Chapter

Alkaloids: The Potential of Their Antimicrobial Activities of Medicinal Plants

Mohammad Barati and Amir Modarresi Chahardehi

Abstract

Given the potential adverse effects of chemical drugs, utilizing natural products with diverse therapeutic and antimicrobial compounds is advisable. Countries can use indigenous flora from their regions in vegetation for medicinal purposes. Several nations exhibit distinctive indigenous flora owing to their geographic positioning and climatic conditions. These plants have been the subject of our research, which has explored their antimicrobial properties against fungi, parasites, bacteria, and viruses. Studies have investigated the therapeutic and antimicrobial effects of plants and their bioactive compounds, such as alkaloids, flavonoids, and terpenoids. Among them are alkaloids, a diverse class of naturally occurring chemicals, such as tropanes, terpenoids, and steroids. Some of these medicinal plants have been found to possess antioxidant and anti-inflammatory properties in addition to their antimicrobial effects. This chapter explores the antimicrobial potential of alkaloids found in medicinal plants.

Keywords: alkaloids, medicinal plants, antimicrobial activity, secondary metabolite, bioactive compounds

1. Introduction

Researchers are discovering infectious diseases are a major threat to world health [1, 2]. For millennia, medicinal plants have yielded an abundance of therapeutic compounds, which have been incorporated into traditional pharmacological practices across the globe [3, 4]. Since the dawn of time, people have known that plants have healing properties, making botanic medicine one of the first forms of therapy [5–7]. Antibacterial medications have traditionally been derived from natural materials. This avenue of inquiry declined in the 1980s as scientists shifted their focus to synthetic compound libraries because of their greater flexibility [8]. Antibiotic and antifungal medication discovery are crucial in the face of the rise of multidrug-resistant (MDR) fungi and bacteria [9]. The emergence of multidrug-resistant organisms is a significant worldwide health concern [10]. The incorrect use of antibiotics in human and animal health care is largely responsible for the rise of MDR strains. Consequently, the

search for alternative, nonantibiotic-dependent solutions to this critical issue has become an urgent and imperative challenge [11]. In particular, each plant produces small quantities of secondary metabolites—tiny compounds like terpenoids, polyphenols, phenolics, alkaloids, essential oils, etc. [12]. The discovery of novel pharmacological compounds that can treat serious ailments has greatly benefited from research into medicinal plants [13]. Some plants, such as mustard, ginger, basil, garlic, cinnamon, sage, curry, and many other crude extracts, for instance, have antibacterial activity against many different forms of bacteria, including gram-positive and gram-negative [14]. Medicinal plants include phytochemicals, often responsible for their biological activity, commonly found in these plant sources [1]. Secondary metabolites found in plants include active chemical molecules with potential therapeutic applications for various diseases [15]. Isolated secondary metabolites in plants are thought to account for fewer than 10% of the total. Metabolites are commonly employed to safeguard against insects, herbivores, and microbes. The diverse range of aromatic substances and their oxygen-substituted derivatives plants synthesize accounts for the extensive variety observed [16]. Recently, drug resistance has emerged as a major issue in healthcare; the rate at which drug-resistant diseases are increasing is far higher than the rate at which new medications are being tested and authorized for human use. Thus, it is crucial to create new antimicrobial drugs [17–19].

Infectious illnesses caused by microorganisms significantly contribute to human suffering and death. About 60% of the biomass on Earth is thought to be composed of microbial species. This, together with their tremendous genetic, metabolic, and physiological variables, renders them a danger to the well-being and progress of human communities everywhere [20]. Hence, nature is the source of a significant proportion of the drugs currently used, derived from microorganisms, flora, or fauna. Identifying and synthesizing novel compounds possessing pharmacological properties depends on the natural environment's biodiversity [12, 21]. Many plant components are available without a prescription from herbal distributors and natural-food stores, and self-administration of these drugs is common even though their purity is often questionable [22]. Chemical analysis of medicinal plants has uncovered various bioactive chemicals, including saponins, tannins, and alkaloids [1, 23]. Also, flavonoids, terpenoids, and alkaloids are the primary constituents of phytochemicals in the plant kingdom [24]. The pharmacologically active compounds encompass a variety of alkaloids that can be categorized into several classes, such as piperidines, pyrrolizidines, quinolizidines, imidazoles, tropanes, pyrrolidines, indoles, isoquinolines, and purines [15]. They belong to a vast group of naturally occurring chemical compounds that include at least one nitrogen atom (particularly in the form of an amino or amido group). The nitrogen atoms often form a ring shape [25]. Alkaloids are plant-derived bioactive compounds typically exhibiting alkaline properties due to their nitrogen atoms [26].

With many plants still waiting to be discovered and examined for their phytochemical compositions, the future of therapeutic plants seems bright. Synthetic medicine design and development have benefited from learning about medicinal plants [1]. Thus, alkaloids are the subject of intensive study because they may constitute a novel class of naturally occurring antibiotics with a broad antibacterial range, few side effects, and a low propensity to result in drug resistance. The present chapter centers on investigating the antimicrobial potential of alkaloids obtained from medicinal plants against human pathogenic microorganisms, specifically emphasizing multi-drug-resistant clinical strains. The chapter elucidates the mechanism of action of these alkaloids when available and underscores their concentrations and usage.

2. Plant products as an antimicrobial agent

Pathogenic bacteria create dangerous and potentially fatal infectious diseases that affect humans [27, 28]. On the other hand, antibiotic resistance is a significant issue in the twenty-first century, and infectious illnesses are still the second-greatest cause of mortality globally despite the success of antibiotic discoveries [1]. The growing incidence of antimicrobials-microbes resistance is causing growing alarm among scientists. The advent of drug-resistant bacteria has increased the difficulty and expense of creating newer antimicrobials from novel chemical compounds [15, 28]. Despite the approval of synthetic antimicrobial agents in numerous countries, using natural compounds derived from microbial, animal, or plant sources has garnered significant interest among researchers [29]. Numerous researchers are currently engaged in the investigation of plants to identify potential antimicrobial agents [15]. The quest for compounds possessing antimicrobial properties is common, and scholars have shown interest in medicinal plants due to their widespread use in traditional medicine as a treatment for various infectious ailments [30]. Hence, the demand for and research into plant-based pharmaceuticals and nutritional aids has increased rapidly in recent years [31]. Studies conducted on plants utilized in traditional medicine have been performed *in vitro* within the realm of microbiology, with a particular focus on the proliferation of infectious bacteria [30]. Betoni et al. found that plant compounds can either act as antimicrobial agents that complement antibiotics or increase a pathogen's susceptibility to an antibiotic that would have otherwise been ineffective [30].

Researchers from fields as diverse as ethnopharmacology, botany, microbiology, and natural products chemistry scour the planet in search of phytochemicals and "leads" that might be refined into effective antimicrobial drugs [31]. New medications can be developed by optimizing the structural makeup of phytochemicals present in plants [1]. Phytochemicals and other substances derived from plants have been used to treat a wide range of infectious diseases because they exhibit good antibacterial action against many human infections [29, 32]. However, it is widely established that several extracts and components of plants have antibacterial activity. Unfractionated extracts are typically used in these studies, despite their low *in vitro* antimicrobial activity. *In vivo* tests were rarely used to verify the results of these investigations [12]. Phytochemicals, which are bioactive organic chemical compounds, are present in medicinal plants [33, 34]. These compounds protect against chronic diseases, including those caused by metabolic or genetic disorders and infectious diseases. They are present in various foods made from plants, including cereals, veggies, and fruits [1]. There are several classes of phytochemicals, including carotenoids, alkaloids, phenolics, organosulfur compounds, and nitrogen-containing compounds [5].

3. Alkaloids

Alkaloids are naturally occurring compounds sourced from various organisms, including plants (which comprise approximately 300 plant families), bacteria, fungi, and animals [12]. The compounds and biomolecules exhibit significant diversity, yet all these chemicals are byproducts of the amino acid biosynthesis process or the transamination reaction [35]. Alkaloids are predominantly solid compounds that are commonly found in higher plants. The aforementioned botanical families, namely Leguminoceae, Papaveraceae, Solanaceae, Ranunculaceae, Annonaceae,

Amaryllidaceae, Liliaceae, Apocynaceae, Boraginaceae, Loganiaceae, Magnoliaceae, Berberidaceae, Piperaceae, Gnetaceae, Rutaceae, Lauraceae, Menispermaceae, and Rubiaceae, are known to exhibit a high prevalence of the subject matter [36]. Certain plant species employ naturally occurring insecticides or pesticides to protect themselves against the harmful effects of select insect species. The synthesis of vegetal alkaloids primarily occurs in herbaceous and vascular plants [12]. The Arabic word al-qali designates the source of soda. German scientist Carl F. W. Meissner developed the term "alkaloid" in 1819 to describe this compound [36]. One of the biggest groups of secondary metabolites in plants, alkaloids are present in some economically relevant plant families [37]. As mentioned, they are present in various kingdoms. However, their distribution is restricted within each domain [8]. Alkaloids are classified into multiple categories. The categorization is founded upon the compounds' heterocyclic ring structure and biosynthetic forerunners. The abovementioned compounds comprise indoles, pyrrolizidines, quinolizidines, pyrrolidines, piperidines, tropanes, isoquinoline, purines, and imidazoles [15]. The amino acids nicotinic acid, L-histidine, L-ornithine, L-tryptophan, L-lysine, L-tyrosine, acetate, L-phenylalanine, anthranilic acid, and L-phenylalanine are all precursors to the alkaloid phenylpropanoid [35]. Alkaloids also exhibit various pharmacological and biological properties and may be found in many herbal treatments [38]. Alkaloids have been the fundamental framework for advancing multiple antibiotics showing a broad activity spectrum [16]. Nicotine, caffeine, and cocaine are just a few examples of alkaloids incorporated into popular culture as drugs used for entertainment or abuse. Certain alkaloids have been identified as possessing high toxicity levels, resulting in numerous instances of human poisoning [16].

Alkaloids have a wide array of pharmacological activities, including antibacterial activity [12]. Most alkaloids exert their effects via efflux pump inhibitor (EPI) activity, which is considered a potential mechanism of antibacterial action [29]. In addition to their use as stimulant medications, alkaloids may be found in many of the foods and drinks we consume regularly. They have shown several pharmacological effects, including those of local anesthetic, anticancer, analgesic, pain-relieving, antifungal, anti-inflammatory, neuropharmacological, and antimicrobial, [25], antimalarial action, oxytocic and vasoconstrictor activity (ergometrine), activity against the central nervous system (brucine), and activity against the cholinergic system (atropine) [16]. Alkaloids, which derive their name from their resemblance to alkalis, can undergo salt formation upon reaction with acids, similar to inorganic alkalis. The nitrogen atoms exhibit basic properties in acid-base responses [25]. Alkaloids are characterized by a nitrogen atom that accepts protons and multiple amine hydrogens that donate protons. Hence, the biological activity of biomolecules is primarily attributed to their ability to establish hydrogen bonds with other biomolecules such as enzymes, receptors, and proteins [12, 24]. Thus, alkaloids can be used for a variety of pharmacological purposes. [24]. Several antibiotics have been developed from alkaloids: the quinolones were discovered by accident during the production of quinine; the structure of metronidazole was altered from that of azomycin; and the quinoline scaffold was utilized to create bedaquiline [8]. Alkaloids can also be found in other medications like linezolid and trimethoprim scaffolding. Academic institutions, private companies, and public-private partnerships continue studying alkaloids to create effective antibacterial drugs [8].

A straightforward quantitative approach for identifying alkaloids in plants was developed by Li et al. [39]. Using tetrahydrofurfuryl methacrylate as the monomer, in situ radical polymerization was used to construct a polymer-based chromatographic

monolithic column. Based on the results of the technique validation, the accuracy of the spiking recovery measures is between 98.89 and 102.06%. These findings demonstrate the constructed monolithic column's viability for avoiding the lengthy analysis time required by conventionally packed C18 columns in quantitatively analyzing alkaloids from actual medicinal and culinary plant foods [39]. Alkaloids are used internally to improve health, physical performance, and the immune system. These entities are common in daily dietary intake, drinks, and supplementary products. Several compounds present in plants exhibit advantageous characteristics. Compounds such as caffeine, guaranine, and mateine, found in various plants, including coffee, have been observed to possess anti-inflammatory, antioxidant, and stimulatory properties. Additionally, cocoa contains theobromine and paraxanthine, which act as antioxidants. Ginger, conversely, contains gingerol and shogaols, which are phenolic alkenones that possess antioxidant, anti-inflammatory, antimicrobial, and antitumoral properties [37]. However, we provide a brief overview of the class of alkaloids concerning antimicrobial activity.

