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Recent Advances in the Discovery of Plant-Derived Antimicrobial Natural Products to Combat Antimicrobial Resistant Pathogens: Insights from 2018–2022

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Abstract

Antimicrobial resistance (AMR) poses a significant global health threat. Thousands of years before antibiotics were first discovered, infections were treated with plants, chosen from traditional medicine practices. Out of Earth's 374,000 plant species, approximately 9% have been used medicinally. As antimicrobial resistance grows, and conventional antibiotics' effectiveness wanes, the demand for innovative drug scaffolds and new targets to combat multidrug-resistant bacteria rises. This review illuminates discoveries of antimicrobial natural products from plants made between 2018 and 2022. It highlights traditional medicinal plant uses showing antibacterial, antivirulence, and antibiofilm activity in lab studies. Additionally, it discusses the development of novel derivatives from well-studied parent natural products, as these have often served as scaffolds for anti-infective agents.

Graphical Abstract

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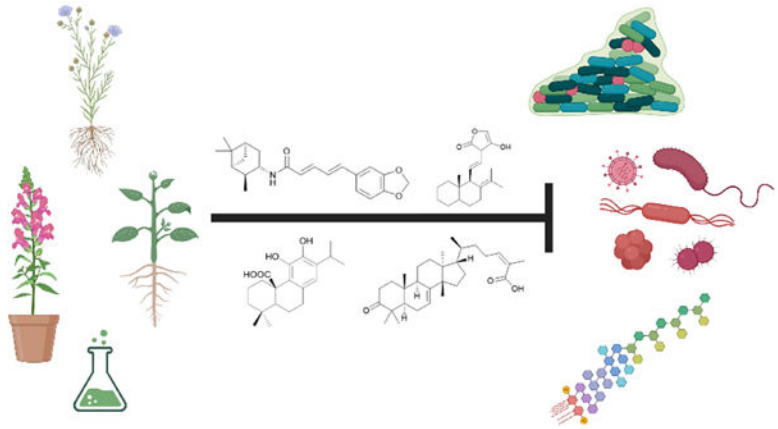
7.·Author Contributions

CLQ and SW wrote synopsis of manuscript. All authors, CLQ, SW, LM, WC, and CJR participated in drafting and editing the manuscript.

8.·Conflicts of Interest

CLQ is a founder and CEO/CSO of PhytoTEK LLC, a company developing plant-derived antibiofilm compounds. CLQ is a founder and CSO of Verdant Scientific LLC, a company developing plant-derived antivirulence compounds. CLQ is an Editor for the Natural Product Reports Special Issue "Botanical Natural Products in Drug Discovery, Past, Present and Future."



Plants produce a wide array of secondary metabolites capable of inhibiting pathways crucial for microbial survival and pathogenicity.

Keywords

Natural products; antimicrobial; antibacterial; antivirulence; antibiofilm; antimicrobial resistance

1. Introduction

Antimicrobial resistance (AMR) poses a significant public health threat in the modern era. As antibiotics lose their effectiveness due to the development of drug resistance, the treatment of recalcitrant infections becomes increasingly challenging, and in some cases, impossible. Researchers from the Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and public health institutions around the world continue to assert that remedial actions must be implemented globally to address the spread of AMR.[1–3] According to the CDC, more than two million AMR infections occur annually in the United States, resulting in an estimated 29,000 deaths; the medical cost for AMR treatment is over $4.7 billion.[2] Although the degree of AMR varies greatly depending on the bacterial species and geographic region, AMR is prevalent across the globe. For example, in the European Union/European Economic Area (EU/EEA) alone, it is estimated that more than 670,000 infections are caused by AMR each year and about 33,000 deaths as a result of it.[4] An assessment of 2019 global data found that an estimated 4.95 million deaths were associated with bacterial AMR, including 1.27 million deaths attributed to bacterial AMR.[5] During the global COVID-19 pandemic, AMR rates have continued to rise. In the period from March to October 2020, nearly 80% of hospitalized patients for COVID-19 received antibiotics, which contributed to this AMR trend.[6]

In February 2017, the WHO published a list of pathogens in urgent need of new antibiotics and provided guidelines to focus researchers' research and development efforts on high-priority targets. Six pathogens, in particular, were issued with priority ratings and named the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *and Enterobacter* spp.).[7, 8] To overcome the challenges of AMR, the development of rapid point-of-care diagnostic methods,

discovery of new drug candidates, and rapid development of existing candidates are all necessary.

