Chapter

Pharmacological Role of Biosynthetic Products

Yakubu Jibira and Paul Atawuchugi

Abstract

A product such as hydrated carbons (carbohydrates), lipids, proteins, and nucleic acids play significant roles in plants metabolically. But there are other natural organic products manufactured by plants, some of the products are complex molecules, which are not primary metabolites. These biosynthetic products have possesses a variety of therapeutic merits in drug discovery. Some biosynthetic products show numerous appreciable therapeutic effects making them beneficial for trimming down polypharmacy and as viable candidates for the management of chronic diseases such as diabetes and hypertension in patients. The chapter discusses the pharmacological role of some biosynthetic products from plants and animals.

Keywords: alkaloids, phytosterols, biosynthesis, amino acids, pharmacological, terpenes

1. Introduction

Natural products are mostly produced by a living organism. A product such as carbohydrates, lipids, proteins, and nucleic acids play significantly impact on the primary role in in plants in terms of their metabolic reactions. Moreover, other natural organic compounds have also been known to be produced by plants, with which some of them are complex molecules, which are not primary metabolites. Different organisms may produce the same compounds through different pathways (e.g., convergent evolution), even if they are widely separated phylogenetically. The same organism may produce some compounds via over one biosynthetic path. There may be over one path available, such as in a changed linear process or metabolic grid. Even if the same compound is present in two different organisms, they may be formed via different pathways. This, however, is more likely for metabolites with simple structures. It derives the major precursors from the metabolism of carbohydrate (sugars), protein (amino acids), and lipid (fatty acid). The pathway derived biosynthetically for aromatic amino acids is an integral source of aromatic compounds such as flavonoids, phenols, and some alkaloids. Glycolysis yields an important metabolite such as acetyl-CoA and also via the beta-oxidation of fatty acids and also used in the tricarboxylic acid cycle (TCA) in the manufacture of organic acids, which are also starting materials for secondary metabolites. Also, acetyl-CoA plays important role in synthesizing terpenes, which forms a distinct class of metabolites.

2. Animal biosynthetic product

Animals contain many unique small molecules, including bioactive secondary metabolites. The compounds are protective, offensive or involved in communication [1]. Most of this product is also biologically effective, and they include the following.

2.1 Terpenes

Terpenes occur widely in nature. They are a large and varied class of hydrocarbons, which are produced by a wide variety of plants and by some animals. Terpenes are biosynthetically derived from isoprene units with the molecular formula C_5H_8. In bacteria and plants, isoprene precursor's dimethylallyl pyrophosphate and isopentenyl pyrophosphate can be made either via the mevalonate or deoxyxylulose phosphate pathways, but in animals' mevalonate is the source of these precursors [2]. The mevalonate pathway is the universal source of the terpenoid C5 precursor's isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP). In this pathway, three molecules of acetyl-CoA are condensed to 3-hydroxy-3-methylglutaryl-CoA with subsequent reduction to mevalonate, which is converted to IPP and DMAPP. Terpenes can exist as hydrocarbons or have oxygen-containing compounds such as hydroxyl, carboxyl, ketone, or aldehyde groups. After chemical modification of terpenes, it refers to the resulting compounds as terpenoids [3].

In the biochemical pathway of terpenoid synthesis, prenyltransferases take part in the condensation of activated forms of isoprene units. They link IPP with an isopentenyl diphosphate isomer of DMAPP in a "head-to-tail" manner. The linear chains of phenyl diphosphates that are formed in the reaction may also be changed through dimerization or cyclization by terpene synthase, forming terpenoids with new functions. They classify the resulting terpenes in order of size into hemiterpene, monoterpenes, sesquiterpenes, diterpene, triterpene, tetra terpenes, and polyterpenes. Hemiterpene comprises a single isoprene unit and changed into oxygen-containing derivatives called hemiterpenoids [3].

We have found terpenoids to be useful in the prevention and therapy of several diseases, including cancer, and also to have antimicrobial, antifungal, antiparasitic, antiviral, anti-allergenic, antispasmodic, antihyperglycemic, anti-inflammatory, and immunomodulatory properties [3].

2.2 Carnitine

Vaz and Wanders, [4] have described that carnitine plays a vital role in energy production in living organisms in terms of metabolism since it enables activated fatty acids to enter the mitochondria, where broken down via β-oxidation. Carnitine is present in all animal species, including other multiple micro-organisms and plants. They maintain its homoeostasis through endogenous synthesis, absorption from dietary sources and efficient tubular reabsorption by the kidney. Animal tissues contain relatively high amounts of carnitine, varying between 0.2 and 6 μmol/g, with the highest concentrations in heart and skeletal muscle. Apart from the diet being the primary source of carnitine, most mammals can synthesize carnitine internally [4].

Carnitine synthesis is from two amino acids; precisely lysine and methionine. Lysine serves as the carbon backbone of carnitine and the 4-N-methyl groups emanate from methionine [5]. Proteins in mammals contain N'trimethyl-lysine (TML) residues. N-methylation of these lysine residues occurs as a post-translational event in proteins such as calmodulin, myosin, actin, cytochrome c and

histones. This reaction mostly catalysed by specific methyltransferase, which uses S-adenosylmethionine as a methyl donor. TML is the first metabolite of carnitine biosynthesis is released through the action of Lysosomal hydrolysis of these proteins. TML is first hydroxylated on the 3-position by TML to yield 3-hydroxy TML (HTML). Aldolytic cleavage of HTML yields 4-trimethylaminobutyraldehyde (TMABA) and glycine, a reaction catalysed by HTML aldolase (HTMLA; EC 4.1.2.'X'). Dehydrogenation of TMABA by TMABA dehydrogenase (TMABA-DH; EC 1.2.1.47) results in the formation of 4-Ntrimethylaminobutyrate (butyrobetaine). In the irrevocable step, butyrobetaine is hydroxylated on the 3-position by γ-butyrobetaine dioxygenase to yield carnitine [4]. Carnitine has an important role in the transport of activated long-chain fatty acids from the cytosol to the mitochondrial matrix where β-oxidation takes place. Second, they involve carnitine in transferring the products of peroxisomal β-oxidation, including acetyl-CoA, to the mitochondria for oxidation to CO2 and H2O in the Krebs cycle.