3.1 Alkaloids classification

At present, the number of identified alkaloids exceeds 18,000 [15]. Natural antibacterial alkaloids have been the subject of research since the 1940s, although most of the earliest studies did not go far enough to determine minimum inhibitory concentrations (MICs). Despite this class's large number of chemicals, only a fraction of their biosynthesis routes have been determined [40]. The chemical makeup or inherent biological source of these entities determines their classification [16]. Chemical structure and characteristics are used to divide alkaloids into several classes. The feasibility of classifying alkaloids based on their natural origin arises because certain alkaloids are limited to specific sources [16]. The chemical structure or biological origin of alkaloids allows for two broad categories:

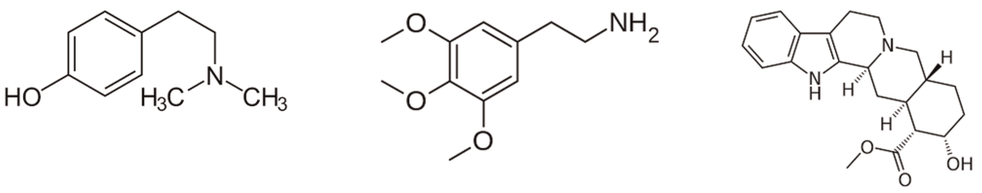
1. The initial category comprises three types: protoalkaloids, or biological amines, nonheterocyclic or unconventional alkaloids. These alkaloids contain nitrogen in their side chains. The following category includes the heterocyclic or conventional alkaloids, also known as true alkaloids, which possess nitrogen within the heterocycle, and pseudoalkaloids [36]. The basic carbon skeleton of pseudoalkaloids is not directly formed from amino acids. Still, it is connected to amino acid processes and is derived via an amination or transamination process from amino acid precursors or postcursors. Common pseudoalkaloids include capsaicin, caffeine, and ephedrine [36].

2. The second division may be subsequently classified into 14 subgroups based on the ring shape due to its deep structural complexity [16, 24].

As mentioned above, there are primarily three classes of alkaloids [36]:

3.1.1 Protoalkaloids

Alkaloids having a closed ring structure are protoalkaloids; they are chemically perfect but have a straightforward molecular structure. Among the alkaloids, they are in the minority [35]. The most notable examples of these alkaloids include yohimbine, mescaline, and hordenine (a phenethylamine) (**Figure 1**). Hordenine, a Tyr-derived



Hordenine Mescaline Yohimbine

Figure 1.
Some examples of protoalkaloids.

phenylethylamine alkaloid, was initially discovered in *Hordeum vulgare* (barley) [41]. They are prescribed for various conditions, from mental illness to chronic pain to neuralgia. The nitrogen atom in these alkaloids comes from a source other than the heterocyclic ring structure; instead, it is generated from an amino acid. Typically, L-tryptophan and L-tyrosine are the precursors to these alkaloids. Simple alkaloids make form the framework of this minor class [36]. Protoalkaloids are compounds where the heterocyclic bond does not include the N atom from an amino acid. One type of alkaloid consists of compounds derived from the amino acids L-tryptophan and L-tyrosine [35].

3.1.2 True alkaloids

These alkaloids and their precursor amino acids both have nitrogen in a heterocyclic ring. These entities exhibit high reactivity and possess significant biological efficacy [36]. These compounds can dissolve in water and form salts soluble in water. Additionally, many of these compounds exhibit a crystalline structure and can undergo conjugation with acids to form salts. Most authentic alkaloids are characterized by their solid state and bitter flavor, except nicotine, a brown liquid. Common true alkaloids include cocaine, morphine, and quinine [36]. Morphine, an alkaloid generated from tyrosine, has a nitrogen-containing heterocyclic ring and is used as a painkiller. It exhibits potent analgesic effects and is widely used as a painkiller in clinical settings [42]. Not all alkaloids show significant biological efficacy; some have no known pharmacological activity [43].

These subgroups have unique properties and uses, making them essential modern medicine and research components. Understanding the classification of alkaloids is an important step in understanding their potential therapeutic applications. For example, various pharmacological effects are associated with indole alkaloids found in plants, many of which are thought to be attributable to the indole nucleus [44]. Common plant families proven to contain indole alkaloids include Loganiaceae, Rubiaceae, Apocynaceae, and Nyssaceae. Preclinical and clinical research has shown that several of the discovered indole alkaloid compounds are particularly effective [44]. According to their antimicrobial activity, the most critical phytocompounds across all alkaloid chemical groups are shown in **Table 1**.

Monoterpenoid indole alkaloids are a class of widely recognized alkaloids that are derived from tryptamine and secologanin. Numerous alkaloids exhibit intricate structures and significant biological properties, rendering them intriguing. Various species belonging to the Apocynaceae family, including *Tabernanthe iboga*, *Voacanga africana*, and multiple *Tabernaemontana* species, synthesize alkaloids, including the ibogan type [116]. Antibiotic and well-known alkaloid tryptanthrin (TRYP) (indolo[2,1-b] quinazolin-6,12-dione) is found in *Candida lypolica*, higher plants, and numerous

Types of alkaloids	Formula	Plant family	Targeted microorganism	Concentrations range (μg/mL)	Reference
Indole alkaloids					
Brassicaceous indoles	$C_{13}H_9N_3O_2S$	Brassicaceae			
Caulilexin A	$C_{10}H_9NOS_2$	Brassicaceae	*Sclerotinia sclerotiorum*, *Leptosphaeria maculans*, *Rhizoctonia solani*	5×10^{-4} M	[45]
Camalexin (3-thiazol-2′-yl-*indole*)	$C_{11}H_8N_2S$	Brassicaceae	*Alternaria brassicae*	80 μg/mL	[46]
β-Carbolines	$C_{11}H_8N_2$				
Borrerine	$C_{16}H_{20}N_2$	Rubiaceae	*Staphylococcus aureus*, *Vibrio cholerae*	50 and 6 μg/mL, respectively	[47]
Borreverine	$C_{32}H_{40}N_4$	Rubiaceae	*S. aureus, V. cholerae*		[47]
Canthin-6-one (canthinone)	$C_{14}H_8N_2O$	Simaroubaceae	*S. aureus*, *Mycobacterium* sp.	8–32 μg/mL	[48]
Rhetsinine	$C_{19}H_{17}N_3O_2$	Rutaceae	*Xanthomonas oryxae* pv *oryzae*, *Xanthomonas oryxae* pv *oryzicola*	1 and 4.5 μg/mL	[49]
Carbazoles	$C_{12}H_9N$				
Glycozolidol	$C_{14}H_{13}NO_2$	Nitrariaceae and Rutaceae	*Proteus vulgaris, Bacillus firmis*, *S. lutea*, *S. aureus*, *Agrobacterium tumefaciens*	200 μg/mL/well	[50]
Benzoisofuranone	$C_8H_6O_2$	Rutaceae	*S. aureus*, *B. subtilis*, *Escherichia coli*, *P. vulgaris*, *Aspergillus niger*, *Candida albicans*	3.13–100 μg/mL	[51]
Harmane	$C_{12}H_{10}N_2$	Nitrariaceae	*V. anguillarum*	3.1 μg/mL	[52]
			Cryptococcus neoformans, *A. niger*, *Cryptococcus gattii, C. albicans*	Very weak inhibited	[53]
Koenigine	$C_{19}H_{19}NO_3$	Nitrariaceae and Rutaceae	*Candida* sp.	MIC_{90}: 12.5–100 μg/mL	[54]
3,3′-[Oxybis(methylene)]bis (9-methoxy-9H-carbazole)	$C_{28}H_{24}N_2O_3$	Nitrariaceae and Rutaceae	*P. vulgaris* and *C. albicans*	6.2 and 25 μg/mL, respectively	[51]
Monoterpenoid indole alkaloids					
Scholarisine	$C_{19}H_{18}N_2O_2$	Apocynaceae	*Gibberella pulicaris* and *Cercospora nicotianae*	MIC: 1.37–1.91 μM	[55]

Types of alkaloids	Formula	Plant family	Targeted microorganism	Concentrations range (μg/mL)	Reference
Kopsiflorine	$C_{23}H_{28}N_2O_5$	Apocynaceae	*S. aureus*	IZ: 9.7 mm	[56]
Erchinines A and B	—	Apocynaceae	*B. subtilis*, *Trichophyton rubrum*	0.78 and 0.78, 12.5 and 6.25, respectively	[57]
Melokhanine A	$C_{19}H_{26}N_2O_3$	Apocynaceae	*Pseudomonas aeruginosa*, *Enterococcus faecalis*	2–5 μM	[58]
Ibogaine	$C_{20}H_{26}N_2O$	Apocynaceae	*E. coli*, *B. subtilis*, *A. flavus*, *A. niger*, *Rhizoctonia phaseoli, K. pneumoniae, S. aureus, S. pneumoniae, A. flavus, C. albicans, and R. phaseoli*	50–60 μg/mL	[59]
Vobasine	$C_{21}H_{24}N_2O_3$	Apocynaceae	*A. niger* and *A. flavus*	50–60 μg/mL	[59]
Voacamine	$C_{43}H_{52}N_4O_5$	Apocynaceae	*R. phaseoli*, *P. chrysogenum*, and *C. albicans*	50–60 μg/mL	[59]
Cadambine	$C_{27}H_{32}N_2O_{10}$	Rubiaceae	Weakly against: *Staphylococcus epidermidis*, *S. aureus*, *B. cereus*, *B. subtilis*, and *C. albicans*	3.3–164 μg/mL	[60]
Strictosidine	$C_{27}H_{34}N_2O_9$	Rubiaceae	*K. pneumoniae, Providencia smaitii,* and *E. coli*	12.5, 25, and 50 μg/mL, respectively	[61]
Tubotaiwine	$C_{20}H_{24}N_2O_2$		*Mycobacterium tuberculosis*	100 μg/mL	[62]
Diterpene alkaloids	$C_{24}H_{39}NO_4$	Ranunculaceae			
Vilmorrianone, panicutine, 8-acetylheterophyllisine	$C_{23}H_{29}NO_4$	Ranunculaceae	*Allescheria boydii*, *A. niger*, *E. floccosum*, *Pleurotus ostreatus*	–	[63]
Miscellaneous					
Tryptanthrin	$C_{15}H_8N_2O2$		*E. floccosum*, *T. mentagrophytes*, *Trichophyton rubrum*, *Trichophyton tonsurans*, *M. gypseum*, and *Microsporum canis*	3.1–6.3 μg/mL	[64]
			C. neoformans, and *Cryptococcus deuterogattii*	MIC/MFC: 2/ > 64 and 8/ 32 μg/mL	[65]
Dehydroevodiamine	$C_{19}H_{15}N_3O$	Rutaceae	*X. oryxae* pv *oryzae*	1.4 μg/mL	[49]
Piperidine Alkaloids					

Types of alkaloids	Formula	Plant family	Targeted microorganism	Concentrations range (μg/mL)	Reference
Piperlongumine	$C_{17}H_{19}NO_5$	Piperaceae	*C. albicans*, *S. aureus* and *P. aeruginosa*	MIC: 3.9 μg/mL	[66]
Piperine	$C_{17}H_{19}NO_3$	Piperaceae	*C. albicans*, *R. solani*, *Fusarium gramineum*, *Alternaria tenuissima*, *Gloeosporium theae-sinensis*, *Phytophthora capsici*, and *Phomopsis adianticola*	100 μg/mL	[66]
Quinolizidine					
Quinolizidine	$C_9H_{17}N$	Nymphaeaceae, Fabaceae	*E. faecalis*, *Enterococcus faecium*, *S. aureus*, and Methicillin-resistant Staphylococcus aureus (MRSA)	2–16 μg/mL	[67]
Phenanthroindolizidine		Lauraceae, Moraceae, Asclepiadaceae			
7-Demethoxytylophorine	$C_{23}H_{25}NO_3$	Apocynaceae	*Penicillium italicum, Penicillium digitatum*	MIC/MFC: 1.5/6.2 and 1.5/12.5 μg/mL, respectively	[68, 69]
Tylophorinine	$C_{23}H_{25}NO_4$	Apocynaceae	*C. albicans*, *Candida krusei*, *Candida glabrata*, and *A. fumigatus*	0.6–5 μg/mL	[68]
Tylophorinidine	$C_{22}H_{23}NO_4$	Apocynaceae	*C. albicans*, *Candida krusei*, *Candida glabrata*, and *A. fumigatus*	2–8 μg/mL	[68]
Securinega alkaloids					
viroallosecurinine	$C_{13}H_{15}NO_2$	Phyllanthaceae	*P. aeruginosa* and *S. aureus*	MIC: 0.4 μg/mL	[70]
Securinine, Allosecurinine	$C_{13}H_{15}NO_2$	Phyllanthaceae	*P. aeruginosa*, *S. aureus*, and *M. smegmatis*	Weak activity	[70]
norsecurinine	$C_{12}H_{13}NO_2$	Phyllanthaceae	filamentous fungi	Inhibited at Low concentrations	[71]
Miscellaneous					
Dihydrodioscorine	$C_{13}H_{21}NO_2$	Dioscoreaceae	*Sclerotium rolfsii*, *C. lunata*, *F. moniliforme*, *Botryodiplodia theobromae*, and *Macrophomina phaseolina*	Inhibited the mycelial growth	[72]
Pandamarilactone-1	$C_{18}H_{23}NO_4$	Dioscoreaceae	*E. coli*, *P. aeruginosa*, and *S. aureus*	Weak activity	[73]