About half of the drugs registered by the FDA between 1981 and 2019 were natural products, mimetics, or derivatives, which was roughly double the share of all synthetic drugs (24.6%).[9] Among these drugs, natural products continue to be an important source for the discovery and development of anti-infective drug candidates. Around 42.3% of all anti-infective agents are derived from natural products, their derivatives, and natural product mimics.[9] Natural products are characterized by a great diversity of scaffolds and high structural complexity. Among plant-derived natural products, alkaloids, phenolic derivatives, and terpenoids are promising sources of antibacterial lead compounds that can help fill the drug development pipeline. In addition to their potential value as classic antibiotics targeting growth and survival, some plant-derived natural products also show promise as synergists, targeting bacterial virulence and pathogenesis pathways, or by sensitizing bacteria to established classes of antibiotics.[10–12]

Bacterial resistance to antimicrobials is enabled through a few core mechanisms, including inactivation or alteration of antibacterial molecules, modification of bacterial target sites, reduction of antibiotic penetration/accumulation, and formation of bacterial biofilms.[13] Plant natural products can act as antibacterial agents through a variety of modes of action targeting these resistance mechanisms and other pathways necessary for bacterial survival. In this paper, we review recent findings from the last five years (Jan 2018 – Sep 2022) on plant natural products that exhibit anti-infective properties against pathogenic bacteria, including growth inhibition, antivirulence, and antibiofilm activity. We also introduce traditional knowledge of medicinal plants used for the treatment of infectious diseases in the study of source material for plant natural product discovery in the context of ethnobotany—the study of local plant and their practical uses through accumulated knowledge of local culture and people.[14] We present a summary of activities for plant-derived natural products exhibiting promising activity as antibiotic, antivirulence, and antibiofilm leads in Tables 1–3. This review will be of critical importance to the natural product community, filling a gap in comprehensive reviews on plant-derived natural products for the treatment of infection.

2. Methods for Review

Our previous comprehensive review of plant derived natural products with antibacterial activity examined the literature from January 1st, 2012 to September 3rd, 2019.[10] This review seeks to build on that by examining the literature for plant-derived and plant-inspired antimicrobial compounds that met our rigorous inclusion criteria from articles published from January 1st, 2018 to September 30th, 2022. This review specifically focuses on recently reported natural products with antibacterial, antivirulence, or antibioflm activity.

Articles were searched on PubMed with specific key words for each type of activity. Antibacterial key terms searched were “(antibiotics) AND (natural product)” and “(antibiotics) AND (isolated) AND (natural product)”, “(natural product) AND (antibiotic) AND (novel)”, “(antibiotic) AND (natural product)”, “(plant) AND (antibiotic) AND (novel compound)”, and “(antibiotics) AND (extract)” and “(antivirulence) AND (plant)”

on PubMed and Google Scholar; Reaxys key terms were “antibiotic, natural product >=2018” and “Pharmacological data, article, antibiotic”. Antivirulence key terms searched were “(virulence) AND (natural product)” on PubMed and Google Scholar; Reaxys key terms were “antivirulence, natural product >=2018” and “Pharmacological data, article, antivirulence”. Antibiofilm key terms searched were “(biofilm) AND (natural product)” and “(biofilm) AND (plant)” on PubMed and Google Scholar; Reaxys key terms were “biofilm, natural product >=2018” and “Pharmacological data, article, biofilm”. As lead hits were selected, similar searches were performed including the compound name and “derivative”.

The initial search yielded thousands of results, prompting us to establish criteria to refine our selection. First, we selected papers to only include terrestrial plant derived natural products with activity specifically against multidrug resistant bacteria. Next, we filtered our results to only include single compounds rather than essential oils or extracts. Additionally, we searched for novel products and allowed for derivatives from well-studied parent compounds (such as myricetin and quercetin), while excluding results that utilized nanoparticle technology. For antibiofilm results, we cross checked with the 2020 *Natural Product Reports* review “Natural products as inspiration for the development of bacterial antibiofilm agents” by R.J. Melander *et al.* to prevent redundant reporting in the literature.[15]

An additional round of literature review on PubMed and Google Scholar was developed after identifying our lead compounds. Our first round was centered on reports of each compound’s mechanism of action in bacteria, then we transitioned to review their bioactivity against other diseases. Finally, we searched records for ethnobotanical information for each plant. The resources for ethnobotanical information included review articles, textbook chapters, and primary field reports as available.