Pharmacologically, carnitine has possessed several effects on bone mass, male infertility, cognitive support, [6] metabolic function improvement, [7] neuroprotective effects in Alzheimer's dementia [8] and Parkinson's disease, [9] protection against oxidative stress damage, [10] congestive heart failure, hypertrophic heart disease, and peripheral arterial disease treatment [11]. They have also shown it to improve peripheral vasodilator activity [12].

From [13] the ability of an agent to control endothelial dysfunction is through upsetting the balance between the production of a vasodilator such as nitric oxide and vasoconstrictor, such as endothelin-1 substances in response to physical or chemical stimuli. This is because it is through that imbalance that leads to endothelial dysfunction, which is one of the initial steps in atherogenesis [14]. They relate endothelial dysfunction to cardiovascular risk factors such as arterial hypertension, dyslipidemia, diabetes, and obesity [15, 16]. They have therefore investigated carnitine gas in rats' models to cause an endothelium-dependent dilatation in arteries, since endothelial nitric oxide seemed to be the main mediator of vasodilatation [17]. For the cardioprotective ability of carnitine to serve as a cardioprotective agent, isolated rat working heart through different antioxidant mechanisms in most of the cases [18]. In terms of insulin resistance, this is where a 20 weeks treatment with carnitine in animal obese models resulted in a reduction in body weight, abdominal adiposity, plasmatic insulin, and liver triglyceride content [19]. Several, studies have been conducted on the antioxidant properties of carnitine and was due mainly to a reduction in both lipid peroxidation and free radical generation [20]. A decreased expression of inducible NO synthase and protein nitration, and inhibition of tubular necrosis and neutrophil infiltration in transplanted kidneys [21] . For antioxidant study [22] also revealed that carnitine and its derivatives fundamental mechanisms as participating in redox signalling that affects transcription factors (Nrf2, PPARα, NF-κB, etc.) and activating the vitagene network.

2.3 Pheromone

Pheromone plays a key role in sexual communication and reproduction in many insects such as the moth's species. In some insects, the pheromone is biosynthesized and released by specialized sex pheromone glands (PGs) that are along the intersegmental membrane between the 8th and 9th abdominal segments of females. Although the general pathway of sex pheromone synthesis in most species has not been established and the molecular mechanisms remain poorly understood [23]. Although de novo synthesis is more prevalent in the species studied to date, there are multiple examples of pheromone components derived from host precursors. Sometimes, such as leucine, used as starting material for fatty-acid derived sex

pheromone biosynthesis by Holomelina spp. (Lepidoptera: Arctiidae), the putative plant-derived precursor is extensively elaborated by a typically de novo pathway. In other cases, it converts a highly elaborated host precursor to a pheromone component through a simple chemical transformation. While they originally reported the utilization of host precursors for pheromone biosynthesis in some insects, subsequent studies showed that pheromone biosynthesis was only or partially de novo [23].

The analysis of different pheromone glands in different species has revealed the occurrence of unusual fatty acids that have been proposed as precursors of pheromone components. Many lepidopteran sex pheromones are produced by P-oxidation steps with desaturase systems. However, only a few studies have a combination of different fatty acyl intermediates been used to show experimentally a pheromone biosynthetic pathway [23].

From [24] sex pheromone biosynthesis in moths begins with a palmitic or stearic acid moiety that is synthesized de novo in the PG through modifications of the fatty acid biosynthetic pathway. Through a series of enzymatic reactions such as desaturation, chain-shortening reaction, reduction, acetylation, and oxidation, it then converts the palmitic or stearic acids to the final pheromone components in a step-wise manner. Therefore, different enzymes are likely to be involved in the different reactions, and to date, the genes encoding 4 different classes of enzymes that are essential for this pathway have been functionally identified desaturases (Des), fatty acid reductases (FARs), fatty acid transport proteins (FATPs), and acyl-CoA-binding proteins (ACBPs) [24].

Pheromones, a chemical or blend of chemicals released by an organism that causes a specific behavioral or physiological reaction in one or more conspecific individuals are important mediators of communication for bacteria, plants, and animals in these environments. Pheromone systems of insects have proved to be some of the richest intellectual sources for the nascent science of chemical ecology the composite pheromones can be classed into six behaviorally functional groups: sex, aggregation, dispersal (spacing or epideictic), alarm, recruitment (trail), and maturation [24].

Pheromones are noted to function as opposite-sex attractants, same-sex repellents, and mother-infant bonding attractants and as menstrual cycle modulators [25]. A review article by [26] concluded that pheromones have aphrodisiac activity.

2.4 Melanin

Melanin is an abundant biological pigment that is present in mammalian which is located in areas such as skin, hair, eyes, ears and the nervous system. Birds' feathers, squid's ink, insects, plants and many other biological systems have been also known to contain melanin. It classifies melanin into three groups: eumelanin, pheomelanin and allomelanins. We term nervous system melanins as neuromelanin. Eumelanin colours commonly present as black or brown in animals [27].

Amino acid tyrosine is needed in the production of melanin, but its actions are catalyzed enzymatically by tyrosinase. In their primary biosynthetic pathway, tyrosine is hydroxylated to form the catecholamine 3,4-dihydroxyphenylalanine (DOPA), which is then oxidized to form 3,4-dioxyphenylalanine (dopa quinone) before cyclization to 5,6-indole quinones and their subsequent polymerization to form melanin [27].