Types of alkaloids	Formula	Plant family	Targeted microorganism	Concentrations range (μg/mL)	Reference
Haloxyline B	—	Chenopodiaceae	*M. tuberculosis* H37Rv	50 μg/mL	[74]
Quinoline Alkaloids					
Simple Quinolines					
4-Methylquinoline	$C_{10}H_9N$	—	*S. aureus*	MIC/MBC values of 12.2/ 50 μg/mL	[75]
4-methoxy-2-phenylquinoline	$C_{16}H_{13}NO$	Rutaceae	*M. tuberculosis* H37Rv	16 μg/mL	[75]
Dictamine	$C_{12}H_9NO_2$	Rutaceae	*Micrococcus luteus* (TISTR 884) and *B. cereus* (TISTR 688)	26 and 64 μg/mL, respectively	[76]
γ-Fagarine	$C_{13}H_{11}NO_3$	Rutaceae	broad-spectrum antibacterial	Moderate activity	[77]
Robustine	$C_{12}H_9NO_3$	Rutaceae	broad-spectrum antibacterial	Moderate activity	[77]
Benzylisoquinolines					
Reticuline	$C_{19}H_{23}NO_4$				
Fuyuziphine	—	Papaveraceae	*Alternaria brassicicola*, *A. solani*, *Alternaria melongenae*, *C. maculans*, *Erysiphe cichoracearum*, and *Helminthosporium pennisetti*	500 ppm	[78]
Bisbenzylisoquinolines					
Tetrandrine	$C_{38}H_{42}N_2O_6$	Menispermaceae	*S. aureus* and MRSA	weakly bactericidal	[79]
Tiliacorinine	$C_{36}H_{36}N2O_5$	Menispermaceae	*M. tuberculosis*	6.2 μg/mL	[80]
2′-nortiliacorinine	$C_{35}H_{34}N_2O_5$	Menispermaceae	*M. tuberculosis*	3.1 μg/mL	[80]
Tiliacorine	$C_{36}H_{36}N_2O_5$	Menispermaceae	*M. tuberculosis* and *A. tenuissima*	3.1 and 100 μg/mL, respectively	[80, 81]
Aporphines					
Aporphine	$C_{17}H_{17}N$	Illiciaceae, Trimeniaceae	bacteria and fungus in plants	suppressed a wide variety of bacteria and fungus	[82]

Types of alkaloids	Formula	Plant family	Targeted microorganism	Concentrations range (μg/mL)	Reference
Liriodenine	$C_{17}H_9NO_3$	Illiciaceae, Trimeniaceae	bacteria and fungus in plants	suppressed a wide variety of bacteria and fungus	[82]
Anonaine	$C_{17}H_{15}NO_2$	Magnoliaceae, Annonaceae	*B. cereus*, *E. coli*, *S. aureus*, and *S. epidermidis*	diameters of 20, 8, 14, and 12 mm, respectively	[83]
Lysicamine	$C_{18}H_{13}NO_3$	Annonaceae	*L. monocytogenes*, Methicillin-resistant Staphylococcus aureus (MSSA), *S. pneumoniae*, *Actinobacillus* sp., and *K. pneumoniae*	1.4–20 μg/mL	[84]
O-methylmoschatoline	$C_{19}H_{15}NO_4$	Annonaceae	*B. subtilis*, *E. coli*, and *Salmonella typhi*	64 μg/mL	[82]
Artabotrine	$C_{20}H_{23}NO_4$	Annonaceae	*K. pneumoniae*	MIC/MBC: 2.5/2.5 μg/mL	[84]
Azaoxoaporphine sampangine	$C_{15}H_8N_2O$	Annonaceae	*C. albicans*, *C. glabrata*, *C. kruseii*, *A. fumigatus*, and *C. neoformans*	3.1, 3.1, 6.2, 6.2, and 0.05 μg/mL, respectively	[85]
Lanuginosine	$C_{18}H_{11}NO_4$	Annonaceae	*B. cereus*, *S. aureus*, *E. coli*, *K. pneumoniae*, and *P. aeruginosa*	IZ: 12, 14, 10, 14, and 12 mm, respectively	[86]
Nordicentrine	$C_{19}H_{19}NO_4$	Menispermaceae	*M. tuberculosis*	12.5 μg/mL	[87]
Dicentrinone	$C_{19}H_{13}NO_5$	Menispermaceae	*M. tuberculosis*	Moderate antimycobacterial	[88]
Oxoaporphine thailandine	$C_{39}H_{62}O_{14}$	Menispermaceae	*S. pneumoniae*, *S. aureus*, *E. faecalis*, and *M. tuberculosis*	30, 30, 60, and 6.2 μg/mL, respectively	[89]
Isoboldine	$C_{19}H_{21}NO_4$	Ranunculaceae	*A. baumanii*, *B. subtilis*, *C. albicans*, *P. aeruginosa*, *E. coli*, *P. mirabilis*, *K. pneumoniae*, and *S. aureus*	Moderate activity	[90]
Roemerine	$C_{18}H_{17}NO_2$	Lauraceae	MRSA, *A. fumigatus*, *C. albicans*, *C. glabrata*, *C. krusei*, *Candida tropicalis*, *Candida parapsilosis*, and *S. aureus*	10 μg/mL for *C. albicans*	[91, 92]
Magnoflorine	$C_{20}H_{24}NO_{4+}$	Menispermaceae	*C. albicans*, *C. parapsilosis* var. *parapsilosis*, *T. rubrum*, and *T. mentagrophytes*	Moderate activity	[93]
Protopines					
Protopine	$C_{20}H_{19}NO_5$	Papaveraceae	*C. albicans*	4 μg/mL	[90]
Allocryptopine	$C_{21}H_{23}NO_5$	Papaveraceae	*P. aeruginosa*, *S. aureus*, *E. coli*, and *S. agalactiae*	Weak activity	[94]

Types of alkaloids	Formula	Plant family	Targeted microorganism	Concentrations range (μg/mL)	Reference
Protoberberines					
Pendulamine A	—	Annonaceae	*B. subtilis*, *P. aeruginosa*, *S. aureus*, *Corynebacterium hoffmanii*, *K. pneumoniae*, *S. typhi*, *Micrococcus lysodickycus*, and *S. paratyphi A*	0.02–2 μg/mL	[95]
Pendulamine B	—	Annonaceae	*Corynebacterium hoffmanii*, *S. faecalis*, *S. aureus*, *S. typhi*, *S. viridans*, *M. lysodickycus*, *P. aeruginosa*, *K. pneumoniae*, and *S. paratyphi* A	0.02–2 μg/mL	[95]
Spirobenzylisoquinolines					
Parfumine	$C_{20}H_{19}NO_5$	Papaveraceae	*A. baumanii*, *B. subtilis*, *K. pneumoniae*, *E. coli*, *P. aeruginosa*, *P. mirabilis*, and *S. aureus*	Moderate activity	[90]
Fumarophycine	$C_{22}H_{23}NO_6$	Papaveraceae	*A. baumanii*, *B. subtilis*, *K. pneumoniae*, *E. coli*, *P. aeruginosa*, *P. mirabilis*, and *S. aureus*	Moderate activity	[90]
Fumariline	$C_{20}H_{17}NO_5$	Papaveraceae	*A. baumanii*, *B. subtilis*, *K. pneumoniae*, *E. coli*, *P. aeruginosa*, *P. mirabilis*, and *S. aureus*	Moderate activity	[90]
Benzophenanthridines					
Stylopine or sanguinarine	$C_{20}H_{14}NO_{4+}$	Papaveraceae	*A. baumanii*, *B. subtilis*, *K. pneumoniae*, *E. coli*, *P. aeruginosa*, *P. mirabilis*, and *S. aureus*	Moderate activity	[90]
Dihydrosanguinarine	$C_{20}H_{15}NO_4$	Papaveraceae	*S. mutans, S. aureus, P. aeruginosa, E. coli*, and *S. agalactiae*	32, 31.3, 250, 62.5, 15.6 μg/mL	[94]
6-Methoxydihydrosanguinarine	$C_{21}H_{17}NO_5$	Papaveraceae	*S. aureus* and MRSA	IZ: 17 mm	[96]
			E. faecalis and *S. aureus*	MIC/MBC: 5/10, 2.5/5 μg/mL	[97]
8-Hydroxydihydrosanguinarine		Papaveraceae	MRSA	MIC range: 0.4 to 7.8 μg/mL, and MBC range: 1.9 to 31.2 μg/mL	[81]
Norsanguinarine	$C_{19}H_{11}NO_4$	Papaveraceae	*A. baumanii*, *B. subtilis*, *K. pneumoniae*, *E. coli*, *P. aeruginosa*, *P. mirabilis*, and *S. aureus*	Moderate activity	[90]

Types of alkaloids	Formula	Plant family	Targeted microorganism	Concentrations range (μg/mL)	Reference
Allocryptopine	$C_{21}H_{23}NO_5$	Papaveraceae	*S. epidermidis*, *S. aureus*, *S. pyogenes*, *B. subtilis*, *K. pneumoniae*, and *E. coli*	6.2/12.5, 12.5/50, 12.5/50, 25/50, 12.5/25, 25/25 μg/mL, respectively	[98]
8-Hydroxydihydrochelerythrine	$C_{21}H_{19}NO_5$	Papaveraceae	MRSA	MIC: 0.9–15.6 μg/mL, MBC: 7.8–62.5 μg/mL	[99]
Dihydrochelerythrine	$C_{21}H_{19}NO_4$	Papaveraceae	MRSA, *E. coli*	8–128 5 μg/mL	[77]
Chelerythrine	$C_{21}H_{18}NO_4$	Papaveraceae	*C. albicans*, *S. cerevisae*, and *C. neoformans*	MIC/MBC: 3.1/3.1, 6.2/6.2, and 3.1/6.2 μg/mL, respectively	[98]
Corynoline	$C_{21}H_{21}NO_5$	Papaveraceae	*Cladosporium herbarum*	3 μg/spot	[100]
Acetylcorynoline	—	Papaveraceae	*C. herbarum*	3 μg/spot	[100]
Norchelerythrine	$C_{20}H_{15}NO_4$	Rutaceae	*M. tuberculosis*	25 μg/mL	[101]
Avicine	$C_{20}H_{14}NO_{4+}$	Rutaceae	*S. epidermidis*, *S. aureus*, *S. pyogenes*, *B. subtilis*, *K. pneumoniae*, and *E. coli*	3.1/12.5, 1.5/25, 1.5/12.5, 1.5/6.2, and 6.2/12.5 μg/mL, respectively	[98]
Rhoifoline B	$C_{21}H_{17}NO_5$	Rutaceae	*S. aureus*, *S. epidermidis*, *E. coli*, *E. cloacae*, *K. pneumoniae*, *P. aeruginosa*, and *S. dysenteriae*	Moderate activity	[102]
Nitidine	$C_{21}H_{18}NO_{4+}$	Rutaceae	*M. luteus*, *S. aureus*, and *M. smegmatis*	Weak activity	[103]
Protoberberines					
Berberine	$C_{20}H_{18}NO_{4+}$	Berberidaceae	*K. pneumonia* and *A. baumanii*	8 μg/mL	[90]
Palmatine	$C_{21}H_{24}NO_{4+}$	Berberidaceae, Papaveraceae, Ranunculaceae, and Menispermaceae	*A. baumanii*, *E. coli*, *P. mirabilis*, *P. aeruginosa*, *K. pneumoniae*, *S. aureus*, and *B. subtilis*	Moderate activity	[90]
Phthalides					
Bicuculline	$C_{20}H_{17}NO_6$	Fumariaceae	*A. brassicae*, *F. udum*, and *Curvularia lanata*	200 ppm	[90]
Hasubanans					

Types of alkaloids	Formula	Plant family	Targeted microorganism	Concentrations range (μg/mL)	Reference
Glabradine	$C_{19}H_{19}NO_7$	Menispermaceae	*S. aureus* and *S. mutans*	50 μg/mL	[104]
Amaryllidaceae Alkaloids		Amaryllidoideae			
Crinamine	$C_{17}H_{19}NO_4$	Amaryllidoideae	Some bacteria	—	[105]
Lycorine	$C_{16}H_{17}NO_4$	Amaryllidoideae	*C. glabrata*, *Candida dubium*, *C. albicans*, *Lodderomyces elongisporus*, and *S. cerevisae*	512, 39, 32, 64, and 97.3 μg/mL	[78]
			Alternaria oleracea, *C. gloeosporioides*, *F. graminearum*, *Colletotrichum ophiopogonis*, and *Pleospora lycopersici*	100 μg/mL	[106]
Lycoricidine		Amaryllidoideae		IZ: 12 mm	[78]
Narciclasine	$C_{14}H_{13}NO_7$	Amaryllidoideae	*Corynebacterium fascians* and *C. neoformans*	Highly growth inhibition	[107]
Tazettine	$C_{18}H_{21}NO_5$	Amaryllidoideae	*L. elongisporus* and *C. dubliniensis*	Weak activity	[108]
Miscellaneous					
Quinolinones					
Antidesmone	$C_{19}H_{29}NO_3$	Euphorbiaceae	Carbendazim-sensitive strains of *S. sclerotiorum*, and Carbendazim-resistant strains of *S. sclerotiorum Botryosphaeria dothidea*, *Pestalotipsis guepinii*, *Colletotrichum musae*, *Colletotrichum orbiculare*, *Pestalotiopsis longiseta Phylophthora nicotianae*	50 μg/mL	[109]
Waltherione C	$C_{22}H_{21}NO_3$	Malvaceae	*B. dothidea*, *Colletotrichum orbiculare*, *Colletotrichum musae*, *Pestalotiopsis longiseta*, *Pestalotipsis guepinii*, *Phylophthora nicotianae*, carbendazim-sensitive strains of *S. sclerotiorum*, and carbendazim-resistant strains of *S. sclerotiorum*	50 μg/mL	[109]
Evocarpine	$C_{23}H_{33}NO$	Rutaceae	MRSA and *S. aureus*	8 μg/mL	[110]
Acridanones					
1-hydroxy-3,4-dimethoxy-10-methylacridan-9-one	$C_{16}H_{15}NO_4$	Rutaceae	*E. coli*	Growth inhibition	[51]