2.1 Data Reporting

2.1.1 Antibacterial—Antibacterial compounds either kill the bacterial cells (bactericidal) or interfere with growth (bacteriostatic). Antibacterial compounds have multiple mechanisms of action broken down into four general classes: cell wall synthesis inhibitors, protein synthesis inhibitors, nucleic acid synthesis inhibitors, and compounds that alter cell membrane function.[16] To compare efficacy between antibacterial compounds, we used the minimum inhibitory concentration (MIC), a standard indicator for the antibacterial potency of a compound. MIC is the lowest concentration of drug that inhibits the visual growth of a microbe *in vitro*. The most common experimental techniques to determine the MIC comprises microtiter dilutions against bacteria in liquid broth, and time-kill assays (which also may inform the mechanism of action).[17] In this review, we highlight some of the latest plant derived and plant inspired natural products that displayed strong (MICs ≤ 20 μg/mL) antibacterial activity.

2.1.2 Antivirulence—Disrupting virulence for the treatment of bacterial infections is an alternative approach for addressing the antibiotic resistance crisis.[18] Bacteria display many different mechanisms of virulence. Virulence is the degree to which the bacteria can infect or damage a host, with virulence factors being defined as products that the bacteria produce to affect this pathogenicity.[19] Ideally, an antivirulent compound mitigates bacterial virulence

or reduces virulence factors while not disrupting growth, thus potentially reducing the rate of resistance acquisition. Potential targets include surface proteins, which may provide more accessible targets than traditional cell-penetrating antibiotics. Virulence factors are broad and can include toxins, secretion systems, adhesin, and siderophores.[18] Some common mechanisms for testing antivirulence include the measurement in reduction of these secreted virulence factors, inhibition of key biosynthetic enzymes, gene reported assays to assess the downregulation of virulence pathways, or reduction in host cell damage upon treatment with pathogenic bacteria. The compounds reviewed in this section are plant-derived secondary metabolites recently reported for antivirulence activity in bacterial pathogens.

2.1.3 Antibiofilm—Biofilms are virulence factors that contribute both to pathogenicity and antibiotic resistance through conferring intrinsic resistance to many antibiotic therapies. Biofilms are composed of extracellular polymeric substances (EPS) that form a matrix enclosing bacterial cells, leaving bacteria cells impenetrable to many therapeutics.[20] Disrupting biofilm is a key target in drug discovery as it can increase the effectiveness of antibiotics and antivirulence drugs. The studies discussed here include promising plant-derived natural products as biofilm inhibitors. Biofilm formation occurs first with attachment (reversible and irreversible), then growth, maturation, and dispersal.[21] The majority of studies discussed herein focus on the inhibition of biofilm growth or damage to mature biofilms. The output of these studies measures the minimum biofilm inhibitory concentration (MBIC) during the initial stages or minimum biofilm eradication concentration (MBEC) when evaluated against a mature biofilm. Staining with crystal violet is a standard method to observe biofilm coverage of well plates in the presence and absence of test compound.[22] Confocal scanning laser microscopy and scanning electron microscopy are examples of methods used to measure biofilm thickness and morphology,[23] The previous methods are primarily static measures of biofilm behavior, while rotary biofilm reactors and biofilm microfluidic devices are used to replicate biofilm formation in a physiologically relevant setting.[23]

2.2 Chemical Structures

Chemical structures reported in this review are based upon the published structure within each manuscript if available and PubChem for those not reported. Structural figures were produced using ChemDraw 21.0.0 by PerkinElmer Informatics.

2.3 Plant Nomenclature

Plant nomenclature is updated periodically, and it is important to differentiate the accepted plant names from common names. The full accepted name of each plant in this review was to include genus, species, author epithet, and family. Each plant mentioned in the literature was verified on World Flora Online (http://www.worldfloraonline.org) to ensure that the nomenclature is current and up to date.

3. Plant-Derived Natural Products with Antimicrobial Activity

3.1 Alkaloids

Alkaloids have been used in botanical medicine for over >3500 years, with the Ebers papyrus (~1500 BCE) mentioning the first recorded medical use of the opium poppy.[24] They are a diverse class of natural products originally documented as basic, organic nitrogen-containing secondary metabolites produced by plants, microbes, and animals. The class is broadened to now include most nitrogen-containing natural products of low molecular weight or their derivatives.[25] The most prevalent class are indole alkaloids, with other classes including, tropane, quinoline, isoquinoline, pyridine, pyrrolidine, pyrrolizidine, and steroidal alkaloids. Many plant alkaloids and their derivatives are still prescribed today for a variety of medical reasons such as severe pain (oxycodone, morphine, fentanyl), as antimalarials (quinine), to treat hypotension (ephedrine), or used recreationally (caffeine, nicotine, cocaine). Medicinal chemists often explore the inclusion of nitrogen into the parent compound due to its remarkable ability to improve the pharmacological profile of new drug derivatives.[26] Several plant natural product alkaloids, or their derivatives, with antibacterial activity are described below.

