary (*Rosmarinus officinalis* L.) has been widely accepted as one of the spices with highest antioxidant activities which appear to be related to their richness of phenolic compounds. This study was undertaken with the aim to estimate the total phenolic content, identify and quantify the polyphenolic compounds of the methanolic extracts from post-distilled rosemary, collected from two different bioclimatic areas from Tunisia. Total phenolic content (TPC) was determined by Folin–Ciocalteu method. Identification and quantification of polyphenolic compounds was performed using high-performance liquid chromatography (HPLC) analysis. TPC ranged from 85.8 to 137.3 mg GAE/g DE in rosemary extracts. HPLC analysis showed the presence of carnosic acid and carnosol, wich were found to be the most abundant compounds in all analyzed extracts (46.3 to 76.4 and 22.4 to 43.5 mg/g of plant dry weight respectively), rosmarinic acid and caffeic acid as phenolic acids, besides some flavonoids such as apigenin, luteolin, genkwanin and hesperidin. This study revealed that rosemary post-distilled residues were shown to be promising with regard to their incorporation into various foods, cosmetics and fragrances.Therefore, supplementing a balanced diet with herbs may have beneficial health effects.

Keywords: *Rosmarinus officinalis* L, total phenolic content, polyphenolic profile, HPLC analysis

1. Introduction

Herbs and plants have been used for a large range of purposes including medicine, pharmaceuticals, nutrition, food preservation, flavorings, beverages, repellents, fragrances and cosmetics. Since prehistoric times, they were the basis for medicinal therapy until synthetic drugs were developed in the nineteenth century [1, 2]. In recent decades, the use of herbs and plants has been of great interest, as

they have been the sources of natural products, commonly named as bioactive compounds, with beneficial activities, namely polyphenols, vitamins, polysaccharides and minerals [3]. Nowadays the use of natural compounds is also increasing around the world due to their mild features and low side effects [4, 5]. Cosmetic preparations from herbal origin are popular among consumers, as these agents are typically non-toxic and possess strong activities [6].

Preliminary studies demonstrated that some herbs extracts are as efficient as the synthetic antioxidants such as butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA), which have carcinogenic effects in living organisms [3, 4, 7]. Several studies have indicated that the consumption of natural antioxidant compounds protect cells against the damage of reactive oxygen species such as singlet oxygen, superoxide, peroxyl radicals, hydroxyl radicals and peroxynitrite (Yang et al., 2013) [8]. Recently numerous reports have described antioxidants and compounds with beneficial activities, would be beneficial for healthy life, present in fruits, vegetables, herbs and cereals extracts [3, 9]. For all the described reasons, during the last decade there has been a growing interest in the formulation of new cosmetic, food and pharmaceutical products containing natural compounds with antioxidant activity and other beneficial properties for healthy life.

The evidence for antioxidant effect of spices and herbs in food systems was initially determined by Chipault et *al.* (1952) [10] studying 32 spices, and among these rosemary and sage were considered the most effective. In general, herbs and plants are rich in compounds with antioxidant properties, such as vitamins (E and C), glutathione, enzymes and phenolic compounds [11]. Specifically, the natural compounds from the Lamiaceae family (thyme, sage and rosemary) has been reported in several studies for its antioxidant, anti-inflammatory, antimicrobial and anti-carcinogenic activities [1, 3, 12, 13]. In particular rosemary extracts possess very useful antioxidant properties, which appear to be related to their content of phenolic compounds [4, 7, 14–18].

Rosemary (*Rosmarinus officinalis* L.) is a perennial shrub belonging to the *Lamiaceae*. Native to the Mediterranean region rosemary is now widely distributed and has been cultivated around the world [19]. Its leaves have been used for thousands of years as a natural food preservative, flavorings, pharmaceuticals, alternative medicine and natural therapies [20, 21] and its applications have ranged from memory enhancement to the treatment of gastrointestinal diseases [22, 23]. Also, rosemary is the most used and economically important aromatic and medicinal plant for its essential oil and phenolic compounds [1, 24–26] and has been widely accepted as one of the spices with highest antioxidant activities of all the herbs and spices that have been investigated [3]. Antioxidant activity of rosemary extracts depends on their richness of phenolic compounds. Several investigators found that rosemary bioactive properties are connected with the presence of phenolic compounds, especially flavonoids and diterpenes, such as carnosic acid and carnosol that characterized with its antioxidant activity [1, 27–33].

Rosemary is among the most promising sources for the recovery of essential oils through hydrodistillation and polyphenols. After extracting the essential oils, the residues remaining postdistillation (wastes of hydro-distillation) is considered a natural source of antioxidants with several biological activites [9, 30]. Up to today, their exploitation for polyphenol recovery has been limited. The residues remaining after essential oil recovery currently disposed as waste, could be extracted to obtain natural extracts rich in phenolic compounds and with a high antioxidant activity [34].

This current study was undertaken with the aim to identify and quantify the polyphenolic compounds (polyphenolic profile) and to determine the total phenolic content of the residues (waste of hydro-distillation) of rosemary aerial parts in

order to revalorize this plant and to increase the economic values of this valuable products as a source of bioactive molecules with beneficial properties that might confer benefits to human health.

2. Materials and methods

2.1 Collection of plant materials

A total of 40 individual samples of wild rosemary shrubs (4 locations with 10 plants/area) from two different bioclimatic areas (Semi-arid superior and lower arid) were randomly collected at the full bloom phenological stage (spring 2017). Voucher specimens of rosemary from every location are deposited at the Herbarium of Laboratory of Aromatic and Medicinal Plants of the Research Group on Rainfed Crops for the Rural Development, Murcia Institute of Agri-Food Research and Development (IMIDA), Murcia, Spain.

Details of collection sites are given in **Table 1**. Fresh aerial parts of plants were firstly dried at room temperature for ten days and afterwards dried in a forced-air drier at 35°C for 48 h, until they reached a constant weight.

2.2 Chemicals

2,2-Diphenyl-1-picrylhydrazyl (DPPH•), ascorbic acid, potassium persulfate, the Folin–Ciocalteu reagent, gallic acid and high purity standards were purchased from Sigma-Aldrich (Madrid, Spain). Methanol, acetonitrile, formic acid, anhydrous sodium carbonate and sodium acetate were supplied from Scharlau Chemie S.A. (Sentmenat, Spain). Methanol was of HPLC grade and other reagents were of analytical grade.

2.3 Extraction of polyphenolic coupounds

After extracting the essential oils, the residues remaining postdistillation (wastes of hydro-distillation) is considered a natural source of antioxidants [35, 36]. In order to avoid interferences from the essential oil components, individual plants were firstly distilled in a Clevenger system for 3 h, after this, the oil free distilled plant material was dried in a forced-air drier at 35°C for 48 h (until it reached a constant weight) and then ground to pass through a 2-mm mesh. Dried samples (0.5 g) were extracted using 150 mL of methanol in a Soxhlet extractor (B-811) (Buchi, Flawil, Switzerland), for 2 h under a nitrogen atmosphere. Methanolic extracts (ME) were taken to dryness at 40°C under vacuum conditions

Collection site	Bioclimatic stage	Rainfall mm/year	Temp °C/year	Geographical location		
				Longitude (N)	Latitude (E)	Altitude (m)
ElKef-Menzel Salem (KMS)	Semi-arid superior	446	16.2	35°51′24.0”	8°28′34.0”	995
Elkef-Sers (KS)	Semi-arid superior	441	16.9	36°4′36.2”	9°1′21.8”	887
Gafsa-Orbata (GO)	Arid lower	223	19.6	34°22′49.8”	9°3′23.4”	1165
Gafsa-Sened (GS)	Semi-arid superior	222	17.3	34°28′1.2”	9°16′1.2”	392

Table 1.
Samples collection sites and their eco-geographic characteristics.

Figure 1.
Preparation of methanolic extracts of post-distilled rosemary plant.

in an evaporator system (Syncore Polyvap R-96) (Buchi, Flawil, Switzerland) (**Figure 1**). The residue was re-dissolved in methanol and made up to 5 mL [37]. The yield of the extracts was expressed in terms of milligrams of dry methanolic extract per gram of dry plant weight. Final extracts were kept in vials at −80°C until their corresponding analyses.

2.4 Determination of the total phenolic content

Total phenolic contents in the extracts were determined by the Folin–Ciocalteu method [38]. A reaction mixture of 15 µL of methanolic extracts, 1185 µL of distilled water and 75 µL of Folin–Ciocalteu reagent were prepared. A vigorous stirring was performed and 225 µL of a sodium carbonate (20%) were added. The tubes were incubated in the dark for 30 min and then the absorbance was measured at 765 nm and 25°C with a Shimadzu (UV-2401PC, Japan) spectrophotometer. Standard curve was prepared by using different concentrations ranging from 100 to 1000 mg/L of gallic acid. Total phenolic content was expressed as mg gallic acid/g dry extract (mg GAE/g DE). Analyses were done in triplicate.

2.5 HPLC analysis

For the HPLC analysis, a method adapted from Zheng and Wang [1] was performed on a reverse phase ZORBAX SB-C18 column (4.6 x 250 mm, 5 µm pore size, Hewlett Packard, USA) using a guard column (ZORBAX SB-C18 4.6 x 125 mm, 5 µm pore size, Hewlett Packard, USA) at ambient temperature. Extracts were passed through a 0.45 µm filter (Millipore SAS, Molsheim, France) and 20 µL were injected in a Hewlett Packard (Germany) system equipped with a G1311A quaternary pump and G1315A photodiode array UV/Vis detector. The mobile phase was acetonitrile (A) and acidified water containing 0.05% formic acid (B). The gradient was as follows: 0 min, 5% A; 10 min, 15%A; 30 min, 25%A; 35 min, 30%A; 50 min, 55%A; 55 min, 90%A; 57 min, 100% A and then held for 10 min before returning

to the initial conditions. The flow rate was 1.0 mL/min and the wavelengths of detection were set at 280 and 330 nm. Identification of the phenolic components was made by comparison of retention times and spectra with those of commercially available standard compounds. For quantification, linear regression models were determined using standard dilution techniques. Phenolic compound contents were expressed in mg per g of dry plant weight.

2.6 Statistical analyses

All data were reported as means ± standard deviation (SD). A one-way ANOVA was carried out to assess for significant differences (significant model was accepted for a p-value <0.05) using the IBM SPSS Statistic Program (v. 25). Next, Fisher's LSD pairwise comparison was performed on the data.

3. Results and discussion

3.1 Determination of total phenolic content (TPC)

Residues of the hydro-distillation process of aromatic plants oils had been studied for their contents of a diversity of biologically active compounds including antioxidants such as phenolic acids and flavonoids, that could be employed to increase the shelf life of food [13, 35]. The total phenolic content (TPC) in the post-distilled rosemary extracts ranged from 85.8 to 137.3 mg GAE/g DE (**Table 2**). Among the studied collection sites, post-distilled plants of GO population had the highest phenolic content (137.3 mg GAE/g DE). GS population had the lowest phenolic content (85.8 mg GAE/g DE). Our result showed higher TPC in comparison with that obtained by Jordan et *al.* (2013) in the case of Spain rosemary [16]. A recent investigation including several rosemary species revealed lower amounts of total phenolics of non-distilled plant material [18, 39].

Alternatively, results reported by Parejo et *al.* (2002) showed that plant material submitted to hydro-distillation has been found to contain a higher amount of phenolic substances than the non-distilled plant material [35]. In certain cases, cell wall phenolics or bound phenolics could be released consequently to heat exposure, thus generating more phenolics to be extracted. In addition, many studies described several biological activities that these non-volatile fractions have, and confirmed that these properties are directly related with the concentration of the principal components present in these polyphenolic extracts [16, 40–43]. Since total phenolic content estimated by the Folin–Ciocalteu procedure does not give a full picture of the quality and quantity of the phenolic constituents, HPLC analyses for determination of individual phenolic constituents is necessary.

3.2 Identification and quantification of polyphenolic compounds by HPLC

The polyphenolic profile of rosemary has been widely described in the scientific literature [4, 5, 16, 17, 29, 31, 33, 39, 44–49]. The polyphenolic profile of these plants is characterized by the presence of carnosic acid, carnosol, rosmarinic acid and hesperidin, as major components. Based on the retention times of calibration standards, methanolic extracts of rosemary showed a phenolic profile composed of 18 identified phenolic compounds (**Table 2**). The polyphenolic profile of rosemary are composed of four phenolic acids (salvianic acid, caffeic acid, rosmarinic acid, and salvianic acid A), five phenolic diterpenes (Rosmadial, 7-CH_3-Rosmanol, carnosol, carnosic acid and12-CH_3-carnosic acid), and nine flavonoids (Luteolin

	Kef Seres	Kef Menzel Salem	Gafsa Orbata	Gafsa Sned
Total phenolic content (TPC, mg GAE/g DE)	85.8 ± 28. 4[a]	109.1 ± 23.1[b]	137.3 ± 15.6[c]	87.8 ± 15.0[a]
Phenolic acids				
Salvianic Acid	1.10 ± 0.13[ab]	1.13 ± 0.23[ab]	1.21 ± 0.39[b]	0.84 ± 0.13[a]
Caffeic Acid	1.00 ± 0.22[b]	0.90 ± 0.11b[ab]	0.74 ± 0.26b[ab]	0.69 ± 0.27[a]
Rosmarinic Acid	29.91 ± 9.33[c]	17.96 ± 3.25[ab]	26.02 ± 5.88[bc]	16.77 ± 7.59[a]
Salvianolic Acid A	1.76 ± 0.44[a]	1.20 ± 0.34[a]	2.62 ± 0.84[b]	1.32 ± 0.40[a]
Flavonoids				
Luteolin –7-O-Rutinoxide	0.98 ± 0.40[b]	0.74 ± 0.18[ab]	0.74 ± 0.37[ab]	0.57 ± 0.25[a]
Luteolin-7-Glucoronide	2.56 ± 0.80[b]	1.89 ± 0.59[ab]	1.15 ± 0.49[a]	1.28 ± 0.62[ab]
Hesperidin	10.41 ± 2.79[a]	14.0 ± 2.69[b]	10.6 ± 2.77[ab]	9.85 ± 3.47[a]
Luteolin	0.77 ± 0.10[a]	0.97 ± 0.13[b]	0.81 ± 0.11[ab]	0.78 ± 0.18[a]
Apigenin	0.23 ± 0.05[a]	0.24 ± 0.06[a]	0.24 ± 0.05[a]	0.2 ± 0.05[a]
Hispidulin	0.34 ± 0.05[a]	0.48 ± 0.09[b]	0.41 ± 0.09[ab]	0.37 ± 0.08[a]
Cirsimaritin	1.21 ± 0.58[a]	1.53 ± 0.48[a]	1.32 ± 0.41[a]	1.16 ± 0.42[a]
Genkwanin	3.30 ± 1.33[a]	2.51 ± 0.71[a]	2.07 ± 0.84[a]	2.05 ± 1.22[a]
Salvigenin	1.05 ± 0.31[a]	1.13 ± 0.3[a]	1.59 ± 0.5[b]	1.22 ± 0.37[ab]
Diterpenes				
Rosmadial	1.83 ± 0.32[a]	2.49 ± 0.41[bc]	2.68 ± 0.54[c]	1.98 ± 057[ab]
7-CH_3-Rosmanol	1.45 ± 0.35[a]	1.49 ± 0.26[a]	3.73 ± 0.75[b]	1.12 ± 0.31[a]
Carnosol	26.94 ± 4.86[ab]	29.95 ± 3.57[b]	43.53 ± 4.18[c]	22.36 ± 4.17[a]
Carnosic acid	57.33 ± 22.37[a]	54.74 ± 9.24[a]	76.36 ± 12.87[b]	46.27 ± 12.01[a]
12-CH_3- Carnosic Acid	9.60 ± 4.86[a]	10.60 ± 4.00[a]	16.70 ± 5.84[b]	10.6 ± 2.78[a]

Contents of phenolic compounds are expressed as as mg compound/g Dry plant weight. Values followed by the same letter did not share significant differences at 5% (Duncan test).

Table 2.
Total phenolic content and polyphenolic profiles of R. officinalis *L. methanolic extracts.*

–7-O-Rutinoxide, luteolin-7-Glucoronide, hesperidin, luteolin, apigenin, cirsimaritin, genkwanin, and salvigenin). Among the mentioned phenolic compounds, carnosic acid and carnosol were the major diterpenic components quantified in rosemary extracts, considering both provenances, (ranging from 46.3 to 76.4 mg/g and 22.4 to 43.5 mg/g respectively) followed by rosmarinic acid and hesperidin. Much lower contents were detected for luteolin, apigenin, cirsimaritin and genkwanin.

In the present study locations belonging to two different bioclimatic regions were prospected, showing, as a general pattern, that the differences in polyphenolic content should be attributed more to the genetic inheritance of the plants, than to the area of prospection. Contrary to this, studies accomplished by Yeddes et *al.* (2019) about the effect of bioclimatic area and season on phenolics and antioxidant activities of rosemary growing wild in Tunisia showed that there was a strong correlation between antioxidant activity and phenolic content depending on bioclimatic and season effects [18]. However, our results are in agreement with those published

previously by Jordán et *al.* (2013) and Luis et *al.* (2007), since as occurs at the present study, for these researchers, variation in the chemical composition of polyphenolic extracts have been attributed to many factors, including abiotic stress,, genetic heritance and the phenological stages of the plants [16, 50].

Several phenolic compounds of rosemary determined in this study were similar in content and concentration to those in previous reports [1, 24, 51]. These phenolic compounds in rosemary extracts are very potent antioxidants and are utilized in many food products. The identified compounds were previously reported in *R. officinalis* extracts: rosmarinic acid and carnosic acid [29, 52], carnosol [52], caffeic acid, ferulic acid, luteolin, apigenin [53]. Differences among phenolic compound levels, compared with our results, can be related to the distillation process, because according to Almela et *al.* [51], the drying and/or distillation treatments of *R. officinalis* strongly affected the content of the two compounds of higher antioxidant activity: rosmarinic and carnosic acid. However, our samples seem to have higher concentrations of carnosic acid compared with previous studies [1, 51].

4. Conclusion

Rosemary (*R. officinalis* L.) is a rich source of phenolic compounds and their properties are derived from its extracts. It is therefore the strong antioxidant compounds in its essential oil and extract that is making *R. officinalis* a plant of great interest in today's food and medical industries. Bioactive compounds of plant origin have been shown to have several beneficial properties. Nowadays the use of natural compounds is also increasing around the world due to their mild features and low side effects. Several studies have indicated that the consumption of natural antioxidant compounds protect cells against the damage of reactive oxygen species such as singlet oxygen, superoxide, peroxyl radicals, hydroxyl radicals and peroxynitrite. Detection of natural antioxidant sources would be beneficial for healthy life. Many plants, such as vegetables, fruits, and herbs, are the main sources of natural antioxidants. Phenolic compounds have attracted particular interest because these compounds demonstrate effective antioxidant potential and other beneficial properties. Unfortunately, due to their structure and nature, certain compounds such as polyphenols, is not stable and may interact easily with the matrices in which they are incorporated. Although it is crucial to benefit from the phenolic compounds, there are unsaturated bonds in the molecular structure of polyphenols and this makes them vulnerable to oxidants, light, heat, pH, water and enzymatic activities. Therefore, the stability and shelf life of phenolic compounds should be increased by being protected from chemical and physical damage prior to its application. In order to minimize aroma degradation or loss during processing and storage, it is beneficial to encapsulate volatile ingredients prior to use in foods or beverages. A bioactive compound encapsulated in a biopolymer can be efficiently protected from harmful environmental agents like light, oxygen or water. Encapsulation is becoming increasingly important in the pharmaceutical, food, cosmetics, textile, personal care, chemical, biotechnology and medicinal industries due to its potential for stabilization and delivery of delicate and precious bioactive compounds.

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Conflicts of interest

The authors declare no conflict of interest.

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Chapter 10

Medicinal Properties of Phytochemicals and Their Production

Aanchal Bansal and Chinmayee Priyadarsini

Abstract

Phytochemicals are produced by plants as a defence mechanism against pathogens. They are used to treat various metabolic, immunological and neurological disorders in humans in various parts of the world as a part of traditional medicine. The use of indigenous plants in commercial medicine is rising with increasing population. The antimicrobial properties of plant extracts led to increased demands. Plant tissue culture on the other hand, has proved to be a reliable alternative for the production of bioactive compounds from plants. Artificial plant culture can enhance the production of phytochemicals in medicinal plants. This review focuses on the medicinal properties of phytochemicals and their in-vitro production.

Keywords: plants, health, phytochemicals, antimicrobial, metabolic, in-vitro

1. Introduction

In the modern era of medicine, plants are still used as traditional mode of healthcare against certain disorders [1]. Plants can protect themselves from pathogenic microorganisms, harmful insects and adverse environmental changes by producing certain chemicals or secondary metabolites which are non-nutritive [2], but useful in defence mechanism. These are known as Phytochemicals, and somewhat essential oils. It can not only protect plants, but also humans and animals against certain diseases which are either caused by microorganisms or toxins produced by the microorganism. This is due to its antimicrobial property [3]. In future, phytochemicals can be used as chemo-preventive agents [4]. Till date, a number of phytochemicals have been discovered based on difference in chemical structure and have been classified as major groups [5]. The major groups of phytochemicals are phytosterols, flavonoids, terpenoids, saponins, alkaloids, carotenoids, aromatic acid, organic acid, essential oils and protease inhibitors [6]. Due to certain properties like antimicrobial, anti-inflammatory, anthelmintic, anticarcinogenic, antigenotoxic, antiproliferative, antimutagenic and antioxidative, the metabolites can provide direct or indirect defensive mechanism against pathogens or harmful ailments [7] (**Figure 1**).

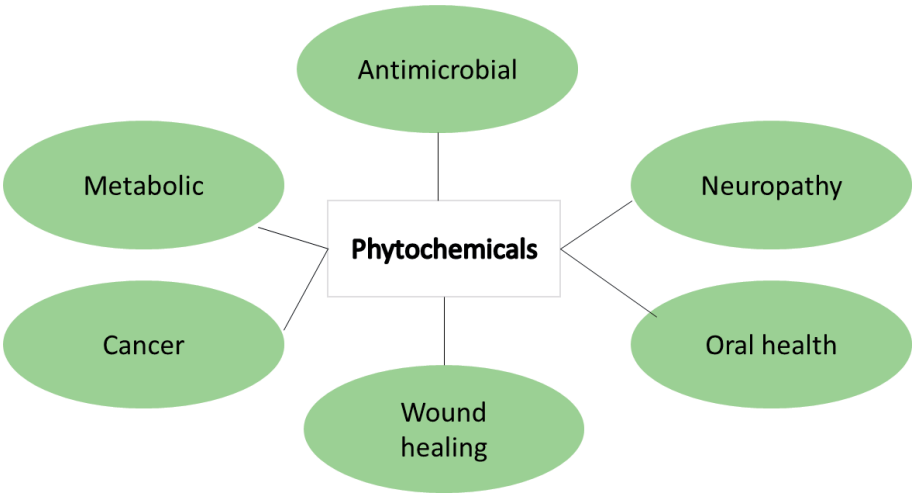

Figure 1.
Medicinal properties of phytochemicals.

2. Antimicrobial properties

2.1 Antibacterial

Helicobacter pylori colonises on the epithelial layer of gastric mucosa and cause peptic ulcers and adenocarcinoma of distal stomach. Successful treatment of *H. pylori* infection has been observed by combination treatment of a proton pump inhibitor with two antibiotics. The bacterium has evolved and become resistant to the antibiotics [8]. Thus, there is a need to find alternative to current antibiotics. Recently, certain plant extracts and substances have been isolated such as alkaloids, polysaccharides and flavonoids which have shown effective cure against *H. pylori* infection. *Daucus carota* (carrot) seed oil has been found most effective against *H. pylori* in vitro [9].

Mycoplasmas are microorganisms lacking a rigid cell wall. Generally, their physiological habitats are plants and animals, but they can cause infection to humans. Furneri et al. [10] in his recent experiment has exposed 25 clinically isolated strains to TTO (Tea Tree Oil). They used broth microdilution assay to determine the MIC values.

Diseases like pneumonia, sinusitis, bronchitis, tonsillitis and viral infections such as common cold develop due to bacterial infection in the respiratory tract and the microorganisms commonly related to this infection are *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae* and *Moraxella catarrhalis*. Traditionally, essential oils have been in use for the treatment of respiratory tract infections. They are either inhaled by steam, administered orally or applied by rubbing on the chest due to its secretolytic and secretomotoric properties. Except *Streptococcus pyogenes*, all other respiratory tract infecting microorganisms are susceptible to essential oils extracted (*in vitro*) from lemon grass (*Cymbopogon citratus*), lemon balm (*Melissa officinalis*), cinnamon bark (*Cinnamomum verum*) and thyme (*Thymus vulgaris*). Essential oils from peppermint (*Mentha piperita*) and eucalyptus (*Eucalyptus globulus*) can also be used but it shows low activity. Most of the active essential oils showed antibacterial effect at a concentration ranging from 1.56 to 6.25 μg/ml in its gaseous phase [11]. Thus, these can used to treat the infection by inhalation. Tea tree oil (TTO) is used worldwide in sectors including skin care cosmetics, nursing, and for successful treatment of bacterial

and fungal infections [12]. It showed high antibacterial activity against *S. aureus* both *in vitro* and in vivo [13].

2.2 Antiviral

Natural products in the form of pure compound or as a plant extract can be used as antiviral drugs due to unmatched availability of chemicals [14]. Besides certain chemicals, natural products can be used as novel therapeutic agents for treatment of various diseases including viral infections. Viral infections have resisted prophylaxis as compared to than other microorganisms which is of major concern worldwide. Currently, very few antiviral medicines are available and there is a need to find new substances showing both extracellular and intracellular antiviral properties. The parameters commonly taken into consideration during evaluation of antiviral property of a substance (may be natural or synthetic) are reduction in the virus yield, inhibition of cytopathic effects, reduction or inhibition of plaque formation, and other viral functions in selected host cell cultures.

Scientific evidences have shown human viral infections can be treated by plant-derived phyto-antiviral agents produced in vitro [8]. To investigate the antiviral activity of essential oils, they were tested against enveloped and non-enveloped RNA and DNA viruses. Most of the tests were performed against the former such as herpes simplex virus type 1 and type 2 (DNA viruses), dengue virus type 2 (RNA virus), influenza virus (RNA virus) and Junin virus (RNA virus). Only a few essential oils such as oregano (*Origanum vulgare*) oil and clove (*Syzygium aromaticum*) oil were tested against non-enveloped viruses such as adenovirus type 3 (DNA virus), poliovirus (RNA virus), and coxsackievirus B1 (RNA virus).

Herpes simplex virus type 1 (HSV-1) causes infections such as herpetic encephalitis, herpetic keratitis, mucocutaneous herpes infections and neonatal herpes. For the treatment of this infection Acyclovir is used which is a nucleoside analogue and a selective anti-herpetic agent. It inhibits the replication of viral DNA through viral thymidine kinase, inhibition its synthesis. But, resistant HSV strains against this drug have been isolate from immunosuppressed hosts, such as patients suffering from AIDs and malignancy, and patients undergoing bone marrow or organ transplants [15]. Recent researches have demonstrated the antiviral effect of certain essential oils against these resistant HSV strains [16].

Currently, Coronavirus disease of 2019 (COVID-19) is a global threat. Unfortunately, very limited drugs have shown effectiveness against SARs-CoV-2 virus and its inflammatory complications [17]. Combinations of certain medicines are used such as antiviral (remdesivir), dexamethasone, antimalarials (chloroquine/hydroxychloroquine), and IL-6 receptor blocking monoclonal antibodies (tocilizumab), for the treatment of the disease. Studies have proposed essential oils showing activity against the SARs-CoV-2 virus due to various properties such as antiviral, anti-inflammatory, broncho dilatory, immuno-modulatory. Since essential oils have lipophilic nature, it can easily penetrate the viral membrane causing its membrane disruption. Essential oils also contain multiple active phytochemicals which can act on multiple viral replication stages inducing positive effect on the host's respiratory system including lysis of mucus and bronchodilation. Thus, a combination of chemo-herbal essential oils could be feasible and effective to combat the pandemic virus.

2.3 Antifungal

Phytochemicals are antifungal as they can induce cytotoxicity in fungi by disrupting the membrane permeability of cell; inhibiting enzymes involved in

Effect	Microbial species	Plant extract	References
Antibacterial	*Helicobacter pylori*	*Daucus carota* (carrot) seed oil	Bergonzelli et al. [9]
	Mycoplasmas	Tea tree oil	Furneri et al. [10]
	Streptococcus pneumoniae, *Streptococcus pyogenes*, *Haemophilus influenzae* and *Moraxella catarrhalis*	Essential oils	Inouye et al. [1]
Antiviral	Herpes simplex virus type 1 (HSV-1)	Essential oils	Schnitzler et al. [16]
	Adenovirus, poliovirus	Oregano oil, clove oil	Reichling et al. [8]
	Coronavirus	Essential oils	Asif et al. [17]
Antifungal	*Aspergillus, Fusarium*	Wild stevia extract Curcumin and ellagic acid	Abdel-Fattah et al. [19] Gowda et al. [20]
	Zearalenone producing species	Lycopene	Aydin et al. [21]

Table 1.
Antimicrobial properties of phytochemicals.

mitochondria, cytoplasm and cell wall synthesis; and altering the cell compartment, and redox and osmotic balance. Some herbal plants showed antifungal and anti-mycotoxigenic activities along with antioxidant activity against phytotoxic fungal strains such as *Fusarium verticillioides*, *spergillus. Ochraceous* and *Aspergillus flavus*. The results reported, use of selected medicinal plants as bio fungicides may prevent food spoilage due to oxidation [18]. Study by Abdel-Fattah et al. reported, the extract of wild stevia shows potential antifungal, anti-mycotoxigenic and antioxidant activities against *Aspergillus flavus*, *Aspergillus ochraceus*, *Aspergillus niger*, and *Fusarium moniliforme* [19]. Besides, essential oils have the ability to regulate the growth of mycotoxigenic fungi including *Aspergillus favus*, *Aspergillus oryzae*, *Aspergillus niger*, *Alternaria alternata*, *Fusarium moniliforme*, *Fusarium graminearum*, *Penicillium citrinum* and *Penicillum viridicatum* and many more to list.

Curcumin and ellagic acid are some phytochemicals used in feed and food supplements [20]. These prevent the Aflatoxin B1 (AFB1) metabolism and increases glutathione-S-transferase activity which are involved in xenobiotic detoxification.

Red fruits and vegetables such as papaya and tomato have a compound named Lycopene. This compound has shown defensive mechanism against reproductive, hormonal damage and ZEN oxidation in mice [21]. It also prevents oxidative stress induced by T-2 toxin and maintains GSH cellular level in vivo. The antibacterial, antiviral and antifungal properties have been described in **Table 1**.

3. Metabolic disorders

3.1 Obesity

Obesity occurs due to high intake of dense energy foods (carbohydrates) along with less physical activity which is required to burn the food [22]. Overweight is related to a number of comorbidities such as type 2 diabetes mellitus, cardiovascular diseases (stroke and heart) and certain cancers (breast, prostate, kidney, colon) [23]. There are various factors which affects our weight and to reduce or maintain weight one must have a healthy lifestyle, physical activity, reduce consumption

of saturated fats, consume less sugars and salts and increase the intake of dietary vegetables and whole grains, as well as pharmacological therapies and surgical interventions [24]. Still obesity treatment is a challenging as only 5–10% of individuals are able to maintain their weight loss over years [25]. The weight loss is reversed when an individual abandons his/her healthy lifestyle or ceases pharmacotherapy [26]; also use of some synthetic drugs have side effects [27]. The pharmacological drugs can be replaced by herbal supplements which are not only efficient but also less expensive and most importantly safe.

3.2 Diabetes mellitus

Diabetes mellitus is a metabolic disorder and has increased rapidly in the past 20 years. Some medicinal plant species (*Tarchonanthus camphoratus*, *Strychnos henningsii*, *Elaeodendron transvaalense*, *Euclea undulata*, *Hypoxis argentae*, *Schkuria pinnata* and *Cissampelo campensis*) have the ability to increase glucose uptake in cultured cells such as hepatic cells, muscle cells and preadipocytes and thus, might show hypoglycemic activity by increasing peripheral glucose uptake [28]. *Cucurbita pepo*, *Senna alexandri*, *Nuxia floribunda* and *Cymbopogon citrutus* are some medicinal plants containing α-glucosidase and α-amylase inhibitors which might help in the reduction of post-prandial hyperglycemia [29]. *H. argentae* and *Carica papaya* are example of antidiabetic plants which has the ability to preserve and increase the regeneration of pancreatic β-cells resulting in increased insulin release [30]. In South Africa, diabetes treatment is done by some medicinal plants such as *Hypoxis hemerocallidea*, *Catharanthus roseus*, *Vernonia amygdalina*, *Sutherlandia frutescens* and *Mimusops zeyheri*. Although traditional practitioners have cited some medicinal plants showing antidiabetic properties, but still very few pharmacological data is available to confirm their efficiency. Also, the interaction of these medicinal plants with modern antidiabetic pharmacological drugs, its effective doses and toxicity levels are still unknown.

3.3 Cardiovascular disease (CVD)

CVD associated complications can be prevented by using anti-hypersensitive regimes to lower high blood pressure. Some traditionally used hyper-sensitive pharmaceutical drugs used are β-blockers, angiotensin receptor blockers, thiazide diuretics, calcium channel antagonists and vasodilators [31]. Several plant extracts have been identified possessing potential to treat CVDs including hypertension, congestive heart failure, ischemic heart disease and atherosclerosis [32].

For hypertension treatment, some healers of South Africa have used orally administered tincture of *Helichrysum ceres*. The hypotensive effect of the extract is due to the presence of diuretic and natriuretic bioactive phytochemical compounds [33]. In vivo studies have shown that *H. ceres* leaf ethanolic extract lowers blood pressure [34]. The extract acts on the vascular smooth muscles resulting in vasodilation which leads to total peripheral resistance (TPR) reduction. The ethanolic extract of *Ekebergia capensis* leaf prevents hypertension development in murine models. This hypotensive effect is due to the modulatory effect on TPR of vascular smooth muscles. Studies have shown that crude leaf extract of *Opuntia megacantha* can overturn the inability of kidney to excrete sodium in a streptozotocin-induced (STZ) diabetic rat model [35]. This indicates the beneficial effects of plant extracts in hypertension management by influencing the ability of kidney to regulate blood volume. *Allium sativum* (phenols and flavonoids) [36], *Sclerocarya birrea* (flavonoids and triterpenes) [37], *Ficus thonningii* (anthraquinones, flavonoids, and saponins) [38], and *Olea europea* (triterpenes, flavonoids, and glycosides) [39] are

some medicinal plants used popularly in South Africa for hypertension management due to their cardioprotective, vasorelaxant and bradycardic effects. Isolated phytochemicals from wild African olive leaves (*Olea europea*) collected from Cape Town showed anti-hypersensitive, diuretic and anti-atherosclerotic effects [40]. When insulin-resistant rat model was treated with *O. europea* extracts for six-weeks, development of hypertension and atherosclerosis was prevented displaying its potential in hypertension management in Africans.

Renin-angiotensin-aldosterone system (RAAS) is a signalling pathway in blood pressure regulation which is targeted by the phytochemical constituents of medical plants showing anti-hypertensive property. During hypertension development, angiotensin I is converted to angiotensin II by an enzyme known as angiotensin-converting enzyme (ACE) and the enzymatic inhibition of ACE is analysed while

Metabolic disorder	Medicinal plant	Mode of action	References
Diabetes mellitus	*Tarchonanthus camphoratus*, *Strychnos henningsii*, *Elaeodendron transvaalense*, *Euclea undulata*, *Hypoxis argentae*, *Schkuria pinnata* and *Cissampelo campensis*)	Increase glucose uptake	Oyedemi et al. [28]
	Cucurbita pepo, *Senna alexandri*, *Nuxia floribunda* and *Cymbopogon citrutus*	Inhibit α-glucosidase and α-amylase and reduces hyperglycemia	Boaduo et al. [29]
	H. argentae and *Carica papaya*	regeneration of pancreatic β-cells	Akinrinde et al. [30]
Cardiovascular Disease (CVD)	*Helichrysum ceres*	Lowers blood pressure	Musabayane et al. [38]
	Ekebergia capensis	Prevents hypertension	KAMADyAAPA et al. [34]
	Opuntia megacantha	Influence kidney to regulate blood volume	Bwititi et al. [35]
	Allium sativum, *Sclerocarya birrea*, *Ficus thonningii*, and *Olea europea*	Hypertension management	Al-Qattan et al. [36]; Braca et al. [37]; Musabayane et al. [38]; Bennani-Kabchi et al. [39]
	Tulbaghia violacea	Inhibition of angiotensin-converting enzyme (ACE)	Ramesar et al. [42]
Non-alcoholic Fatty Liver Disease	*Hoodia gordonii*	Suppresses the appetite	Smith et al. [44]
	S. frutescens	Modifies lipid metabolism in 3 T3 adipocytes	MacKenzie et al. [45]
	Aloe vera	Hepatoprotective activity, reduces lipid accumulation	Bhalla et al. [46]; Misawa et al. [47]

Table 2.
Mode of action of plant extracts against metabolic disorders.

screening for anti-hypertensive medicines [41]. In vitro studies have been done on South African medicinal plants to evaluate their inhibition potential against ACE. Ethanolic and aqueous extract of some medicinal plants have demonstrated inhibition activity against ACE, and they are *Tulbaghia violacea*, *Amaranthus ybridus*, *Amaranthus dubius*, *Galinsoga parviflora*, *Stangeria eriopus*, *Oxygonum sinuatum*, *Physalis viscosa*, *Justicia flava* and *Oxygonum sinuatum*. Among these medicinal plants, *T. violacea* exhibited highest activity [42]. The inhibition activity observed, is due to the presence of tannins in most of these plants as tannins interferes with the activity of ACE [43].