Types of alkaloids	Formula	Plant family	Targeted microorganism	Concentrations range (μg/mL)	Reference
Phenanthrene Alkaloids					
Aristolochic acid	$C_{17}H_{11}NO_7$	Aristolochiaceae	*Moraxella catarrhalis*	MIC and MBC: 25/50 μg/mL	[111]
1-N-monomethylcarbamate-argentinine-3-O-β-D-glucoside	—	Menispermaceae	MRSA	500 μg/disk, IZ: 8 mm	[112]
Pyrrolidines and Imidazole Alkaloids		Piperaceae			
Pyrrolidines		Piperaceae			
Brachyamide B	$C_{20}H_{25}NO_3$	Piperaceae	*C. albicans*	IC_{50}: 41.8 μg/mL	[113]
Pandanus lactones			*C. neoformans*	IC_{50}: 7.1 μg/mL	[114]
Pandamarilactonine A	$C_{18}H_{23}NO_4$	Pandanaceae	*E. coli*, *P. aeruginosa*, and *S. aureus*	Moderate activity	[73]
Diterpene Alkaloids		Ranunculaceae			
8-acetylheterophyllisine	$C_{24}H_{35}NO_5$	Ranunculaceae	*Pleurotus ostreatus*, *Allescheria boydii*, *A. niger*, and *E. floccosum*	Growth inhibition	[63]
Vilmorrianone	$C_{23}H_{27}NO_5$	Ranunculaceae	*Pleurotus ostreatus*, *Allescheria boydii*, *A. niger*, and *E. floccosum*	Growth inhibition	[63]
Panicutine	$C_{23}H_{29}NO_4$	Ranunculaceae	*Pleurotus ostreatus*, *Allescheria boydii*, *A. niger*, and *E. floccosum*	Growth inhibition	[63]
Steroidal Alkaloids					
N-formylconessimine	—	Apocynaceae	MSSA	32 μg/mL	[115]
Conimine	$C_{22}H_{36}N_2$	Apocynaceae	MRSA	128 μg/mL	[115]
Isoconkuressine	—	Apocynaceae	MSSA and MRSA	Growth inhibition	[115]

IZ: inhibition zone; and MIC: minimum inhibitory concentration.

Table 1.
Classification of alkaloids in plants family based on their antimicrobial activity.

marine microbes [117]. Various biological and pharmacological qualities are related to the several structural scaffolds, and a wide variety of functional group modifications is found in the broad class of plant-specific metabolites known as benzylisoquinoline alkaloids. N-Methylation is a widely used modification technique that forms intermediates and final products in the tertiary and quaternary metabolic pathways [118].

3.2 Some selected alkaloids with antimicrobial activity

Various alkaloids found in nature have been shown to have antimicrobial effects against a wide range of diseases [15]. Some selected alkaloids with potent antimicrobial activity include berberine, quinine, and vincristine. The potential for these particular alkaloids' antibacterial action to expand therapy choices for infectious disorders caused by drug-resistant microbes or those not responding to conventional therapies has been widely discussed [16]. Hence, this review focuses on alkaloids with antibacterial activity against MDR microorganisms. Also, this article describes the most influential alkaloids with potent antibacterial properties. Here are some selected examples of these compounds:

3.2.1 Berberine

The natural isoquinoline alkaloid berberine has been shown to have minimal toxicity [119]. Berberine, derived from *Berberis* spp., is a prominent quaternary ammonium salt of protoberberines. It exhibits various antimicrobial properties, particularly against Gram-negative bacteria [24]. *Berberis vulgaris*, *Coptis chinensis*, *Hydrastis canadensis*, *Coptidis rhizoma*, *Xanthoriza simplicissima*, *Phellodendron amurense*, and *Chelidonium majus* all contain it, among many others, making them useful as therapeutic herbs [119]. Berberine is an effective antibacterial agent that may one day replace conventional antibiotics and help combat the problems caused by antibiotic resistance. Methanol extract of *Pancratium illyricum* L. bulbs yielded the isoquinoline alkaloid ungeremine. Its antimicrobial qualities have been well-praised. As mentioned earlier, the compound can induce a significant augmentation in DNA cleavage through its selective targeting and inhibition of bacterial topoisomerase IA [29]. Herpes, influenza, and respiratory syncytial viruses are susceptible to berberine's antiviral actions [34, 119]. Berberine's mechanism of action against *V. cholerae* and *E. coli*-induced diarrhea has been thoroughly investigated. The effects of *E. coli* and *V. cholerae* enterotoxins were found to be directly inhibited by berberine *in vitro* as early as 1982 [120]. Berberine's antibacterial activity against *S. aureus* has been shown in *in vitro* investigations [121]. As reported in reference, berberine and CinA can undergo self-assembly, forming nanoparticles (NPs) that exhibit bacteriostatic properties against MRSA and potentially eliminate biofilms [40]. Cinnamaldehyde (CinA) is a principal constituent of the *Cinnamomi cortex*, a traditional spice that finds extensive usage in everyday routines [122].

The alkaloid berberine sulfate is harvested from the bark and roots of several plants. It exhibits antibacterial, antifungal, and antiprotozoal properties. Berberine sulfate disrupts fimbrial formation in *Streptococcus pyogenes*, impeding bacterial attachment to mucosal or epithelial surfaces [123]. On the other hand, L-Tyr is widely recognized as the biosynthesis precursor of berberine. 13 different enzymatic processes are involved in the production of berberine from L-Tyr. Notably, biochemical analysis has been performed on all of the enzymes in this pathway [24].

3.2.2 Caffeine

Numerous plant species derive caffeine (1,3,7-trimethyl xanthine) from methylated alkaloids. It is structurally related to uric acid [124]. However, recent studies have shown that caffeine also has antimicrobial properties, which has led to increased interest in its potential use as an alternative to traditional antibiotics. Understanding caffeine's antimicrobial activity is crucial in developing new treatments for drug-resistant infections, making it an important area of research. Another study by Ibrahim et al. found that growth inhibition was most noticeable at concentrations of 0.50% and above against *E. coli* [124]. Also, caffeine concentrations in coffee extracts are high enough to concern human health, with 50% antibacterial activity against *S. enterica* [125].

3.2.3 Capsaicin (CAP)

The berries of virtually all peppers in the genus *Capsicum* contain capsaicin, also known as 8-methyl-N-vanillyl-6-nonenamide [12]. Peppers, especially chili peppers, are members of the Solanaceae plant family, responsible for their distinctive flavor [11]. *Capsicum annuum* powder is a commonly utilized seasoning in various culinary traditions across the globe. Apart from its gastronomic application, CAP is employed for analgesic purposes in different severe and persistent medical conditions [12]. Pepper fruits may contain capsaicin at a rate of up to 1% of their total weight. It is naturally produced in the epidermal cells of the placenta, which are located close to the seeds. The compound tends to accumulate in the form of "blisters" on the surface of the placenta. The molecule is a potent agonist of the transient receptor potential vanilloid ion-channel receptor 1 (TRPV1), eliciting its characteristic hot, burning sensation. However, the beneficial effects of capsaicin and the TRPV1 receptor cannot be attributed primarily to this interaction [11]. In an *in vitro* investigation [126], six capsaicin derivatives were developed, each possessing phenolic hydroxyl, a benzene ring, and amide structures. These derivatives were subsequently evaluated for their antibacterial properties against *E. coli* and *S. aureus*. Two powerful chemicals found in *Capsicum* species were shown to have antimicrobial capabilities, and Cichewicz and Thrope identified them. The experiment results showed that the plain and heated extracts displayed different levels of inhibition against *Streptococcus pyogenes*, *B. subtilis*, *B. cereus*, *Clostridium tetani*, and *Clostridium sporogenes* [127].

3.2.4 Colchicine

Colchicine has been around longer than most other pharmaceuticals [128]. The use of colchicine as a pharmacological agent in humans has been permitted by the Food and Drug Administration (FDA). It is a safe and productive anti-inflammatory medication derived from the *Colchicum* and *Gloriosa* plant species. Colchicine has been utilized in treating cardiovascular ailments due to its distinctive effectiveness as an anti-inflammatory agent [24]. The chemical origins of colchicine have been the subject of extensive research, facilitated by numerous feeding studies utilizing isotope-labeled substrates in Colchicum plants. Furthermore, a well-defined biosynthetic hypothesis has been established thanks to structural study of colchicine-related alkaloids isolated from several members of the Colchicaceae family [24]. The first biosynthetic studies on colchicine were performed by Leete in 1960 [129].

The medical application of colchicine in cancer chemotherapy is restricted due to its comparatively high toxicity, despite its potency as an anticancer agent. Nevertheless, colchicine is currently utilized in therapy [130]. Colchicine's potential anticancer impact on hypo-pharyngeal carcinoma was studied. Colchicine dose-dependently suppressed hypo-pharyngeal human cell proliferation [128]. Colchicine inhibited adhesion, migration, and cell invasion via decreasing expression of MMP9, uPA, and FAK/SRC [128]. Researchers have shown that colchicine inhibits the reproduction of the Flaviviridae family of viruses by blocking microtubule polymerization. Researchers believe colchicine, a well-known anti-inflammatory medication, can cure COVID-19 by decreasing inflammation [131].

3.2.5 Piperine

Piperine has been extracted from various species of the Piperaceae botanical family [132], as shown chemically in **Figure 2** [132]. Piperine is a major compound of black pepper (*Piper nigrum*) and long pepper (*Piper longum*), two species of the Piperaceae family. Studies suggest piperine exhibits bioavailability-enhancing properties for select nutritional substances [133]. The biting quality that is distinct from black pepper is attributed to piperine. Piperine exhibits numerous pharmacological properties and confers various health advantages, particularly for chronic ailments. These benefits include mitigation of anti-inflammatory effects, insulin resistance, amelioration of hepatic steatosis [134], anti-aging, antidiabetic, cardioprotective, antimicrobial, and anti-obesity [132]. When ciprofloxacin and a piperidine-type alkaloid from

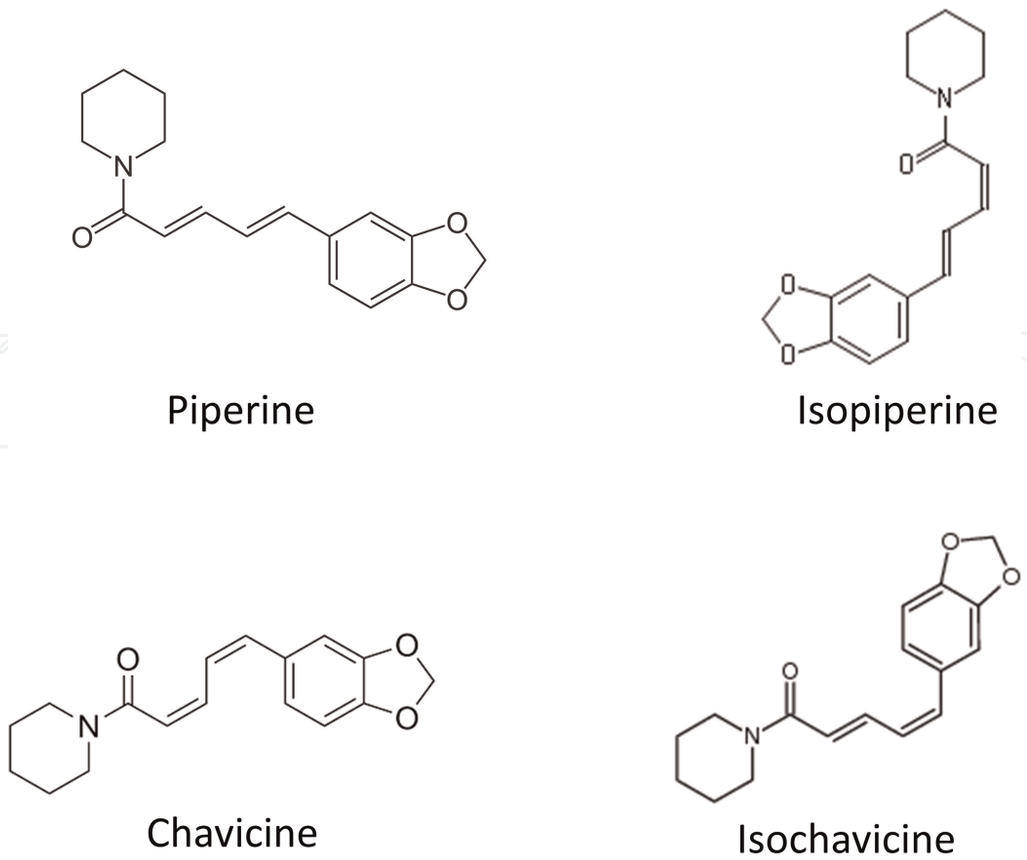


Figure 2.
Piperine and its structural isomers (adapted from Ul-Haq et al. [132]).

the plants. Together, *P. longum* and *P. nigrum* were able to inhibit the development of a mutant *S. aureus* and considerably reduce MIC values for *S. aureus* [135].