Mason-Raper pathway can also produce melanin, and it started by the usage of tyrosine to form dihydroxyphenylalanine by tyrosinase through an oxidation reaction. The product (dihydroxyphenylalanine) formed is then oxidized by the same enzyme to dopa quinone, which rearranges spontaneously to leuco dopa chrome and then to dopa chrome. An unusual trait of dopa chrome that of decolorizing slowly if held

under a vacuum allowed the identification of the subsequent intermediate 5,6-dihydroxy indole-2 carbolic acid, which loses its carboxyl group to become 5,6-dihydroxy dole. Upon exposure to air 5,6-dihydroxy indole is oxidized to indole 5,6-quinone and then to melano chrome, a purple compound that polymerizes to melanin [27].

Similar to the biosynthesis of eumelanin, melanin known as pheomelanin is biologically synthesized, except that it incorporates a precursor containing sulphur in the structure.

It has revealed melanin from natural sources to exhibit a broad spectrum of biological activities such as UV radiation protection, enzymatic lysis, and damage by oxidants, and resistance to drugs by pathogens, protection of insects against bacteria and antiviral protection. They have shown melanin to chelate metal ions and to act as a physiological redox buffer [27]. With this in mind, several studies have pharmacologically shown that melanin is indeed effective as an antioxidant, [28–30] Immunomodulatory and enhancement, [31–34] hepatoprotective, [35] anticarcinogenic effects, [36] and anti-inflammatory [37].

Studies conducted in *Nigella sativa* L. by [38, 39] which contains a lot of melanin in its seeds had the potential of treating imbalanced cytokine production and unconcern cancer and other immunotherapies. This was possible because melanin induced TNF-alpha, IL-6 and VEGF mRNA expression.

Melanins from various sources exhibit significant antioxidant activity, melanin protects pigmented cells and adjacent tissues by adsorbing potentially harmful substances, which are then slowly released in nontoxic concentrations, Besides, melanin could also interact with orally administered drugs and a vehicle for drug delivery, Melanin extracted from different species of tea displays protective effects against hydrazine-induced liver injury, a remarkable anti-inflammatory effect of melanin has been reported [34].

2.5 Cholesterol

The most ubiquitous sterol in the animal system is present as cholesterol. But plant lack cholesterol notwithstanding, they contain structurally similar other sterol and similar biosynthetic pathway exist both in plants and animals and some prokaryotes. In humans, Normal healthy adults synthesize cholesterol at a rate of approximately 1 g/day and consume approximately 0.3 g/day. A relatively constant level of cholesterol in the body (150–200 mg/dL) is maintained primarily by controlling the level of de novo synthesis, which is partly regulated in part by the dietary intake of cholesterol [40].

Cholesterol is biosynthesized from a 2-carbon metabolic intermediate, acetyl-CoA hooked end to end involving several enzymatic reactions and finally gets converted into the 27-carbon molecule of cholesterol. Metabolism (catabolism) of lipids, carbohydrates and proteins leads to the formation of AcetylCoA. The process of cholesterol synthesis has five major steps where the conversion of Acetyl-CoAs to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) is the first. HMG-CoA is converted to mevalonate, followed by the formation of an isoprene-based molecule, isopentenyl pyrophosphate (IPP), with the concomitant loss of CO2 from mevalonate. It, therefore, converts the IPP to squalene, where cholesterol is formed from squalene as the last step. The reaction is repeated with the units of Acetyl-CoA. Two moles of acetyl-CoA are condensed in a reversal of the thiolase reaction, forming acetoacetyl-CoA. Acetoacetyl-CoA and the third mole of acetyl-CoA are converted to HMG-CoA by the action of HMG-CoA synthase. HMG-CoA is converted to mevalonate by HMG-CoA reductase, HMGR (it binds this enzyme in the endoplasmic reticulum, ER). HMGR requires NADPH as a cofactor, and two moles of NADPH are consumed during the conversion of HMG-CoA to mevalonate.

The reaction catalyzed by HMGR is the rate-limiting step of cholesterol biosynthesis. Mevalonate is then activated by three successive phosphorylations, yielding 5-pyrophosphomevalonate. Phosphorylation mevalonate and successive reactions maintain their solubility since otherwise, these are insoluble in water [40].

Cholesterol from both diet and synthesis is utilized in the formation of membranes and the synthesis of the steroid hormones and bile acids, regulating membrane fluidity and permeability as a cell membrane structural component, formatting lipid rafts with sphingolipid to mediate cell-to-cell recognition, adhesion, and communication [40].

3. Biosynthesis of plant origin

Different plants not only synthesize different aromatic secondary metabolites but also synthesize varying amounts of them at specific times and in specific subcellular compartments. One would expect that regulation of the differential biosynthesis of sometimes very complex molecular structures might involve regulation of the supply of the precursors influencing the rate-limiting step for carbon flow through the shikimate pathway. Recent data on transgenic potatoes give some sign that this is indeed the case [41].

3.1 Biosynthesis of terpenoid compounds

Some terpenoids play an important role in plant growth and development, such as gibberellin, as plant hormones regulate plant development. Other terpenoids play a role in the interaction between plants and the environment, such as participating in plant defence systems as phytoalexins and interspecies competition as interspecific sensing compounds. Terpenoids make up one of the largest and structurally diverse groups of naturally occurring compounds [42]. Mevalonic acid is mostly employed as a terpenoid synthetic racemate; however, mevalonic acid dimethoxy acetal may be resolved as its quinine salt. The acetates of the individual enantiomers of mevalonolactone are much less soluble than the racemate, and these may determine the purity and chirality of biosynthetic mevalonate. The steric course of many terpenoid biosynthetic processes has been followed using the stereospecifically deuterated and tritiated 2R,3R- [2-'H]-, 2S,3R- [2-3H]-, 3R,4R- [4–3 H] -, 3R,4S- [4- HI-, and 3R,5R- [S 3 H]-mevalonate. Several routes for preparing 5S-[5-3H] mevalonate have been described. [l-3H] Isopentenal is a substrate for liver alcohol dehydrogenase and this affords 1 s- [l-3H] isopentenyl, which may then be converted into mevalonic acid. Alternatively, [5-3H] mevalonic acid can be reduced enzymatically with mevalonate reductase to afford 5S-[5-3H] mevalonic acid. The hemithioacetal of mevalonate and coenzyme-A is reduced by 3-hydroxy-3-methylglutaryl COA reductase." The steric course of this reduction is now known and they can also adapt this to afford 3R,5S- [5-3H] mevalonic acid. They have reported a mevalonate kinase assay [13]. An enzyme system capable of forming the mono- and pyro-phosphates of mevalonic acid, isopentenyl pyrophosphate and dimethylallyl pyrophosphate has been isolated 'From orange-juice vesicles and shown to convert isopentenyl pyrophosphate and dimethylallyl pyrophosphate into linalool [42].