3.4 Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is a major cause of morbidity and mortality. The disease is generally related with obesity, but recent studies show it can also develop independent of metabolic syndrome. *Hoodia gordonii*, a succulent plant was used as an appetite suppressant and due to its appetite-suppressing property, the succulent plant can be potentially used for NAFLD management. Recent studies have shown, *Hoodia gordonii* extracts have reduced the body mass of obese rats along with reduction in muscle mass and adipocyte size [44].

S. frutescens, a legume has various medicinal properties. It not only exhibits anti-diabetic properties but recent studies have shown, it also has the ability to modify lipid metabolism in 3 T3 adipocytes as well as in insulin-resistant rats [45]. Studies have also shown, the aqueous extract of the plant can reverse fructose induced hepatic steatosis in vivo.

Aloe vera is well known for its medicinal properties against hepatic steatosis and it has also been demonstrated that its extract improves this condition in rats. Kaempferol is a bioactive compound in *A. vera* which exhibits hepatoprotective activity [46]. Lophenol and cycloartenol are some other *A. vera* phytosterols which when administered to Zucker diabetic fatty rats shows significant decrease of lipogenic gene expression and reduced hepatic lipid accumulation [47]. The mechanism of effectiveness of plant extracts in metabolic disorders is given in **Table 2**.

4. Cancer

Cancer involves uncontrolled cell growth which can be initiated by various factors. Chemoprevention is a treatment makes use of natural, biological or synthetic agents to suppress, prevent or reverse carcinogenesis in its initial phase or prevent the invasion of premalignant cells [48]. Carcinogenesis occurs in three steps, initiation, promotion and progression. At molecular level, chemoprevention has been distinguished by altering these three pathways [49]. FDA has recently approved ten new agents for the treatment of precancerous lesions, reducing the risk of cancer [50]. Clinically, chemoprevention has be grouped as primary, secondary and tertiary. The primary chemoprevention is for people with no cancer, as well as for those who have the risk of developing cancer in future. The secondary chemoprevention is suitable for patients with pre-malignant lesions which in future may lead to invasive cancer. The tertiary prevention is to cure or prevent recurrence of cancer [49].

Capsaicin (trans-8-methyl-N-vanilly l-6-nonenamide), an active and pungent alkaloid found in Capsicum [51]. It has been reported that capsaicin has been used as an anticancer, tumour suppressing, chemopreventive and radio sensitising agent in various cancer models [52]. Capsaicin exhibited its ability to reduce pain and effective against osteoarthritis when applied topically [53]. It has been used as an

alternative for oral non-steroidal anti-inflammatory drugs which had side effects. Capsaicin can be used as cancer treatment due to its properties such as carcinogens activity inhibition and inducing apoptosis in several cancer cell lines in vitro and in rodents [54].

Catechins are found in various beverages such as green tea [55]. These are naturally occurring dietary phytochemical and polyphenols. Very few studies have been reported showing association of cancer with consumption of dietary phytochemicals [56]. Major components of green tea are Catechin (C), epicatechin (EC), epigallocatechin (EGC) and epigallocatechin-3-gallate (EGCG) [57]. It has been reported that EGCG could enhance the activity of several anticancer drugs such as retinoids [58]. A synthetic retinoid, AM80, has been clinically used for relapsed and intractable acute promyelocytic leukaemia patients. A study demonstrated the use of AM80 and EGCG in combinations, induced apoptosis and upregulated the expression of inducible gene of damaged DNA including death receptor 5 (DR5), GADD153 and p21waf1 in lung cancer. The combination also showed downregulation of deacetylase 4, –5, and – 6, inducing apoptosis in lung cancer by Am80 and EGCG.

Lycopene is an antioxidant and thus shows protective effect against various diseases including cancer, hypertension, osteoporosis, cardiovascular diseases and neurodegenerative diseases [59]. Studies have been reported that lycopene accumulates in prostate tissue as compared to other tissues and this might be responsible for its anti-prostate cancer activity [60]. A study showed lycopene exhibits anti-angiogenic activity in in vitro as well as in vivo, suggesting the mechanism may involve modulation of PI3K-Akt and ERK/p38 signalling pathways [61]. Several studies have demonstrated use of lycopene and melatonin in combination showed strong chemopreventive activity through antioxidant and anti-inflammatory activities [62].

Isoflavones are isoflavonoids present in plants of leguminosae family [63]. It is extensively found in lentil, chickpeas, beans, soy and have importance in mammals as phytoestrogens. Isoflavones have several health benefits and are used for treating hormone-dependent medical conditions such cancer, cardiovascular disease, menopause and osteoporosis. Isoflavones extracted from soy, such as genistein, have been developed to have significant anticancer effects against as lymphoma, leukaemia, breast, prostate gastric and non-small cell lung cancer [64]. Studies have reported genistein showing anticancer effects in various cancer models such as breast cancer, lung cancer, ovarian cancer, prostate cancer, bladder cancer, renal cancer, cervical cancer, liver cancer, and head and neck squamous cell carcinoma [65].

Chemotherapy is an approach for cancer treatment but has several undesired side effects, including chemotherapy-induced peripheral neuropathy (CIPN) [66]. Recent studies have reviewed the preclinical and clinical studies on the efficiency of herbal medicines in CIPN. Cinnamon (*Cinnamomum cassia* (L.) D. Don), chamomile (*Matricaria chamomilla* L.), sage (*Salvia officinalis* L.), and sweet flag (*Acorus calamus* L.) are some medicinal plants, and curcumin, thioctic acid and matrine are some phytochemicals which have shown effective properties in CIPN animal models.

5. Oral health

Oral health reflects the physical and social well-being of an individual. The food consumed affects the oral health as they are naturally bioactive and is composed of minerals, vitamins and antioxidants [67]. Aromatic vegetables and spices used in it are not only appetising and savoury but also has therapeutic and preservative properties. Foods we consume have a number of benefits such as antibiotic,

anti-inflammatory, anticarcinogenic and immunogenic properties. A study shows, vegetables (more than 440 g/day), fruits and spices rich diet can prevent 20% of all cancers [68]. According to a WHO report, there is 15% chance of suffering from oropharyngeal cancers due to dietary imbalance or deficiencies [69]. The people of Asia, USA and Europe suffer from oral squamous cell carcinoma due to low antioxidant and fibre intake. Many studies have proved that antioxidants and fibres exhibit chemotherapeutic and chemo-preventive properties.

In Mexico, various herbal therapies are used for the treatment of oral disorders such as mouth infection, teeth discoloration, gingivitis and periodontitis [70]. Even though, very less research has been performed demonstrating the antiplaque, antimicrobial and antibacterial effects of Mexican herbs, they can still me used for treating several periodontal diseases or as anticarcinogenic agent [70].

6. Wound healing

Wounds are injuries caused physically due to skin rupture which may lead to anatomical or functional disorders. Wound healing is a complex and dynamic process leading to reformation of tissue integrity and homeostasis [71]. The process involves inflammation, tissue formation, neovascularization, reepithelization, extracellular matrix remodelling and wound contraction. The process is coordinated by various signalling mechanism involving numerous growth factors, chemokines and cytokines. During the process, cell proliferation is necessary for tissue repair and its regeneration [72].

For more than 500 years, "Ayurveda" has been practiced in India to prevent and cure diseases. The process utilises plants for disease prevention and cure. Traditional Chinese medicine system has been in use all over eastern Asia for over 3000 years and it uses numerous medicinal plants [73]. Modern science has analysed the traditional medicinal plant species to identify bioactive constituents present in it and as many as 12 medicinal plants have undergone clinical trials with regard to their wound healing property.

7. Production

Plants immediately activate their defence mechanism when they are attacked. This also includes the biosynthesis of phytochemicals which occurs rapidly resulting in reduction of nutrients and amino acids. But the optimization of mass production of phytochemical is still unknown.

An efficient way for phytochemical production is creation of metabolic highways through protein complexes known as metabolons. Three decades ago, the existence of metabolons was first proposed. But it's in vivo protein–protein interaction and structures are still challenging. Metabolons are involved in metabolic pathways, mostly primary and secondary including lignin, Krebs cycle and flavonoid pathways [74]. For the biosynthesis of toxic cyanogenic glucoside dhurrin which highly gets accumulated in sorghum, metabolons are essential (*Sorghum bicolor*) [75]. Metabolons can efficiently produce inducible phytochemicals. The biosynthesis efficiency can be increased by assembling the sequential enzymes of a pathway into a single protein complex and would also limit release of harmful or reactive intermediates. In these protein complexes, the phytochemical intermediates are released only when the metabolon is disassembled. Th 2019, Mucha et al. studied if a metabolon channels the biosynthesis of an essential defence metabolite in Arabidopsis (*Arabidopsis thaliana*), known as camalexin [76]. The biosynthesis of camalexin is an

enzyme catalysed multi-step reaction and from tryptophan (Trp) various intermediates are generated which have been detected in knockout genotypes [77].

In vitro plant production is a solution which is favoured by biotechnologists. The in vitro technology allows to produce plants uniformly by controlled manipulation of environmental condition, growth regulators, and strategies that can enhance production as well as overall yield of phytochemicals. The naturally occurring instable chemical composition in plants can avoided by growing them on media prepared according to strict recipes for plant's nutritional necessities under controlled environmental conditions including temperature, light duration and intensity [78].

The most efficient method for in vitro secondary metabolite production is plant micropropagation. This is a technique that uses clonal propagation to produce plants which are identical genetically as well as free from pathogens and contaminants, and this process requires very less space, time and supplies. A study demonstrated in vitro culture of tansy (*Tanacetum vulgare*) from seeds collected from natural population for production of secondary metabolites such as essential oils and methanol extracts [79]. Studies have reported, the use of plant growth regulators exogenously (auxin and cytokinin) might hinder genetical stability leading to somaclonal variation, which is undesirable for in vitro plant production when used for isolation of secondary metabolites [80].

8. Conclusion and future perspectives

The non- nutritive part of the plants that is, phytochemicals have antimetabolic, anti-cancer, anti-neurological and wound healing properties. They also help in maintaining oral health. The antimicrobial nature of phytochemicals has led to its increased demand. To meet the requirements of modern medicine, plants and their extracts are cultured in vitro. The use of huge bioreactors and mass propagation has led to the establishment of inexpensive and efficient method for phytochemical production. The regulation of in-vitro conditions to multiplication can be a promising technique for medicine.

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Chapter 11

The Structure and Function of Alkamides in Mammalian Systems

Stephanie E. Johnstone and Scott M. Laster

Abstract

Alkamides, or alkylamides, are fatty acid amides produced by plants from the genera *Echinacea, Acmella, Spilanthes,* and *Heliopsis* among others. Alkamides contain varying head groups, an amide moiety, and a fatty acid tail with varying numbers of carbons and double and triple bonds. Extracts from these plants have been used worldwide by native peoples for the treatment of numerous medical disorders, including bacterial and viral infections, inflammation, liver and kidney disorders, and pain. *In vitro*, these molecules display a variety of different activities depending on the cell type tested. Studies with neurons, macrophages and mast cells have revealed interactions between alkamides and a number of different cells surface receptors and intracellular signaling molecules. Generally, the alkamides have been found to exert suppressive effects, inhibiting cellular activation. In this report we introduce the structure of alkamides and review their effects in a number of different cellular systems. We also describe structure:function studies that have been performed with alkamides. While these studies have not as yet revealed general rules for alkamide activity, interesting insights have been revealed. The stage is set for the development of synthetic, designer alkamides with targeted *in vivo* activities.

Keywords: alkamide, inflammation, immunity, nocioception

1. Introduction

The alkamides, also known as alkylamides, are fatty acid amides which vary in structure and function. Alkamides are found in nature in over 100 plant species, where they are thought to act as a defense against herbivory [1]. Alkamides contain a fatty acid tail, which can vary in the number of carbons and unsaturations, an amide group, and a variable headgroup. The structure of the alkamide dodeca-2E,4E-dienoic acid isobutylamide (A15) from *Echinacea,* which contains an isobutyl headgroup is shown in **Figure 1**. The structures of several other alkamides that have been studied extensively are also shown in **Figure 1**, including spilanthol, pellitorine, sanshool, and capsaicin. Spilanthol, which is found in many plants, including several species in the *Acmella* and *Spilanthes* genera and *Heliopsis longipes*, has 10 carbons and three double bonds in the fatty acid region. Historically, the most common usage for spilanthol has been as an analgesic. Plants containing spilanthol are often called "toothache plants" where the plant matter is chewed, causing a local numbing sensation in the mouth [2]. Pellitorine, found in plants from the *Piper* genus, is similar in structure to A15 from *Echinacea*, with two less carbons and two unsaturations in the fatty acid chain. Sanshool is found in plants in the *Zanthoxylum* genus which includes the Szechuan peppercorn. A number of analogs of sanshool have been identified

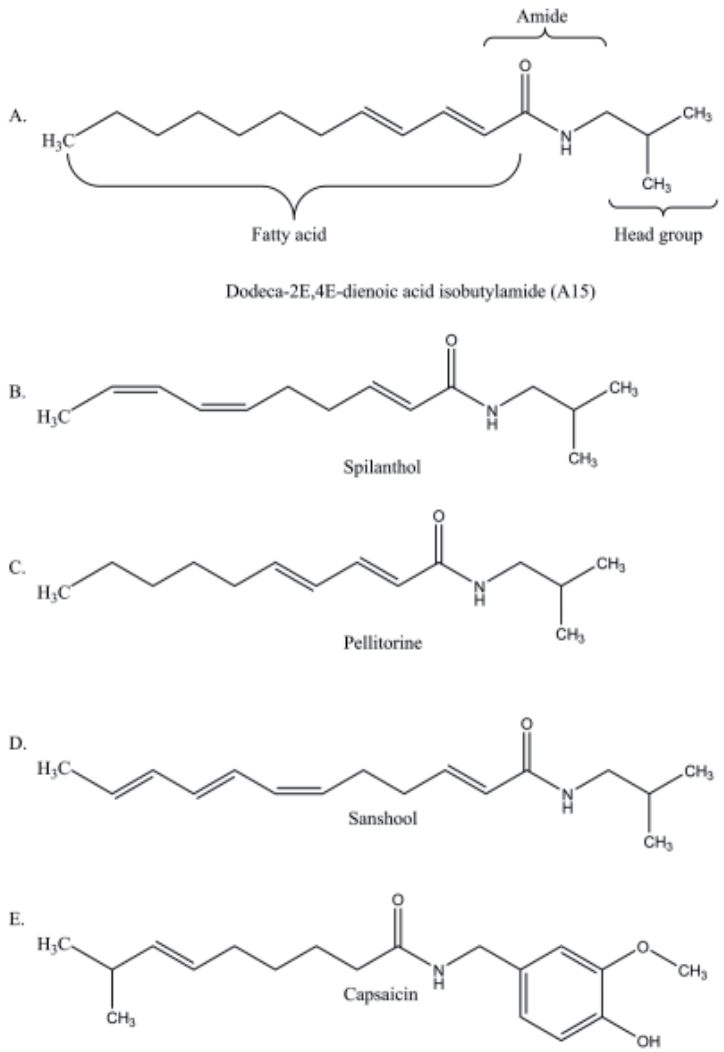

Figure 1.
General structure of alkamides. A. Dodeca-2E,4E-dienoic acid isobutylamide (A15) is shown above as a representation for the general alkamide structure. Other alkamides from Acmella/Spilanthes *(spilanthol) (B),* Piper nigrum *(pellitorine) (C),* Zanthoxylum *(sanshool) (D), and* Capsicum *(capsaicin) (E). Structures B-E are from Boonen et al. [1].*

with hydroxy-α-sanshool believed to be the major bioactive compound in most plant extracts [3]. Hydroxy-α-sanshool contains 12 carbons with multiple double bonds in the fatty acid chain and a hydroxyl group for the headgroup. Capsaicin, which contains a nine-carbon fatty acid, contains methyl groups on the fatty acid chain and an unsaturation at the sixth carbon. Capsaicin also contains an aromatic head group, and through its ability to activate the transient receptor potential (TRP) TRPV1 receptor, is responsible for the painful sensation associated with "hot peppers" [4].

2. Alkamides in plants used in traditional medicine

2.1 Echinacea

Alkamides occur in the flowering plants of the *Echinacea* genus, including the species *purpurea*, *angustifolia*, and *pallida* [5]. Alkamide containing *Echinacea*

extracts have been used historically by a variety of peoples including numerous Native American tribes for a wide range of purposes including treatment of infected wounds, rabies, or painful conditions such as toothaches or snakebites [6]. In 1805, Lewis and Clark learned about the use of this medicinal plant on their famous expedition and mailed seeds and roots to President Jefferson noting it as one of their important finds [6]. Today, *Echinacea* extracts are used to treat a variety of conditions- most often the common cold, but also bronchitis, upper respiratory infections, and more generally as an anti-inflammatory [7, 8]. Recently, the role of the alkamides in the uses for *Echinacea* have been studied by a number of labs.

Alkamides from *Echinacea,* such as A15, have been shown to act on a variety of cell types, including many immune cells such as macrophages, mast cells, and T cells, and also neurons [9–11]. In immune cells, A15 suppresses activation of pro-inflammatory responses such as production of pro-inflammatory cytokines and chemokines, which may account for the reduction of symptoms when *Echinacea* is used to treat respiratory infections [11]. In addition to the modulation of important inflammatory cytokines, alkamides from *Echinacea* are useful in inhibiting activation of mast cells and T cells, which has been linked to the inhibition of calcium-dependent signaling [10]. In neurons, alkamides have been shown to block ion channel activity leading to analgesia, which further reinforces their use to relieve symptoms caused by the common cold or respiratory infections [9]. *Echinacea* extracts have also been tested successfully in clinical trials to treat eczema where a significant reduction in local inflammation was noted [12].

2.2 *Piper longum* and *Piper nigrum*

Plants containing alkamides have not only been used by Native Americans, but they have also been used by people around the globe in China, Mexico, Brazil, Africa, Europe, and India [13]. *Piper* species, such as the long pepper, have been used in traditional medicine to treat a range of conditions such as chronic bronchitis, asthma, viral infections, and diarrhea and their use first appeared in texts by Hippocrates [14]. The plant *Piper longum* L., which contains 16 known alkamides, has been used to treat stomach conditions in ancient Chinese medicine and in traditional Indian medicine to treat abdominal pain and disease, among other diseases and disorders [15, 16]. Modern research has shown that these alkamides can increase melanin content and tyrosinase activity in melanoma cells [15] leading to suggestions that *Piper* extracts might produce an anti-melanoma affect. In addition, pellitorine displayed a strong cytotoxic activity in a study with two tumor-derived cell lines [17]. Alkamides isolated from *Piper longum* have also been shown to suppress NF-κB activation and inhibit the activity of COX-1 and -2 [18]. Inhibition of prostaglandin synthesis was also observed in ionophore stimulated leukocytes treated with pellitorine containing *Piper* extracts [19]. Finally, pellitorine has also been shown to be an effective insecticidal agent against the housefly and *Aedes aegypti* mosquito [20, 21].

2.3 *Phyllanthus*

Traditional healers in India have used the plant *Phyllanthus fraternus* to treat liver disorders, mixing the plant into a paste or using a plant extract [22]. Aqueous extracts from the plant, which are used by Indian healers, possess antioxidant activity and can prevent the oxidation of lipids and proteins [23]. In isolated hepatocyte mitochondria, the extracts are protective against alcohol induced oxidative stress [24]. *Phyllanthus sp.* have also been used in Ghana as an anti-malarial treatment and two alkamides E,E-2,4-octadienamide and E,Z-2,4-decadienamide (both of which lack the alkyl residue on the amine group) are thought to contribute to their anti-malarial activity [25].

2.4 *Spilanthes*

In Mexico, alkamide containing *Spilanthes* plants have been used as insecticides as well as analgesics [26]. In Africa and India, *Spilanthes acmella* is used as a medication to treat malaria [27]. In regions of Brazil, extracts from these plants have also been used as a female aphrodisiac [28]. Spilanthol is the predominant alkamide found in *Spilanthes sp.* with several other alkamides reported in lesser quantities [29]. Commercial preparations of spilanthol are as available for use as oral analgesics and to provide a long-lasting mint flavor in toothpastes [2]. In animal models, analgesia was demonstrated using a *Spilanthes* extract and was found to reduce murine hind paw edema and acetic acid induced tail flick in a dose dependent manner [30]. Spilanthol displays structural similarities to capsaicin, the ligand for the nociceptor channel TRPV1, which may account for its analgesic properties [23]. Isolated spilanthol also displays immunomodulatory properties *in vitro* causing dose dependent reduction in macrophage activation and nitric oxide (NO) production, as well as inhibition of cytokine production and NF-κB activation [31]. Other uses for spilanthol have been investigated including as an antipyretic, antimicrobial, antifungal, diuretic, and vasorelaxant [32].

2.5 *Zanthoxylum clava-herculis*

Zanthoxylum clava-herculis, also known as the toothache tree, Hercules' club, or prickly ash, has been used as a medical plant by Native Americans. In East Asia this plant is used as an analgesic, an antimicrobial, and for the treatment of kidney and liver disorders (Pawlus et al.; [33]). For example, extracts from the bark of *Zanthoxylum* display antimicrobial activity against Gram negative and Gram positive bacteria, and yeast *in vitro* [34]. Several alkamides have been isolated from *Zanthoxylum clava-herculis* including α-sanshool, and the presence of these molecules may explain the activities of this plant [35]. The alkamides in *Zanthoxylum clava-herculis* extracts have been shown to bind cannabinoid receptors, perhaps suggesting the mechanism of analgesic action [36].

2.6 Additional plants

Alkamides have been identified from a variety of other plants representing over 30 different plant families [23] although the role of the alkamides in the activity of the plant extracts has not been thoroughly defined. A few come from the *Solanaceae* family such as *Capsicum annuum* L. which has been used to treat otitis, infections, rheumatism, and headache [1]. Alkamides have also been identified in another plant from the same family, *Nicotiana tabacum* L., which is used in Africa to treat convulsions and as a stimulant [1]. Extracts of *Ricinus communis* L., which is a member of the *Euphorbiaceae* family, contains alkamides and is used by Mediterranean and African cultures to treat respiratory illness, rheumatic pain, and acne [37].

3. Alkamide cellular activities

3.1 Macrophages

Macrophages are important innate immune cells involved in organ homeostasis and defense against microbes [38]. Excess macrophage activation can, however, result in pathophysiological damage [39] and, therefore, it is necessary to identify immunomodulatory compounds which can dampen macrophage responses. Alkamides have been shown to display this activity *in vitro*. For example, alkamides have been shown

to inhibit LPS-induced TNF-α production by human monocytes/macrophages [40]. The authors propose that this effect is mediated by alkamides binding to type 2 cannabinoid receptors (CB2) and altering downstream signaling via cAMP, p38/MAPK, and JNK molecules [40]. CB2 is highly expressed on innate and adaptive immune cells, with the capability to down-regulate cellular activity, and has been proposed as an important therapeutic target [41]. Subsequently, it was shown that the alkamides dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide and dodeca-2E,4E-dienoic acid isobutylamide bind the CB2 receptor directly, with a higher affinity than endogenous cannabinoids, and that binding was associated with increased intracellular calcium level and IL-6 expression. However, contradictory to previous work, it was shown subsequently that the effect on TNF-α, IL-1β, and IL-12p70 expression was independent of CB2 binding [42]. Therefore, there may be multiple cellular targets of alkamides resulting in inhibition of both CB2-dependent and CB2-independent pathways leading to modulation of cytokine production. Taken together, these results demonstrate that alkamides are able to directly bind an important cell surface receptor, with known anti-inflammatory activity, as well as inhibit pro-inflammatory cytokine production through alternative, undefined mechanisms.

Alkamide effects on macrophages have also been studied during viral infection. During infection with influenza A, macrophages are key in elimination of the virus and can also contribute to the symptoms and pathology of influenza A by causing overproduction of inflammatory mediators [43]. It was found that alkamides undeca-2Z,4E-diene-8,10-diynic acid isobutylamide, dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide, dodeca-2E,4E-dienoic acid isobutylamide, and undeca-2E-ene-8,10-diynoic acid isobutylamide from *Echinacea* were able to inhibit influenza-induced TNF-α and prostaglandin production, with dodeca-2E,4E-dienoic acid isobutylamide also strongly inhibiting chemokine CCL2, CCL3, and CCL5 production [44]. The inhibition of these mediators may explain the relief from symptoms seen in certain individuals when *Echinacea* extracts are used to treat influenza A.

3.2 T cells

Thymus-derived lymphocytes, or T cells, are a type of lymphocyte whose activity is critical to the immune response to infection, allergic reactions, and cancer [45]. Alkamides have been shown to inhibit IL-2 production in a dose dependent-manner from Jurkat T cells and the effects were independent of cytotoxicity [46]. IL-2 production is an important signaling molecule in T cell function and differentiation and decreasing IL-2 production may limit T cell activation and proliferation reducing the adaptive immune response. On the other hand, reducing IL-2 production in certain situations may have a beneficial effect by decreasing production of pro-inflammatory cytokines [47]. In support of this hypothesis, mitogen-stimulated splenocytes harvested from mice treated with *Echinacea*, produced significantly less IL-1β and TNF-α [48]. These mice also showed enhanced levels of T cell proliferation, both mitogen-induced and in the absence of mitogens. Stimulation of T cell proliferation was also observed using a commercial preparation of *Echinacea augustifolia* in which murine T cells were stimulated with anti-CD3 and the commercial *Echinacea* product [49]. Finally, T cell calcium responses were also found to be inhibited follow ionophore stimulation upon treatment with dodeca-2E,4E-dienoic acid isobutylamide (T. V. [10]).

3.3 Mast cells

Alkamides have been shown to be biologically active against mast cells. Mast cells are myeloid derived immune cells with key roles in regulation of vascular homeostasis, immune responses, and angiogenesis and have important functions in diseases such as

allergy, asthma, cardiovascular disorders, and gastrointestinal diseases [50]. A15 from *Echinacea* was demonstrated to inhibit mast cell degranulation, histamine release, and calcium influx in both primary bone marrow-derived mast cells and the mast cell-like cell line RBL-2H3 [10]. Because A15 was able to block granule release following ionophore stimulation, as well as FCεRI crosslinking, A15 must act on molecular targets regulating both stimulation pathways. Additionally, A15 inhibited TNF-α and prostaglandin E_2 production following ionophore stimulation. In an atopic dermatitis model, mast cell tissue infiltration was diminished following treatment with spilanthol [51]. *In vivo*, oral administration of N-(2-hydroxyethyl) hexadecanamide downregulated mast cell activation and pathology associated with mast cell activation such as edema [52]. In an asthmatic model using OVA-sensitized guinea pigs, *Echinacea* treated animals displayed a significant reduction in exhaled nitric oxide which has been shown to be partially produced by mast cells in asthmatic disease [53].

3.4 Neurons

A popular therapeutic use for alkamides is as pain relievers. Numerous groups have now reported on the analgesic effects of alkamides *in vitro* and *in vivo*. There are multiple types of pain receptors, with different specific receptors mediating mechanical and thermal pain. The neurons bearing these receptors are categorized as C-fibers, which are unmyelinated and small in diameter, and A-fibers, which are myelinated and quick to respond to stimuli mediating "initial fast-onset pain" [54]. Using the alkamide hydroxy-α-sanshool, from the *Zanthoxylum* plant, a selective inhibition of mechanical pain via inhibition of voltage-gated sodium channels on Aδ mechanonociceptors was observed in mice under both naïve and inflammatory conditions, with no influence on thermal pain [55]. Hydroxy-α-sanshool also altered activity levels of cool-sensitive fibers and cold nociceptors in extracellular nerve recording from the lingual nerve in rats [56]. Sanshool was also found to target channels TRPV1 and TRPA1 [57]. Alkamides from *Acmella oleracea* and a synthetic isobutylalkylamide showed long lasting *in vivo* analgesic efficacy when mice were pretreated with the alkamide 15 minutes prior to carrageenan injection to induce pain [58]. Alkamide dodeca-2E,4E-dienoic acid isobutylamide was demonstrated to be biologically active in the central nervous system in mice following intraperitoneal injection and dependent on interaction with the voltage-gated sodium channel, particularly Nav1.8 [59]. TRPV1, a non-specific cation channel that is the receptor for capsaicin and found on neurons, has been shown to be sensitive to isobutylalkylamides [60]. Using *in vitro* dorsal root ganglion cultures, neurons responded to the application of a synthetic isobutylalkylamide with an increase in intracellular calcium in a manner similar to activation by capsaicin [61]. This supports the analgesic effects observed with alkamides due to TRPV1 repeat activation of the channel leading to desensitization and lack of responsiveness [62]. Alkamides, such as pellitorine, also directly inhibit TRPV1 activation by acting as an antagonist which additionally explains the commonly observed analgesic effects [12]. This points to dual actions of alkamides as both TRPV1 agonists and antagonists, which can both lead to channel inactivation and pain relief. Interestingly, low dose synthetic isobutylalkylamide administration was shown the be anti-nociceptive, whereas high doses induced nociceptive behaviors in mice, with the authors suggesting the anti-nociceptive effects arising from blocking of ion channels [63]. Further, lingual application of synthetic isobutylalkylamide activated mechanosensitive neurons through modulation of potassium channels in human testing and caused a tingling sensation, while repeated exposure to the isobutylalkylamide causes desensitization of the channels and lessened tingling [64] supporting the concept of inhibition of neuron activities through desensitization of ion channels.

3.5 Liver and pancreatic cells

Alkamides have be tested as therapeutics for dietary and nutritional disease, particularly in diabetes. For example, daily oral administration of alkamides to diabetic rats was shown to significantly decrease fasting blood glucose level, and total liver cholesterol, and to relieve organ enlargement through activation of the AMPK signaling pathway which reduced fatty acid synthesis [65, 66]. Additionally, alkamides from *Zanthoxylum* were found to cause activation of the mTOR pathway in diabetic rats and ameliorate their protein metabolism disorder [65, 66]. Alkamides from the same plant also increased glucose metabolism preventing hyperglycemia and pancreatic dysfunction through modulation of the main enzymes regulating gluconeogenesis as well as improved amino acid metabolism [67, 68].

3.6 Cancer cells

Alkamides have also been investigated as treatments for cancer. For example, alkamide derivatives of bexarotene were able to induce apoptosis and prevent cell migration and proliferation in triple-negative breast cancer cells, while showing no cytotoxic effects against normal mammary epithelial cells [69]. In addition, a panel of alkamides with varying structure and molecular weights were able to induce differentiation of human leukemia cells to granulocyte-like cells [70].

4. Structure: function studies

4.1 Fatty acid chain saturation

The differences in cellular uptake based on structure could also explain the differences seen in biological activities of alkamides. A number of labs have asked how the structure of various alkamides contributes to their activities. For example, the importance of double bonds in the fatty acid chain was evaluated by measuring inhibition of cytokine production from LPS-stimulated RAW 264.7 macrophage-like cells. Similar levels of inhibition of TNF-α was observed with synthetic versions of dodeca-2E,4E-dienoic acid isobutylamide which all have 12-carbon tails with zero, one, or two double bonds indicating that unsaturated bonds are not required for inhibitory effect [71]. Further, 11–12 carbon isobutylamides containing a double bond at position C2 were found to inhibit chemically induced TNF-α production from human blood, RAW 264.7 macrophage-like cells, and other cell lines [1, 44].

The presence of multiple alkyne groups in the fatty acid chain was also investigated. Alkamides with multiple alkyne groups inhibited the activity COX enzymes, and at higher levels, inhibited prostaglandin E_2 production [44, 72]. Both alkamide A15 and pellitorine, which have highly similar structures, including their fatty acid chain inhibit ionophore stimulated prostaglandin production [19]. Interaction with the endocannabinoid receptor CB2 has been shown to occur with unsaturated alkamides with 11–14 carbons, but there was no affinity observed for *all-trans* tetradeca-2E,4E,8E,10E-tetraenoic acid IBA, indicating specific structural requirements for alkamide receptor interaction [1]. One group showed alkamides required a double bond at the C2 position for interaction with CB2 receptors with a second double bond at C4 increasing affinity, but not required for receptor interaction [1, 59]. Finally, a possible role for double bonds came from studies of the endocannabinoids where it was noted that the alkamide N-benzyl-(9Z,12Z)-octadecadienamide double bonds closely mimic those in endocannabinoid substrates [73].

The number and placement of double bonds has also been shown to impact the ability of alkamides to cross cell barriers. Using a Caco-2 cell monolayer, spilanthol and pellitorine, both 10 carbon alkamides but variable in position and number of double bonds, were tested for their ability to cross the monolayer. Spilanthol transport was significantly better than was the transport of pellitorine, suggesting that the placement and number of double bonds can affect transport [74]. A systematic analysis of bond number and position, and how they affect transport has not been performed.

Positioning of double bonds in spilanthol analogs between carbons two and five altered the physiological activity, with most activity resulting from double bonds at positions two and four [75]. The necessity of double bonds in the fatty acid chain was also evaluated for the activity of α-hydroxysanshool. Unsaturations were found to be required for interaction with TRPA1, but not TRPV1, perhaps indicating that different regions of the alkamide interact with the two receptors [57].

4.2 Fatty acid chain length

Experiments with alkamides using RAW 264.7 macrophages found that the number and placement of double bonds did not affect the activity, however, the length of the fatty acid chain did impact activity with these cells, with shorter fatty acid chains eliminating anti-inflammatory activity [71]. The length of the fatty acid chain was investigated using synthetic variants of dodeca-2E,4E-dienoic acid isobutylamide in an LPS activated RAW 264.7 cell model system. Alkamides with fatty acid tails shorter than 12 carbons did not significantly inhibit LPS-stimulated TNF-α cytokine production, indicating that longer fatty acid chains are required for this activity [71].

Alkamide fatty acid chain length was also evaluated in mast cells with alkamide analogs of varying chain lengths tested for their ability to inhibit intracellular calcium influx and mast cell degranulation. It was found that the shortest (four carbon) and longest (15 carbon) analogs were poor inhibitors of both degranulation and intracellular calcium influx [76]. Interestingly, there seemed to be differences in the optimum chain length and maximum inhibition for calcium influx and degranulation, perhaps suggesting different cellular targets responsible for inhibitory effects. For degranulation, the optimum chain length was eight carbons and for inhibition of calcium influx it was 12 carbons.

4.3 Head group

The head group was also investigated using LPS-stimulated RAW 264.7 cells and results indicated that head group substitutions were well tolerated with biological activity retained with most substitutions [71]. Addition of a carbon into the isobutyl head group did not significantly affect cytokine inhibition, and replacement of the isobutyl group with a benzyl group or six-carbon alkyl chain lessened inhibition, but the molecule was still biologically active [71]. Finally, altering of the amide functional group through addition of a thiazole group rendered the molecule inactive, thus demonstrating the importance of the amide [71]. In other studies using alkamides with benzyl headgroups, some showed affinity for CB2 receptors, which had been previous reported for isobutyl headgroups, with most activity seeming to come from the presence of an alkyl chain with 2 double bonds, rather than the identity of the headgroup [1]. Together, these studies suggest that fatty acid chain length and the amide are the critical determinants of alkamide activity.