In the case of absorption, it is noteworthy that piperine exhibits no metabolic transformations upon absorption, as evidenced by its presence in both intestinal tissues and serosal fluid. This suggests that piperine remains unaltered throughout the absorption process [132].

3.2.6 Reserpine

Reserpine, an indole alkaloid extracted from the plant Rauwolfia serpentina, is well-known for its potent EPI action. The co-administration of reserpine has improved the antibiotic susceptibility of various bacterial species, such as *Micrococcus* spp., *Streptococcus* spp., and *Staphylococcus* spp. [29]. Combining reserpine with other commercially available antibiotics has been shown to improve the antibiofilm response and eradicate a sizable amount of bacterial biofilm in a urinary catheterization model, as reported by Parai et al. [136]. In another study, many acyl reserpine derivatives were made and tested for their antimycobacterial and antioxidant activities against *Mycobacterium* TB, strain H (37) Rv. This was done because reserpine is thought to have therapeutic benefits. According to the findings, 10 of 18 derivatives exhibited more significant suppression of antimycobacterial activity than reserpine [137]. On the other hand, reserpine inhibits AcrB. Acriflavine resistance protein B (AcrB) is an MDR efflux transporter that belongs to the Resistance-nodulation-division (RND) superfamily [138].

3.2.7 Tomatidine

Steroid alkaloid tomatidine is harvested from nightshade plants, including tomatoes, potatoes, and eggplant. As monotherapy or in combination with aminoglycosides, there is evidence that it is highly effective as an antibacterial agent against *S. aureus* [29]. Tomatoes and tomatidine, as found by Silva-Beltrán et al., have great promise as a source of several bioactive chemicals, antioxidants, and antibacterial agents [139]. Tomatidine exhibited bacteriostatic activity against small-colony variants linked to their impaired electron transport system. The electron transport inhibitor 4-hydroxy-2-heptylquinoline-N-oxide (HQNO) increased the sensitivity of typical *S. aureus* strains to tomatidine [140].

3.2.8 Conessine

Holarrhena antidysenterica, a member of the Apocynaceae family, has a long history of medical usage for treating dysentery, diarrhea, fever, and bacterial infections [141]. Conessine is a steroidal alkaloid. The therapeutic actions of *H. antidysenterica* barks are due to the presence of alkaloids, specifically the steroidal alkaloid conessine. There is preliminary evidence that this compound can kill gram-positive and gram-negative bacteria [141]. Based on the existing evidence, it can be inferred that the steroidal crude extract of *H. antidysenterica* and conessine exhibit properties of efflux pump inhibitors (EPIs). Recently, it has been reported that the steroidal extract and alkaloid conessine can augment the efficacy of antibiotics by impeding the AdeIJK efflux pump in *A. baumannii* [142].

Other alkaloid classes, namely indolizidine, pyrrole-imidazole alkaloid, quinoline, aaptamine, indole, isoquinoline, piperazine, polyamine, bisindole, quinolone, indole-

quinoline, agelasine, aaptamine-indole, pyridoacridine, and bispyrrole have been reported to exhibit antibacterial activity [37].

4. Alkaloids derived from medicinal plants and their antimicrobial activities

The distribution of alkaloids within plant tissues is heterogeneous, as mentioned previously, with varying concentrations observed across plant parts such as roots, seeds, leaves, fruits, and bark. Distinct alkaloid types may exist in various parts of a single plant [12]. The alkaloids are the most abundant secondary metabolites in the *Zanthoxylum* genus, and they exhibit a wide variety of biological functions due to their structural diversity [143]. A study by Farouk et al. indicated that *Eurycoma longifolia* leaf extracts were tested for antibacterial efficacy against *Pseudomonas aeruginosa* and *S. aureus* bacteria. The extracts were prepared using various solvents, including acetone, ethanol, phosphate buffer, and methanol at 5–100 mg/mL concentrations. Several extracts inhibited bacterial growth, with the widths of the inhibition zones ranging from 7 to 25 mm [144]. In addition to causing serious side effects, treating fungal infections with antifungal drugs often leads to drug-resistant strains of the fungus. This highlights the critical need to investigate potential new antifungal medicines. It has been shown that alkaloids isolated from the leaves of *Ruta graveolens* L. are fungi toxic [145]. Flavonoids and quinoline alkaloids isolated from the roots of *Waltheria indica* L. showed that to have antifungal activity against *Candida albicans* [146]. **Table 2** summarizes some selected medicinal plants that possess alkaloids with antimicrobial properties.

In a study by Erdemoglu et al. [154], capillary GC-MS identified 15 alkaloids. 13α-hydroxylupanine (50.78%) and lupanine (23.55%) were assessed to be the significant alkaloids in the aerial parts of *L. angustifolius*. Ammodendrine, tetrahydrorhombifoline, isoangustifoline, α-isolupanine, 5,6-dehydrolupanine, 11,12-dehydrolupanine, 13α-tigloyloxylupanine, 13α-acetoxylupanine, angustifoline, 13α-isovaleroyloxylupanine, 13α-valeroyloxylupanine, 13α-*cis*-cinnamoyloxylupanine, and 13α-*cis*-cinnamoyloxy-17-oxolupanine were analyzed as the minor alkaloids of the substances in this plant. The alkaloid extract showed modest effectiveness against *E. coli,* while a strong point against *B. subtilis*, *S. aureus*, and *P. aeruginosa*. The extract was only moderately effective against *Candida albicans* and *C. krusei* [154]. Although native to the Middle East and Mediterranean regions, *Peganum harmala* has been introduced to Australia and the United States [155]. The alkaloids of *P. harmala* are concentrated in its roots and seeds. All 13 Gram-positive (*S. pyogenes*, *S. epidermidis*, *S. aureus*, *L. monocytogenes B. pumilus*, *B. cereus*, and *B. anthracis*) and Gram-negative (*Brucella melitensis*, *P. aeruginosa*, *Salmonella typhi*, *Klebsiela pneumoniae*, *E. coli*, and *P. mirabilis*) bacteria tested showed inhibition by methanol extract [155]. *Papaver somniferum,* belonging to the Papaveraceae botanical family, has been the subject of extensive research due to its benzylisoquinoline alkaloids (BIAs), which have been utilized for medicinal purposes since ancient times. It is notable for being the sole commercial source of morphine and codeine and is regarded as the model plant for BIA research. *P. somniferum* synthesizes vital alkaloids, such as sanguinarine, papaverine, and noscapine [162].

Native to Oman, *Ficus sycomorus* has had its leaf extracts investigated for their ability to eradicate *Haemophilus influenzae*, *S. aureus*, *E. coli*, and *Proteus* spp. [152]. *Ficus sycomorus* is abundant in flavonoids, alkaloids, tannins, and phenolic compounds.

Plant and family	Common name	Part of plant	Extraction solvent	Method of detection	Bioactive compound	Ref.
Antibacterial						
Alchornea laxiflora / *Euphorbiaceae*	Three-veined bead string, Lowveld bead string, Venda bead string,	Leaf	Methanol and distilled water	—	—	[147]
Amaryllis belladonna/ *Amaryllidaceae*	Jersey lily	Bulb	Chloroform, Ethanol, and n-butanol	HPTLC	(-)-Amarbellisine, (-)-lycorine, (-)-pancracine, (+)-vittatine, (+)-11-hydroxyvittatine, and (+)-hippeastrine	[148]
Stephania glabra/ Menispermaceae	Hairless tape vine	Tuber	Ethanol	—	gindarine, gindaricine, gindarinine, columbamine, jatrorrhizine and magnoflorine	[149]
Zanthoxylum spp./Rutaceae	Pricklyash	—	—	—	Quinoline, isoquinoline, indole, quinazoline, indolopyridoquinazoline	[143]
Eurycoma longifolia/ *Simaroubaceae*	Tongkat Ali	Leaf	Acetone, methanol, and ethanol			[144]
Morus alba/Moraceae	Mulberry	Root	Water extract	NMR	piperidine	[150]
Glycyrrhiza glabra L./Fabaceae	Licorise	Aerial parts	Methanol	—	—	[151]
Ficus sycomorus/Moraceae	Mulberry Fig, Sycamore Fig	Leaf	Methanol	—	—	[152]
Telosma (Pergularia) pallida/ Apocynaceae	Telosma vine	Air-dried roots	—	—	pergularinine and tylophorinidine	[153]
Lupinus angustifolius L./ Fabaceae	Lupine	Aerial parts	Dichloromethane	GC-MS	13α-Hydroxylupanine (50.78%) and lupanine (23.55%)	[154]
Murraya koenigii (L) Spreng/ Rutaceae	Curry tree	The stem barks	Petroleum ether	UV, IR, MS, and a series of 1D and 2D NMR	Benzoisofuranone and carbazole	[51]
Peganum harmala/Nitrariaceae	Wild rue, Syrian rue, esfand, espand, harmel	Root and seed	Methanolic extract	TLC	Pegamine, vasicine, harmine, harmane, harmaline, harmalol, and vasicinon	[155]

Plant and family	Common name	Part of plant	Extraction solvent	Method of detection	Bioactive compound	Ref.
Phoenix dactylifera L./Arecaceae	Date palm	Leaf and pit	Methanol and acetone	—	—	[156]
Antifungal						
Ruta graveolens L./Rutaceae	Rue, common rue, herb-of-grace	Leaf	Hexane	(1)H and (13)C NMR	1-methyl-2-[6'-(3″,4″-methylenedioxyphenyl) hexyl]-4-quinolone	[145]
Waltheria indica/Malvaceae	Sleepy morning	Aerial parts	Dichloromethane	COSY, HSQC, HMBC, NOESY NMR, UV, IR, and HRESIMS	Waltheriones and 5®-vanessine	[146]
Antiviral						
Phellodendron amurense/ Rutaceae	Amur cork tree	Bark	Aqueous and ethanol	—	Berberine	[157]
Moringa oleifera/Moringaceae	ben oil tree, drumstick tree, horseradish tree, and benzolive tree	Leaf	Water extract	LC-MS	Gentiatibetine	[158]
Nuphar lutea/Nymphaeaceae					thiobinupharidines and thiobinuphlutidines	[159]
Antiparasitic						
Argemone Mexicana/ Papaveraceae	Mexican poppy	Leaves and stems	Methanolic extract	Dragendorff's reagent	Berberine	[160]
Spondias mombin/ Anacardiaceae	Yellow mombin	Bark and leaves	Aqueous and ethanol	—	—	[161]

Table 2.
Selected medicinal plants possess antimicrobial activity based on their alkaloids as components.

The leaves were subjected to methanol extraction, and subsequent extraction with various solvents. The disk diffusion technique results showed that at concentrations of 0.22–2.02 mg/mL, the crude leaf extracts showed antibacterial activity against *E. coli*, with inhibition diameters ranging from 0 to 9 mm [152].

The Apocynaceae plants, *Catharanthus roseus*, and *Rauwolfia serpentina* are known for their production of significant alkaloids, including serpentine, vinblastine, vincristine, ajmalicine, reserpine, and ajmaline. These plants are role models for understanding how monoterpene indole alkaloids (MIA) are synthesized. Considerable knowledge exists regarding the physiological and ecological factors producing MIA in *C. roseus* [37].

The date palm is widely distributed throughout the Arabian Peninsula and is recognized as a significant economic crop. Date palms possess various chemical compounds such as vitamins, flavonoids, steroids, alkaloids, tannins, and carbohydrates. Except for *E. faecalis*, both the methanol and acetone extracts showed potent antibacterial activity [156].