3.1.1 Pharmacology of terpenoids

Antitumour, [43] anti-inflammatory, antibacterial effects, cardiovascular effects, antimalarial, hypoglycemic effect, and transdermal absorption promotion have been investigated to give such pharmacological activities. Other activities apart

from the mentioned above include insect resistance, immunoregulation, anti-oxidation, antiaging, and neuroprotection have also been known [3].

3.1.2 Works done on terpenoids

They have conducted several studies on terpenoids and their outcomes are promising. For antitumour activity, they have shown that perillyl alcohol which contains terpenoids plays a preventive and therapeutic role in cancer. The results showed that the administration of perillyl alcohol in rats can significantly reduce the incidence and multiplicity of colonic invasive adenocarcinoma caused by the injection of carcinogen azomethane [43]. Paeoniflorin which is a monoterpene glycoside compound isolated from the root of *Paeonia lactiflora* gave significant levels of anti-inflammatory activity. It could also dose-dependently inhibit the production of inflammatory factor nitric oxide (NO), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) induced by lipopolysaccharides (LPS) [44]. Besides, menthol, which is a cyclic monoterpene, has been shown to have antibacterial activity [45], they found that menthol showed significant inhibitory activity of biofilm when studying the effects of plant-derived terpenoids on *Candida albicans*. Several studies have also shown that terpenoids, particularly artemisinin which is a sesquiterpene lactone compound isolated from *Artemisia annua* Linn, has an effective antimalarial activity and currently in use [3]. The latest findings suggest that tanshinone IIA (TS) which is a terpenoid can prevent the formation of atherosclerosis and the damage and hypertrophy of the heart. This is because of its ability to inhibit the oxidation of low-density lipoprotein and the expression of proinflammatory factors, and TS also has certain activity and potential to stabilize atherosclerotic plaque [46].

3.2 Biosynthesis of pinocembrin

In plant propolis, pinocembrin is one of the most abundant flavonoid, and it could also be commonly found in a most plants. Biological synthesis plays a significant part in synthesizing pinocembrin owing to its increased yield and low cost in production. They can extract pinocembrin from product of nature but that methodology is of high production cost and reduced yield. Biological synthesis from microorganisms features the advantages of low cost and large product yield, which compensate for the lack pinocembrin natural sources [47]. *Escherichia coli* has been known to be used in the production of pinocembrin. Recently, efficient way of producing pinocembrin has been the main goal of most researchers. Biological production of pinocembrin mostly requires that one needs to supplement an expensive phenylpropanoid starting materials, resenting a key problem in previous studies. Genetic engineering is now the breakthrough in the synthesis of pinocembrin biosynthesis, where there is the usage of bacteria to construct the synthesis of pinocembrin from glucose. To manufacture the flavonoid precursor (2S)-pinocembrin directly from glucose, four-vectors have been assembled, 3-deoxy-D-arabinoheptulosonate-7-phosphate synthase, chorismite mutase/pre-phenate dehydratase, phenylalanine ammonia-lyase (PAL), 4-coumarate: CoA ligase (4CL), chalcone synthase (CHS), chalcone isomerase (CHI), malonate synthetase, malonate dehydratase, and malonate carrier protein. Pinocembrin synthesis from glucose can be achieved through adjustment of other corresponding parameters in the synthetic pathways [47].

3.2.1 Pharmacological activities

Pharmacologically, pinocembrin can exhibit anti-inflammatory, [48] antioxidant, [49] antibacterial [50] and neuroprotective activities [51]. They mainly use

Pinocembrin for the treatment of ischemic stroke. Moreover, current studies have shown that pinocembrin may have an effect of reversing Parkinson's disease (PD) and Alzheimer's disease (AD) in affected patients [52]. It has also been shown to exhibit anti-pulmonary fibrosis and vasodilating effects. Pinocembrin undergoes several pathways to perform its pharmacological effects. In addition, pinocembrin could also ease blood brain barrier (BBB) disruption and neurological injury by interfering and reducing the levels of inflammatory factors and reactive oxygen species (ROS). Also, pinocembrin is known to preserve mitochondrial integrity via the activation of the signal-regulated kinase/nuclear factor erythroid 2-related factor 2 (Erk1/2-Nrf2) pathway extracellularly [53]. Pinocembrin also attenuates apoptosis by affecting the p53 pathway, influencing the Bax-Bcl-2 ratio and cytochrome C release [54].

3.2.2 Works done on pinocembrin

The brain of rats has been demonstrated to be protected against apoptosis and oxidation induced by ischemia–reperfusion both in vivo and in vitro. Pinocembrin attenuates blood–brain barrier injury induced by global cerebral ischemia–reperfusion in rats [55]. Further research work is also showing that Pinocembrin has the potential of giving positive outcomes in the treatment of ischemic stroke. This is because it can significantly cause a reduction in the regions of cerebral infarction in rats and cerebral ischemia and reduce the level of cerebral oedema and apoptosis of the cells in the nerve [47]. Shen et al., [47] concluded that pinocembrin exhibits several effects on, Parkinson's disease, ischemic stroke, solid tumors, Alzheimer's disease, and some other diseases because of possibility of releasing inflammatory factors by halting several signaling pathways, such as PI3K/AKT and MAPK. Antioxidant role is also known in pinocembrin because of its ability to reduce the release of NO, nNOS, ROS and iNOS.

