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Ethnobotany and the Role of Plant Natural Products in Antibiotic Drug Discovery

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Abstract

The crisis of antibiotic resistance necessitates creative and innovative approaches, from chemical identification and analysis to the assessment of bioactivity. Plant natural products (NPs) represent a promising source of antibacterial lead compounds that could help fill the drug discovery pipeline in response to the growing antibiotic resistance crisis. The major strength of plant NPs lies in their rich and unique chemodiversity, their worldwide distribution and ease of access, their various antibacterial modes of action, and the proven clinical effectiveness of plant extracts from which they are isolated. While many studies have tried to summarize NPs with antibacterial activities, a comprehensive review with rigorous selection criteria has never been performed. In this work, the literature from 2012 to 2019 was systematically reviewed to highlight plant-derived compounds with antibacterial activity by focusing on their growth inhibitory activity. A total of 459 compounds were included in this review, of which 50.8% were phenolic derivatives, 26.6% were terpenoids, 5.7% were alkaloids, and 17% were classified as other metabolites. A selection of 183 compounds were further discussed regarding their antibacterial activity, biosynthesis, structure-activity relationship, mechanism of action, and their potential as antibiotics. Emerging trends in the field of antibacterial drug discovery from plants are also discussed. This review brings to the forefront key findings on the antibacterial potential of plant NPs for consideration in future antibiotic discovery and development efforts.

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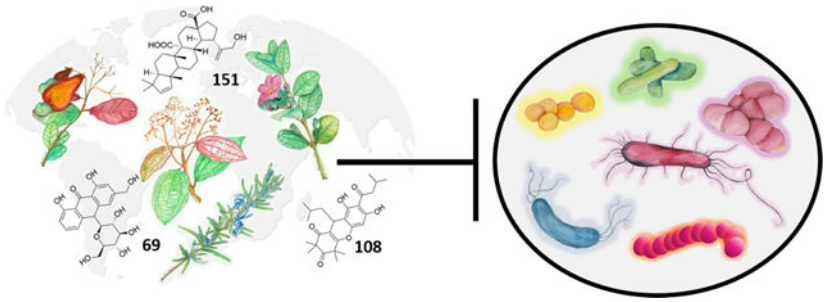
Supporting Information

Supporting Information File on antibacterial compounds: chemical class, compound name, SMILES, MICs, plant source, and references.

Graphical Abstract



1. Introduction

The ability to successfully treat infectious diseases is threatened due to the rise of antimicrobial resistance (AMR). According to the Centers for Disease Control and Prevention (CDC), about 2.9 million antibiotic-resistant infections occur in the United States each year, resulting in 35,900 deaths.[1] The CDC lists sixteen bacteria and two fungi as urgent, serious or concerning threats, including *Mycobacterium tuberculosis*, of which there are extensively drug-resistant strains, resistant to two of four first-line antibiotics and at least one of the three second-line antibiotics.[2]

Several factors are involved in the rise of antibiotic resistance, especially the overuse and misuse of antibiotics in human and animal health and the lack of development of new antibiotics. The field of antibiotic discovery and development is in dire need of innovation in order to reinvigorate the pipeline that has not seen a new class of drugs discovered and approved by the FDA since the late 1980s.[3] This status quo can be in large part explained by the economics of antibiotics post-approval, which has become so unfavorable to companies and investors that antibiotic start-ups and large pharmaceutical companies alike are unable to survive in the antibiotics development space.[4]

In the search for novel antibiotics, the screening of synthetic combinatorial compound libraries has failed to meet expectations and has consequently demonstrated the importance of exploring the biologically relevant chemical space.[5,6] Compounds that occupy this space in chemistry are already able, unlike the majority of synthetic compounds, to interact with biological machinery and potentially act as drugs.[7] Natural products (NPs) have a strong tendency to occupy this space, in part due to their core purpose of interacting with biological systems and their vast range of chemical and structural diversity that reach complexities above what many synthetic compound libraries possess.[5]

Historically, the discovery of penicillin by Alexander Fleming in the 1920s was made from a culture of the fungus *Penicillium notatum*.[8] To date, of the 162 antibacterial agents approved by the U.S. Food and Drug Administration from 1981 to 2019, about 50% are from or derived from NPs.[9] Almost all of these have a microbial source rather than a plant source in part due to former limited accessibility of plant natural products for drug discovery.[10] The more recent improvement in accessibility of plant NPs is due to enhanced compatibility with

high throughput screening (HTS) and advances in lead optimization, compound isolation, dereplication, and plant sample acquisition.[5,7,11,12]

Plants are particularly interesting as sources for antibiotic leads because they have developed complex defense mechanisms against microbes, such as the use of chemical defenses involving a wide range of structurally unique secondary metabolites.[13] Plants also possess other distinctive features promising for drug discovery, including their rich chemodiversity across the approximately 374,000 species of plants worldwide,[14] the proven clinical effectiveness of plant extracts in long-standing traditional medicinal practices across the world,[15] their ease of access, and the potential for synergistic interactions between phytochemicals and other bioactive compounds.[16]

Ethnobotany is the scientific study of the interactions between humankind and the plant kingdom; it has also been defined as the science of survival.[17] The field encompasses studies on how humans use plants for food, medicine, art, construction, music, ritual, and more. The history of medicine is rich in records of plants used to treat myriad ailments, including infectious diseases. Today, between 70–95% of people in the developing world continue to rely on plants for their primary pharmacopeia.[18] According to the Medicinal Plant Names Services (MPNS), 28,187 species are used in medicine, representing nearly 7.5% of all plant life on Earth.[19] Through focusing on those species already in use in traditional therapies for the treatment of infectious disease, a more targeted approach to identifying plant NPs with antibacterial properties can be achieved; this is known as the ethnobotanical approach to drug discovery.

Plant NPs can act as antibacterials through various modes of action. All antibiotics currently in the clinic work by inhibiting bacterial growth, either in a bactericidal or bacteriostatic fashion, and this is achieved by drug-mediated perturbation of an essential cellular process. One of the main drawbacks of growth inhibition is the inevitable selection for resistance due to the rapid evolution of the bacterial genome under selective pressure on essential cellular processes.[20] Given the threat of antibiotic resistance, a growing body of research is focused on the development of drugs that target bacterial virulence, a non-essential cellular process. Antivirulence drug candidates target systems such as biofilm formation and quorum sensing, potentially exerting less selective pressure for resistance and less detrimental effects on commensal microbes.[21] The potential of plant compounds to exert such antivirulence activities is covered in an exhaustive review by Silva et al.[22] Also, of note, the engineering of natural products by synthetic chemistry was explored in depth by Rossiter et al.[23]

1.1 Scope and Terminology

We discuss the growth inhibitory activity of plants and define antimicrobials here as an agent that kills or limits the growth of microorganisms (bacteria, fungi, parasites, viruses). We specifically use the terms ‘antibacterial’ or ‘antibiotics’ when describing agents that kill or inhibit the growth of bacteria. We focused on plant-derived compounds with an emphasis on the minimum inhibitory concentration (MIC) value, which is commonly used as an indicator of antibacterial potency. The minimum inhibitory concentration (MIC) is defined as the lowest concentration of an antimicrobial agent that inhibits the visible growth of a microorganism in vitro.[24] To provide a comprehensive analysis on the topic, we performed a

thorough literature review by using electronic databases (Web of Science, PubMed, SciFinder) and specific keywords: “plant,” “inhibitory concentration,” and “antibacterial,” covering the period between January 1, 2012 to September 3, 2019. We then used rigorous inclusion and exclusion criteria to select plant-derived compounds with significant antibacterial activity defined as MICs ≤ 100 μg/mL. In this review, we refer to the antimicrobial activity of compounds with MICs ≤ 10 μg/mL as high and MICs of 11–100 μg/mL as moderate.

All plant names were checked for accuracy with The Plant List,[25] and plant family assignments follow the Angiosperm Phylogeny Group IV guidance.[26] All reported bacterial names were cross-checked for accuracy and updated in accordance with the List of Prokaryotic names with Standing in Nomenclature.[27]

Of the 459 plant-derived compounds extracted from 198 scientific articles included, we decided to focus on the 183 compounds with the best MIC values, representing compounds of interest for further study. Finally, we discuss recent technological developments in the field of chemistry and pharmacology useful for improving the drug discovery process from plant materials.

2. Plant-Derived Compounds with Antibacterial Properties

2.1 Overview

We identified 459 botanical antibacterial compounds with a total of 1,394 MIC values reported in μg/mL (Supporting Information File 1). These were isolated from 73 plant families, 152 plant genera, and 183 different species. Data were also deposited in the Shared Platform for Antibiotic Research and Knowledge (SPARK) with Pew Charitable Trusts, accessible at https://app.collaborativedrug.com/vaults/4724/protocols. Registration for a SPARK account is free and available at http://www.pewtrusts.org/spark-antibiotic-discovery.

2.1.1 Major Chemical Classes Investigated—Antibacterial plant NPs were categorized into four major chemical classes: alkaloids, phenolic derivatives, terpenoids, and other metabolites. Of the compounds tested, 50.8% (233/459) belong to the major class phenolic derivatives. Terpenoids compromise 26.6% (122/459) of the compounds, other metabolites account for 17% (79/459) of compounds, and alkaloids account for the fewest compounds at 5.7% (26/459). The antibacterial activity data on the most active 183 compounds is presented in Table 1.

2.2 Alkaloids

Alkaloids are one of the largest groups of plant NPs, including more than 20,000 different molecules with a vast diversity of structures and routes to biosynthesis. Alkaloids are low-molecular-weight nitrogen-containing compounds and, due to the presence of a heterocyclic ring containing a nitrogen atom, are typically alkaline.[150]

Alkaloids are biosynthetically derived from amino acids such as phenylalanine, tyrosine, tryptophan, ornithine, and lysine. Building blocks from the acetate, shikimate, or deoxyxylulose phosphate pathways are also frequently incorporated into alkaloid structures.

The biogenesis of alkaloids is used for their classification, as this is directly linked to their molecular skeleton; for example, the largest groups are indole alkaloids and isoquinoline alkaloids. Other relevant groups are tropane alkaloids, steroidal alkaloids, pyridine, and pyrrolizidine alkaloids. The botanical origin of the alkaloids is also used as a classification method, e.g., *Papaver* (opium) alkaloids, *Cinchona* alkaloids, *Rauvolfia* alkaloids, and others.[151]

Alkaloids are known for their numerous pharmacological effects. They impact different metabolic systems, and their mechanism of action (MOA) may be through enzymatic alterations affecting physiological processes. Such processes include inhibition of DNA synthesis and repair mechanisms by intercalating nucleic acids.[152]

2.2.1 Overview—Isoquinolines, aporphines, and phenanthrenes represent 46.1% of the alkaloid compounds reported in this review, while quinolines represent 26.9% of alkaloid compounds and indoles represent 11.5% of alkaloid antibacterial compounds. One piperidine compound was noted amongst the antibacterial alkaloids, representing 3.8% of the class (Figure 1). Interesting antibacterial activity (<10 ug/mL)was noted among the alkaloids discussed below.

2.2.2 Quinolines—Quinoline alkaloids are important nitrogen-containing heterocyclic aromatic compounds with a broad range of bioactivities, such as antitumor, antimalarial, antibacterial, antifungal, antiparasitic and insecticidal, antiviral, anti-inflammatory, and antiplatelet activities.[153] Quinoline alkaloids occur mainly in the Rutaceae family and are biosynthetically derived from 3-hydroxyanthranilic acid, a metabolite formed from tryptophan through a sequence of enzymatic reactions. Specifically, the condensation reaction of 3-hydroxyanthranilic acid and malonyl-SCoA, followed by a cyclization, yields the quinoline alkaloids.[154] Biological activities of hundreds of quinolines have been reported, many of which are promising in terms of their potential as antibacterial agents. Some of them are described below.

8-hydroxyquinoline (**2**) is a strong metal ion chelator and represents an excellent scaffold with a broad spectrum of pharmacological applications, which include antimicrobial properties. It is one of the oldest antibacterial agents with documented antiseptic uses dating back to 1895,[155] and anti-infective uses in humans predating the age of modern antibiotics.[156] Houdkova et al.[29] investigated the growth inhibitory activity of 8-hydroxyquinoline against bacteria associated with respiratory system infections, with 8-hydroxyquinoline displaying high activity against *S. aureus* and *Haemophilus influenzae* and moderate activity against *Streptococcus pneumoniae*. Furthermore, 8-hydroxyquinoline derivatives have been identified as a major hit cluster against *Mycobacterium tuberculosis*, with more than 200 active analogues (concentration range from 0.1 to 50 μg/mL).[157] With regards to the bacterial growth inhibitory effect, Anjaneyulu et al.[158] proposed that the high lipophilicity of 8-hydroxyquinoline allows it to penetrate bacterial cell membranes in order to reach its target site of action. The charged 8-hydroxyquinoline metal complex can bind and block the metal-binding sites on bacterial enzymes, which gives rise to the antimicrobial effect; at the same time, the free ligand, having a strong chelating ability, can bind metallic cofactors of microbial enzymes thereby leading to the inhibition of bacterial enzymatic activity.[158,159]

Evocarpine (**3**), a quinolone alkaloid with a 13-carbon alkenyl chain substituent, was isolated from the fruits of *Tetradium ruticarpum* (A.Juss.) T.G.Hartley (Rutaceae); evocarpine demonstrated high activity against *S. aureus* and MRSA.[30]

Of the seven quinolines included in this review, only two (i.e., 8-hydroxyquinoline, evocarpine) showed a strong in vitro antibacterial activity (MIC ≤ 10 μg/mL) as defined by Kuete et al.[160] In vitro experiments represent the first step towards the pharmacological validation of the anti-infective properties of compounds of interest. However, in vitro assays are less clinically relevant than in vivo tests, which must be considered as a second step in the validation process to ensure the safe and effective use of plant-derived compounds. Finally, clinical trials are the last step in the process of verifying or refuting the antibacterial activity.[161] Here, only the antibacterial activity of 8-hydroxyquinoline and its derivatives have been further pursued. 8-hydroxyquinoline derivatives are perhaps the most promising antibacterial agents from the alkaloid class. Many 8-hydroxyquinoline derivatives have been developed, and some of them are already commercially available against bacterial disorders. For example, nitroxoline is used for the treatment of urinary tract infections in Europe and Asia.[162] More recently, a quinoline-based compound (bedaquiline) was approved for the treatment of multi-drug resistant tuberculosis in the U.S.[163] Future research should focus on developing safe and effective 8-hydroxyquinoline derivatives targeting multi-drug resistant bacteria, especially those considering as urgent threat by the CDC.[1]

2.2.3 Isoquinolines, Aporphines, and Phenanthrenes—Isoquinoline alkaloids constitute one of the largest groups of natural substances and are derived from phenylalanine and tyrosine; their skeleton includes an isoquinoline or a tetrahydroisoquinoline ring as a basic structural feature.[164] This group of alkaloids is not structurally homogenous. Based on different degrees of oxygenation and intramolecular rearrangements, their distribution, and the presence of additional rings connected to the main system, they may be divided into eight subgroups.[165] Isoquinolines are widely distributed among plants coming from the families Papaveraceae, Berberidaceae, Fumariaceae, Menispermaceae, Ranunculaceae, Rutaceae, and Annonaceae (in the dehydro forms). A few plant species which belong to the Magnoliaceae and Convolvulaceae are also rich in these alkaloids.[165]

Aporphine alkaloids are one subgroup of alkaloids and are characterized by the incorporation of a biphenyl system in their skeleton. They can be di-, tri-, tetra-, penta- and hexa-substituted derivatives where the substituents are hydroxyl, methoxyl, and methylenedioxy groups that can be situated over all four rings. Plants of the families Berberidaceae, Fumariaceae, Magnoliaceae, Papaveraceae, Ranunculaceae, and others are rich in these alkaloids.[166] Furthermore, aporphine alkaloids have a close relationship with phenanthrene alkaloids. The phenanthrene alkaloids are derivatives of 1-(2-aminoethyl) phenanthrene, and although they do not contain a nitrogen heterocycle, they are considered alkaloids because they are derived from aporphines (by oxidative degradation), and they occur in the same plant families.[167] Compounds belonging to this group showed the potential to be used as effective antibacterial agents and are described below.

Research by Tan et al.[31] on a chloroform extract of *Artabotrys crassifolius* Hook.f. & Thomson (Annonaceae) bark led to the isolation of three aporphine alkaloids: lysicamine

(**4**), artabotrine (**5**) and liridine (**6**). Lysicamine exhibited high activity against *L. monocytogenes* and *S. pneumoniae,* and *S. agalactiae*. Artabotrine displayed high activity against a broad array gram-positive bacteria, including *B. cereus*, *L. monocytogenes*, *Staphylococcus* sp., and *S. aureus*. They also found that liridine displayed high activity against *Bacillus subtilis*, *L. monocytogenes*, *Staphylococcus* sp., and *Streptococcus agalactiae*. All three compounds (liridine, lysicamine, and artabotrine) were highly active against extended-spectrum beta-lactamase-producing *K. pneumoniae* (ESBL-KP). Additionally, *Proteus vulgaris* growth was significantly inhibited by lysicamine and artabotrine.

Hamound et al.[32] investigated the benzophenanthridine alkaloid sanguinarine (**7**), which can be isolated from several members of the Papaveraceae family, including *Sanguinaria canadensis* L., *Macleaya cordata* (Willd.) R.Br., and *Eschscholzia californica* Cham. The authors found that the antibacterial activity of sanguinarine was strongest against gram-positive bacteria, with high activity against *Staphylococcus epidermidis* and vancomycin-resistant *Enterococcus faecalis*. Additionally, sanguinarine inhibited the growth of gram-negative bacteria with high activity against *Escherichia coli* and moderate activity against *Acinetobacter baumannii* and *Klebsiella pneumoniae*.[32] Furthermore, the authors observed synergistic activity against a panel of clinically relevant gram-positive and gram-negative strains with a drug cocktail consisting of sanguinarine, an antibiotic (streptomycin), and a chelating agent (ethylenediaminetetraacetic acid, EDTA).

Sanguinarine has been tested as an antibacterial in several clinical trials for the treatment of oral diseases such as gingivitis and periodontitis, but a number of studies found sanguinarine to have no significant benefit over the vehicle control.[168] An extract of *Sanguinaria canadensis*, with sanguinarine as the active ingredient, was formulated into Viadent® toothpaste and mouthwash,[169,170] which was later found to be associated with leukoplakia and was subsequently removed from Viadent® products.[170,171] Due to its quaternary nitrogen, polycyclic and planar structure, sanguinarine can react with nucleophilic and anionic groups of amino acids in several biomolecules, receptors, enzymes and also exhibits strong DNA intercalating activity. Sanguinarine's interaction with biological molecules and its DNA intercalating ability may be the cause of the negative effects associated with its use and lowers its appeal as a drug candidate.

Four quaternary benzylisoquinoline alkaloids, isolated from *Berberis integerrima* Bunge (Berberidaceae) roots, including berberine (**8**), jatrorhizine (**9**), columbamine (**10**), and palmatine (**12**) were investigated by Azimi et al.[33] for growth inhibition against *Brucella abortus*. This study found these compounds to all have high activity against *B. abortus*, with jatrorhizine being the most effective. Another phytochemical study reported that palmatine, isolated from *Tinospora sagittata* Gagnep (Menispermaceae), showed a bactericidal effect and high growth inhibitory activity against *Helicobacter pylori*, both in vitro and in a murine model.[36] In addition, Xie et al.[34] evaluated the antibacterial efficacy of berberine against selected endodontic pathogens using a multispecies biofilm tooth model. They found berberine to have high activity against *Prevotella intermedia* and moderate activity against *Fusobacterium nucleatum*. Additionally, in a randomized controlled clinical trial of patients

with diarrhea due to enterotoxigenic *E. coli* or *Vibrio cholerae*, berberine sulfate treatment was found to produce a significant reduction in stool volume.[172]

The antibacterial activity of berberine has been attributed to its ability to act as a hydrophobic cation that increases membrane permeability, and the positive charge on berberine facilitates its accumulation in bacterial cells, which enhances its antimicrobial activity.[33,173] Berberine was also found to inhibit the bacterial cell division protein FtsZ, with FtsZ inhibition increasing with the addition of a 9-phenoxyalkyl substituent group at the C9 position of berberine.[174] However, one of the major drawbacks of berberine is its ability to be extruded by bacterial efflux pumps (e.g., multidrug resistance pump NorA). Naturally occurring (e.g., 5′-methoxyhydnocarpin) and hybrid synthetic compounds (e.g., Berberine-INF55) have been reported to inhibit efflux pumps and thus improve the antibacterial activity of berberine.[175,176] The bioavailability of berberine in vivo was reported to be less than 1%, and many studies have focused on developing derivatives to improve berberine's bioavailability.[177,178] Although berberine seems to be safe at clinical doses, a number of drug interactions have been reported with both antagonistic and synergistic effects.[178] Berberine is a well-known drug and has promise as an antibacterial agent, but further work is needed to confirm its efficacy and improve its pharmacokinetic profile.

A SAR study examining quaternary protoberberine alkaloids revealed that growth inhibitory activity was more influenced by the type of the oxygen substituents on rings A, C, and D and especially the position of the oxygen functions on ring D.[179] Azimi et al.[33] also observed similar results; all of four isolated alkaloids showed potent antibacterial activity against *B. abortus,* but jatrorhizine and columbamine, with a free hydroxyl group on C-3 or C-2, showed stronger activity than berberine and palmatine, which have no free hydroxyl groups.[33]

Tankeo et al.[35] isolated the benzophenanthridine alkaloid, buesgenine (**11**); it is one of the main active constituents of the roots of *Zanthoxylum gilletii* (De Wild.) P.G.Waterman (Rutaceae). The authors found buesgenine to have high activity against a panel of gram-negative bacteria, including multidrug-resistant (MDR) phenotypes. Buesgenine was found to have high activity against *E. coli* and *K. pneumoniae*, and moderate activity against *Enterobacter aerogenes*, *P. aeruginosa* and *Providencia stuartii*. Additionally, buesgenine was found to be nontoxic to mouse hepatocytes.[180]

Twelve isoquinolines, aporphines, and phenanthrenes are included in our review, of which nine (artabotrine, berberine, buesgenine, columbamine, jatrorrhizine, liridine, lysicamine, palmatine, sanguinarine) showed high in vitro antibacterial activity. Although promising as lead compounds, some of them present safety concerns (e.g., palmatine, sanguinarine), have pharmacokinetic issues (e.g., berberine and palmatine have a poor intestinal absorption due their interaction with p-glycoprotein, jatrorrhizine blood distribution is limited due to its binding with human serum albumin) or are poorly studied and need further pharmacological and toxicological investigations (e.g., artabotrine, buesgenine, columbamine, liridine, lysicamine).[181–184] Despite its drawbacks, berberine is the most studied compound from this

group, and more clinical research should be performed to evaluate its potential in the treatment of multi-drug resistant bacterial infections.

2.2.4 Other Alkaloid Derivatives—A phytochemical investigation by Yu et al.[37] on the lateral roots of *Aconitum carmichaelii* Debeaux (Ranunculaceae) led to the isolation of a vakognavine-type C_{20}-diterpenoid alkaloid, carmichaedine (**13**). The authors found carmichaedine to have high antibacterial activity against *Bacillus subtilis.* Of the three other alkaloids derivatives found in our review, carmichaedine is the only one exhibiting a high in vitro antibacterial activity. This compound was discovered in 2017,[37] and no studies have yet investigated its efficacy in animal models or humans. Further research is needed to confirm its potential as an antibacterial agent.

2.3 Phenolic Derivatives

Phenolic compounds are a large class of plant secondary metabolites and are found across all plant families.[185] These secondary metabolites are formed via the shikimic or phenylpropanoid pathways.[186] The simplest phenolic, phenol, is an aromatic ring with a single hydroxyl group. Polyphenols consist of two or more of these phenolic units and show a wide diversity of structures. Phenolic compounds are associated with several plant processes, such as pigmentation, pollinator attraction, herbivory deterrence, and preventing UV tissue damage.[187] This large class of compounds has equally diverse bioactivities. To better present this chemical class, it is further subdivided in the discussion below.

2.3.1 Overview—Flavonoids made up 31.6% of phenolic derivative antibacterial compounds reported in this review. The high ranking of “other phenolic compounds”, 28.6% of all phenolic derivatives, is likely due to the large diversity of phenolic acids, simple phenols and other phenolic phytochemicals included in this group. The next most relevant chemical class was the quinones and related compounds, at 15.3%. Anthocyanins were the least represented chemical class among phenolic derivatives, at 0.9% (Figure 2A).

The Fabaceae family had the most phenolic derivatives investigated in the studies reviewed (Figure 2B). Since Fabaceae is the third-largest botanical family,[188] the number of available species for study may contribute to this high ranking. Fabaceae contains legumes, economically important food and cover crops, with an annual production of 77 million tons in 2014.[189] However, most of the top 10 species studied in this family are not major food crops, suggesting that the Fabaceae produces an array of interesting phenolics across its genera.

2.3.2 Chalcones—Chalcones are found throughout nature and share a common chemical structure, a chalconoid or 1,3-diaryl-2-propen-1-one.[190] Plants synthesize chalcones from a precursor produced by the shikimate pathway, cinnamoyl-coenzyme A (CoA) C_6C_3. This precursor is elongated by condensation of three acetate groups from malonyl-CoA catalyzed by chalcone synthase.[191] There is no general mechanism of action (MOA) for chalcones; rather chalcones have a diverse set of biological targets for their anti-cancer, anti-inflammatory, neuroprotective and anti-microbial activities.[192]

The activity of 4-hydroxylonchocarpin (**14**) and isobavachalcone (**15**), isolated from the twigs of *Dorstenia barteri* Bureau (Moraceae) and found in the twigs of many other *Dorstenia* species,[193] against MRSA and a susceptible *S. aureus* was investigated by Dzoyem et al.[38] 4-hydroxylonchocarpin and isobavachalcone were found to have high activity against *S. aureus* strains, including MRSA. The growth-inhibiting effects of 4-hydroxylonchocarpin and isobavachalcone are attributed to their ability to depolarize the cellular membrane and cause cell membrane damage. Additionally, toxicity studies using silkworms (*Bombyx mori*) found 4-hydroxylonchocarpin to be relatively safe with no signs of toxicity after 24 hours.[38]

Licochalcone A (**16**), isolated from the roots of *Glycyrrhiza inflata* Batalin (Fabaceae) and found in *Glycyrrhiza glabra* L.,[194] was found to strongly inhibit the growth of *S. aureus.*[39] Kinoshita et al. found that licochalcone A disrupts the bacterial respiratory chain by inhibiting NADH oxidase and effectively inhibited the growth of gram-positive bacteria.[195] Concomitantly, the authors found that while licochalcone A did inhibit NADH oxidase in the outer membranes of gram-negative bacteria, no growth inhibitory effect was noted. This is likely due to the inability of licochalcone A to penetrate gram-negative bacterial cells. Licochalcone A was found to be well tolerated by human liver cells and African green monkey kidney cells, with a LD_{50} of 36.6 and 26.9 μg/mL, respectively.[196] Currently, a clinical trial is studying the effects of licochalcone A in combination with decanediel, L-carnitine and salicylic acid against *Acne vulgaris* (Table 2).[197]

Xanthoangelol (**17**) was found to be most effective against *Enterococcus faecium* and *S. aureus*, with high activity against *E. faecalis*.[40] MOA studies found that xanthoangelol treatment causes perforations in the membrane of gram-positive bacteria and a loss of membrane potential leading to cell death.[199] This same study found xanthoangelol to be well tolerated with LD_{50} values of 21.5–58.8 μM against two human cell lines.[199] Kuraridin **(18)** was found to have high activity against *S. aureus*[41] and was well tolerated by human liver cells.[200]

Of the ten chalcones identified in our review, five (4-hydroxylonchocarpin, kuraridin, isobavachalcone, licochalcone A, xanthoangelol) showed high in vitro antibacterial activity, but none were examined either in vivo or in clinical trials. One of the main drawbacks of chalcones is their poor solubility leading to low oral bioavailability.[201] Isobavachalcone has also been involved in drug-drug interactions[202] and is subject to export via efflux pump mechanisms.[203] However, the toxicity of chalcones is low, which could support their development as potential antibacterial agents.[204] One chalcone-based compound, sofalcone, has already been approved in Japan for treating peptic ulcer, and this activity may partially be explained by its antibacterial effects against *H. pylori*.[205] Overall, natural or synthetic chalcones are promising antibacterial lead compounds, and future trends include molecular hybridization, combination approaches, antibacterial mechanisms study, and improvement of physicochemical properties.[206]

2.3.3 Coumarins—Coumarins are found in over 30 different plant families and 150 plant species,[207] and share a common structure of a benzene fused to an α-pyrone ring. They are found in the highest concentrations within fruits and flowers of plants and play a role in

defense against herbivory and microbial infections.[208] Plant biosynthesis of coumarins begins with the ortho-hydroxylation of cinnamic acid to produce 2-coumaric acid. The side chain undergoes a *trans-cis* isomerization from *trans* to the *cis* form, and enzyme-mediated lactone formation occurs to produce coumarin.[191]

Zuo et al.[42] investigated the activity of coumarins isolated from the roots of *Zanthoxylum nitidum* (Roxb.) DC. (Rutaceae) against the growth of susceptible and drug-resistant strains of *S. aureus*. Of the coumarins isolated, artanin (**19**), phellopterin (**20**), and 5-geranyloxy-7-methoxy-coumarin (**21**) were found to have the highest level of activity. 5-geranyloxy-7-methoxy-coumarin and artanin were the most effective, with high activity against both *S. aureus* and MRSA. Similarly, phellopterin displayed high activity against a susceptible strain of *S. aureus*, but only moderate activity against MRSA.