5. Alkaloids' antibacterial mechanism of action

Alkaloids have been observed to affect various metabolic systems in animals, and their toxic mechanism of action can display considerable variability. Toxicity may present itself via enzymatic alterations that affect physiological functions, obstruction of DNA synthesis and repair mechanisms by intercalating with nucleic acids, or modulation of the nervous system. Various alkaloids can exert an influence on different physiological processes [37]. However, bactericidal drugs are those that, in the absence of confounding variables, result in a 99.9% reduction in bacterial viability at doses no higher than four times the MIC [96]. Most research shows that alkaloids are antibacterial, not bacteriostatic, though this might vary depending on the species of specific alkaloids (such as chelerythrine and prosopilosidine) [8, 15]. The MIC values of squalamine have been demonstrated to be bactericidal within 1–2 hours, killing 99.99% or more of gram-positive and gram-negative bacteria [8]. Their primary antibacterial methods involve blocking bacterial metabolism, altering membrane permeability, and blocking the creation of nucleic acids and proteins [17]. Techniques involving the controlled introduction of pathogens or herbivores, the physical or chemical stimulation of their presence, and the subsequent monitoring of gene expression, enzyme activity, and concentrations of precursors and the alkaloid itself have proven effective [37]. The distinct classes of alkaloids exhibit varying mechanisms of action as antibacterial agents [37]. The antibacterial properties of pergularinine and tylophorinidine, which belong to the indolizine class of alkaloids, are attributed to their ability to inhibit the dihydrofolate reductase enzyme, thereby impeding the synthesis of nucleic acids [153]. Agelasines alkaloids affect bacterial hemostasis by inhibiting the dioxygenase enzyme BCG 3185c, contributing to their antibacterial action. Agelasine D is an alkaloid with antimycobacterial activities, and its overexpression and binding affinity in studies led to the result mentioned above [163]. The respiratory inhibition effects of synthetic quinolone alkaloids, as well as the cell division inhibition effects of isoquinolines, including protoberberine, berberine, benzophenanthridine, and sanguinarine through perturbation of the Z-ring, have been documented. Additionally, the phenanthridine isoquinoline alkaloid ungeremine has been found to inhibit nucleic acid synthesis. In contrast, the indolizidine alkaloids pergularinine and tylophorinidine have been

shown to suppress nucleic acid synthesis by inhibiting dihydrofolate reductase [37]. The mechanisms of action about antibacterial activity exhibit variation across distinct alkaloids. The following examples are being examined [16]:

1. Disruption of the bacterial membrane.

   Several alkaloids from herbal plants have been discovered to exhibit antimicrobial activity by disrupting the bacterial membrane. For example, herbal alkaloids like berberine and palmatine have been proven to cause bacterial cell death by rupturing their membrane [164, 165]. Additionally, squalamine is a polyamine alkaloid with a detergent-like mode of action, depolarizing Gram-positive bacteria membranes and disrupting Gram-negative bacteria's outer membranes [16]. The cytoplasmic membrane is disturbed by phenanthroindolizidine alkaloids [166]. For instance, berberine attacked the mitochondrial membrane of fungi and resulted in cytoplasmic damage in *Streptococcus agalactiae* (CVCC 1886 strain, obtained from the Microbiological Lab of Sichuan Agricultural University, Ya'an, China), whereas liriodenine caused cytoplasmic changes and cell wall destruction in *Paracoccidioides brasiliensis* [9].

2. Interfering with cell division.

   Pergularinine and tylophorinidine, two phenanthroindolizidine plant alkaloids, can block the production of nucleic acids. Protein, RNA, and DNA synthesis rely on pyrimidine and purine precursors, produced by the crucial enzyme dihydrofolate reductase [16]. DNA-protein cross-linking and DNA cross-linking are two mechanisms through which certain alkaloids, such as aristolochic acids, can cause mutations [167]. Interaction with DNA is thought to be the primary mechanism by which quinoline alkaloids exert their antibacterial and antifungal effects [9]. Another example is berberine, which was effective against *Actinobacillus pleuropneumoniae* and *Streptococcus agalactiae* (CVCC 1886) by inhibiting DNA synthesis and preventing synthesis [168].

3. Bacterial enzyme and respiratory system inhibition:

   Alkaloids from herbal plants have been reported to inhibit bacterial enzymes and respiratory systems. For example, inhibiting the respiratory system of bacteria, including *S. aureus*, has been demonstrated for the alkaloid tetrandrine, which is present in several medicinal plants [15]. Additionally, berberine can inhibit bacterial enzymes like DNA gyrase leading to cell death [15]. Also, the alkyl methyl quinolone alkaloids exhibit potent and selective antibacterial properties against *H. pylori* using respiratory inhibition [169].

4. Modulating the expression of virulence genes.

   The regulatory protein ToxT has been identified in *V. cholerae.* It plays a crucial role in activating various virulence determinants, including the genes responsible for encoding virulence factors. Additionally, Yang et al. report that cholera toxin and ToxT co-regulated pilus [170]. The isoquinoline alkaloid known as virstatin has been found to effectively inhibit ToxT, which

subsequently results in the inhibition of virulence factors. The research showed that it prevented *V. cholerae* from colonizing the intestines of newborn mice models [16].

On the other hand, the majority of quinoline and indole-based antifungal and antibacterial alkaloids discovered in Asian angiosperms, respectively, target DNA, topoisomerases, and the cytoplasmic membrane as their primary sites of action [9].

6. Conclusions and future

Alkaloids comprise a vast and heterogeneous category of compounds that exhibit a broad-spectrum of biological functions that hold immense significance for plants, animals, and humans. These compounds possess remarkable pharmacological properties. The advent of antibiotic-resistant microorganisms has substantially compromised antibiotic effectiveness. To date, a new approach to tackling antibiotic resistance is urgently needed. In the coming years, bioactive compounds will likely be discovered using phytochemicals, which exhibit a variety of chemical structures and methods of action. Alkaloids exhibit varying primary functions across different plant species, and their metabolic profiles are often associated with distinct environmental factors and developmental cues, thereby providing evident adaptive advantages. Concerning potential toxicity to other organisms or the production of bioactive metabolites for therapeutic applications, the variation in plant alkaloid metabolism and accumulation is crucial. Alkaloids are effective in this review report as an alternate therapy for combating the emergence and spread of multidrug-resistant infections and the harmful effects of some antibiotics. The following compounds have been identified as primary candidates due to their MIC of less than 1 μg/mL: 8-Acetylnorchelerythrine, cryptolepine, sampangine, 8-hydroxydihydrochelerythrine, 6-methoxydihydrosanguinarine, 2′-nortiliacorinine, tiliacorine, rhetsisine, pendulamine A and B, tylophorinine, tryptanthrin, viroallosecurinine, and vallesamine.

Author details

Mohammad Barati and Amir Modarresi Chahardehi*
Infectious Diseases Research Center, AJA University of Medical Sciences, Tehran, Iran

*Address all correspondence to: amirmch@gmail.com

References

[1] Ugboko HU et al. Antimicrobial importance of medicinal plants in Nigeria. ScientificWorldJournal. 2020; **2020**:7059323

[2] Barati, M., I. Sharifi, and F. SHarififar, In vitro evaluation of anti-leishmanial activities of Zataria multiflora Boiss, Peganum Harmala and Myrtus Communis by colorimetric assay. Journal of Kerman University of Medical Sciences. 2010;**16**(1):32-42

[3] Gong X et al. Plant pharmacophylogeny: Review and future directions. Chinese Journal of Integrative Medicine. 2022;**28**(6):567-574

[4] Cruz Martinez C, Diaz Gomez M, Oh MS. Use of traditional herbal medicine as an alternative in dental treatment in Mexican dentistry: A review. Pharmaceutical Biology. 2017; **55**(1):1992-1998

[5] Aiyegoro O, Okoh A. Use of bioactive plant products in combination with standard antibiotics: Implications in antimicrobial chemotherapy. Journal of Medicinal Plants Research. 2009;**3**(13): 1147-1152

[6] Ghaderi A et al. Evaluation of antileishmanial effect of the plant extract of alpha-pinene (Pistacia atlantica) in vitro and in vivo. Scientific Journal of Kurdistan University of Medical Sciences. 2018;**23**(5):32-44

[7] Modarresi Chahardehi A et al. Antidepressant-like effects of selected crude extracts of Pilea microphylla in mice model of depression. American Journal of Agricultural and Biological Sciences. 2013;**8**(1):75-81

[8] Cushnie TPT, Cushnie B, Lamb AJ. Alkaloids: An overview of their antibacterial, antibiotic-enhancing and antivirulence activities. International Journal of Antimicrobial Agents. 2014; **44**(5):377-386

[9] Sulaiman M et al. Antibacterial and antifungal alkaloids from Asian angiosperms: Distribution, mechanisms of action, structure-activity, and clinical potentials. Antibiotics. 2022;**11**(9):1146

[10] Shin J, Prabhakaran VS, Kim KS. The multi-faceted potential of plant-derived metabolites as antimicrobial agents against multidrug-resistant pathogens. Microbial Pathogenesis. 2018;**116**: 209-214

[11] Fuchtbauer S et al. Antibacterial properties of capsaicin and its derivatives and their potential to fight antibiotic resistance-A literature survey. European Journal of Microbiology and Immunology (Bp). 2021;**11**(1):10-17

[12] Alibi S, Crespo D, Navas J. Plant-derivatives small molecules with antibacterial activity. Antibiotics (Basel). 2021;**10**(3):231

[13] El-Saber Batiha G et al. Traditional uses, bioactive chemical constituents, and pharmacological and toxicological activities of Glycyrrhiza glabra L. (Fabaceae). Biomolecules. 2020;**10**(3): 352

[14] Gonelimali FD et al. Antimicrobial properties and mechanism of action of some plant extracts against food pathogens and spoilage microorganisms. Frontiers in Microbiology. 2018;**9**:1639

[15] Thawabteh A et al. The biological activity of natural alkaloids against herbivores, cancerous cells and

pathogens. Toxins (Basel). 2019;**11**(11): 656

[16] Othman L, Sleiman A, Abdel-Massih RM. Antimicrobial activity of polyphenols and alkaloids in Middle Eastern plants. Frontiers in Microbiology. 2019;**10**:911

[17] Yan Y et al. Research Progress on antibacterial activities and mechanisms of natural alkaloids: A review. Antibiotics (Basel). 2021;**10**(3):318

[18] Modarresi-Chahardehi A et al. Screening antimicrobial activity of various extracts of Urtica dioica. Revista de biologia tropical. 2012;**60**(4): 1567-1576

[19] Modarresi Chahardehi A. Infectious Diseases; Along with a Set of Questions and Explanations of Key Words. Tehran, Iran: Royan Pazhouh Publication; 2023

[20] Radulovic NS et al. Antimicrobial plant metabolites: Structural diversity and mechanism of action. Current Medicinal Chemistry. 2013;**20**(7): 932-952

[21] Modarresi, Chahardehi A et al. Effects of ethyl acetate extract of Urtica dioica on Bacillus subtilis strain ATCC 6633: Structural degeneration study. In: National Postgraduate Seminar (NPS 2014). Fostering Collaborative for the Advancement of Microbiology. Malaysia: Universiti Putra Malaysia; 2014

[22] Cowan MM. Plant products as antimicrobial agents. Clinical Microbiology Reviews. 1999;**12**(4): 564-582

[23] Modarresi Chahardehi A, et al. Cytotoxicity activity of Elatostema umbellatum against cancer cell lines. In: The 2nd Annual International Conference in Conjunction with the 8th IMT-GT UNINET Bioscience Conference; Darussalam, Banda Aceh, Indonesia. Banda Aceh: Universitas Syiah Kuala; 2012

[24] Huang W et al. Biosynthesis investigations of terpenoid, alkaloid, and flavonoid antimicrobial agents derived from medicinal plants. Antibiotics. 2022; **11**(10):1380

[25] Joanna K. Chapter 1, Introductory chapter: Alkaloids-their importance in nature and for human life. In: Joanna K, editor. Alkaloids. Rijeka: IntechOpen; 2019

[26] Ti H et al. Progress of plant medicine derived extracts and alkaloids on modulating viral infections and inflammation. Drug Design, Development and Therapy. 2021;**15**: 1385-1408

[27] Zhao Y et al. Antimicrobial effects of chemical compounds isolated from traditional Chinese herbal medicine (TCHM) against drug-resistant bacteria: A review paper. Mini Reviews in Medicinal Chemistry. 2019;**19**(2): 125-137

[28] Hashemi A et al. Antibacterial effects of methanolic extracts of Zataria multiflora, Myrtus communis and Peganum harmala on Pseudomonas aeruginosa producing ESBL. Journal of Arak University of Medical Sciences. 2011;**14**(4):104-112

[29] Khameneh B et al. Review on plant antimicrobials: A mechanistic viewpoint. Antimicrobial Resistance & Infection Control. 2019;**8**(1):118

[30] Betoni JE et al. Synergism between plant extract and antimicrobial drugs used on Staphylococcus aureus diseases. Memórias do Instituto Oswaldo Cruz. 2006;**101**(4):387-390

[31] Evans SM, Cowan MM. Plant products as antimicrobial agents. In: Cosmetic and Drug Microbiology. U.S.A.: CRC Press; 2016. pp. 227-254

[32] Barati M et al. Anti-leishmanial activity of Gossypium hirsutum L., Ferula assa-foetida L. and Artemisia aucheri Boiss. Extracts by colorimetric assay. Anti-Infective Agents. 2014;**12**(2): 159-164

[33] Chahardehi AM et al. Baja citotoxicidad, y actividad antiproliferativa sobre las celulas cancerosas, de la planta Senna alata (Fabaceae). Revista de Biología Tropical. 2021;**69**(1):317-331

[34] Ghaffari H et al. Inhibition of herpes simplex virus type 1 infection by Sambucus ebulus extract in vitro. Medical Journal of the Islamic Republic of Iran. 2021;**35**:9

[35] Aniszewski T. Chapter 1-definition, typology, and occurrence of alkaloids. In: Aniszewski T, editor. Alkaloids. 2nd ed. Boston: Elsevier; 2015. pp. 1-97

[36] Dey P et al. Analysis of alkaloids (indole alkaloids, isoquinoline alkaloids, tropane alkaloids). Recent Advances in Natural Products Analysis. 2020;**2020**: 505-567. DOI: 10.1016/B978-0-12-816455-6.00015-9

[37] Matsuura HN, Fett-Neto AG. Plant alkaloids: Main features, toxicity, and mechanisms of action. In: Gopalakrishnakone P, Carlini CR, Ligabue-Braun R, editors. Plant Toxins. Dordrecht: Springer Netherlands; 2015. pp. 1-15

[38] Yu X et al. An innovative extraction strategy for herbal medicine by adopting p-sulphonatocalix[6]/[8]arenes. Phytochemical Analysis. 2022;**33**(7): 1068-1085