3.3 Biosynthesis of polyphenols

Polyphenols constitute an integral class of key secondary metabolites with multiple phenolic hydroxyl groups including flavonoids, stilbenes, phenolic acids, and tannins (hydrolysable and condensed) [56] synthesized mainly by a metabolic pathway termed phenylpropanoid [57].

The biological synthetic routes of polyphenols involve the phenylpropanoid and shikimic acid metabolism pathways [58]. In Salvia species, polyphenols found are mainly reduced by the phenylpropanoid metabolic pathway [57–60] and most derivatives have synonymous basic structures [61].

Tyrosine and Phenylalanine are precursor compounds of the phenylpropanoid metabolic pathway, and their biosynthetic pathways make up two (2) parallel branches of this pathway involving five rate-limiting enzymes [62, 63]. These enzymes consist of phenylalanine ammonia-lyase (PAL); which is a key regulatory enzyme in plant metabolism, cinnamic acid-4-hydroxylase (C4H) and 4-coumarate: coenzyme A (COA) ligase (a peculiar regulatory enzyme in the phenylalanine branch), rosmarinic acid synthase (a key enzyme in catalytic synthesis) and tyrosine aminotransferase (the initial key enzyme and rate-limiting enzyme in tyrosine metabolism pathway), [64].

Caffeic acid derivatives are phenolic acids derived from Salvia species which are mostly produced via esterification of caffeic acid with danshensu [65, 66]. Caffeic acid originates from the class of phenyl propionic acid, [67] and it is the fundamental structural unit of phenolic acids [68]. Phenylalanine is the precursor compound of caffeic acid, which helps in the production of caffeic acid through the action of C4H and PAL enzymes.

It plays a key role in the metabolic pathway of phenylpropanoid and is a precursor compound of rosmarinic acid [69, 70]. Studies have speculated that, catalysis of caffeoyl CoA in the main synthetic route of rosmarinic acid, caffeic acid. Subsequently, caffeoyl CoA and 4-hydroxyphenyl acetic acid is catalysed by hydroxycinnamoyl-CoA: hydroxyphenyllactate hydroxycinnamoyl transferase (rosmarinic acid synthase (RAS)) to earn caffeoyl-40-hydroxy phenylacetic acid (caffeoyl-40-HPLA).

The reaction is finally catalyzed by CYP98A14 to rosmarinic acid [71]. Rosmarinic acid is employed in the formation of Salvianolic acid E under the action of enzymes and other reactions which are then transformed into salvianolic acid B and other compounds. This observation seeks to infer that rosmarinic acid is the core constituent unit of a series of complex phenolic acids, such as salvianolic acids [72, 73]. Complex phenolic compounds formation is based mostly on rosmarinic acid synthesis [61].

The phenylpropanoid metabolic pathway is an important upstream pathway for producing flavonoids such as anthocyanins, isoflavonoids, and flavonoids [74].

3.3.1 Pharmacology of polyphenols

They exhibit numerous pharmacological activities, such as anti-cardiovascular, [75] anti-oxidation [76], anti-tumor [77] anti-inflammatory [78]. Other pharmacological activities exhibited by polyphenols include; anti-hypertensive (caffeic acid, chlorogenic acid and salvianolic acid A), memory and cognitive impairment improvement (rosmarinic acid, total salvianolic acid), hypoglycemic (Salvianolic acid B), antiviral (Protocatechuic aldehyde, Magnesium lithospermate B, rosmaric acid), prevents and treats cancer (Danshensu, Protocatechualdehyde) [79].

3.3.2 Works done on polyphenols

Chang et al., [80] have illustrated that phenolic acids exhibit better antioxidant properties because of their mechanism of action including, inhibition of free radical generation, free radical scavenging and lipid peroxidation. A study showed that rosmarinic acid, danshensu and caffeic acid were as effective as the positive control (quercetin), which scavenged 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals in a concentration-dependent way. On the other hand, ferulic acid was less effective [81]. Other studies have shown that danshensu and salvianolic acid B showed greater scavenging activities against HO·, –, DPPH, O2-, and 2,20-and-bis (3-ethylbenzothiazoline-6-sulphonic acid (ABTS) than the other constituents. Among them, the half-maximal inhibitory concentration (IC50) of salvianolic acid B and danshensu were not significantly different, and there was no obvious difference in the scavenging actions of hydroxyl radicals [82]. Thus, hydroxyl radical scavengers are phenolic acids are.

Studies on inhibition of spontaneous lipid peroxidation in liver tissue of polyphenols in mice lead to the formation to the following order after testing all the seven polyphenols. Rosmarinic emerged the most efficacious followed by caffeic acid, protocatechuic aldehyde, chlorogenic acid, ferulic acid, and danshensu. 3-hydroxycinnamic acid was studied in hydrogen peroxide -induced liver lipid peroxidation in rodents' model. Also, other in vitro studies confirmed the antioxidants effects of these phenolic acids [83].

Salvianolic acid B was found to be effective in the reduction of myocardial ischemia–reperfusion injury. Ischemia–reperfusion model was established by ligating the left circumflex artery in Sprague–Dawley (SD) rats against myocardial ischemia–reperfusion injury and the concentration and apoptotic index of

the plasma level of myocardial enzymes (cardiac troponins (CTn) I and creatine kinase-MB (CKMB)), endothelin (ET), superoxide dismutase (SOD), nitric oxide (NO), malondialdehyde (MDA), and histological changes of the heart were determined. The outcome was observed that salvianolic acid B significantly increased the plasma levels of CTn I, CKMB, MDA, and ET contents; decrease in T-SOD and NO contents; reduction in infarct size; and improved myocardial ultrastructure. It was concluded that salvianolic acid B has an impact against conditions such as myocardial ischemia–reperfusion injury via the regulation of reducing oxidative stress, active oxygen metabolism, and myocardial apoptosis [84]. A study conducted by [85] also stated that salvianolic acid which is a phenolic could also be effective in alleviating ischemic-reperfusion injury. It could also prevent myocardial ischemia–reperfusion injury through an increased glucose condition by adjusting the NADPH oxidase 2 (Nox2)/reactive oxygen species (ROS)/phosphorylated-c-Jun N-terminal kinase 2 (p-JNK2)/NF-κB pathway to reduce transient receptor potential cation channel, member 6 (TRPC6)/Ca2+ influx, subfamily C [86].