Twelve coumarins were reported in our review, among which four exhibited high in vitro antibacterial activity: 4′-senecioiloxyosthol, 5-geranyloxy-7-methoxy-coumarin, artanin, and phellopterin. All of these NPs are poorly studied, and further investigations are needed to ensure their safety and explore their potential for applications in humans. Of note, one coumarin-based compound: novobiocin has been isolated from *Streptomyces* species, and is used as an antibiotic (Albamycin®) in the U.S.[209]

2.3.4 Flavonoids—Flavonoids are ubiquitous polyphenolic compounds in plants and are composed of two benzene rings connected by a pyran ring. Flavonoids are versatile plant NPs known to aid in attracting pollinators and fruit dispersers by imparting color and aroma to flowers and fruits. Within plants, flavonoids also have roles as responses to stressors, phytoalexins, antimicrobials, and signaling molecules.[210] Flavonoid biosynthesis often begins with a chalcone as the precursor, after which it is enzyme-catalyzed into a variety of flavonoid derivatives.[191] The biological activity of individual flavonoids depends on their structure, which can be quite varied. A general MOA for flavonoids revolves around their ability to complex with bacterial cell walls, with highly lipophilic flavonoids also disrupting bacterial membranes.[211] Flavonoids have been found to have a wide range of therapeutic uses, such as anti-oxidant, anti-bacterial, antiviral, anti-inflammatory and anti-cancer applications.[212]

The growth inhibitory activity of two flavones, 3′,4′,7-trihydroxyflavone (**23**) and 6-prenylpinocembrin (**29**), isolated from the seeds of *Myristica fragrans* Houtt. (Myristicaceae), were investigated by Dzotam et al.[44] 3′,4′,7-trihydroxyflavone displayed high activity against *P. stuartii* and *E. coli*, with moderate activity against *K. pneumoniae*.[44] The authors also demonstrated that 6-prenylpinocembrin displayed high activity against *E. coli*, *K. pneumoniae*, and *S. aureus*; with moderate activity against *E. faecalis* and *P. aeruginosa*.[44] With regards to pharmacokinetics, Riyazuddin et al.[213] demonstrated that 3′,4′,7-trihydroxyflavone, from an extract of *Senna occidentalis* (L.) Link (Fabaceae), was eliminated from rodents after 12 hours.[213] A separate toxicity study found 6-prenylpinocembrin to be cytotoxic at 21.87 μg/mL against African green monkey kidney epithelial cells.[214] While 6-prenylpinocembrin was highly active against a wider range of bacteria, the mammalian cytotoxicity of the compound lowers its appeal as a drug lead. In

addition to being found in the Myristicaceae family, 6-prenylpinocembrin has also been found in members of the Fabaceae family, notably *Eriosema robustum* Baker.[215]

Quercetin (**25**) is a ubiquitous flavonoid found in a variety of fruits and vegetables, and it is commonly studied for its antioxidant and anticancer activity, among other applications.[216] There is speculation that quercetin, and other flavonoids, contribute to the longevity and cardiovascular health associated with the Mediterranean diet.[217] Biosynthesis of quercetin from glucose is accomplished by way of the shikimic acid pathway.[217] As an antibacterial, quercetin has shown high activity in vitro against *Streptococcus pyogenes* and moderate activity against many bacteria including *S. aureus*, *M. tuberculosis*, *P. aeruginosa*, *Aggregatibacter actinomycetemcomitans,* and *K. pneumoniae*.[47–49] A SAR study of quercetin and other flavonoids suggested that hydroxylation of the 2' position of ring B of polyhydroxyflavones is associated with increased antibacterial activity; since quercetin is unsubstituted at this position, analogues of quercetin may be more potent.[218] However, quercetin may have a larger role as a synergist with other antibacterials than as a single compound.[219] For example, combinations of quercetin and ceftazidime synergistically inhibited growth of *S. pyogenes* (fractional inhibitory concentration index, FICI = 0.27) and *S. aureus* (FICI < 0.21), with quercetin acting by inhibiting β-lactamase and increasing the permeability of the cytoplasmic membrane.[220,221]

In addition to inhibition of bacterial growth, quercetin has been found to inhibit a variety of bacterial virulence factors, including quorum sensing in *Chromobacterium violaceum* and biofilm formation and exopolysaccharide (EPS) production in *K. pneumoniae*, *P. aeruginosa*, and *Yersinia enterocolitica*; in silico analysis suggests that quercetin may achieve this activity by binding to LasR, a receptor protein associated with bacterial quorum sensing.[222] In general, the toxicity of quercetin is not a concern for humans: the average US diet includes approximately 1 g of flavonoids and 25–50 mg of quercetin per day, with high quercetin content in foods such as onions (284–486 mg/kg), kale (110 mg/kg), broccoli (30 mg/kg) and apples (21–72 mg/kg).[217] Some studies have found mutagenicity in *Salmonella* in vitro and rats in vivo, but these results are not generalizable, and the International Agency for Research on Cancer has categorized quercetin as non-carcinogenic.[216] To our knowledge, quercetin has not been tested in clinical trials for bacterial diseases, but there have been many trials of quercetin for other conditions; for example, a trial of 500 and 1000 mg/day quercetin supplements for upper respiratory tract infections found no effect overall but noted a reduction in the severity of upper respiratory tract infections for some demographics relative to the placebo treatment.[223] Quercetin's safety profile and its promising synergistic and antibacterial properties support its elevation as an antibacterial compound for further analogue development and lead optimization.

Myricetin (**26**) was isolated from the leaves of *Triclisia gilletii* (De Wild.) Staner (Menispermaceae) and investigated by Tiam et al.[50] for its bioactivity. Myricetin is found in many plant species in the families Anacardiaceae, Myricaceae, Pinaceae, Polygonaceae, and Primulaceae, particularly in fruits.[224] Myricetin was found to have high inhibitory growth activity against *Mycobacterium tuberculosis*.[50] An in vitro study by Jayaraman et al.[225] found that myricetin paired with sulfamethoxazole displayed synergistic growth inhibitory activity against three *P. aeruginosa* strains.

Pseudarflavone A (**27**), isolated from the whole plant *Pseudarthria hookeri* Wight & Arn. (Fabaceae). *P. hookeri* is traditionally used in Africa to treat pneumonia, coughing, and wounds,[226] while also being used to treat gastrointestinal disorders, such as diarrhea and stomach pain.[227] Dzoyem et al.[51] found pseudarflavone A to have high activity against *E. coli* and *S. aureus*. This same study also found pseudarflavone A to have moderate activity against *P. aeruginosa*, *K. pneumoniae,* and *E. faecalis*.[51] While the bacterial growth inhibitory properties of pseudarflavone A are promising, a cytotoxicity assay in this same study found pseudarflavone A to be cytotoxic against two cancer cell lines at low concentrations (3.59 μg/mL and 7.94 μg/mL).[51] The low therapeutic index of pseudarflavone A against these mammalian cell lines warrants further cytotoxicity studies to determine the full safety profile of pseudarflavone A.

Mbaveng et al.[52] examined the growth inhibitory activity of compounds from Cameroonian plants: the isoflavone neobavaisoflavone (**28**) isolated from the bark of *Erythrina sigmoidea* Hua (Fabaceae)[52,53]; the flavanone candidone (**32**) isolated from the rhizomes of *Echinops giganteus* A. Rich. (Asteraceae); and neocyclomorusin (**41**) isolated from the roots of *Milicia excelsa* (Welw.) C.C. Berg (Moraceae). The authors found that all three (**28, 32**, **41**) compounds displayed high activity against *E. faecalis*, *E. coli,* and *K. pneumoniae*.[52] Additionally, neobavaisoflavone and neocyclomorusin both displayed high activity against *P. stuartii* and *P. aeruginosa*.[52] Amongst the three compounds, neocyclomorusin was the only one to be highly effective against *E. aerogenes.*[52] From this same study, a SAR analysis[52] found that the antibacterial activity of neobavaisoflavone was dependent on a prenyl group and α-β-unsaturated ketone; loss of either of these two functional groups reduced the antibacterial activity of neobavaisoflavone. Concomitantly, it was found that the presence of an α,β-unsaturated double bond in candidone and a cyclic prenyl moiety in the heterocyclic portion of neocyclomorusin increased their bioactivities. While a mechanism of action is not identified in the literature, the high lipophilicity of these compounds suggests that they are complexing with targets within the bacterial membrane and compromising its integrity.

Zuo et al.[63] isolated the pyranoflavonoid cyclocommunol (**31**) and two prenylflavonoids: morusin (**37**) and kuwanon E (**40**), from the root bark of *Morus alba* L. (Moraceae). In the same study, the investigators also isolated two flavones: multicaulisin (**50**) and albanin G (**52**) and the flavanone sanggenon G (**51**). In Traditional Chinese Medicine, the root bark of *M. alba* is known as Sang-Bai-Pi and is used for treating shallow cuts, respiratory problems, and pulmonary disease.[228] Ferraria et al.[229] previously isolated and identified compounds multicaulisin and sanggenon G from *M. alba* in 2000, and multiple groups have isolated albanin G in the early 1980's.[230] Multicaulisin, albanin G, and sanggenon G were found to be highly active in inhibiting the growth of MRSA, with multicaulisin being the most effective.[63] While the MOA for multicaulisin and sanggenon G is currently unknown, albanin G is believed to work against MRSA by increasing bacterial membrane permeability and lowering the proton motor force of ATP synthesis, leading to cell death.[231]

Cyclocommunol has also been found in other species from the Moraceae family, notably within the genus *Artocarpus*.[232,233] The antibacterial activity of cyclocommunol was found to be high against a suspectable strain of *S. aureus* and a drug-resistant MRSA strain.[55] This same study found cyclocommunol to be cytotoxic against human liver cells at 27.4 μg/mL.

Kuwanon E has been found in other *Morus* species[234] and displayed high growth inhibition activity against both methicillin-sensitive *S. aureus* and MRSA.[55] The authors also found that morusin had high activity against MRSA, but only moderate activity against a susceptible *S. aureus* strain.[55] Another study examining the metabolism of morusin, found that morusin is rapidly absorbed in the intestines of rats and is mainly metabolized through glucuronidation.[235] It is believed that the phenyl group of kuwanon E and morusin, and the geranyl group of cyclocommunol, facilitates their antimicrobial effect.[55] A separate study suggests that the antibacterial action of morusin is via attachment to the bacterial cell membrane, compromising its structural integrity leading to increased permeability and ultimately cell lysis.[236]

Pereira et al.[56] isolated two bioactive flavanones, chamanetin (**35**) and dichamanetin (**46**) from the root and bark of *Cleistochlamys kirkii* (Benth.) Oliv. (Annonaceae), a plant traditionally used in Mozambique, Africa to treat wound infections and tuberculosis.[56] Dichamanetin was found to effectively inhibit the growth of three drug-resistant bacterial strains: with high activity against MRSA, vancomycin-resistant *S. aureus* (VRSA) and vancomycin-resistant *E. faecalis*.[56] According to Urgaonkar et al., dichamanetin inhibits the GTPase activity of FtsZ, a bacterial homologue for tubulin, leading to disruption of bacterial cell division.[237] Dichamanetin has also been isolated from *Piper sarmentosum* Roxb. (Piperaceae)[238].

Lupinifolin (**36**) is a flavanone isolated from the bark and wood of *Albizia myriophylla* Benth. (Fabaceae)[57,59,239] and from the stems of *Derris reticulata* Craib (Fabaceae).[58] Thai traditional remedies use *A. myriophylla* to treat dental carries.[57,59,240] Lupinifolin was found to effectively inhibit the growth of various gram-positive bacteria; with high activity against *Streptococcus mutans*[57] and *Staphylococcus aureus*[58], and moderate activity against *B. cereus*.[59] It was hypothesized that lupinifolin inhibits bacterial cell growth by permeating the bacterial cell wall and plasma membrane, which then causes leakage of the cytoplasmic membrane.[239]

Dzoyem et al.[38] isolated the flavanone 6–8-diprenyleriodictyol (**38**) from the aerial parts of *Dorstenia mannii* Hook.f. (Moraceae). The authors found that 6–8-diprenyleriodictyol was highly active against *S. aureus*, displaying one of the lowest MICs of all the flavonoid compounds listed in this review. Plants from the genus *Dorstenia* have uses in African and South American traditional medicine for the treatment of snake bites and infectious diseases. Harborne et al.[241] previously isolated **38** from the leaves of *Vellozia coronata* L.B.Sm. and *Vellozia nanuzae* L.B.Sm. & Ayensu (Velloziaceae).

Sophoraflavanone G (**39**) is a flavanone isolated from the roots of *Sophora flavescens* Aiton (Fabaceae) and other *Sophora* species.[242,243] Biosynthesis of sophoraflavanone G is thought to occur in plastids and begin in the pathway for isopentenyl diphosphate (IPP) and 1-deoxy-D-xylulose-5-phosphate (DOXP),[244] with the final 2'-hydroxlyation being catalyzed by cytochrome P450 monooxygenase at the endoplasmic reticulum.[245] Sophoraflavanone G was reported by Chan et al.[41] to have high activity against *S. aureus*. It was proposed that sophoraflavanone G binds directly to peptidoglycan in the cell wall of *S. aureus*, damaging and killing the bacterium.[246] Additionally, prompted by cases of hepatoxicity from the

ingestion of capsules containing *Sophora flavescens* extracts, a study by Yu and Cheng[247] identified sophoraflavanone G as a hepatoxic compound. The hepatoxicity of sophoraflavanone G reduces its appeal as a lead antimicrobial compound.

A phytochemical study of *Ludwigia leptocarpa* (Nutt.) H. Hara (Onagraceae) was conducted by Mabou et al.[60] and led to the isolation of two flavonoids, luteolin-8-*C*-glucoside (**44**) and (2*R*,3*S*,2′′*S*) 3′′′,4’,4′′′,5,5′′,7,7′′-heptahydroxy-3,8”-biflavanone (**49**). These flavonoids have been commonly found in edible plants and have been identified in at least twenty plant families worldwide.[248] In regards to their antibacterial activity, (2*R*,3*S*,2′′*S*) 3′′′,4’,4′′′,5,5′′,7,7′′-heptahydroxy-3,8”-biflavanone and luteolin-8-*C*-glucoside were found to have high activity against *S. aureus*.[60] This same study found that both of these flavonoids were highly active against *Shigella flexneri* and moderately active against *V. cholerae*. It is hypothesized that these compounds produce their antibacterial effect by forming complexes with extracellular and soluble bacterial proteins and also with components of the bacterial cell wall.[211]

Two studies noted the antibacterial effects of the flavonoid isoquercetin (**45**) isolated from the flowers of *Trollius chinensis* Bunge (Ranunculaceae)[47] and the aerial parts of *Aster yomena* Makino (Asteraceae).[249] In Korean traditional medicine, *A. yomena* is used to treat asthma and colds, and in traditional Chinese and Mongolian medicine, *T. chinensis* is used to treat viral and bacterial infections.[249] Yun et al.[249] found isoquercetin to have high activity against *E. coli*. A separate study found isoquercetin to have high activity against *P. aeruginosa* and moderate activity against *S. aureus*.[47] Currently, there is one clinical trial underway for isoquercetin to investigate its ability to prevent blood clots in patients with small-cell lung cancer or colorectal cancer, but no trials are testing its antimicrobial properties.[198] One possible area of future research is to investigate the antiviral properties of isoquercetin, as the plants containing it are used in traditional medicine to treat the symptoms of viral infections.

Amentoflavone (**47**), an ingredient commonly used in traditional Chinese medicine,[250] was isolated from the whole plant of *Selaginella tamariscina* (P.Beauv.) Spring (Selaginellaceae) and investigated for its bioactivity by Hwang et al.[61] The authors found amentoflavone to have a high level of growth inhibitory activity against *S. aureus*, *E. faecium*, *E. coli*, and *P. aeruginosa*. A cytotoxicity study by Srividhya et al.[251] found amentoflavone to be toxic to human liver cells with an LD_{50} of 25.3 μg/mL. While amentoflavone is widely distributed in many plant families and over 120 different plant species,[250] the in vitro hepatoxicity of amentoflavone warrants further studies into the drugs pharmacokinetic properties.

Chukwujekwu et al.[62] isolated a neoflavonoid 3″-epidiphysin (**48**) from the aerial parts of *Ormocarpum trichocarpum* (Taub.) Engl. (Fabaceae), a plant traditionally used in parts of Africa as an emetic and in the treatment of tuberculosis, gastrointestinal disorders and strokes.[62] The authors found that 3″-epidiphysin displayed high activity against *S. aureus* and moderate activity against *B. subtilis*.[62]

In our review, 74 flavonoids were reported, and 25 had high in vitro antibacterial activity. Of these, only three compounds (amentoflavone, myricetin, and quercetin) were evaluated with

in vivo models of bacterial infections,[252–255] and only two compounds (quercetin and isoquercetin) were evaluated in clinical trials, albeit not for their antibacterial activity. This indicates the lack of thorough investigation of flavonoid compounds for antibacterial activity. Pharmacokinetic and pharmacodynamic issues have also been noted for some highly active compounds such as a low bioavailability after oral administration (e.g., amentoflavone, quercetin, lupinifolin, morusin), a susceptibility to high temperature and certain conditions of pH (e.g., myricetin), and an induction effect on CYP3A4, potentially responsible for drug-drug interactions (e.g., neobavaisoflavone).[202,256,257] Due to their high diversity, their presumable low toxicity, and a large number of antibacterial mechanisms of action, flavonoids can be considered as promising compounds, but further studies are needed to assess their antibacterial potential in animal models and humans.

2.3.5 Lignans—Plant biosynthesis of lignans begins via the shikimic pathway from cinnamic acid. Alcohol derivatives of cinnamic acid, such as coniferyl alcohol and *p*-coumaryl alcohol, dimerize to form lignans.[191] Further modifications of these dimers produce a wide range of structurally different lignan types.

Three antimicrobial lignans were isolated from leaves of *Larrea tridentata* (Sesse & Moc. ex DC.) Coville (Zygophyllaceae): 3′-demethoxy-6-*O*-demethylisoguaiacin (**53**), 4-*epi*-larreatricin (**54**) and dihydroguaiaretic acid (**55**) by Favela-Hernandez et al.[64] Mexican traditional medicine has used *L. tridentata* in remedies to treat urinary tract infections.[258] The compound 3′-demethoxy-6-*O*-demethylisoguaiacin was found to have moderate activity against a drug resistant strain of *M. tuberculosis* and MRSA, while also having moderate activity against the susceptible strains of *E. coli* and *E. faecalis*.[64] The authors also found 4-*epi*-larreatricin to have moderate activity against a MDR strain of *M. tuberculosis* and susceptible strains of *M. tuberculosis* and *E. faecalis*.[64] Dihydroguaiaretic acid had moderate activity against a drug-resistant and susceptible strain of *M. tuberculosis* and MRSA.[64] The MOA for 3′-demethoxy-6-*O*-demethylisoguaiacin against MRSA is thought to be through downregulation of a gene associated with a lipoprotein for releasing ATP-binding proteins, three genes associated with ABC transporters and another gene associated with a subfamily of transport proteins.[259] Downregulation of these genes is believed to reduce MRSA's ability to effectively remove 3′-demethoxy-6-*O*-demethylisoguaiacin from within the cell. Against *M. tuberculosis*, dihydroguaiaretic acid is thought to act upon an enzyme in the geraniol degradation pathway, the alpha subunit of coenzyme A transferase (CoAt-Mt). Inhibition of this enzyme leads to intracellular accumulation of 1- and 2-methylnaphthalene.[260] These two intermediate products have previously been shown to be toxic to cyanobacteria[261] and their accumulation may lead to toxicity in *M. tuberculosis*. The ability of 3′-demethoxy-6-*O*-demethylisoguaiacin to interfere with bacterial ABC transporters raises the appeal of this compound to be further optimized for potential use as an adjunct synergistic treatment with conventional antibiotics.

Six lignans were found in our literature search, but none of them showed high antibacterial activity (MIC ≤ 10 μg/mL). Overall, lignans are poorly studied for their antibacterial activity, and more effort should be dedicated to assessing their potential role as future antibacterial agents.

2.3.6 Quinones and Related Compounds—Quinones are aromatic rings with two ketone substitutions, and these metabolites are potentially derivable by oxidation of suitable phenolic compounds like catechols (1,2-dihydroxybenzenes), giving rise to *ortho*-quinones and quinols (1,4-dihydroxybenzenes) and yielding *para*-quinones. Consequently, quinones can be formed from phenolic systems generated by either the acetate or shikimate pathways.[262]

Quinones are characteristically highly reactive and known for providing a source of stable free radicals and forming irreversible complexes with nucleophilic amino acids, often leading to a loss of function of vital proteins in the microbial organism. Probable targets in the microbial cell could be surface-exposed adhesins, cell-wall peptides, and membrane-bound enzymes. Differences in cell wall structures between gram-positive bacteria and gram-negative bacteria can play an important role in the antibacterial activity and explain why some quinones can destroy the cell wall and cell membrane of bacteria. Quinones may also render substrates unavailable for the proliferation of the microorganism.[211] We have selected quinones with potent antibacterial effects, described below.

Thymoquinone (**56**), a benzoquinone, is a biologically active compound from *Nigella sativa* L. (Ranunculaceae) seeds.[263] The presence of this compound has also been confirmed within several genera of Lamiaceae, such as *Monarda*, and Cupressaceae, such as *Juniperus*.[264] Thymoquinone exists in tautomeric forms, including the enol form, the keto form and mixtures, and it exhibits antibacterial activity, particularly against gram-positive cocci.[265] The antibacterial activity of thymoquinone was reported to be high against MRSA[65] and *H. influenzae,*[29] with moderate activity against *S. pneumoniae*.[29] Additionally, thymoquinone possesses selective antibacterial and resistance-modifying activity against oral bacteria. The oral strains of *S. aureus*, *S. mutans,* and *S. salivarius* were highly to moderately sensitive to thymoquinone.[266] It also demonstrated synergistic effects in combination with antibacterial agents such as tetracycline and benzalkonium chloride.[266] In vivo studies demonstrated that acute bacterial prostatitis induced by *E. coli* and *P. aeruginosa* could regress following administration of thymoquinone, improving the general histologic structure and downgraded the degree of inflammation in prostatic tissue.[29,267]

Uc-Cachon et al.[268] obtained four naphthoquinones (**57**, **66**, **67**, **68**) from a non-polar extract of *Diospyros anisandra* S.F. Blake (Ebanaceae). They found that plumbagin (**57**) and its dimers 3,3'-biplumbagin (**66**) and maritinone (**67**) had high antibacterial activity against sensitive and drug-resistant *M. tuberculosis* strains. Studies have suggested that naphthoquinones can interact with enzymes in the mycobacterial electron transport chain due to their structural similarity to the natural redox cycler in *M. tuberculosis*.[269,270] Another proposed mechanism for this class of compounds is the inhibition of DNA gyrase in *M. tuberculosis*.[271,272] It was also noted that 3,3'-biplumbagin and maritinone were not cytotoxic to mammalian cells and emerged as candidates for further development as novel anti-tuberculosis drugs for their potential against drug-resistant strains.[66] A separate study by Omosa et al.[67] reported on the antibacterial potential of plumbagin against a panel of sensitive and MDR gram-negative and gram-positive bacteria. Plumbagin displayed high activity against various *E. coli*, *K. pneumoniae,* and MRSA strains; moderate activity was

observed for one MRSA strain.[67] In addition, Cesari et al.[68] and Nair et al.[69] described the high and moderate antibacterial activity of plumbagin against *S. pneumoniae* and *S. aureus*.

The anthraquinones emodin (**63**) and aloe-emodin (**64**) are mainly reported in three plant families: Fabaceae (*Cassia* spp.), Polygonaceae (*Rheum*, *Rumex,* and *Polygonum* spp.), and Rhamnaceae (*Rhamnus* and *Ventilago* spp.). However, a comprehensive literature survey revealed that emodin had been identified in at least 17 plant families worldwide.[273–275] Emodin is reported to have high activity against the growth of MRSA and moderate activity against *E. coli* and *K. pneumoniae*.[67,72] Furthermore, the effects of emodin on virulence factors of *S. mutans* have been investigated, revealing that emodin significantly attenuated the growth, acid production, and insoluble glucan synthesis of *S. mutans* in vitro and suppressed the development of dental caries of rats in vivo.[276] The MOA of bioactive anthraquinonoids derived from plants is still unknown but may be related to the destruction of the integrity of the bacterial cell wall and cell membrane, leading to loss of intracellular components.[211]

Antibacterial-guided fractionation of *Senna alata* (L.) Roxb. (Fabaceae) led to the isolation of aloe-emodin, which exhibited high activity against *S. aureus* and also moderately inhibited the growth of MDR *S. flexneri* and *V. cholerae*.[73] Another study demonstrated that aloe-emodin exhibited no bactericidal activity against *S. aureus* but affected *S. aureus* biofilm formation in a dose-dependent manner.[277] Wang et al.[278] reported that aloe-emodin inhibited the arylamine *N*-acetyltransferase enzyme and growth of *H. pylori* cultures in a dose-dependent manner.

Yoshikawa et al.[71] isolated the phenanthrendione ephemeranthoquinone B (**61**) from the roots of the orchid hybrid *Cymbidium* Great Flower Marie Laurencin (Orchidaceae). Ephemeranthoquinone B has been found in other members of the Orchidaceae family, such as the orchid hybrid *Odontioda* Marie Noel ‘Velan’ and *Cymbidium finlaysonianum* Lindl.[279,280] Ephemeranthoquinone B had high activity against *B. subtilis*.[71,279,280] A cytotoxicity study found ephemeranthoquinone B to be cytotoxic against human leukemia cells (HL-60);[71] the cytotoxicity of ephemeranthoquinone B may hinder its development into an antibacterial drug.

Two *C*-glycosylated anthrones characterized as aloin A/B (**69**) and aloin-6’-*O*-acetate A/B (**70**) were isolated from leaves of *Aloe trigonantha* L.C. Leach (Asphodelaceae), an endemic Ethiopian plant. Aloin A/B and aloin-6’-*O*-acetate A/B possess broad antibacterial activities against several gram-negative and gram-positive bacteria. In particular, aloin A/B showed high activity against *V. cholerae*,[75] *E. coli*, *Salmonella enterica* serotype *Typhi*, and *Shigella dysenteriae*.[76] Additionally, aloin-6’-O-acetate A/B demonstrated high antibacterial activity against *B. subtilis*, *S. enterica* ser. *Typhi* and *V. cholerae*.[75]

A total of 36 quinones and related compounds were reported, and 17 exhibited high in vitro antibacterial activity. Of the latter, only three compounds (i.e., aloe-emodin, emodin, and thymoquinone) have been studied with in vivo models of bacterial infections,[276,281–283] and two (emodin, thymoquinone) have been evaluated in clinical trials for other conditions than bacterial infections. While emodin has some toxicological issues (mainly nephrotoxicity and

hepatotoxicity) that limits its therapeutic use,[273] thymoquinone presents a good safety profile[284] and could be a potential antibacterial lead. Further studies are needed to improve its bioavailability and to assess its antibacterial MOA with in vivo models.

2.3.7 Xanthones—Xanthones, represented as the C_6-C_1-C_6 system, are secondary metabolites restricted in occurrence to only a few families of higher plants and some fungi and lichens. The majority of xanthones have been found in four families of higher plants, the Clusiaceae, Gentianaceae, Moraceae, and Polygalaceae.[285] Xanthones can be classified based on their oxygenation, prenylation, and glucosylation patterns.[286]

Xanthones are biosynthesized from a mixed shikimate-acetate pathway. The main steps in their biosynthesis involve the condensation of shikimate and acetate moieties, which constitute a benzophenone intermediate followed by a regioselective, oxidative mediated intramolecular coupling to form the xanthone ring.[287] Naturally occurring xanthones have emerged as an important class of organic compounds due to their remarkable pharmacological and biological activities. Xanthones with promising antibacterial activity are described below.

One of the more promising xanthones, α-mangostin (**74**), was isolated from *Garcinia x mangostana* L. (Clusiaceae).[288] α-mangostin exhibited high activity against *S. aureus* and oxacillin-resistant *Staphylococcus saprophyticus*.[79] It also exhibited moderate activity against *Leptospira interrogans* serovar Javanica and *Leptospira interrogans* serovar Saigon.[80] The bactericidal activity of α-mangostin has been linked to the disruption of cytoplasmic membrane integrity leading to membrane breakdown and leakage of intracellular components. Isoprenyl groups from α-mangostin are directly involved in this activity as they trigger penetration into the hydrophobic region of the bacterial membrane.[289] In addition to membrane perturbation, another study demonstrated α-mangostin downregulated genes involved in the fatty acid biosynthetic pathway, cell division, DNA replication, homologous recombination, mismatch repair, resistance development, biofilm, oxidative stress, and cellular stress responses in *S. epidermidis*.[290] It was also hypothesized that α-mangostin could inhibit β-lactamase activity.[79] Glycosides of α-mangostin were synthesized, and their antibacterial activity against gram-positive bacteria was largely improved by glycosylation at the C-3 position.[291] A separate study found that the presence of hydroxyl groups at C-3 and C-6 positions are essential for the antibacterial activity against MRSA and vancomycin-resistant *E. faecalis*.[292] Additionally, an ethanol extract of *Garcinia x mangostana* was found to promote wound healing and a reduction of MRSA colonies in vivo. This same study found α-mangostin to be ineffective in vivo. It was then hypothesized that other compounds such as β and γ-mangostin could act in synergy with α-mangostin to produce the antibacterial and wound-healing effect observed for the plant extract.[293] Further in vivo studies should be performed to confirm the role of α-mangostin as an antibacterial agent.

Phytochemical investigation of *Garcinia cowa* Roxb. Ex Choisy (Clusiaceae) stem bark led to the isolation of a variety of xanthones, norcowanin (**75**), cowanin (**79**), cowanol (**80**), cowagarcinone E (**81**) and a rearranged triprenylxanthone, garciniacowone (**78**); these were evaluated for their antibacterial activity against gram-negative and gram-positive bacteria

strains. Cowanol, garciniacowone, cowanin, and cowagarcinone E each displayed high activity against MRSA.[81]

Of the 20 xanthones found in our review, ten have high in vitro antibacterial activity. Of the latter, only one, α-mangostin, has been studied in an animal model of bacterial infections.[293] While α-mangostin seems to have a good safety profile,[294] its poor oral bioavailability[295] and the lack of clear in vivo antibacterial efficacy necessitates a more thorough investigation of this compound.

2.3.8 Other Phenolic Compounds—Phenolic derivatives represent one of the most abundant groups of organic compounds in the plant kingdom with enormous structural variability. The diversity of structures is related to a variety of properties associated with specific roles in plants, hence their specific distribution. The site(s) and number of hydroxyl groups on the phenol group are thought to be related to their relative toxicity to microorganisms, with evidence that increased hydroxylation results in increased toxicity.[296] In addition, some authors have found that more highly oxidized phenols are more inhibitory.[297] The mechanisms thought to be responsible for phenolic toxicity to microorganisms include enzyme inhibition by the oxidized compounds, possibly through reaction with sulfhydryl groups or through more nonspecific interactions with the proteins.[298] In addition to the groups described above, several other phenolic compounds are highlighted in this review.

Two phenols, pyrocatechol (**82**) and pyrogallol (**84**) a structural constituent of many polyphenols were screened against periodontopathic bacteria,[48] and pyrogallol showed high antibacterial activity against *A. actinomycetemcomitans* and *Streptococcus mitis*. Similar results were obtained for pyrocatechol, which possessed high activity against *A. actinomycetemcomitans*.[299] This study also reported the structure-function relationship against *A. actinomycetemcomitans*, the most susceptible of the tested strains, finding that increased hydroxylation of the benzene ring in phenolic acids and benzene alcohols is associated with an increase in antibacterial activity. Polyphenols containing a pyrogallol moiety in their chemical structure were more potent inhibitors of the growth of *A. actinomycetemcomitans* than compounds containing 1,2 dihydroxyphenyl (pyrocatechol) groups.[299]

Due to the localized hydroxyl groups, pyrogallol is capable of rapidly and robustly forming noncovalent interactions such as hydrogen bonds and hydrophobic interactions. Thus, a fundamental property of pyrogallol-containing molecules is strong affinity for a variety of proteins, peptides, DNA/RNA, and polysaccharides.[300] Another feature is the oxidation of two hydroxyl groups adjacent to the reactive “quinone” form under physiological and weak basic conditions, leading to antioxidant effects. The quinone further reacts with amine and thiol groups, enabling the covalent modification of biomolecules via Michael addition or Schiff base formation. Additionally, two adjacent hydroxyl groups contribute to coordination bonds with transition metal ions, such as iron, copper, and others.[301] Recent investigations have documented that the pyrogallol moiety exhibits a broad spectrum of pharmacological and health-promoting effects in various animal disease models. Baruah *et al*.[302] reported that

pyrogallol elicits a prooxidant action (e.g., generation of hydrogen peroxide, H_2O_2) that induces protein Hsp70 production to generate protective immunity.[302]

An investigation by Zeng et al.[303] examined the main phenylethanol component present in the fruit and leaf of the olive (*Olea europaea* L., Oleaceae) and isolated hydroxytyrosol (**85**). Hydroxytyrosol has also been found in the stems of another Oleaceae species, *Sargentodoxa cuneata* (Oliv.) Rehd. et Wils.[84] Hydroxytyrosol is found free, in acetate form, or as a part of more complex compounds such as oleacein, oleuropein, and verbascoside.[304] Hydroxytyrosol showed high antibacterial activity against *S. aureus*.[84]

3,4-dihydroxyphenylacetic acid (**86**), also known as DOPAC or homoprotocatechuic acid, is a phenolic acid present in *Thymus vulgaris* L. (Lamiaceae) and *Eucalyptus globulus* Labill. (Myrtaceae).[305,306] 3,4-dihydroxyphenylacetic acid was found to have high activity inhibiting the growth of *A. actinomycetemcomitans*.[48] Interestingly, 3,4-dihydroxyphenylacetic acid is largely studied as a metabolite of dopamine and a useful marker compound in mammalian physiology[307]; for example, rats experiencing a conditioned stress response were found to have increased levels of 3,4-dihydroxyphenylacetic acid in their brains.[308] As such, 3,4-dihydroxyphenylacetic acid has been analyzed in several clinical trials as an outcome or marker, but not as an intervention.