[39] Li M et al. Simple quantitative analytical methods for the determination of alkaloids from medicinal and edible plant foods using a homemade chromatographic monolithic column. Journal of Chromatography. B, Analytical Technologies in the Biomedical and Life Sciences. 2019;**1128**: 121784

[40] Huang X et al. Self-assemblies based on traditional medicine berberine and cinnamic acid for adhesion-induced inhibition multidrug-resistant Staphylococcus aureus. ACS Applied Materials & Interfaces. 2019;**12**(1): 227-237

[41] Schenck CA, Maeda HA. Tyrosine biosynthesis, metabolism, and catabolism in plants. Phytochemistry. 2018;**149**:82-102

[42] Szántay C, Dörnyei G, Blaskó G. Chapter 2 the morphine alkaloids. In: Cordell GA, Brossi A, editors. The Alkaloids: Chemistry and Pharmacology. Maryland, U.S.A.: National Institutes of Health Bethesda; Academic Press; 1994. pp. 127-232

[43] Ding Y et al. Phytochemical and biological investigations of Amaryllidaceae alkaloids: A review. Journal of Asian Natural Products Research. 2017;**19**(1):53-100

[44] Omar F et al. Plant-based indole alkaloids: A comprehensive overview from a pharmacological perspective. Molecules. 2021;**26**(8):2297

[45] Pedras MSC et al. The phytoalexins from cauliflower, caulilexins A, B and C: Isolation, structure determination, syntheses and antifungal activity. Phytochemistry. 2006;**67**(14):1503-1509

[46] Jimenez LD, Ayer WA, Tewari JP. Phytoalexins produced in the leaves of

Capsella bursa-pastoris (shepherd's purse). Phytoprotection. 1997;**78**(3): 99-103

[47] Maynart G et al. Antibacterial effect of borreverine, an alkaloid isolated from Borreria verticillata (Rubiaceae). Comptes Rendus des Seances de la Societe de Biologie et de Ses Filiales. 1980;**174**(5):925-928

[48] O'Donnell G, Gibbons S. Antibacterial activity of two canthin-6-one alkaloids from Allium neapolitanum. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2007;**21**(7):653-657

[49] Su X-L et al. Three new quinazolines from Evodia rutaecarpa and their biological activity. Fitoterapia. 2018;**127**: 186-192

[50] Bhattacharyya P, Chakrabartty P, Chowdhury B. Glycozolidol, an antibacterial carbazole alkaloid from Glycosmis pentaphylla. Phytochemistry. 1985;**24**(4):882-883

[51] Rahman MM, Gray AI. A benzoisofuranone derivative and carbazole alkaloids from Murraya koenigii and their antimicrobial activity. Phytochemistry. 2005;**66**(13):1601-1606

[52] Aassila H et al. Identification of harman as the antibiotic compound produced by a tunicate-associated bacterium. Marine Biotechnology. 2003; **5**:163-166

[53] Cruz KS et al. Screening and antifungal activity of a β-Carboline derivative against Cryptococcus neoformans and C. gattii. International Journal of Microbiology. 2019;**2019**: 7157845

[54] Joshi T et al. Pyranocarbazoles from Murraya koenigii (L.) Spreng. as antimicrobial agents. Natural Product Research. 2018;**32**(4):430-434

[55] Wang W, Cheng MH, Wang XH. Monoterpenoid indole alkaloids from Alstonia rupestris with cytotoxic, anti-inflammatory and antifungal activities. Molecules. 2013;**18**(6):7309-7322

[56] Xu S, Bian R, Chen X. Methods of Pharmacology Experiment. Beijing, China: People's Sanitation Press; 2003. pp. 1651-1653

[57] Yu HF et al. Nepenthe-like indole alkaloids with antimicrobial activity from Ervatamia chinensis. Organic Letters. 2018;**20**(13):4116-4120

[58] Cheng GG et al. Bioactive monoterpenoid indole alkaloids with diverse skeletons from Melodinus khasianus. Journal of Natural Products. 2016;**79**(9):2158-2166

[59] Singh B, Sharma RA, Vyas GK. Antimicrobial, antineoplastic and cytotoxic activities of indole alkaloids from Tabernaemontana divaricata (L.) R. Br. Current Pharmaceutical Analysis. 2011;**7**(2):125-132

[60] Karaket N et al. Chemical and bioactivity evaluation of the bark of Neonauclea purpurea. Natural Product Communications. 2012;**7**(2):169-170

[61] Qin X-J et al. Indole alkaloids with antibacterial activity from aqueous fraction of Alstonia scholaris. Tetrahedron. 2015;**71**(25):4372-4378

[62] Kawakami J et al. Antibacterial and antifungal activities of tryptanthrin derivatives. Transactions of the Materials Research Society of Japan. 2011;**36**(4):603-606

[63] Atta ur, R., et al., Antifungal diterpenoid alkaloids from Delphinium

denudatum. Journal of Natural Products. 1997;**60**(5):472-474

[64] Hao Y et al. Discovery of tryptanthrins as novel antiviral and anti-phytopathogenic-fungus agents. Journal of Agricultural and Food Chemistry. 2020;**68**(20):5586-5595

[65] Wu JY et al. Topoisomerase I inhibitor evodiamine acts as an antibacterial agent against drug-resistant Klebsiella pneumoniae. Planta Medica. 2013;**79**(1):27-29

[66] Wang J et al. Natural phenolic derivatives based on piperine scaffold as potential antifungal agents. BMC Chem. 2020;**14**(1):24

[67] Silva Teles MMR et al. Alkaloids of the Lauraceae. The Alkaloids. Chemistry and Biology. 2019;**82**:147-304

[68] Xin Z et al. Isolation of antofine from Cynanchum atratum BUNGE (Asclepiadaceae) and its antifungal activity against Penicillium digitatum. Postharvest Biology and Technology. 2019;**157**:110961

[69] Peng L et al. Antibacterial activity and mechanism of berberine against Streptococcus agalactiae. International Journal of Clinical and Experimental Pathology. 2015;**8**(5):5217-5223

[70] Mensah JL et al. Antibacterial activity of the leaves of Phyllanthus discoid us. Journal of Ethnopharmacology. 1990; **28**(1):129-133

[71] Singh AK, Pandey MB, Singh UP. Antifungal activity of an alkaloid Allosecurinine against some fungi. Mycobiology. 2007;**35**(2):62-64

[72] Adeleye A, Ikotun T. Antifungal activity of dihydrodioscorine extracted from a wild variety of Dioscorea bulbifera L. Journal of Basic Microbiology. 1989;**29**(5):265-267

[73] Laluces HMC et al. Antimicrobial alkaloids from the leaves of Pandanus amaryllifolius. Journal of Applied Pharmaceutical Science. 2015;**5**(10): 151-153

[74] Bibi N et al. In vitro antituberculosis activities of the constituents isolated from Haloxylon salicornicum. Bioorganic & Medicinal Chemistry Letters. 2010;**20**(14):4173-4176

[75] Kim MG et al. Antimicrobial potentials of active component isolated from Citrullus colocynthis fruits and structure-activity relationships of its analogues against foodborne bacteria. Journal of the Science of Food and Agriculture. 2014;**94**(12):2529-2533

[76] Aguinaldo AM et al. Quinoline alkaloids from Lunasia amara inhibit Mycobacterium tuberculosis H37Rv in vitro. International Journal of Antimicrobial Agents. 2007;**29**(6): 744-746

[77] Tantapakul C et al. Antibacterial compounds from Glycosmis puberula twigs. Natural Product Communications. 2014;**9**(12):1705-1707

[78] Pandey MB et al. Inhibitive effect of Fuyuziphine isolated from plant (Pittapapra) (Fumaria indica) on spore germination of some fungi. Mycobiology. 2007;**35**(3):157-158

[79] Zhang H et al. Synergistic anti-candidal activity of tetrandrine on ketoconazole: An experimental study. Planta Medica. 2010;**76**(1):53-61

[80] Sureram S et al. Antimycobacterial activity of bisbenzylisoquinoline alkaloids from Tiliacora triandra against multidrug-resistant isolates of

Mycobacterium tuberculosis. Bioorganic & Medicinal Chemistry Letters. 2012; **22**(8):2902-2905

[81] Singh K et al. Tiliacorinine, a new systemic fungicide effective against Alternaria blight of pigeon pea (Cajanus cajan)/Tiliacorinine, ein neues systemisches Fungizid mit Wirkung gegen die Alternaria-Blattfleckenkrankheit an Taubenerbsen (Cajanus cajan). Zeitschrift für Pflanzenkrankheiten und Pflanzenschutz/Journal of Plant Diseases and Protection. 1991;**98**(2):213-219

[82] Rahman MM et al. Antibacterial and cytotoxic compounds from the bark of Cananga odorata. Fitoterapia. 2005; **76**(7–8):758-761

[83] Paulo Mde Q et al. Antimicrobial activity of benzylisoquinoline alkaloids from Annona salzmanii D.C. Journal of Ethnopharmacology. 1992; **36**(1):39-41

[84] Tan KK et al. Antibacterial alkaloids from Artabotrys crassifolius Hook.f. & Thomson. Natural Product Research. 2015;**29**(24):2346-2349

[85] Agarwal AK et al. Role of heme in the antifungal activity of the azaoxoaporphine alkaloid sampangine. Eukaryotic Cell. 2008;**7**(2):387-400

[86] Khan M, Kihara M, Omoloso A. Antimicrobial activity of the alkaloidal constituents of the root bark of Eupomatia laurina. Pharmaceutical Biology. 2003;**41**(4):277-280

[87] Lekphrom R, Kanokmedhakul S, Kanokmedhakul K. Bioactive styryllactones and alkaloid from flowers of Goniothalamus laoticus. Journal of Ethnopharmacology. 2009;**125**(1): 47-50

[88] Camacho-Corona MdR et al. Evaluation of some plant-derived secondary metabolites against sensitive and multidrug-resistant Mycobacterium tuberculosis. Journal of the Mexican Chemical Society. 2009;**53**(2):71-75

[89] Makarasen A et al. Cytotoxic and antimicrobial activities of aporphine alkaloids isolated from Stephania venosa (Blume) Spreng. Planta Medica. 2011; **77**(13):1519-1524

[90] Orhana I et al. Antiviral and antimicrobial profiles of selected isoquinoline alkaloids from Fumaria and Corydalis species. Zeitschrift fur Naturforschung-Section C Journal of Biosciences. 2007;**62**(1–2):19-26

[91] Ma C et al. Potent activities of Roemerine against Candida albicans and the underlying mechanisms. Molecules. 2015;**20**(10):17913-17928

[92] Agnihotri VK et al. Constituents of Nelumbo nucifera leaves and their antimalarial and antifungal activity. Phytochemistry Letters. 2008;**1**(2):89-93

[93] Kim J et al. Antifungal activity of magnoflorine against Candida strains. World Journal of Microbiology and Biotechnology. 2018;**34**(11):167

[94] Kosina P et al. Phytochemical and antimicrobial characterization of Macleaya cordata herb. Fitoterapia. 2010;**81**(8):1006-1012

[95] Faizi S et al. New antimicrobial alkaloids from the roots of Polyalthia longifolia var. pendula. Planta Medica. 2003;**69**(4):350-355

[96] Choi JG et al. Antibacterial activity of Hylomecon hylomeconoides against methicillin-resistant Staphylococcus aureus. Applied Biochemistry and Biotechnology. 2010;**160**(8):2467-2474

[97] Xue X et al. TLC bioautography-guided isolation and antimicrobial, antifungal effects of 12 alkaloids from Hylomecon japonica roots§. Natural Product Communications. 2017;**12**(9): 1439-1442

[98] Tavares Lde C et al. Structure-activity relationship of benzophenanthridine alkaloids from Zanthoxylum rhoifolium having antimicrobial activity. PLoS One. 2014; **9**(5):e97000

[99] Zuo GY et al. Synergistic antibacterial and antibiotic effects of bisbenzylisoquinoline alkaloids on clinical isolates of methicillin-resistant Staphylococcus aureus (MRSA). Molecules. 2011;**16**(12):9819-9826

[100] Guang Ma W, Fukushi Y, Tahara S. Fungitoxic alkaloids from Hokkaido corydalis species. Fitoterapia. 1999; **70**(3):258-265

[101] Phatchana R, Yenjai C. Cytotoxic coumarins from Toddalia asiatica. Planta Medica. 2014;**80**(8–9):719-722

[102] Hu J et al. Alkaloids from Toddalia asiatica and their cytotoxic, antimicrobial and antifungal activities. Food Chemistry. 2014;**148**:437-444

[103] Gu JQ et al. Cytotoxic and antimicrobial constituents of the bark of Diospyros maritima collected in two geographical locations in Indonesia. Journal of Natural Products. 2004;**67**(7): 1156-1161

[104] Semwal DK et al. The genus Stephania (Menispermaceae): Chemical and pharmacological perspectives. Journal of Ethnopharmacology. 2010; **132**(2):369-383

[105] Adesanya SA et al. Stilbene derivatives from Cissus quadrangularis. Journal of Natural Products. 1999; **62**(12):1694-1695

[106] Shen JW et al. Lycorine: A potential broad-spectrum agent against crop pathogenic fungi. Journal of Microbiology and Biotechnology. 2014; **24**(3):354-358