Anti-thrombotic effects which are through its actions on blood rheology has also been known to be a possible action of salvianolic acid in *S. miltiorrhiza*. It also acts as to prevent platelet aggregation by targeting P2Y1 or P2Y12 receptors, which are novel target receptors required for anti-platelet aggregation. Salvianolic acid B experimentally, only antagonizes the action of platelet P2Y12 receptors, while salvianolic acid A and C are P2Y12 and P2Y1 receptor inhibitors [87].

Other studies by [88] have also illustrated that caffeic acid can inhibit platelet-mediated thrombosis by P-selectin expression, repression of ADP-induced platelet aggregation, ATP release, and Ca2+ mobilization and attenuate the activation of ERK, p38, JNK, and integrin αIIbβ3. It could also increase cAMP expression levels.

Better antiplatelet and anti-thrombotic therapeutic efficacy have also been demonstrated in Danshensu when compared to other constituents. Several contributions have been made through its ability to selectively suppress balancing the ratio of thromboxane A2 (TXA2)/prostacyclin (PGI2) and the expression of cyclooxygenase (COX)-2 [89].

Several studies have been conducted on the anti-liver injury activity of polyphenols and from [90] salvianolic acid B protects liver cells by enhancing lysosome-associated membrane protein 1 (LAMP1) expression and preserving lysosomal membrane integrity through scavenging ROS. Salvianolic A has also been concluded by [91, 92] that it protects acute hepatic injury after inducing mice models with concanavalin A. The outcome of the liver function markers, alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) showed that salvianolic acid A significantly reduced ConA-induced AST and ALT activity. Also, there was a reduction in the hepatotoxic cytokine levels, such as interferon (IFN)-γ and tumor necrosis factor (TNF)-α; improvement in the increased NF-κB level and cleaved caspase-3; and reversal of B-cell lymphoma-extra-large (Bcl-xL) expression [79].

Wang et al. [90] concluded that salvianolic acid B seems to be effective and safe, and it could develop this natural component into a potential therapeutic agent for the management of glioma. This is because of its inhibitory actions on the human glioma U80 cells, which its initiation leads to p38-activation-mediated ROS production.

Reviews conducted by Rasouli et al. [93] throws more light on the importance of polyphenols from foods. This because they are beneficial in most health conditions including pernicious human diseases (HDs). Also, people who followed a specific diet particularly polyphenol-rich diets are of lower risk of several ranges of chronic diseases, such as diabetes, obesity, cancer, and heart disease.

3.4 Biosynthesis of berberine

Berberine is a quaternary ammonium salt and it's from a group of isoquinoline alkaloids termed 2,3–methylenedioxy-9,10-dimethoxyprotoberberine chloride; C20H18NO4+. It is highly concentrated in the roots, stem bark, rhizomes and of numerous plants including *Rhizoma coptidis, Tinospora cordifolia, Coptis chinensis, Hydrastis canadensis, Berberis vulgaris, Berberis aquifolium, Berberis aristata, Arcangelisia flava* and *Cortex rhellodendri* [94].

Berberine comprises of several derivatives such as berberrubine, jatrorrhizine thalifendine, and demethyleneberberine [94].

3.4.1 Pharmacological activity

Pharmacologically, almost all parts of the plant have been shown to have several properties. These pharmacological properties of berberine includes antiemetic, antipyretic, tonic, antimicrobial, antipruritic, antiarrhythmic, sedative, antioxidant, anti-inflammatory, hypotensive, antinociceptive, anticholinergic and cholagogue actions, and it has been used sometimes like dysentery cholecystitis, cholelithiasis, leishmaniasis, jaundice, malaria and gall stones [95]. Berberine has been used for treating diarrhoea and gastrointestinal disorders for a long time [96, 97]. It has multiple pharmacological effects including; antimicrobial activity against 54 microorganisms, [98] inhibition of intestinal ion secretion and smooth muscle contraction, inhibition of ventricular tachyarrhythmia, reduction of inflammation, stimulation of bile secretion and bilirubin discharge [99]. Moreover, [100] have reviewed that berberine to possess pharmacological activities such as insulin secretion promotion, insulin resistance reduction, increased insulin secretion, inhibiting gluconeogenesis in the liver, stimulating glycolysis in peripheral tissue cells, reducing intestinal absorption of glucose, and regulating lipid metabolism, and modulating gut microbiota. Also, it is significant in the treatment of diabetic nephropathy, diabetic neuropathy, and diabetic cardiomyopathy because of its anti-inflammatory and antioxidant activities, in inflammatory diseases.

3.4.2 Works done on berberine

Antidiabetic activity of berberine has been conducted by Pang et al., [101] His review article highlighted several mechanisms with which berberine act to improve glucose control. A bibliometric review conducted between 1985–2018 also outlines that berberine has significant antibacterial and antipyretic effects and is a commonly used drug for treating infectious diarrhoea and amoebiasis. Berberine has significant antipyretic and antibacterial effects and its commonly used for the treatment of diarrhea associated with infections.