5. Summary

Alkamides have been in use in traditional medicine for centuries across cultures worldwide. Alkamides are found in a large number of plant species including those in the genera *Echinacea*, *Piper*, *Phyllanthus*, *Zanthoxylum*, and *Spilanthes*, among others. Some alkamide containing products have made to commercialization in the 21st century such as splinathol in oral products and capsaicin creams. Currently, significant progress has been made into understanding alkamide activity and their use as therapeutics, although many questions regarding the molecular mechanism of alkamide action remain unanswered. At a cellular level, alkamides act on a variety of cell types including mast cells, macrophages, T cells, and neurons and alkamides are able to cross important cellular barriers including the blood–brain-barrier and the gut epithelial barrier. Modulation of cellular activity results in changes in cytokine and chemokine production, as well as cellular activation and signaling. Alkamides may be useful in dietary and nutritional settings with some studies demonstrating efficacy in mitigating effects of diabetes in mice. Additionally, some progress has been made in linking alkamide structure to activity, which could aid in the development of highly targeted drugs. Overall alkamides provide a promising class of plant derived compounds which should be considered when designing and evaluating novel therapeutics.

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Chapter 12

The Contribution of Javanese Pharmacognosy to Suriname's Traditional Medicinal Pharmacopeia: Part 1

Dennis R.A. Mans, Priscilla Friperson, Meryll Djotaroeno and Jennifer Pawirodihardjo

Abstract

The Republic of Suriname (South America) is among the culturally, ethnically, and religiously most diverse countries in the world. Suriname's population of about 600,000 consists of peoples from all continents including the Javanese who arrived in the country between 1890 and 1939 as indentured laborers to work on sugar cane plantations. After expiration of their five-year contract, some Javanese returned to Indonesia while others migrated to The Netherlands (the former colonial master of both Suriname and Indonesia), but many settled in Suriname. Today, the Javanese community of about 80,000 has been integrated well in Suriname but has preserved many of their traditions and rituals. This holds true for their language, religion, cultural expressions, and forms of entertainment. The Javanese have also maintained their traditional medical practices that are based on *Jamu*. *Jamu* has its origin in the Mataram Kingdom era in ancient Java, some 1300 years ago, and is mostly based on a variety of plant species. The many *Jamu* products are called *jamus*. The first part of this chapter presents a brief background of Suriname, addresses the history of the Surinamese Javanese as well as some of the religious and cultural expressions of this group, focuses on *Jamu*, and comprehensively deals with four medicinal plants that are commonly used by the Javanese. The second part of this chapter continues with an equally extensive narrative of six more such plants and concludes with a few remarks on the contribution of Javanese *jamus* to Suriname's traditional medicinal pharmacopeia.

Keywords: Suriname, Javanese, ethnopharmacology, medicinal plants, ethnobotanical uses, phytochemistry, pharmacology

1. Introduction

The Republic of Suriname is a small independent country in South America that is renowned for its ethnic, cultural, and religious diversity [1]. The Javanese are currently the fourth most numerous ethnic group in Suriname, after the Hindustanis, the Creoles, and the Maroons [1]. The Javanese are the descendants of indentured laborers from particularly the Indonesian island of Java who were attracted by the Dutch colonizers from the former Dutch East Indies - modern-day Indonesia - at the

end of the 19th century to work on the sugar cane plantations in Suriname following the abolition of slavery in the year 1863 [2, 3]. They had signed contracts for five years, and although some returned to their home country and others relocated to The Netherlands [2, 3], most remained in Suriname and settled in the district of Commewijne (**Figure 1**) where the first groups of Javanese had been put to work [2, 3].

Today, only five generations later, the Javanese have integrated well in Suriname, actively participating in all sections of the society including politics, arts, entertainment, and sports. For instance, Iding and Willy Soemita and Paul Somohardjo were prominent Surinamese Javanese politicians. Iding Soemita was born in West Java and came as an indentured laborer to Suriname, and founded the political party *Kerukunan Tulodo Pranatan Inggil* (KTPI) in 1949, giving Surinamese Javanese for the first time a political voice. Iding Soemita's son Willy succeeded his father as chairman of the KTPI in 1972 and served several times as a minister until 1996. As a more outspoken and assertive alternative to the KTPI, Paul Somohardjo founded the Javanese party *Pendawa Lima* in 1977 that was superseded in 1998 by the *Pertjajah Luhur*. Somohardjo became the first-ever Javanese Speaker of the National Assembly in 2005 and also served several terms as a minister.

The Surinamese-Javanese writer Karin Amatmoekrim studied Modern Literature at the University of Amsterdam, graduated with a thesis on 'The ethnicity in literature in Suriname', and won the 2009-Black Magic Woman Literature Prize for her novel 'Titus'. The Surinamese-Javanese singers Ragmad Amatstam, Oesje Soekatma, and Eddy Assan are among the greatest and most beloved musicians Suriname has brought forth. Specializing in pop-Jawa songs, they reached a broad audience in both Suriname and The Netherlands. Notable Surinamese-Javanese sports heroes are Andy Atmodimedjo, Virgil Soeroredjo, and Mitchel Wongsodikromo. Andy Atmodimedjo was an impressive professional football player and became the successful manager of several clubs in Suriname's highest soccer league as well as the head coach of the country's senior and under-21 national soccer teams. And Virgil

Figure 1.
Location of Suriname with respect to its neighboring countries French Guiana, Brazil, and Guyana, as well as its poisoning in South America (insert) (modifed from: https://goo.gl/images/F77jgS).

Soeroredjo and Mitchel Wongsodikromo were among the world's top badminton players who excelled on various national, Caribbean, Central American, and South American competitions.

Nevertheless, the Javanese have preserved their own identity, speaking their own language and adhering to their own specific religious and cultural customs. This also holds true for their traditional medical customs which are based on *Jamu*, the centuries-old traditional form of medicine from Indonesia that mainly involves the use of plants with medicinal properties. The first part of this chapter gives some background on Suriname; then addresses some of the religious and cultural expressions of Surinamese Javanese; focuses on *Jamu*, and concludes with an extensive account of the traditional, phytochemical, and pharmacological aspects of four medicinal plants that are mainly used by Surinamese Javanese. The second part of the chapter continues with a comprehensive narrative about six additional popular 'Javanese' medicinal plants and concludes with the contribution of the Javanese pharmacognostic knowledge to Suriname's traditional medicinal pharmacopeia.

2. Background on Suriname

2.1 Geography, population, and economy

The Republic of Suriname is located in the north-eastern part of South America, bordering the Atlantic Ocean to the north, French Guiana to the east, Guyana to the west, and Brazil to the south (**Figure 1**). It is the smallest sovereign country in South America with a land area of about 165,000 km^2 that can be distinguished into a relatively narrow northern coastal region and a large, sparsely inhabited hinterland that is mainly covered by savanna grassland and pristine Amazon rain forest [4]. Suriname's capital and largest city is Paramaribo that is located in the coastal area near the mouth of the Suriname River (**Figure 1**) and harbors, together with the other cities in the coastal area, approximately 80% of the population [1]. The hinterland encompasses more than three-quarters of the country's surface and [4] and is home to the remaining 20% of Suriname's inhabitants [1].

The population is among the ethnically most varied in the world, comprising Amerindians, the original inhabitants; Maroons, the immediate descendants of enslaved Africans shipped from western Africa between the 17th and 19th centuries; mixed people descending from enslaved Africans and mostly Europeans called Creoles; the descendants from indentured laborers attracted from China and India in addition to Java (Indonesia) between the second half of the 19th century and the first half of the 20th century; and immigrants from various European, South American, and Caribbean countries [1]. According to the 2012 census, the largest groups are represented by the Hindustanis, Maroons, Creoles, and Javanese, making up roughly 27, 22, 17, and 16%, respectively, of the total Surinamese population [1].

Suriname is situated on the Guiana Shield, a Precambrian geological formation estimated to be 1.7 billion years old and one of the regions with the largest expanse of undisturbed tropical rain forest in the world, with an extraordinary high animal and plant biodiversity [4]. The high mineral density of Suriname's soil contributes to its ranking as the 17th richest country in the world in terms of natural resources and development potential [5]. Suriname's most important economic means of support are crude oil drilling, gold mining, agriculture, fisheries, forestry, and ecotourism [5]. These activities contributed substantially to the gross domestic product in 2019 of USD 3,697 billion and the gross per capita income in that year of USD 5,420 [6]. This positions Suriname on the World Bank's list of upper-middle income economies [6].

2.2 Brief history

Although many history text books discuss Suriname starting from 1492 (the year Christopher Columbus 'discovered' South America's 'Wild Coast'), archeological finds in Suriname's deep south-west have demonstrated the presence of human beings in Suriname as far back as 5,000 years ago [7]. The artifacts have been ascribed to nomadic Amazon tribes who then lived in that region and who may represent the ancestors of the present-day Indigenous tribes who still populate Suriname's hinterland. One of these nomadic tribes are the Arawaks, who are generally believed to be Suriname's original inhabitants [8], but there are no written documents to support this assumption.

Dozens of years after Columbus, the first Europeans arrived in Suriname in the early 1600s. They were Spanish, English, French and Dutch fortune hunters who were in search of El Dorado, a mythical city of immense wealth somewhere at the 'Wild Coast' ruled by a chieftain covered with gold dust [9]. The area was first colonized in 1630 by British settlers led by Captain John Marshall [10], and they called the occupied region 'Surinam' after the Surinen indigenous people they had encountered. Their attempt to set up tobacco plantations failed and they abandoned the colony by 1645 [10].

A second English operation undertaken in 1651 was more successful when permanent sugar cane plantations were established in the colony that had been named Willoughbyland in honor of their patron Lord Francis Willoughby, the then governor of Barbados [10]. Initially, cheap labor to work on the plantations was mainly provided by captured Indigenous tribespeople from the hinterland. However, because of the increasing need for laborers, the British started importing enslaved Africans in 1663 from Dutch centers for slave trading in western Africa [10]. In the resulting conflict, the Dutch invaded and captured Willoughbyland in 1667 [10]. This eventually led to settlements in which Suriname was assigned to The Netherlands in exchange for New Amsterdam in North America [11]. The Dutch renamed Willoughbyland Dutch Guiana, while the English renamed New Amsterdam New York after the Duke of York [11].

From 1683 onwards, the Dutch ruled over their newly acquired colony in South America, elevating the plantation economy to unprecedented heights by producing cocoa, coffee, cotton, sugar, and indigo [12]. The Dutch also dominated the trans-Atlantic slave trade for a long time, transporting a total of approximately 300,000 Africans to Suriname [12]. However, treatment of the enslaved Africans was notoriously brutal, and many escaped to Suriname's hinterland [13]. These Maroons preserved much of their cultural concepts and established a new and unique culture that was highly successful and exists until today [13].

Slavery was officially abolished in 1863, but the enslaved Africans who had remained on the plantations were obliged to conduct ill-paid work over the next ten years. As soon as they became truly free, the majority abandoned the plantations and settled in Paramaribo [14]. To make up for the shortage of workers on the plantations after 1873, indentured laborers were brought in, first from India then from the then Dutch East Indies [2]. In addition, between 1850 and 1860, small numbers of (mostly male) laborers had been brought in from China and the Middle East [15]. From the mid-20th century onwards, various immigrants from South American and Caribbean countries immigrated to Suriname [5]. These developments are the reason that Suriname has become one of the ethnically and culturally most diverse countries in the world notwithstanding its relatively small population. It also explains the large variety of traditional forms of medicine practised in the country.

3. Surinamese Javanese

3.1 The first arrivals

The first group of 94 Javanese indentured laborers was from the countryside of the city of Surakarta in Java (also known as Solo) and left on May 21, 1890, for Suriname on the steamship Prins Willem II [16]. This was an initiative of the Netherlands Trading Society (Nederlandsche Handel-Maatschappij, abbreviated NHM), one of the primary ancestors of ABN AMRO Bank NV, the third-largest bank in The Netherlands. The Prins Willem II arrived 70 days later, on August 9, 1890, in Suriname [16]. Lately, this date has been proclaimed a national holiday in commemoration of the Javanese immigration. The new arrivals were set to work on the sugar cane plantations at Mariënburg (district Commewijne) which were then owned by the NHM.

The NHM initiative was considered successful, and by 1894 the Dutch colonial government took over the task of recruiting Javanese hands starting with signing up 584 additional Javanese in that year [16]. The workers (and their families) arrived in small groups and in two stages, *i.e.*, first from the Dutch East Indies to The Netherlands and from there to Paramaribo [16] (**Figure 2**). They came from the then overpopulated villages in central and western Java, Batavia, Surabaya, and Semarang, and awaited their departure in depots in Batavia, Semarang, and Tandjong Priok, where they were inspected and registered and signed their contract [16]. The transport of Javanese indentured laborers continued until 13 December 1939, when it was discontinued by the outbreak of World War II [16].

Figure 2.
Arrival of one of first groups of Javanese indentured laborers in Suriname (from: https://images.app.goo.gl/cwD6eX97BovonbgR6).

In total, 32,956 Javanese arrived in Suriname. Most of them were recruited to work on the plantations, but a group was also specifically recruited to work at the Colonial Railways, while another group was assigned to the Suriname Bauxite Company in Moengo during World War I [16]. Only 20 to 25% of the Javanese migrants returned to their home country before World War II [2, 3]. In 1954, an additional 1,200 Javanese, encouraged by Iding Soemita's rival Salikin Hardjo, returned to Indonesia to start an agricultural co-operative in Tongar in western Sumatra [2, 3]. And in the 1970s, 20,000 to 25,000 Surinamese Javanese went to The Netherlands for fear of social-economic insecurity in an independent Suriname that was due in 1975 [2, 3]. However, the great majority of Javanese immigrants settled permanently in Suriname,

Nevertheless, many Javanese identified and still identify with their country of origin, even though very few have ever visited Java or maintain family connections there. This strong adherence to their origin is partly due to the major socio-economic disadvantages they had to face in an often hostile environment [16, 17]. In addition, the firm commitment of many Javanese to their own customs and traditions is for an important part directly attributable to Dutch colonial policies to control the immigrants [16, 17]. This was done through the so-called 'Indianisation' project implemented in the 1930s and involved, among others the creation of small Indonesian-styled Javanese farm villages - *desas* - in the countryside, each headed by its own village head (the *lurah*) and religious and civic leaders [16, 17]. Obviously, this secluded lifestyle strengthened the group identity and helped them to maintain the rich culture they had brought with them from Java [16, 17]. Indeed, some of the *desas* were situated in locations that are still mainly populated by Javanese such as Tamanredjo, Kampong Baru, Sidoredjo, and Kuwarasan as well as Lelydorp, Domburg, and Meerzorg.

3.2 Javanese culture

The social, economic, linguistic, cultural, and religious challenges the Javanese indentured laborers had to cope with, obviously contributed to the consolidation of the group cohesion and the preservation of their customs and traditions. For instance, the Surinamese Javanese still speak their own language in addition to Dutch, the official language of government, business, media, and education, as well as Surinamese or Sranan Tongo, the widely used English- and Portuguese-based lingua franca [18]. The language spoken by this group is Surinamese-Javanese that is derived from the original Javanese language called *Basa Jawa* spoken in the central and eastern parts of Java [19]. However, after more than a century, Surinamese-Javanese has become influenced by Dutch and Sranan Tongo and has developed differently from *Basa Jawa* [19].

Most Javanese are Muslim, and one of the central values in their philosophy about life is *rukun* that involves a commitment to harmony and togetherness, not only among people but also between the human world and that of the gods and the spirits. The importance of *rukun* manifests in Javanese everyday-life in, for instance, the pursuit of good relations with others, an attitude of modesty, courtesy, politeness, formality, and avoiding conflicts whenever possible. *Rukun* is also expressed in several ceremonies and rituals for maintaining good relations with the gods and the spiritual world [20]. This is mainly done by making sacrifices and holding ritual sacrificial meals or *slametans*. A *slametan* is headed by a religious leader called *kaum* who asks God to bless the various dishes spread out on the table, each with a specific ritual meaning based on the purpose of the *slametan* [20].

Unique cultural expressions from the Javanese are the *gamelan* music, the *wayang* shadow puppet show, and the *ludruk* theater. *Gamelan* (**Figure 3**) is the

Figure 3.
Gamelan *ensemble (from: https://images.app.goo.gl/p3ZFZ9JKJbyp87s39).*

traditional ensemble music of Javanese and is predominantly performed by different percussion instruments such as metallophones and xylophones played by mallets, chimes, and hand-played drums called *kendhang* to register the beat, as well as melodic instruments like bamboo flutes, strings, and vocalists called *sindhen* if female or *gerong* if male [21]. The earliest known records of *gamelan* were found in the reliefs of the Borobudur Temple located near Central Java, the world's largest Buddhist temple, dating it back as far as the 9th century [21]. Gamelan is commonly played in many religious rituals, traditional ceremonies, and informal events, including, among others, *wajang* puppet shows and *ludruk* theater [21].

Wajang is an ancient form of storytelling by theater play that dates back to medieval times [22]. The form most practiced is called *wajang kulit* that depicts dramatic mythological stories as well as local adaptations of cultural legends using flat leather shadow puppets [22]. A *wajang* is played out by the *dalang*, the puppeteer who sits behind the screen and sings and narrates the dialogs of the different characters of the story [22]. The *dalang* is highly respected for his knowledge and art, and as a spiritual person capable of bringing to life the spiritual stories in the religious epics [22]. *Ludruk* theater is the old Javanese tradition of storytelling presented by a group of actors (or comedians) on a stage, through slow, graceful, and expressive dances [23]. *Ludruk* presumably dates as far back as the 13th century [23]. It tells stories about everyday life, mostly that of the underprivileged, and is particularly appreciated by a working-class audience [23].

Other characteristic Javanese cultural expressions are *djarang kepang* and *pentjak silat*. *Djarang kepang* (**Figure 4**) is a spectacular cultural religious tradition where young males dance on hobby horses and suddenly become entranced, behaving like horses and eating grass [24]. It is generally performed in a cordoned-off area, with the audience separated from the dancers [24]. The origin of *djarang kepang* is uncertain, but it may be based on the wars fought between native Javanese and the colonial Dutch Empire in the dying days of the Sultanate of Mataram at the end of the 19th century and during the Diponegoro War from 1825 to 1830 [24]. *Pentjak silat* is the indigenous ritual martial art of Indonesia intended for self defense [25]. It is believed to be founded as early as the 6th century and has extensively been practised during the epoch of the powerful kingdom of Sri Vijaja on Sumatra in the 11th century [25]. *Pentjak silat* is based on the movements and stances of tigers,

Figure 4.
Performers of djarang kepang *(https://images.app.goo.gl/KVF2xzwUAzqmr8ac6)*

eagles, snakes, crocodiles, monkeys, scorpions, and dragons [25]. As a result, some of the stances and styles have been named after animals, such as *harimau* (tiger) and *garuda putih* (white eagle) [25].

3.3 Jamu

The Surinamese Javanese have also maintained their traditional medical customs which are mainly based on medicinal plants and, as mentioned above, are referred to as *Jamu* [20]. *Jamu* is widely practiced in Indonesia and probably has its origin in the Mataram Kingdom era in ancient Java, some 1300 years ago [26, 27]. *Jamu* products called *jamus* are in Indonesia traditionally available from (particularly female) peddlers and street-side vendors, entrepeneurs who operate on a made-to-order basis out of their home, as well as medium-sized and large firms that produce and retail pre-made *jamus* in dried form, sachet packaging, and as tablets, capsules, and liquid drinks [26, 27]. The many different *Jamu* brands are united in the Indonesian Herbal and Traditional Medicine Association locally known as *Gabungan Pengusaha Jamu* that had sales worth USD 74 million in 2014 [26, 27].

There are *jamus* against almost every ailment, ranging from remedies for treating sick children and managing post-childbirth conditions to a large variety of beauty products and remedies for sexual problems [28]. The medicine book from Mataram from the 18th century even has 3,000 entries of *jamu* recipes [28]. An example is *jamu kunirasem* that contains as main ingredients the rhizome from the turmeric *Curcuma longa* L. (Zingiberaceae) called *kunjit* or *kunir* in Javanese,

and parts from the tamarind *Tamarindus indica* L. (Caesalpiniaceae) called *asem* in Javanese [28]. Another example is *jamu beraskentjur* that has as basic ingredients rice (*beras* in Javanese) and the rhizome from the sand ginger *Kaempferia galanga* L. (Zingiberaceae) called *kentjur* in Javanese [28]. However, depending on the desired benefits, various other ingrededients are added, such as ginger rhizome, cardamom seeds, cinnamon, pomegranate, lemon, and/or nutmeg [28]. To improve the (sometimes bitter or sour) taste, natural sweeteners such as brown sugar, granulated sugar, rock sugar or honey may be added [28].

Jamu is practiced in both Indonesia and Suriname by highly respected medicinal practitioners known as *dukuns* [20, 26, 29]. The *dukun* is very influential and holds extensive knowledge about the preparation of the large variety of sometimes rather complicated *jamus* [20, 26]. An example is the very popular *jamu galian* consisting of different parts of eight plants that is widely used in Suriname as a general health-promoting tonic [20, 26, 29]. The *dukun* also plays an important role during, for instance, *njuwuk*, a ritual to bring a person at ease by praying over and blowing three times over a glass of water that then must be drunk by the client [20, 26, 29]. *Njuwuk* is often performed prior to examinations, circumcisions, or giving birth [20, 26].

4. Plants used in Javanese pharmacognosy

Hereunder, four medicinal plants that are traditionally mainly used by Surinamese Javanese, have in detail been assessed for their phytochemical contents and pharmacological activities in order to provide a scientific rationale for their ethnopharmacological applications. The plants have been selected on the basis of the number of times they have been dealt with in a number of comprehensive publications describing the use of medicinal plants in the country [30–38]. In part 2 of this chapter, six additional plants are equally extensive addressed. All the plants and their main traditional use by Surinamese Javanese are given in **Table 1**.

4.1 Acanthaceae - *Strobilanthes crispa* Blume

The black face general *S. crispa*, known as *ketji beling* in Suriname (**Figure 5**), is native to the region between Madagascar and Indonesia but is now found in many countries throughout south-eastern Asia. It is a woody spreading shrub that carries yellow-colored flowers, attains a height of 50 centimeters to 1 meter, and can be found on riverbanks and abandoned fields. The leaf is eaten as a vegetable but has for centuries been used medicinally in Indonesian and Malaysian folk medicine. More recently, some products prepared from *S. crispa* leaf have entered the health-food market as nutraceuticals in the form of sachets containing the raw crude powder for preparing a tea, as an additive in coffee, or as capsules for oral intake. *S. crispa* has probably been introduced in Suriname from Java in 1956 [32], and mainly the leaf is used as an ingredient of popular *jamus* for lowering elevated blood sugar levels [34]. In Suriname, it is also used as a diuretic, against kidney stones and renal colics, and to lower elevated blood sugar levels in diabetes mellitus [34], either separately or in combination with, for instance, the leaves from the cat's whiskers *Orthosiphon grandiflorus* Bold. (Lamiaceae) [34].

Some of these traditional uses are supported by experimental data and pharmacological studies. The use of the leaf as a mild diuretic [39] can be attributed to the many cystoliths of calcium carbonate in this part of the plant [40], which make an infusion slightly alkaline. Support for the anti-urolithiatic properties of *S. crispa* and its efficacy against renal colics came from the inhibitory activity

Family	Species (vernacular names in English; Surinamese-Javanese)	Part(s) used	Traditional indications	References
Acanthaceae	*Strobilanthes crispa* Blume (black face general; *ketji beling*)	Leaf	Disorders of the urinary system; diabetes mellitus	[34]
Araceae	*Acorus calamus* L. (sweet flag; *dlingo*)	Rhizome	Gastrointestinal disorders, intestinal parasites, common cold, convulsions and seizures in children, evil eye and evil spirits	[33, 34, 38]
Arecaceae	*Cocos nucifera* L. (coconut; *klapa*)	Coconut oil, coconut meat, coconut water, husk fibers	Respiratory problems, pimples, shingles due to herpes, diabetes mellitus, hypertension, gastrointestinal disorders, skin and hair care, skin lesions, burns, sprains, sore muscles, evil eye and luck	[32–36]
Asclepiadaceae	*Calotropis gigantea* (L.) Aiton (crown flower; *bidari*, *widuri*)	Latex, stem	Bleeding, skin lesions, burns, toothache, tonsillitis, colds, heart conditions	[36, 38]
Asteraceae	*Ageratum conyzoides* L. 1753 not Hieron. 1895 nor Sieber ex Steud. 1840 (goatweed; *wedusan*)	Whole plant leaf, root	Symptioms of flu, gastrointestinal problems, gynecological disorders, gonorrhea, itching, skin lesions, burns, allergic conjunctivitis	[32, 35, 37, 38]
Caesalpiniaceae	*Tamarindus indica* L. (tamarind; *asem*)	Leaf, fruit pulp	Health-promoting *jamus*, fever, gynecological conditions, gastrointestinal disorders, itching, skin lesions	[30, 34, 38]
Fabaceae	*Sesbania grandiflora* (L.) Poiret (vegetable hummingbird; *turi*)	Leaf, bark	Abdominal disorders, throat and oral infections	[38]
Portulacaceae	*Portulaca oleracea* L. (green purslane; *krokot*)	Whole plant leaf	Skin lesions, sprains, swellings, stiff joints, pain, bronchitis, conjunctivitis, anemia	[31, 35, 38]
Zingiberaceae	*Curcuma longa* L. (turmeric; *kunjit*)	Rhizome	Health-promoting *jamus*, gynecological disorders, gastrointestinal diseases, fever, inflamed gums, conjunctivitis, skin lesions, pinworm infection	[34, 38]
Zingiberaceae	*Zingiber officinale* Roscoe (ginger; *djahe*)	Rhizome	Health-promoting *jamus*, overweight, respiratory diseases, gastrointestinal disorders, gynecological problems, bruises, rheumatic joints, sore muscles	[34, 38]

Table 1.
Plants commonly used in Javanese traditional medicine addressed in this chapter, parts preferentially used, and traditional indications in the Surinamese-Javanese community.

Figure 5.
The black face general Strobilanthes crispa *Blume (Acanthaceae) (from: https://images.app.goo.gl/8miNujrV KRRNs5N79).*

of methanolic and ethyl acetate leaf extracts against the aggregation of calcium oxalate crystals and their stimulatory effects on the dissolution of the crystals [41]. The results from a clinical trial with a polyherbal formulation containing *S. crispa* suggested that it was safe and effective in the treatment of urolithiasis [42]. It has been suggested that the phenolic compounds in the leaf are responsible for the anti-urolithiatic activity of the plant, as these compounds have been found to inhibit the growth of calcium oxalate crystals *in vitro* [43].

The use of *S. crispa* against diabetes mellitus is supported by the antihyperglycemic activities of hot water extracts of fermented and/or unfermented leaf tea in normal and streptozotocin-induced diabetic laboratory rats [44]. Both fermented and unfermented *S. crispa* tea improved lipid profile in the animals [44]. Comparable results were obtained with *S. crispa* juice in diabetic and normal rats [45]. Interestingly, the fresh juice from *S. crispa* leaf stimulated the healing of incision wounds on the back of normal and streptozotocin-induced hyperglycemic rats [46]. These observations are in accordance with the stimulatory effects of a topically applied ethanol extract of *S. crispa* leaf on excision wounds in the posterior neck area rats [47].

4.2 Acoraceae - *Acorus calamus* L. 1753

The sweet flag *A. calamus*, also called *dlingu* in Surinamese-Javanese (**Figure 6**), is a species of flowering plant that is widely spread from the Caucasus through western Asia and Siberia to China, India and south-eastern Asia, as well as North America, where it can be found in swampy and marshy habitats. It is a stemless herbaceous perennial that grows about 2 meters tall and is characterized by clusters of leaves arising from a spreading rhizome. The plant has diploid forms (mainly in parts of northern Asia and much of North America), triploid forms (mainly in Europe and south-western Asia to the Himalayas), and tetraploid forms (mainly in central Asia, through India, Japan and tropical Asia) [48]. Each of these forms has a distinct chemistry, particularly with respect to the composition up of the essential oil in leaf and rhizome [49].

A. calamus has been known since the ancient Egyptians who appreciated the sweet, cinnamon-like scent of the essential oil and incorporated extracts from

Figure 6.
The sweet flag Acorus calamus *L. 1753 (Acoraceae) (from: https://images.app.goo.gl/Rt334C1iRQEvLjaT8).*

these parts of the plant into perfumes and aromatic vinegars [50]. In Suriname, *A. calamus* is only used by the Javanese [34] who incorporate the dried rhizome as a spice in a herbal paste called *bumbus* [34]. The dried rhizome is also prepared into a tea for treating abdominal cramps, stomach problems, and dysentery [38]; as an ingredient of a number of *jamus* [34] such as *jamu sawanang* that is given to children as a deworming treatment and against pinworms; the macerated rhizome mixed with aniseed is placed on the forehead of children with the common cold; as an ingredient of an ointment for treating convulsions and seizures in children; and the grated rhizome is rubbed behind the ears and on the forehead of children to ward off the evil eye and provide protection from evil spirits [34, 38].

Phytochemical studies of *A. calamus* have shown the presence of a wide variety of chemical constituents in the rhizome and other parts of the plant, including a volatile oil that consists of the phenylpropanoids α-asarone and β-asarone as well as saponins, lectins, sesquiterpenoids, lignans, and steroids [49]. β-Asarone is responsible for the characteristic odor and flavor of *A. calamus* rhizome and leaf [49] and is present in varying amounts in the essential oils from the diploid, triploid, and tetraploid forms the plant. The oil from the tetraploid form consists for 90 to 95% of β-asarone, that of the triploid form has only relatively small amounts of β-asarone, while the diploid form is devoid of this compound [49]. β-Asarone is potentially carcinogenic and hepatotoxic [51] and can cause hallucinations, as well as severe and prolonged nausea and vomiting [52]. For these reasons, *A. calamus*-derived products such as the rhizome oil have been banned in the USA and their concentrations as flavorings in, for instance, bitters, have been limited to 115 μg per day [53].

Nevertheless, a great number of pharmacological studies provided support for various Surinamese-Javanese traditional applications of *A. calamus*. The traditional use of the dried rhizome for gastrointestinal conditions [38] is supported by the inhibitory effects of an ethanolic rhizome extract on gastric secretion in rats and the protective effect of this preparation on the animals' gastroduodenal mucosa against damage caused by pyloric ligation, indomethacin, reserpine, cysteamine administration, and cytodestructive agents such as ethanol [54]. A 50%-ethanol extract

of the rhizome also showed antispasmodic activity in an isolated guinea pig illeum assay in mice [55], while a crude rhizome extract inhibited spontaneous and high K^+-induced contractions in an isolated rabbit jejunum preparation, accomplishing spasmolytic activity that might be mediated through calcium channel blockade [56]. Furthermore, a methanolic rhizome extract the considerably reduced induction time of castor oil-induced diarrhea and total weight of the feces in mice [57].

The incorporation of *A. calamus* rhizome in, among others, *jamu sawanang* in order to remove intestinal worms and pinworms [34] is justified by the inhibitory effects of extracts of the essential oil against the large roundworm *Ascaris lumbricoides* [58], the causative agent of ascariasis that causes abdominal swelling, abdominal pain, and diarrhea, as well as poor weight gain, malnutrition, and learning problems in children [59]. Notably, administration of the dried rhizome powder to 147 children aged between 5 and 11 years with round worm infestation produced complete cures in 83% of cases [60]. *A. calamus* essential oil also displayed nematicidal activity against the root-knot nematode *Meloidogyne incognita* [61] that arouses large, usually irregular galls on roots of trees [62].

Support for an anticonvulsant activity from *A. calamus* came from the protective effect of the essential oil on convulsions produced by electroshocks in laboratory rats and mice [63], the reduction in the severity of maximum electric shock-induced seizure in rats by aqueous and alcohol extracts from the rhizome [64], and the significant increase in the pentylenetetrazole-induced seizure latency caused by these extracts [64]. These calming effects of *A. calamus* preparations may also account, at least partially, for their use to ward off the evil eye and protect against evil spirits [34, 38].

4.3 Arecaceae - *Cocos nucifera* L.

The coconut tree *C. nucifera*, known as *klapa* in Surinamese-Javanese (**Figure 7**), presumably originates from Indonesia, Malaysia, the Philippines, as well as the many islands between the Indian and the Pacific Ocean. It has subsequently been brought to India, Africa, and the Americas, and is now found in most tropical regions throughout the world. The plant is an evergreen arborescent monocotyledonous tree that can range in height from 2 meters up to 30 meters. *C. nucifera* is grown for decoration but also for the many culinary, non-culinary, and medicinal uses of virtually every part of the plant. Indeed, coconut oil; coconut milk; coconut water; preparations from the dried coconut meat, husk fiber, leaf, inflorescence, stem, and root; leaves and roots of young plants are widely used in many traditional medical systems throughout the world.

In Suriname, small amounts of coconut oil are included in in preparations to fight colds, flu, fever, bronchitis, and astma [32, 34]. Coconut meat is eaten against pimples, or applied on shingles due to herpes zoster infection after it has been macerated by chewing [34]. A tea from the husk fibers is drunk to manage the symptoms of diabetes mellitus and hypertension [38]. Diarrhea and dysentery are treated by drinking coconut water or an infusion of cocos meat with allspice and clove [35]. Coconut water would also stop vomiting and fever [36]. Externally, coconut oil is used for skin and hair care, skin wounds, insect bites, burns, sprains, sore muscles, to massage the abdomen of pregnant women, to promote the health of newborn babies [34], and to protect newborn babies against the evil eye and to command luck in their life [33].

Phytochemical studies showed the presence of many phytochemicals and bioactive compounds in various parts of *C. nucifera* including, among others, flavonoids and other phenolic compounds having antioxidant properties, condensed tannins with potential antihelminthic activity, macronutrients such as lauric acid that may

Figure 7.
Coconut tree Cocos nucifera L. (Arecaceae) (from: https://images.app.goo.gl/47JmZznFpMu9eebL7).

be involved in the antiprotozoal, antifungal, antibacterial, and antiviral properties of the plant, and micronutrients such as manganese, copper, iron, and selenium [65]. The presence of these compounds in the plant could support some of its traditional applications and could help explain some of its pharmacological activities dealt with hereunder.

The use of *C. nucifera* preparations against infections of the respiratory tract in Suriname [32, 34] may be attributed to their antibacterial, antifungal, and antiviral properties. Support for the former activity particularly came from the inhibitory effects of preparations from the dried and macerated husk fibers against common oral pathogens like cariogenic bacteria, periodontal pathogens, and candidal organisms albeit the less than that of the disinfectant and antiseptic chlorhexidine [66]; cultures of a broad range of both Gram-positive and Gram-negative pathogenic bacteria [67, 68] including methicillin-resistant *Staphylococcus aureus* [69]. Other studies also found antimicrobial activities of preparations from the endocarp [70] and the mesocarp [71]. The antibacterial activities may be associated with phenolic compounds, terpenoids, phytosterols, and unsaturated fatty alcohols [67, 71], and their mechanism of action may involve perturbation of the bacterial cytoplasmic membrane [68].

Indications for antimycotic activity of *C. nucifera* were provided by the *in vitro* activity of an alcoholic extract of the shell against a wide diversity of fungal species [72]; that of the virgin oil from the coconut pulp and a teas from the husk fiber against *Candida albicans* [69, 73]; and that of coconut oil - either incorporated into a Viscogel tissue conditioner or not - against *Candida albicans* [74], a frequent cause of oral candidiasis and denture stomatitis. The antifungal activity has mainly been attributed to the presence of phenolic compounds in these preparations [72]. That *C. nucifera* may also exert antiviral activity is indicated by the inhibitory activity of a crude catechin-rich husk fiber extract against acyclovir-resistant herpes simplex virus type 1 [67] and the efficacy of coconut oil against a variety of viruses with lipid capsules such as visna virus, cytomegalovirus, and Epstein–Barr virus [75]. It has been suggested that the medium chain saturated fatty acids from coconut oil destroy and break the membranes and interfere with viral maturation [75]. Importantly, the apparent antiviral activity of *C. nucifera* may also account for the application of finely chewed coconut meat on shingles caused by herpes zoster infection [34].

The use of coconut meat against impurities in the face [34] and that of coconut oil for skin and hair care, skin lesions, sprains, and sore muscles [34] may mainly have its rationale in the analgesic and antiinflammatory properties of these parts of the plant. Support for an analgesic effect is provided by the inhibitory effects of orally administered husk fiber extracts as well as two aqueous subfractions derived therefrom on acetic acid-induced writhing, heat-induced tail flicking, and formalin-induced paw licking in mice [69, 76]. Comparable results were obtained with an ethanolic root extract that, in addition, potentiated the sleeping time of mice induced by pentobarbital sodium, diazepam, and meprobamate, potentiated analgesia induced by morphine and pethidine in the animals, and protected them from convulsions caused by pentylenetetrazole [77]. The latter action may also tentatively explain the putative protective effects of coconut oil in newborns against symptoms ascribed to the evil eye [33]. Administration of the opioid antagonist naloxone counteracted the antinociceptive effects of the *C. nucifera* preparations, indicating that they might act on opioid receptors [76]. Indications for antiinflammatory activity of the extracts were provided by their inhibitory effects on carrageenan carrageenan-, histamine-, and serotonin-induced paw edema and on cell migration, extravasation of protein, and TNF-α production following subcutaneous injection of air in rats [69, 76].