[107] Pettit GR, Melody N, Herald DL. Antineoplastic agents. 450. Synthesis of (+)-pancratistatin from (+)-narciclasine as relay(1a). The Journal of Organic Chemistry. 2001;**66**(8):2583-2587

[108] Nair JJ, van Staden J. Antifungal constituents of the plant family Amaryllidaceae. Phytotherapy Research. 2018;**32**(6):976-984

[109] Liang C et al. Broad-spectrum antifungal activity of dichloromethane extract of Waltheria indica stems and isolated compounds. Industrial Crops and Products. 2019;**142**:111855

[110] Adams M et al. Cytotoxicity and p-glycoprotein modulating effects of quinolones and indoloquinazolines from the Chinese herb Evodia rutaecarpa. Planta Medica. 2007;**73**(15):1554-1557

[111] Suliman Mohamed M et al. Activity of Aristolochia bracteolata against Moraxella catarrhalis. International Journal of Bacteriology. 2014;**2014**:481686

[112] Zeng YB et al. Antimicrobial glycoalkaloids from the tubers of Stephania succifera. Archives of Pharmacal Research. 2017;**40**(4): 429-434

[113] Tuntiwachwuttikul P et al. Chemical constituents of the roots of Piper sarmentosum. Chem Pharm Bull (Tokyo). 2006;**54**(2):149-151

[114] Shi YN et al. Antifungal amide alkaloids from the aerial parts of Piper

flaviflorum and Piper sarmentosum. Planta Medica. 2017;**83**(1–02):143-150

[115] Zhou LN et al. Antibacterial steroidal alkaloids from Holarrhena antidysenteriaca. Chinese Journal of Natural Medicines. 2017;**15**(7):540-545

[116] de Lourdes FD et al. Chapter 9-Biological activity and 13C NMR spectral data of iboga-type skeleton alkaloids. In: Atta ur R, editor. Studies in Natural Products Chemistry. Vol. 72. Karachi, Pakistan: Center for Molecular Medicine and Drug Research University of Karachi, Elsevier; 2022. pp. 287-369

[117] Kirpotina LN et al. Therapeutic effects of Tryptanthrin and Tryptanthrin-6-Oxime in models of rheumatoid arthritis. Frontiers in Pharmacology. 2020;**11**

[118] Morris JS, Facchini PJ. Isolation and characterization of reticuline N-methyltransferase involved in biosynthesis of the aporphine alkaloid magnoflorine in opium poppy. The Journal of Biological Chemistry. 2016; **291**(45):23416-23427

[119] Warowicka A, Nawrot R, Goździcka-Józefiak A. Antiviral activity of berberine. Archives of Virology. 2020; **165**(9):1935-1945

[120] Sack RB, Froehlich JL. Berberine inhibits intestinal secretory response of Vibrio cholerae and Escherichia coli enterotoxins. Infection and Immunity. 1982;**35**(2):471-475

[121] Wang D et al. Global transcriptional profiles of Staphylococcus aureus treated with berberine chloride. FEMS Microbiology Letters. 2008;**279**(2): 217-225

[122] Guzman JD. Natural cinnamic acids, synthetic derivatives and hybrids with antimicrobial activity. Molecules. 2014;**19**(12):19292-19349

[123] Sun D, Courtney HS, Beachey EH. Berberine sulfate blocks adherence of Streptococcus pyogenes to epithelial cells, fibronectin, and hexadecane. Antimicrobial Agents and Chemotherapy. 1988;**32**(9):1370-1374

[124] Ibrahim SA et al. Application of caffeine, 1,3,7-trimethylxanthine, to control Escherichia coli O157:H7. Food Chemistry. 2006;**99**(4):645-650

[125] Almeida AAP et al. Antibacterial activity of coffee extracts and selected coffee chemical compounds against Enterobacteria. Journal of Agricultural and Food Chemistry. 2006;**54**(23): 8738-8743

[126] Wang X et al. Synthesis of amide derivatives containing capsaicin and their antioxidant and antibacterial activities. Journal of Food Biochemistry. 2019;**43**(12):e13061

[127] Cichewicz RH, Thorpe PA. The antimicrobial properties of Chile peppers (capsicum species) and their uses in Mayan medicine. Journal of Ethnopharmacology. 1996;**52**(2):61-70

[128] Dhyani P et al. Anticancer potential of alkaloids: A key emphasis to colchicine, vinblastine, vincristine, vindesine, vinorelbine and vincamine. Cancer Cell International. 2022;**22**(1): 206

[129] Leete E, Nemeth PE. The biogenesis of the alkaloids of colchicum. I. The incorporation of phenylalanine into colchicine1. Journal of the American Chemical Society. 1960;**82**(23): 6055-6057

[130] Huczyński A et al. Synthesis, antiproliferative and antibacterial

evaluation of C-ring modified colchicine analogues. European Journal of Medicinal Chemistry. 2015;**90**:296-301

[131] Golpour M et al. The effectiveness of colchicine as an anti-inflammatory drug in the treatment of coronavirus disease 2019: Meta-analysis. International Journal of Immunopathology and Pharmacology. 2021;**35**

[132] Haq IU et al. Piperine: A review of its biological effects. Phytotherapy Research. 2021;**35**(2):680-700

[133] Atal CK, Dubey RK, Singh J. Biochemical basis of enhanced drug bioavailability by piperine: Evidence that piperine is a potent inhibitor of drug metabolism. The Journal of Pharmacology and Experimental Therapeutics. 1985;**232**(1):258-262

[134] Derosa G, Maffioli P, Sahebkar A. Piperine and its role in chronic diseases. Advances in Experimental Medicine and Biology. 2016;**928**:173-184

[135] Khan IA et al. Piperine, a phytochemical potentiator of ciprofloxacin against Staphylococcus aureus. Antimicrobial Agents and Chemotherapy. 2006;**50**(2):810-812

[136] Parai D et al. Reserpine attenuates biofilm formation and virulence of Staphylococcus aureus. Microbial Pathogenesis. 2020;**138**:103790

[137] Begum S et al. Antimycobacterial and antioxidant activities of reserpine and its derivatives. Natural Product Research. 2012;**26**(22):2084-2088

[138] Shaheen A et al. Reserpine is the new addition into the repertoire of AcrB efflux pump inhibitors. Molekuliarnaia Biologiia (Mosk). 2019;**53**(4): 674-684

[139] Silva-Beltrán NP et al. Total phenolic, flavonoid, tomatine, and tomatidine contents and antioxidant and antimicrobial activities of extracts of tomato plant. International Journal of Analytical Chemistry. 2015;**2015**:284071

[140] Mitchell G et al. Tomatidine inhibits replication of Staphylococcus aureus small-colony variants in cystic fibrosis airway epithelial cells. Antimicrobial Agents and Chemotherapy. 2011;**55**(5):1937-1945

[141] Siriyong T, Voravuthikunchai SP, Coote PJ. Steroidal alkaloids and conessine from the medicinal plant Holarrhena antidysenterica restore antibiotic efficacy in a Galleria mellonella model of multidrug-resistant Pseudomonas aeruginosa infection. BMC Complementary and Alternative Medicine. 2018;**18**(1):285

[142] Siriyong T et al. Holarrhena antidysenterica extract and its steroidal alkaloid, conessine, as resistance-modifying agents against extensively drug-resistant Acinetobacter baumannii. Microbial Drug Resistance. 2016;**22**(4): 273-282

[143] Wei WJ et al. A review on classification and biological activities of alkaloids from the genus Zanthoxylum species. Mini Reviews in Medicinal Chemistry. 2021;**21**(3):336-361

[144] Farouk A, Nawi M, Hassan S. Antibacterial peptides from Euycoma longifolia (Tongkat Ali) and Labisia pumila (Kacip Fatimah) leaves in Malaysia. Science Brun. 2008;**9**: 55-63

[145] Oliva A et al. Natural fungicides from Ruta graveolens L. leaves, including a new quinolone alkaloid. Journal of Agricultural and Food Chemistry. 2003;**51**(4):890-896

[146] Cretton S et al. Antifungal quinoline alkaloids from Waltheria indica. Journal of Natural Products. 2016;**79**(2):300-307

[147] Akinpelu DA et al. Evaluation of antibacterial and antifungal properties of Alchornea laxiflora (Benth.) Pax. & Hoffman. Evidence-based Complementary and Alternative Medicine. 2015;**2015**:684839

[148] Evidente A et al. (−)-Amarbellisine, a lycorine-type alkaloid from Amaryllis belladonna L. growing in Egypt. Phytochemistry. 2004;**65**(14): 2113-2118

[149] Semwal DK, Semwal RB. Efficacy and safety of Stephania glabra: An alkaloid-rich traditional medicinal plant. Natural Product Research. 2015;**29**(5): 396-410

[150] Asano N et al. N-containing sugars from Morus alba and their glycosidase inhibitory activities. Carbohydrate Research. 1994;**259**(2): 243-255

[151] Sultana S et al. Antimicrobial, cytotoxic and antioxidant activity of methanolic extract of Glycyrrhiza glabra. Agriculture and Biology Journal of North America. 2010;**1**(5):957-960

[152] Al-Matani SK, Al-Wahaibi RNS, Hossain MA. Total flavonoids content and antimicrobial activity of crude extract from leaves of Ficus sycomorus native to Sultanate of Oman. Karbala International Journal of Modern Science. 2015;**1**(3):166-171

[153] Rao KN, Venkatachalam SR. Inhibition of dihydrofolate reductase and cell growth activity by the phenanthroindolizidine alkaloids pergularinine and tylophorinidine: The in vitro cytotoxicity of these plant alkaloids and their potential as antimicrobial and anticancer agents. Toxicology In Vitro. 2000;**14**(1):53-59

[154] Erdemoglu N, Ozkan S, Tosun F. Alkaloid profile and antimicrobial activity of Lupinus angustifolius L. alkaloid extract. Phytochemistry Reviews. 2007;**6**(1):197-201

[155] Darabpour E et al. Antibacterial activity of different parts of Peganum harmala L. growing in Iran against multi-drug resistant bacteria. EXCLI Journal. 2011;**10**:252-263

[156] Perveen K, Bokhari NA, Soliman DA. Antibacterial activity of Phoenix dactylifera L. leaf and pit extracts against selected Gram negative and Gram positive pathogenic bacteria. Journal of Medicinal Plants Research. 2012;**6**(2):296-300

[157] Wang W et al. In vitro antioxidant, antimicrobial and anti-herpes simplex virus type 1 activity of Phellodendron amurense Rupr. From China. The American Journal of Chinese Medicine. 2009;**37**(1):195-203

[158] Rahayu I, Timotius KH, Analysis P. Antimutagenic and antiviral activity of Moringa oleifera L. leaf infusion: In vitro and in silico studies. Molecules. 2022;**27** (13):4017

[159] Weiss S et al. In vitro and in vivo therapeutic potential of 6,6'-Dihydroxythiobinupharidine (DTBN) from Nuphar lutea on cells and K18-hACE2 mice infected with SARS-CoV-2. International Journal of Molecular Sciences. 2023;**24**(9):8327

[160] Elizondo-Luévano JH et al. Berberine: A nematocidal alkaloid from Argemone mexicana against Strongyloides venezuelensis.

Experimental Parasitology. 2021;**220**: 108043

[161] Agbaje EO, Onabanjo AO. Toxicological study of the extracts of anti-malarial medicinal plant Enantia chlorantha. The Central African Journal of Medicine. 1994;**40**(3):71-73

[162] Hagel JM, Facchini PJ. Benzylisoquinoline alkaloid metabolism: A century of discovery and a brave new world. Plant & Cell Physiology. 2013; **54**(5):647-672

[163] Arai M et al. Identification of the target protein of agelasine D, a marine sponge diterpene alkaloid, as an anti-dormant mycobacterial substance. Chembiochem. 2014;**15**(1):117-123

[164] Luo Y et al. Berberine prevents non-alcoholic steatohepatitis-derived hepatocellular carcinoma by inhibiting inflammation and angiogenesis in mice. American Journal of Translational Research. 2019;**11**(5): 2668-2682

[165] Brahma U et al. Antimicrobial and anti-biofilm activity of hexadentated macrocyclic complex of copper (II) derived from thiosemicarbazide against Staphylococcus aureus. Scientific Reports. 2018;**8**(1):8050

[166] Chen C et al. Inhibitory effect of 7-Demethoxytylophorine on Penicillium italicum and its possible mechanism. Microorganisms. 2019;**7**(2):36

[167] Kuete V et al. Antimycobacterial, antibacterial and antifungal activities of the methanol extract and compounds from Thecacoris annobonae (Euphorbiaceae). South African Journal of Botany. 2010;**76**(3):536-542

[168] Kang S et al. The antibacterial mechanism of berberine against Actinobacillus pleuropneumoniae. Natural Product Research. 2015;**29**(23): 2203-2206

[169] Tominaga K et al. In vivo action of novel alkyl methyl quinolone alkaloids against Helicobacter pylori. The Journal of Antimicrobial Chemotherapy. 2002; **50**(4):547-552

[170] Yang J, Tauschek M, Robins-Browne RM. Control of bacterial virulence by AraC-like regulators that respond to chemical signals. Trends in Microbiology. 2011;**19**(3):128-135