Zhao et al., [102] also added., that berberine has an improved activity in improving nonalcoholic fatty liver disease by halting glucogenesis and comprehensively regulating lipid metabolism, and its effect on inhibiting lipogenesis in the liver was much stronger. He also suggested that weight loss may partly mediate the improvement and would be a drug of choice for NAFLD patients and glucose metabolic disorder. But they, therefore, require future clinical trials to confirm these effects.

The review article by Zhu et al., [103] threw more light on the mechanism of action of berberine. It was stated that berberine potentially works through an increase in insulin sensitivity, LDLR mRNA stabilization, improvement of mitochondrial function, regulation of adenosine monophosphate-activated protein kinase (AMPK) pathway, alleviation of oxidative stress, and regulation of gut microenvironment being the major targets of berberine in the treatment of NAFLD.

Also, the reduction of DNA methylation and that of proprotein convertase subtilisin/Kexin 9 (PCSK9) expression is also involved in the pharmacological mechanisms of berberine involved in the management of NAFLD. Several mechanisms such as the immunologic mechanism in relation to the treatment of NAFLD, drug combinations, development of berberine derivative, delivery routes, and drug dose can be considered for further research.

From Cicero and Baggioni, [104] a good deal of preclinical evidence supports the role of berberine in the management of cerebral ischemia, Alzheimer's disease, anxiety, mental depression, and schizophrenia. However, most of these data have been obtained purely through experimental models [105]. Of particular interest is the potential antidepressant activity of berberine, it was found to inhibit the immobility time in mice in both tail suspension test and forced swim test. These two antidepressant models all gave effects in a dose-independent manner [106]. Regarding the bioactivities of berberine reported, monoamine oxidase (MAO)-A activity is noted to be inhibited. From Kong et al., [107] (MAO)-A is an enzyme needed to catalyze the deamination of catecholamines oxidatively, and thus inhibiting degradation of these neurotransmitters. Levels of norepinephrine, serotonin and dopamine, neurotransmitters are increased due to induction by MAO-A enzyme after acute and chronic administration of berberine in mice [107]. Under Kulkarni and colleague's data, Arora and Chopra [106] revealed the protective antidepressant-like activity of berberine against the reserpine-induced biogenic amine depletion (a monoamine depletion) mostly employed in the induction of depression in animals.

However, to there is therefore no conclusive data on the evaluation of the potential antidepressant effects of berberine in higher mammals such as humans [108].

The review article by Td et al., [100] has shown that berberine has the potential of reversing neurodegenerative effects in diseases such as Alzheimer, Huntington's disease, Parkinson's and because of its antioxidant activity. They have also conducted antiviral activity on berberine by Warowicka et al., [94] and he observed berberine could regulate the MPK/mTOR, MEK–ERK, and NF-κB signaling routes, which are needed for viral replication. It is deduced that it provides adequate supports to the host immune response, thus leading to viral clearance. Berberine and its derivatives might promise agents to be considered in future in the fight against the recent pandemic SARS-CoV-2, which is the causative agent responsible for causing COVID-19.

3.5 Biosynthesis of aristolochic acid

Roots and rhizomes of most Aristolochia species contain mixtures of nitro phenanthrene-carboxylic acids. The key acid is the aristolochic acid I. The aristolochic acids; a group of substituted 10-nitro-1-phenanthrene acids have been known to occur in most species of the genus Aristolochia, and other members of the family Aristolochiaceae [109, 110]. Aristolochic acids emanate from aporphines through oxidative cleavage of the hetero ring. They stated that the results were consistent with the observation that the aristolochic acids rises from aporphines via oxidative cleavage of the hetero ring. Because the pathway from tyrosine to the product runs through dopa, which is an amino acid that undergoes reversible transamination in plants [111].

In all cases, aristolochic acid I and the structurally related alkaloid magnoflorine could be shown in the roots and rhizomes. The biogenetic relationship with the aporphine alkaloids was due to both the structure of aristolochic acid and its occurrence with magnoflorine. Aporphine skeleton could yield aristolochic acids through oxidative cleavage of the heterocyclic ring. Benzylisoquinoline norlaudanosoline is a key intermediate in the biosynthetic pathway, which can be formed from tyrosine or a biochemical equivalent. Aporphine skeleton is also produced from norlaudanosoline through the phenol oxidation and dienol-benzene rearrangement [110].

Aristolochiaceae family of plants produces aporphine alkaloid, 4,5-dioxoaporphine, which is referred to as possible intermediates of the precursors of aristolochic acids and aristo lactams [112].

3.5.1 Pharmacological activities of aristolochic acid

It has been reported by Okhale et al., [112] that Aristolochic acid antirheumatics, as diuretics, in the treatment of oedema, to facilitate childbirth, in wound healing and for less common conditions such as cough, hemorrhoids, and asthma. Aristolochic acids also possess antibacterial [113, 114] antifungal, antiviral, and antitumor effects and in more recently, have been used in the pharmaceutical industry as convention usage [115, 116]. Herbal preparations with active constituents being aristolochic acids have been used for different illnesses such as urinary tract infection, hepatitis, vaginitis, oedema, upper respiratory tract infection, eczema, bronchitis, headache, oral ulcer, neuralgia, dysmenorrhea, arthralgia, hypertension, cerebrovascular accident, heart failure and pneumonia [117].

3.5.2 Works done on aristolochic acid

Aristolochia species that contain aristolochic acid is Aristolochia triangularis. Oliveira et al., [118] had revealed several studies such as the antiproliferative effect, and his conclusions show its outcomes are very desirable.

Several studies have reported that aristolochic acid is the potential of causing carcinogenic effects in humans [119]. Nephrotoxic effects of the renal cortex and further damage to the liver and bladder when much of it is ingested; likely because of the formation of bulky chemical DNA adducts. AA is dA-AA formation is the most abundant and mutagenic form of DNA adduct associated with. In exons 2–11 of TP53, mutation results from bulky chemical DNA adducts, primarily of A: T base pairs [120, 121] have also conducted potential nephrotoxic effects of aristolochic acids and also proposed possible molecular mechanism of such effect. This is through induction of oxidative/nitros active stress and mitochondrial dysfunction, apoptosis induction, inflammatory responses induction, and fibrosis. A pharmacokinetic study conducted by [122] also added up that Aristolochic nephrotoxicity comprises dose-dependent and progressive tubular damage, even though significant changes in the morphology of glomeruli was not seen.