The usefulness of *C. nucifera* against diabetes mellitus [38] is supported by the decrease in fasting blood glucose and insulin levels as well as the restoration of all other biomarker as well as enzymes in streptozotocin- and alloxan-induced diabetic rats treated with a purified coconut kernel protein isolated from dried coconut kernel [78], a hydro-methanol or methanol extract of the immature inflorescence [79], or lyophilized mature coconut water [80]. The hypoglycemic effect of coconut water was comparable to that caused by glibenclamide [79, 80], and the antidiabetic activity of the purified coconut kernel protein has been attributed to the beneficial effects on pancreatic β cell regeneration of the relatively high levels of arginine in the protein [78]. And the traditional use in Suriname of a tea from the husk fibers to manage hypertension [38] is supported by the vasorelaxant activity of an ethanolic extract of the endocarp on isolated rat aortic rings and the blood pressure-lowering effect of the extract in deoxycorticosterone acetate salt-induced hypertensive rats [81]. This effect has been attributed to the direct activation of the nitric oxide/guanylate cyclase pathway as well as stimulation of muscarinic receptors and/or the cyclooxygenase (COX) pathway [81] and might be attributed to phenolic compounds in the extract [81].

4.4 Apocynaceae - *Calotropis gigantea* (L.) Dryand

The crown flower *C. gigantea* (**Figure 8**) called *bidari* or *widuri* in Surinamese-Javanese, is a fast-growing, evergreen, flowering shrub that can reach a height of 2 meters and that is native to Indonesia, India, southern China, and Malaysia. The vernacular name 'crown flower' is derived from the shape of the flower that consists of five pointed petals and a small crown-like structure rising from the center that holds the stamen. *C. gigantea* has extensively been cultivated in eastern Asian countries as an ornamental, for the fiber obtained from its stems, and for its medicinal uses, but easily naturalizes and is often found as a weed in uncultivated urban areas. It is an important religious plant in Hinduism where it is sacred to the God Shiva, and is used in various traditional medical systems throughout the world.

C. gigantea has presumably been introduced in Suriname by Hindustani indentured laborers but its medicinal properties have also been recognized by other ethnic groups in the country including the Javanese. The milky latex is used to stop bleeding, and for treating minor wounds, boils, scabies, itches, bruises, cuts, sores,

Figure 8.
The crown flower Calotropis gigantea *(L.) Dryand (Apocynaceae) (from: https://images.app.goo.gl/AtQjN2XqM77NsXbo9).*

and burns [38]. The latex is also rubbed against the gums to ease toothache or put on a piece of gauze that is placed in a cavity to stop caries [38]. The dried stem is burned, placed in the nostrils, and the released vapors are inhaled for treating inflamed tonsils [36]. And preparations from the leaf are taken orally for severe chest colds and heart conditions [38].

Phytochemical studies showed a variety of bioactive compounds in various parts of the plant which may account for some of its pharmacological activities [82], providing support for some of the traditional uses. For instance, the milky latex and the leaf contain, among others, cardiac glycosides such as calotropin, gigantin and uscharin that exerted a digitalis-like action on the heart [83], possibly accounting for the traditional use of leaf preparations against heart conditions [38]. Another group of glycosides in the plant exhibited, along with certain flavonoids, phenolic compounds, and triterpenoids, antimicrobial and antioxidant properties [84] that may help explain the traditional use of the latex against a variety of skin lesions [38].

Further evidence to support the use of the plant to stop bleeding and treat various types of wounds [38] is provided by the apparent wound healing stimulating effects of the plant. For instance, the use of the latex led to a smaller wound area, faster epithelization, increased granuloma breaking strength, and improved wound contraction in excision and incision wounds in Wistar rats [85, 86]. And an ethanol extract of *C. gigantea* rootbark formulated as an ointment base for topical application, also stimulated the healing of incision, excision, and dead space wounds in albino rats, as judged by the increased percentage of wound contraction, the decreased degree of fibrosis, and the increased breaking strength [86].

The use of *C. gigantea* latex against toothache, caries, and chest colds [38], and that of the dried and burned stem against inflamed tonsils [36] is supported by the substantial inhibitory effects of aqueous and/or ethanolic extracts of the sap of the plant on the growth of various pathogenic bacteria as well as yeast species [87, 88]. Aqueous, methanol, ethanol, and petroleum ether extracts of the leaves of the plant also exerted broad antimicrobial activity against cultured bacterial strains [88], clinical isolates of *Candida* species [89], and the plant-pathogenic

fungus *Fusarium mangiferae* that can cause serious damage to mango cultivations [90]. Additionally, a methanol extract from the rootbark and its petroleum ether, chloroform, and ethyl acetate fractions, as well as crude aqueous, ethanolic, and acetone extract also displayed broad *in vitro* antibacterial activity [89, 91].

Possibly contributing to the above-mentioned therapeutic efficacies of *C. gigantea* are the anti-inflammatory, antioxidant, analgesic, and antipyretic activities reported in various laboratory models. An ethanol extract of the leaf inhibited carrageenan-induced paw edema in Wistar albino rats to a greater extent than ibuprofen [92]; a hydroalcohlic leaf extract displayed notable DPPH radical-scavenging activity, reducing power activity, and nitric oxide scavenging activity [93]; an orally administered ethanolic extract of the flower produced a substantial decrease in the frequency of writhing and paw licking in laboratory rodents [94, 95]; and intraperitoneal administration of a water:ethanol extract of the root led to a reduction of the fever and normalization of the body temperature in yeast- and typhoid vaccine-induced pyrexia in Albino Swiss rats and rabbits [96].

5. Concluding remarks

The Javanese have been in Suriname for over a century. They have been brought to that country as poor and unaccustomed indentured laborers but have become successful individuals who have integrated well into the Surinamese community, actively participating in all its sections. Indeed, the Javanese are full-fledged citizens of the country and an integral part of the vibrant color palette represented by its unique cultural, religious, and ethnic diversity. This is reflected by the presence of the small, often family-owned Javanese restaurants called *warungs* in the smallest of towns, where widely appreciated savory dishes such as *bami goreng* (fried noodles), *nasi goreng* (fried rice), *pityel* (mixed blanched vegetables with a peanut sauce dressing), *teloh* (fried cassava), *pejeh* (prawn crackers), and *saoto* soup (chicken broth, meat, and vegetables) can be enjoyed, and can be washed down with refreshing beverages such as the lemongrass-, corn starch-, and coconut milk-based *dawet*.

Nevertheless, the Javanese have maintained most of their cultural traditions. This particularly holds true for their ancient form of medicine that is based on centuries-old *Jamu*. *Jamu* has added a unique element to the array of traditional forms of medicine throughout the Caribbean and Latin America, most of which are based on practices from the Indigenous American peoples as well as those from Africa, China, India, and various European countries. The influence of *Jamu* is already noticeable. The use of an infusion of the cat's whiskers or *kumis kutjing Orthosiphon aristatus* (Blume) Miq. (Lamiaceae) for treating kidney stones and renal colics is no longer limited to Indonesia and Suriname but has expanded into many other parts of the world. It is foreseeable that many more *Jamu* recipes will one day contribute to Suriname's traditional medicinal pharmacopeia as well as to the development of novel mainstream drugs for treating human diseases.

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Chapter 13

The Contribution of Javanese Pharmacognosy to Suriname's Traditional Medicinal Pharmacopeia: Part 2

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Abstract

The Republic of Suriname (South America) is among the culturally, ethnically, and religiously most diverse countries in the world. Suriname's population of about 600,000 consists of peoples from all continents including the Javanese who arrived in the country between 1890 and 1939 as indentured laborers to work on sugar cane plantations. After expiration of their five-year contract, some Javanese returned to Indonesia while others migrated to The Netherlands (the former colonial master of both Suriname and Indonesia), but many settled in Suriname. Today, the Javanese community of about 80,000 has been integrated well in Suriname but has preserved many of their traditions and rituals. This holds true for their language, religion, cultural expressions, and forms of entertainment. The Javanese have also maintained their traditional medical practices that are based on *Jamu*. *Jamu* has its origin in the Mataram Kingdom era in ancient Java, some 1300 years ago, and is mostly based on a variety of plant species. The many *Jamu* products are called *jamus*. The first part of this chapter presented a brief background of Suriname, addressed the history of the Surinamese Javanese as well as some of the religious and cultural expressions of this group, focused on *Jamu*, and comprehensively dealt with four medicinal plants that are commonly used by the Javanese. This second part of the chapter continues with an equally extensive narrative of six more such plants and concludes with a few remarks on the contribution of Javanese *jamus* to Suriname's traditional medicinal pharmacopeia.

Keywords: Suriname, Javanese, ethnopharmacology, medicinal plants, ethnobotanical uses, phytochemistry, pharmacology

1. Introduction

The Republic of Suriname is a small independent country in South America that is renowned for its ethnic, cultural, and religious diversity [1]. The Javanese are currently the fourth most numerous ethnic group in Suriname, after the Hindustanis, the Creoles, and the Maroons [1]. The Javanese are the descendants of indentured laborers from particularly the Indonesian island of Java who were attracted by the

Dutch colonizers from the former Dutch East Indies - modern-day Indonesia - at the end of the 19th century to work on the sugar cane plantations in Suriname following the abolition of slavery in the year 1863 [2, 3]. They had signed contracts for five years, and although some returned to their home country and others relocated to The Netherlands [2, 3], most remained in Suriname and settled in the district of Commewijne where the first groups of Javanese had been put to work [2, 3].

Today, only five generations later, the Javanese have integrated well in Suriname, actively participating in all sections of the society including politics, arts, entertainment, and sports. For instance, Iding and Willy Soemita and Paul Somohardjo were prominent Surinamese Javanese politicians. Iding Soemita was born in West Java and came as an indentured laborer to Suriname, and founded the political party *Kerukunan Tulodo Pranatan Inggil* (KTPI) in 1949, giving Surinamese Javanese for the first time a political voice. Iding Soemita's son Willy succeeded his father as chairman of the KTPI in 1972 and served several times as a minister until 1996. As a more outspoken and assertive alternative to the KTPI, Paul Somohardjo founded the Javanese party *Pendawa Lima* in 1977 that was superseded in 1998 by the *Pertjajah Luhur*. Somohardjo became the first-ever Javanese Speaker of the National Assembly in 2005 and also served several terms as a minister.

The Surinamese-Javanese writer Karin Amatmoekrim studied Modern Literature at the University of Amsterdam, graduated with a thesis on 'The ethnicity in literature in Suriname', and won the 2009-Black Magic Woman Literature Prize for her novel 'Titus'. The Surinamese-Javanese singers Ragmad Amatstam, Oesje Soekatma, and Eddy Assan are among the greatest and most beloved musicians Suriname has brought forth. Specializing in pop-Jawa songs, they reached a broad audience in both Suriname and The Netherlands. Notable Surinamese-Javanese sports heroes are Andy Atmodimedjo, Virgil Soeroredjo, and Mitchel Wongsodikromo. Andy Atmodimedjo was an impressive professional football player and became the successful manager of several clubs in Suriname's highest soccer league as well as the head coach of the country's senior and under-21 national soccer teams. And Virgil Soeroredjo and Mitchel Wongsodikromo were among the world's top badminton players who excelled on various national, Caribbean, Central American, and South American competitions.

Nevertheless, the Javanese have preserved their own identity, speaking their own language and adhering to their own specific religious and cultural customs. This also holds true for their traditional medical customs which are based on *Jamu*, the centuries-old traditional form of medicine from Indonesia that mainly involves the use of plants with medicinal properties. The first part of this chapter gave some background on Suriname; then addressed some of the religious and cultural expressions of Surinamese Javanese; focused on *Jamu*, and concluded with an extensive account of the traditional, phytochemical, and pharmacological aspects of four medicinal plants that are mainly used by Surinamese Javanese. This second part of the chapter continues with a comprehensive narrative about six additional popular 'Javanese' medicinal plants and concludes with the contribution of the Javanese pharmacognostic knowledge to Suriname's traditional medicinal pharmacopeia.

2. Plants used in Javanese pharmacognosy

Hereunder, six medicinal plants that are traditionally mainly used by Surinamese Javanese - in addition to four that have been addressed in the first part of this chapter - have in detail been assessed for their phytochemical contents and pharmacological activities in order to provide a scientific rationale for their ethnopharmacological applications. The plants have been selected on the basis of the

number of times they have been dealt with in a number of comprehensive publications describing the use of medicinal plants in the country [4–12]. All the ten plants and their main traditional use by Surinamese Javanese have been given in **Table 1**.

2.1 Asteraceae - *Ageratum conyzoides* L. 1753 not Hieron. 1895 nor Sieber ex Steud. 1840

The goat weed *A. conyzoides*, called *wedusan* in Surinamese-Javanese (**Figure 1**), is an annual herb that is native to northern Brazil. It is sometimes grown as an ornamental plant but has become a common invasive weed in many tropical regions in the Americas, the Caribbean, and Africa. It grows to a height of about 1 meter, has an erect stem covered with white hairs, carries leaves and flowers that emit a strong, unpleasant smell, and is commonly found in gardens and open spaces. The pungent smell from the leaf and flower is due to the presence of an essential oil with a strong nauseating odor [13]. Nevertheless, a decoction of fresh shoots and leaves is used as an ingredient of an 'anti-ageing' herbal shampoo [14]. *A. conyzoides* produces hepatotoxic pyrrolizidine alkaloids [15] that are regularly encountered as contaminants in, among others, grains, honey, milk, organ meats, and eggs [16]. For this reason, *A. conyzoides* is not consumed by humans except when taken for medicinal purposes.

In Suriname, an infusion from the whole plant is drunk against a sore throat, colics, and atony of the digestive tract [11], as well as gynecological diseases and gonorrhea [9]. A tea prepared from the root as well as the juice from the leaf are also used against a sore throat and, in addition, for reducing fever and fighting colds [12]. Itching all over the body, diarrhea, and chest conditions are treated by drinking a tea from the leaves [6]. A concentrated leaf decoction is used against chiggers [17], the juvenile forms of a type of mite (Trombiculidae) that are also known as berry bugs and that produces itching and blisters on the skin [18]. An infusion from the leaves is externally used against allergic conjunctivitis [6]. And a paste from the crushed leaves is applied on abscesses or burn wounds [6].

Most of the traditional uses and supporting pharmacological activities of *A. conyzoides* have been attributed to its essential oil [19]. The oil contains monoterpenes and sesquiterpenes that are mainly responsible for its fragrance [19], as well as important bioactive constituents such as flavonoids, alkaloids, steroids, benzofurans, tannins, chromenes, and coumarins [19]. A number of alkaloids and flavonoids have been encountered in other parts of the plant [19]. Several of these compounds may be associated with some its traditional uses and pharmacological activities.

The use of preparations from *A. conyzoides* against a sore throat, fever, and colds [11, 12] may have its rationale in the analgesic, antiinflammatory, antimicrobial, and wound healing activities of the plant. Evidence for analgesic activity was provided by the inhibitory effects of aqueous and ethanolic whole-plant or leaf extracts on acetic acid-induced writhing and/or formalin-induced licking in laboratory rodents, and the increase in the threshold of pain the animals experienced on a hot plate [20, 21]. Notably, an aqueous extract of the whole plant had been reported to accomplish analgesic effects and improvements in articulation mobility in patients with arthrosis [22]. The antinociceptive effects of *A. conyzoides* might be due to saponins and/or flavonoids in the plant [20, 23].

Indications for antiiflammatory effects of *A. conyzoides* came from the significant reduction in carrageenin-induced hind paw edema in rats by methanolic and ethanolic root, whole-plant, aerial, and leaf extracts of the plant [21, 23]. A leaf extract also exerted antiinflammatory effects in cotton pellet-induced granuloma and formaldehyde-induced arthritis models of inflammation in rats [24].

Family	Species (vernacular names in English; Surinamese-Javanese)	Part(s) used	Traditional indications	References
Acanthaceae	*Strobilanthes crispa* Blume (black face general; *ketji beling*)	Leaf	Disorders of the urinary system, diabetes mellitus	[8]
Araceae	*Acorus calamus* L. (sweet flag; *dlingo*)	Rhizome	Gastrointestinal disorders, intestinal parasites, common cold, convulsions and seizures in children, evil eye and evil spirits	[7, 8, 12]
Arecaceae	*Cocos nucifera* L. (coconut; *klapa*)	Coconut oil, coconut meat, coconut water, husk fibers	Respiratory problems, pimples, shingles due to herpes, diabetes mellitus, hypertension, gastrointestinal disorders, skin and hair care, skin lesions, burns, sprains, sore muscles, evil eye and luck	[6–10]
Asclepiadaceae	*Calotropis gigantea* (L.) Aiton (crown flower; *bidari*, *widuri*)	Latex, stem	Bleeding, skin lesions, burns, toothache, tonsillitis, colds, heart conditions	[10, 12]
Asteraceae	*Ageratum conyzoides* L. 1753 not Hieron. 1895 nor Sieber ex Steud. 1840 (goatweed; *wedusan*)	Whole plant, leaf, root	Symptioms of flu, gastrointestinal problems, gynecological disorders, gonorrhea, itching, skin lesions, burns, allergic conjunctivitis	[6, 9, 11, 12]
Caesalpiniaceae	*Tamarindus indica* L. (tamarind; *asem*)	Leaf, fruit pulp	Health-promoting *jamus*, fever, gynecological conditions, gastrointestinal disorders, itching, skin lesions	[4, 8, 12]
Fabaceae	*Sesbania grandiflora* (L.) Poiret (vegetable hummingbird; *turi*)	Leaf, bark	Abdominal disorders, throat and oral infections	[12]
Portulacaceae	*Portulaca oleracea* L. (green purslane; *krokot*)	Whole plant, leaf	Skin lesions, sprains, swellings, stiff joints, pain, bronchitis, conjunctivitis, anemia	[5, 9, 12]
Zingiberaceae	*Curcuma longa* L. (turmeric; *kunjit*)	Rhizome	Health-promoting *jamus*, gynecological disorders, gastrointestinal diseases, fever, inflamed gums, conjunctivitis, skin lesions, pinworm infection	[8, 12]
Zingiberaceae	*Zingiber officinale* Roscoe (ginger; *djahe*)	Rhizome	Health-promoting *jamus*, overweight, respiratory diseases, gastrointestinal disorders, gynecological problems, bruises, rheumatic joints, sore muscles	[8, 12]

Table 1.
Plants commonly used in Javanese traditional medicine addressed in this chapter, parts preferentially used, and traditional indications in the Surinamese-Javanese community.

Figure 1.
The goat weed Ageratum conyzoides *L. 1753 not Hieron. 1895 nor Sieber ex Steud. 1840 (Asteraceae) (from: https://images.app.goo.gl/1tsLVnadhCW6kXSr6).*

The antiinflammatory activity of *A. conyzoides* might be attributed to certain flavonoids [25]. This supposition is based on the amplification of the inhibitory effect of a methanol extract of the aerial part of the plant on the carrageenan-triggered edema in rats by a flavonoid fraction [25].

Support for antimicrobial activities of *A. conyzoides* was provided by the broad activity of aqueous, methanolic, and ethanolic extracts from the leaf and the whole plant as well as the essential oil of the plant against both Gram-positive and Gram-negative pathogenic bacteria [26, 27]. The plant extracts were also active against bacteria from wound isolates [28], methicillin-resistant *Staphylococcus aureus* [29], and clinical isolates of *Helicobacter pylori* [30]. Furthermore, the essential oil exhibited meaningful fungitoxic effects [26, 31] including activity against *Microsporum gypseum*, the causative agent of ringworm [32], *Candida* spp. [26], and the aflatoxin B1-producing A*spergillus flavus* [33]. That *A. conyzoides* may possess, in addition, would healing properties, has been suggested by the improved rates of epithelialization and wound contraction as well as the increased tensile strength of open excision wounds in Wistar rats accomplished by aqueous, methanolic, and ethanolic extracts of the leaf [34].

The analgesic, antiinflammatory, antimicrobial, and wound healing properties of *A. conyzoides* may also (partially) explain the traditional use of leaf preparations against burning eyes and skin lesions [6], itchy skin [6, 11], gonorrhea [9] as well as against gastrointestinal disorders caused by infectious microorganisms [6, 11]. The latter use is further supported by the *in vitro* schistosomicidal effect of the essential oil of the plant against the blood fluke *Schistosoma mansoni* [35]; the protective activity of aqueous and ethanolic leaf extracts against ethanol-induced gastric lesions in rats [36]; and the spasmolytic effect of an aqueous leaf extract on isolated rat intestine smooth muscles [37].

2.2 Caesalpiniaceae - *Tamarindus indica* L.

The tamarind *T. indica*, called *asem* in Surinamese-Javanese (**Figure 2**), is a long-lived, slow-growing, evergreen tree that can reach a height of 20 meters. The plant has a dense, spreading crown and an extensive root system that makes it very tolerant of windy conditions and drought. Its origin is uncertain but is thought to lie in tropical Africa. From there, it has long ago been introduced in more than fifty tropical and subtropical parts throughout the world. *T. indica* has fragrant flowers and is extensively cultivated for its edible, sweet–sour-tasting seedpods due to their relatively high concentrations of tartaric acid and reducing sugars. The pods, along with the young leaves, seedlings, and flowers, are extensively used for preparing a large variety of dishes, beverages, and confections, and the dried seeds can be roasted and ground as a coffee substitute.

T. indica also has a wide range of medicinal applications in various traditional systems throughout Asia, Africa, and the Americas. The plant has presumably been introduced in Suriname by enslaved Africans who used it to fight fever, diarrhea, and worm infections on board of the slave ships [11]. Since then, it is abundantly used medicinally in this country. Javanese use the leaves, together with the rhizomes from *Curcuma* spp., in various health-promoting *jamus*, and drink an infusion from the fruit pulp to ease menstrual pain and vaginal discharge [8]. The pulp is used

Figure 2.
The tamarind Tamarindus indica *L. Caesalpiniaceae (from: https://images.app.goo.gl/ViLrKniuZfAGExDb7).*

for treating constipation as well as skin conditions, heartburn, and jaundice [4]. Preparations from the leaf are drunk to stimulate perspiration in patients with fever [4] and in herbal baths to ease itching and skin irritation caused by measles, chicken pox, or rubella [12]. And Maroon women who have recently given birth incorporate *T. indica* leaves in a hot steam bath to cleanse the uterus and the vagina [12], presumably because of the presence of astringent, antimicrobial, and wound healing properties of the tannins in the plant [38].

T. indica contains a variety of phytochemicals with nutritious and pharmacological properties which can account, at least partially, for the traditional uses of the plant and for the pharmacological studies supporting these uses [39]. Important bioactive constituents in the plant are terpenoids and phenolic compounds including tannins; citric, malic, and tartaric acid; pectin and various pentoses and hexoses; many essential dietary minerals; as well as amino acids and proteins [39].

The incorporation of *T. indica* parts in *jamus* for improving well-being [35] may be associated with its antioxidant, weight-reducing, and immunomodulatory properties. Evidence for the former property was provided by the potent antioxidant activity exhibited by seed, pericarp, and fruit pulp preparations in various *in vitro* assays [40–42], and the improved efficiency of the antioxidant defense system in hypercholesterolemic hamsters treated with an ethanolic extract of the seed coat [41]. The antioxidant activity could be attributed to the polyphenolic compounds such as proanthcyanidins in the preparations [40, 42].

Indications for weight-reducing properties of *T. indica* came from the hypolipidemic and antioxidant activities of the fruit pulp or a fruit extract in rats on a cholesterol-rich diet [41] and the hypolipidemic and slimming effects of an ethanolic fruit pulp extract in obese rats on a cafeteria diet or on sulpiride (an antipsychotic drug that causes weight gain) [43]. And suggestions for immunomodulatory activity of *T. indica* were given by the stimulatory effects of a polysaccharide isolated from the fruit pulp on the uptake of foreign bodies by phagocytes, the promotion of lymphocyte proliferation, and the inhibition of leukocyte proliferation *in vitro* [44], as well as the increase in total white blood cell count, CD4+ T-cell population, and bone marrow cellularity in BALB/c mice which had receiving the polysaccharide intraperitoneally [45].

The use of *T. indica* against skin lesions [12] as well as menstrual pain and vaginal discharge [8] may be accounted for by the analgesic, antiinflammatory, and antimicrobial properties of the plant. Indications for both former activities came from the increase in reaction time of laboratory rodents in a tail immersion, acetic acid-induced writhing, tail flicking, and hot-plate assay, and the reduction in carrageenan-induced hind paw edema in the animals accomplished by a petroleum ether stembark extract, an aqueous fruit extract, a hydroethanolic leaf extract, and a methanolic seed extract [46, 47]. Evidence for antimicrobial activity came from the broad *in vitro* antibacterial and antifungal activity of preparations from various parts of the plant [48–50]. The analgesic and antiinlammatory activities of *T. indica* have been attributed to sterols, triterpenes, and phenolic compounds in the plant [46, 47]. The antimicrobial activities have mainly been associated with phenolic compounds and the essential oil [48].

Further support for the traditional uses of *T. indica* mentioned in the preceding alinea lesions [12] are its antihistaminic potential as suggested by the inhibitory effects of a leaf methanolic extract on the histamine-induced contraction of goat tracheal chain and guinea pig ileum [51], and its wound healing activity, as indicated by the accelerated wound closure, epithelial migration, and re-epithelialization of various types of wounds in laboratory rodents caused by water and methanolin seed extracts seed [52], the fruit paste [53], and the cork and seed ash [54].

The claims of efficacy of *T. indica* against gastrointestinal problems [4] is supported by the efficacy of preparations from the fruit pulp against constipation [55] due to the presence of relatively high amounts of tartaric acid and malic acid in their salt form which improve the movement of the bowel and act as a mild laxative [38]. Furthermore, a methanolic seed coat extract elicited meaningful antiulcer effect on ibuprofen-, alcohol-, and pyloric ligation-induced gastric lesions in rats when compared to the antipeptic agent ranitidine [56]. Finally, the use of *T. indica* against fevers [4] is supported by the antipyretic activity of a water-soluble crude polysaccharide fraction from the fruit pulp against the raised body temperature in rats and mice which had subcutaneously been injected with yeast or intraperitoneally with a lipopolysaccharide (LPS) from *Escherichia coli*, respectively [57].

2.3 Fabaceae - *Sesbania grandiflora* (L.) Poiret

The vegetable hummingbird *S. grandiflora*, known as *turi* in Surinamese-Javanese (**Figure 3**), is a fast-growing, relatively short-lived, highly branched tree that can grow to about 4 meters tall, and has rounded leaves, white, red, or pink flowers, as well as flat, long, thin, and green bean-like fruits. The plant probably originates from Indonesia and/or Malaysia, but is abundantly found in other hot and humid locations throughout the world. It is cultivated in various countries for its many edible parts. *S. grandiflora* also has many traditional medicinal uses in various parts of the world [58]. In Suriname, the plant is mainly used by Javanese, who cook the flowers, leaves, and young pods and eat them as a vegetable [12]. They also prepare a tea from the astringent bark for treating abdominal disorders and use the leaf juice as a gargle against a sore throat and mouth sprue [12].

Phytochemical studies revealed the presence of several bioactive in *S. grandiflora* that may account for its traditional uses including alkaloids, flavonoids, tannins, terpenoids, glycosides, steroids, and saponins [59]. Some of these compounds have been associated with, among others, the antimicrobial, hepatoprotective, antioxidant, and hypolipidemic activities of the plant [60–62].

Figure 3.
The vegetable hummingbird Sesbania grandiflora *(L.) Poiret (Fabaceae) (from: https://images.app.goo.gl/8oo6WbZ8MJsEr5e2A).*

Pharmacological support for the use of a concoction from *S. grandiflora* stembark against gastrointestinal disorders [12] is provided by the preventive action of an ethanolic extract of this part of the plant against acute gastric injury in rats caused by stress or non-steroidal anti-inflammatory drugs [63]. Of note, the extract did not modify the volume, pH, and hydrochloric acid contents of the gastric secretion of the animals [63]. Importantly, ethanolic extracts of the leaf substantially inhibited the development of ulcers in adult albino rats caused by pylorus ligation and ethanol when compared to omeprazole [64]. Furthermore, the seed oil showed considerable anthelmintic activity [65], speaking in favor of its traditional use to expel parasitic worms and other internal parasites from the gastrointestinal tract. Moreover, an *S. grandiflora* ethanolic leaf extract exerted a substantial protective effect on liver injury in rats produced by the antibiotic erythromycin estolate [61].

The use of the leaf juice against conditions of the throat and the oral cavity [12] may be accounted for by the antibacterial and wound healing activity of this preparation. Support for the former suggestion came from the notable activity of extracts from the leaf - but also from the stembark, the flower, and other parts of the plant - against a variety of bacterial strains [66–68]. The antimicrobial activity was most prominent with extracts prepared with organic solvents [66–68] and was also directed against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci, either in culture or in silkworms infected with these pathogens [68]. In some cases, the antimicrobial properties of the plant have been associated with the presence of bioactive constituents such as tannins, sterols, saponins, phenolic compounds including flavonoids, and alkaloids [66, 68, 69].

Indications for wound healing activity of *S. grandiflora* came from the rapid repair of excision and/or incision wounds in Wistar albino rats following the topical application of a methanolic extract of the stembark or an ethanolic extract from the flower when compared to the topical antibiotics framycetin sulphate and nitrofurazone, respectively [70, 71]. Furthermore, the use of a semi-purified extract of the stembark significantly stimulated the healing of incision wounds on the mucosa of the lower lip of rats when compared to the topical antiseptic and disinfectant dequalinium chloride [72]. This activity has been attributed to the astringent and antimicrobial properties of the stembark and has been interpreted as support for the traditional use of the plant against mouth ulcers [72]. As well, an ethanolic extract of *S. grandiflora* flower showed potent *in vitro* activity against *Streptococcus mutans* - that is commonly found in the human oral cavity and is a significant contributor to tooth decay - that was comparable to that of erythromycin [73].

2.4 Portulacaceae - *Portulaca oleracea* L.

The green purslane *P. oleracea*, called *krokot* in Surinamese-Javanese (**Figure 4**), is an erect annual succulent herb that can reach a height of about 40 centimeters. The origin of this plant is uncertain but may lie in western Asia, India, and/or even Africa. *P. oleracea* was probably one of the first plants to be domesticated as a food crop. Now, it often grows as a weed in fields, waste grounds, roadside verges, and cultivated grounds in many temperate tropical parts of the world. However, it is among the richest vegetable sources of omega-3 fatty acids and also contains high levels of vitamins C and E, β-carotene, and dietary minerals such as potassium, magnesium, calcium, phosphorus, and iron [74].

P. oleracea has also been used in various folk medicinal systems since ancient times and is still one of the most widely used medicinal plants in the world [75]. In Suriname, individuals from all ethnic groups including those from Javanese ancestry, mainly use preparations from *P. oleracea* as a dressing on abscesses and sores; as an ointment with coconut oil for sprains, swellings, stiff joints, as well as

Figure 4.
The green purslane Portulaca oleracea *L. (Portulacaceae) (from: https://images.app.goo.gl/wmwxjiB8FvgpzF7JA).*

back and neck pain; to stop bronchitis, and against conjunctivitis [5, 9]. The plant is also widely used against anemia [12] because of its relatively high iron content [74]. Incidentally, administration of *P. oleracea* seeds to adolescent females with iron deficiency anemia led to appreciable increases in the girls' hemoglobin, hematocrit, and mean corpuscular volume [76].

Some of the traditional uses may be associated with the presence in the plant of potent bioactive compounds such as flavonoids and alkaloids [77, 78]. Some of the flavonoids have been associated with antibacterial, antiviral, antiinflammatory, and/or antioxidant activities of the plant [77–79]. Potent alkaloids identified in the plant are dopa, dopamine, and noradrenalin as well as oleracimines which have been associated with the antiinflammatory properties of the plant [77, 78, 80].

The apparent usefulness of *P. oleracea* as a dressing on abscesses and sores and for treating sprains, swellings, stiff joints, and back and neck pain [12] may be explained by the wound healing, antiinflammatory, analgesic, antioxidant, and/or antimicrobial activity elicited by preparations of parts of the plant. Support for the wound healing-promoting properties of *P. oleracea* came from the stimulation of contraction, the decrease in surface area, and the increase in tensile strength of excision wounds in mice following topical treatment with an extract of the aerial parts of the plant [81]. An ethanolic extract of the aerial parts of the plant also accelerated the healing of excision wounds in streptozotocin-induced albino rats by stimulating wound contraction and promoting granulation and organization formation [82].

Indications for antiinflammatory and analgesic activities of *P. oleraceae* were provided by the inhibitory effects of extracts from aerial-parts, leaf, and seed extracts of the plant in the paw edema and ear edema tests, as well as the paw licking, writhing, tail flicking, and hot plate tests [83, 84]. Importantly, intraperitoneal administration of the alkaloid allantoin isolated from the seed gave comparable results [85]. The anti-inflammatory and analgesic efficacies of the plant-derived products were similar to those found with diclofenac and aspirin [83–85]. Furthermore, aqueous extracts of the dried aerial parts of the plant prevented the TNF-α-induced vascular inflammatory events in cultured human umbilical vein endothelial cells (HUVECs) [86], and

substantially inhibited the protein expression of iNOS as well as the production of PGE2, IL-6, and TNF-α in LPS-activated cultured RAW 264.7 murine macrophages [87]. The antiinflammatory activities of the *P. oleracea* preparations have been attributed to oleracimines, since these compounds inhibited the secretion of various inflammatory mediators by LPS-stimulated macrophages [88].

Indications for antioxidant activity of *P. oleracea* have been provided by the protective effects of an aerial-parts aqueous extract against DNA strand breakage in human lymphocytes caused by hydrogen peroxide [89], and of aqueous and ethanolic seed extracts against hemolysis of erythrocytes caused by the free radical initiator 2,2′-azobis hydrochloride [90]. Furthermore, administration of leaf and stem preparations prevented oxidative damage in the liver of laboratory mice treated with steptozotocin [79] or fed with a high-fat diet, among others, by modulating blood and liver antioxidant enzyme activities [91]; increased the levels of reduced glutathione, catalase, superoxide dismutase, glutathione reductase, glutathione-S-transferase and glutathione peroxidase, and inhibited lipid peroxidation and nitric oxide in liver, kidney, and testis of male Wistar albino rats [92]; and improved serum levels of superoxide dismutase and catalase in sensitized rats [93]. The latter results were also achieved with the use of α-linolenic acid, one of the constituents of the leaf and stem of the plant [93].

P. oleracea probably also possesses antibacterial, antifungal, and antiviral activities. These suppositions are supported by the growth-inhibitory activity of extracts of the leaf and stem against a wide range of both Gram-negative and Gram-positive pathogenic bacteria [94, 95] as well as *Candida albicans* [94]. An ethyl acetate extract of the aerial parts of the plant also inhibited the growth of dermatophytes of the genera *Trichophyton* [96]. And a polysaccharide isolated from the aerial part of the plant was active against herpes simplex virus type 2 [97] and a methanolic extract of the aerial parts against hepatitis C virus genotype-3a infected in cultured Huh-7 human liver cells [98]. The apparent antiviral activities of *P. oleracea*, along with the above-mentioned antibacterial and antifungal properties of the plant may account for its traditional use in Suriname against conjunctivitis [5] and bronchitis [9].

2.5 Zingiberaceae - *Curcuma longa* L.

The turmeric *C. longa*, known as *kunjit* in Surinamese-Javanese (**Figure 5**), is an erect, herbaceous, perennial plant that grows to a height of about 1.5 meters. It is believed to have arisen in southern or south-eastern Asia by selection and vegetative propagation of a hybrid between the wild turmeric *Curcuma aromatica* Salisb. and other closely related species. As a result, *C. longa* is not found in the wild and is only known as a domesticated plant. The maternal plant carries yellow-white flowers that do not produce viable seed and multiplies by producing new sprouts from its underground rhizomes. The plant is abundantly cultivated for its pulpy orange-yellow rhizome in Indonesia and India as well as many other tropical and subtropical parts of the world. The pungent and bitter-tasting rhizome is dried and ground into a yellow powder, an essential ingredient of curry powders and pastes for coloring and flavoring many meat and fish dishes in Asian cuisine and as a bright yellow constituent that is used in the food industry as a natural food colorant.