3.1.1 Amide alkaloids—Piperine (**1**) and piperlongumine (**2**) are amide alkaloids found in many species of *Piper*. *Piper betle* L. in the Piperaceae family has been used extensively in Ayurvedic medicine in many applications with some examples being as an antihelminthic, astringent, and to treat diarrhea.[27] Several different species of *Piper* are used throughout Peru, Brazil, Panama, and Mexico for treating a variety of ailments such as toothaches, dysentery, coughs, wound healing, and more.[28] In addition to these traditional uses, piperine has multiple biological uses and has been found to have anti-tumor, antifungal, analgesic, and anti-depressant properties.[29]

Mgbeahuruike *et al*. found **1** and **2** to have antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*.[30] Philipova *et al*. synthesized a series of piperine derivatives with different cyclic amines.[31] These piperine derivatives **1a** – **1e** were found to have potent anti-bacterial activity against *Mycobacterium tuberculosis* with MICs between 0.15 – 0.36 μM. **1e** was the most promising compound with an MIC of 0.18 μM and cytotoxicity IC_{50} of 249.8 μM (vs HEK293) and a selectivity index of >1300. The authors also conducted quantitative structure-activity relationship studies and found that quaternary carbons were necessary for anti-tuberculosis activity.

While the mechanism of action (MOA) for these compounds has not been identified, it has been theorized that piperine's antibacterial activity occurs through an increase in mTORC1 signaling. A study reported that mTORC signaling led to an increase in the bacterial phagocytic ability of peritoneal macrophages in mice and the subsequent increase in bacterial clearance.[32]

3.2 Phenolics

The oldest historical record of plant phenolic compounds used as medicine comes from the *Ebers Papyrus* (~1500 BCE), where ancient Sumerians and Egyptians recorded the uses

of what is now known as willow for treating pain and fever.[33] Thousands of years later, salicin and salicylic acid were isolated and later derivatized to acetylsalicylic acid. Better known by its generic name, Aspirin, it has since become the most used drug in the world,[33] providing one of the ultimate examples of ethnobotanical records guiding the discovery of a new drug. There are over 8,000 known plant phenolic compounds[34], making it the largest class of plant secondary metabolites.[35] They are seemingly ubiquitously expressed in plants and play many roles, from defense and signaling to pigment biosynthesis and regulation growth.[35] Phenolics are classified as having at least one hydroxyl group directly bonded to a mono or polycyclic aromatic hydrocarbon and are biosynthesized through shikimate or phenylpropanoid pathway[36]. The phenolic compounds highlighted below are those that exhibit antibacterial properties.

3.2.1 Lignans—Ligustchuanes A and B (**3**, **4**) are two novel epimeric lignan trimers containing a unique neolignan linkage, ferulic acid, and ethoxyl groups isolated from the rhizomes of *Ligusticum striatum* DC., Apiaceae, each in a racemic mixture.[37] Lignans are a structurally diverse group of phenols characterized by β,β' linkages of phenyl propane units. Diversity stems from varying degrees of side-chain oxidation, diversity of the aromatic ring, or changes in the linkage of the two or more units.[38] Compounds **3** and **4** (tested in respective racemic mixtures) disrupt the virulence of *Staphylococcus* aureus through the disruption of α-Hemolysin. This toxin facilitates the penetration of host cells by forming pores on the membrane.[39] Molecular docking studies show that both enantiomers of ligustchuane B can bind to α-Hemolysin heptamer, indicating a possible mechanism of action. Despite the structural similarity between ligustchuanes A and B, ligustchuane B exhibits a 32-fold increase in activity, emphasizing the importance of the chiral centers of the molecule. *L. striatum* (common name chuanxiong) has been used in Traditional Chinese Medicine (TCM) for thousands of years, first recorded in Shennong's Classic of *Materia Medica,*[40] a text containing 365 medicinal compiled during the end of the Eastern Han Dynasty (25–220 AD).[41] The rhizomes of *L. striatum* have been traditionally used to treat gynecological diseases, irregular menstruation, amenorrhea, dysmenorrhea, headache, rheumatism arthralgia and hemiplegia caused by stroke, coronary heart disease, and possess anti-inflammatory properties.[37, 40, 42] Most medicinal preparations with chuanxiong are combined with other plants, commonly *Angelica sinensis* (Oliv.) Diels (Apiaceae), *Paeonia lactiflora* Pall. (Paeoniaceae), and Borneolum syntheticum (a processed product produced from a combination of turpentine and camphor),[40] however, it is also used in treatment as a stand-alone ingredient.