Methyl gallate (**87**) is a phenolic compound found in a variety of plant species such as *Sedum aizoon* L. (Crassulaceae) and *Terminalia chebula* Retz. (Combretaceae).[86,309] It is an ester of gallic acid and is biosynthesized from dehydroshikimate.[310] Methyl gallate has high activity against the growth of *S. aureus* and moderate activity against *V. cholerae* and *E. coli*.[86,309] In a mouse model of cholera, oral administration of non-toxic doses (23.80 to 95.23 mg/kg) of methyl gallate significantly decreased inflammation, *V. cholerae* colonization and fluid accumulation in the intestines.[86] It has been proposed that the antibacterial activity of methyl gallate against *V. cholerae* is by its action against the bacterial membrane, reducing cytoplasmic pH, increasing membrane polarization, and decreasing ATP production.[311] A SAR study of alkyl esters of gallic acid against *Ralstonia solanacearum*, a plant-pathogenic bacterium, found that methyl gallate has better antibacterial activity than gallic acid and that activity decreases as the length of the alkyl chain increases; however, it should be noted that different trends have been observed in other bacteria.[312]

4,5-(methylene-dioxy)-*o*-coumaroylputrescine (**88**) and 4,5-(methylene-dioxy)-*o*-coumaroyl-4'-*N*-methylputrescine (**89**) are phenylpropanoids isolated from the stems and bark of *Drypetes staudtii* (Pax) Hutch (Putranjivaceae), a plant traditionally used in Nigeria for wound treatment.[87] A study by Grace et al.[87] found **88** and **89** to have high activity against *S. aureus* and *S. agalactiae* and moderate activity against *E. coli* and *P. aeruginosa*.

A study by Zeng et al.[84] reported on the phenylethanoid, 2-(3,4-dihydroxyphenyl) ethyl-*O*-β-D-glucopyranoside (**91**), that was isolated from the stems of *Sargentodoxa cuneate* (Oliv.) Rehder & E.H.Wilson (Lardizabalaceae). Compound **91** displayed high growth inhibition against *S. aureus* and significant inhibition of cell viability in two target cell lines, resulting in an antiproliferative rate of about 85% at the concentration of 64 μg/mL.[84]

Phloroglucinols (**92**, **93**, **95**, **96**) were isolated from *Hypericum* species (Hypericaceae) and tested for inhibition of bacterial growth against a panel of clinically relevant pathogens.[88] The results show that compounds **92**, **93**, **95**, and **96** demonstrated high antibacterial activity against gram-positive bacteria. A benzoyl derivative, 2-geranyloxy-4,6-dihydroxybenzophenone (**101**), isolated from *Hypericum densiflorum* Pursh exhibited the most potent growth inhibition activity, in this series, with high activity against MRSA and *S. epidermidis*. They also found that compounds **92**, **93**, **95**, **96**, and **101** were inactive against gram-negative bacteria (*E. coli*, *P. aeruginosa*, *A. baumannii*) at the highest test concentration (125 μg/mL). Additionally, compounds **92**, **93**, **95**, **96**, and **101** displayed indistinguishable growth inhibitory effects against biofilm-producing and non-biofilm-producing *S. epidermidis* strains.[88] Previous SAR studies with similar acylphloroglucinol compounds from *Hypericum beanii* N.Robson reported that compounds lacking the geranyl chain were two to fourfold less active against *S. aureus*, highlighting the importance of the geranyl structural feature.[313]

Detailed investigation of the secondary metabolites contained in a bioactive extract of dry fruits of *Amorpha fruticosa* (Fabaceae) resulted in the isolation of bibenzyl compounds amorfrutin A (**94**), amorphastilbol (**98**), 2-geranyl-5-(2-phenylethyl) resorcin (**99**), 2-[(*E*)-styryl]-5-geranylresorcin-1-carboxylic acid (**104**) and amorfrutin B (**106**). These were evaluated by Muharini et al.[40] for their antibacterial activity against a panel of human pathogenic gram-positive bacteria. The geranylated bibenzyl derivatives **98**, **99**, and **106** showed high antibacterial activity against vancomycin-resistant *E. faecalis* and *E. faecium*. Likewise, the five bibenzyl metabolites (**94**, **98**, **99**, **104**, and **106**) exhibited high activity against *S. aureus*, with amorphastilbol displaying the most effectiveness. The authors also used SAR assessments of these geranylated bibenzyl derivatives and found that isoprenoid derived side chain length seems to be important for the antibacterial activity against *E. faecalis* and *E. faecium* strains. This was exemplified by the relatively weak activity of amorfrutin A, which only differs from amorfrutin B by an isoprene versus a geranyl side chain.[40]

The acylphloroglucinol olympicin A (**97**) was isolated from the aerial parts of the plant *Hypericum olympicum* L. cf. *uniflorum* (Hypericaceae) by Shiu et al.[89] and investigated for its antibacterial activity. Olympicin A exhibited high antibacterial activity against MSSA and MRSA strains and was also highly active against a variety of *Mycobacterium* strains. The activity of olympicin A was higher than the control antibiotics against MDR strains. They also show that olympicin A was inactive against the gram-negative species that were included in this study. The authors suggest that this may be due to the impermeability of the compound to the outer membrane of the gram-negative bacteria or the different efflux pumps gram-negative bacteria express.[89]

Chemical investigation of *Bletilla striata* (Thunb.) Rchb.f. (Orchidaceae) rhizomes by Jiang et al.[90] led to isolation of bibenzyl derivatives bulbocol (**100**) and shancigusin B (**107**). These compounds were evaluated for their antibacterial activities against gram-positive and gram-negative bacteria. Both shancigusin B and bulbocol exhibited high inhibitory activity against *S. aureus*. In addition, shancigusin B moderately inhibited the growth of MRSA and

B. subtilis, while bulbocol had moderate activity against MRSA. Both compounds were inactive against gram-negative strains.[90]

Curcumin (**102**), a bis-α,β-unsaturated β-diketone was first isolated in 1815. It is one of the curcuminoids from *Curcuma* species, especially *C. longa* L. (Zingiberaceae), for which it represents 2 to 8% of the total content.[314] Curcumin was effective against periodontal pathogens and demonstrated high growth inhibitory activity against *Porphyromonas gingivalis* and moderate activity against *F. nucleatum* and *S. mitis*.[315] The antibacterial effect of curcumin could be due to its ability to inhibit bacterial cytokinesis by targeting the assembly dynamics of FtsZ in the Z-ring.[316] Many in vivo studies demonstrated therapeutic effect of curcumin for bacterial infections, especially against *H. pylori*-induced gastric damage,[317] and *K. pneumoniae*-induced lung infection,[318] and on virulence factors produced by *P. aeruginosa,*[319] on *S. mutans* adherence to tooth surfaces,[320] and on a bacterial septicemia model with *Vibrio vulnificus* infection.[321] Besides animal model studies, a total of 218 clinical trials mentioned the use of curcumin for a wide range of conditions.[198] Among the completed clinical trials, two focused on the effect of curcumin on patients with *H. pylori* infection. These studies showed an improvement of dyspeptic symptoms and reduction of gastric inflammation serologic signs, but fail to demonstrate an effect on eradication of *H. pylori*.[322,323] Another study demonstrated the effect of curcumin associated with lactoferrin on the reduction of respiratory tract infections in children, finding beneficial immunomodulatory effects.[324] In combination with quercitin, *Serenoa repens* (W.Bartram) Small (Arecaceae), and *Urtica dioica* L. (Urticaceae), curcumin was able to improve the efficacy of prulofloxacin in patients with chronic bacterial prostatitis.[325] Also, a recent study shows that topical application of 5% curcumin is as effective as 0.1% triamcinolone for treating recurrent aphthous stomatitis, an oral mucosal disease that may be caused by bacterial pathogens.[326] Despite these interesting results, curcumin has low solubility in water and poor bioavailability, thus limiting its use as an antibacterial agent. To overcome these drawbacks, structural analogues have been synthetized and nanoparticle-based approaches have been developed.[327,328] Further research on these new formulations are required to confirm their therapeutic values.

A prenylated benzopyran, 3,4-dihydro-5-hydroxy-2,7dimethyl-8-(3”-methyl-2”-butenyl)-2-(4’-methyl-1’,3’-pentadienyl)-2H-1-benzopyran 6-carboxylic acid (**103**), was isolated by Ruiz Mostacero et al.[92] from *Peperomia obtusifolia* (L.) A. Dietr. (Piperaceae) aerial parts. Compound **103** displayed high antibacterial activity against *S. aureus*, three MRSA isolates, *E. faecalis*, and *S. epidermidis*. Based on the data obtained, the authors suggested that compound **103** may act on gram-positive bacteria by a different mechanism than β-lactams or glycopeptide antibiotics. In order to propose a possible MOA for **103**, zeta potential experiments on *S. aureus* were conducted, and membrane damage was confirmed by fluorescent microscopy experiments. The results indicated that **103** was able to interact directly with bacterial membranes due to its amphipathic characteristics. The isoprenoid chains could interact with the phospholipid membrane, and the carboxylic acid moiety may possibly expose its negative charge to the interface, explaining the increase of the negative charge of both the *S. aureus* and liposomal surface.[92]

Tetraceranoate (**105**) was isolated from a stem bark extract of *Tetracera potatoria* Afzel. ex G.Don (Dilleniaceae). Tetraceranoate exhibited the high antibacterial activity against *Mycobacterium smegmatis* and was as effective as rifampicin, a first-line drug used for tuberculosis treatment. The cyclic structure of tetraceranoate and the presence of lipophilic domains may explain its anti-mycobacterial activity. Anti-mycobacterial activity is frequently enhanced by increased lipophilicity, which helps penetration through the highly lipophilic mycobacterial outer envelope and cell wall.[329] Another hypothesis suggests that tetraceranoate may have the same mode of action as rifampicin: inhibiting bacterial DNA-dependent RNA polymerase.[330]

Rhodomyrtone (**108**), a member of the acylphloroglucinols isolated from *Rhodomyrtus tomentosa* (Aiton) Hassk. (Myrtaceae) leaves, displayed antibacterial activity against many bacterial pathogens.[331] Studies conducted by Limsuwan et al. demonstrated the high activity of rhodomyrtone against oral microorganisms, including *S. mutans* and *Staphylococcus aureus*.[94] Based on the excellent antibacterial activity of rhodomyrtone against gram-positive bacteria,[332,333] Saising et al.[95] investigated the efficacy of rhodomyrtone against *C. acnes*, finding a high level of growth inhibition with low toxicity on human skin cells.

Rhodomyrtosone B (**109**), an isomer of **108**, was also isolated from the leaves of *R. tomentosa* and exhibited a high level of activity against gram-positive bacteria, including *S. aureus*, *C. acnes*, *E. faecalis*, *S. epidermidis,* and clinically relevant multidrug-resistant pathogens such as MRSA and vancomycin-resistant *Enterococcus* (VRE).[96] This study also showed that rhodomyrtosone B had low mammalian cytotoxicity, and its MOA appeared to be associated with increased permeability into the bacterial cell membrane. In addition, compound rhodomyrtosone B profoundly attenuated skin ulcer formation in a murine model of MRSA infection with an efficacy comparable to or superior to the effects of vancomycin. These results suggested that rhodomyrtosone B might be a promising natural antibiotic to combat drug-resistant (MRSA and VRE) infections.[96]

Biloa Messi et al.[97] isolated the polyisoprenylated benzophenone 7-*epi*-clusianone (**110**) from the hexane extract of the fruits of *Garcinia preussii* Engl. (Clusiaceae). The authors found that 7-*epi*-clusianone exhibited high antibacterial activity against *S. aureus* and *E. faecalis*. In previous investigations, 7-*epi*-clusianone has been shown to be a promising compound for the treatment of multidrug-resistant *S. aureus* infections.[334] In addition, 7-*epi*-clusianone was found to affect the biofilm formation and acid tolerance of the cariogenic gram-positive bacteria *S. mutans*.[335] The MOA of this compound is unknown; however, due to their specificity to gram-positive bacteria, the effect may be related to the characteristics of the cell envelope.[97]

The polycyclic polyprenylated acylphloroglucinol (PPAP), hypercalin B (**113**), was isolated from *Hypericum acmosepalum* N.Robson (Hypericaceae) and had high activity against the MDR *S. aureus* strain, SA-1199B.[100,336] The majority of the over 400 known PPAPs are limited to the Hypericaceae family, with hypercalin B reported in only three genera.[336–339] PPAPs, including hypercalin B, derive from a mixed mevalonate and polyketide biosynthetic pathway.

Kim et al.[101] isolated a growth-inhibiting benzofuran, chalcomoracin (**114**), from the leaves of *Morus alba* L. (Moraceae)[101], and it has also been found in *Morus wittiorum* Hand.-Mazz (Moraceae).[340] Chalcomoracin was found to have high activity against both MRSA and MSSA.[101] Chalcomoracin is believed to inhibit the growth of *S. aureus* by targeting the bacterial fatty acid system II. Specifically, chalcomoracin inhibits an isoform of enoyl-ACP reductase, FabI, a catalyst required for fatty acid synthesis.[101]

A phenylpropanoid glycoside identified as martynoside (**115**), was isolated from *Boscia albitrunca* (Burch.) Gilg & Benedict (Capparaceae) leaves.[102] The same study found martynoside to have high antibacterial activity against *B. subtilis* and moderate activity against *K. pneumoniae.* Pendota et al. concluded that the antibacterial activity of martynoside provides rationale for the ethnomedicinal uses of the plant and suggested that this compound could be helpful in the management of eye infections.[102]

Of the 67 other phenolic compounds included in our review, 33 exhibited a high in vitro antibacterial activity. Of these, five compounds (curcumin, methyl gallate, pyrogallol, rhodomyrtone, rhodomyrtosone B) have demonstrated an in vivo antibacterial activity, two compounds (curcumin, hydroxytyrosol) have been investigated in clinical trials for conditions other than bacterial infections, and only one (curcumin) has been tested in clinical trials for bacterial infections (*H. pylori* infection).[86,96,302,317–321,341–344] Rhodomyrtone and rhodomyrtosone B represent two promising antibacterial lead compounds, discovered in 2002 and 2008, respectively.[345,346] Studies focusing on their potential for clinical applications (e.g., pharmacokinetic parameters, toxicity) are needed. On the other hand, hydroxytyrosol has been widely studied, but few studies have examined its potential as an antibacterial agent; further work should explore its efficacy and safety in animal models of infection. Overall, methyl gallate and curcumin exhibit the greatest potential as therapeutic agents for the treatment of bacterial infections in humans. They have demonstrated promising results in different in vivo models of bacterial infections, and they exhibit a good safety profile.[347,348] Despite their great efficacy and safety, both compounds have some pharmacokinetic issues with low oral bioavailability and poor stability under physiological conditions. Thus, more research is needed to evaluate the antibacterial activity of synthetic analogues and pharmaceutical formulations with improved pharmacokinetics in animal models and humans.

2.4 Terpenoids

Formed by condensation of isoprene or isopentane units, terpenoids represent the largest chemical class of plant NPs and most are multicyclic structures that differ from one another on the basis of carbon skeleton and different functional groups [349] Plants form terpenoids via the mevalonate pathway from mevalonic acid or deoxyxylulose phosphate by the methylerythritol 4-phosphate pathway (MEP), also referred to as mevalonate independent pathway. These precursors form isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP).

2.4.1 Overview—Triterpenoids and saponins make up 33.6% of terpenoid antibacterial compounds documented in our literature search. Diterpenoids represented 30.3% of all

terpenoid compounds. Monoterpenoids and sesquiterpenoids were seen less frequently, at 17.2% and 19% respectively (Figure 3).

2.4.2 Monoterpenoids—In the creation of monoterpenoids, the enzyme prenyl transferase converts the precursors into geranyl pyrophosphate (GPP). GPP ionizes to its isomers, linalyl diphosphate, and neryl diphosphate. These three isomers become the linear monoterpenoids and act as substrates for various cyclases which yield monoterpene ring systems.[191]

Carvacrol (**116**) is a monoterpenoid common to many aromatic plants. It is approved for human consumption, and it is often used as both a flavoring agent and for its anti-bacterial properties in many prepared foods.[350] One study reported that carvacrol increases cell membrane permeability and depolarizes the membrane potential in *L. monocytogenes*; this leads to cell death.[351] This study also found antibacterial synergy with nisin.

Thymol (**117**) is the phenolic isomer of carvacrol present mainly in essential oils (EOs) from plants of the Lamiaceae family. Thymol has shown moderate growth inhibitory effect on eleven different bacterial species, including *Proteus mirabilis*, *B. cereus*, *M. flavus*, *S. aureus*, *S. enteritidis,* and *P. aeruginosa*.[103,352] Thymol induces the permeabilization and depolarization of the cytoplasmic membrane and thus disrupts the membrane integrity resulting in leakage of intracellular materials and cell death.[353] Catheters impregnated with thymol (400 mg/mL) and chloroxylenol (150 mg/mL) have demonstrated in vitro antibacterial activity against uropathogens and in vivo antibacterial activity against *Enterobacter cloacae*, which suggests that thymol could be used to prevent catheter-associated urinary tract infection.[354] A thymol-enriched bacterial cellulose hydrogel showed in vitro antibacterial activity against burn specific pathogens, as well as an improvement of wound healing in vivo and is proposed to be used as a delivery system for third-degree burns.[355] A clinical trial evaluated the effectiveness of a topical lavender-thymol oil preparation in 60 postpartum women with episiotomy and showed a reduction in pain and improvement in dyspareunia for patients treated.[356] Finally, a randomized clinical trial comparing the traditional Listerine® mouthwash with thymol and other EOs to an alcohol-free mouthwash Listerine Zero® with thymol showed that both products reduce plaque formation and biofilm thickness.[357] Although thymol shows great potential as an antibacterial agent, its low bioavailability, along with its potential toxicity, limits its use.[353] Further comprehensive studies should be performed to assess its safety in vivo.

Linalool (**118**) is a monoterpenoid with a tertiary alcohol group. This volatile oil was isolated from many plants, including *Lavandula* spp. (Lamiaceae), *Cinnamomum camphora* (L.) J.Presl (Lauraceae), and *Cannabis sativa* L. (Cannabaceae).[358–360] Linalool isolated from *Ligustrum compactum* (Wall. ex G.Don) Hook.f. & Thomson ex Brandis (Oleaceae) flowers had high antibacterial activity against *Salmonella enteritidis, B. cereus, B. subtilis, E. coli, P. aeruginosa,* and *S. sonnei*.[106] Alves et al. [361] isolated linalool from *Coriandrum sativum* (Apiaceae) and determined it had moderate antibacterial activity against *A. baumannii.* The antibacterial MOA of linalool against *P. aeruginosa* is multifaceted, like many other EOs; linalool changes cell morphology, destroys the cell wall, decreases

membrane potential, interferes with cellular respiration, and causes nucleic acid leakage due to cell membrane damage. The culmination of these effects is cell death.[362]

The volatile monocyclic monoterpenoid alcohol α-terpineol (**119**) is one of 5 isomers of terpineol, which differ only in the position of the double bond. The compounds α-terpineol and terpinen-4-ol are the most common naturally-occurring terpineols.[363] Additionally, α-terpineol is present in many aromatic plant substances, including orange juice[364], and smells like lilac.[363] Antibacterial activity of α-terpineol is high against *B. subtilis, S. epidermidis*, *S. aureus*, *P. aeruginosa*, and *E. coli*.[365] The MOA of α-terpineol against *S. aureus* does not involve gross membrane damage, as is seen with other terpenoids and EOs. Rather, α-terpineol causes the loss of membrane-bound autolytic enzymes, which leads to cytoplasm leakage and an inability to osmoregulate. The combination of these effects over time induces cell lysis.[365]

Citronellol (**120**) usually occurs naturally as a mixture of enantiomers, (+)-citronellol and (-)-citronellol[366]. It was ineffective against *S. aureus*, but highly active against *E. coli.*[109] The cell surface tension properties and surface charge of *E. coli* and *S. aureus* are altered when citronellol is applied, becoming more hydrophobic, having a less negative zeta potential and deteriorating membrane integrity.[109]

Twenty-one monoterpenoids were reported in our review, among which ten exhibited high in vitro antibacterial activity. All of them were found in EOs from plants and have received much attention for their significant antibacterial activity, with four compounds (α-terpineol, carvacrol, eucalyptol, and thymol) being investigated with in vivo models of bacterial infections,[354,367–369] and six (α-pinene, carvacrol, eucalyptol, linalool, terpinen-4-ol, and thymol) tested in clinical trials (Table 2) related to infectious and inflammatory conditions (e.g., gingivitis, sore throat, episiotomy, acute bronchitis, blepharitis).[198,356,370] Although highly active, these compounds present some drawbacks reducing their use as antibacterial agents, especially their unfavorable physico-chemical profile with high volatility leading to instability and a short half-life, a low water solubility leading to a poor bioavailability after oral administration, an unpleasant taste and smell, and potential toxicity due to poor knowledge concerning the optimal safe dose to be administered. Future research directions include improvement of physicochemical properties, the examination of acute and chronic toxicity as well as teratogenicity, development of standardized formulations with multiple compounds, and realization of clinical trials focused on multi-drug resistant bacterial infections.

2.4.3 Sesquiterpenoids and Derivatives—Sesquiterpenoids form via the mevalonate pathway from the addition of an IPP group to geranyl pyrophosphate (GPP) to form farnesyl diphosphate (FPP). FPP can form acyclic and cyclic sesquiterpenoids with varied stereochemistry.[191] These compounds are usually less volatile than other terpenoids, and as they oxidize their aroma changes.[371]

The roots of *Iostephane heterophylla* (Cav.) Benth. (Asteraceae) yielded several compounds with antibacterial activity, including the bisabolane-type sesquiterpenoid xanthorrhizol (**121**) and the diterpenoid *ent*-trachyloban-19-oic acid (**127**)[110]. Compound **127** had high

antibacterial activity against *S. mutans*, and also inhibited the formation of *S. mutans* biofilms. Xanthorrhizol and **127** were determined to have moderate to high antibacterial activity against *P. gingivalis*.[110] The effectiveness of xanthorrhizol against gram-negative bacteria is improved when used in combination with polymyxin B nonapeptide, nisin, carvacrol (**116**), or thymol (**117**).[372]

Onopordopicrin (**122**), a germacranolide sesquiterpenoid lactone, was isolated from *Onopordum acanthium* L. (Asteraceae) and exhibited moderate activity against *B. subtilis, Lactobacillus plantarum, Vibrio fischeri,* and *Xanthomonas euvesicatoria*.[111]

The sesquiterpenoid 8,9-oxoisopropanyldshamirone (**123**) along with 27 other sesquiterpenoids were isolated from *Ferula ferulioides* (Steud.) Korovin (Apiaceae). It had high activity against both MRSA and tetracycline-resistant *S. aureus*; however, it was not active against other strains.[112]

Of the 19 sesquiterpenoids included in our review, only three (i.e., 8,9-oxoisopropanyldshamirone, onopordopicrin, xanthorrhizol) showed high in vitro antibacterial activity. However, none of them have been investigated either in animal models of bacterial infections or in clinical trials. Further research including in vivo pharmacological and toxicological studies are needed to assess the potential of sesquiterpenoids in the treatment of bacterial infections.

2.4.4 Diterpenoids—Diterpenoids form from the addition of isopentenyl diphosphate (IPP) to geranylgeranyl diphosphate (GGPP); cyclization, and Wagner-Meerwein rearrangements produce the diversity seen in this chemical class.[191] One of the most ubiquitous diterpenoids is the acylic diterpene alcohol, phytol. It is a required sidechain in chlorophyll and is also necessary for the biosynthesis of vitamin E, tocopherol, and vitamin K, phylloquinol.[373]

Three abietane diterpenoids exhibited antibacterial activity: abieta-7,9(11)-dien-13-β-ol (**124**), dehydroabietic acid (**125**), and carnosic acid (**138**). A recent review of the antibacterial activity of these compounds and their relatives covers much of the existing knowledge on the MOA and SAR of abietane diterpenoids.[374] Dehydroabietic acid is a defense metabolite in the resin of *Pinus* species (Pinaceae) and other conifers.[114,375] Biosynthesis of dehydroabietic acid involves cyclization of copalyl diphosphate, followed by oxidation mediated by cytrochrome P450.[375] From in vitro assays, dehydroabietic acid had high activity in *P. gingivalis* and moderate activity against *Actinomyces naeslundii*, *C. acnes*, *S. mitis*, *Bacteroides fragilis,* and *P. intermedia*.[114,115] Dehydroabietic acid was less potent than the oleoresin from which it was isolated, suggesting that synergy among compounds in the oleoresin may be important for antibacterial activity.[115]

Carnosic acid (**138**)—sometimes classified as a polyphenol due to its catechol moiety—is found in the plant family Lamiaceae; it was first isolated from *Salvia officinalis* L., commonly known as sage, and is widely used and studied for its antibacterial and antioxidant properties.[376] The biosynthesis of carnosic acid is not entirely clear, but several possible intermediates have been identified.[376] A methyl ester of carnosic acid (20-methyl

carnosate) is also found in Lamiaceae, specifically *S. officinalis* and *Salvia lanigera* Poir.[123] An SAR study of carnosic acid and its methyl ester indicated the hydroxyl at C12 is needed for activity and that the methylation of C20 decreased the MIC against *E. faecalis* and MRSA.[123] In another study with *E. faecalis* and *S. aureus*, the antibacterial MOA for carnosic acid was found to be inhibition of efflux pumps, suggesting possibilities for synergy with existing antibiotics.[377] Several in vivo experiments have found carnosic acid to have an antioxidant effect, and rosemary extracts containing carnosic acid and carnosol (**137**) are approved in the European Union as antioxidant food additives.[376] The wide availability of carnosic acid will facilitate further study of its antioxidant and antibacterial properties; cultivars of *Rosmarinus officinalis* (Lamiaceae) have been developed with up to 10% content of carnosic acid by weight in dried leaves.[376]

Serrulatane diterpenoids 8,19-dihydroxyserrulat-14-ene (**126**) and 8-hydroxyserrulat-14-en-19-oic acid (**131**) were isolated from the plant genus *Eremophila*, which is used in wound healing in Australian traditional medicine.[116] Their in vitro antibacterial activity is generally against gram-positive bacteria; both compounds had high activity against *B. subtilis*, *S. pneumoniae*, MRSA, and the gram-negative bacterium *Moraxella catarrhalis*.[116] However, they both exhibited cytotoxicity against Vero cells, indicating that toxicity may be a barrier to the use of these compounds as therapeutics.[116] When tested in a mouse model of foreign body infection, **131** exhibited neither antibacterial activity nor toxicity, putatively due to binding to albumin.[378] A patent application for the use of serrulatane diterpenoids in antimicrobial coatings on medical devices has been abandoned.[379]

Kaurenoic acid (**128**) and its enantiomer, *ent*-kaurenoic acid, are tetracyclic kaurane diterpenoids. They are composed of a perhydrophenantrene unit and cyclopentane ring. Like other diterpenoids, these are formed via the mevalonate pathway from geranylgeranyl pyrophosphate (GGPP).[191] Under acidic conditions, GGPP can cyclize into two enantiomeric perhydronaphtalene bicyclic intermediates with stereocenters on C-5, C-9, and C-10; resulting in “normal” and *ent*- diterpenoids.[380] This class of diterpenoids occurs in many plant families, including Asteraceae, Annonaceae, Apiaceae, Celastraceae, Chrysobalanaceae, Erythroxylaceae, Euphorbiaceae, Fabaceae, Lamiaceae, Jungermanniaceae, Rhizophoraceae, Rutaceae, and Velloziaceae.[380] Kaurenoic acid is an intermediate for many other diterpenoids, including the gibberellins, a class of plant hormones involved in development.[381,382] Many bioactivities have been attributed to kaurenoic acid, including anti-diabetic properties,[383] genotoxicity against some tumor cells,[384–386] antifungal activity against *Trichophyton rubrum*, *T. metagrophytes* and *Epidermpphyton floccosum,*[387] and as a phagostimulant.[388] It has also shown activity against the botanical gray mold, *Botrytis cinerea.*[389] A 2007 review of the kaurane diterpenoids discusses their bioactivities and synthesis in detail.[380] Kaurenoic acid isolated from *Copaifera langsdorffii* Desf. (Fabaceae) oleoresin had moderate to high antibacterial activity against *B. cereus* and *S. epidermidis*.[390] Several bacteria linked to dental caries are inhibited by *ent*-kaurenoic acid, including *S. mitis*, *S. mutans*, *Prevotella melaninogenica*, *P. gingivalis,* and *Prevotella nigrescens*.[118,391]

The labdane diterpenoid copalic acid (**129**) is the primary biomarker of the plant genus *Copaifera* (Fabaceae) and a major constituent of the terpene-rich medicinal oleoresin of that

genus.[392] In in vitro assays, copalic acid had high activity against *S. epidermidis* and *S. pneumoniae,* and moderate activity against MRSA, demonstrating better activity against gram-positive bacteria than gram-negative bacteria.[117] A methylated analogue of copalic acid exhibited MICs an order of magnitude higher than those of copalic acid, supporting the theory that diterpenoids with a single hydrogen bond donor group have more potent antibacterial activity than those with two such groups.[393]

The clerodane diterpenoid 16α-hydroxycleroda-3,13(14)*Z*-dien-15,16-olide (**133**), isolated from *Polyalthia longifolia* (Sonn.) Thwaites (Annonaceae) showed moderate antibacterial activity against several clinical isolates of MRSA.[121,122] When used in combination with a β-lactam, oxacillin, tetracycline, daptomycin, and linezolid, synergistic interactions are observed in vitro, with the β-lactam showing a 10–80 fold reduction in the MIC depending on the strain tested.[122] Similar synergistic activity was observed for several fluoroquinolones in vitro and for norfloxacin in vitro.[121] A downregulation of major facilitator superfamily (MFS) and multidrug and toxin extrusion (MATE) efflux genes in the presence of **133** and norfloxacin demonstrates that **133** acts as an efflux pump inhibitor, allowing increased intercellular concentrations of the antibiotic.[121]

A total of 37 diterpenoids were reported in our review, among which 13 had high in vitro antibacterial activity. Only one compound (i.e., 8-hydroxyserrulat-14-en-19-oic acid) has been studied in animal model of bacterial infections but it did not demonstrate any antibacterial activity.[378] None of these compounds have been tested in clinical trials. More research is needed to confirm the antibacterial activity of diterpenoids using in vivo models.