C. longa preparations have also a centuries-long medicinal use in various traditional systems, particularly in Indonesian Jawa and Indian Ayurveda, Unani, and Siddha [99]. In Suriname, *C. longa* rhizome is an essential ingredient of many *jamus* to promote health and fitness and to enhance mental functioning and well-being, as well as in *jamus* for treating inflamed gums, abscesses, menstrual pains, and skin rash [8]. In addition, drinking a tea from the fresh rhizome would purify the

Figure 5.
The turmeric Curcuma longa *L. (Zingiberaceae) (from: https://images.app.goo.gl/1QbEoBg45CR8ub2m6).*

blood and treat stomach pain, chewing on the fresh rhizome and swallowing the sap would help against diarrhea, drinking the sap mixed with chalk would help against menstrual pains, and having children drink the sap of the grated rhizome mixed with that of other plants would take care of pinworm infection [12]. Moreover, the sap from the fresh rhizome is rubbed on the abdomen to ease bellyache and fever, dripped on watering eyes and inflamed eyelids, and used to disinfect pierced ears and the navel of newborn babies [12].

The main constituents of *C. longa* rhizome that may be associated with these beneficial effects are polyphenolic compounds such as diarylheptanoids and diarylpentanoids, as well as terpenoids such as sesquiterpenes, monoterpenes, diterpenes, and triterpenoids [100, 101]. The most common diarylheptanoids are the yellow-colored curcuminoids curcumin along with its derivatives demethoxycurcumin and bisdemethoxycurcumin [100, 101]. These constituents impart the characteristic color and flavor to preparations from this part of the plant [100, 101]. The sesquiterpenes are the main constituents of the rhizome essential oil, while the monoterpenes dominate the essential oils from the leaves and the flowers [101]. The major volatile principles of the rhizome oil are the aromatic compounds α- and β-turmerone [101].

Several lines of evidence support the inclusion of *C. longa* rhizome in *jamus* to promote health and fitness and to enhance mental functioning and well-being [8]. Firstly, rhizome preparations reduced the deposition of plaques similar to those seen in Alzheimer's disease in the brains of aged mice and the oxidative damage and amyloid pathology in transgenic mouse models of Alzheimer's disease [102]. Secondly, curcumin therapy produced favorable responses in a transgenic mouse model of Alzheimer's disease [103], and both curcumin and dimethoxycurcumin lessened lead-induced memory deficits in Wistar rats [104]. Furthermore, a water extract of the rhizome exerted anti-stress effects in laboratory rats which were comparable to those caused by the antidepressant fluoxetine [105]. Importantly, the results from clinical studies suggested that the daily intake of this extract had a positive influence on emotional fatigue in healthy individuals [106], that curcumin intake reduced fatigue, tension, anger, confusion, and total mood disturbance following 4 weeks of supplementation in non-depressed healthy elderly people [107, 108], and that curcumin reduced depressive symptoms in individuals suffering from depression [109].

The usefulness of *C. longa* against (inflammatory) gastrointestinal conditions [12] is sustained by the inhibitory effects of curcumin on the damage caused by indomethacin to the gastric mucosa of laboratory rats [110] and the production

of inflammatory cytokines, intercellular adhesion molecule 1, and TNF-α in the animals [110]. Furthermore, curcumin substantially improved the profile of inflammatory markers, severity of diarrhea, and colonic architecture in laboratory mice with colitis induced by trinitrobenzenesulfonic acid [111]. Clinical trials indeed showed beneficial effects of curcumin or a standardized *C. longa* rhizome extract in patients with peptic ulcers [112] or inflammatory bowel disease [113]. In fact, a Cochrane analysis revealed that curcumin may be a safe and effective therapy for the maintenance of remission in quiescent ulcerative colitis [114].

These apparent antiinflammatory activities of *C. longa* also support its traditional use against primary dysmenorrhea [12]. The substantial reduction in the level of pain during menstruation accomplished by rhizome preparations in various clinical studies (see, for instance, ref. [115]) was presumably due to blockade of prostaglandin production by curcumin [116], producing analgesic and antiinflammatory effects [116, 117]. The same mechanisms may be involved in the apparent beneficial effects of *C. longa* preparations against inflamed gums, abscesses, pain, inflammatory skin conditions, and conjunctivitis [8], as well as the application of a *C. longa*-based Javanese ointment called *bobok* for alleviating the discomfort of, among others, toothache [8].

The aseptic properties of *C. longa* may contribute to these effects. Indeed, both rhizome preparations and curcumin inhibited the growth of various standard bacterial strains [118, 119] including common periopathogens [120], as well as pathogenic fungi such as *Candida albicans* [121] and *Aspergillus flavus* [122]. Curcumin and its derivatives were also active against a broad variety of pathogenic viruses [123] including the influenza virus [124], accounting for its traditional use for fighting fever [12]. Finally, the broad antiparasitic activity of curcumin [125] may explain the Surinamese-Javanese custom of including *C. longa* rhizome in preparations for treating pinworm infection in children [8].

2.6 Zingiberaceae - *Zingiber officinale* Roscoe

The ginger *Z. officinale*, called *djahe* in Surinamse-Javanese (**Figure 6**), is a slender, erect, herbaceous perennial plant that grows to a height of about 2 meters. It has a thick, branched rhizome that grows horizontally near the soil surface and gives rise to leafy shoots that grow close together. *Z. officinale* has a long history of cultivation and use, with records going back almost 2,000 years [126]. It has probably first been domesticated in tropical Asia, presumably China, and is believed to have spread via south-eastern Asia and Africa to the Neotropics. In all these parts of the world it is abundantly cultivated for its succulent, aromatic, and pungent rhizome. This part of the plant is widely used as a hot, spicy flavoring for a variety of oriental dishes, as well as cakes, candies, and hot and cold beverages. *Z. officinale* also has a very long use as a medicinal herb in many traditional systems, particularly those from Indonesia, India, and China, where the fresh or dried rhizome and the essential oil are ingredients of numerous medicaments [127].

Z. officinale has probably been introduced in Suriname by Javanese indentured laborers [8]. The rhizome is an ingredient of many health-promoting *jamus* including those for maintaining the functioning of heart, muscles, blood vessels, and intestines, as well as those to stimulate fertility, reduce the risk of diabetes mellitus, and decrease stress [8]. Furthermore, all ethnic groups in Suriname also use *Z. officinale* rhizome for treating coughing, influenza, cold, sore throat, hoarseness, laryngitis, and pneumonia; stomach cramps and other abdominal problems; overweight; menstrual pain and to cleanse the uterus after delivery; and externally to massage bruised limbs, rheumatic joints, and sore muscles [12].

Figure 6.
The ginger Zingiber officinale *Roscoe Zingiberaceae (from: https://images.app.goo.gl/ETuwvyrgdVMDP5eY9).*

The distinctive odor and flavor of *Z. officinale* rhizome is mainly the result of a combination of volatile oils and non-volatile phenolic compounds [128]. The volatile oils predominantly consist of zingiberol and other sequiterpene hydrocarbons [128], while the non-volatile phenolic phytochemicals comprise, among others, gingerols, shogaols and paradols [128]. Gingerols, including 6-gingerol - the best studied phytochemical in *Z. officinale* - are the major pungent compounds in the fresh rhizome [128]. The gingerols are thermally labile and easily undergo dehydration reactions during drying, heating, or prolonged storage of the rhizome to form the corresponding shogaols which are about twice as pungent as the gingerols [128].

Both gingerols and shogaols exhibit a host of biological activities [129, 130], supporting some of the traditional claims of *Z. officinale* [8, 12]. The incorporation of *Z. officinale* in many health-promoting *jamus* [8] may be related to the ameliorating effects of the essential oil on the antioxidant capacity, inflammatory response, and the building up of fat in the liver in cases of high-fat diet-induced non-alcoholic fatty liver disease [131]. The antioxidant compounds in *Z. officinale* rhizome are primarily gingerols, shogaols, and some related diarylheptanoids [132], and may help protect the cells from oxidative stress [133]. In addition, *Z. officinale* preparations accomplished hypocholesterolemic, hypolipidemic, and antiatherosclerotic effects in cholesterol-fed rabbits and rats [134] and inhibited LDL oxidation and attenuated the development of atherosclerosis in apolipoprotein E-deficient mice [133].

Furthermore, crude rhizome methanol extracts elicited potent positive-inotropic effects in an isolated guinea pig left atria preparation [135]. These extract also induced a dose-dependent fall in blood pressure in anesthetized rats, inhibited the spontaneous force and beating rate of atrial contractions in guinea pig atria similarly to the calcium antagonist verapamil, and caused endothelium-independent vasodilation in rabbit and rat aorta [136]. These apparent cardiotonic activities have been ascribed to the gingerols and the shogaols in the preparations [125, 136]. Additional support for the inclusion of *Z. officinale* rhizome in health-enhancing *jamus* is provided by the ameliorating activity of 6-gingerol on the genotoxicity

(chromosomal aberrations and sister chromatid exchanges) caused in cultured human lymphocyte chromosomes by norethandrolone and oxandrolone [137], and the chemopreventive activities of gingerols and shogaols in animals treated with laboratory carcinogens [138].

The folkloristic use of *Z. officinale* for treating conditions of the respiratory system is supported by the broad *in vitro* antibacterial properties of rhizome preparations as well as gingerols against both Gram-positive and Gram-negative human pathogenic bacteria and fungi [139] including those associated with respiratory tract infections [140]; the potentiation of the antibacterial effect of some commonly used antibiotics by the rhizome extract [141]; and the activity of these substances and compounds against the influenza A/Aichi/2/68 virus [142], the human respiratory syncytial virus (HRSV) [143], and the influenza A (H1N1) virus [144].

Several pieces of evidence support the traditional use of *Z. officinale* against gastrointestinal disorders [12]. Firstly, preparations from the rhizome inhibited the growth of several strains of *Helicobacter pylori* [145] and improved dyspeptic symptoms in patients with *H. pylori*-positive functional dyspepsia [146]. Secondly, rhizome preparations had a stimulatory effect on antiinflammatory cytokines and an inhibitory effect on proinflammatory cytokines in inflammations associated with the alimentary channel such as colitis and inflammatory bowel disease [147]. The antiinflammatory activities have been associated with potent inhibitory effects on prostaglandin, thromboxane, and leukotriene biosynthesis [148] and COX-2 activity [149]. Furthermore, methanolic and aqueous extracts from the rhizome exerted meaningful activity against larvae of the rat long worm *Angiostrongylus cantonensis* and those of the parasitic fish nematode *Anisakis simplex*, the causative agents of angiostrongyliasis, the most common causes of eosinophilic meningitis or meningoencephalitis in south-eastern Asia and the tropical Pacific islands [150], and anisakiasis, a gastrointestinal infection characterized by severe abdominal cramps [151], respectively. This suggests that *Z. officinale* also has activity against parasites of the alimentary tract, further supporting its traditional use against conditions of this organ system [12].

3. Concluding remarks

The Javanese have been in Suriname for over a century. They have been brought to that country as poor and unaccustomed indentured laborers but have become successful individuals who have integrated well into the Surinamese community, actively participating in all its sections. Indeed, the Javanese are full-fledged citizens of the country and an integral part of the vibrant color palette represented by its unique cultural, religious, and ethnic diversity. This is reflected by the presence of the small, often family-owned Javanese restaurants called *warungs* in the smallest of towns, where widely appreciated savory dishes such as *bami goreng* (fried noodles), *nasi goreng* (fried rice), *pityel* (mixed blanched vegetables with a peanut sauce dressing), *teloh* (fried cassava), *pejeh* (prawn crackers), and *saoto* soup (chicken broth, meat, and vegetables) can be enjoyed, and can be washed down with refreshing beverages such as the lemongrass-, corn starch-, and coconut milk-based *dawet*.

Nevertheless, the Javanese have maintained most of their cultural traditions. This particularly holds true for their ancient form of medicine that is based on centuries-old *Jamu*. *Jamu* has added a unique element to the array of traditional forms of medicine throughout the Caribbean and Latin America, most of which are based on practices from the Indigenous American peoples as well as those from Africa, China, India, and various European countries. The influence of *Jamu* is already

noticeable. The use of an infusion of the cat's whiskers or *kumis kutjing Orthosiphon aristatus* (Blume) Miq. (Lamiaceae) for treating kidney stones and renal colics is no longer limited to Indonesia and Suriname but has expanded into many other parts of the world. It is foreseeable that many more *Jamu* recipes will one day contribute to Suriname's traditional medicinal pharmacopeia as well as to the development of novel mainstream drugs for treating human diseases.

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Chapter 14

Medicinal Plants, Bioactive Compounds, and Dietary Therapies for Treating Type 1 and Type 2 Diabetes Mellitus

Chinaza Godswill Awuchi

Abstract

Medicinal plants, bioactive compounds, and dietary measures have been found to be effective in the treatment of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). About 463 million people have diabetes worldwide; estimates project 700 million people by 2045. While T1DM is caused by the loss of beta cells of pancreatic islets that produce insulin, resulting in the deficiency of insulin, T2DM, which constitutes over 90 to 95% of all DM cases, is caused by insulin resistance, and could relatively combine reduction in the secretion of insulin. *Aloe vera, Terminalia chebula, Perilla frutescens, Curcuma longa, Zingiber zerumbet, Nigella sativa, Gongronema latifolium, Pachira aquatic, Caesalpinioideae, Azadirachta indica, Artemisia dracunculus, Artemisia herbaalba, Vachellia nilotica, Abelmoschus moschatus, Cinnamomum verum, Salvia officinalis, Tinospora cordifoli, Pterocarpus, Ocimum tenuiflorum, Mangifera indica, Syzygium cumini, Coccinia grandis, Caesalpinia bonduc, Gymnema sylvestre, Carthamus tinctorius, Allium sativum,* and *Trigonella foenum-graecum* are among the medicinal plants shown to be effective in controlling and treating T1DM and T2DM. Bioactive compounds such as lycopene, vitamin E, vitamin D, genistein, quercetin, resveratrol, epigallocatechin-3-gallate, hesperidin, naringin, anthocyanin, etc. are useful in treating T1DM and T2DM.

Keywords: medicinal plants for treating diabetes type 1 and 2, bioactive compounds for treating diabetes type 1 and 2, dietary measures for managing diabetes, diabetes mellitus, herbal therapy for diabetes

1. Introduction

Diabetes mellitus (DM), simply called diabetes, are metabolic disorders characterized by varying or persistent hyperglycemia (high levels of sugar in the blood) over an extended time period. The most common symptoms of DM usually include increased appetite, increased thirst, and frequent urination. If not treated or when poorly managed, DM can result in several complications. While acute complications of DM often include hyperosmolar hyperglycemic state, diabetic ketoacidosis, or even death, severe chronic complications include cognitive impairment, damage to the eyes, damage to the nerves, foot ulcers, chronic kidney disease, stroke, and cardiovascular disease [1]. Diabetes mellitus (DM) manifest by hyperglycemia,

defects in insulin secretion, glucose intolerance, and/or failure of insulin activity to boost uptake of glucose. Diabetes mellitus (DM) causes global burden as a result of its high morbidity/mortality rates, as well as the capital intensity required for its treatment and management. About 463 million people have DM worldwide, while estimates project 700 million people by 2045 [2].

Globally, epidemiological studies showed that diabetes is more prevalent in middle- and low-income countries with about 50 percent of cases unreported and undiagnosed [2, 3]. Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are the most common types of DM. Over 90 to 95% of DM cases are T2DM [2, 4], while the remain 5 to 10% are other types of DM, including T1DM, the gestational diabetes, and other minor specific types rarely encountered. Worldwide, there has been serious search for cost effective and potent drug against T1DM and T2DM in order to reduce the annual death rate [5]. Various antidiabetic therapeutics and treatments that make use of conventional medications are often laborious as they are not single-dose treatment regimen; some are taken throughout lifetime. In recent years, medicinal plants, bioactive compounds, and dietary measures have been found to be effective in the treatment of T1DM and T2DM.

The increasing awareness of the safety and efficacies of medicinal plants, dietary therapy, and bioactive compounds in treatment of various metabolic diseases is gradually reshaping treatment measures for many metabolic diseases [6–8], including DM. Medicinal plants and their bioactive constituents play important role in regulating metabolisms in humans, usually resulting in improved health and general wellbeing. They can be largely found in fruits and vegetables, medicinal plants [9–16], whole grains [11], etc., and could be consumed every day. The health benefits of bioactive compounds are commonly reported in animal and cell studies, which often include regulating cell signaling pathway, scavenging free radicals, and decreasing inflammation [17, 18]. Natural materials containing bioactive compounds have been traditionally employed in the treatment of diabetes mellitus (DM). Due to their safety, availability, and tolerable side effects, bioactive compounds applications have been suggested for reducing incidences or delaying progression of many diseases, such as T1DM and T2DM, constipation, Alzheimer's disease, etc. [19, 20]. This chapter provides detailed descriptions and efficacies of the medicinal plants, bioactive compounds, and dietary nutrients shown to be effective in treating T1DM and T2DM. Although the medicinal plants, bioactive compounds, and dietary nutrients discussed in this chapter are mainly focused on T1DM and T2DM, they could also be effective against the less common types of DM such as the gestational diabetes and other minor specific types rarely encountered.

2. Causes and complications of T1DM and T2DM

Type 1 diabetes mellitus (T1DM) is caused by the loss of beta cells of pancreatic islets that produce insulin, resulting in the deficiency of insulin. T1DM can be additionally classified as idiopathic or immune-mediated. Most T1DM has the nature of the immune mediation, where an autoimmune attack mediated by T-cell results in loss of beta cells and consequently insulin [21]. The majority of the affected individuals are otherwise mostly healthy, with healthy weight during the onset occurrence. Responsiveness and sensitivity to insulin are often normal, particularly in initial stages. Though T1DM is often referred to as "juvenile diabetes" due because of the regular onset in children, most people with T1DM are currently adults. T1DM could be accompanied by unpredictable, irregular high levels of blood sugar, and potentials for serious low levels of blood sugar or diabetic ketoacidosis. Other T1DM complications are endocrinopathies (such as Addison's disease),

gastroparesis (that results in irregular dietary carbohydrates absorption), infection, and impairment in the counterregulatory responses to low levels of blood sugar. These usually occur in 1–2% of those with T1DM [22]. T1DM is in part hereditary, with several genes, such as some HLA genotypes, having influence on T1DM risks. In those with genetic susceptibility, the onset of DM could be caused by at least environmental factors, including diet, stress, or viral infection [23]. Although many viruses have been reported, however, no reliable evidence has supported their potentials to cause DM in humans [23, 24]. Among dietary factors, it has been reported that gliadin (a gluten protein) can be a factor in the development of T1DM, although the mechanism has not been established, at least not entirely. T1DM occurs at any stage of life; significant percentage has been detected in adulthood. Latent autoimmune diabetes of adults (LADA) is a term used when T1DM occurs in adulthood, and has slower onset than T1DM in children. Due to this difference, few people make use of the unofficial term "type 1.5 diabetes" in place of T1DM in adults. Adults with latent autoimmune diabetes of adults are often misdiagnosed as having T2DM initially, due to age instead of cause [25].

On the other hand, type 2 diabetes mellitus (T2DM), which constitutes over 90 to 95% of all DM cases, is caused by insulin resistance, and could combine relative reduction in the secretion of insulin. The defects in body tissues response to insulin is considered to be related the insulin receptors. Cases of DM with known defects are categorized separately. Many individuals with T2DM present clinical prediabetes evidence (such as impaired glucose tolerance and/or impaired fasting glucose) prior to developing T2DM [26]. Prediabetes progression to overt T2DM could be reversed or slowed by lifestyle medications/changes, which enhance sensitivity to insulin or decrease the production of glucose in the liver [27]. T2DM is mostly because of lifestyle and environmental factors, as well as genetics [28]. Some lifestyle factors result in T2DM development, such as obesity (body mass index ≥30), urbanization, stress, poor diet, and lack of physical activities. Dietary factors, including sugar-sweetened drinks, have been correlated with increased risks of T2DM. Fat types in the food are also significant; trans fats and saturated fat increase the risks, while monounsaturated and polyunsaturated fat reduce the risks [28]. Excessive consumption of carbohydrates dense foods such as white rice may increase risks of DM [29]. Lack or insufficient physical activities can increase risks of DM in some individuals. Adverse childhood experiences (ACEs), such as neglect, abuse, and household challenges, increase possibility of T2DM by 32% later in life, with neglect reported to have the most significant effects [30].

3. Medicinal plants for T1DM and T2DM treatment

Several medicinal plants have been shown to be effective in treating and managing DM. *Aloe vera, Terminalia chebula, Perilla frutescens, Symplocos, Symphytum, Cactaceae, Zingiber zerumbet, Chrysanthemum morifolium, Tinospora cordifolia (guduchi), Nigella sativa, Gongronema latifolium, Pachira aquatic, Caesalpinioideae, Azadirachta indica, Artemisia dracunculus, Artemisia herbaalba, Andrographis paniculata L, Asphodelaceae, Mentha, Fabaceae, Achyranthes, Vachellia nilotica, Abelmoschus moschatus, Cinnamomum verum, Panax, Salvia officinalis, Tinospora cordifoli, Pterocarpus, Ocimum tenuiflorum, Momordica charantia, Mangifera indica, Syzygium cumini, Coccinia grandis, Caesalpinia bonduc, Liriope, Sarcopoterium, Swertia, Combretum, Gymnema sylvestre, Bauhinia, Ferula assafoetida, Carthamus tinctorius, Allium sativum*, and *Trigonella foenum-graecum* are among the medicinal plants shown to be effective in controlling and treating T1DM and T2DM [31]. **Table 1** shows the list of plants known to be effective in treating T1DM and T2DM.

Scientific name of plant	Common name	Parts used	Effectiveness and mechanisms against T1DM and T2DM	Type of study	Reference
Allium sativum	Garlic	Bulb	Antihyperlipidemic and antihyperglycemic effects. Lowers FBG, improves glycemic control via increased secretion of insulin and improved sensitivity to insulin	In vivo	[32]
Aloe vera	Aloe vera	Leaves	Prevents changes in insulin levels. Diabetic kidney shows distinctive changes resulting in kidney failure or renal insufficiency. Major alteration was mostly reported in kidney tissue proximal tubules in diabetic animal models	In vitro	[33]
Bauhinia forficate	Brazilian orchid tree	Leaves	After treatment for 31 days using decoction, in T2DM group, urinary glucose and plasma glucose levels reduced significantly	In vitro	[31]
Caesalpinia Bonducella	Gray Nicker	Seeds	The 50% ethanolic and aqueous extracts of seeds of *Caesalpinia bonducella* had hypolipidemic and antihyperglycemic activities in streptozotocin-induced diabetic rats. Both ethanolic and aqueous extracts indicated potent hypoglycemic properties in chronic T2DM rats. The antihyperglycemic properties of the seed extracts could be because of the glucose absorption blockage	In vitro	[31]
Carthamus tinctorius	Safflower	Flower	The hydroalcoholic extracts from flower of *Carthamus tinctorius* can treat T1DM and T2DM. The flower of *Carthamus tinctorius* is rich in flavonoids, including kaempferol and quercetin, with hypoglycemic and antioxidant effects	In vivo	[34]
Cinnamomum verum	Cinnamon	Whole plant	*Cinnamomum verum* in diet reduces risks of cardiovascular diseases and DM. *Cinnamomum verum* reduced HbA1C (hemoglobin A1c) by 0.83% in comparison to the usual care alone, which reduced hemoglobin A1c by 0.37% in T2DM patients in a controlled, randomized trial	In vivo	[32]
Combretum Micranthum	Kinkeliba, geza'	Leaves	Hypoglycemic properties of *Combretum Micranthum* extracts were studied using fasting blood sugar and glucose tolerance in healthy rats. The aqueous extracts from leaf of *Combretum Micranthum* has antidiabetic properties against T1DM and T2DM	In vitro	[31, 35]
Ferula asafoetida	Asafoetida	Gum	With the presence of antioxidants, gum of *Ferula assafoetida* decrease the free radical levels in cells, and stimulates insulin secretion and synthesis in T2DM, and residual pancreatic cells hyperplasia and reduction of glucose level in blood	In vivo	[35]

Scientific name of plant	Common name	Parts used	Effectiveness and mechanisms against T1DM and T2DM	Type of study	Reference
Ginseng	Ginseng	Root, berries, stalk, leaves	Ginseng significantly reduced fasting blood glucose (FBG) and insulin resistance in patients with T2DM. Amongst 30 T2DM patients treated using Renshen tangtai (injection containing Ginseng polysaccharides and polypeptide), 86.7% presented significant effects on symptoms of T1DM and T2DM	In vivo and in vitro	[31, 32]
Gymnema sylvestre	Cowplant	Leaf	The crude extracts of *Gymnema sylvestre* and dihydroxy gymnemic triacetate (a compound obtained from *Gymnema sylvestre*) have hypoglycemic effects in streptozotocin-induced diabetic rats in time- and dose-dependent manners	In vitro	[35]
Liriope spicata	Monkey grass	Leaves	Aqueous extracts of *Liriope spicata* resulted in significant reduction in levels of fasting blood sugar and significantly improved glucose tolerance and insulin in streptozotocin-induced diabetic mice.	In vitro	[35]
Mangifera indica	Mango	Leaves	Extracts of mango leaves have hypoglycemic properties, possibly because of decrease in intestinal glucose absorption	In vitro	[31]
Momordica charantia	Bitter melon	Fruit	*Momordica charantia* reduced postprandial and fasting serum levels of glucose in patients with T2DM. Bitter melon showed antihyperglycemic effects by increasing the expression of glucose transporter type 4 (GLUT4), activating AMPK, inhibiting protein tyrosine phosphatase 1B (PTP1B), promoting beta cells recovery and insulin-mimicking action	In vivo	[32]
Sarcopoterium spinosum	S. spinosum	Root	*Sarcopoterium spinosum* root aqueous extracts induce antidiabetic effects on progressive hyperglycemia in mice with T1DM and T2DM. Aqueous root extracts of *Sarcopoterium spinosum* has insulin-like action in target tissues	In vitro	[35]
Swertia punicea	Swertia	Whole plant	Mechanism *Swertia punicea* hypoglycemic effects has been established by ameliorating insulin resistance in mice with T1DM and T2DM	In vitro	[35]
Trigonella foenum graecum	Fenugreek	Seed	Powdered fenugreek (15 g) administered to T2DM patients decreased Darqndkhvn sense	In vivo	[36]
Urtica dioica	Stinging nettle	Leaves	*Urtica dioica* leaves' aqueous extracts enhanced glycemia levels in rats with T2DM, and is mediated by essential effects on the pancreatic beta-cells functional status	In vivo	[37]

Scientific name of plant	Common name	Parts used	Effectiveness and mechanisms against T1DM and T2DM	Type of study	Reference
Zingiber zerumbet	Bitter ginger	Root	Ethanol extracts of bitter ginger rhizome were administered to streptozotocin-induced diabetic rats. After 3 months of diabetic conditions, weight gain in streptozotocin-induced diabetic rats was significantly less in comparison with healthy rats, while the glucose levels in the blood were significantly higher. Body weight reduction was unnoticeable in streptozotocin-induced diabetic rats receiving ethanol extracts of bitter ginger rhizome during study period	In vitro	[38]

Table 1.
Medicinal plants effective against T1DM and T2DM.

4. Bioactive compounds and dietary nutrients with effectiveness against T1DM and T2DM

Many dietary nutrients and bioactive compounds have effectiveness in the treatment of T1DM and T2DM. This section discusses the most common bioactive compounds and dietary nutrients for treating DM, with more focus on type 1 and type 2 DM. **Figure 1** shows the complex mechanisms of cell signaling targeted by T1DM and T2DM therapeutic strategies and bioactive compounds of plants.

4.1 Vitamins

Vitamins are bioactive organic compounds which are essential micronutrients organisms required in small quantities, usually within micrograms to milligrams, for the proper functioning of body metabolisms [39]. Here are some vitamins for treating T1DM and T2DM.

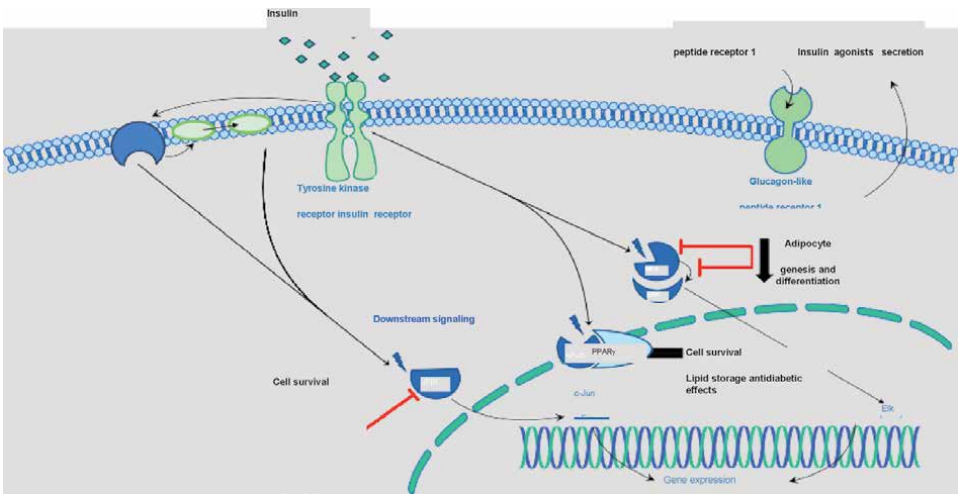

Figure 1.
Few complex mechanisms of cell signaling targeted by T1DM and T2DM therapeutic strategies and bioactive compounds of plants.

4.1.1 Vitamin A for T1DM and T2DM treatment

Vitamin A has been known to be important in treating DM. it is a group of unsaturated organic compounds essential to organisms, e.g. retinol, retinal, as well as many provitamin A carotenoids [39]. Retinol (or Vitamin A) is essential nutrient required for vision, normal growth, and reproduction. Retinoic acid (RA) is a metabolite of vitamin A with physiological importance. Retinol is converted intracellularly to 9-cis-retinoic acid or retinal all-trans-RA [40]. Mechanisms by which vitamin A influence T1DM and T2DM include adipose and obese biology regulation, increasing insulin sensitivity, β cells regeneration, and oxide radicals' chelation [40]. It has been reported that all-trans-retinoic acid may enhance insulin signaling through preventing the activity of protein kinase C (PKC) by binding to isozymes of PKC [40]. Protein kinase C was reportedly high in DM and blocked insulin signaling [40]. Retinoic acid increases secretion of insulin and levels of insulin mRNA in cultured islets, through raising pancreatic glucokinase by the glucokinase promoter activation. Retinol and retinoic acid are uncoupling protein 1 (UCP-1) positive regulators, and the UCP-1 overexpression may enhance insulin resistance and glucose transport of skeletal muscle [41]. For diabetic patients that have altered retinoid biology, vitamin A could not be effective intervention; it has been reported that insulin treatment may reverse retinoid metabolic availability. Also, intakes of vitamin A in large doses interfere with bone metabolisms and have been associated with osteoporosis [40]. Berry and Noy [42] showed that all-trans-RA has suppressive effects on insulin resistance and obesity through inducing retinoid acid receptor (RAR) gene expression and PPARβ/δ gene expression. In 2018, a study carried out by [43] reported that rats with vitamin A deficiency that were fed with diets had decreased monounsaturated fatty acid and stearoyl-CoA desaturase 1 (SCD1) levels, which alter function and structure of pancreas and increase ER stress-induced apoptosis.

4.1.2 Vitamin E for T1DM and T2DM treatment

Vitamin E is a significant constituent of antioxidant systems in every body tissue. α-tocopherol is most active type of vitamin E. Vitamin E is a group of about 8 fat soluble vitamins which four tocotrienols and four tocopherols. Vitamin E, because of its antioxidant activity, is believed to be promising therapeutic alternative T1DM and T2DM. Supplementation with vitamin E has been reported to ameliorate mouse hyperglycemia through improving secretion of insulin from alloxan-treated islet [44]. In vivo, rats with streptozotocin-induced DM were shown to present significant decrease in glucose level and improved antioxidant enzymes activities, including glutathione reductase, glutathione peroxidase, and catalase, after vitamin E supplementation. However, results obtained from human studies have been inconsistent. Vitamin E only showed effectiveness in patients that have insufficient glycemic control baseline or low-serum concentrations of vitamin E [45]. Vitamin E plays significant role in the treatment of T1DM and T2DM.

4.1.3 Vitamin D for T1DM and T2DM treatment

The most important forms of Vitamin Ds in humans are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Vitamin D is a group of fat soluble secosteroids responsible for various biological functions, including intestinal absorption of calcium, phosphate, magnesium, and other biological functions. Vitamin D3 is obtained from diets and also synthetically made in skin from 7-dehydrocholesterol when exposed to radiation of solar UVB. It is converted in the

kidney to the active vitamin D, 1,25-(OH)2 VD3 [46]. Vitamin Ds are mediated by vitamin D receptor (VDR), their nuclear receptor. Vitamin D plays significant roles in modulating T1DM and T2DM risks through having influence on inflammation, insulin sensitivity, and β-cell function [47]. Vitamin D can promote the survival of β-cell through modulating the activity and generation of cytokines via downregulation of Fas or NF-κB-related pathways. Currently, one study reported that vitamin D has increasing effects on insulin secretion stimulated by glucose through improving influx of calcium through upregulating the expression of "R-type voltage-gated calcium channel" (VGCC) genes in human and mouse islets. Treating STZ-induced diabetic rat using diet with vitamin D supplementation increased levels of insulin, decreased fasting blood glucose levels, as well as restored pancreatic islets injured by streptozotocin [48]. Meerza et al. [49] showed that treating 1,25-(OH)2 VD3 has significant changing effects on the concentrations of blood glucose and calcium, and glucose metabolic enzymes activities, such as fructose 1,6-bisphosphatase (FBPase), hexokinase, and glucose-6-phosphatase (G6Pase) in mice with induced DM. Vitamin D can have effect on insulin sensitivity in peripheral insulin-target cell through stimulating insulin receptor expression via VDR interaction or by other channels [50]. Calcium plays crucial role for any insulin-mediated intracellular process, and the extracellular and intracellular concentrations of calcium are, to a large extent, regulated by vitamin D to influence sensitivity of insulin [51].

4.2 Lycopene

Lycopene, a natural occurring carotenoid, is commonly found in tomatoes, pink grapefruit, etc.; it gives the red color. Several in vivo examinations indicated the health benefits of lycopene on T1DM and T2DM, and its accompanying complications [52, 53]. The antioxidant and anti-inflammatory properties of lycopene may be connected with its antidiabetic functions. Ali and Agha [54] carried out study with diabetic rats where lycopene supplementation resulted in a dose-dependent reduction of hydrogen peroxide (H_2O_2), lipid peroxidation, and NO, and also increased antioxidant enzymes activities, which led to decreased levels of glucose, increased levels of insulin, and enhanced profiles of serum lipids. Lycopene antioxidant properties have also indicated to solve diabetic endothelial dysfunctions in rats with induced diabetes [52]. Lycopene was evaluated for its capability to reduce cognitive decline associated with T2DM. Kuhad [55] showed dose-dependent responses to chronic treatments using lycopene, which eased cognitive impairments, decreased TNF-α and NO, alleviated cholinergic dysfunctions, and increased activity of acetylcholinesterase in rats on streptozotocin-induced diabetes. Endothelial progenitor cells (EPCs) dysfunctions are implicated in vascular complications associated with diabetes [56]. Zeng et al. [57] reported that lycopene improved AGE-induced oxidative autophagy and endothelial progenitor cells apoptosis, thereby damaging EPCs functions and number. Based on the knowledge about lycopene and T2DM, it is clear that lycopene could have promising potentials for improving T2DM vascular complications. Li et al. [53] carried out a study on rats with streptozotocin- (STZ) induced diabetes for studying lycopene specific therapeutic effects on diabetic nephropathy. They reported that lycopene has protective effects on kidney against DM-induced morphological destructions as well as impairments of functions through regulating growth factor of connective tissue, increasing protein kinase B (Akt) phosphorylation, and improving oxidative status. A different study showed that lycopene ameliorates renal functions through interruption of the Advanced glycation end products (AGE)-receptor for advanced glycation end-products (RAGE) (AGE-RAGE) axis [58].

Table 2 shows bioactive compounds, dietary nutrients, and their sources for T1DM and T2DM treatment.