Phillygenin is a phillyrin aglycone lignan.[43] Li *et al.* reported phillygenin (**5**) isolated from *Forsythia suspensa* Vahl, Oleaceae, to prevent biofilm formation at 100–150 μg/mL in *Helicobacter pylori.* Additional studies on **5** show it can act as an antioxidant, protect high density lipoprotein and low density lipoprotein lipid peroxidation, and may also have anti-inflammatory activity.[44–46] The fruit from *Forsythia suspensa* has a rich history in Chinese traditional medicine, with uses including the treatment of gonorrhea, inflammation, cough, ulcers, and parasites.[47]

3.2.2 Anthraquinones—Quinones are composed of aromatic rings with two ketone substitutions in the structure,[10] and this chemical class can be divided into subcategories of benzoquinone, naphthoquinone and anthraquinone. Among them, anthraquinones are found throughout nature and have been isolated from fungi, plants, and bacteria. Anthraquinones contain an anthracene skeleton with keto groups on the 9′ and 10′ position of the tricyclic ring. They display a wide range of bioactivities such as anticancer, anti-arthritic, and laxative properties.[48] Compound **6** is an anthraquinone derivative that was isolated from the stem bark of *Stereospermum fimbriatum* DC., Bignoniaceae; **6** displayed potent activity against MRSA with an MIC of 6.25 μg/mL.[49] *S. fimbriatum* has been traditionally used in Malaysia to treat earaches, itchy skin, and dermatosis.[50] The antibacterial mechanism of action for **6** is unknown, but it has been noted for other anthraquinones against gram-positive bacteria, that as carbon number increases so does the antibacterial activity.[51] This trend suggests that lipophilicity and the ability to permeate/disrupt the bacterial membrane is one major factor in the antibacterial activity of anthraquinones against gram-positive bacteria.

Rhein (**7**), rhein-8-*O*-*β*-D-glucopyranoside (**8**), emodin (**9**), *N*′-((4,5-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)methylene) benzenesulfonohydrazide (an aloe emodin-conjugated sulfonyl hydrazone) (**10**), chrysophanol (**11**), and hypericin (**12**) are all examples of this diverse and rich class of biofilm inhibitors.

Anti-biofilm activity of anthraquinone rhein (**7**), which can be isolated from traditional medicinal plants *Rheum palmatum* L. (Polygonaceae), *Senna tora* (L.) Roxb. (Fabaceae), *Reynoutria multiflora* (Thunb.) Moldenke (Polygonaceae), and *Aloe vera* (L.) Burm.f. (Asphodelaceae), was discovered by Folliero *et al.*[52] This study identified **7** to eradicate biofilm formation against *Streptococcus mutans* with an $MBEC_{50}$ of 6.31 μg/mL and $MBEC_{90}$ > 50 μg/mL. At 6.25 μg/mL, inhibition of biofilm formation and decreased thickness of the biofilm was observed. In addition to its antibiofilm activity, studies have shown that rhein also demonstrates growth inhibition of various bacteria strains.[53–55] Rhein is also neuro and hepatoprotective, as well as anti-cancer and anti-inflammatory.[56]

A related compound, (**8**) was also reported to have anti-biofilm properties.[57] Zhang *et al.* studied **8**, which is isolated from the roots of *Aucklandia costus* Falc. (Asteraceae) and the roots of *Rheum palmatum.* A dose-dependent effect of **8** was seen against *S. mutans*, with 60% inhibition of biofilm formation at 10 μg/mL of **8** and complete inhibition at 50 ug/mL. Zhang *et al.* also observed a decrease in the expression of the genes *brpA* and *luxS,* which engage in biofilm and may be one MOA through which **8** inhibits biofilm formation. Studies have reported that **8** inhibited the activity of PTP1B, prevents apoptosis, and promotes the purgative activity of sennoside A.[58–60]