2.4.5 Nor-triterpenoids—Nimbolide (**142**) is a limonoid triterpenoid isolated from the leaves of *Azadirachta indica* A. Juss (Meliaceae). Nimbolide exhibited high activity against MRSA.[127] A potential MOA for nimbolide against MRSA is thought to be targeting of the bacterial cell membrane, resulting in increased membrane permeability, the disintegration of the cell envelope, and bacterial cell lysis.[127] However, a cytotoxicity assay found nimbolide to be cytotoxic to BeWo human choriocarcinoma cells, indicating a potential barrier to its utility as an antibacterial therapy.[394] Due to its poor oral bioavailability and its cytotoxicity, the therapeutic application of nimbolide in bacterial infections seems to be limited.[395]

2.4.6 Triterpenoids and Saponins—While most terpenoids (mono-, di- and tetra-) are formed in the chloroplasts and use the methylerythritol 4-phosphate (MEP) pathway, the mevalonate pathway occurring in the cytosol forms triterpenoids, steroids, and some sesquiterpenoids. Indeed, the biosynthetic pathways for terpenoids (MEP and mevalonate) are compartmentalized, so that the chloroplast and cytosol represent two distinct locations for biosynthesis. Accordingly, triterpenoids are formed by converting the cytosolic pool of isopentenyl phosphate (IPP) to the C15 farnesyl pyrophosphate (FPP), then joining two FPP units tail-to-tail to yield the linear triterpene squalene. Squalene undergoes a cyclization via an intermediary 2,3-oxidosqualene, which through cyclized ring expansions and Wagner-Meerwein migrations yields triterpene alcohols or aldehydes including α- and β-amyrin and lupeol. Ursolic acid (**147**) contains the α-amyrin skeleton, β-amyrin is found in oleanolic acid (**148**), while betulinic acid (**149**) and betulin (**144**) are two oxidized versions of lupeol.[191]

Friedelane-3,11-dione (**143**) is a triterpenoid with high activity against clinically isolated, isoniazid resistant *M. tuberculosis*.[50] It has been isolated from the stems of *Drypetes molunduana* Pax & K. Hoffm (Putranjivaceae)[396] and leaves of *Triclisia gilletii* (De Wild.) Staner (Menispermaceae). The low polarity of **143** may explain its action against the hydrophobic cell wall of *M. tuberculosis* and validate its history as an anti-tubercular agent.[50]

Two *nor*lupane triterpenoids, ceanothenic acid (**145**) and 29-hydroxyceanothenic acid (**151**), were isolated from the leaves of *Alphitonia xerocarpus* Baill (Rhamnaceae). Both showed moderate antibacterial activity against *E. faecalis* and high activity against *S. aureus*, as well as cytotoxicity against a human carcinoma cell line.[397]

Moronic acid (**146**) is a pentacyclic triterpenoid isolated from the aerial parts of *Schinus lentiscifolius* Marchand (Anacardiaceae). Moronic acid showed high growth inhibitory activity against *B. subtilis*, *S. aureus* and *S. pyogenes*. Some derivatives of moronic acid tested against these bacteria showed much higher MICs, indicating the importance of the carbonyl group for antibacterial activity.[129]

Ursolic acid (**147**) is an ursane-type pentacyclic triterpenoid isolated from various plant species including apple (*Malus domestica* Borkh., Rosaceae), coffee (*Coffea arabica* L., Rubiaceae), cranberry (*Vaccinium macrocarpon* Aiton, Ericaceae), guava (*Psidium guajava* L., Myrtaceae), marjoram (*Origanum majorana* L., Lamiaceae), olive (*Olea europaea*, Oleaceae) and thyme (*Thymus vulgaris*, Lamiaceae).[398] Ursolic acid showed high growth inhibitory activity against *E. faecalis*, *L. monocytogenes*, and *M. tuberculosis*, and moderate activity against extremely drug-resistant (XDR) *M. tuberculosis*, *K. pneumoniae*, *P. aeruginosa,* and *V. cholerae*.[83,131,132,399,400]

Ursolic acid has been extensively studied against human pathogenic bacteria; however, its MOA is not yet fully elucidated. It relies on modulating microbial genes, interfering in the mycolic acid biosynthesis, inhibiting peptidoglycan turnover, damaging cell membrane integrity, inhibiting biofilm formation, inducing stress responses and cell autolysis.[401–403] To improve its low water solubility and its antibacterial activities, chemical modifications were performed in the C-3, C-17, and C-28 positions. Acetylation of ursolic acid at the C-3 position afforded ursolic acetate, which exhibited higher antimycobacterial activity.[404] Introducing two hydroxyl groups to ursolic acid at positions C-1 and C-2 together with a methyl ester group at C-17 position afforded methyl 1α,2β,3β-trihydroxy-urs-12-en-28-oate, which showed better growth inhibitory activity against *S. aureus* and *B. subtilis*.[405] Incorporation of isopropyl or *n*-butyl chain onto the C-28 position led to derivatives able to reverse the resistance against multi-drug resistant *E. coli* by inhibiting efflux pumps.[406] Other derivatives containing an aminoguanidine moiety at C-3 or at C-28 position led to better antibacterial activities against multi-drug resistant *S. aureus.*[407,408] Finally, the incorporation of a carbazole moiety, as well as a *N*-(dimethylamino) propyl amide side chains at C-28 position had a beneficial effect on the antibacterial activity of ursolic acid.[409]

A mixture of ursolic acid and oleanolic acid (**148**) (3:1) was administered three times per week for 30 and 60 days to mice infected with *M. tuberculosis* and results showed a

significant reduction of bacterial loads, improvement in lung histopathology and immunostimulatory effects.[410] In a murine model of subcutaneous MRSA infection, a local administration of ursolic acid in combination with nafcillin every eight hours for 56 hours reduced the size of necrotic skin lesions and the production of the proinflammatory cytokine IL-1β.[411] Although ursolic acid has been studied in some clinical trials—none focused on its effect on bacterial infectious disorders. Further studies should be performed to confirm the efficacy of ursolic acid and its derivatives as antibacterial agents.

Oleanolic acid (**148**) often occurs in combination with its isomer, ursolic acid (**147**), and has been isolated from more than 1,620 plant species, especially in plants belonging to the Oleaceae family.[412] Oleanolic acid demonstrated moderate to high growth inhibitory activity against *E. faecalis*, *L. monocytogenes*, *B. cereus,* and *M. tuberculosis*.[130,413] Derivatives of oleanolic acid with antibacterial activity have been isolated from a variety of plant species; this is the case of compound **156** (3-*O*-β-D-glucuronopyranosyloleanolic acid 28-*O*-β-D-glucopyranosyl ester) and compound **154** (3−*O*−β−D−glucuronopyranosyl−oleanolic acid), both isolated from *Melanthera elliptica* O.Hoffm. Compounds **156** and **154** showed moderate activity against multidrug-resistant *E. coli*, *S. flexneri* and *S. aureus*.[136] Compound **155** (3-*O*-β-D-glucopyranosyl(1→6)-β-D-glucopyranosyloleanolic acid) is another derivative of oleanolic acid and was isolated from *Paullinia pinnata* L. (Sapindaceae). Compound **155** showed moderate to high antibacterial activity against *E. coli*, *K. pneumoniae*, *E. aerogenes,* and *S. enterica* ser. *Typhi*.[137] A set of oleanolic acid C-28 amide derivatives were synthesized and it was shown that a longer chain length improved antibacterial activity on gram-positive bacteria.[414] Unlike ursolic acid, oleanolic acid inhibits peptidoglycan turnover, thus affecting the cell membrane of bacteria.[415] Oleanolic acid also showed a synergistic effect in combination with conventional antibiotics against MRSA.[416] Although oleanolic acid is one of the most investigated plant-derived compounds and has been approved as an OTC hepatoprotective drug in China,[417] few in vivo studies and clinical trials have been undertaken to evaluate the use of oleanolic acid and its derivatives as antibacterial agents.

Pseudolarolide B (**150**), a cycloartane triterpenoid lactone and pseudolarolide Q (**152**), a triterpenoid cycloperoxide[418], were isolated from the seeds of *Pseudolarix amabilis* (Nelson) Rehd (Pinaceae). Pseudolarolide Q and B exhibited high antibacterial activity against *S. aureus* and *E. coli*.[134] Cytotoxicity studies of pseudolarolide B found toxicity against KB (nasopharyngeal), A-549 (lung), HCT-8 (colon) and P-388 (leukemia) tumor cell lines.[419]

Of the 41 triterpenoids and saponins included in our review, 12 showed high in vitro antibacterial activity. Of these, only two compounds (i.e., oleanolic acid and ursolic acid) have been studied in animal models of bacterial infections and tested in clinical trials for conditions other than infectious disorders.[410,411,420] The development and therapeutic application of these two pentacyclic triterpenoids have been limited by their low oral bioavailability and their short half-life; thus many derivatives have been synthesized and tested using in vitro antibacterial assays. More in vivo studies are needed to explore their full potential as antibiotics.

2.5 Other Metabolites

Aliphatic compounds were the most abundant chemical class amongst other metabolites at 37.7%. Cyclic compounds and steroids were seen at the same rate, 14.3%. While lipids and organosulfurs and derivatives both occurred at 12%. Peptides and quinones and related compounds were the least represented chemical classes at 1.3%, each having a single compound in the subclass. (Figure 4).

2.5.1 Aliphatic Compounds—Aliphatic compounds are non-aromatic hydrocarbons. They are found as straight chains or branched compounds with a variety of single or double bonds throughout. These highly lipophilic compounds most likely exhibit their effect by compromising the bacterial membrane.

Fujita et al.[138] examined the antibacterial components of EO from plants in the genus *Polygonum* (Polygonaceae)[138] for activity against *Salmonella*, identifying *2E*-undecenal (**157**), undecanol (**158**), 2*E*-dodecenal (**159**), and dodecanol (**160**), as having antibacterial properties. 2*E*-dodecenal has previously been found in the EO of *Marrubium thessalum* Boiss. & Heldr. (Lamiaceae).[421] Dodecanol has also been found in the EO of *Phlomoides laciniata* (L.) Kamelin & Makhm. (Lamiaceae).[422] *2E*-undecenal has been found in the EO of species within the genus *Geranium.*[423] Undecanol was found in the EO of *Senecio belgaumensis* (Wight) C.B.Clarke (Asteraceae).[424] The nonspecific MOA of these alkanals and alkanols is thought to occur by acting as a surfactant, denaturing integral proteins in the membrane and disturbing their normal function.[138] All four of these inhibited *S. enterica* growth. One clinical trial examined the effects of a moisturizing hand wash solution containing dodecanol as one ingredient and compared differences in development of hand dermatitis to typical hand wash solutions.[198]

Guzman et al.[139] investigated the roots of *Levisticum officinale* W.D.J.Koch (Apiaceae) and found the aliphatic compound falcarindiol (**161**) to have moderate to high activity against *Mycobacterium tuberculosis* and *M. bovis*. Falcarindiol is also found in many other members of the Apiaceae family.[425–430] The biosynthesis of falcarindiol occurs from crepenynic acid in the crepenynate pathway.[431] A cytotoxicity study by Dall'Acqua et al.[432] found falcarindiol to be cytotoxic against a panel of cancer cell lines: promyelocytic leukemia, human fibrosarcoma, and human intestinal adenocarcinoma. A clinical study examined the bioavailability of dietary compounds found in carrots, including falcarindiol, and another clinical trial studied the effects of these dietary compounds in preventing cellular and DNA damage.[198]

Perianayagam et al.[135] examined the roots of *Trichodesma indicum* (Boraginaceae), yielding the antibacterial aliphatic compound *n*-dotriacont-9-one-13-ene (**162**). *T. indicum* has been used in traditional medicine in India to treat many ailments, including dysentery and skin disease.[135] Compound **162** was found to have a wide range of antibacterial activity against both gram-negative and gram-positive bacteria, with moderate activity against *B. subtilis*, *S. aureus*, *S. epidermidis*, *K. pneumoniae*, *E. coli,* and *P. aeruginosa*.

Twenty-nine aliphatic compounds were found in our review, and four (i.e., 2*E*-dodecenal, dodecanol, falcarindiol, *n*-dotriacont-9-one-13-ene) showed high in vitro antibacterial

activity. Of these, falcarindiol is the only aliphatic compound studied in an in vivo model of bacterial infection.[433] However, the toxicological profile of this compound is poorly studied, which limits our ability to draw any conclusions. More research is needed to assess the role of falcarindiol and other aliphatic compounds as antibacterial agents.

2.5.2 Ceramides—Ceramides are long-chain amino alcohols, or sphingosines, attached to a fatty acid. The synthesis of ceramides begins with the formation of an amide linkage, catalyzed by ceramide synthase, between a long-chain amino alcohol and fatty acyl-CoA.[434]

Teinkela et al.[74] isolated ficusoside B (**163**) from the wood of *Ficus elastica* Roxb. ex Hornem. (Moraceae). Thus far, ficusoside B and a related compound, ficusoside, have only been found in *F. elastica*. Ficusoside B displayed high activity against *S. aureus* and *P. vulgaris*, and moderate activity against *P. stuartii* and *P. aeruginosa*.[74] A cancer study found ficusoside B to have a weak cytotoxic effect against a panel of human cancer cell lines.[435]

Of the two ceramides found in our review, only ficusoside B exhibited high in vitro antibacterial activity. However, only one study focused on assessing its in vitro antibacterial activity. Further in vitro experiments should be performed to confirm these results.

2.5.3 Cyclic Compounds—Cyclic compounds are a large and diverse category of compounds defined by the presence of a ring. Cyclic compounds with significant antibacterial activity that do not belong to the previously discussed classes are described below.

Yu et al.[106] isolated the cyclic compound 2-phenylethanol (**164**) from the flowers of *Ligustrum compactum* (Wall. ex G.Don) Hook.f. & Thomson ex Brandis (Oleaceae). It has also been found in roses (*Rosa* spp.) and strawberries (*Fragaria* spp.) in the Rosaceae family and contributes to their aromatic scent.[436] The biosynthesis of 2-phenylethanol occurs from the conversion of L-phenylalanine to phenylacetaldehyde by the enzyme aromatic amino acid decarboxylases (AADC), which is then reduced by phenylacetaldehyde reductases (PAR) into 2-phenylethanol.[437] The MOA for 2-phenylethanol is currently unknown. It displayed high activity against *S. enteritidis*, *S. sonnei*, *B. cereus*, *P. aeruginosa*, *L. plantarum*, *Leuconostoc mesenteroides,* and *S. aureus*.[106] 2-phenylethanol has been used in clinical trials as an odorant but has not been assessed for its antimicrobial properties in humans.[198]

Panyo et al.[140] isolated an antibacterial dipyridyl disulfide, 2,2’-dithiodipyridine (**165**) from the stems of *Ixora megalophylla* Chamch. (Rubiaceae). It has previously been found in the genus *Allium* (Amaryllidaceae), which includes onion and garlic.[438] 2,2’-dithiodipyridine was found to have high activity against *S. mutans* and *S. mitis*.[140]

Of the 11 cyclic compounds included in our review, three compounds (2,2’-dithiodipyridine, (-)-cleistenolide, 2-phenylethanol) exhibited high in vitro antibacterial activity, but none of them have been studied in animal models or humans. More effort should be dedicated to assessing the therapeutic value of cyclic NPs in the treatment of bacterial infections.

2.5.4 Glycosides—The formation of glycosides occurs through the process of glycosylation. Glycosylation begins with the synthesis of a nucleoside diphosphosugar. Uridine diphosphoglucose (UDP-glucose) is often used for this process. The biosynthesis of UDP occurs from glucose 1-phosphate, uridine triphosphate, and the enzyme UTP-glucose 1-phosphate uridylyltransferase. What follows is an SN_2 attack of UDP-glucose producing the respective *O*-β-D-glucoside.[191]

Lunga et al.[137] identified two bacterial growth inhibiting glycosides, pinnatoside A (**167**) and 3-*O*-β-D-glucopyranosyloxy-4-methyl-2(5H)-furanone (**168**). Compound **168** and pinnatoside A were isolated from the stems of *Paullinia pinnata* (Sapindaceae). *P. pinnata* has been traditionally used to treat a wide range of bacterial infections, malaria, and erectile dysfunction.[137] Compound **168** was found to have high activity against *E. aerogenes*, *P. aeruginosa*, and *K. pneumoniae*, and moderate activity against *S. enterica* ser. *Typhi*.[137] Pinnatoside A was found to have high activity against *E. coli*, *E. aerogenes*, *K. pneumoniae*, and *P. aeruginosa*, and moderate activity against *S. enterica* ser. *Typhi*.[137]

The two glycosides identified in our review showed a high in vitro antibacterial activity. However, the lack of in vivo and clinical studies calls for a better investigation of these compounds.

2.5.5 Fatty Acids—Fatty acids are a large and diverse group of organic compounds that are characterized by their solubility in organic solvents and lack of solubility in water. Many endogenous lipids are bioactive and play key roles in physiological processes such as inflammation[439].

Dodec-9,11-diynoic acid (**169**), (12*E*)-heptadec-12-en-8,10-diynoic acid (**170**), and exocarpic acid (**171**), are all fatty acids obtained from *Thesium chinense* Turcz. (Santalaceae).[141] Exocarpic acid demonstrates high activity against *F. nucleatum* and *P. gingivalis*, and moderate activity against *S. mutans*. Compounds **169** and **170** have moderate to high activity against *F. nucleatum* and *P. gingivalis*.

3-(dodecanoyloxy)-2-(isobutyryloxy)-4-methylpentanoic acid (**172**) is another fatty acid isolated from the aerial parts of *Sigesbeckia glabrescens* (Makino) Makino (Asteraceae); it has moderate to high activity against *B. subtilis*, *E. faecalis*, *S. aureus,* and *S. pyogenes*.[142] It is a lauryl ester with a laurate group, which may account for its antibacterial activity. A study on lauric acid and monolaurin, which also contain a laurate group, also indicated significant antimicrobial activity, particularly against gram-positive bacteria.[440]

Of the ten fatty acids included in our review, four compounds (discussed above) showed a high in vitro antibacterial activity. To date, none of them have been studied in animals or humans, and further research is needed to assess the potential of fatty acids from plants as antibacterial agents.

2.5.6 Organosulfurs and Derivatives—Organosulfurs are organic compounds characterized by the presence of a sulfur atom. Some of the best-known organosulfurs are

the essential amino acids cysteine and methionine, antibacterials such as penicillin, the sulfonamides, and the chemical warfare agent sulfur mustard.

Diallyl thiosulfinate, or allicin (**174**), is a sulfur-containing compound produced when *Allium sativum* L. (Amaryllidaceae), garlic, is cut or damaged.[441] It contains both carbon and sulfur stereochemistry, although it occurs naturally as a racemate. Allicin is present in most *Allium* spp. It was first isolated in 1944 by Cavallito and Bailey and shown to be the major antibacterial compound in garlic.[442] However, garlic has a long history of medicinal uses before 1944. The Ebers papyrus, dated from the reign of the Egyptian Pharaoh Amenhotep I, circa 1534 BCE, describes 32 illnesses that can be treated with garlic.[443] Interestingly, even though allicin represents up to 70% of the thiosulfinates present; it is not present in raw garlic. Rather, after the tissue is injured, alliin is formed by the enzymatic hydrolysis of alliinase and then spontaneously condenses into allicin.[441] Allicin has shown a wide range of biological effects, including antifungal,[444] antiparasitic,[445] and antiviral[446] activities. It exhibits high antibacterial activity against *Burkholderia cenocepacia, B. cepacia* and *B. pyrrocinia*.[144] *Burkholderia* spp. can cause bacteremia, especially in young children, [447] and is one of the major bacteria involved in cystic fibrosis along with *S. aureus* and *P. aeruginosa*.[448] Allicin shows synergistic and adjuvant activity with conventional antibiotics such as oxacillin and cefazolin.[449] Additionally, allicin is stable in simulated intestinal fluid, [450] but was shown to have a relatively short half-life in aqueous solution at room temperature.[451] However, the biological half-life of allicin was longer than its chemical decomposition half-life; indicating that even the degradation products of allicin are biologically active.[451] The MOA for allicin was studied in red blood cells and synthetic membranes and was found to easily diffuse through the membrane and does not cause cell leakage or membrane fusion.[452] In *E. coli*, allicin reacts with intercellular glutathione, reducing the availability of this antioxidant, and reduces overall thiol-containing molecules and inhibits key enzymes of cell metabolism by reacting with cysteine residues. The culmination of these activities is cell death.[453]

In vivo efficacy of allicin was evaluated in a rabbit model of prosthetic joint infection caused by *S. epidermidis*. Allicin inhibited biofilm formation and enhanced the bactericidal effect of vancomycin in this model, suggesting that allicin in combination with vancomycin may be useful for the treatment of prosthetic joint infection.[454] In another in vivo study using a short-time hernia-repair rabbit model infected by *S. aureus*, a polypropylene mesh pretreated with a combination of allicin and chlorhexidine did not improve bacterial clearance compared to meshes treated with chlorhexidine alone, and the authors suggested that allicin could interfere with the necessary inflammatory process.[455] A clinical study evaluated the possible role of allicin in the eradication of *H. pylori*. Sixty patients with *H. pylori* positive biopsies, randomized to two groups, received a standard antibiotic course either alone or in combination with allicin at 4,200 μg/day for 14 days. This treatment led to the eradication of *H. pylori* in 20 patients (66.6%) in the first group and 27 patients in the second group (90%), indicating that allicin may be effective in the treatment of *H. pylori*.[456] Major drawbacks of allicin include its poor solubility, its sensitivity towards heat and alkaline, and its pungent odor. Therefore, the development of synthetic analogues and new delivery systems have recently been the main research foci for allicin.[457,458]

Propyl-propane-thiosulfonate[145] (**175**) is another organosulfur compound commonly found in the Amaryllidaceae family. This compound is commonly used as an additive in animal feed to improve livestock health in place of antibiotic growth promoters.[459] Propyl-propane-thiosulfonate was isolated from *Allium* spp. and shows high activity against *E. faecalis*, MRSA and *S. agalactiae*.[145]

Of the ten organosulfurs and derivatives found in our review, five (10,11-*erythro*-xanthopappin D, 10,11-*threo*-xanthopappin D, allicin, benzyl isothiocyanate, propyl-propane-thiosulfonate) showed high in vitro antibacterial activity. Allicin is the only compound from this group that was tested in animal models and clinical trials for the treatment of bacterial infections. Despite its great potential as an antibacterial agent, some concerns were raised regarding its pharmacokinetic (poor oral bioavailability, volatility, instability), organoleptic (pungent odor), and pharmacodynamic (herb-drug interactions) properties.[460–462] Still, allicin represents one of the most promising antibacterial leads from the organosulfurs and derivatives, and further research should focus on improving its physicochemical properties and evaluating its toxicological profile.

2.5.7 Peptides—Peptides are short chains of amino acids, typically under 40 amino acid residues in length, linked via a peptide bond. Peptide biosynthesis occurs at ribosomes, where mRNA is translated into its corresponding amino acid sequence before being post-translationally modified.

A phytochemical study by Daneshmand et al.[147] isolated the antibacterial peptide snakin-Z (**178**) from the fruit of *Ziziphus jujuba* Mill. (Rhamnaceae). Snakin-Z is a defensin-like cationic peptide. Plant defensin peptides typically lack antibacterial activity,[463] but snakin-Z had moderate activity against *B. subtilis*, *S. aureus*, *E. coli*, and *K. pneumoniae*.[147] The MOA for snakin-Z is currently unknown.

Only one peptide has been included in our review, but it exhibited moderate antibacterial activity. Overall, antibacterial peptides from plants represent an understudied group, with a small number of individuals discovered so far.[464] Because it has been suggested that bacterial resistance might not occur, antibacterial peptides represent an interesting group to explore, and more effort should be made to identify them in plants.[465] However, some limitations should also be considered such as their susceptibility to proteolytic degradation affecting their oral administration, a lack of information regarding their potential toxicity, and the high cost of peptide development and manufacturing.[466]

2.5.8 Steroids—Steroids are a group of lipids distinguished from other lipids by their quatracyclic structure. The most common endogenous steroid is cholesterol, which is a precursor to many biomolecules, including Vitamin D, testosterone, and estrogen. Most lipid hormones are steroid hormones, which are usually ketones or alcohols.

β-stigmasterol[93] (**179**) is a sterol with moderate activity against *M. aurum* and *M. smegmatis*. β-stigmasterol was isolated from the stem bark of *Tetracera potatoria* (Dilleniaceae) and shows potential for tuberculosis,[93] urinary tract infection, and typhoid

fever treatments.[467] Stigmast-22-ene-3,6-dione[148] (**180**) is a steroid that was isolated from *Salvinia auriculata* Aubl. (Salviniaceae) that is moderately active against *S. aureus*.

Stigmast-5-en-3β-ol-23-one[135] (**181**) and stigmast-5-en-3β-ol-21(24)-olide[135] (**182**) are moderately active against *B. subtilis*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus,* and *S. epidermidis*. Both were isolated from the root of *Trichodesma indicum* (Boraginaceae). Compound **182** is a lipophilic aliphatic ester that may be important in microbial membrane disruption.[468]

Eleven steroids were found in our review, among which four (i.e., polyphyllin G, stigmast-22-ene-3,6-dione, stigmast-5-en-3β-ol-21(24)-olide, stigmast-5-en-3β-ol-23-one) exhibited high antibacterial activity. None of them have been studied in animal models highlighting the need to better assess their role as antibacterial agents.

2.6 Summary of Antibacterial Compounds

MIC values of 459 compounds included in this review (reported in μg/mL), were classified into four main chemical classes (phenolic derivatives, terpenoids, alkaloids, and other metabolites) and selected for further analysis. This represents a total of 1,394 MIC values, including 887 MIC values for gram-positive bacteria, and 507 MIC values for gram-negative bacteria. Alkaloids, phenolic derivatives, terpenoids, and other metabolites showed overall mean MIC values of 20.8, 32.3, 36,6, and 34.4 μg/mL, respectively. Alkaloids had significantly better overall growth inhibitory activity ($P < 0.01$ or better) than each of the other chemical classes (Figure 5A). For gram-positive bacteria, alkaloids also had the lowest mean MIC, 19.7 μg/mL, compared to 29.7 (no significant difference), 35.0 ($P < 0.001$), and 35.5 μg/mL ($P < 0.01$) for phenolic derivatives, terpenoids and other metabolites, respectively (Figure 5B). For gram-negative bacteria, alkaloids again showed the lowest mean MIC value, 23.2 μg/mL, while other metabolites ranked second (33.4 μg/mL), phenolic derivatives ranked third (37.0 μg/mL), and terpenoids ranked fourth (40.0 μg/mL) (Figure 5C). However, significant differences in the superior activity of alkaloids for both gram-positive and -negative bacteria were only noted in comparison to terpenoids ($P < 0.05$).

Further examination of the MIC data was performed on the six most represented bacteria species (i.e. *Staphylococcus aureus, Escherichia coli*, drug-resistant strains of *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*), but no major patterns emerged from this analysis. While not statistically significant, alkaloids had the lowest mean MIC against *S. aureus, E. coli, and K. pneumoniae* (Figure 6A, **B** and **F**). For drug-resistant strains of *S. aureus,* the phenolic derivatives have the lowest mean MIC (Figure 6C) and other metabolites for *B. subtilis* (Figure 6D).

Another analysis was performed for the compounds with the lowest mean MICs tested against at least three different bacterial species. Overall, rhodomyrtone (**108**), allicin (**174**), and rhodomyrtosone B (**109**) had the lowest mean MICs with values of 0.56, 0.72, and 1.07 μg/mL, respectively. For gram-positive bacteria, rhodomyrtone (**108**), rhodomyrtosone B (**109**), and xanthoangelol (**17**) had the lowest mean MICs with values of 0.56, 1.07, and 1.63 μg/mL. For gram-negative bacteria, allicin (**174**), 2-phenylethanol (**164**), and pinnatoside A

(**167**) had the lowest mean MICs with value of 0.72, 3.61 and 5.31 μg/mL. Further descriptive statistics on all compounds are reported in Table 3.

Bacterial genera can be divided into three clusters based on the number of compounds that have been used to target them: (1) *Staphylococcus* was targeted by the most compounds by far, 289, (2) *Bacillus* and *Escherichia* were targeted by 110 and 112 compounds, respectively and (3) *Mycobacterium, Streptococcus, Enterococcus, Pseudomonas* and *Klebsiella* were targeted by 59–67 compounds each. All other bacterial genera were targeted by 45 compounds or fewer (Figure 7A). Of the 289 compounds used to target *Staphylococcus* species, 281 were specifically active against either antibiotic susceptible or resistant strains of *S. aureus* (Figure 7B).

Analyzing the bacterial species on the number of compounds screened against them: antibiotic susceptible strains of *Staphylococcus aureus* was targeted by the most compounds, 242, while MDR strains of *S. aureus* were screened against 100 compounds, and *Escherichia coli* was targeted by 113 compounds. All other bacterial species were targeted by 86 compounds or fewer (Figure 7B).

Based on this analysis, alkaloids stand out as the most promising botanical NP antibacterial candidate based on the mean MIC value, especially considering they represent only 6% of all the compounds in this review and showed the lowest average MIC values against both gram-positive and gram-negative bacteria. It must be noted that if the total number of compounds with high antibacterial activity is considered, rather than the mean MIC values, the phenolic derivatives are more promising lead molecules. However, this is heavily biased, since phenolic derivatives represent 47% of the compounds screened. Lastly, since *Staphylococcus* species are so heavily represented as a test organism, any generalization about potential compound class activity relationships will be influenced by this single genus representing 62% of the reported antibacterial testing data.

3. Emerging Trends

In the area of plant NP drug discovery, much progress is being made in the generation and analysis of large chemical datasets. In parallel, our understanding of antibacterial activity is being broadened by assays for bacterial virulence inhibition and the study of synergy and other interactions between plant NPs. Together, these increasingly sophisticated chemical and pharmacological approaches are beginning to open up the complexities of ethnobotanical antimicrobials to useful scientific investigation. Perhaps more than any other space in drug development, antibiotic development is in dire need of innovation in order to reinvigorate a waning pipeline. Small molecules remain the primary focus of drug discovery for antibiotics. While it is essential to consider innovations beyond this realm, such as bacteriophage therapy and fecal microbiota transplant, we have focused on innovations connected to small molecule discovery and development for this review.

Ethnobotany is uniquely positioned to fill in a portion of the preclinical antibiotic innovation gap thanks to both: (1) its utilization of established traditional medicinal knowledge to hone in on promising plants and to (2) the unique and promising region of the biologically

relevant chemical space occupied by plant NPs. At the same time, it must be noted that most studies cited in this review tend to use similar experimental approaches depending on whether extracts or purified compounds are under investigation. These approaches include classical bioassay-guided fractionation and structure elucidation by NMR after compound isolation and purification. In this section, we outline some emerging trends in drug discovery that are particularly well-suited for adoption into ethnobotanical approaches to antibiotic drug discovery. As the technological capacity of laboratories across the world grows, many of these trends will be adopted extensively and contribute to a streamlining of laboratory workflows.

3.1. Chemical Innovations

Plant NPs occupy a vast and largely untapped portion of the biologically relevant chemical space. Many chemical innovations for drug discovery can be explicitly applied to ethnobotanical drug discovery of antibiotics in order to advance the field.