Plants and sources of the compounds	Bioactive Compound	Phytochemical class	T1DM and T2DM properties	References
Asparagus, buckwheat, figs, apples, etc.	Rutin	Polyphenol (flavonoid)	Rutin reduced levels of blood glucose in insulin-resistant mouse by improving GLUT4 translocation and activities of insulin-dependent receptor kinase	[59]
Vitamin D3 (Cholecalciferol) is obtained from diets (fatty fishes, cooked egg yolk, liver, fungi) or synthetically made in skin when exposed to solar UVB.	Vitamin D	Vitamin	Treating streptozotocin-induced diabetic rat using diet with vitamin D supplements decreased fasting blood glucose levels, increased levels of insulin, as well as restored pancreatic islets injured by STZ	[48]
Citrus fruits, such as lemons, oranges, etc., and few plants	Hesperidin	Polyphenol (flavonoid glycoside)	It has protective effects in diabetic nephropathy, often through inhibiting transforming growth factor-β1- (TGF-β1-) integrin-linked kinase- (ILK-) Akt signalling	[60, 61]
Cod liver oil, carrots, broccoli leaf, liver (fish, pork, beef), sweet potato, spinach, etc.	Vitamin A, including provitamin A compounds	Vitamin	Increases levels of insulin mRNA and secretion of insulin in cultured islets, through raising pancreatic glucokinase by activating glucokinase promoter. Retinol and retinoic acid are uncoupling protein 1 (UCP-1) positive regulators; UCP-1 overexpression could enhance insulin resistance and glucose transport	[41]
Fruits, flowers, vegetables, etc.	Anthocyanin	Polyphenol (flavonoid)	In STZ-induced diabetic rats, pelargonidin (an anthocyanin) injection improved glucose tolerance, normalized elevated levels of blood glucose, and improved serum insulin level	[62]
Grapefruit, pumelo, tomatoes, grapefruit juices, etc.	Naringin	Polyphenol (flavonoid)	Naringin protects cells against high glucose-induced destruction. Naringin inhibits high inflammatory reaction induced by glucose through mediating oligomerization and nucleotide-binding domain-related receptors family of inflammasome of pyrin domain-containing 3 in mesangial cells of rat	[63]
Grapefruit, oranges, lemon, tomatoes, etc.	Naringenin	Polyphenol (flavonoid)	Naringenin ameliorated structural changes and renal damages, including glomerulosclerosis in STZ-	[64]

Plants and sources of the compounds	Bioactive Compound	Phytochemical class	T1DM and T2DM properties	References
			induced diabetic rats, possibly via downregulating IL-1 and TGF-β1 through decreasing oxidative stress, modulating production of proinflammatory cytokines and apoptotic events	
Green tea, black tea, white tea, onions, apple skin, plums, etc.	Epigallocatechin gallate	Polyphenol (Catechin)	Epigallocatechin gallate supplementations have influence on expression of the genes involved in metabolism of lipid and glucose in liver, such as through increasing glucose kinase by mRNA expression and reducing mRNA expressions of G6Pase, fatty acid synthases, as well as PEPCK	[65]
Turmeric plant (*Curcuma longa*)	Curcumin	Polyphenol	Curcumin oral administration reduced blood glucose levels, increased levels of plasma insulin, and reduced body weight	[66]
Red onions, apples, tea, broccoli, etc.	Quercetin	Polyphenol (flavonoid)	Quercetin increased glucose uptakes in cultured skeletal muscle cell by stimulating GLUT4 translocation through 5' AMP-activated protein kinase activation. Quercetin has activities on homeostasis of glucose in skeletal muscle and liver.	[67]
Red wines, grape skins, seeds, groundnut skins, etc.	Resveratrol	Polyphenol	In insulin-secreting cell, treatment with resveratrol improved mitochondrial activity, improved insulin secretion stimulated by glucose, and enhanced glucose metabolism.	[68]
Soybeans, fava beans, chickpeas, etc.	Genistein	Polyphenol (isoflavone)	Supplementation with genistein alleviated hyperglycemia induced by streptozotocin and improved insulin levels and glucose tolerance	[69]
Tomatoes, pink grapefruit, etc.	Lycopene	Carotenoid	Lycopene antioxidant activities have demonstrated to solve diabetic endothelial dysfunctions in diabetic rats	[52]
Wheat germ oil, sunflower oil, rapeseed/canola oil, almonds, g hazelnut oil, etc.	Vitamin E	Vitamin	After vitamin E supplementation, rats with streptozotocin-induced DM, in vivo, were shown to present significant reduction in glucose level and improved	[44]

Plants and sources of the compounds	Bioactive Compound	Phytochemical class	T1DM and T2DM properties	References
			antioxidant enzyme activities, such as catalase, glutathione peroxidase, and glutathione reductase.	

Table 2.
Medicinal plants, bioactive compounds, nutrients with effectiveness against T1DM and T2DM.

4.3 Polyphenolic compounds and their properties against T1DM and T2DM

Several polyphenols have been directly linked to treatment of T1DM and T2DM, including resveratrol, epigallocatechin-3-gallate (EGCG), quercetin, genistein, hesperidin, naringin, anthocyanins, curcumin, rutin, naringenin, etc.

4.3.1 Resveratrol properties against T1DM and T2DM

This polyphenol occurs naturally in red wines, seeds, grape skins, and groundnut (peanut) skins. In insulin-secreting cell, treatment with resveratrol improved insulin secretion stimulated by glucose, improved mitochondrial activity, and enhanced glucose metabolism [68]. The effects depend on active Sirtuin 1-induced key genes upregulation for β-cell functions [68]. Resveratrol exhibits anti-inflammatory and antioxidant properties, and also maintains metal homeostasis and increases mitochondrial function [70]. Resveratrol lower production of hepatic glucose, improve insulin sensitivity, and normalize hyperglycemia through Sirtuin 1 activation [71]. A study done recently suggest that T2DM was improved by resveratrol through the regulation of lipid metabolism, mitochondrial biogenesis, and β cells via SIRT1 activation [72]. Animal and cell studies suggest that resveratrol could have potentials in T1DM and T2DM treatment [73]. A NAD + -dependent deacetylase known as Sirtuin 1 (SIRT1) is known to be involved in regulating several factors which affect T2DM; resveratrol has been shown to be SIRT1 activator [71].

4.3.2 Epigallocatechin-3-Gallate (EGCG) properties against T1DM and T2DM

Epigallocatechin-3-gallate, a polyphenol, is obtained from numerous plants, especially green teas, black tea, white tea, and apple skin. Studies have been done on green tea health benefits, with the benefits associated with epigallocatechin-3-gallate, which is most abundant constituent. EGCG has strong antioxidant activities. Han [74] reported that epigallocatechin-3-gallate protected cells of RINn5F against β-cell damage caused by cytokines. The molecular mechanisms may include suppressing expression of iNOS via the inhibition of the activation of NF-κB. Consequently, epigallocatechin-3-gallate can improve pancreatic functions. Cytokines made by immune cell might cause damage of β-cell in insulin-dependent DM, and have been attributed to NO and iNOS generation in the cells. EGCG antioxidant effects are contentious; some evidence suggested that EGCG is prooxidant [75]. A typical example is the report of the work done by [75] showed that EGCG mediated the H_2O_2 production and triggered the formation of Fe2 + −dependent toxic radicals, which caused cell apoptosis and reduced the viability of cell in pancreatic β cells of HIT-T15.

4.3.3 Quercetin properties against T1DM and T2DM

Quercetin is a flavonoid which occurs naturally in many foods such as red onions, tea, apples, etc. A study indicated that treatment with quercetin enhanced lipid and

glucose metabolism, as well as eased hepatic histomorphological damage in rats with STZ-induced DM, which possibly connected to the SIRT1 activity upregulation by quercetin and its impacts on Akt signaling pathways [76]. Vascular complications have been associated with most mortality and morbidity in T1DM and T2DM patients [77]. Youl et al. [78] carried out research and reported that quercetin improved secretion of glucose-induced insulin and protected β-cell viability/function from hydrogen peroxide-induced oxidative damages in cells of INS-1. The effects are mediated by extracellular signal regulated kinase (ERK1/2) phosphorylation, which suggest that activation of extracellular signal regulated kinase take part in quercetin action [78]. Quercetin has antiapoptotic, anti-inflammatory, and antioxidant effects, and has been shown to have potentials for diabetes treatment, as well as its health complications [67, 76, 77]. Quercetin also has influence on homeostasis of glucose in skeletal muscle and liver; quercetin increased glucose uptakes in cultured skeletal muscle cell by stimulating GLUT4 translocation through 5' AMP-activated protein kinase (AMPK) activation [67]. In the same way, quercetin in hepatocytes activated 5' AMP-activated protein kinase, and was associated with glucose-6-phosphatase suppression, finally reducing the production of hepatic glucose [67].

4.3.4 Genistein properties against T1DM and T2DM

Genistein, a naturally occurring compound, structurally belongs to a group of compounds known as isoflavone. Genistein is found in many plants such as soybeans, chickpeas, etc. [79]. Evidence support genistein as a therapeutic potential and preventive treatment for T1DM and T2DM [69, 80, 81]. Genistein dietary supplementation enhanced mass of β-cell through reducing apoptosis and increasing the proliferation of β-cell [69]. The genistein supplementation alleviated hyperglycemia induced by streptozotocin (STZ) and improved insulin levels and glucose tolerance [69]. Recently, [82] showed that genistein decreased fasting glucose levels, prevented cytosolic phosphoenolpyruvate carboxy kinase (PEPCK), and activated ERK1/2 and AMPK pathways in mice with alloxan-induced diabetes, which could, as a result, improve dysfunctions in T1DM and T2DM associated hepatic gluconeogenesis. Mass loss in functional β-cell, which reduces secretion of insulin, is important for T2DM development. The β cells mass is regulated by balance between apoptosis, proliferation, transdifferentiation, and neogenesis [80]. Ae Park et al. [81] studied genistein antidiabetic effects on C57BL/KsJ-db/db mice that share human-like T2DM metabolic features. HbA1c and blood glucose were reported to be significantly lower in groups of genistein, whilst glucagon-insulin ratio and glucose tolerance were also enhanced in the group of genistein in comparison with control group [81]. Also, the supplements of genistein improved the total cholesterol, free fatty acid, HDL-cholesterol, and plasma triglyceride levels in the mice. The effects could be due to increased activities of hepatic glucokinase, and also due to the decreased activities of G6Pase, β-oxidation, and hepatic fatty acid synthase [81]. Consequently, genistein could have antidiabetic effects against T1DM and T2DM through improving the metabolism of glucose and lipid. Fu et al. [69] showed that incubation of genistein induced increase in the proliferation of human islet β-cell and INS-1 through activating cAMP/PKA-dependent extracellular signal regulated kinase (ERK1/2) signaling pathway. Studies involving animal models showed that genistein has antidiabetic effects; particularly, [69] showed that STZ-induced diabetes reduced mass of β-cell and caused cell architecture disruption.

4.3.5 Hesperidin properties against T1DM and T2DM

Hesperidin, a flavonoid glycoside, is commonly found in citrus fruits, e.g. lemons and oranges, in rich quantity. Hesperidin oral administration significantly

decreased HbA1c and glucose levels and raised serum insulin, vitamin E, and vitamin C levels in rats with HFD/STZ-induced diabetes [83]. The effects were most likely as a result of decline in producing oxidants and proinflammatory cytokines, including IL-6 and TNF-α [83]. In vivo and in vitro studies showed that hesperidin helps in T2DM treatment and prevention, and complications associated with T1DM and T2DM, via its antidepressant, anti-inflammatory, and antioxidant properties [61, 83, 84]. In pancreatic islet cells of rat, hesperidin has been reported to protect against IL-1β-induced oxidative stress, thus improving islet cells function and restoring insulin secretion and biosynthesis [84]. Hesperidin treatment in rats with STZ-induced diabetes attenuated plasma and retina abnormalities, such as increased breakdown of blood retina and decreased retina thickness, through its anti-inflammatory and antioxidant properties, and the inhibition of AGEs production and high aldose reductase [85]. Hesperidin treatment in rats on high fat diet (HFD)/STZ-induced diabetes decreased hyperglycemia through increasing the uptake of peripheral glucose, which may be attributed to GLUT4 mRNA expression upregulation [84].

4.3.6 Naringin properties against T1DM and T2DM

Naringin, also a flavonoid, is commonly seen in some grapefruits and citrus species. It is known for its antihyperglycemic, antioxidant, and anti-inflammatory properties [86]. Numerous studies recently conducted demonstrated that naringin may improve T1DM and T2DM and ameliorate the severity of their associated health complications; their mechanism is understood [63, 86]. In vitro studies showed that naringin protects cells against high glucose-induced destruction. A typical example is the work done by [63], which showed that naringin inhibits high inflammatory reaction induced by glucose through mediating the oligomerization and nucleotide-binding domain-related receptors family of inflammasome of pyrin domain-containing 3 (NLRP3) in mesangial cells of rat. Sharma et al. [87] showed that naringin ameliorated kidney damage and hepatic steatosis, and attenuated β-cell dysfunction and insulin resistance through reducing inflammation and oxidative stress by upregulating PPARγ, heat shock protein-72, as well as heat shock protein-27. Li et al. [88] showed that naringin can protect the endothelial cells of humans against high damage induced by glucose through improving mitochondrial function, downregulating chemokine (C-X3-C motif) ligand 1 (CX3CL1), and inhibiting oxidation. In addition, many studies have showed naringin beneficial effects on complications of diabetes such as diabetes-associated anemia, atherosclerosis, cognitive decline, and kidney damage [89, 90]. Mahmoud [89] showed that naringin protected rats with HFD/STZ diabetes from diabetes-induced anemia through stimulation of adiponectin expression and reducing the production of proinflammatory cytokine. In rats with NA/STZ-induced DM, naringin significantly ameliorated the serum glucose levels and profile of the lipid, including low density lipoprotein cholesterol (LDL), and free fatty acids (FFAs) [86]. The effects could be potentiated through elevation in glycogen phosphorylase and liver G6Pase activities, enhancing response to insulin secretion, and improving GLUT4 expression, adiponectin, and insulin receptor, in addition to reducing oxidative stress [86].

4.3.7 Anthocyanins properties against T1DM and T2DM

Anthocyanins (ANTs) are flavonoids mostly responsible for purple, blue, and red colors of fruits, flowers, and vegetables [91]. Most anthocyanins have strong antioxidant properties which may play role in their antidiabetic activities against

T1DM and T2DM. In rats with STZ-induced diabetes, pelargonidin (an anthocyanin) injection improved serum insulin level, improved glucose tolerance, and normalized elevated levels of blood glucose [62]. Yan et al. [92] reported that anthocyanins pre-treatment attenuated β-cell autophagy mediated by H_2O_2 through antioxidant transcription factor Nrf2 activation. In cells of HepG2, mulberry anthocyanins extracts were reportedly found to alleviate insulin resistance through PI3K/Akt pathways activation [93]. Zhang et al. [94] indicated that anthocyanins from extracts of Chinese bayberry upregulated expression of HO-1 through activating ERK1/2 and PI3K/Akt signaling in cells of INS-1. Consequently, anthocyanins protected the cells against β-cell injury induced by H_2O_2.

4.3.8 Curcumin properties against T1DM and T2DM

Curcumin, a polyphenol, is extracted from dried root of turmeric plant (*Curcuma longa*). Curcumin has numerous pharmacological activities in which anti-inflammatory and antioxidant properties are most notable properties [95]. The main factors in T1DM- and T2DM-related hepatic fibrogenesis are hepatic stellate cells (HSCs) [96]; in HSCs, AGEs induce gene expression of RAGE that may stimulate HSCs activation [96]. Lin et al. [95] showed that curcumin inhibited AGE stimulation possibly through increasing PPARγ gene expression which ameliorated RAGE expression, and eased oxidative stress. A study showed that curcumin oral treatment increased levels of plasma insulin, reduced blood glucose levels, and reduced body weight [63]. Study indicated that curcumin ameliorated glucose/lipid metabolic disorder and enhanced insulin resistance in diabetic rats; the effects may be attributed to the decrease in the TNF-α and free fatty acid in serum [97]. Curcumin has significant effects against T1DM and T2DM. Through scavenging free radicals, curcumin protects pancreatic islet against oxidative stress induced by streptozotocin. Curcumin increased insulin secretion, increased islet viability, reduced concentration of ROS, reduced NO generation, and inhibited poly ADP-ribose polymerase-1 overactivation. Oral curcumin in db/db mice alleviated hyperglycemia-induced kidney/liver damage via mitochondrial function normalization, by suppressing lipid peroxidation and NO synthesis [98].

4.3.9 Rutin properties against T1DM and T2DM

Rutin is a flavonoid commonly found in several fruits and vegetables, including asparagus, buckwheat, figs, and apples. Rutin is known to have many biological properties such as antioxidant, neuroprotective, antihyperglycemic, and anti-inflammatory properties [99], and all support its potential applications in the prevention and treatment of T1DM and T2DM and their associated health complications. Rutin reduced glycogen phosphorylase and G6Pase activities and increased hepatic hexokinase activities [47]. To this effect, rutin might decrease output of hepatic glucose. In rats with nicotinamide-STZ-induced diabetes, rutin administration decreased serum glucose levels, ameliorated glucose tolerance significantly, ameliorated oxidative stress, and also improved serum lipid variables, including serum total lipids, triglycerides, VLDL-cholesterol, and LDL-cholesterol. Rutin antihyperglycemic effects could be accomplished through increasing the uptake of glucose by peripheral tissue, stimulating secretion of insulin, suppressing gluconeogenesis in liver, and improving insulin resistance. Hsu et al. [59] showed that rutin decreased levels of blood glucose in insulin-resistant mouse by improving GLUT4 translocation and activities of IRK (insulin-dependent receptor kinase).

4.3.10 Naringenin properties against T1DM and T2DM

Naringenin, another flavonoid, naturally occur in citrus fruits, including oranges, tomatoes, grapefruits, and lemons [100]. Due to its beneficial effects in treating T1DM and T2DM and their associated health complications, naringenin has recently gained more attention. Several studies have evaluated naringenin role in complications associated with T1DM and T2DM, including vascular disease, neuropathy, hepatotoxicity, cardiac hypertrophy, and nephropathy [101, 102]. Kapoor and Kakkar [101] showed that increased apoptotic proteins expression, mitochondria dysfunction, increased ROS generation, altered antioxidant status, and altered activities of kidney and liver enzymes; may induce diabetic hepatopathy and liver damage in rats with T2DM; all the effects were completely rescued after treatment with naringenin. Consequently, naringenin has promising potentials for diabetic hepatopathy treatment. Naringenin functioned as cholinesterase inhibitor and as antioxidant, ameliorating diabetes-induced dysfunctions in memory of rats [103]. Roy et al. [64] reported that naringenin ameliorated renal damage and structural changes, including glomerulosclerosis in rats with STZ-induced diabetes, likely via downregulating IL-1 and TGF-β1 through decreasing oxidative stress, modulating the production of proinflammatory cytokines and apoptotic events. They reported that naringenin ameliorated endothelial dysfunctions induced by glucose through reducing apoptosis and oxidative stress through NO and ROS/caspase-3 pathways in endothelial cell [64, 102]. In rats with STZ-induced diabetes, naringenin oral administration improved VLDL concentrations, normalized LDL, and reduced blood glucose levels, as well normalized oxidative stress in pancreas and liver; the effects have been associated with increased mRNA expression and increased protein levels of PPARγ and GLUT4 by naringenin [104].

5. Epigenetic modification actions of bioactive compounds and dietary nutrients in T1DM and T2DM

Epigenetic modification is heritable and persistent changes in DNA which regulate how the expression of genes are done, with no effects on the sequence of the nucleotide itself. Epigenetic modification includes DNA methylation, microRNA regulation, and histone modification. It has been generally acknowledged that epigenetic and genetic factors predispose to T1DM and T2DM. The main genes which regulate the differentiation of β-cell, including GLP1 receptor, PDX1, and PAX4, are epigenetically regulated. To prevent or alleviate symptoms of hyperglycemia, preventive strategies using nonpharmacological measures have been employed. Weight loss, regular exercise, and healthy diet can help manage glucose serum level and also enhance normal metabolism of glucose. Pancreatic islets can be transplanted [105]. Epigenetic modification encourages insulin resistance via having pro-inflammatory effects on numerous biological factors, such as osteopontin, NF-kB, and Toll-like receptors [106, 107]. Some of the bioactive compounds and dietary nutrients associated with the epigenetic modification in T1DM and T2DM are shown in **Table 3**.

Bioactive compounds, including EGCG, resveratrol, curcumin, sulforaphane, lycopene, etc., have been reported to modify epigenetic mechanisms, which could result in increased cells sensitivity to conventional agents [118]. Quercetin is a bioactive compound in buckwheat and citrus fruits. The bioactive compound functions as DNMT1 inhibitor through repressing TNF-induced NFkappa transcription factor and also encourages Fas ligand associated apoptosis through histone H3 acetylation, in addition to potential inhibition of HDAC [119]. Quercetin has been reported to take part in glucose uptake stimulation via MAPK insulin-dependent

Plants and natural sources of the compounds	Bioactive compound	Phytochemical group	Epigenetic modification effect	Reference
Apples, black tea, grapes, blackberries, etc.	Epigallocatechin gallate	Polyphenol (flavonoids)	Chromatin remodelling, histone acetylation, DNA methylation	[108, 109]
Broccoli, cabbages, Brussels sprouts, etc.	Sulforaphane	Isothiocyanate	DNA methylation	[110]
Cod liver oil, liver, carrots, broccoli leaf, sweet potato, spinach, etc.	Vitamin A	Vitamin	Changes chromatin structure	[111]
Fatty fishes, liver, fungi, cooked egg yolk. Synthetically made in skin when exposed to solar UVB	Vitamin D	Vitamin	Changes chromatin structure	[112]
Grapes, chocolate, grape skins, red wines, seeds, peanut skins, etc.	Resveratrol	Polyphenol	miRNA levels modifications, chromatin remodelling, histone modifications	[113]
Turmeric plant (*Curcuma longa*)	Curcumin	Polyphenol	miRNA levels modifications, chromatin remodelling, histone modifications	[114]
Red onions, broccoli, apples, tea, etc	Quercetin	Polyphenol (flavonoid)	Histone modifications	[67]
Rice, fat fraction of bran, rice bran oil, etc.	ϒ-oryzanol	Lipid	DNA methylation	[115]
Soybeans, chickpeas, beans, fava, etc.	Genistein	Polyphenol (isoflavone)	Histone modifications, DNA methylation	[116]
Soybeans, chickpeas, fava, etc.	Genistein	Polyphenol (isoflavone)	DNA methylation	[116]
Tomatoes, pink grapefruit, etc.	Lycopene	Carotenoid	DNA methylation	[117]

Table 3.
Medicinal plants, nutrients, and bioactive compounds in epigenetic modification in T1DM and T2DM.

mechanisms. This is achieved in muscles through translocating GLUT4 transporters and in the liver through downregulating key enzymes of gluconeogenesis [67]. Resveratrol is a polyphenol which naturally occurs in grapes, chocolate, etc. Resveratrol activates a NAD-dependent HDAC, called sirtuin 1 (SIRT1); administration of SIRT1 to animals with insulin resistance regulates insulin sensitivity and improves glucose homeostasis [113]. Curcumin inhibits DNMTs, HDACs, and HATs. It inhibits or activates many miRNAs [120]. Epigallocatechin gallate (EGCG), an abundant catechin in green tea, is known to affect T1DM and T2DM. Epigenetic action mechanism of EGCG involves DNA methylation, histone acetylation, and deacetylation. Epigallocatechin gallate upregulates activities of anti-inflammation of regulatory T cell [108]. Genistein, a polyphenol obtained from soybean, induces active histone modifications and reverses hypermethylation [121]. Genistein appears to modulate on T1DM and T2DM through having direct effects on protection against apoptosis, glucose-stimulated insulin secretion, and β-cell proliferation. These have been reported to modulate through epigenetic

mechanisms and to involve cascades of cAMP/PKA signaling [116]. Sulforaphane obtained from broccoli is a bioactive compound with epigenetic effects. Sulforaphane was reported to inhibit HDACs, decrease promoter methylation, and inhibit expression of DNMT1 in T2DM [122]. *in vivo* studies of cell culture, co-expression network analysis, and analysis of genetic data of liver tissues indicated that sulforaphane inhibits production of glucose via nuclear translocation mechanisms of "nuclear factor erythroid 2-related factor 2" (NRF2) as well as inhibiting gene expression of essentials enzymes involved in gluconeogenesis [110]. Lycopene in tomatoes and organosulfur compounds in allium and garlic have anti-diabetic effects, especially against T2DM. These bioactive substances were reported to modulate through inducting histone acetylation in numerous malignancies. Lycopene is a carotenoid in tomatoes which has potent antioxidant properties. Studies reported a usefulness in using lycopene to ameliorate oxidative stress in patients with T1DM and T2DM [117]. Lycopene was reported to act through gene methylation. Bioactive compounds have epigenetic modification role in T1DM and T2DM.

6. Conclusion and future perspective

Diabetes mellitus (DM), simply called diabetes, are metabolic disorders characterized by varying or persistent hyperglycemia (high levels of sugar in the blood) over an extended time period. About 463 million people have diabetes worldwide; estimates project 700 million people by 2045. Over 90 to 95% of DM cases are T2DM, while the remain 5 to 10% are other types of DM, including T1DM, the gestational diabetes, and other minor specific types rarely encountered. Medicinal plants, bioactive compounds, and dietary measures have been found to be effective in the treatment of T1DM and T2DM. While T1DM is caused by the loss of beta cells of pancreatic islets that produce insulin, resulting in the deficiency of insulin, T2DM is caused by insulin resistance, and could combine relative reduction in the secretion of insulin. *Aloe vera, Terminalia chebula, Perilla frutescens, Curcuma longa, Zingiber zerumbet, Nigella sativa, Gongronema latifolium, Pachira aquatic, Caesalpinioideae, Azadirachta indica, Abelmoschus moschatus, Cinnamomum verum, Salvia officinalis, Tinospora cordifoli, Pterocarpus, Ocimum tenuiflorum, Mangifera indica, Syzygium cumini, Coccinia grandis, Caesalpinia bonduc, Gymnema sylvestre, Carthamus tinctorius, Allium sativum,* and *Trigonella foenum-graecum* are among the medicinal plants shown to be effective in controlling and treating T1DM and T2DM. Bioactive compounds such as lycopene, vitamin E, vitamin D, genistein, quercetin, resveratrol, epigallocatechin-3-gallate, hesperidin, naringin, anthocyanin, etc. are useful in treating T1DM and T2DM. There is need to explore other treatment measures, both medicine and alternative medicine, for T1DM and T2DM treatment. Medicinal plants and their bioactive constituents provide excellent potentials for the development of drugs and therapeutic measures for treating diabetes mellitus in general.

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Conflict of interest

The author declares no conflict of interest.

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Chapter 15

An Overview on Antiviral Potential of Traditional Medicines

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Abstract

Traditional medicines can serve as the source of potential new drug candidates and initial research focuses on the isolation of bioactive lead compounds. Medicinal plants have a combination of secondary metabolites that are naturally occurred by giving different therapeutic benefits. Phytoconstituents have been recognized as an important role in the drug discovery process moreover the other sources. Presently, over hundred natural product-derived pharmaceuticals are being used in modern medicine. Plants and their secondary metabolites, with activity against targets associated with the viral infections could provide valuable leads for the development into drugs for the novel antiviral drugs. Some of them play as important tools in the immune system exhibiting antiviral potentials. The objective of this review is to conduct information regarding the potential of traditional medicines to which have shown antiviral activity against SARS-CoV-2 infection.

Keywords: Antiviral, traditional medicine, medicinal plants, phytoconstituents, SARS-CoV-2

1. Introduction

Medicinal plants produce various secondary metabolites in their normal metabolic pathways and these metabolites play an important role for providing the activities of different therapeutic benefits. Medicinal plants have been considered for many years as an essential source of drugs such as morphine, digoxine, quinine, taxol, galantamine, artemisinine *etc*. for the treatment of several diseases and these natural products are still popular main stream stage for researchers to discovery of novel bioactive compounds with recent advancement in science and technology. Furthermore, FDA-approved antiviral drugs (famciclovir, ganciclovir, sorivudine, zidovudine, didanosine, zalcitabine, stavudine and ivermectin) are originally modeled on a natural product parent. The potential utilization of plant extracts and their secondary metabolites to combat the development of antiviral agents is considered to be one of the most important approaches toward effective therapy for viral infections by inhibiting the replication cycle of various DNA and RNA viruses. Among the viral infections, Human Immunodeficiency Virus type 1 (HIV-1) and 2 (HIV-2) as genetic variabilities that causes *Acquired Immunodeficiency Syndrome* (AIDS) which is one of the most dangerous infectious disease all over the world and has led to the death of many people. The anti-HIV potential of the 717 plant species belonging to 151 families were summarized for 206 HIV-reverse transcription (HIV-RT), 254 HIV-protease (HIV-PR) and 43 species as HIV-integrase (HIV-IN); among them *Calendula officinalis, Justicia gendarussa* and *Sceletium tortuosum* might

be useful potential sources for new lead compounds in the development of new candidates with anti-HIV properties of therapeutic interest reported by Salehi *et al*. [1]. 16 ethanolic extracts of Turkish medicinal plants were evaluated for their antiviral activities against Herpes Simplex Virus (HSV) and Sindbis virus (SINV); according to results, the extracts of *Galanthus elwesii* and *Rheum ribes* showed the most potent anti-HSV activities as well as *Galanthus elwesii* and *Leucojum aestivum* were found to be the most potent anti-SINV [2]. Moreover, 14 herbal products with confirmed clinical safety features were attractive starting material for the identification of new antiviral activities and their identified compounds for the eradication of viral diseases were also reported [3]. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Influenza A Virus (IAV), and Noro Virus (NV) are highly pathogens that affected the health of the worldwide community. SARS-CoV-2 is an enveloped RNA virus (genus *Betacoronavirus*, subgenus *Sarbecovirus*) that was originated in December 2019 in patients with infectious pneumonia in Wuhan, China. Despite of intense efforts relevant to experimental and clinical studies since the start of the COVID-19 pandemic, no disease-specific drug is available, yet. Several treatment strategies including already known antiviral drugs, interpherons, interleukin inhibitors, and other drugs acting through different mechanims are being implemented in COVID-19 patients. Moreover, the traditional medicines can serve as the source of potential new drug candidates and initial research focuses on the isolation of antiviral lead compounds. This review particularly presents a survey of recent studies on traditional medicines, medicinal plants and phytoconstituents that have indicated antiviral activity for SARS-CoV-2 infection.

2. Traditional medicines

Traditional medicine is being frequently used all over the world. Treatment with traditional medicine is still esteemed highly, particularly by those who have no access to modern health-care. Traditional medicine is to be understood as the total of the knowledge, practices based on theories and experiences indigenous to different cultures used to maintain and improve health, to prevent and diagnose illnesses. Traditional medicine can be included in medical systems and folk medicine along with health knowledge. The numbers of medicinal plants from various medical systems like Ayurveda, Siddha, Unani, Traditional Chinese Medicine, Kampo, *etc*. could be taken into consideration as an inspiring source for bioactive phytochemicals as drug designing as well as nutraceuticals and functional foods for wellness. Based on Lipinski factors and lower binding energies, numbers of compounds from medicinal plants were analyzed for their pharmacological and biological characteristics. Some selected bioactives were found to have lower toxicity with a higher gastrointestinal absorption rate and potent anti-inflammatory and anti-viral activities against targets of COVID-19 which is an infectious pandemic caused by the SARS-CoV-2 virus. The critical target components of SARS-CoV-2 are the Spike protein (S-protein) and the Main protease (Mpro). Mpro is required for the maturation of the various polyproteins involved in replication and transcription. S-protein helps the SARS-CoV-2 to enter the host cells through the Angiotensin-Converting Enzyme 2 (ACE-2). Since ACE-2 is required for the binding of SARS-CoV-2 on the host cells, ACE-2 inhibitors and blockers have got wider attention, in addition to S-protein and Mpro modulators as potential therapeutics for COVID-19. So far, no specific drugs have shown promising therapeutic potential against COVID-19. Therfeore, several studies were undertaken to evaluate the therapeutic potential of traditional medicinal plants against COVID-19.

2.1 Traditional Chinese medicine

Based on the frequency of appearance of each medicinal herb and their corresponding pharmacological activities from Traditional Chinese Medicines (TCM), one of the TCM formula was reconstructed with the potential of treating COVID-19 infection. This TCM formula contains herbs with evidenced antiviral activity along with reducing fever, removing dampness, expelling phlegm, and arresting coughing. It includes *Bupleurum chinense*, *Ramulus cinnamomi*, *Scutellaria baicalensis*, *Glycyrrhiza glabra*, *Atractylodes macrocephala*, Rhizoma Zingiberis, *Agastache rugosa*, *Stephania tetrandra* root, *Polygonum cuspidatum*, *Rheum palmatum*, Tangerine Peel, Semen Armeniacae Amarum and *Ophiopogon japonicus* root. These herbs have the effect of eliminating dampness, for relieving cough and lung symptoms. In addition, in modern pharmacology, *Rheum palmatum* and *Polygonum cuspidatum* have significant antiviral effects due to their rich emodin content. Full prescription of 12 drugs are evaluated for the clinical treatment of COVID-19 [4]. On the other hand, a medicinal plant library containing 32,297 potential antiviral traditional Chinese medicinal plants compounds were analyzed the 3-Chymotrypsin-Like protease (3CLpro) sequence which plays a critical role in the replication of virus particles and unlike structural/accessory protein-encoding genes constructed its 3D homology model. These analyses revealed that the top nine hits might serve as potential anti-SARS-CoV-2 lead molecules for further optimisation and drug development process to combat COVID-19. The proteolytic processing is mediated by Papain-Like protease (PLpro) and 3CLpro. The 3CLpro cleaves the polyprotein at 11 distinct sites to generate various non-structural proteins that are important for viral replication [5].

In Asian countries, *Saxifraga* species (Saxifragaceae) are used as medicinal herbs for treatment of various types of disorders. With respect to antiviral activities, *Saxifraga melanocentra* inhibited the activity of hepatitis C virus serine protease. The virucidal activity of pyrogallol compounds obtained from *Saxifraga spinulosa* have also suggested against SARS-CoV-2, Influenza A (IAV), as well as Feline Calici Virus (FCV) and Murine Noro Virus (MNV) [6].

2.2 Traditional Persian medicines

In Iran, some medicinal plants have great potential value for treatment of COVID-19 based on the therapeutic approaches of Traditional Persian Medicine (TPM) is one of the most ancient medical doctrines mostly known as "wi", several of which have also been confirmed by pharmacological studies in modern medicine. Among them, Amla (*Phyllanthus emblica* L.), Chicory (*Cichorium intybus* L.), Clove [*Syzygium aromaticum* (L.) Merr. and L.M.Perry], Damask Rose (*Rosa* × *damascena* Herrm.), Fenugreek (*Trigonella foenum-graecum* L.), Galangal (*Alpinia galanga* (L.) Willd., *A. officinarum* Hance), Garlic (*Allium sativum* L.), Grape and Raisin (*Vitis vinifera* L.), Licorice (*Glycyrrhiza glabra* L., *G. uralensis* Fisch.), Rhubarb (*Rheum palmatum* L., *R. officinale* Baill.) and Saffron (*Crocus sativus* L.) were determined as promising plant species. However, preclinical mechanistic studies as well as clinical trials are necessary to confirm the safety and efficacy of these plants for the management of SARS-CoV-2 infection [7].

2.3 Ayurveda

For nearly 5000 years Ayurveda, an ancient Indian medicine method, has been practiced in India, relying heavily on plants to formulate it. Ayurvedic herbal supplements and immunity boosters showing the way to a broad-spectrum

antiviral drug that is the need of the hour. Antiviral properties of *Glycyrrhiza glabra, Andrographis paniculata, Phyllanthus spp., Zingiber officinale, Withania somnifera*, and *Curcuma longa* have been reported [8]. Whereas, *Tinospora cordifolia* and *Emblica officinalis* have the properties to enhance immunity. It has been shown that *Coptidis rhizome, Meliae cortex, Sanguisorbae radix, Cimicifuga rhizome,* and *Phellodendron cortex* exhibit anti-coronavirus activity. *Sophorae radix*, *Torilis fructus,* and *Acanthopanacis cortex* decreased intracellular viral RNA levels with corresponding viral protein decreases [9]. The antiviral activity of some phytoconstituents present in traditional medicinal plants from Ayurveda were also investigated against spike glycoprotein of SARS-COV-2 as well as its host ACE-2 receptor. Some parameters like drug-likeness, pharmacokinetics, and toxicity were also determined to ensure the safety and efficacy of active constituents. Based on the findings amarogentin, eufoliatorin, α-amyrin, caesalpinins, kutkin, β-sitosterol, and belladonnine were found the top ranked molecules have the highest affinity toward both the spike glycoprotein and ACE-2 [10]. Further, fourthy-one plant-derived compounds from Indian medicinal plants were screened for their inhibitory effect on Main protease (Mpro) of SARS-CoV-2 using the molecular docking approach. Among them amentoflavone, lectin, glycyrrhizic acid, hypericin and torvoside H exhibited high binding energy. Amentoflavone isolated from *Torreya nucifera* showed the highest binding energy of 10.0 kcal/mol with the SARS-CoV-2 Mpro [11]. Furthermore, free energy calculations on these compounds performed by using the molecular docking procedure. The results suggested that amentaflavone, hypericin, and Torvoside H respectively complexed with SARS-CoV-2 Mpro show better binding with stabilizing interactions and provided valuable information in developing new, novel and natural anti-viral drugs for COVID-19 [9]. In addition, taraxerol isolated from *Clerodendrum* species has shown potential antiviral activities with desirable pharmacological features [12]. Withanolide A active constituent of ayurvedic herb from *Withania somnifera* has shown promising antiinfluenza properties by targeting neuraminidase of H_1N_1 Influenza as well as the highest binding affinity with S-protein and ACE-2 receptor [13]. AYUSH Ministry of Health, India, has recommended the use of the aqueous extract of *Withania somnifera* as a preventive and prophylactic for treating COVID-19 infection. Withametelin isolated from *Datura innoxia* plant, has shown a better binding affinity against Mpro, S-protein and ACE-2. However, the pharmacological analysis revealed its toxicity to health. Other compound known as Daturaolone also isolated from *Datura innoxia*, has shown lower toxicity and potent antiviral and anti-inflammatory activities. These compounds can be further developed and assessed as phytoformulations against SARS-CoV-2 infection [8].