3.6 Biosynthesis of canthaxanthin

Canthaxanthin is a carotenoid, and it's one class identified to possess a lot of colouration. Canthaxanthin is biologically synthesized from the precursor, β-carotene, ketolase enzyme (BKT in algae and CRTW in bacteria) serves as the enzyme for the reaction. The allylic 4-position to a carbonyl group is oxidized in the β-ring, producing echinenone as intermediate product. The same enzyme sequentially transforms the 40-carbon atom in the second β-ring to a carbonyl [123, 124]. This is also a substrate for the synthesis of another keto carotenoid astaxanthin which is of commercial interest. The enzyme β-carotene hydroxylase introduces hydroxyl (OH) groups into the canthaxanthin rings at positions 3,30, resulting in astaxanthin formation [125].

3.6.1 Pharmacological activities of canthaxanthin

Antioxidant and free radical scavenging properties [125]. Canthaxanthin alters the onset of many diseases such as cataracts, atherosclerosis, multiple sclerosis, age-related macular degeneration, and cancer [126].

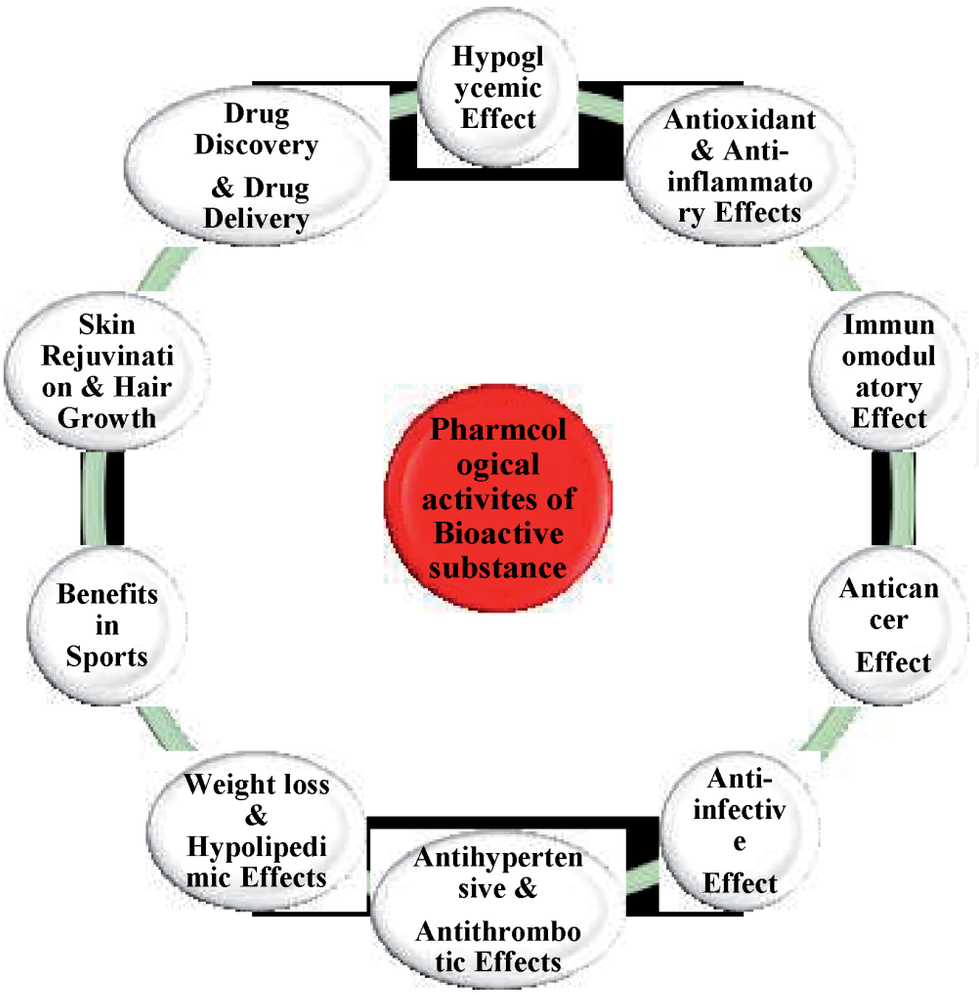

Figure 1.
A summary of biological activities and health-promoting properties of biological metabolite.

3.6.2 Works done on canthaxanthin

Studies have shown that canthaxanthin show significantly higher free radical scavenging and antioxidant properties than other xanthophylls and carotenes, and they can also scavenge reactive oxygen species and quench singlet oxygen. Also, it has been revealed in in vivo experiments that the supplementation of canthaxanthin led to a significant decrease in lipid peroxidation to preventing induced rats liver DNA damage [126]. They have also found it in cell detoxification of lipopolysaccharides. With respect to uses of canthaxanthin in humans, less comprehensive studies have been conducted to elucidate its effects and safety. It is popularly employed as natural skin-tanning agent, and cosmetics (**Figure 1**).

4. Conclusion

It employs most of these bioactive products in complementary medicine, and others are under clinical study. They can source bioactive products from plants, animal and some micro-organisms. They are produced mostly via a sequence of physiological processes or synthesized exogenously. Many biosynthetic products exhibit one therapeutic effect. These several biosynthetic metabolites have many pharmacological effects, thus making them useful candidates for drug discovery.

DOI: http://dx.doi.org/10.5772/intechopen.96977

IntechOpen

Author details

Yakubu Jibira* and Paul Atawuchugi
Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

*Address all correspondence to: jyakubu2@st.knust.edu.gh; yakjab21@gmail.com

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