3.1.1. Machine Learning—Machine learning (ML), a subset of artificial intelligence (AI), can be used to streamline decision-making by utilizing abundant, high-quality data to answer well-specified questions.[469] Very recently, ML has been successfully utilized for the identification of a structurally divergent antibiotic lead, halicin, which has demonstrated potent broad-spectrum antibiotic activity in vitro and in mouse models of infection. The investigators first trained a directed-message passing deep neural network model on a group of 2,335 compounds binarized as hit or non-hit for *E. coli* growth inhibition. The investigators used the in silico model to screen >107 million compounds, and of the top hits, 99 were obtained and screened in vitro by the investigators, whose workflow ultimately yielded halicin.[470]

In this breakthrough example, ML was utilized in the drug screening stage to identify a small group of compounds with a high probability of antibiotic activity against *E. coli*. ML can be applied at all stages of drug discovery and can be based on any of a wide variety of data such as images, text, chemical structures, spectroscopic data, and omics data.[469] AI has only in the last few years begun to see a practical application in drug discovery, much of this progress is due to advances in ML algorithms such as deep learning.[470] The hope in the pharmaceutical industry is that the application of ML will increase drug development success rates and lower costs, and it is being utilized by most large biopharma companies.[469,471]

Academic research labs are also increasingly applying ML to drug discovery efforts, with several studies having been done on plant NPs specifically. A recent study reported the success of a deep recurrent neural network model in *de novo* molecule generation of new chemical entities that modulate the retinoid X receptor (RXR).[472] This deep learning model was trained on the SMILES strings of a set 541,555 bioactive molecules from ChEMBL; by transfer learning, this model could generate new molecular structures based on template compounds. The investigators selected six known plant NP RXR ligands, and of the 1,000 SMILES strings generated, 201 were predicted as RXR agonists by self-organizing map-based prediction of drug equivalence relationships (SPiDER) target prediction software.[473]

Four compounds were chosen for synthesis and characterization in vitro for modulatory activity on the three RXR subtypes. Of the four, one demonstrated full agonistic activity on RXRα and RXRβ with low micromolar EC_{50} values. This early success, as well as the success of halicin should not, however, draw attention away from the progress yet to be made with ML. A recent review paper, for example, recommends the use of AI to correlate natural product 2D structure with biological function.[474] The ability to predict biological function of a NP would greatly streamline bioassay-guided fractionation efforts, but as of now, only a foundation has been laid for the pursuit of this goal. Furthermore, not all AI approaches have enjoyed market success. For example, due to poor financial returns, IBM is stopping development and sales of its AI technology Watson for Drug Discovery, though Pfizer continues to use it for hypothesis generation.[475]

ML will occupy a growing role in plant NP antibiotic development as it possesses the potential to aid the emerging trends below in answering important questions. For a more in-depth discussion of how ML can be applied to drug discovery and development, refer to the review by Vamathevan et al.[469]

3.1.2. Molecular Networking and Dereplication—Since its introduction in 2012, molecular networking (MN) has emerged as a revolutionary tool in natural product isolation, streamlining the process immensely.[476] This dereplication technique allows for rapid identification of compounds in complex mixtures by visualizing and organizing tandem MS/MS data sets and annotating them based on data sets of known compounds. As such, MN-based dereplication relies on the quality and availability of MS/MS data, for which the world's largest repository and data analysis tool is Global Natural Products Social Molecular Networking (GNPS).[477,478] Two ways to improve dereplication when relevant MS/MS data is unavailable are via in-house experimental MS/MS data and via in silico MS/MS data.[476] The idea behind the former is that using natural product samples enriched for a particular chemical class generated in one's lab, one can generate an MS/MS database on which a new dataset can be annotated for the identification of chemicals of that class and their derivatives. This strategy was pioneered by Fox Ramos et al. [479] and was used to isolate three new and three known monoterpene indole alkaloids from the bark of *Geissospermum laeve* (Vell.) Miers (Apocynacaeae) as well as dereplicate five known compounds previously undescribed in the genus. As for using in silico MS/MS data, the goal is to generate new databases to annotate on by using ML to generate MS/MS data of known compounds that lack experimental MS/MS data. The first in silico databases (ISDBs) were created by Allard et al. by using the ML-based tool CFM-ID v. 1.10 to generate MS/MS data for >220,000 compounds in the Dictionary of Natural Products and >170,000 compounds in the Universal Natural Products Database.[480–484] Several studies have since used these ISDBs for successful targeted plant natural product isolations.[485,486]

MN allows other layers of information besides MS/MS to be mapped over networks, including analytical, taxonomical and biological details and this has been increasingly leveraged to inform NP prioritization.[487–489] For example, one investigation by Olivon et al. [488] used MN embedding both bioactivity and taxonomic data to identify potentially bioactive scaffolds from 292 Euphorbiaceae extracts from New Caledonia. The collection was screened against the oncogenic Wnt signaling pathway and chikungunya virus (CHIKV)

replication. Crude extract activity levels in each assay were assigned a unique color tag and applied to the MN; as such, clusters of potentially bioactive metabolites became easily visualized. To better narrow down potential bioactive candidates and exclude ubiquitous compounds, extracts' genus/species and plant part were also assigned a unique color tag which was applied to the MN. This way, four bioactive clusters related to the leaves of *Bocquillonia nervosa* Airy Shaw (Euphorbiaceae) were identified as being associated with high efficacy in both bioassays. Ultimately, the investigators' workflow led to the isolation of a daphnane diterpene orthoester and four 12-deoxyphorbols with potent bioactivities. For an expanded discussion on natural product MN strategies and natural product prioritization, refer to reviews by Fox Ramos et al. and Wolfender et al.[476,490]

A tool of great interest that works well with dereplication protocols is the liquid micro junction surface sampling probe (LMJSS), which enables the in situ analysis of metabolites from a biological sample.[491] The LMJSS works by depositing a solvent droplet on a sample such as a leaf; this droplet extracts the metabolites from the area it covers, and the microextract is injected into LC-MS. There are, in fact, many iterations of mass spectrometry imaging (MSI) that allow for such in situ analyses, such as DESI-MSI (desorption electrospray ionization), MALDI-MS (matrix assisted laser desorption ionization) and LAESI-MS (laser ablation electrospray ionization).[492–495] The LMJSS distinguishes itself in that it uses chromatography while the others do not; it requires no sample preparation (as does LAESI), can sample any surface, and does not damage the sample. Additionally, the droplet probe can perform repeated sampling to concentrate microextractions by retaining a droplet on the top of the syringe. It cannot, however, take spatial measurements at high resolution due to the droplet size and so the other three techniques are superior at imaging. The droplet probe has been used to rapidly identify and differentiate acetogenin analogues and even isomers from the various organs of *Asimina triloba* (L.) Dunal (Annonaceae) through coupling to UPLC-PDA-HRMS/MS.[496] In a later study also by the Oberlies group, the investigators successfully identified cytotoxic prenylated xanthones from an herbarium voucher specimen of *Garcinia mangostana* (Clusiaceae) without damaging the specimen.[497] Although MS/MS data acquired from droplet probe experiments have yet to be used for prioritization of natural product isolation via MN, the possibility now exists of doing so without performing bulk extractions.

Although molecular networking is typically thought of as utilizing MS data, NMR spectroscopy is the other major analytical platform that yields highly specific fingerprints for a given compound.[498] A new tool has been developed for molecular networking with NMR data, Metabolomics And Dereplication By Two-dimensional Experiments (MADByTE).[499] MADByTE utilizes HSQC and TOCSY data to construct spin systems of a compound. Spin systems represent particular fragments of a compound; while MS/MS fragments also represent fragments, the two concepts are different. The spin systems are treated as features, and a sample is a collection of its features. If a compound is present in two samples, those samples will share features that correspond to it. From spin system features, MADByTE can generate a number of association networks and then output them as a graphML file for visualization in Cytoscape or Gephi. MADByTE is also capable of mapping bioactivity metadata over networks to visualize bioactivity profiles for sample prioritization. For MN, MADByTE does not use a centralized database of NMR spectra; rather, investigators can

query against in-house experimental data.[500] Other functions are currently being developed, including integration of MS data and the utilization of *in silco* databases for tentative structure elucidation.[499]

3.1.3. Metabolite Generation—The ability to efficiently produce desired natural products is of great importance to drug discovery. Typically, such production is done in bioreactors by reconstituting biosynthetic machinery in species such as *E. coli* and *Saccharomyces cerevisiae*. A challenge in this process, however, is that many biosynthetic pathways are not fully characterized. Genome mining is a strategy by which biosynthetic pathways are computationally predicted and prioritized for further studies such as natural product isolation.[501] A number of bioinformatics tools exist for the identification of natural product biosynthetic pathways from sequenced DNA.[502] Two examples are antiSMASH,[503] a comprehensive pipeline used for bacterial and fungal genomes and plantiSMASH,[504] an antiSMASH derivative that includes plant-specific cluster detection rules, co-expression analysis, and comparative genomic analysis. It is worth expanding on the latter two analyses. Co-expression analysis uses genes of known biosynthetic enzymes as bait and ranks other genes by correlation coefficient to the bait to identify candidate genes of biosynthetic enzymes. Rajniak et al.[505] successfully used a combination of untargeted metabolomics and co-expression analysis to identify 4-hydroxyindole-3carbonyl nitrile (4-OH-ICN), a previously unknown *Arabidopsis thaliana* (L.) Heynh. (Brassicaceae) cyanogenic metabolite and elucidate its biosynthesis by using the *CYP82C2* gene as bait. Comparative genomic analysis, on the other hand, uses phylogenetic profiling to find co-occurrence across genomes. CLIME (clustering by inferred models of evolution) is an algorithm that performs this analysis and it has been used to predict new members of a number of biosynthetic pathway based on shared inferred ancestry.[506]

While missing enzyme identification can be performed within the native species, similar enzymes in other organisms can be found via genome mining to construct an artificial pathway. Biosynthetic enzyme discovery studies often utilize genomic databases such as the Kyoto Encyclopedia of Genes and Genomes (KEGG) and the Medicinal Plant Genome Project, as well as transcriptomic databases such as the 1000 Plants (1KP) project.[507–509] Luo et al.[510] used the Medicinal Plant Genomics Resource, among other tools, to select six *Cannabis* (Cannabaceae) enzymes with potential geranylpyrophosphate:olivetolate geranyltransferase (GOT) activity, necessary for the biosynthesis of a precursor to several cannabinoids. Ultimately, the investigators constructed the complete biosynthesis of several major cannabinoids from galactose in *S. cerevisiae*.[510,511] For a thorough discussion on computational tools for discovering and engineering natural product biosynthetic pathways, refer to the review by Ren et al.[502]

The ability to generate NP derivatives has also been an emerging trend in the field of plant NPs. After identifying and engineering a suitable host organism and planning and engineering a metabolic pathway, many routes are possible to generating novel NPs; these steps are elaborated on in a review by Cravens et al.[512] Unnatural substrates can be fed to engineered microorganisms when the relevant biosynthetic enzymes are able to accommodate these structures for reactions.[513–515] Additionally, biosynthetic enzymes can be replaced, added, or removed from a pathway to alter metabolite production.[516–518]

Finally, novel enzymes can be incorporated into a biosynthetic pathway, with protein engineering likely needed to facilitate substrate accommodation.[519–521] While few studies have actually performed these feats, advancements in metabolic and protein engineering, discussed in dedicated review papers, will greatly enable the further pursuit of these strategies.[512,522–525]

Another system that can be thought of as a bioreactor for producing desired plant NPs are plants themselves. Cyber-agriculture is the growth of plants in contained environments under artificial climate control.[526] It has been developed to address challenges in agriculture, including optimizing the flavor and nutrient content of edible plants and reducing waste and costs. A proof-of-principle study has shown that by combining cyber-agriculture with metabolomics phenotyping, or chemotyping and predictive ML, the flavor profile of common sweet basil (*Ocimum basilicum* var "Sweet", Lamiaceae) could be optimized.[527] Johnson et al. grew basil plants in a Food Server, which is a large, multi-tray, multi-rack hydroponic configuration of the Food Computer the size of a shipping crate. By experimenting with different growth conditions, or climate recipes, a condition was identified in which the production of volatile flavor-active compounds was increased. Possible future uses for cyber-agriculture include experimentation on different plants and the analysis of different conditions such as stressors to modulate the production of compounds of interest. This strategy will use ML to determine optimal recipes to contribute to the emerging field of ethnophytotechnology.[528]

3.1.4. Endophytic Fungi—The ability of endophytes to alter and contribute to their host plant's chemistry is well known, though the intricacies of this phenomenon remained poorly understood until recently.[529] Endophytes are endosymbiotic microorganisms that reside in internal plant tissues beneath the epidermal cell layer without causing disease.[530,531] They have been shown to enhance host drought tolerance, growth, nutrient gain, and resilience to stressors and pests.[532,533] Because of the chemistry they confer to plants, endophytes, mainly fungal and bacterial, have long been of great interest to drug discovery.[534,535] Some fungal endophytes have even been shown to produce the same bioactive compounds as their hosts, which called more into question the extent to which plants alone are the sources of some botanical compounds.[536–538] Other studies have demonstrated that the presence of endophytes in plants does, in fact, alter the in vitro bioactivity of their extracts.[539,540] More recent ecological studies have explored in greater depth how endophytes interact with plants and play roles in their physiology. Khare et al. [541] discuss endophytism and the latest insights in the field. While much progress has been made in understanding the biology endophytes, Khare et al.[541] call for the exploration of the vast majority of endophytes that remain untouched, deduction of the biochemistry and physiology of endophytes up to genomic and metabolomics levels and the creation of a database for endophytic microorganisms and their metabolites.

A recent review by Martiez-Klimova et al.[542] covers antimicrobials isolated from endophytes between 2006–2016. Indeed, endophytes have evolved mechanisms to compete with other microbes inside plants and, as such, represent promising sources of antimicrobial compounds. Recent studies have capitalized on progress in the field and have discovered antibiotic compounds from endophytes. For example, Ibrahim et al. [543] describe their

collections from wild and highbush blueberry plants of the novel endophytic fungus *Xylaria ellisii*, the genus of which is unique in its diverse production of secondary metabolites. By dereplicating extracts against the Dictionary of Natural Products, Antibase, and NORINE and performing comparative analysis against known fungal metabolites, 11 previously reported compounds were identified. Following this, eight new proline-containing cyclic nonribosomal pentapeptides were identified named ellisiiamides A–H; ellisiiamide A was active against *E. coli* (MIC = 100 μg/mL), a first report for this scaffold. Further investigation of plant endophytes, and especially those plants identified through the ethnobotanical approach as being used in traditional medicine for infections, holds great potential for future antibiotic discovery.

3.1.5. Structure Elucidation—The field of anisotropic NMR has recently seen significant advancements that greatly improve its accessibility to natural product chemists. Residual dipolar couplings (RDCs) and residual chemical shift anisotropies (RCSAs) are examples of anisotropic NMR data, the former reporting the relative angles between internuclear vectors, usually C–H bonds and the latter reporting the relative orientations of carbon chemical shift tensors.[544–549] As such, these two anisotropic techniques complement each other and are particularly useful for structure elucidation in proton-deficient organic molecules. They have been used to unequivocally determine the 3D configurations of several complex natural products, the structures of which having previously been questioned.[550] To obtain anisotropic NMR data, an anisotropic sample environment is needed, and this can be achieved by an alignment medium such as compressed or stretched polymeric gels. An anisotropic environment precludes fully random molecular rotation, which renders dipolar coupling (DC) and chemical shift anisotropy (CSA) unobservable; consequently, residual DC and CSA are observable. RDCs and RCSAs are measurable by eliminating the isotopic contribution to the interactions via a control under an alternative alignment. In a recent publication, Liu et al.[551] describe the 2–3 day synthesis of two such gels and the sample setup as well as the 0.5–4 day experiments. Their results make the utilization of anisotropic NMR more accessible than ever to non-experts and hence more available for addressing complex structural assignment questions. Anisotropic NMR data can especially be used to aid in the structure elucidation of complex natural products by Computer-Assisted Structure Elucidation (CASE), which has less success determining the structures of proton-poor compounds.

CASE programs reduce the rate of error in natural product structure elucidation by generating all possible structures that agree with the input data, usually 2D COSY and HMBC data, and ranking them by probability.[552] In the case that a CASE program generates multiple probable structures, further experimentation is done to select between the alternatives.[553] To read about new developments in CASE methodology and future directions in the field, refer to the recent review by Burns et al.[554] Most CASE programs do not solve for absolute configuration, but only for planar structures. As mentioned above, by combining RDC and RCSA data 3D structures can be unequivocally determined for complex natural products.[550] To make use of these anisotropic NMR data, computational chemistry methods such as density functional theory (DFT) are used to generate 3D conformers based on probable 2D constitutions and 3D configurations. This strategy has

already been implemented by the development of StereoFitter by Mestrelab, the first to our knowledge to take advantage of anisotropic NMR data to introduce 3D conformational and configurational analysis into CASE.[555] Currently, StereoFitter accepts RDC, Nuclear Overhauser Effect (NOE), *J*-coupling, and chemical shift data to calculate 3D structure. Structure elucidation is often the rate-limiting step in natural products research.[556] The ability to rapidly determine the 3D structure of a compound computationally based on NMR data promises to further streamline natural product drug discovery efforts.

A key emerging trend in structure elucidation is the continuation of the NMR Raw Data Initiative, begun in 2016, which aims to address the urgent need for public availability of raw NMR data.[557] For further discussion on this need, the layers of the rationale behind it and action items for implementation, refer to the review by McAlpine et al.[558] In brief, raw NMR data is necessary for: structure revisions, impurity detection and quantification, dereplication, enabling new methodologies such as the new analysis of published data by optimal processing of the free induction decay (FID), assigning signals from other nuclei such as ^{19}F, building data repositories for purposes such as dereplication (via MADByTE, for example) and clinical applications such as magnetic resonance spectroscopy (MRS). While McAlpine et al. [558] outline several action items, the ultimate action item is the creation of a global and unified repository for raw NMR data.

Another emerging trend is the increased use of the cryo-electron microscopy (cryo-EM) technique microcrystal electron diffraction (microED), which has proven to be of astounding utility for the structure elucidation of small molecules, including NPs.[559] With microED, the structure of a small molecule in nanocrystal form on an EM grid can be solved. A nanocrystal is a crystal thousands of times smaller and much easier to produce than the crystals X-ray diffraction requires, and nanocrystals often spontaneously occur in simple powders. Two breakthrough studies published back-to-back in late 2018 demonstrate that microED can in minutes obtain structures with atomic resolution, in many cases better than 1 Å, from pure powder samples, pure rotary evaporated samples and even heterogeneous mixtures by selecting single crystals off of the EM grid.[560,561]

3.2. Pharmacological Innovations

A number of advancing areas in pharmacology stand to guide plant NP antibiotic drug discovery. Given the complex formulations and diverse applications of plant-based anti-infectives in traditional medicine, knowledge of the interactions between compounds and consideration of a variety of biological mechanisms are necessary for a full understanding of the potential of ethnobotanical antibacterials.

3.2.1. Drug Delivery Systems—Innovative drug delivery systems are a developing area of research for antibacterial agents, including compounds derived from plants. The purpose of drug delivery systems is to lower the dose of a drug required for a therapeutic effect and to localize the drug to the site of action, minimizing side effects. In the case of wounds and other dermatological conditions, topical treatment is often used, allowing for localization of a drug and decreased risk of systemic toxicity.[562,563] This approach is consistent with the historical medical tradition of using balms and poultices, often botanical.

[564] An emerging technology in topical treatments is the hydrogel, a moist polymeric mesh that provides a favorable environment for wound healing and can be impregnated with antibiotics.[565] For systemic use of antibacterials, a variety of nanoscale systems are being investigated as delivery mechanisms.[566] For example, the antibacterial flavone apigenin was found to have lowered MICs against both gram-positive and gram-negative bacteria when encapsulated in a liposome that allowed it to more easily enter cells.[567] Beyond delivering a drug to the site of action, drug delivery systems can be used to facilitate drug administration. One example is microneedle patches, which have been developed to address the need for administering drugs with the ease of oral administration and the delivery efficacy of an injection.[568] The continued development of precise drug delivery systems is crucial to the safe and effective use of plant-derived antibacterials.[470]

3.2.2. Synergy—The study of synergy and other interactions between plant compounds is also a growing research area in the field of ethnobotanical drug discovery.[569,570] The evolutionary ecology of plants lends itself to the production of compounds that interact synergistically on bacterial targets; as sessile organisms, plants produce mixtures of secondary metabolites for defense and these metabolites often interact to produce a more potent effect.[571]

The main limitation in studying synergy is the inherent complexity that comes from studying two compounds together rather than one,[16] a complexity that multiplies with the addition of more elements and is particularly daunting in the case of plant extracts, which can contain hundreds or thousands of potentially interacting compounds. Ethnobotanical drug discovery poses an even greater challenge, as combinations of diverse plant species are common among traditional formulations.[569] Currently, there are very few methods developed for studying higher-order interactions, or interactions between more than two agents.[572] Metabolomics approaches have recently arisen to systematically assess synergy in plant extracts, but with limitations on the complexity of the interactions that can be studied.[16,573] Omics approaches may, therefore, be particularly useful in the search for compounds that synergize with existing antibiotics.

3.2.3 Alternative Microbial Targets—Much of the research in plant-derived antibacterials is spurred by the rise of resistance to existing antibiotics.[574] Investigation of plant extracts may result in the discovery of antibiotics with novel mechanisms of action.[575] Alternatively, existing antibiotics may be modified to bypass certain types of resistance; approaches for developing natural product antibiotics that are effective against resistant bacteria are discussed in a review by Rossiter et al.[23]

Given the threat of antibiotic resistance, a growing amount of research is focused on the development of drugs that can combat bacterial virulence by mechanisms such as biofilm or quorum sensing inhibition, resulting in less evolutionary pressure for resistance and less harm to the commensal microbiome.[21] The role of plant NPs in these alternative antibacterial pathways is covered in a review by Silva et al.[22]

4. Conclusions and Future Perspectives

The antibacterial compounds reported herein represent dozens of unique scaffolds with abundant possibilities for derivatization for lead optimization. For antibacterial drug development, this is particularly true for some of the compounds with single-digit μg/mL MIC values and lower. Plant NPs that are poor candidates for lead optimization include those such as citronellol; they demonstrate potent activity in one or more bioassays but are likely not selective drugs due to their small molecular weight and a higher proportion of freely rotating bonds.[576] The MIC values of NPs listed herein are predominantly reported for only one or a few bacterial strains and often without toxicological data against mammalian cells. Therefore, establishing the selectivity of these NPs remains a crucial next step for preliminary justification for further drug development.

There are other aspects of the current state of antibacterial discovery from plants that speak to its still being in its early stages, one being that plant NPs are still largely unexplored. There are approximately 374,000 species of plants in the world today,[14] and 28,187 of them are estimated to be used by humans for medicine.[19] The most common types of bioassays employed in laboratory studies of plant NPs are those that explore inhibition of bacterial growth, and the compounds reported for antibacterial activity herein were isolated from 183 plant species and 73 families. This reflects the minuscule proportion of plants that were studied at all for antibacterial activity and highlights the need for increased research volume and rigor, both of which can be aided with the adoption of new technologies emerging in the field.

Of the 459 compounds with reported antibacterial activity, phenolic derivatives (mainly flavonoids) represented about half of them, while terpenoids represented roughly one-quarter. Interestingly, Silva et al. [56] found antivirulence activity against bacteria to be similarly distributed among plant natural product classes. In their study, they found that phenolics made up 59% of the total antivirulence compounds reported, among which flavonoids were the most represented (~50%). In a review of plant NPs used as adjuvants to antibacterial drugs, Zacchino et al.[577] showed that polyphenols were the most reported chemical class. The predominance of phenolics among antibacterial compounds from plants can be attributed to the unique features of this chemical class. Indeed, the number and positions of hydroxyl groups attached to the aromatic ring have been reported to be important for the antibacterial activity.[578] Cushnie and Lamb[579] reported that the antibacterial activity of flavonoids, in particular, could be mainly attributed to six structures out of 14: the flavones, chalcones, flavonols, flavan-3-ols, flavanones, and flavolans. Plants have developed the production of flavonoids for preventing much of the intercellular damage caused by free radicals and reactive oxygen species.[210] Flavonoids are readily oxidized by reactive species, consequently quenching them;[580] as such, many plant flavonoids are intrinsically reactive. Plant phenolic compounds also exhibit a wide range of MOAs, including cytoplasmic membrane damage, inhibition of nucleic acid synthesis, inhibition of energy metabolism, inhibition of cell wall synthesis, and efflux pump inhibition.[578,579]

In comparison to the other chemical classes, alkaloids demonstrated the lowest mean MIC value against reported bacteria. Alkaloid distribution is restricted in plants, with only 300

families producing these compounds.[581] They are also known to be highly toxic in animals and to possess allelopathic effects on plants.[582] A number of antibacterial drugs are alkaloids, including the antituberculosis medicine bedaquiline with its quinoline scaffold and the synthetic quinolones derived from quinine.[581] Many alkaloids also fall well within the parameters for being considered drug-like by Lipinksi's Rule of Five, and they have more skeletal structural and functional group diversity than other chemical classes.[583] Cordell et al.[583] noted that only 702 out of 21,120 known alkaloids have been evaluated in more than five bioassays and that many new alkaloid skeletons could be discovered from plant families that are already studied for alkaloids. Alkaloids thus represent a promising source of antibacterial compounds, and further research should be performed while considering their potential toxicity at an early stage of the drug discovery process.

Several chemical scaffolds are shared by a number of antibacterial plant natural products, and the relationship between their structures and reported MIC values makes clear the promising utility of more extensive SAR studies on lead optimization. For example, 2-hydroxy-anthraquinone has a structure very similar to that of digiferruginol: the latter has a methoxyl group instead of the hydroxyl group and an additional hydroxyl group on the same ring. Digiferruginol, reported in the same study as 2-hydroxy-anthraquinone, is approximately twice as potent at inhibiting *B. subtilis* growth. While modification of plant NPs by medicinal chemistry can yield derivatives with improved potency, it is also critical to assess subsequent changes in pharmacokinetics and toxicity. Such studies are largely yet to be undertaken in the field, and it is likely that they will be the next research frontier that plant NP chemists engage in order to bring candidate compounds through lead optimization. Derivatization is required in any case for patenting of NPs in the United States.[576]

Although many plant NPs present promising antibacterial activities, some also have drawbacks that limit their therapeutic use. For instance, many are poorly bioavailable when administered as single compound therapies. This is the case for a large portion of the most investigated plant compounds, such as allicin, berberine, curcumin, emodin, linalool, oleanolic acid, quercetin, and thymol. Other disadvantages associated with plant-derived compounds include a high volatility (e.g., linalool), low chemical stability (e.g., quercetin), pungent odor (e.g., allicin) and toxicity (e.g., sanguinarine). One solution is to improve their physicochemical properties through structural modifications; another is to load them onto drug delivery systems. The development of analogues by medicinal chemistry is key, particularly for performing SAR studies.

Despite NPs commonly violating Lipinski's rules[584] and often not meeting the solubility and permeability desired for druggable compounds, they occupy a vast area of chemical space that is unexplored, even in comparison to bioactive medicinal chemistry compounds.[585] Therefore, NPs represent a large reservoir of understudied compounds with novel chemistry, from biological systems, to explore in the search for novel pharmaceuticals.

It is important to note that unlike the random sampling approaches common to the broader field of NP research (e.g., mining soil, water, terrestrial and marine organisms for novel chemical scaffolds), the ethnobotanical approach to drug discovery for infection control is uniquely targeted,[586] relying on human knowledge and practice in the use of plant resources

to treat infections, sometimes over periods spanning centuries or even millennia. Importantly, human interactions with nature can vary greatly between different cultural groups—even for communities living in the same environment with access to the same natural resources.[587] Thus, further primary ethnobotanical field studies are also necessary to capture the full scope of human knowledge pertaining to medicinal plants across different environmental and cultural contexts. Lastly, the application of emerging technologies in drug discovery from plant NPs is likely to prove incredibly useful to fueling the antibiotic discovery pipeline in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Biographies

Gina Porras, Ph.D. received her BSc in chemistry from the National University, Costa Rica in 2007. She obtained her Ph.D. from La Laguna University, Spain in 2013, where she studied the isolation and structural elucidation of biologically active secondary metabolites from marine invertebrates and associated microorganisms under the guidance of Dr. Mercedes Cueto and Dr. José Darias. She returned to Costa Rica and worked as Bioprospection Unit Coordinator at National Center for Biotechnological Innovations, CENAT-CONARE, Costa Rica until 2017. In 2018, she joined to Quave Research Group at Emory University as a postdoctoral fellow, where her current research involves the isolation and structure elucidation of bioactive natural products from plants.

François Chassagne, Pharm.D., Ph.D. graduated from a School of Pharmacy in Paris Descartes University (Paris, France) in 2008, and he holds a M.Sc. in Biodiversity, Ecology and Evolution from Paul Sabatier University (Toulouse, France) obtained in 2009. During his studies, he became passionate about mycology and botany, and thus decided to explore their medicinal potential in various research projects. His first ethnobotanical survey started in Vietnam as part of a research program with the Hanoi University of Pharmacy in 2010. Then, he carried out other ethnobotanical surveys in Cambodia and Lao PDR during his PhD program that he completed in 2017 under the guidance of Dr. Eric Deharo and Dr. Geneviève Bourdy. Curious to understand the pharmacology and chemistry behind these traditional uses, he undertook postdoctoral training with Dr. Guillaume Marti, an expert in metabolomics, and Dr Guillaume Cabanac, informatician in 2017. In 2018, he then joined the Quave Research Group at Emory University as a postdoctoral fellow where he studied the antimicrobial properties of plant extracts. In 2020, he was selected by the French Research Institute for Sustainable Development (IRD) to lead his own research group in the field of ethnopharmacology in France.

James T. Lyles, Ph.D. graduated from Rhodes College in 2001 with a B.S. in biochemistry. He earned his Ph.D. in plant sciences with Dr. Edward J. Kennelly in 2011 from The Graduate Center of the City University of New York's joint program with the New York Botanical Garden. During this time, he studied natural products chemistry, pharmacognosy, botany, systematics, and field collection. He then developed a natural product research library consisting of botanicals, fungi, lichens, and seaweeds for The North Carolina Arboretum. While there, he also developed botanical authentication and adulteration testing for raw plant material and finished dietary supplements. Afterward, he undertook a post-doctoral fellowship at Emory University's Center for the Study of Human Health. In 2018, he was hired as an Associate Academic Research Scientist in the Phytochemical Research Laboratory of Cassandra L. Quave at Emory University.

Lewis Marquez received his Bachelor of Science in Cell and Molecular Biology from California State University, Northridge in 2018. He is currently a doctoral student in the Molecular and Systems Pharmacology program at Emory University. In 2019, he accepted a fellowship through The Jones Center at Ichauway and began his research under Dr. Cassandra Quave and Dr. Kier Klepzig. His work focuses on isolating and identifying the bioactive small molecules within plants used in traditional medicine by Southeast Native American tribes for use against drug-resistant microbes.

Micah Dettweiler earned his B.S. in Biology from Emory University in 2017 and worked as a Research Specialist in the Quave Research Group. He is currently pursuing his PhD in Agronomy at the University of Florida. His interests include the historic use of plant medicines in wound healing and the role of synergy in the activity of complex plant extracts.

Akram M. Salam received his Bachelor of Science in Biochemistry in 2015 from the University of Rochester in Rochester, New York, where he did combinatorial chemistry research for HIV drug discovery under Dr. Benjamin L. Miller. He then matriculated into Emory University's Molecular and Systems Pharmacology doctoral program and began research under Dr. Cassandra Quave on the discovery of plant natural products that inhibit quorum sensing in *Staphylococcus aureus*.

Tharanga Samarakoon, Ph.D. is Collections Manager of the Emory University Herbarium. She received her Bachelor of Science in Botany from the University of Peradeniya, Sri Lanka, in 2004. She completed her Ph.D. in Biology at the University of Southern Mississippi in 2015 with Dr. Mac Alford. Her graduate research was on a study of the phylogenetic relationships of the tropical family Samydaceae (former Flacourtiaceae) and the preparation of a monograph of the genus *Casearia* in south-central Asia. Her research interests are in plant systematics, including floristics, molecular phylogenetics, and phytogeography, particularly in southern and southeastern Asia.