2.4 Siddha medicine

During molecular docking and simulation analysis for the prevention and cure of COVID-19 infection on some phytoconstituents of Siddha medicine were determined as potential candidates. Among them orientin, bis-andrographolide, cucurbitacin B, cucurbitacin E, isocucurbitacin B, vitexin, berberine, bryonolic acid, piperine and magnoflorine were identified as potential lead molecules that have been shown to possess the ability to interact with the components that block the viral replication in SARS-CoV-2. Moreover, the immune-enhancing properties of these compounds without any adverse side effects could provide natural immune power to resist COVID-19 infections [14]. Several plants have been found to act on the ACE-2 receptor, which could become promising antiviral agents and can help in combatting COVID-19 pandemic. *Rheum palmatum, Polygonum multiflorum, Cerasus avium, Alcea digitata, Rubia tinctorum, Citrus aurantium, Berberis integerrima, Peganum*

harmala and Allium sativum have the potential to act on the ACE-2 receptor and are well-known for blocking the transmission or entry of Coronoviruses. These plants can possibly be used for the combinational therapeutic management of COVID-19 by inhibiting various protein targets of SARS-CoV-2 (**Table 1**) [15].

Traditional medicines	Medicinal plants	Antiviral compounds	Virus	References
Traditional Chinese Medicine	*Agastache rugosa*, *Atractylodes macrocephala*, *Bupleurum chinense, Citrus reticulata*, *Glycyrrhiza glabra*, *Ophiopogon japonicus, Polygonum cuspidatum*, *Prunus armeniaca* var. *ansu* *Ramulus cinnamomi, Rheum palmatum*, *Saxifraga melanocentra, Scutellaria baicalensis*, *Stephania tetrandra, Zingiber officinale*	Emodin, Pyrogallol	SARS-CoV-2, Influenza A (IAV), Feline Calici Virus (FCV) and Murine Noro Virus (MNV)	[4–6]
Traditional Persian Medicine	*Allium sativum*, *Alpinia galanga* *Alpinia officinarum* *Cichorium intybus* *Crocus sativus* *Glycyrrhiza glabra* *Glycyrrhiza uralensis* *Phyllanthus emblica* *Rheum officinale* *Rheum palmatum* *Rosa damascena* *Syzygium aromaticum* *Trigonella foenum-graecum* *Vitis vinifera*	—	SARS-CoV-2	[7]
Ayurveda	*Acanthopanax gracilistylus, Andrographis paniculata, Cimicifuga racemosa* *Clerodendrum* species, *Coptis chinensis* *Curcuma longa, Datura innoxia, Glycyrrhiza glabra, Melia azedarach* *Phellodendron amurense* *Phyllanthus spp., Sanguisorba officinalis* *Sophora flavescens*, *Torilis arvensis, Torreya nucifera, Withania somnifera*, *Zingiber officinale*	Amarogentin Amentoflavone, α-Amyrin, β-sitosterol, Belladonnine, Caesalpinins, Daturaolone, Eufoliatorin, Glycyrrhizic acid, Hypericin, Kutkin, Lectin, Torvoside H, Taraxerol, Withanolide A, Withametelin	SARS-CoV-2, H_1N_1 Influenza	[8–13]

Traditional medicines	Medicinal plants	Antiviral compounds	Virus	References
Siddha medicine	*Alcea digitata, Allium sativum Berberis integerrima, Cerasus avium, Citrus aurantium, Peganum harmala Polygonum multiflorum Rheum palmatum, Rubia tinctorum*	Berberine, Bis-andrographolide Bryonolic acid, Cucurbitacin B, Cucurbitacin E, Isocucurbitacin B, Magnoflorine, Orientin, Piperine Vitexin	SARS-CoV-2	[14, 15]
Thai traditional medicine	*Boesenbergia rotunda*	Panduratin A	SARS-CoV-2	[16]
African traditional medicine	*Abrus precatorius Acacia senegal, Achyranthes aspera Allium sativum*, *Annona muricata Artemisia afra*, *Azadirachta indica Cryptolepis sanguinolenta*, *Curcuma longa, Euphorbia hirta Garcinia kola*, *Glycyrrhiza glabra*, *Hypoxis hemerocallidea, Moringa oleifera* Lam., *Nigella sativa* L., *Psidium guajava Sutherlandia frutescens, Xysmalobium undulatum, Zingiber officinale*	Arabic acid, Hypoxoside, L-Cnavanine, Uzarine	SARS-CoV-2	[17]
Traditional South American Countries Medicine	*Althaea officinalis*, *Commiphora molmol*, *Glycyrrhiza glabra*, *Hedera helix, Sambucus nigra Uncaria tomentosa,*	3-dihydrocadambine, 3isodihydrocadambine Proanthocyanidin C1, Proanthocyanidin B4, Proanthocyanidin B2 Proanthocyanidin C1, Speciophylline Uncarine acid, Uncaric F	SARS-CoV-2	[18, 19]
Phytoconstituents			SARS-CoV-2, H_1N_1 Influenza	[20–30]
Alizarine, Aloe-Emodin, Amaranthin, Anthrarufin, Calceolarioside B, Curcumin, Dantron, Emodin, Harman, Harmalol, Hypericin, Licoleafol, Lycorine, Methyl rosmarinate, Mycophenolate Mofetil, Myricetin, Myricitrin, Ouabain, Resveratrol, Scutellarein, Silvestrol, Tylophorine, Vasicine, Vasicinone, 5,7,3′,4′-tetrahydroxy-2′-(3,3-dimethylallyl) isoflavone, 3,5,7,3′,4′,5′-hexahydroxy flavanone-3-*β*-D-glucopyranoside, (2S)-eriodictyol 7-*O*-(6″-*O*-galloyl)-*β*-D-Glucopyranoside, 3-*O*-*β*-D-glucopyranoside				

Table 1.
The list of traditional medicines for antiviral activities.

2.5 Thai traditional medicine

Among 122 Thai traditional medicines, *Boesenbergia rotunda* extract and its compound, known as panduratin A exhibited the potent anti-SARS-CoV-2 activity by using the high-content imaging system coupled with the plaque reduction assay. Treatment with *Boesenbergia rotunda* extract and panduratin A after viral infection drastically suppressed SARS-CoV-2 infectivity in Vero E6 cells with IC_{50} of 3.62 μg/mL (CC_{50} = 28.06 μg/mL) and 0.81 μM (CC_{50} = 14.71 μM), respectively. Also, the treatment of panduratin A at the pre-entry phase inhibited SARS-CoV-2 infection with IC_{50} of 5.30 μM (CC_{50} = 43.47 μM). Therefore, Panduratin A exerted the inhibitory effect against SARSCoV-2 infection at both pre-entry and post-infection phases as the novel natural candidate [16].

2.6 African traditional medicine

Fifteen African ethnomedicinal herbs (*Abrus precatorius* L. Gaertn, *Achyranthes aspera* L., *Allium sativum* L., *Annona muricata* L., *Artemisia afra* Jacq. ex Willd, *Azadirachta indica* A. Juss., *Cryptolepis sanguinolenta* (Lindl.) Schltr., *Curcuma longa* L., *Euphorbia hirta* L., *Garcinia kola* Heckel, *Glycyrrhiza glabra* L., *Moringa oleifera* Lam., *Nigella sativa* L., *Psidium guajava* L., *Zingiber officinale* Roscoe) used in African traditional medicine from different countries in Africa were investigated in the prevention, treatment and management of COVID-19 infection [17]. From them, *Glycyrrhiza glabra* was reported to be successful inhibitor for SARS-CoV replication and was recommended for the management COVID-19. Due to the complex nature of SARS-CoV-2 and clinical presentation of COVID-19 disease, combining two or more extracts with various pharmacological activity from these herbs in a standard dosage form such as capsule, tablets, syrups, and injections is necessary in the management of the disease. This combination would improve adherence but care must be taken to ensure that all ingredients in the formulation are compatible otherwise it may lead to therapeutic failure or toxicity. These findings will serve as a source of information for future research in the selection of herbs which could be used in the management of COVID-19 [17].

2.6.1 African medicinal plants

Sixty-two alkaloids and hundred terpenoids isolated from some African medicinal plants were docked to the 3-Chymotrypsin-Like protease (3CLpro) controled coronavirus replication as a promising drug target for combating the coronavirus infection. The twenty alkaloids and terpenoids with high binding affinities to the SARS-CoV-2 3CLpro were further docked to the 3CLpro of SARS-CoV by comparing with the reference inhibitors (Lopinavir and Ritonavir). From them, 10-hydroxyusambarensine, cryptoquindoline, 6-oxoisoguesterin and 22-hydroxyhopan-3-one showed potent activity against SARS-CoV-2 3CLpro [31].

2.6.2 Nigerian medicinal plants

Fifty Nigerian medicinal plants and their 9 phytoconstituents were investigated against symptoms related to COVID-19. Their specific therapeutic actions are administered to combat the key players in the pathogenesis of the disease [32].

2.6.3 Moroccan medicinal plants

The molecular docking studies on sixtyseven phytoconstituents from Moroccan medicinal plants were evaluated for their *in vitro* and *in vivo* antiviral activity against SARS-COV-2 Main protease before clinical trial. The results of molecular docking studies showed that three compounds (crocin, digitoxigenin, and *β*-eudesmol) were proposed as inhibitors against the coronavirus based on the energy types of interaction between these compounds and studied protein [33].

2.6.4 South African medicinal plants

Twentynine phytoconstituents isolated from commonly used South African traditional medicinal plants were examined against SARS-CoV-2 using molecular docking and molecular dynamics. Molecular docking identified arabic acid from *Acacia senegal* and L-canavanine found in *Sutherlandia frutescens* were determined as a potential inhibitor 3C-Like main protease (3CLpro) of SARS-CoV-2. Similarly, hypoxoside isolated from *Hypoxis hemerocallidea* and uzarin from *Xysmalobium undulatum* were also identified as a potential inhibitor of SARS-CoV-2 receptor binding domain and SARS-CoV-2 RNA-dependent polymerase (SARS-CoV-2 RdRp). In addition, these compounds exhibited favorable binding orientations characterized by strong molecular interactions within respective inhibitors binding pockets of the target enzymes [34].

2.7 Traditional medicinal plants of South American countries

Uncaria tomentosa (cat's claw) is traditionally used medicinal plant in South American countries. Twentysix phytoconstituents of *Uncaria tomentosa* were docked on the binding interface of the ACE-2 and SARS-CoV-2 spike protein of novel corona virus. From these compounds namely Proanthocyanidin C1, 3-isodihydrocadambine, Uncarine F and Uncaric acid had a good predicted binding affinity for interface of the ACE-2 as compared to the sulfated Heparin OctaSaccharide (HepOS). Likewise, 3-dihydrocadambine, Proanthocyanidin B4, Proanthocyanidin B2 and Proanthocyanidin C1 had the highest docking score on SARS-CoV-2 spike glycoprotein in their open state. Virtual prediction ADME revealed that Speciophylline, Uncarine F and Uncaric acid presented values of drug ability according to Lipinski rule, demonstrating their potential bioavailability as likely orally active antiviral. *Uncaria tomentosa* can be performed as an herbal supplement with the safety and efficacy parameters at both preclinical and clinical stages to evaluate its effectiveness in the treatment of novel coronavirus disease (COVID-19) [18].

Thirty-nine herbal medicinal plants known in the America and Europe for the management of respiratory conditions, mainly regarding the symptoms cough, pain and fever were studied for their therapeutic potential alongwith the limitations for their use and possible risks. For five out of the 39 herbal drugs a positive benefit/risk assessment was determined. The level of evidence for *Althaea officinalis*, *Commiphora molmol*, *Glycyrrhiza glabra*, *Hedera helix* and *Sambucus nigra* are suggested a potential clinical use as adjuvants in the treatment of early/mild cases of COVID-19. Another twelve herbal medicines were classified as promising plant species [19].

3. Various phytoconstituents

Various phytoconstituents occured in living organisms in a high structural diversity have antiviral activities by inhibiting different stages in the replication

of various viruses. Their different antiviral mechanisms like virus adsorption, virus-cell fusion, reverse transcription, protease and integrase inhibition have been reported in recent studies [20, 21]. Lycorine, hypericin, emodin, tylophorine, ouabain, mycophenolate mofetil, silvestrol, myricetin and scutellarein were also reported for their inhibitory effects against SARS-CoV-2 and other human coronaviruses [22]. Some phytoconstituents such as myricitrin, methyl rosmarinate, 5,7,3′,4′-tetrahydroxy-2′-(3,3-dimethylallyl) isoflavone, 3,5,7,3′,4′,5′-hexahydroxy flavanone-3-*β*-D-glucopyranoside, (2*S*)-eriodictyol 7-*O*-(6″-*O*-galloyl)-*β*-D-glucopyranoside, calceolarioside B, myricetin, 3-*O*-*β*-D-glucopyranoside, licoleafol, and amaranthin were reported as potential lead candidates to develop novel anti-SARS-CoV-2 drugs [23].

Moreover, anthraquinone derivatives were screened on the basis of binding energy against N-Terminal Domain (NTD) of SARS-CoV-2. Emodin, Anthrarufin, Alizarine, Aloe- emodin, and Dantron showed the good binding affinity at three different active sites of N-Terminal Domain of SARS-CoV-2 nucleocapsid phosphoprotein. These compounds prevent the assembly of virus particles and stop the infection. They are suggested as potential drugs for COVID-19 treatment [24]. From secondary metabolites, curcumin as the main constituent of *Curcuma longa* L. (turmeric), is the reputed compound displaying remarkable biological activities for human health. It has been shown to have an inhibiting effect against SARS-CoV-2 [25]. Synthesized resveratrol derivatives have been shown to suppress SARS-CoV replication and reduce its clinical symptoms [26]. Some *beta*-carboline alkaloids including harman, harmalol and quinazoline-type alkaloids like vasicine and vasicinone have showed antiviral effect against influenza virus [27].

Among the secondary metabolites, essential oils interfere with the virus envelope or masking viral compounds which are necessary for adsorption or entry into host cells. Essential oils have long been known to have antiviral properties and are being proposed to have activity against SARC-CoV-2 virus [28]. Owing to their lipophilic nature, essential oils are advocated to penetrate viral membranes easily leading to membrane disruption. Moreover, essential oils contain multiple active phytochemicals that can act synergistically on multiple stages of viral replication and also induce positive efects on host respiratory system including bronchodilation and mucus lysis. Their antiviral properties were shown by computer-aided docking and *in vitro* studies for anti-SARC-CoV-2 [29, 30].

4. Conclusion

Plants and their secondary metabolites provide valuable leads for the development into drugs for the novel antiviral activities. Ivermectin is the FDA approved drug and inhibited the replication of SARS-CoV-2 [35]. Although there is an increase in the use of traditional medicine worldwide, researches in traditional medicines are insufficient. Assessments of the quality, safety, and efficacy of traditional medicines are needed to provide scientific information that regulations need. In the present review, antiviral activity mainly against coronaviruses of traditional medicines along with their phytoconstituents through the literature data relevant to their enzyme and receptor interactions given by different assays. Pre-clinical studies would provide deep insight into mechanism of actions and also drug ability of the antiviral candidates for the treatment of COVID-19 infection. Besides, vast range of double-blinded clinical studies with strict protocols is required to estimate the accurate potential of antiviral phytochemicals against COVID-19 with the aim of ensuring the fulfillment of international acceptable standards. Therefore, phytoconstituents will play an important role and continue to support in developing potential drugs against SARS-CoV-2.

Conflict of interest

The authors declare no conflict of interest.

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Chapter 16

Current Updates on Global Phytoceuticals and Novel Phyto Drug Delivery System in Herbal Medicine

Selvakumari Sreenathkumar

Abstract

The acceptance of the herbal drugs globally is increased in the modern era, is due to its potent active molecules and also its usage as excipients from natural origin in the pharmaceutical industries is remarkable. Due to complex structure, poor solubility, instability and lacuna in the standardization protocol, there is always a hindrance in the usage of herbal medicine at par with modern drugs. The formulation of phytomedicine in the area of Novel drug delivery system should be focused in basic research and also in the clinical trials, to overcome the solubility and bioavailability challenges in the phytoceuticals. This chapter gives the in-depth perception of phytomolecules, formulated in the domain of novel drug delivery system, especially in nano dosage forms in specific to nano-emulsion, methods of formulation, challenges in formulating nano-emulsion including characterization techniques, colon specific drug carriers and the usage of excipients from natural origin in formulation of modern drugs in the pharmaceutical industries globally.

Keywords: Phytomedicine, Phytoceuticals, Excipients, Colon specific drug delivery Nano phyto dosage forms

1. Introduction

The contribution of natural products to human kind is tremendous in modern drug discovery and its usage is well known before the era of Christ. Lead molecules from plants and microbial origin are significant [1]. In the global pharmaceutical industry, about 34% of the medicines originated from natural molecules. Among the 34%, 6% were natural products, 27.5% were natural products derivatives, thus played important source of lead molecules in manufacturing therapeutic agents in pharmaceutical industries globally [2, 3].

2. Remarkable contribution of Phytomolecules as API in pharmaceutical sector

Based on the survey in the dispensing area of union territory of Puducherry, India, the potent phyto molecules as Active Pharmaceutical Ingredient (API) is being prescribed by modern physicians, are

- Atropine, a tropane alkaloid (*Atropa belladonna* - Solanaceae) is a parasympatholytic drug with anticholinergic properties, prescribed for organophosporous & carbamate poisoning, in bradycardia and as ophthalmic dosage form, administered for eye examination that produces mydriasis and cycloplegia. The formulations available are Atropine oinment USP & IP, Atropine eyedrops BP, Atropine sulphate tablets USP, Atropine dermal plasters, Atropine sulphate intravenous, intramuscular and subcutaneous injections.

- Pilocarpine, an imidazole alkaloid (*Pilocarpus jaborandi* - Rutaceae) is a cholinergic agonist used in the treatment of glaucoma. Pilocarpine hydrochloride tablets USP and pilocarpine ophthalmic solution USP available pharmaceutically.

- Morphine, a phenanthrene alkaloid (*Papaver somniferum* - Papaveraceae) is a narcotic analgesic used in the management of acute and chronic pain, in relief of dyspnoea of left ventricular failure and in pulmonary oedema. Morphine sulphate extended release tablets, morphine sulphate intramuscular injection available pharmaceutically.

- Codeine, a phenanthrene alkaloid (*Papaver somniferum* - Papaveraceae) is an antitussive agent– acts through brain and supress the cough reflux. Codeine phosphates syrups and tablets are available.

- Digoxin, a cardiac glycoside (*Digitalis lanata* – Scrophulariaceae), is a cardenolide in the name of Lanoxin, used in the treatment of atrial fibrillation, atrial flutter & atrial tachycardia. Digoxin tablets USP, digoxin intramuscular injection, digoxin elixer for pediatric use is available.

- Vincristine sulphate, an indole alkaloid, (*Catharanthus roseus* - Apocynaceae), is an anticancer drug, used in the treatment of acute lymphocytic leukemia, acute myeloid leukemia, Hodgkin's disease, neuroblastoma and small cell lung cancer and Vinblastine sulphate, an indole alkaloid, (*Catharanthus roseus* - Apocynaceae) used in the treatment of Hodgkin's lymphoma, non-small cell lung cancer, bladder cancer, brain tumor, melanoma, and testicular cancer. Vincristine & Vinblastine sulphate intramuscular and intravenous injections are available.

- Taxol, a diterpene alkaloid (*Taxus brevifolia* - Taxaceae) renamed to paclitaxel, is being used in the treatment of cancers for metastatic breast cancer, advanced ovarian cancer, non-small cell lung cancer and Kaposi's sarcoma, available as Paclitaxol injection IP.

- Caffeine, a purine alkaloid (*Coffea Arabica* - Rubiaceae) is an API finds important drug combinations with antihistamic drugs to counteract the sedative effect available as tablet in pharmaceutical market.

- Ergometrine, an indole alkaloid (*Claviceps pupurea* - Clavicipitaceae) used for uterus contraction in labour and in postpartum hemorrhage. Ergometrine maleate injections are available.

- Capsaicin, a pungent principle (*Capsicum annum* - Solanaceae) is used as counter irritant to relieve joint pain, stiffness and swelling caused by osteoarthritis of the knees. Pharmaceutically available as an ointment.

- β – Carotene, a tetraterpene (*Daucus carota* – Apiaceae) hydrolyses into two molecules of vitamin-A upon the action of the enzyme cholesterol ester

hydrolase and pancreatic lipase in duodenum thus serve as a precursor of vitamin –A. β – Carotene is available as a tablet pharmaceutically.

- Antibiotics - Penicillin from *Penicillium notatum* - Trichocomaceae, Streptomycin, macrolide antibiotics/aminoglycoside from *Streptomyces griseus* - Streptomycetaceae, Tetracyclins – broad spectrum antibiotics from *Streptomyces aureofacians*, *S. rimosus* – Streptomycetaceae are active against communicable diseases.

- The important milestone of natural molecules in the time travel of drug discovery and also in global pharmaceutical market is, they act as precursors for some of the semisynthetic molecules [4–6].

- Chloroquine, semisynthetic derivative of quinine (*Cinchona species* – Rubiaceae, quinoline alkaloid) antimalarial drug active against *Plasmodium falciparum*.

- Diosgenin, a steroidal saponin (*Dioscorea deltoida* - Dioscoreaceae) is used for the commercial synthesis of cortisone, pregnenolone, progesterone and other steroid products.

Table 1 gives the remarkable contribution of pharmaceutical phyto API, is being prescribed in modern medicine along with formulation.

3. Contribution of Phytomolecules as excipients in pharmaceutical industry

Excipients in formulating different dosage forms are pharmacologically inert thereby promotes the therapeutic activity of API. Bioavailability, safety, efficacy and stability of the dosage forms is depend on the nature of excipients. Excipients are classified as diluents, binders, surfactants, preservatives, sweeteners etc. [7]. The usage of herbal excipients as phytomolecules is veiled due to the popularity of synthetic molecules in the domain of pharmacy.

3.1 Advantage of phytomolecules as herbal excipients

- Natural excipients are biodegradable in nature

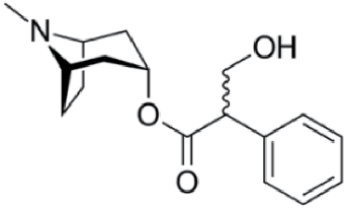
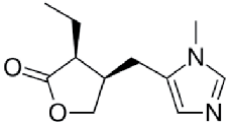
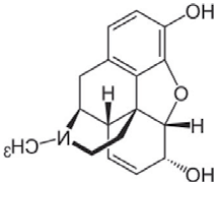
- As ecofriendly in the aspect of pharmaceutical effluents

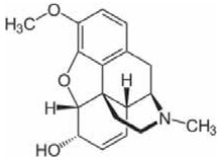
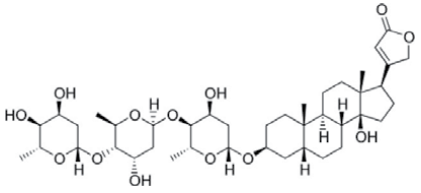
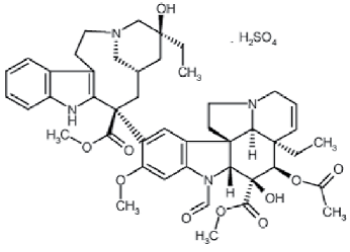
- Most of the herbal excipients are carbohydrate in nature and hence they are non-toxic in nature

- Cost of the excipients are cheaper when compared to synthetic molecules

- Natural excipients are easily available from different natural sources.

Though natural excipients are advantageous, in some aspects they do possess some limitations, in the source of raw materials as herbal excipients. Possibility of attack of microbial contamination in contact with external environment, availability as raw material is varied depending upon climatic conditions and geographical origin, more importantly heavy metal contaminations. These are the challenges faced in herbal excipients as a source of raw materials in pharmaceutical industries.

S.No.	Name of pharmaceutical phyto API	Biological source & family	Formulation available in global market
1.	Atropine sulphate (Tropane Alkaloid) 	*Atropa belladonna*-Solanaceae 	Oinment USP  Dermal Plaster 
2.	Pilocarpine (Imidazole alkaloid) 	*Pilocarpus jaborandi*-Rutaceae 	Opthalmic solution 
3.	Morphine (Phenanthrene alkaloid) 	*Papaver somniferum*-Papaveraceae 	Extended release tablets 

S.No.	Name of pharmaceutical phyto API	Biological source & family	Formulation available in global market
4	Codeine (Phenanthrene alkaloid) 	*Papaver somniferum* -Papaveraceae 	Syrup  Tablets 
5	Digoxin (Lanoxin - Cardiac glycoside) 	*Digitalis lanata* –Scrophulariaceae 	Lanoxin Pediatric Elixer 
6.	Vincristine sulphate (Dimeric indole alkaloid) 	*Catharanthus roseus* - Apocynaceae 	Vincristine sulphate injection USP 

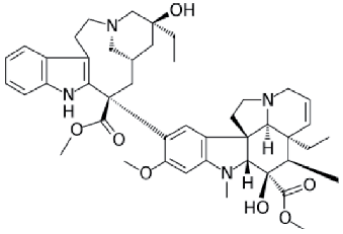
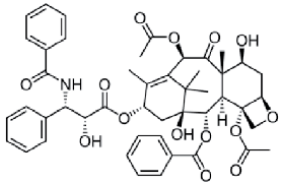
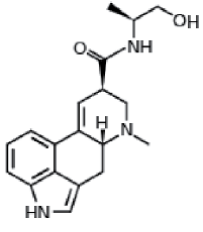
S.No.	Name of pharmaceutical phyto API	Biological source & family	Formulation available in global market
7.	Vinblastine sulphate (Dimeric indole alkaloid) 	*Catharanthus roseus*- Apocynaceae 	Vinblastine sulphate injection USP 
8.	Taxol (Diterpene alkaloid) 	*Taxus brevifolia* - Taxaceae 	Paclitaxel Injection IP 
9.	Ergometrine (Indole alkaloid/amino alkaloid-Lysergic acid derivative) 	*Claviceps pupurea*-Clavicipitaceae 	Ergometrine maleate injection 

Table 1.
Pharmaceutical phyto API in modern medicine.

The requirement of human community is the source of the drug should always from natural resources instead of synthetic origin not only the API but also the excipients.

4. Herbal excipients in pharmaceutical dosage forms

4.1 Acacia

***Acacia Arabica* – Leguminosae**

***Acacia* tears**

Acacia is the dried gummy exudation obtained from the stem and branches of wild *Acacia arabica*, *Acacia Senegal* (Leguminosae). It occurs as rounded or ovoid, colorless (the best grade) or amber tears, or as a white powder. The gummy exudation principally consist of arabin, is a complex mixture of calcium, magnesium and potassium salts of arabic acid. Arabic acid on hydrolysis gives L-arabinose, L-rhamnose, D-galactose and D-glucuronic acid. It also contains an enzyme oxidase and peroxidase [8].

Therapeutic indication: It is used as a demulcent, as a good protective colloid.

As an excipient: Acacia is compatible with hydrocolloids of other plants as well as starches and carbohydrates. Acacia is the suspending agent due to colloidal property and it is useful in the mixtures containing resinous tincture. It is used in the formulation of Lozenges, Pastilles and compressed tablets. It is a emulsifying agent for fixed oils, volatile oils and liquid paraffin. Acacia is the best emulsifying agent for the externporaneous preparation of oral emulsions. Preparation of good quality, appearance and adequate stability, can be made with only a mortar and pestle. This is because the concentrated emulsion produced in the initial stage of preparation is very viscous and sticky and therefore, the oil cannot escape the vigorous sharing action of the pestle and is easily reduced to fine globules.

Because of the low viscosity of acacia emulsions, creaming occurs rather quickly and thickening agents tragacanth, sodium alginate and agar are used as stabilizers. Acacia emulsions are palatable and thereby are stable over a wide pH range (2–10), but they are too sticky for external use.

Compound tragacanth powder contains acacia (20%), tragacanth (15%), starch (20%) and sucrose. It is generally used in the form of compound powder (about 2 g per 100 ml of mixture) or as the mucilage (10 to 20 ml per 150 ml of product). The compound powder is always used as a vehicle other than water or chloroform water to avoid displacement of part of a medicinally active vehicle by the mucilage.

Novel drug dosage form: Acacia in combination with gelatin, used to form coacervates for microencapsulation of drugs.

4.2 Tragacanth

***Astragalus gummifier* (Leguminosae)**

Tragacanth tears

Tragacanth is the dried gummy exudation obtained by incision from stems and branches of *Astragalus gummifer* (Leguminosae). It occurs as thin, white or yellowish white, ribbon like flakes or as a white powder. With water it forms viscous solutions or gels. It is much better thickener than acacia. It is used as a powder or mucilage or as compound tragacanth powder. It suspends heavy indiffusible powders. It is also useful for mixtures containing resinous tinctures.

As an excipient: Tragacanth produces less sticky mucilage than acacia and hence it is more suitable for external preparations. It is used in jellies, lotions, pastes and creams. Tragacanth is used as a emulsifying agent and is higher viscous in nature due to its mucilage. Due to coarse emulsion it is mainly used as an emulsion stabilizer. In industry hog and *Sterculia* gums are sometimes used as cheap substitutes for tragacanth.

Tragacanth jellies sometimes called bassorin pastes since the hydrophilic component of tragacanth that forms gels in water is been named bassorin. As a lubricant 2–3% is adequate, 5% is necessary for dermatological vehicle. Bassorin paste consist of tragacanth 5%, alcohol 10%, glycerol 2% and water made upto 100 ml, is been used as a vehicle for Ichthammol, resorcinol, salicylic acid and other medicaments. Tragacanth based catheter lubricants and electrode and contraceptives jellies have been developed.

The disadvantage of tragacanth jelly is

I. They vary in viscosity, due to geographical origin of the gum and variations in milling and storage.

II. It tends to flake when the film left on the skin.

III. When the pH range alters from 4 to 5 to 7, the viscosity is lost.

IV. They are susceptible to microbial degradation.

4.3 Agar

***Gelidium amansii* - Gelidaceae**

Powdered agar

Agar is the dried gelatinous substance obtained from *Gelidium amansii* (Gelidiaceae). It is available as white powder or grayish white strips or shreds. Agar consist of two different polysaccharides agarose chemically D-galactose and 3, 6 unianhydro L- galactose units (responsible for gel strength) and agaropectin chemically believed to be a sulphonated polysaccharide in which galactose and uronic acid units are partly esterfied with sulfuric acid (responsible for viscosity).

As an excipient: It was used as an emulsion stabilizer in liquid paraffin emulsions prepared with acacia. The solubility is in boiling water, producing solutions of high viscosity. On cooling, it becomes thin gel with 0.5% mucilage. Only low concentration can be used if the product remains pourable.

Agar used as a gelling agent, thickening agent and stabilizer in liquid dosage forms. It is used as emulsifying agent and bulk laxatives. It is used in the manufacturing of jellies and confectionary items. In microbiology, it is used in the preparation of bacteriological culture medium.

4.4 Pectin





Citrus species (Rutaceae) | ***Malus domestica*** (Rosaceae) | ***Daucus carota*** (Apiaceae) | ***Helianthus annuus*** (Asteraceae) | **Powdered Pectin**

The source of pectin is from plants of different families. The important sources of pectin are *Citrus* (Rutaceae), *Malus domestica* (Rosaceae), *Daucus carota* (Apiaceae), *Helianthus annuus* (Asteraceae). Pectin is the purified carbohydrate product obtained by acid hydrolysis from inner portion of the rind of *Citrus limon* or *Citrus aurantium* (Rutaceae). Chemically pectin is a complex carbohydrate found in the middle lamella of plant cells. Pectin is a neutral methoxy ester of pectic acid. Pectins are polyuronides. Complete hydrolysis of pectin yields D-Galacturonic acid, methyl alcohol, small amount of galactose and arabinose.

Pectin is obtained from the inner rind of citrus fruits or from apple pulp remaining after cider making. It is extracted with dilute acid and purified. Pectin dissolves in about 20 parts of water, producing a viscous opalescent acid solution. It is good emulgent in acid media but degraded at alkaline pH.

Therapeutic indication: It is used as adsorbent in the treatment of diarrhea and as a haemostatic for internal or external hemorrhage. It is also used as a plasma substitute.

As an excipient: To replace acacia, it is been used in the proportion of 0.1 g per gram of acacia fully or partly in internal emulsions. It is used for the preparation or stabilizing pharmaceutical and cosmetic lotions and creams. Pectin is used as protective colloids. Pectin used as medical adhesive, as a demulcent and stabilizer. It is used as an emulsifying agent, a gelling agent in acid medium.

Novel drug dosage form: Pectin is used as a drug carrier in targeted drug delivery system. Pectin in combination with gelatin has been used as an encapsulating agent in pharmaceutical formulations to promote sustained release.

4.5 Lecithin


Glycine max **– Fabaceae** | **Powdered Lecithin**

Lecithin is obtained from soybean oil *Glycine max* (Fabaceae). It is also available in several vegetable seeds, egg yolk, corn and from animal brain and nervous tissue. Chemically lecithin contains glycerol, fatty acids, phosphoric acids and choline. Lecithins contain a saturated fatty acid at α-position and an unsaturated fatty acid at β-position.

Therapeutic Indication: Lecithin with the combination of proteins, it forms lipoproteins of plasma and cells. Acetylcholine formed from choline part is responsible for transmission of nervous impulses across the synapses. It is a

lipoprotic agent and prevent formation of fatty liver and lowers the surface tension of lung alveoli.

As an excipient: In the formulation of pharmaceutical dosage forms it is used as an emulsifying agent, dispersing agent, wetting agent, penetrating agent, stabilizing agent.

Novel drug dosage form: It is employed in Encapsulation.

4.6 Gelatin

Gelatin

Soft gelatin capsules

Gelatin is a protein, extracted by partial hydrolysis of animal collagenous tissue such as skins, tendons, ligaments and bones with in boiling water. Chemically gelatin contains different amino acids in which lysine is major essential amino acid. It does not contain tryptophan, gelatin composed of gluten protein.

Therapeutic indication: Gelatin is used in the form of absorbable gelatin sponge as haemostatic. It is recommended for the treatment of brittle finger nails and non-mycotic defects of the nails.

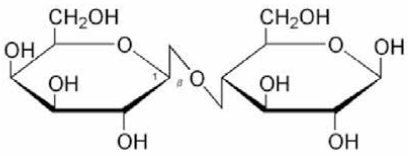
As an excipient: Gelatin used in the manufacture of hard and soft capsule shells. It is used in preparing lozenges, pessaries, pastes, pastiles and suppositories. It is used as vehicle for injections like heparin in the form of Pitkin menstrum that contains dextrose, acetic acid and water.

Novel drug dosage form: Gelatin is employed for encapsulation of drugs.

In bacteriological culture media, gelatin is used in the form of absorbable gelatin sponge and gelatin film.

4.7 Lactose

Lactose



Structure of Lactose

Lactose is a natural disaccharide contains galactose and glucose obtained from milk of mammals. Chemically lactose monohydrate is monohydrate of O-β-D galactopyranosyl – (1–4)-α-D glucopyranose.

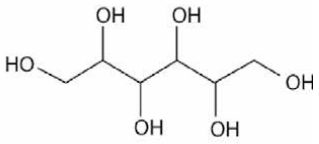
As an excipient: Lactose is widely used as filler and diluents in tablets, capsules. Fine grades of lactose are used in the preparation of tablet by wet granulation method. Direct compression grades of lactose are used in combination with micro-crystalline cellulose or starch and for tablet lubricant as 0.5% magnesium stearate.

Novel drug dosage form: Lactose is used as diluent especially in dry powder inhalations.