Sarah Shabih is projected to graduate from Emory University in May 2021 with a Bachelor of Arts in Human Health. In 2019, she joined the Quave Research Group, where she undertakes research on the phytochemical makeup and antimicrobial activity of medicinal plants.

Darya Raschid Farrokhi is currently earning her Bachelor of Science in Biology at Emory University and is due to graduate in 2020. She is an undergraduate student that began her research with Dr. Quave in the Fall of 2019 after transitioning to Emory University from Oxford College of Emory University, where she earned her Associates of Arts. Her undergraduate research focuses on aiding in the isolation of fungal compounds with antibiofilm formation properties against a common human pathogen.

Cassandra Quave, Ph.D. is Curator of the Herbarium and Associate Professor of Dermatology and Human Health at Emory University, where she leads antibiotic drug discovery research initiatives and teaches courses on medicinal plants, microbiology, and pharmacology. Her research focuses on the documentation and biochemical analysis of plants used in the traditional medical treatment of infectious and inflammatory skin disease. She applies this unique approach to natural products drug discovery in her search for new antibiotics that target multidrug-resistant pathogens. She earned her B.S. in Biology and Anthropology from Emory University in 2000, her Ph.D. in Biology from Florida International University in 2008 in the laboratory of Dr. Bradley Bennett, and completed post-doctoral fellowships in Microbiology at the University of Arkansas for Medical Sciences (2009–2011) with Dr. Mark Smeltzer and Human Health at Emory University (2012) with Dr. Michelle Lampl. Her research has been supported by the National Institutes of Health, Fortune 100 industry contracts, and philanthropy. Dr. Quave has authored more than 100 scientific works and is the co-founder and CEO/CSO of PhytoTEK LLC, a drug discovery company dedicated to developing solutions from botanicals for the treatment of recalcitrant antibiotic-resistant infections. Quave is a Fellow of the Explorers Club, a past President of the Society for Economic Botany, a recipient of the Emory Williams Teaching Award and Charles Heiser, Jr. Mentor Award. She is the creator and host of *Foodie Pharmacology*, a podcast dedicated to exploring the links between food and medicine. Her research has been the subject of feature profiles in the *New York Times Magazine*, *BBC Focus, National Geographic Magazine, Brigitte Magazin*, National Geographic Channel, National Public Radio (NPR), and several major news outlets.

List of Abbreviations

1KP	1000 Plants (initiative for plant gene sequencing)
AADC	Aromatic Amino Acid Decarboxylases
ABC transporters	ATP-binding cassette transporters
AI	Artificial Intelligence
AMR	Antimicrobial Resistance
AntiSMASH	Platform for rapid genome-wide identification, annotation and analysis of secondary metabolite biosynthesis gene clusters
ATP	Adenosine Triphosphate
BCE	Before the Common Era

BeWo	Human choriocarcinoma cell line
Caco-2	Human epithelial colorectal adenocarcinoma cell line
CASE	Computer-Assisted Structure Elucidation
CDC	Centers for Disease Control
CFM-ID	Competitive Fragmentation Modeling-ID
ChEMBL	Curated chemical database of bioactive molecules with drug-like properties
CHIKV	Chikungunya Virus
CLIME	Clustering by Inferred Models of Evolution
CoA	Coenzyme A
COSY	Correlated Spectroscopy
CoAt-Mt	coenzyme A transferase of *M. tuberculosis*
Cryo-EM	Cryo-electron Microscopy
CSA	Chemical Shift Anisotropy
DC	Dipolar Coupling
DESI	Desorption Electrospray Ionization
DFT	Density Functional Theory
DMAPP	dimethylallyl diphosphate
DNA	Deoxyribonucleic Acid
DOPAC	3,4-dihydroxyphenylacetic acid
DOXP	1-deoxy-D-xylulose-5-phosphate
EC_{50}	Effective Concentration 50%
EDTA	Ethylenediaminetetraacetic Acid
EO	Essential Oil
EPS	Exopolysaccharide
ESBL-KP	extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*
FDA	Food and Drug Administration
FICI	Fractional Inhibitory Concentration Index
FID	free induction decay

FPP	farnesyl pyrophosphate
FtsZ	Filamenting temperature-sensitive mutant Z
GGPP	Geranylgeranyl Pyrophosphate
GNPS	Global Natural Products Social Molecular Networking
GOT	Geranylpyrophosphate:olivetolate Geranyltransferase
GPP	Geranyl Pyrophosphate
GTP	Guanosine Triphosphate
GTPase	Guanosine Triphosphate Hydrolase
HepG2	Human liver cancer cell line
HIV	Human Immunodeficiency Virus
HL-60	Human leukemia cell line
HL-7702	Human liver cell line
HMBC	Heteronuclear Multiple Bond Correlation
HSQC	Heteronuclear Single Quantum Coherence Spectroscopy
HTS	High Throughput Screening
IPP	Isopentyl Pyrophosphate or Isopentyl Diphosphate
ISDB	In Silico tandem mass spectrometry database
ISM&H	Indian Systems of Medicine and Homoeopathy
KB	human nasopharyngeal cell line
KEGG	Kyoto Encyclopedia of Genes and Genomes
LAESI	Laser ablation electrospray ionization
LC-MS	Liquid Chromatography-Mass Spectrometry
LD_{50}	Lethal dose 50%
MADByTE	Metabolomics And Dereplication By Two-dimensional Experiments
MALDI	Matrix Assisted Laser Desorption Ionization
MDR	Multidrug-resistant
MEP	Methylerythritol 4-phosphate
MFS	Major Facilitator Superfamily

MIC	Minimum Inhibitory Concentration
Micro-ED	Microcrystal Electron Diffraction
ML	Machine Learning
MN	Molecular Networking
MOA	Mechanism of Action
MPNS	Medicinal Plant Names Services
MRS	Magnetic Resonance Spectroscopy
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSI	Mass Spectrometry Imaging
MS/MS	Tandem mass spectrometry
MSSA	Methicillin-Sensitive *Staphylococcus aureus*
NADH	Reduced form of NAD (nicotinamide adenine dinucleotide)
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
NorA	*Staphylococcus aureus* multidrug efflux pump
NORINE	Database platform of nonribosomal peptides
NP	Natural Product
ORCNS	Oxacillin-resistant Coagulase-negative Staphylococci
OSCNS	Oxacillin-sensitive Coagulase-negative Staphylococci
OTC	Over-the-Counter
PAR	Phenylacetaldehyde Reductases
plantiSMASH	Platform for plant secondary metabolite analysis
PPAP	Polycyclic Polyprenylated Acylphloroglucinol
RCSA	Residual Chemical Shift Anisotropy
RDC	Residual Dipolar Couplings
RNA	Ribonucleic Acid
RXR	Retinoid X Receptor
SAR	Structure-Activity Relationship
SMILES	Simplified Molecular-Input Line-Entry System

S_N2	a reaction mechanism common in organic chemistry
SPiDER	Self-organizing map-based prediction of drug equivalence relationships
TOCSY	Total Correlated Spectroscopy
UDP-glucose	Uridine diphosphoglucose
UPLC-PDA-HRMS/MS	Ultra-Performance Liquid Chromatography–High-Resolution Tandem Mass Spectrometry
US	United States
UTP	Uridine Triphosphate
UV	Ultraviolet
VISA	Vancomycin-Intermediate *Staphylococcus aureus*
VRE	Vancomycin-Resistant Enterococci
VRSA	Vancomycin-Resistant *Staphylococcus aureus*
XDR	Extensively Drug-Resistant

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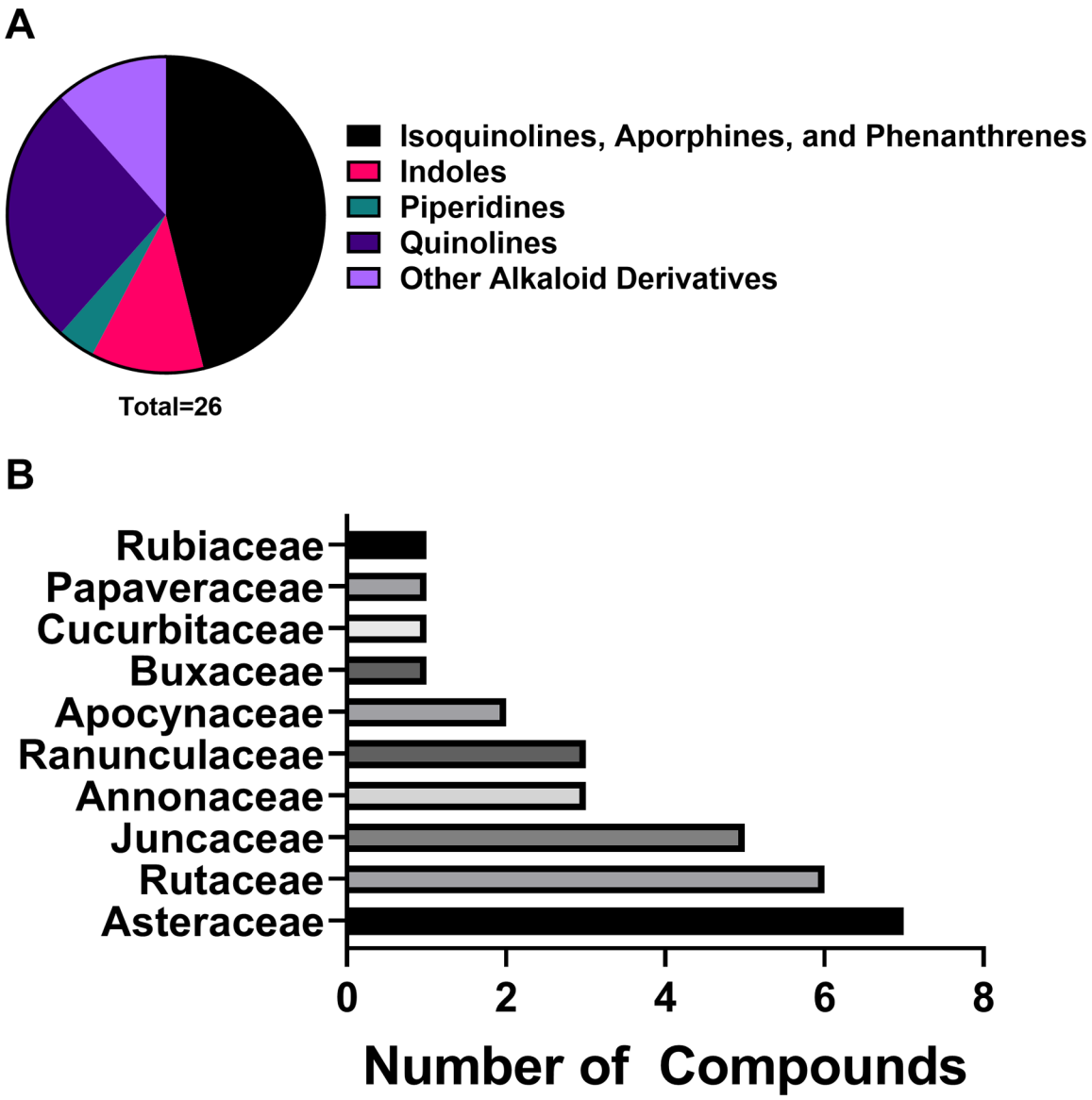


Figure 1.

A) Chemical classes of alkaloids investigated for antibacterial activity and B) top ten plant families yielding antibacterial alkaloids under the study parameters.

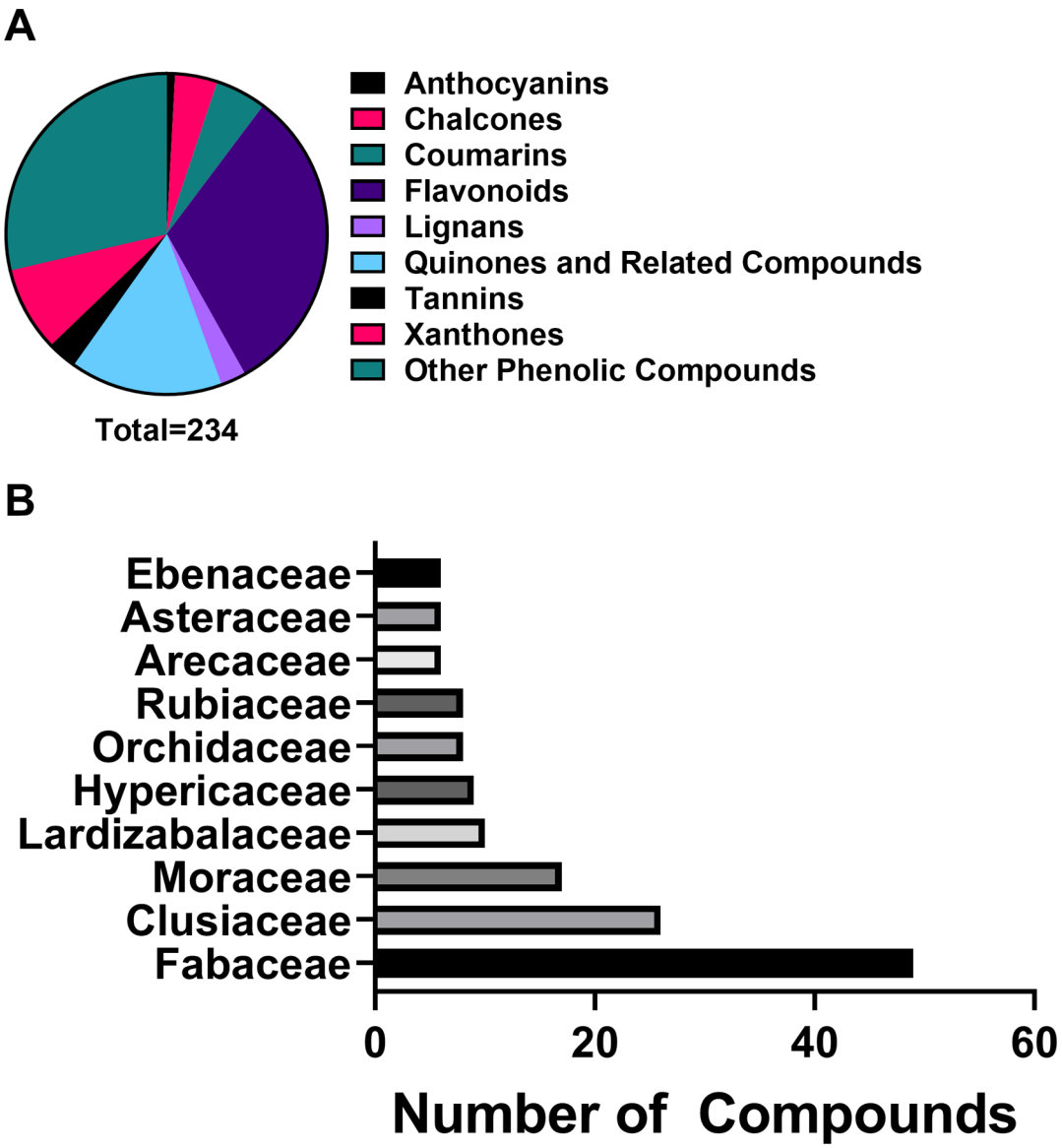


Figure 2.

A) Chemical classes of phenolic derivatives investigated for antibacterial activity and B) top ten plant families yielding antibacterial phenolic derivatives.

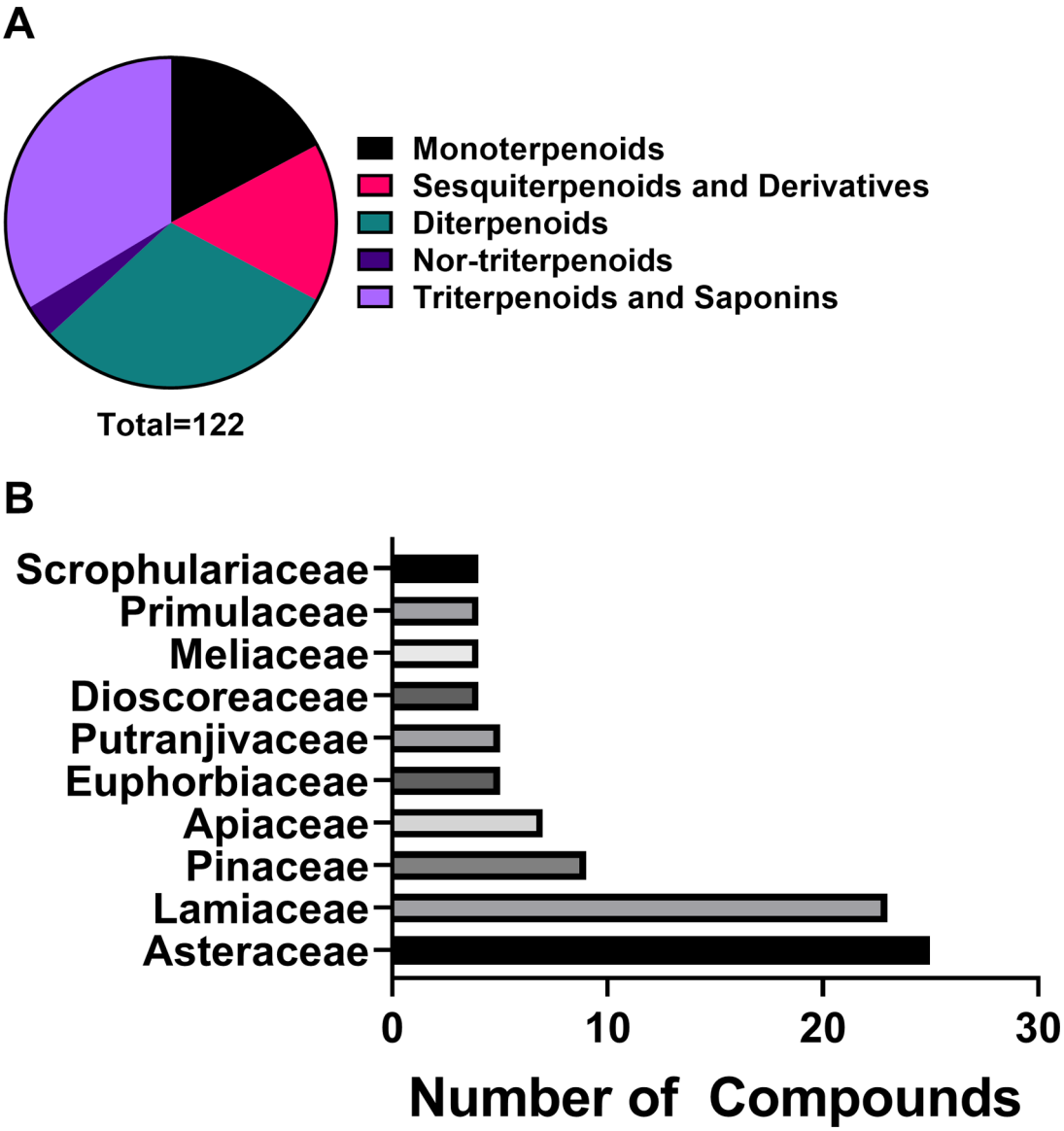


Figure 3.

A) Chemical classes of terpenoids investigated for antibacterial activity and B) top ten plant families yielding antibacterial terpenoids.

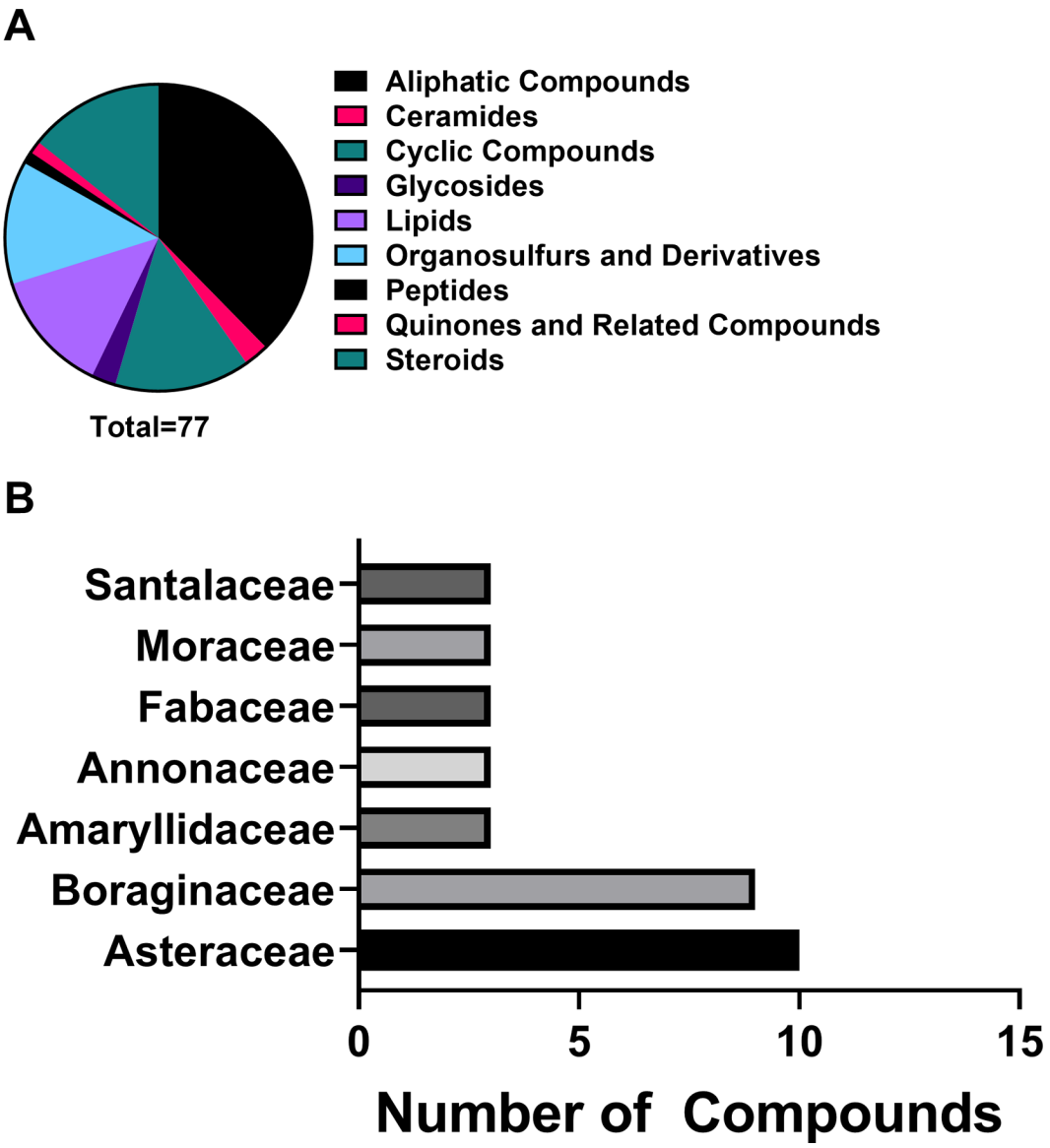


Figure 4.

A) Chemical classes of other metabolites investigated for antibacterial activity and B) top seven plant families yielding other antibacterial metabolites. The remaining 20 plant families had less than three compounds each represented in the data.

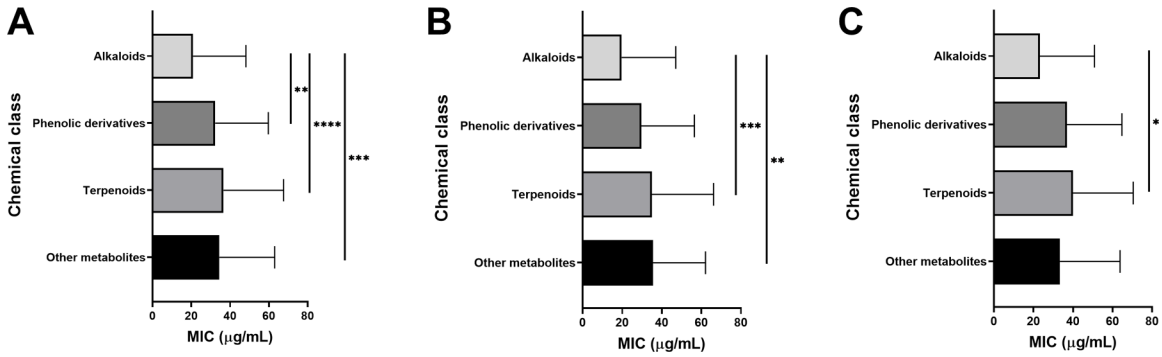


Figure 5.

Mean and standard deviation of minimum inhibitory concentration (MIC) of compounds for each of the four chemical classes, with significant differences in MIC values (μg/mL) for A) all bacteria; B) gram-positive bacteria and C) gram-negative bacteria. P-values: *: $P < 0.05$, **: $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

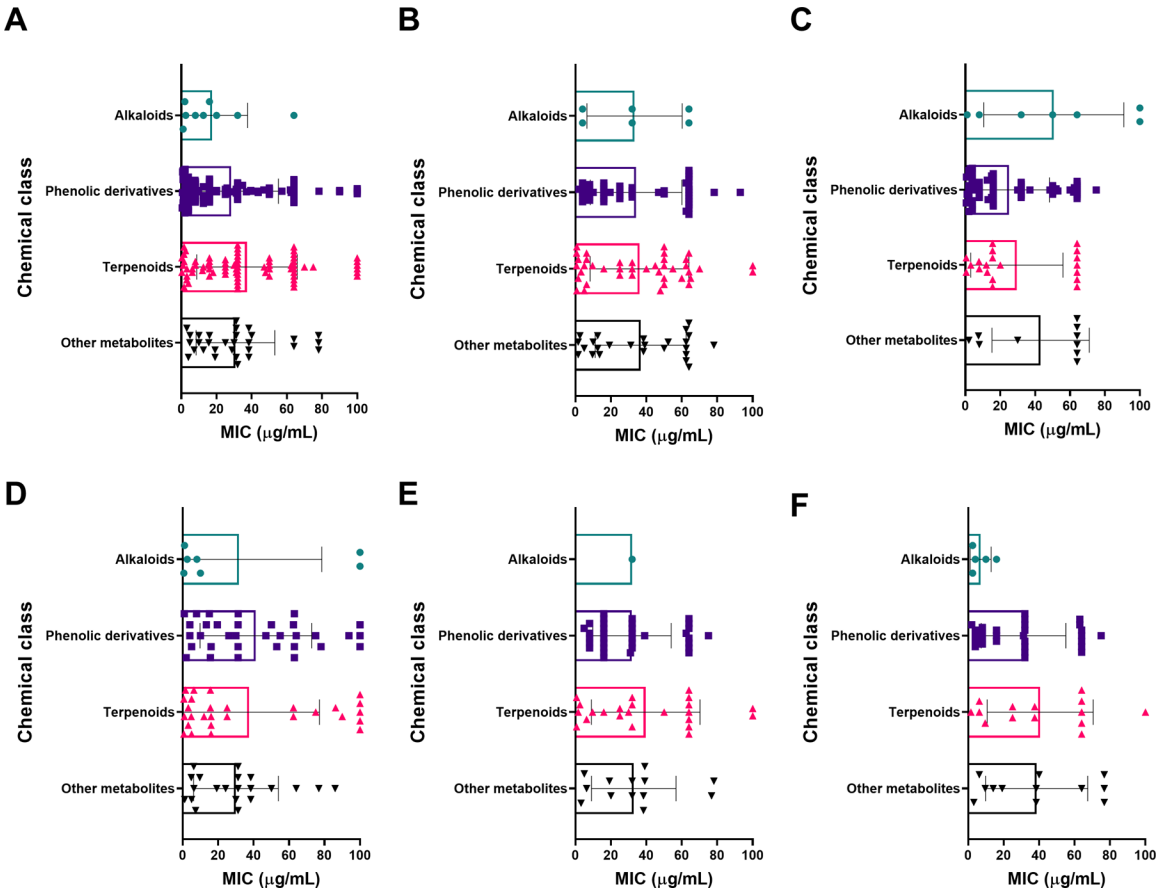


Figure 6.

Minimum inhibitory concentration (MIC) of compounds reported by chemical class, with significant differences in MIC values for A) *Staphylococcus aureus,* B) *Escherichia coli*, C) all drug resistant strains of *Staphylococcus aureus*, D) *Bacillus subtilis*, E) *Pseudomonas aeruginosa*, and F) *Klebsiella pneumoniae*. No significant difference was observed between the chemical classes for each bacterium.

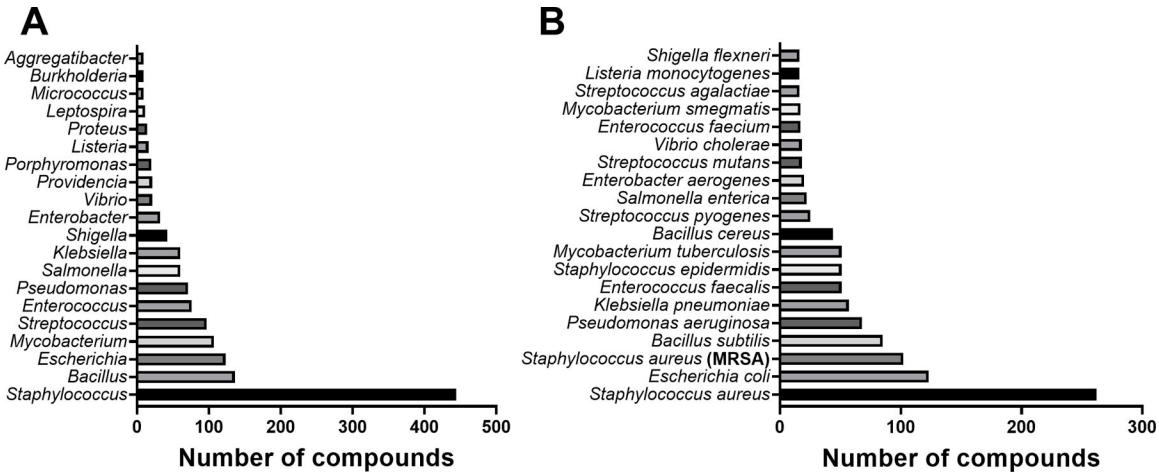
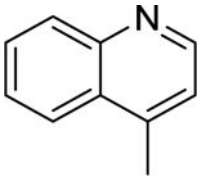
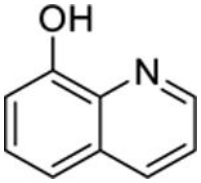
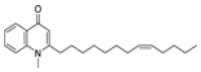
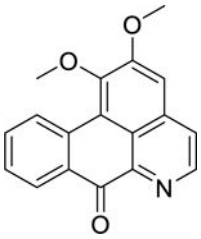
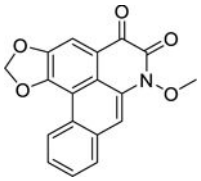


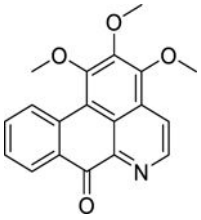
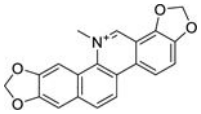
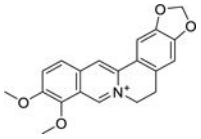
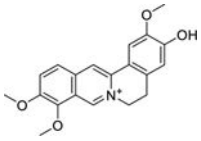
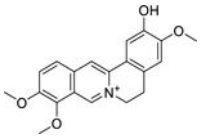
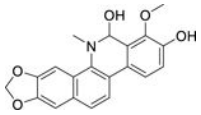
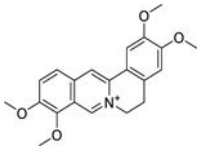
Figure 7.