DOI: http://dx.doi.org/10.5772/intechopen.97671

4.8 Mannitol

Sugary exudation from stem of *Fraxinus ornus* Oleaceae)



Structure of Mannitol

Mannitol is a hexahydric alcohol obtained by isolation from stem of *Fraxinus ornus* (Oleaceae). Chemically mannitol is a sugar alcohol.

Therapeutic indication: Mannitol is a diuretic and isotonic agent. Mannitol does not metabolized and is eliminated by glomerular filtration and hence used as diagnostic and as an osmotic diuretic.

As an excipient: Mannitol used as a diluent, tonicity agent, stabilizer, as cryoprotectant and excipient for chewable tablets.

4.9 Starch

***Zea mays* (Graminae)**

***Oryza sativa* (Graminae)**

***Triticum aestivum* (Graminae)**

***Manihot esculenta* (Euphorbiaceae)**

***Solanum tuberosum* (Solanaceae)**

Starch is a polysaccharide granules obtained from grains of maize (*Zea mays* Linn.,), rice (*Oryza sativa* Linn.,) or wheat (*Triticum aeestivum* Linn.,) belongs to Graminae, tapioca (*Manihot esculenta*) family Euphorbiaceae and from the tubers of potato (*Solanum tuberosum* Linn.,) family solanaceae. Starch contains chemically two different polysaccharides. Amylose (β-amylose, water soluble) and amylopectin (α-amylose in water, soluble but swells responsible for gelatinising property) in the proportion of 1:2.

Therapeutic indication: starch is used as a nutritive, demulcent, protective and as an absorbent. In talcum powder starch is one of the ingredient for application over skin. It is used as an antidote in iodine poisoning.

As an excipient: Starch used as a disintegrant, diluent, binder and lubricant in the formulation of solid dosage forms. Glycerin of starch is used as an emollient and as a base for suppositories.

Sometimes starch is used with other suspending agents because of the high viscosity of the mucilage. It is an ingredient of compound tragacanth powder. Starch is a poor emulsifying agent. Its emulsions are suspensions of large globules prevented from coalescing by the high viscosity of mucilage. It is occasionally used for preparing enemas containing oils.

4.10 Bees wax

Yellow Bees wax

***Apis mellifera* (Apidae)**

Yellow bees wax is purified wax obtained from the honey comb of bees *Apis mellifera* and other species of *Apis* (Apidae). It occurs as yellow or white discs or blocks. The yellow beeswax is used in the preparation of dark colored ingredients. The white beeswax is bleeched and preferred when the ingredients are colorless, white or like calamine a pastel shade.

Chemically bees wax is the esters of straight chain monohydric alcohols with straight chain acids. The chief constituent of the bees wax is myricyl palmitate (about 80%). In addition cerotic acid (15%), small quantity of melissic acid and aromatic substance cerolein present along with chief constituent.

Beeswax contains sterol containing substances. Higher alcohols (eg., cetyl and steary) form w/o emulsion. The chief constituent of beeswax is myricyl palmitate, is a ester of higher alcohol and responsible for emulsifying properties partly. In addition, beeswax contains small amounts of esters of cholesterol (a sterol producing w/o emulsions) and free cerotic acid ($C_{25}H_{51}COOH$) reacts with borax producing soap used as an emulgent in cold creams.

As an excipient: Bees wax is not a very good emulgent but is useful stabilizer for w/o creams in facilitating incorporating water. Pharmaceutically it is used as an ingredient of Paraffin ointment IP. It is used as an stiffening agent and ointment base in semisolid dosage forms.

4.11 Lanolin/wool fat

Lanolin Wax

Ointment

Lanolin is a waxy substance secreted by sebaceous glands of wool bearing animals. Hydrous wool fat is the purified fat like substance obtained from the wool of the sheep *Ovis aries* Linn. (Bovidae). It is a pale yellow, greasy, sticky material with 36–42°C melting point. Wool fat will be deposited onto the wool fibers. Chemically hydrous wool fat is the complex mixture of esters and polyesters of 33 molecular weight alcohols and 36 fatty acids. It contains mainly esters of cholesterol and isocholesterol with carnaubic, oleic, myristic, palmitic, lignoceric and lanopalmitic acids. It also contains 50% of water.

As an excipient: It is poorly absorbed by skin but along with soft paraffin or vegetable oils produce creams that penetrate well and assist absorption of medicaments. It absorb 50% of water but when mixed with other fatty substances, it emulsify several times on its own weight of aqueous or hydro alcoholic liquid and the emulsions are w/o in type.

It is too sticky in nature to use alone and generally mixed with hydrocarbons as in the official eye ointment base and simple ointment B.P. The above products absorb appreciable amount of aqueous liquids. Example is the B.P alkaloidal eye ointments are prepared by incorporating aqueous solution of the alkaloidal salt into base thus forming a stable semi-solid emulsion.

It does not rancidify readily. It is used in creams and ointments and as an emulsion stabilizer and in lotions. Retaining its properties and to improve the physical characteristics and stability of wool fat, the following process can be done

I. Hydrogenation: Hydrogenated wool fat is a white, odorless and non-sticky in nature and spreads easily on skin and absorbs 50% of water.

II. Fractionation**:** They are viscous liquids consist of esters and called as liquid lanolins. They are used as emulgents and emulsion stabilizers and they are virtually free from stickiness.

III. Treatment with ethylene oxide**:** The polyoxyethylene derivatives are known as water soluble lanolins are non – ionic, water soluble and promote the formation of o/w emulsions.

Pharmaceutically in semi-solid dosage form, lanolin is used as water absorbable ointment base. It is a common ingredient and base for many water soluble creams and cosmetic preparations. It is used in topical liniments, as a lubricant and employed in rust preventive coatings.

Wool alcohols are obtained by crude fractionation of wool fat. Small amounts upto 2.5% used as a stabilizer in o/w emulsions. High concentrations cause phase inversion.

4.12 Theobroma oil (cocoa butter)

Cacao Butter

***Theobroma cacao* Sterculiaceae**

Theobroma oil or Cacao butter is the fat obtained from roasted seeds of *Theobroma cacao* family Malvaceae. It is yellowish white solid with chocolate like odor. Chemically *Theobroma* oil consists of stearic 34%, palmitic 25%, oleic 37% acids along with small amount of arachidic and linoleic acid. The non greasiness of the fat is due to glyceride structure. Melting point range is 30–36°C, hence it is solid at room temperature but melts in body. Readily liquefy on warming and rapid setting on cooling.

As an excipient: *Theobroma* oil is a suppository fatty base and ointment base, used in manufacturing creams and toilet soaps.

4.13 Sodium carboxy methyl cellulose / sodium cellulose glycosallate

Sodium carboxy methyl cellulose

Wood and cotton fibre
***Gossypium hirsutum* (Malvaceae)**

Sodium carboxy methyl cellulose is the sodium salt of poly carboxy methyl ether of cellulose from wood and cotton fiber *Gossypium hirsutum* (Malvaceae).

As an excipient: Sodium carboxy methyl cellulose used as a protective colloid, film forming agent, stabilizing agent, suspending agent, thickening agent and binding agent. It is used in concentrations from 0.25 to 1% for suspending powders in parenteral, oral and external products. Autoclaving at 125°C for 15 minutes reduces the viscosity by about 25% and allowance for this must be made when it is used in heat sterilized injections. It can be sterilized by dry heat at 160°C but this reduced the viscosity.

4.14 Sodium alginate /Algin

Sodium alginate

Brown sea weeds

Sodium alginate is the sodium salt of alginic acid, a polyuronic acid obtained from the algal growth of the species of family Phaeophyceae. The common algae are *Macrocystis pyrifera*, *Laminaria hyperborean*, *Laminaria digitata* and *Ascohyllum nodosium*. It occurs as a white or buff powder. Algin is purified carbohydrate extracted from brown sea weed (algae) by treatment with dilute alkali.

Alginic acid present in cell wall. The algae are harvested, dried, milled and extracted with dilute sodium carbonate solution results in a pasty mass. It is diluted to separate insoluble matter. Only soft water is used for extraction process. Further it is treated with calcium chloride or sulfuric acid for converting into calcium alginate. Purification can be done through washing. The next step is treating with hydrochloric acid. Alginic acid collected is treated with sodium carbonate for neutralization and conversion into sodium salt.

Sodium alginate is used as a stabilizing agent for emulsion, in the formulation of buccal tablets, as a cross linking polymer in enzyme immobilization. It is employed as a binding and disintegrating agent in tablet and lozenges, thickening and suspending agent in liquid dosage forms.

Novel drug dosage form: In the formulation of microspheres.

4.15 Chondrus (Irish Moss, carrageen)

Carrageenan Powder

Irish Moss

Irish moss is dried seaweed, red algae *Chondrus crispus* family Gigartinaceae. It occurs as yellowish, horny masses. Chemically carrageenan is sulfated galactans. Sodium alginate is a linear polysaccharide deriveative of alginic acid comprised of 1,4-β-d-mannuronic (M) and α-l-guluronic (G) acids. It is a cell wall component of marine brown algae, and contains approximately 30 to 60% alginic acid.

As an excipient: Sodium aliginate is used as an emulsifying agent. For small scale emulsification it is not suitable because preparation of mucilage is time consuming and the emulsification must be homogenized. Mucilage is prepared by washing the

seaweed. Digesting it with boiling water for 15 minutes, staining while hot through cotton wool in a hot jacketed funnel and adjusting to volume and mixed. 3% solution produces a gel on cooling and 2–5% mucilage will emulsify an equal volume of fixed oil. Very stable emulsions can be made by mechanical methods and *Chondrus* has been used industrially as an inexpensive emulgent for fixed oils, particularly for cod liver oil. It is also a useful emulsion stabilizer.

4.16 Peppermint oil

***Mentha piperita* (labiatae)**

Peppermint oil

Peppermint oil is obtained by steam distillation of fresh flowering tops of *Mentha piperita* (Labiatae). To isolate the oil, the air dried material is packed into galvanized iron or mild steel still. The still designed for this purpose has a false perforated bottom. The steam under pressure, generated with the help of boiler, is then passed through the drug. It takes about 3-4hours for distillation. More than 80% of the oil is distilled off during the first half of distillation. Distillation should be completed carefully, as menthol of medicinal and commercial uses comes later part of distillation process. The condenser should be made up of either aluminum or stainless steel and should be coiled because of increase in the area of condensation. The mentha oil is insoluble in water and having lower density than water can be easily decanted and filtered.

As an excipient: Aromatic waters are used mainly for their flavoring properties although some are mildly therapeutic and or preservative in action. For peppermint aromatic water the dilution in parts by volume is 1 ml with 39 ml of water. Used as flavor, carminative and weak preservative.

4.17 Liquorice liquid extract

Liquorice root

Liquorice liquid extract

Liquorice liquid extract is obtained from the dried, unpeeled, roots and stolons of *Glycyrrhiza glabra* Linn., (Fabaceae). The solvent used for extraction process is hydroalcohol. The chief constituent of liquorice is a triterpenoid saponin glycyrrhizin.

Therapeutic indication: Traditionally liquorice is being used as an expectorant and demulcent. It is used in the treatment of peptic ulcer due to presence of yellow colored flavonoids liquiritin and isoliquiritin. It is used in cough mixtures.

As an excipient: Used as a flavoring agent and for disguising the taste of saline ingredients, such as ammomium salts and alkali iodides in cough mixtures.

4.18 Lemon spirit

Citrus limonis **(Rutaceae)** **Lemon spirit**

Lemon spirit is obtained by maceration of lemon peel which is the outer part of the pericarp of ripen fruits of *Citrus limonis* family rutaceae, in alcohol. Lemon peel consists of volatile from 2 to 4%, hesperidin, pectin, calcium oxalate and bitter substances. The chief constituents of volatile oil are limonene 90%, citral 4%, geranyl acetate and terpineol.

As an excipient: Pharmaceutically lemon oil is used as flavoring agent and lemon spirit is used to mask the taste of alkaline citrates.

4.19 Orange syrup and compound orange spirit

Citrus aurantium **(Rutaceae)** **compound orange spirit**

Orange syrup and compound orange spirit is prepared from fresh or dried outer peel of the ripen or nearly ripen fruits of *Citrus aurantium* family Rutaceae. Outer peel consists of 2.5% of volatile oil, hesperidin, isohesperidin, neohesperidin, vitamin C and pectin. Aurantiamarin and aurantimaric acid are glycosidal compounds responsible for bitter taste.

Therapeutic indication: Orange peels are used as stomachic, aromatic and carminative.

As an excipient: It is used as a flavoring agent in oral liquid preparations and to disguise the metallic and astringent tastes of iron salts in childrens mixture.

5. Novel phyto drug delivery system (NPDDS) in herbal medicine

Earth is gifted by creator with rich heritage of botanicals in terms of natural products. Some of the natural products are potential in its therapeutic action for the betterment of mankind. Exploring the unexplored potential phytomolecules and converting it into novel formulation is the need of the hour to combat the challenging diseases and disorders.

Novel drug delivery in modern phytoceutical research can pave a way to determine its pharmacokinetic property, mechanism and site of action, accurate dose required to exert the desired therapeutic action. Phytomolecules can be incorporated into novel drug carriers as nanoparticles, nano and micro emulsions, matrix

systems, solid dispersions, liposomes, solid lipid nanoparticles and the like. Improving phytodrug delivery to the receptor target improves the efficacy thereby minimize the toxicity due to delivery of precise dose at the site of action.

6. Challenges in formulating novel phyto drug dosage form

Exploring the novel phytomolecules as pharmacophores to combat various diseases and disorders is been realized due to resentment on synthetic molecules. The limited clinical usage of herbal medicine is due to hydrophobic nature of phytomolecules results in poor absorbable nature thereby leads to low bioavailability [9] and lower lipid solubility results in increased systemic clearance. In other fringe at the site of administration, the phytomolecules are not stable at acidic pH in stomach, results in degradation leads to loss of desired therapeutic action [10].

In order to overcome these challenges, developing novel phyto dosage forms will pave a way to deliver the potent phytomolecules at receptor target with improvement in bioavailability, specificity, efficacy and stability and to control the rate of release of phytodrug thereby reduction in dosage frequency, enhances solubility as well as absorption of phytomolecules.

Novel drug delivery strategies include modified drug in terms of sustained and controlled release (polymers, miscelles, liposomes, ethosomes, and nanotechnology), prodrugs, transdermal drug delivery systems, ocusert, insulin jet and micropump, patient controlled analgesia, drug eluting stents, gene therapy and personalized medicine.

Phytometabolites also act as carriers to deliver the drug into different sites (Brain, stomach, colon, lungs, etc.). The aim of thischapter is to articulate the current updates in the area of drug carriers in specific to colon target and the data mining on the nano engineered phytomolecules in pharmaceutical research in the area of phytopharmaceuticals.

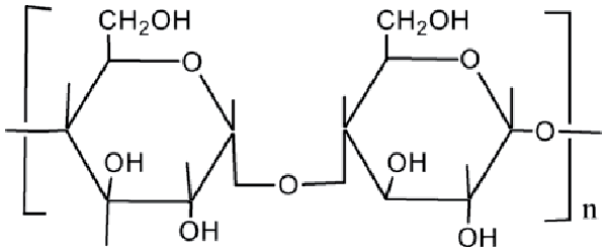
7. Natural polysaccharides based colon-specific drug delivery

The delivery of drugs into gastrointestinal tract is difficult due to physiological challenges like motility, hepatic clearance, acidic degradation, efflux mechanism, mucous turnover etc. Localizing orally administering drugs into the colon is complicated due to prediction of exact residence time of solid dosage forms in the stomach and small intestine. Also the residence time of the drugs depends on fed/fasted patterns, meal compositions and intensity of peristalsis. Solid dosage form may stay few minutes to 8 hour in stomach and 3 to 5 hour in bowel. Hence the colonic route of drug delivery can be used for systemic administration of drugs. Various approaches can be exploited to target the release of drug to colon by coating the drug with pH sensitive polymers, biodegradable polymers, embedding in biodegradable matrices and hydrogels, timed release systems, osmotic systems and bio adhesive systems [11].

Drug delivery systems targeted to colon by using natural polysaccharides finds superior over other systems. Moreover the uniqueness of polysaccharides are, retains their integrity and prevent the release of drug during its travel through GI tract and finally when it come in contact with colonic fluid it is digested by microorganism thereby the entrapped drug will be liberated. The polysaccharides been explored in colon specific drug release from plant origin are amylose, pectin, guar gum, alginates from algal origin, inulin, locust bean gum and pectin.

7.1 Amylose

Amylose is a component of starch, a polysaccharide obtained from plant source. Chemically amylose is glycopyranose residues linked by α-(1–4) bonds. It is a poly (1–4-α-D-glucopyranose).

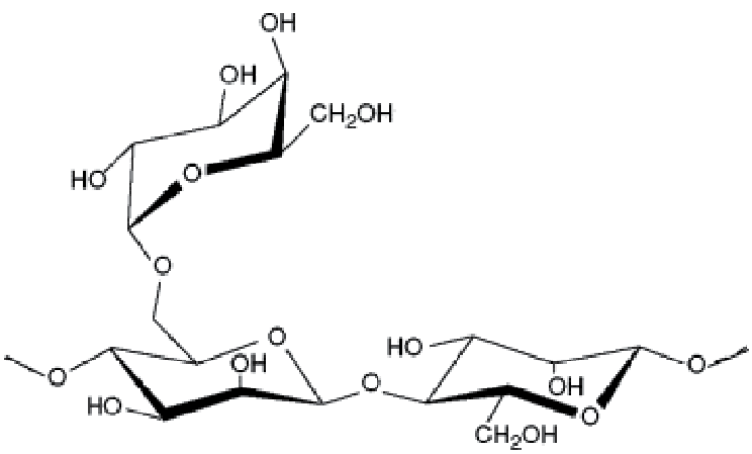


Chemical structure of amylose.

Natural polysaccharide	Reference
In-vitro potential of Amylose-Ethycel (1:4) coated 5-aminosalicylic acid pellet is prepared for colon targeted delivery, to protect drug release in stomach and intestine	[12]
Amylose & Ethecol (1:4) coated pellets containing 300 mg (^{13}C) glucose is developed for colonic drug delivery	[12]
Epichlorhydrin treated crosslinked amylase investigated for colon target drug delivery	[13]

7.2 Guar gum

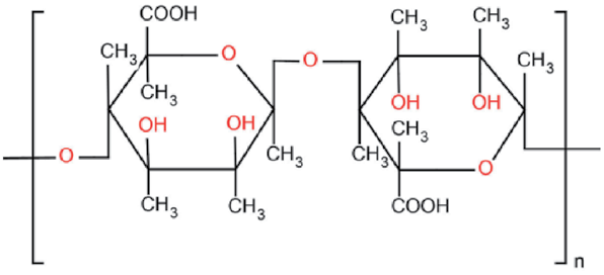
Guar gum is the powdered endosperm of the seeds of *Cyamopsis tetragonalobus* Linn, family Fabaceae. Chemically guar gum consist of linear chain of β-D-mannopyranosyl units linked (1 ➔ 4) with single member α-D-galactopyranosyl units occurring as side branches having molecular weight of approximately 1,000,000 giving it a high viscosity in solution.



Natural polysaccharide	Reference
Matrix tablet of guar gum with dexamethasone & budesonide investigated for colon targeted drug delivery.	[14]
Matrix tablet containing various proportions of guar gum is prepared by wet granulation technique using starch as a binder and colecoxib as a drug	[15]

7.3 Alginates

Alginates are natural hydrophilic polysaccharide derived from seaweeds. Chemically aliganates are 1 ➔ 4 linked D-mannuronic acid and L-glucuronic acid residues.



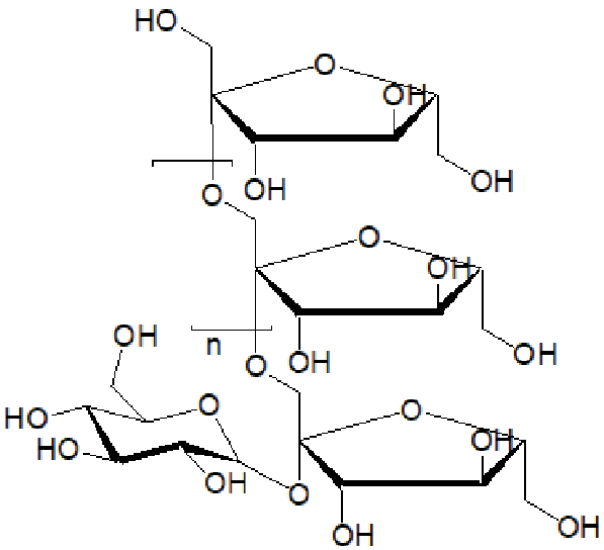
Alginates

Natural polysaccharide	Reference
Calcium alginate beads prepared as cores and 5-amino salicylic acid coated on them, act as controlled drug release.	[16]
Calcium alginate coated with Aquacoat®, a pH independent polymer followed by 2% w/w coating of Eudragit® resisted the release of drug in acidic media and drug release triggered at alkaline pH, act as sustain release in colon.	[17]

When drug coated with calcium alginate beads swells due to osmotic gradient and the film bursts and release the drug. The delivery of the drug will be to the distal intestine with minimum initial leak and thus provides sustained release in the colon.

7.4 Inulin

Inulin is a polysaccharide which is a chemotaxonomic marker of the plants belongs to compositae family. Chemically inulin is β 2–1 linked D-fructose having glucosyl unit at the reducing end. Mostly fructose chains have glucose unit as the initial moiety.

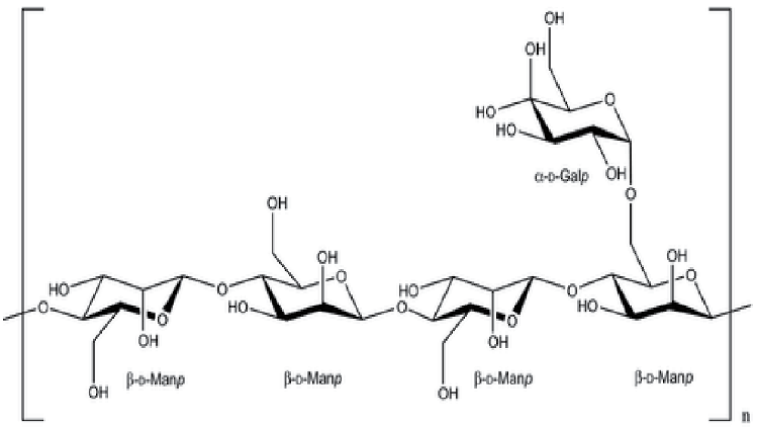


Structure of Inulin.

Natural polysaccharide	Reference
Inulin incorporated into Eudragit® RS films resist degradation in the upper GI tract and digested in human fecal medium	[18]
Inulin reacted with glycidyl methacrylated in N,N-dimethyl formamide in presence of dimethylaminopyridine as catalyst results in formation of hydrogel, degraded by inulinase enzymes causes bulk degradation.	[19]

7.5 Locust bean gum

Carob gum is the synonym of Locust bean gum obtained from seeds of *Ceratonia siliqua* family Fabaceae. Chemically locust bean gum is β-1,4-D-galactomannan units. It requires heat to achieve full hydration and maximum viscosity.

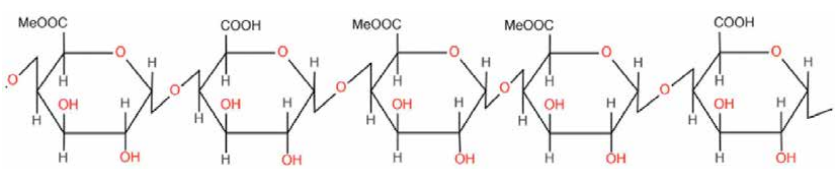


β-o-Manp-β-o-mannopyranosyl unit.
α-o-Galp-α-o-galactopyranosyl unit.
Polysaccharide units of locust bean gum.

Locust bean gum and chitosan (2:3, 3:2 & 4:1) in combination used as a polymer for colon specific drug delivery. Invitro drug release and invivo studies revealed the core tablet is capable of protecting the drug release in stomach, small intestine. Further susceptible to colonic bacterial enzyme results in drug release [20].

7.6 Pectin

Pectin is obtained from *Citrus* (Rutaceae), *Malus domestica* (Rosaceae), *Daucus carota* (Apiaceae), *Helianthus annuus* (Asteraceae). Chemically pectin is a polysaccharide consist of α-1,4 D-galacturonic acid and 1,2 D-rhamnose with D-galactose and D-arabinose side chains with average molecular weight between 50,000-1,50,000. Depending on the plant source and preparation they contain varying degree of methyl ester substituents.



Structure of Pectin.

Natural polysaccharide	Reference
Coating with pectin in presence of additives and hydrophobic polymers remains unaffected in gastric and small intestinal enzymes and digested in presence of colonic bacterial enzymes	[21]
Insoluble salt of calcium pectinate by deesterification is utilized for the preparation of matrix tablets and incorporating indomethacin as water insoluble drug marker in the invitro release experiments. The release of indomethacin is significantly increased in rat caccal contents.	[22]

Natural molecules other than plant source also plays important role in pharmaceutical sector. Chitosan high molecular weight polycationic polysaccharide obtained from chitin (Cuticles of various crustaceans, principally crabs and shrimps), chondroitin sulphate, a mucopolysaccharide consist of D-glucuronic acid linked to acetyl D – galactosamide obtained from extracts of cartilaginous cow and pig tissues and other sources such as shark, fish, and bird cartilages, cyclodextrins, an enzymatic conversion of starch, dextrans, a colloidal, hydrophilic and water soluble linear chains of α-D- glucose molecules obtained from microorganisms of the lactobacillus *Leuconostocmesenteroides* are being used as natural polysaccharides based colon specific drug delivery.

Colon based drug delivery strategies are exploited to target the drug release to the colon. Several approaches is been and being investigated to achieve site specificity to colon. In this context, the presence of polysaccharides in the colon provides platform for the delivery of drugs to the colon. Specifically the natural polysaccharides remains intact in the pH condition of stomach and small intestine and when reaches the colon, the drug loaded natural polysaccharides are cleaved by polysaccharidases enzymes, due to presence of large number of derivatizable groups, wide range of molecular weights, varying chemical compositions, low toxicity and high stability. Challenges faced in use of polysaccharides as drug carriers ishydrophilicity that results in drug release slowly in upper GI tract. This can be overcome by crosslinking of the polysaccharides with epichlorhydrin, glutaraldehyde and STMP. In this aspect the crosslinking agents should not alter the biodegradability of the polysaccharide matrix in colon.

8. Phytomolecules in nano dosage form

Phytomolecules are complex in structure contributes to its polarity. Non polar phytoconstituents are steroids, terpenoids, volatile oils, alkaloids and fixed oil, flavonoids are moderate polar constituent, alkaloidal salt, tannins, glycosides, phenols, gums, resins, mucilage are highly polar constituents. Employing novel drug delivered strategy for varied polar Phytoconstituents illuminate the focus of phytodrug in the global pharmaceutical sector. The advantage of converting phytomolecules into nano size results in increase in solubility in the systemic circulation thereby increase in bioavailability, physical stability, improving tissue macrophage distribution, protection from physical and chemical degradation, dose proportionality, smaller dosage form, smaller particle size with greater surface area provides higher absorption rate including lipophilic non polar phytomolecules, as a substitute for liposomes and vehicles. More importantly the nano sized phytomolecules potentially enhances the therapeutic action that ends in innovative therapeutic strategies for herbal medicines.

Nanotechnology is the engineered technology applied for the drug molecules at the nano size of 1-100 nm.Designing of drugs especially phytodrugs in nano dosage

forms offers greater efficacy and cell specificity. Nanodosage forms are one of the significant novel drug delivery systems.

9. Nanoemulsions

Plants containing volatile oils can be easily formulated into nanoemulsion. Nanoemulsions constitute vehicles for volatile oil with sizes ranging from 20 to 200 nm. Nanoemulsions are colloidal dispersion system mixed with emulsifying agents, surfactants and co-surfactants to form single phase. Nanoemulsions are classified into o/w type (oil dispersed in aqueous phase), w/o type (water dispersed in oil phase) and bicontinuous (microdomains of water and oil are interdispersed within the system). Multiple emulsion is also included in the types of nanoemulsion wherein both o/w and w/o emulsion present in one system. Hydrophobic and lipophilic surfactants are used for stability.

Following is the perception of phytonanoemulsion, formulation methods (**Table 2**), characterization techniques (**Table 3**).

S.No.	Method	Type	Principle
1	Low energy emulsification	Phase inversion method	Using low temperature and high temperature
		Phase inversion composition method	Magnetic stirring and evaporation of the water miscible solvents under vacuum
		Solvent displacement method	Membrane contractor liquid phase forced through membrane pores leads to formation of droplets
2	High pressure emulsification	Ultrasonication	Sonicator probe contacts the liquid and it generates mechanical vibration leads to Cavitation
		High Pressure homogenization	500-5000 psi
		Microfluidiser	500–20,000 psi

Source: (Sunil [23–26]).

Table 2.
Formulation methods in nanoemulsion.

S.No	Parameters	Characterization method
1.	Droplet size analysis	Diffusion method using light scattering particle size analyzer
2.	Viscosity	Brookfield viscometer
3.	Dilution	The Nanoemulsion is diluted with water and observed for phase inversion
4.	Drug content	HPLC method
5.	Poly dispersity	Photon correlation spectroscopy
6.	Refractive index	Refractometer
7.	Dye test	The water soluble dye is added in an o/w type nanoemulsion and it takes up the color uniformly. Similarly, the emulsion is w/o type and the water soluble dye being added and the emulsion is not uniformly colored.
8.	pH	pH meter
9.	Zeta potential	Zeta sizer / zeta analyzer
10.	Fluorescence test	Many oils exhibit fluorescence when exposed to UV light

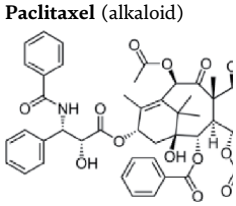
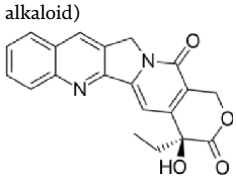
S.No	Parameters	Characterization method
11.	Percentage transmittance	UV visible spectrophotometer
12.	Conductance measurement	Conductometer
13.	Filter paper test	Nanoemulsion dropped onto filter paper and observed for migration
14.	Morphology and structure	TEM (Transmission Electron Microscopy)
15.	Invitro skin permeation studies	Kesharychien-diffusion cell
16.	Stability studies	Heating cooling cycle (the formulation were subjected to refrigerator (six cycles) at the temperature 4 °C and 45°C) stable formulation subjected to centrifugation test& Centrifugation (stable formulation were centrifuged at 3500 rpm)
17.	Interaction study	Fourier transform infrared spectroscopy spectral analysis
18.	Surface morphology	Atomic force microscope
19.	Invitro drug release study	Dissolution test apparatus

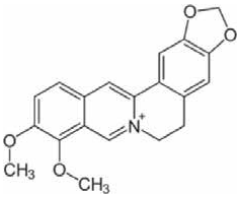
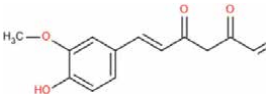
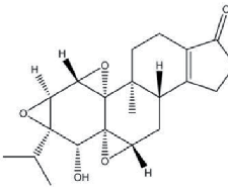
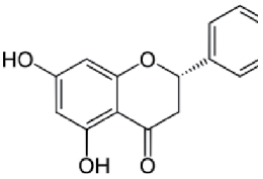
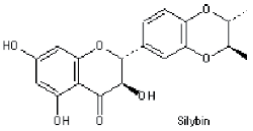
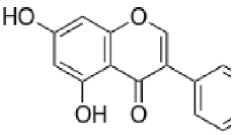
Source: [27].

Table 3.
Characterization parameters for formulated Nanoemulsion.

10. Phytomolecules in novel drug dosage form

Phytomolecules is been formulated as novel dosage forms and over two decades it is been concentrated in scientific research. The plant actives and extracts are formulated into polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microspheres, transferosomes, and ethosomes. Secondary metabolites formulated as novel phyto drug nano dosage forms (**Table 4**) and **Table 5** gives the insight view of plant actives and extracts formulated into various novel dosage forms [48].

S.No	Phytomolecules	Biological source & Family	Formulation Method & Pharmacological action
1	**Paclitaxel** (alkaloid) 	*Taxus brevifolia* (Taxaceae) 	Nanoprecipitation Acts against several tumors, ovarian and breast cancer [28, 29]
2	**Camptothecin** (Quinoline alkaloid) 	*Camptotheca acuminata* (Nycaceae) 	Encapsulation Potent anticancer [30]

S.No	Phytomolecules	Biological source & Family	Formulation Method & Pharmacological action
3	**Berberine** (Isoquinoline alkaloid) 	*Berberis vulgaris* (Berberidaceae) 	Emulsion, ionic gelation. Inflammation and several cancers [25]
4	Curcumin (Polyphenol) 	*Curcuma longa* (Zingiberaceae) 	Wet-milling technique Potent anticancer and antitumor [31, 32]
5	**Triptolide** (Diterpenoidtriepoxide) 	*Tripterygium wilfordii* (Celastraceae) 	Nanoensapsulation In inflammation and autoimmune diseases, especially for rheumatoid arthritis [30, 33]
6	**Naringenin** (Flavonone) 	*Vitis vinifera (Vitaceae)* 	Nano precipitation Acts against several tumors and Hepatoprotective [34]
7	**Silymarin** (Flavonolignans) 	*Silybum marianum*L.Gaertner (Asteracecae) 	Cold homogenization In several liver diseases, breast cancer [35]
8	Genistein (Isoflavone) 	*Genista tinctoria* (Fabaceae) 	Nanoemulsion and chitosan microsphere Used in cardiovascular diseases, breast and uterine cancer also in osteoporosis [36]

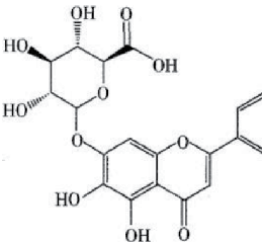
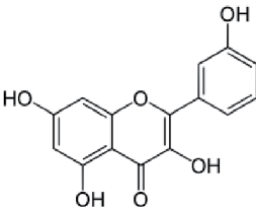
S.No	Phytomolecules	Biological source & Family	Formulation Method & Pharmacological action
9	Breviscapine (Flavonoid) 	*Erigeron breviscapus* (Asteraceae) 	Lipid encapsulation In cerebrovascular and Cardiovascular diseases also against pulmonaryfibrosis [37]
10	Quercetin (Flavonol) 	*Sambucus nigra* (Adoxaceae) 	Gelatin and chitosan loaded Potent anticancer and antioxidant [38]
11	Crude extract of *Ginkobiloba* (Ginkgoaceae)- Terpenic lactones 	*Ginko biloba* (Ginkgoaceae) 	Combination of dryand wet process.(Gas phase andliquid phasegrinding) Acts against loss ofmemory, thinking, language [39]

Table 4.
Secondary metabolites formulated as novel phyto drug nano dosage form.

S.No	Formulation	Method	Pharmacological action	Reference
1	Liposome encapsulated Silymarin	Reverse evaporation technique	Hepatoprotective	[40]
2	Breviscapine liposome	Sustained delivery of breviscapine	To treat ischemic cerebrovascular and cardiovascular diseases	[41]
3	Paclitaxel liposome	Thin film hydration method	Anticancer	[42]
4	Berberine-loaded nanoparticles	Ionic gelation method	Anticancer	[43]
5	Glycyrrhizic acid-loaded nanoparticles	Rotary-evaporated film ultrasonication method	Anti-inflammatory & antihypertensive	[44]
6	Taxal loaded nanoparticles	Emulsion solvent evaporation method	Anticancer	[45]
7	Silybin phytosome	Silybin-phospholipid complexation	Hepatoprotective, antioxidant for liver and skin	[46]
8	Berberine nanoemulsion	Drawing ternary phase diagram	Hypolipidemic agent	[47]

Table 5.
Phytomolecules in novel dosage forms.

11. Conclusion

Natural products either as a drug or pharmaceutical substance played vital role in the treatment and prevention of diseases in humans. Pharmacognosy is the established pharmaceutical science and is a mother of pharmacy wherein, phytochemistry and molecular pharmacology, is the heart of the drug discovery process. Investigation of plant products will give a way to enter as a lead molecule as pharmacophores in drug discovery process or as a drug carrier to receptor target rather than placing the herbs in traditional pharmacognosy.

Today pharmacognosy discipline is the carrier of potent traditional herbs that acts as a bridge and as a vehicle that transports to the site of modern drug discovery. Focusing pharmacognosy research not only identifies new chemical entities (NCE's), but also exploring the biomolecules from natural sources as drug carriers, in formulating novel phyto drug dosage forms equivalent to the synthetic drug dosage forms in the area of pharmaceutical sciences.

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