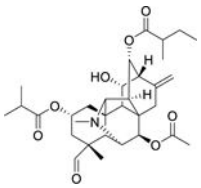
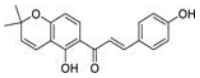
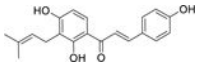
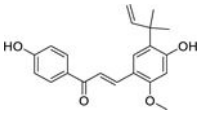
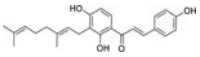
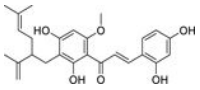
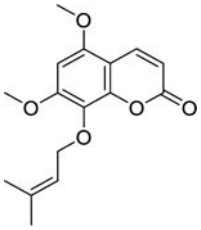
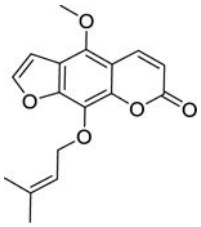
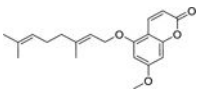
The most targeted A) bacterial genera and B) bacterial species by antibacterial plant compounds.

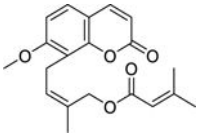
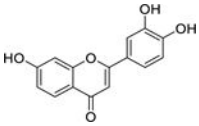
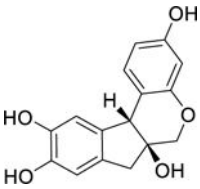
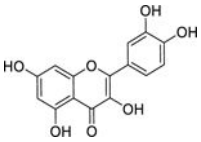
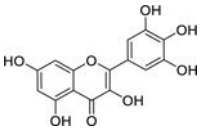
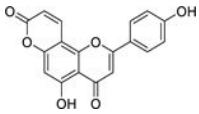
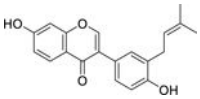
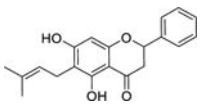
Table 1.

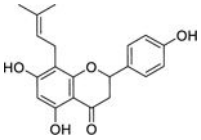
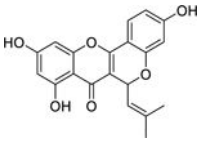
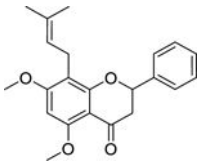
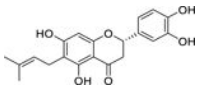
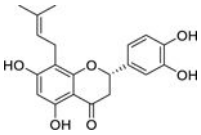
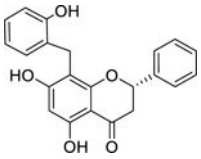
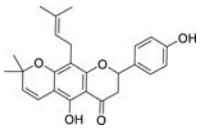
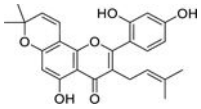
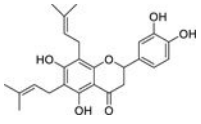
Summary of antibacterial activity for select plant NPs. Compounds are presented with the stereochemistry and configurations determined from the original citation. However, for structures that underwent revisions or for which additional stereochemistry is necessary to differentiate it from other isomers, these clarifications and corrections are included in this table.

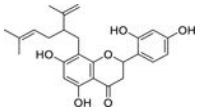
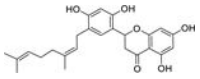
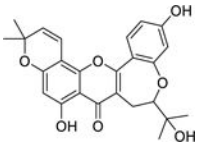
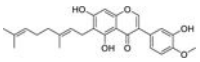
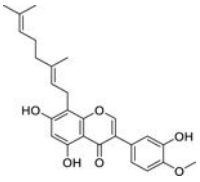
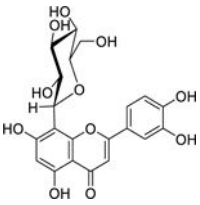
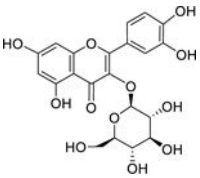
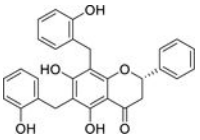
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
ALKALOIDS					
Quinolines					
1		4-methylquinoline	*Staphylococcus aureus*	12.5	28
			Listeria monocytogenes	25	
			Bacillus cereus	50	
			Salmonella enterica serotype *Typhimurium*	75	
			Shigella sonnei	100	
2		8-hydroxyquinoline	*Staphylococcus aureus*	2	29
			Haemophilus influenzae	8	
3		evocarpine	*Staphylococcus aureus*	8	30
			Staphylococcus aureus (MRSA)	8	
Isoquinolines, Aporphines, and Phenanthrenes					
4		lysicamine	*Listeria monocytogenes*	2.5	31
			Streptococcus pneumoniae	2.5	
			Streptococcus agalactiae	5	
			Klebsiella pneumoniae (ESBL-KP)	10	
			Proteus vulgaris	10	
5		artabotrine	*Bacillus cereus*	1.25	31
			Listeria monocytogenes	1.25	
			Proteus vulgaris	1.25	
			Staphylococcus sp. (ORCNS)	1.25	
			Staphylococcus aureus	2.5	
			Klebsiella pneumoniae (ESBL-KP)	2.5	

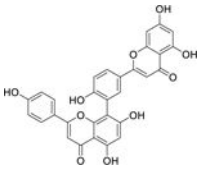
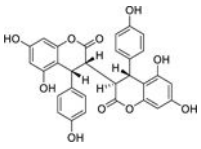
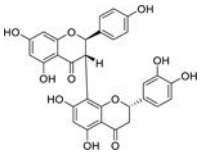
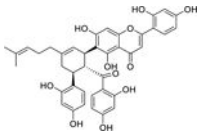
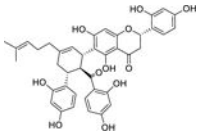
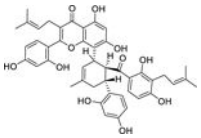
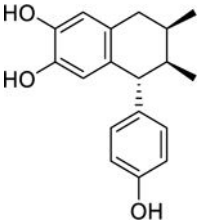
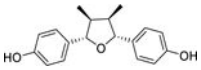
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
6		liridine	*Bacillus subtilis*	0.625	31
			Listeria monocytogenes	1.25	
			Staphylococcus sp. (OSCNS)	1.25	
			Streptococcus agalactiae	1.25	
			Klebsiella pneumoniae (ESBL-KP)	2.5	
7		sanguinarine	*Staphylococcus epidermidis*	0.5	32
			Staphylococcus aureus (MRSA)	1	
			Enterococcus faecalis (Vancomycin-R)	8	
			Escherichia coli	4	
			Acinetobacter baumannii	16	
			Klebsiella pneumoniae	16	
8		berberine	*Brucella abortus*	1.56	33
			Prevotella intermedia	3.8	34
			Fusobacterium nucleatum	31.25	
9		jatrorhizine	*Brucella abortus*	0.78	33
10		columbamine	*Brucella abortus*	3.12	33
11		buesgenine	*Escherichia coli*	4	35
			Klebsiella pneumoniae	4	
			Enterobacter aerogenes	16	
			Pseudomonas aeruginosa	32	
12		palmatine	*Helicobacter pylori*	3.12	36
			Brucella abortus	6.25	33
Other Alkaloid Derivatives					

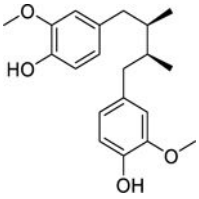
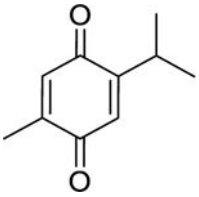
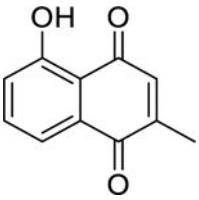
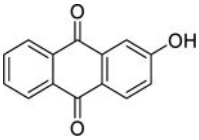
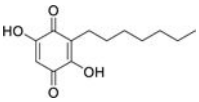
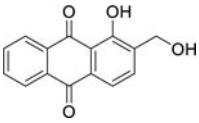
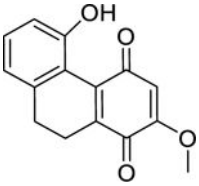
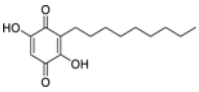
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
13		carmichaedine	*Bacillus subtilis*	8	37
		PHENOLIC DERIVATIVES			
		Chalcones			
14		4-hydroxylonchocarpin	*Staphylococcus aureus*	1	38
15		isobavachalcone	*Staphylococcus aureus*	2	38
16		licochalcone A	*Staphylococcus aureus*	1	39
17		xanthoangelol	*Staphylococcus aureus*	1.2	40
			Enterococcus faecium	1.2	
			Enterococcus faecalis	2.5	
18		kuraridin	*Staphylococcus aureus*	2	41
		Coumarins			
19		artanin	*Staphylococcus aureus*	8	42
			Staphylococcus aureus (MRSA)	8	
20		phellopterin	*Staphylococcus aureus*	8	42
			Staphylococcus aureus (MRSA)	16	
21		5-geranyloxy-7-methoxy-coumarin	*Staphylococcus aureus*	8	42
			Staphylococcus aureus (MRSA)	8	

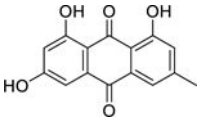
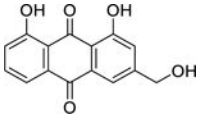
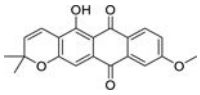
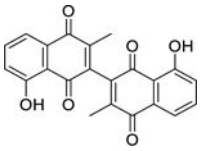
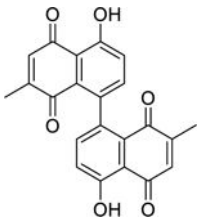
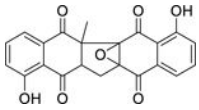
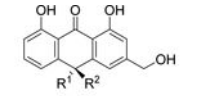
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
22		4′-senecioiloxyosthol	*Bacillus subtilis*	5	43
		Flavonoids			
23		3′,4′,7-trihydroxyflavone	*Providencia stuartii*	4	44
			Escherichia coli	8	
			Klebsiella pneumoniae	32	
24		brazilin	*Bacillus subtilis*	31.3	45
			Cutibacterium acnes	15.6	46
			Staphylococcus epidermidis	31.2	
			Staphylococcus aureus	62.5	
25		quercetin	*Streptococcus pyogenes*	8	47
			Pseudomonas aeruginosa	16	
			Staphylococcus aureus	16	
			Aggregatibacter actinomycetemcomitans	31.25	48
			Mycobacterium tuberculosis	32	49
			Klebsiella pneumoniae	32	47
26		myricetin	*Mycobacterium tuberculosis*	7.81	50
27		pseudarflavone A	*Escherichia coli*	4	51
			Staphylococcus aureus	8	
			Pseudomonas aeruginosa	16	
			Klebsiella pneumoniae	32	
			Enterococcus faecalis	64	
28		neobavaisoflavone	*Enterococcus faecalis*	4	52
			Providencia stuartii	4	
			Escherichia coli	8	52,53
			Pseudomonas aeruginosa	8	
			Klebsiella pneumoniae	8	
29		6-prenylpinocembrin	*Escherichia coli*	4	51
			Klebsiella pneumoniae	8	
			Staphylococcus aureus	8	
			Enterococcus faecalis	16	

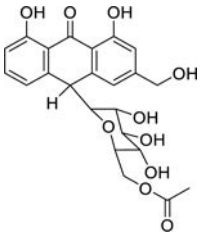
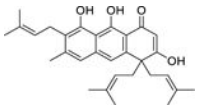
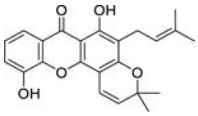
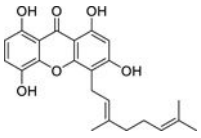
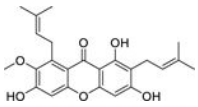
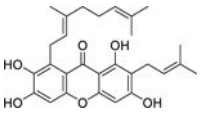
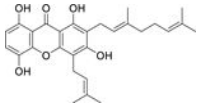
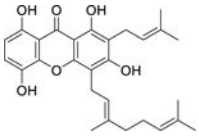
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
			Pseudomonas aeruginosa	32	
30		8-prenylnaringenin	*Staphylococcus aureus*	12.5	[54]
			Staphylococcus epidermidis	12.5	
31		cyclocommunol	*Staphylococcus aureus* (MSSA)	4	[55]
			Staphylococcus aureus (MRSA)	8	
32		candidone	*Enterococcus faecalis*	4	[52]
			Escherichia coli	4	
			Klebsiella pneumoniae	4	
			Enterobacter aerogenes	16	
33		5,7,3',4'-tetrahydroxy-6-(3',3'-dimethylallyl)-flavanone	*Staphylococcus aureus*	12.5	[54]
			Staphylococcus epidermidis	50	
34		5,7,3',4'-tetrahydroxy-8-(3',3'-dimethylallyl)-flavanone	*Staphylococcus aureus*	12.5	[54]
			Staphylococcus epidermidis	25	
35		chamanetin	*Staphylococcus aureus* (MSSA)	7.5	[56]
			Staphylococcus aureus (MRSA)	15	
			Staphylococcus aureus (VISA)	15	
			Enterococcus faecalis	15	
			Bacillus subtilis	15	
36		lupinifolin	*Streptococcus mutans*	1	[57]
			Staphylococcus aureus	8	[58]
			Bacillus cereus	15.63	[59]
37		morusin	*Staphylococcus aureus* (MRSA)	8	[55]
			Staphylococcus aureus (MSSA)	16	
38		6–8-diprenyleriodictyol	*Staphylococcus aureus*	0.5	[38]

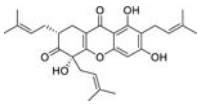
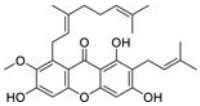
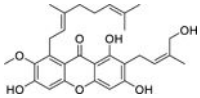
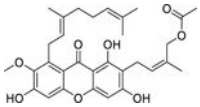
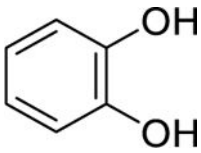
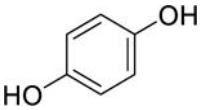
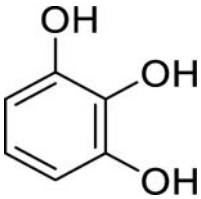
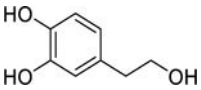
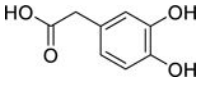
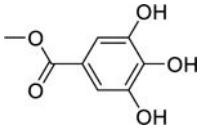
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
39		sophoraflavanone G	*Staphylococcus aureus*	1	41
40		kuwanon E	*Staphylococcus aureus* (MSSA)	4	55
			Staphylococcus aureus (MRSA)	4	
41		neocyclomorusin	*Enterococcus faecalis*	4	52
			Klebsiella pneumoniae	4	
			Enterobacter aerogenes	8	
			Escherichia coli	8	
			Providencia stuartii	8	
42		6-geranyl-5,7,3′-trihydroxy-4′-methoxyisoflavone	*Enterococcus faecium*	5.5	40
			Enterococcus faecalis	10.9	
			Staphylococcus aureus	43.7	
43		8-geranyl-5,7,3′-trihydroxy-4′-methoxyisoflavone	*Enterococcus faecium*	10.9	40
			Enterococcus faecalis	21.8	
			Staphylococcus aureus	43.7	
44		luteolin-8-*C*-glucoside	*Staphylococcus aureus*	4	60
			Shigella flexneri	4	
			Vibrio cholerae	16	
45		isoquercetin	*Pseudomonas aeruginosa*	8	47
			Staphylococcus aureus	16	
46		dichamanetin	*Staphylococcus aureus* (MRSA)	1	56
			Staphylococcus aureus	2	
			Staphylococcus aureus (VRSA)	2	
			Bacillus subtilis	4	
			Enterococcus faecalis (Vancomycin-R)	7.5	

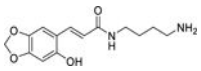
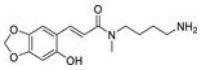
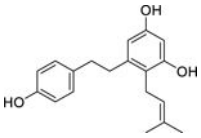
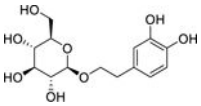
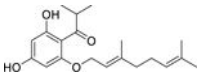
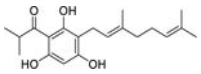
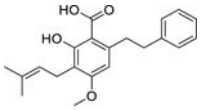
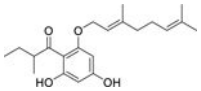
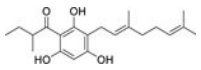
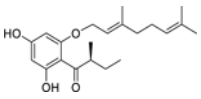
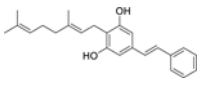
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
47		amentoflavone	*Staphylococcus aureus*	4	61
			Enterococcus faecium	8	
			Escherichia coli	8	
			Pseudomonas aeruginosa	8	
			Streptococcus mutans	32	
48		3″-epidiphysin	*Staphylococcus aureus*	2.17	62
			Bacillus subtilis	19.5	
49		(2*R*,3*S*,2′′*S*)-3′′′,4′,4′′′,5,5′′,7,7′′-heptahydroxy-3,8”-biflavanone	*Staphylococcus aureus*	2	60
			Shigella flexneri	4	
			Vibrio cholerae	8	
50		multicaulisin	*Staphylococcus aureus* (MRSA)	2	63
51		sanggenon G	*Staphylococcus aureus* (MRSA)	4	63
52		albanin G	*Staphylococcus aureus* (MRSA)	4	63
		Lignans			
53		3′-demethoxy-6-*O*-demethylisoguaiacin	*Enterococcus faecalis*	12.5	64
			Mycobacterium tuberculosis (MDR)	12.5	
			Staphylococcus aureus (MRSA)	12.5	
			Escherichia coli	50	
54		4-*epi*-larreatricin	*Enterococcus faecalis*	12.5	64
			Mycobacterium tuberculosis (MDR)	25	
			Mycobacterium tuberculosis	50	

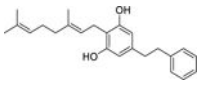
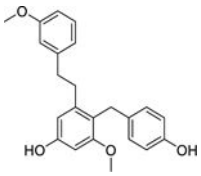
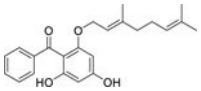
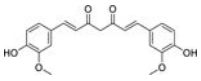
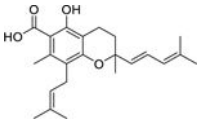
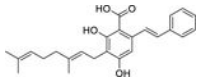
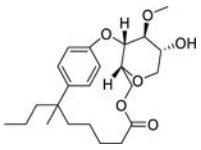
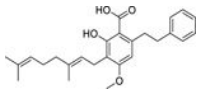
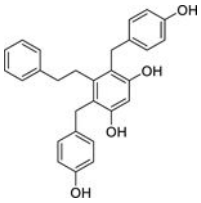
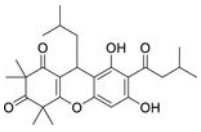
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
55		dihydroguaiaretic acid	*Mycobacterium tuberculosis* (MDR)	12.5	64
			Mycobacterium tuberculosis	50	
			Staphylococcus aureus (MRSA)	50	
Quinones and Related Compounds					
56		thymoquinone	*Haemophilus influenzae*	8	29
			Staphylococcus aureus (MRSA)	8	65
			Staphylococcus aureus	16	29
			Streptococcus pneumoniae	16	
57		plumbagin	*Mycobacterium tuberculosis* (XDR)	1.56	66
			Escherichia coli	2	67
			Klebsiella pneumoniae	2	
			Staphylococcus aureus (MRSA)	2	
			Streptococcus pneumoniae	5	68
			Staphylococcus aureus	5	69
58		2-hydroxy-anthraquinone	*Bacillus subtilis*	1.9	70
			Bacillus cereus	62.5	
59		2,5-dihydroxy-3-heptyl-2,5-cyclohexadiene-1,4-dione	*Enterobacter aerogenes*	4	67
			Escherichia coli	4	
			Klebsiella pneumoniae	4	
			Staphylococcus aureus	4	
60		digiferruginol	*Bacillus subtilis*	0.9	70
61		ephemeranthoquinone B	*Bacillus subtilis*	1.1	71
62		homoembelin	*Staphylococcus aureus*	4	67
			Enterobacter aerogenes	8	
			Pseudomonas aeruginosa	16	

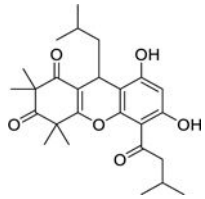
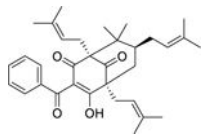
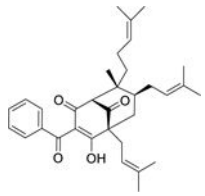
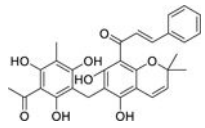
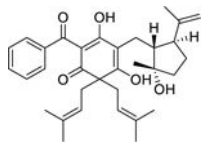
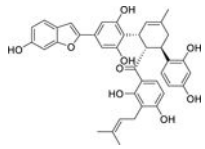
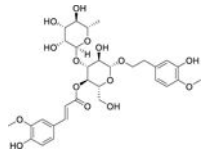
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
			Escherichia coli	32	
63		emodin	*Staphylococcus aureus* (MRSA)	4	67
			Escherichia coli	16	
			Staphylococcus aureus	20	72
			Klebsiella pneumoniae	32	67
64		aloe-emodin	*Staphylococcus aureus*	4	73
			Shigella flexneri	16	
			Vibrio cholerae	64	
65		elastiquinone	*Providencia stuartii*	4.9	74
			Pseudomonas aeruginosa	4.9	
			Proteus vulgaris	9.8	
			Staphylococcus aureus	9.8	
			Escherichia coli	19.5	
66		3,3′-biplumbagin	*Mycobacterium tuberculosis* (XDR)	3.13	66
			Mycobacterium tuberculosis	3.13	
67		maritinone	*Mycobacterium tuberculosis* (XDR)	3.13	66
			Mycobacterium tuberculosis	3.13	
68		zeylanone epoxide	*Mycobacterium tuberculosis* (XDR)	12.5	66
			Mycobacterium tuberculosis	25	
69	 R^1 = H, R^2 = Glc, aloin A R^1 = Glc, R^2 = H, aloin B	aloin A/B	*Vibrio cholerae*	10	75
			Escherichia coli	10	76
			Salmonella enterica serotype *Typhi*	10	
			Shigella dysenteriae	10	
			Staphylococcus aureus	25	
			Bacillus subtilis	50	75

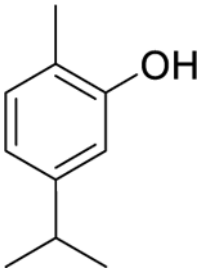
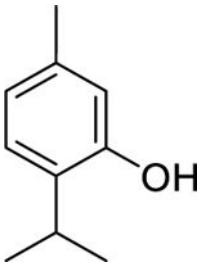
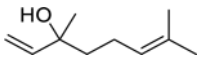
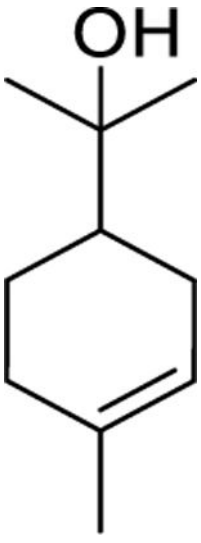
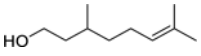
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
70		aloin-6'-*O*-acetate A/B	*Bacillus subtilis*	10	75
			Salmonella enterica serotype *Typhimurium*	10	
			Vibrio cholerae	10	
			Bacillus pumilus	25	
			Shigella dysenteriae	25	
			Staphylococcus aureus	25	
71		ferruginin A	*Enterococcus faecalis*	4	77
			Escherichia coli	4	
			Klebsiella pneumoniae	4	
			Enterobacter aerogenes	8	
Xanthones					
72		ananixanthone	*Enterococcus faecalis*	2	78
			Staphylococcus aureus	32	
			Pseudomonas aeruginosa	64	
			Bacillus cereus	64	
73		cheffouxanthone	*Enterococcus faecalis*	8	78
			Bacillus cereus	32	
			Escherichia coli	64	
			Staphylococcus aureus	64	
74		α-mangostin	*Staphylococcus aureus*	4	79
			Staphylococcus saprophyticus	8	
			Leptospira interrogans serovar Saigon	100	80
			Leptospira interrogans serovar *Javanica*	100	
75		norcowanin	*Staphylococcus aureus*	8	81
			Staphylococcus aureus (MRSA)	16	
			Escherichia coli	64	
76		4-prenyl-2-(3,7-dimethyl-2,6-octadienyl)-1,3,5,8-tetrahydroxyxanthone	*Mycobacterium tuberculosis*	8	82
			Enterobacter aerogenes	64	
			Escherichia coli	64	
			Providencia stuartii	64	
			Pseudomonas aeruginosa	64	
77		1,3,5,8-tetrahydroxy-2-(3-methybut-2-enyl)-4-(3,7-dimethyloct-2,6-dienyl) xanthone	*Enterococcus faecalis*	8	78
			Pseudomonas aeruginosa	16	
			Escherichia coli	32	
			Salmonella enterica serotype *Typhimurium*	64	
			Staphylococcus aureus	64	

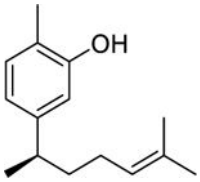
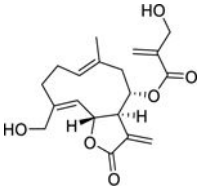
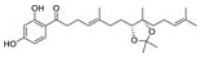
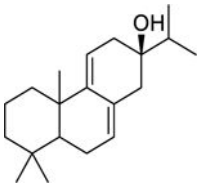
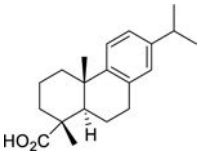
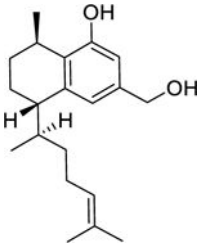
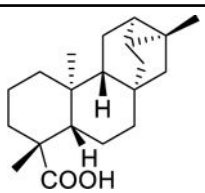
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
78		garciniacowone	*Staphylococcus aureus* (MRSA)	2	81
			Staphylococcus aureus	2	
79		cowanin	*Staphylococcus aureus* (MRSA)	4	81
			Staphylococcus aureus	32	
80		cowanol	*Staphylococcus aureus* (MRSA)	2	81
			Staphylococcus aureus	8	
81		cowagarcinone E	*Staphylococcus aureus* (MRSA)	8	81
		Other Phenolic Compounds			
82		pyrocatechol	*Aggregatibacter actinomycetemcomitans*	4.88	48
83		hydroquinone	*Mycobacterium tuberculosis*	12.5	83
			Mycobacterium smegmatis	50	
			Mycobacterium tuberculosis (XDR)	50	
84		pyrogallol	*Aggregatibacter actinomycetemcomitans*	2.4	48
			Streptococcus mitis	9.76	
85		hydroxytyrosol	*Staphylococcus aureus*	2	84
86		3,4-dihydroxyphenyl-acetic acid	*Aggregatibacter actinomycetemcomitans*	4.88	48
87		methyl gallate	*Staphylococcus aureus*	7.8	85 86
			Vibrio cholerae	64	
			Escherichia coli	93	85

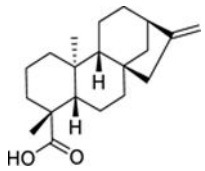
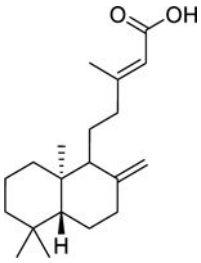
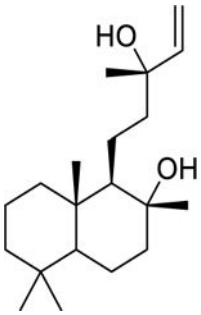
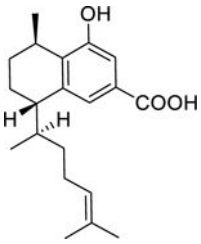
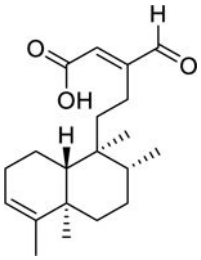
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
88		4,5-(methylene-dioxy)-*o*-coumaroylputrescine	*Staphylococcus aureus*	8	87
			Streptococcus agalactiae	8	
			Escherichia coli	16	
			Pseudomonas aeruginosa	16	
89		4,5-(methylene-dioxy)-*o*-coumaroyl-4'-*N*-methylputrescine	*Staphylococcus aureus*	8	87
			Streptococcus agalactiae	8	
			Escherichia coli	16	
			Pseudomonas aeruginosa	16	
90		2-(3-methyl-2-butenyl)-3,5,4'-trihydroxy-bibenzyl	*Staphylococcus epidermidis*	12.5	54
			Staphylococcus aureus	50	
91		2-(3,4-dihydroxy)-phenyl-ethyl-*O*-β-D-glucopyranoside	*Staphylococcus aureus*	8	84
92		2-geranyloxy-1-(2-methylpropanoyl) phloroglucinol	*Staphylococcus aureus*	3.91	88
			Staphylococcus aureus (MRSA)	7.81	
			Staphylococcus epidermidis	7.81	
93		3-geranyl-1-(2-methylpropanoyl) phloroglucinol	*Staphylococcus aureus* (MRSA)	3.91	88
			Staphylococcus aureus	7.81	
			Staphylococcus epidermidis	7.81	
94		amorfrutin A	*Staphylococcus aureus*	2.1	40
			Enterococcus faecalis	8.5	
			Enterococcus faecium	8.5	
95		2-geranyloxy-1-(2-methylbutanoyl) phloroglucinol	*Staphylococcus aureus*	3.91	88
			Staphylococcus epidermidis	3.91	
			Staphylococcus aureus (MRSA)	7.81	
96		3-geranyl-1-(2-methylbutanoyl) phloroglucinol	*Staphylococcus aureus* (MRSA)	3.91	88
			Staphylococcus epidermidis	3.91	
			Staphylococcus aureus	7.81	
97		olympicin A	*Staphylococcus aureus* (MRSA)	0.5	89
			Staphylococcus aureus	1	
			Mycobacterium phlei	4	
			Mycobacterium smegmatis	4	
			Mycobacterium fortuitum	8	
98		amorphastilbol	*Staphylococcus aureus*	1.1	40
			Enterococcus faecalis	2.2	
			Enterococcus faecium	2.2	

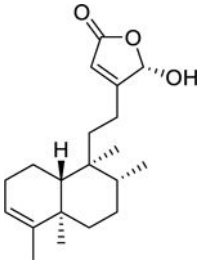
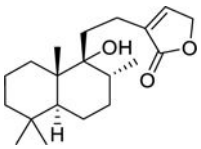
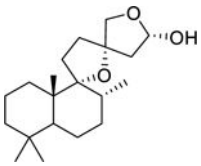
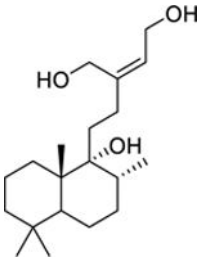
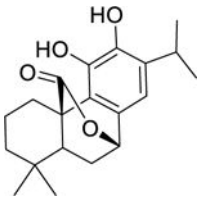
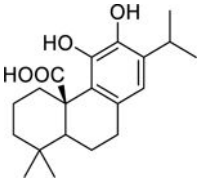
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
99		2-geranyl-5-(2-phenylethyl) resorcin	*Staphylococcus aureus*	2.2	40
			Enterococcus faecalis	4.4	
			Enterococcus faecium	4.4	
100		bulbocol	*Staphylococcus aureus*	9	90
			Staphylococcus aureus (MRSA)	37	
101		2-geranyloxy-4,6-dihydroxybenzo-phenone	*Staphylococcus aureus*	1.95	88
			Staphylococcus aureus (MRSA)	3.91	
			Staphylococcus epidermidis	3.91	
102		curcumin	*Porphyromonas gingivalis*	7.81	48
			Fusobacterium nucleatum	31.25	
			Streptococcus mitis	62.5	
			Bacillus subtilis	78	91
103		3,4-dihydro-5-hydroxy-2,7-dimethyl-8-(3”-methyl-2”-butenyl)-2-(4’-methyl-1’,3’-pentadienyl)-2H-1-benzopyran-6-carboxylic acid	*Enterococcus faecalis*	4	92
			Staphylococcus aureus (MRSA)	4	
			Staphylococcus aureus	4	
			Staphylococcus epidermidis	8	
104		2-[(*E*)-styryl]-5-geranylresorcin-1-carboxylic acid	*Staphylococcus aureus*	4.1	40
			Enterococcus faecalis	9.8	
			Enterococcus faecium	9.8	
105		tetraceranoate	*Mycobacterium smegmatis*	7.8	93
106		amorfrutin B	*Enterococcus faecalis*	2.6	40
			Enterococcus faecium	2.6	
			Staphylococcus aureus	5.1	
107		shancigusin B	*Staphylococcus aureus*	3	90
			Staphylococcus aureus (MRSA)	13	
			Bacillus subtilis	26	
108		rhodomyrtone	*Streptococcus mutans*	0.39	94
			Cutibacterium acnes	0.5	95

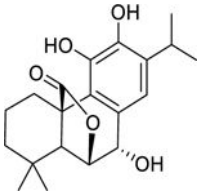
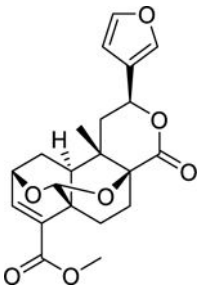
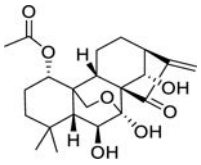
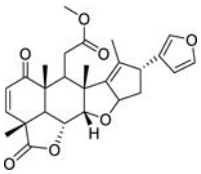
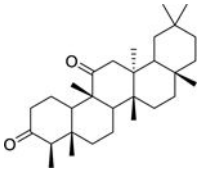
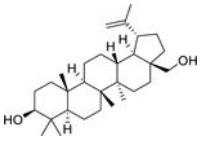
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
			Staphylococcus aureus	0.78	94
109		rhodomyrtosone B	*Staphylococcus aureus*	0.62	96
			Staphylococcus aureus (MRSA)	0.62	
			Bacillus cereus	0.62	
			Cutibacterium acnes	0.62	
			Enterococcus faecalis	1.25	
110		7-*epi*-clusianone	*Enterococcus faecalis*	2	97
			Staphylococcus aureus	2	
111		chamuangone	*Streptococcus pyogenes*	7.8	98
			Helicobacter pylori	15.6	
			Streptococcus viridans	15.6	
			Bacillus subtilis	31.2	
			Staphylococcus aureus	31.2	
112		rottlerin	*Enterococcus faecalis*	1	99
			Staphylococcus aureus (Norfloxacin-R)	2	
			Staphylococcus aureus (MRSA)	2	
			Bacillus subtilis	4	
			Staphylococcus aureus	4	
113		hypercalin B	*Staphylococcus aureus* (MRSA)	2	100
114		chalcomoracin	*Staphylococcus aureus* (MRSA)	2	101
			Staphylococcus aureus	4	
115		martynoside	*Bacillus subtilis*	7.81	102
			Klebsiella pneumoniae	31.2	
TERPENOIDS					
Monoterpenoids					

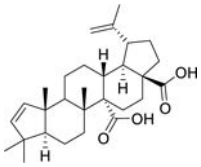
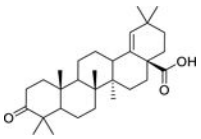
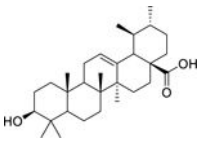
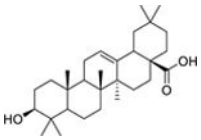
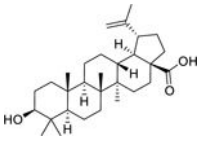
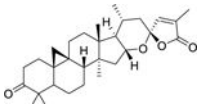
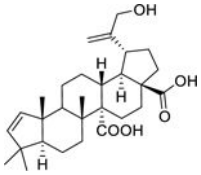
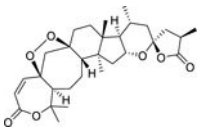
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
116		carvacrol	*Micrococcus flavus*	2.5	103
			Bacillus cereus	12.5	
			Staphylococcus aureus	25	
			Escherichia coli	50	
			Pseudomonas aeruginosa	50	
			Salmonella enterica serotype *Typhimurium*	50	
117		thymol	*Bacillus cereus*	25	103
			Staphylococcus aureus	25	
			Proteus mirabilis	10	
			Staphylococcus epidermidis	32	104
			Salmonella enteritidis	32	
			Escherichia coli	45	105
118		linalool	*Bacillus cereus*	10	106
			Bacillus subtilis	5	
			Escherichia coli	5	
			Pseudomonas aeruginosa	2.5	
			Salmonella enteritidis	10	
119		α-terpineol	*Bacillus subtilis*	0.87 μL/mL	107
			Staphylococcus epidermidis	1.56 μL/mL	
			Pseudomonas aeruginosa	1.56 μL/mL	
			Klebsiella pneumoniae	1.56 μL/mL	
			Staphylococcus aureus	1.56 μL/mL	108
			Escherichia coli	55	105
120		citronellol	*Escherichia coli*	5	109
Sesquiterpenoids and Derivatives					

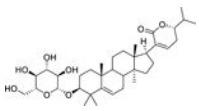
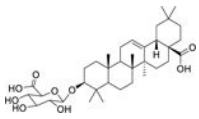
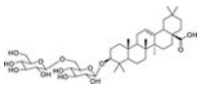
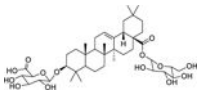
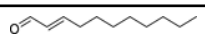
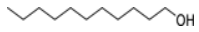
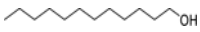
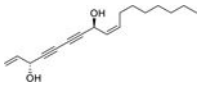
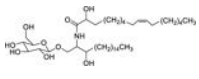
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
121		xanthorrhizol	*Streptococcus mutans*	4.1	110
			Porphyromonas gingivalis	6.8	
122		onopordopicrin	*Bacillus subtilis*	86.2	111
			Vibrio fischeri	2.2	
123		8,9-oxoisopropanyl-dshamirone	*Staphylococcus aureus* (MRSA)	0.5	112
			Staphylococcus aureus (Tetracycline-R)	0.5	
Diterpenoids					
124		abieta-7,9(11)-dien-13-β-ol	*Staphylococcus aureus*	0.98	113
			Bacillus cereus	31.2	
			Enterococcus faecalis	31.2	
			Salmonella enterica serotype *Typhimurium*	62.5	
125		dehydroabietic acid	*Actinomyces naeslundii*	12.5	114
			Cutibacterium acnes	12.5	
			Porphyromonas gingivalis	6.2	
			Bacteroides fragilis	12.5	
			Prevotella intermedia	12.5	
			Streptococcus mitis	25	115
126		8,19-dihydroxyserrulat-14-ene	*Bacillus subtilis*	3.1	116
			Staphylococcus aureus (MRSA)	3.1	
			Streptococcus pneumoniae	3.1	
			Moraxella catarrhalis	3.1	
127		*ent*-trachyloban-19-oic acid	*Streptococcus mutans*	8.9	110
			Porphyromonas gingivalis	57.6	

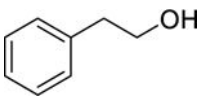
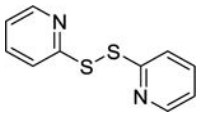
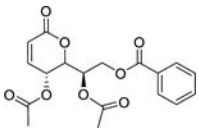
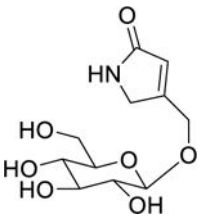
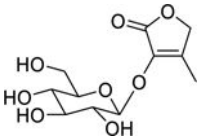
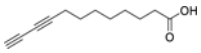
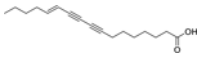
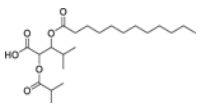
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
128		kaurenoic acid	*Bacillus cereus*	12	117
			Staphylococcus epidermidis	8	
			Streptococcus pneumoniae	5	
			Cutibacterium acnes	6.25	118
			Prevotella melaninogenica	6.25	
			Porphyromonas gingivalis	12.5	
129		(-)-copalic acid	*Staphylococcus epidermidis*	0.5	117
			Streptococcus pneumoniae	2	
			Staphylococcus aureus (MRSA)	15.6	
130		labd-14-ene-8,13-diol	*Mycobacterium tuberculosis*	10.85	119
131		8-hydroxyserrulat-14-en-19-oic acid	*Bacillus subtilis*	3.1	116
			Streptococcus pneumoniae	6.2	
			Staphylococcus aureus (MRSA)	12.5	
			Moraxella catarrhalis	6.2	
132		16-oxo-cleroda-3,13(14)-*E*-diene-15-oic acid	*Staphylococcus aureus* (MRSA)	20	120
			Streptococcus mutans	16	

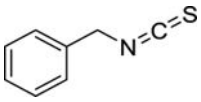
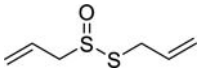
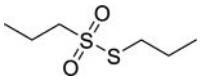
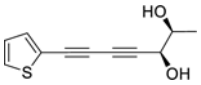
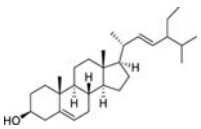
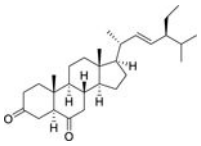
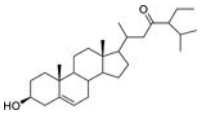
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
133		16α-hydroxycleroda-3,13(14)-*Z*-dien-15,16-olide	*Staphylococcus aureus* (MRSA)	15.63	121,122
134		9-hydroxylabd-13-en-16,15-olide	*Mycobacterium tuberculosis*	19.67	119
135		9,13:15,16-diepoxylabdan-15-ol	*Mycobacterium tuberculosis*	14.88	119
136		labd-13*Z*-ene-9,15,16-triol	*Mycobacterium smegmatis*	30.57	119
137		carnosol	*Staphylococcus aureus* (MRSA)	15.6	123
			Enterococcus faecalis	62.5	
138		carnosic acid	*Staphylococcus aureus* (MRSA)	7.8	123
			Enterococcus faecalis	15.6	
			Staphylococcus aureus (MRSA)	12	124

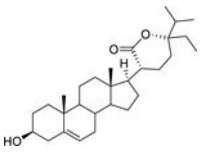
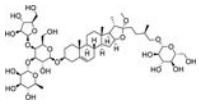
N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
139		rosmanol	*Staphylococcus aureus* (MRSA)	15.6	123
			Enterococcus faecalis	62.5	
140		bafoudiosbulbin C	*Escherichia coli*	16	125
			Enterobacter aerogenes	64	
			Klebsiella pneumoniae	64	
			Mycobacterium smegmatis	8	
			Mycobacterium tuberculosis	8	
141		lasiodin	*Bacillus cereus*	8	126
			Listeria monocytogenes	16	
			Staphylococcus aureus	16	
			Pseudomonas aeruginosa	16	
Nor-Triterpenes					
142		nimbolide	*Staphylococcus aureus* (MRSA)	8	127
Triterpenes and Saponins					
143		friedelane-3,11-dione	*Mycobacterium tuberculosis*	3.9	50
144		betulin	*Mycobacterium aurum*	15	93
			Mycobacterium smegmatis	15	

N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
145		ceanothenic acid	*Staphylococcus aureus*	8	128
			Enterococcus faecalis	16	
146		moronic acid	*Bacillus subtilis*	1.52	129
			Staphylococcus aureus	1.52	
			Streptococcus pyogenes	1.52	
147		ursolic acid	*Enterococcus faecalis*	1	130
			Listeria monocytogenes	2	
			Mycobacterium tuberculosis	10	83
			Mycobacterium tuberculosis (XDR)	25	
			Klebsiella pneumoniae	25	131
			Pseudomonas aeruginosa	25	
			Vibrio cholerae	100	132
148		oleanolic acid	*Enterococcus faecalis*	4	130
			Listeria monocytogenes	8	
			Bacillus cereus	16	
			Mycobacterium tuberculosis	50	
149		betulinic acid	*Mycobacterium aurum*	15	93
			Mycobacterium smegmatis	15	
			Staphylococcus aureus (MRSA)	64	133
150		pseudolarolide B	*Staphylococcus aureus*	25	134
			Escherichia coli	6.3	
151		29-hydroxyceanothenic acid	*Staphylococcus aureus*	4	128
			Enterococcus faecalis	16	
152		pseudolarolide Q	*Staphylococcus aureus*	3.1	134
			Escherichia coli	50	

N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
153		lanast-5-en-3β-D-glucopyranosyl-21 (24)-olide	*Staphylococcus aureus*	2.4	135
			Bacillus subtilis	4.8	
			Staphylococcus epidermidis	4.8	
			Escherichia coli	9.6	
			Klebsiella pneumoniae	9.6	
			Pseudomonas aeruginosa	9.6	
154		3-*O*-β-D-glucuronopyranosyl-oleanolic acid	*Staphylococcus aureus*	8	136
			Shigella flexneri	16	
			Escherichia coli	32	
155		3-*O*-β-D-glucopyranosyl (1→6)-β-D-glucopyranosyl-oleanolic acid	*Escherichia coli*	6.25	137
			Klebsiella pneumoniae	6.25	
			Enterobacter aerogenes	25	
			Salmonella enterica serotype *Typhi*	100	
156		3-*O*-β-D-glucurono-pyranosyloleanolic acid 28-*O*-β-D-glucopyranosyl ester	*Shigella flexneri*	16	136
			Staphylococcus aureus	16	
			Escherichia coli	32	
Other Metabolites					
Aliphatic compounds					
157		2*E*-undecenal	*Salmonella enterica*	12.5	138
158		undecanol	*Salmonella enterica*	12.5	138
159		2*E*-dodecenal	*Salmonella enterica*	6.25	138
160		dodecanol	*Salmonella enterica*	6.25	138
161		falcarindiol	*Mycobacterium bovis*	5	139
			Mycobacterium tuberculosis	20	
162		*n*-dotriacont-9-one-13-ene	*Bacillus subtilis*	9.6	135
			Staphylococcus aureus	19.2	
			Staphylococcus epidermidis	19.2	
			Klebsiella pneumoniae	19.2	
			Escherichia coli	38.4	
			Pseudomonas aeruginosa	38.4	
Ceramides					
163		ficusoside B	*Staphylococcus aureus*	4.9	74
			Proteus vulgaris	4.9	
			Providencia stuartii	19.5	
			Pseudomonas aeruginosa	39.1	

N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
Cyclic compounds					
164		2-phenylethanol	*Bacillus cereus*	5	106
			Lactobacillus plantarum	10	
			Leuconostoc mesenteroides	10	
			Staphylococcus aureus	10	
			Salmonella enteritidis	2.5	
			Shigella sonnei	2.5	
			Pseudomonas aeruginosa	5	
165		2,2'-dithiodipyridine	*Streptococcus mutans*	2	140
			Streptococcus mitis	4	
166		(-)-cleistenolide	*Staphylococcus aureus* (MRSA)	7.5	56
			Enterococcus faecalis (Vancomycin-R)	30	
			Staphylococcus aureus	30	
			Staphylococcus aureus (VRSA)	30	
Glycosides					
167		pinnatoside A	*Escherichia coli*	1.562	137
			Enterobacter aerogenes	3.125	
			Klebsiella pneumoniae	3.125	
			Pseudomonas aeruginosa	6.25	
			Salmonella enterica serotype *Typhi*	12.5	
168		3-*O*-β-D-glucopyranosyloxy-4-methyl-2(5H)-furanone	*Enterobacter aerogenes*	1.562	137
			Pseudomonas aeruginosa	3.125	
			Klebsiella pneumoniae	6.25	
			Salmonella enterica serotype *Typhi*	25	
Fatty Acids					
169		dodec-9,11-diynoic acid	*Porphyromonas gingivalis*	1.2	141
			Fusobacterium nucleatum	9.6	
170		(12*E*)-heptadec-12-en-8,10-diynoic acid	*Porphyromonas gingivalis*	1.63	141
			Fusobacterium nucleatum	26	
171		exocarpic acid	*Streptococcus mutans*	13.7	141
			Porphyromonas gingivalis	0.86	
			Fusobacterium nucleatum	3.4	
172		3-(dodecanoyloxy)-2-(isobutyryloxy)-4-methylpentanoic acid	*Staphylococcus aureus*	3.12	142
			Bacillus subtilis	6.25	
			Streptococcus pyogenes	6.25	
			Enterococcus faecalis	25	

N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
Organosulfurs and derivatives					
173		benzyl isothiocyanate	*Enterococcus faecalis*	40	143
			Staphylococcus aureus	40	
			Escherichia coli	10	
			Pseudomonas aeruginosa	20	
			Klebsiella pneumoniae	40	
			Salmonella pullorum	40	
174		allicin	*Burkholderia cenocepacia*	0.5	144
			Burkholderia cepacia	0.5	
			Burkholderia pyrrocinia	0.5	
175		propyl-propane- thiosulfonate	*Enterococcus faecalis*	4	145
			Streptococcus agalactiae	4	
			Staphylococcus aureus	8	
			Escherichia coli	64	
176		10,11-*erythro*-xanthopappin D	*Staphylococcus aureus*	7.25	146
			Bacillus cereus	15.5	
			Escherichia coli	12.5	
177		10,11-*threo*-xanthopappin D	*Bacillus subtilis*	7.25	146
			Bacillus cereus	62.5	
			Escherichia coli	62.5	
Peptides					
178	Cys-Ala-Arg-Leu-Asn-Cys-Val-Pro-Lys-Gly-Thr-Ser-Gly-Asn-Thr-Glu-Thr-Cys-Pro-Cys-Tyr-Ala-Ser-Leu-His-Ser-Cys-Arg-Lys-Tyr-Gly	snakin-Z	*Bacillus subtilis*	24.2	147
			Staphylococcus aureus	28.8	
			Escherichia coli	13.6	
			Klebsiella pneumoniae	14.1	
Steroids					
179		β-stigmasterol	*Mycobacterium aurum*	15	93
			Mycobacterium smegmatis	31	
180		stigmast-22-ene-3,6-dione	*Staphylococcus aureus*	10	148
181		stigmast-5-en-3β-ol-23-one	*Staphylococcus epidermidis*	9.6	135
			Bacillus subtilis	19.2	
			Staphylococcus aureus	19.2	
			Escherichia coli	19.2	

N°	Structure	Compound	Bacteria[a]	MIC (μg/mL)	Ref.
			Klebsiella pneumoniae	38.4	
			Pseudomonas aeruginosa	38.4	
182		stigmast-5-en-3β-ol-21(24)-olide	*Bacillus subtilis*	4.8	135
			Staphylococcus aureus	4.8	
			Staphylococcus epidermidis	9.6	
			Escherichia coli	9.6	
			Klebsiella pneumoniae	9.6	
			Pseudomonas aeruginosa	19.2	
183		polyphyllin G	*Bacillus subtilis*	6.2	149
			Enterococcus faecalis	52.3	
			Staphylococcus aureus	78	
			Salmonella enteritidis	13.1	
			Proteus mirabilis	26.2	
			Escherichia coli	52.3	

[a]**Abbreviations:** ESBL-KP: Extended-spectrum β-lactamase *Klebsiella pneumoniae*, MDR: Multi-drug resistant, MRSA: methicillin-resistant *Staphylococcus aureus*, MSSA: methicillin-sensitive *Staphylococcus aureus*, Norfloxacin-R: Norfloxacin-resistant, ORCNS: Oxacillin-resistant coagulase-negative staphylococci, OSCNS: Oxacillin-sensitive coagulase-negative staphylococci, Tetracycline-R: Tetracycline resistant, Vancomycin-R: Vancomycin-resistant, VISA: Vancomycin Intermediate *Staphylococcus aureus,* VRSA: Vancomycin Resistant *Staphylococcus aureus,* XDR: Extensively-drug resistant.

Table 2.

List of compounds (from Supporting Information File 1) in clinical trials for infectious disorders.[198]

Compound names	Nº clinical trials related to infectious disorders	Indications
andrographolide	3	Acute tonsillitis. Acute bronchitis. Acute exacerbation of chronic bronchitis
berberine	3	Gastric Ulcer, *Helicobacter pylori* Infection, Gastritis
curcumin	7	Acute Pulpitis. Periodontitis. Positivity for *Helicobacter pylori* infection. HIV infections. Mucositis.
ellagic acid	1	HPV infection.
epigallocatechin gallate	3	Epstein-Barr virus reactivation. HIV infection.
eucalyptol	7	Cough due to infectious origin. Periodontitis. Gingivitis.
licochalcone A	2	Acne vulgaris.
quercetin	3	Chronic hepatitis C. Oral mucositis. Cystic fibrosis.
silymarin	9	Chronic hepatitis C. HIV infection. Tuberculosis
thymol	6	Periodontitis. Gingivitis. Ear infection.

Table 3.

Descriptive statistics for the MIC data (μg/mL) on compounds discussed in this review with 3 or more MIC values reported.

	No. MIC Values	Mean MIC	Min MIC	Max MIC	Std. Deviation
Alkaloids					
artabotrine (**5**)	12	2.4	1.25	5	1.4
liridine (**6**)	9	2.8	0.625	10	3.0
sanguinarine (**7**)	10	6.0	0.5	16	6.0
lysicamine (**4**)	12	9.6	2.5	20	5.7
berberine (**8**)	3	12.2	1.56	31.25	16.5
buesgenine (**11**)	5	17.6	4	32	14.0
palmatine (**12**)	3	28.1	3.12	75	40.6
4-methylquinoline (**1**)	5	52.5	12.5	100	35.8
Phenolic derivatives					
rhodomyrtone (**108**)	3	0.6	0.39	0.78	0.2
rhodomyrtosone B (**109**)	7	1.1	0.62	2.5	0.7
xanthoangelol (**17**)	3	1.6	1.2	2.5	0.8
amorphastilbol (**98**)	3	1.8	1.1	2.2	0.6
rottlerin (**112**)	5	2.6	1	4	1.3
2-geranyloxy-4,6-dihydroxybenzophenone (**101**)	3	3.3	1.95	3.91	1.1
dichamanetin (**46**)	5	3.3	1	7.5	2.6
amorfrutin B (**106**)	3	3.4	2.6	5.1	1.4
olympicin A (**97**)	5	3.5	0.5	8	3.0
2-geranyl-5-(2-phenylethyl) resorcin (**99**)	3	3.7	2.2	4.4	1.3
(2*R*,3*S*,2’’*S*)- 3’’’,4’,4’’’,5,5’’,7,7’’-heptahydroxy-3,8”-biflavanone (**49**)	3	4.7	2	8	3.1
3,4-dihydro-5-hydroxy-2,7dimethyl-8-(3”-methyl-2”-butenyl)-2-(4’-methyl-1’,3’-pentadienyl)-2H-1-benzopyran 6-carboxylic acid (**103**)	4	5.0	4	8	2.0
2-geranyloxy-1-(2-methylbutanoyl) phloroglucinol (**95**)	3	5.2	3.91	7.81	2.3
3-geranyl-1-(2-methylbutanoyl) phloroglucinol (**96**)	3	5.2	3.91	7.81	2.3
ferruginin A (**71**)	5	5.6	4	8	2.2
amorfrutin A (**94**)	3	6.4	2.1	8.5	3.7
2-geranyloxy-1-(2-methylpropanoyl) phloroglucinol (**92**)	3	6.5	3.91	7.81	2.3
3-geranyl-1-(2-methylpropanoyl) phloroglucinol (**93**)	3	6.5	3.91	7.81	2.3
lupinifolin (**36**)	4	6.7	1	15.63	6.7
2-[(*E*)-styryl]-5-geranylresorcin-1-carboxylic acid (**104**)	3	7.9	4.1	9.8	3.3
luteolin-8-*C*-glucoside (**44**)	3	8.0	4	16	6.9
neobavaisoflavone (**28**)	11	9.5	4	32	7.6
elastiquinone (**65**)	5	9.8	4.9	19.5	6.0

	No. MIC Values	Mean MIC	Min MIC	Max MIC	Std. Deviation
2,5-dihydroxy-3-heptyl-2,5-cyclohexadiene-1,4-dione (**59**)	6	10.7	4	32	11.5
neocyclomorusin (**41**)	6	10.7	4	32	10.6
isoquercetin (**45**)	4	11.2	4.64	16	5.8
plumbagin (**57**)	10	11.3	1.56	64	19.4
4,5-(methylene-dioxy)-*o*-coumaroyl-4'-*N*-methylputrescine (**89**)	4	12.0	8	16	4.6
4,5-(methylene-dioxy)-*o*-coumaroylputrescine (**88**)	4	12.0	8	16	4.6
amentoflavone (**47**)	5	12.0	4	32	11.3
thymoquinone (**56**)	4	12.0	8	16	4.6
chamanetin (**35**)	5	13.5	7.5	15	3.4
6-prenylpinocembrin (**29**)	5	13.6	4	32	11.2
shancigusin B (**107**)	3	14.0	3	26	11.5
hydroquinone (**83**)	8	15.6	12.5	25	5.8
candidone (**32**)	6	18.0	4	64	23.3
emodin (**63**)	4	18.0	4	32	11.5
homoembelin (**62**)	5	18.4	4	32	13.1
3′-demethoxy-6-*O*-demethylisoguaiacin (**53**)	5	20.0	12.5	50	16.8
6-geranyl-5,7,3′-trihydroxy-4′-methoxyisoflavone (**42**)	3	20.0	5.5	43.7	20.7
chamuangone (**111**)	6	22.1	7.8	31.2	10.4
aloin A/B (**69**)	20	22.8	10	50	13.7
pseudarflavone A (**27**)	5	24.8	4	64	24.4
aloe-emodin (**64**)	3	28.0	4	64	31.7
4-*epi*-larreatricin (**54**)	3	29.2	12.5	50	19.1
norcowanin (**75**)	3	29.3	8	64	30.3
3′,4′,7-trihydroxyflavone (**23**)	5	34.4	4	64	29.1
brazilin (**24**)	7	35.4	13.3	62.5	20.0
1,3,5,8-tetrahydroxy-2-(3-methylbut-2-enyl)-4-(3,7-dimethyloct-2,6-dienyl) xanthone (**77**)	5	36.8	8	64	26.3
curcumin (**102**)	5	37.5	7.81	78	31.9
dihydroguaiaretic acid (**55**)	3	37.5	12.5	50	21.7
apigenin	10	38.1	15.62	64	20.1
aloin-6'-*O*-acetate A/B (**70**)	20	39.0	10	100	29.1
ananixanthone (**72**)	4	40.5	2	64	29.8
cheffouxanthone (**73**)	4	42.0	8	64	27.2
ellagic acid	7	44.2	16	64	19.6
4-prenyl-2-(3,7-dimethyl-2,6-octadienyl)-1,3,5,8-tetrahydroxyxanthone (**76**)	5	52.8	8	64	25.0
α-mangostin (**74**)	4	53.0	4	100	54.3
methyl gallate (**87**)	4	57.2	7.8	93	35.7
epigallocatechin gallate	3	58.7	32	80	24.4

	No. MIC Values	Mean MIC	Min MIC	Max MIC	Std. Deviation
quercetin (**25**)	14	58.8	8	100	36.1
silymarin	3	60.0	60	60	0.0
gallic acid	5	100.0	100	100	0.0
γ-mangostin	3	100.0	100	100	0.0
Terpenoids					
terpinen-4-ol	3	2.1	1.562	3.125	0.9
α-terpineol (**119**)	11	6.4	0.78	55	16.1
lanast-5-en-3*β*-D-glucopyranosyl-21 (24)-olide (**153**)	6	6.8	2.4	9.6	3.2
linalool (**118**)	8	8.1	2	20	5.9
8,19-dihydroxyserrulat-14-ene (**126**)	14	9.1	3.1	50	12.2
α-pinene	6	11.1	0.313	64	25.9
carnosic acid (**138**)	3	11.8	7.8	15.6	3.9
(-) copalic acid (**129**)	15	12.1	0.5	50	13.4
lasiodin (**141**)	5	14.4	8	16	3.6
3-*O*-β-D-glucuronopyranosyl-oleanolic acid (**154**)	3	18.7	8	32	12.2
kaurenoic acid (**128**)	10	18.8	5	100	28.8
ent-kaurenoic acid	11	19.3	6.25	100	27.2
oleanolic acid (**148**)	4	19.5	4	50	20.9
moronic acid (**146**)	5	21.2	1.52	100	44.0
3-*O*-*β*-D-glucuronopyranosyloleanolic acid 28-*O*-*β*-D-glucopyranosyl ester (**156**)	3	21.3	16	32	9.2
ursolic acid (**147**)	24	27.4	1	100	28.4
abieta-7,9(11)-dien-13-β-ol (**124**)	4	31.5	0.98	62.5	25.1
bafoudiosbulbin C (**140**)	5	32.0	8	64	29.4
8-hydroxyserrulat-14-en-19-oic acid (**131**)	14	36.8	3.1	100	37.4
dehydroabietic acid (**125**)	17	37.1	6.2	100	33.1
betulinic acid (**149**)	4	39.5	15	64	28.3
carvacrol (**116**)	12	45.5	2.5	64	21.0
3-*O*-β-D-glucopyranosyl(1→6)-β-D-glucopyranosyloleanolic acid (**155**)	5	47.5	6.25	100	48.5
thymol (**117**)	16	54.0	10	100	28.7
andrographolide	5	90.0	50	100	22.4
Other metabolites					
allicin (**174**)	9	0.7	0.5	1	0.3
2-phenylethanol (**164**)	14	5.2	2.5	10	2.9
pinnatoside A (**167**)	5	5.3	1.562	12.5	4.4
exocarpic acid (**171**)	3	6.0	0.86	13.7	6.8
3-*O*-β-D-glucopyranosyloxy-4-methyl-2(5H)-furanone (**168**)	5	7.5	1.562	25	10.0
stigmast-5-en-3*β*-ol-21(24)-olide (**182**)	6	9.6	4.8	19.2	5.3

	No. MIC Values	Mean MIC	Min MIC	Max MIC	Std. Deviation
10,11-*erythro*-xanthopappin D (**176**)	3	11.8	7.25	15.5	4.2
3-(dodecanoyloxy)-2-(isobutyryloxy)-4-methylpentanoic acid (**172**)	8	13.7	3.12	25	9.7
ficusoside B (**163**)	5	14.7	4.9	39.1	15.1
propyl-propane-thiosulfonate (**175**)	4	20.0	4	64	29.4
snakin-Z (**178**)	4	20.2	13.6	28.8	7.5
stigmast-5-en-3β-ol-23-one (**181**)	6	24.0	9.6	38.4	11.8
n-dotriacont-9-one-13-ene (**162**)	6	24.0	9.6	38.4	11.8
(-)-cleistenolide (**166**)	5	25.5	7.5	30	10.1
benzyl isothiocyanate (**173**)	6	31.7	10	40	13.3
polyphyllin G (**183**)	9	41.3	6.2	78	27.6
10,11-*threo*-xanthopappin D (**177**)	3	44.1	7.25	62.5	31.9