Rhein and **8** are isolated primarily from *Rheum palmatum,* which has a rich history in traditional Chinese medicine.[61] Traditional use includes it in preparations to treat fever, and eliminate blood stasis, burns, and cancer.[61]

Đukanović *et al.* demonstrated the antibiofilm of emodin (**9**) isolated from *Frangula alnus* Mill. (Rhamnaceae) bark activity against methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* strains.[62] Significant biofilm formation inhibition was observed in

both strains at concentrations as low as 0.05 μg/mL with the highest concentration tested at 3.125 μg/mL. Emodin was also evaluated on mature biofilms to determine its potential to eradicate biofilm. Methicillin-resistant strains demonstrated 30% biofilm eradication at a concentration of 12.5 μg/mL. Additionally, this study found some strains displayed a decrease in *ica* genes, which polysaccharide intercellular adhesin is dependent upon and plays a key role in biofilm formation.[63] Emodin also demonstrates antioxidant, anti-inflammatory, antiviral, anti-diabetic, and anticancer.[64] *F. alnus* has traditional medicinal use in Europe with the bark used as a laxative or to induce vomiting.[65]

A similar compound derived from aloe emodin, aloe emodin-conjugated sulfonyl hydrazone 5a (**10**), reportedly demonstrates anti-biofilm properties as well.[66] Aloe emodin is a key component in much of Chinese traditional medicine and can be derived from *Rheum palmatum* and *Senna obtusifolia* (L.) H.S.Irwin & Barneby (cassia seed). Significant biofilm reduction (40%) by this compound was observed at 4 μg/mL in methicillin-resistant *S. aureus*. In addition to biofilm inhibition, the compound also demonstrated dispersion of the biofilm into the planktonic culture which led to decreased resistance. The method of action in which this specific emodin derivative acts as a biofilm inhibitor remains to be explored.

Another phenolic compound found within *Rheum palmatum* that also demonstrates antibiofilm activity is chrysophanol (**11**).[67] This study reports inhibition of biofilm formation (around 60%) in *Staphylococcus suis* at concentrations as low as 0.112 μg/mL. SEM results demonstrated a single molecule state of the bacteria cells with a lack of interconnection to create a biofilm, however, the exact mechanism of antibiofilm action needs to be further explored. Studies report chrysophanol also has uses in treating cardiovascular disease, treating cancer, providing neuroprotection, and preventing inflammation.[68]

Hypericin (**12**) derived from *Hypericum perforatum* L. (Hypericaceae) was reported by Wang *et al.* to inhibit biofilm formation (~ 60%) in *S. aureus* at 8 μg/mL.[69] This study reports that hypericin decreases gene expression of *sarA,* a key gene for biofilm formation, but still requires further mechanism of action studies. Additional studies report hypericin has anticancer activity and antiviral activity.[70, 71] *Hypericum perforatum* has a history dating back the ancient Greek physicians for wound healing, promoting diuresis, and eliminating parasites.[72] As its use spread throughout Europe in the 1500s, it was also used to treat anxiety and depression.[72]

3.2.3 Coumarins—Umbelliferone (**13**), a common secondary metabolite primarily isolated from plants from the Apiaceae family, was recently reported by Swetha *et al.* to inhibit biofilm formation (~50%) in *Staphylococcus epidermidis* at 200 μg/mL.[73] Umbelliferone is a coumarin, a class of compounds composed of a α-pyrone ring that is fused to a benzene.[10] This study also demonstrates inhibition of biofilm adherence at 500 μg/mL. Additionally, genetic studies revealed the downregulation of key genes for biofilm formation via adhesion (icaD, aap, and bph). Amin et al. studied compounds having a moiety of umbelliferone isolated from *Ferula narthex* Boiss., Apiaceae exudate against *S. epidermidis* and found faselol (**14**), to have a minimum biofilm inhibitory concentration (MBIC) of 174 μg/mL and 87 μg/mL against *S. aureus.*[74] These results suggest further

modification of umbelliferone may lead to discovery of a more potent antibiofilm compound. In addition to its antibiofilm properties, **13** also demonstrates anti-fungal, antioxidant, and antidiabetic activities.[75] The Apiaceae family contains many traditional medicinal plants, and some examples of plants with ethnobotanical uses in Iran include *Cuminum cyminum* L. (cumin), *Ferula gummosa* Boiss. (galbanum), *Foeniculum vulgare* Mill. (fennel), *Anethum graveolens* L. (dill) and *Pimpinella anisum* L. (anise).[76] *Ferula narthex* has historical use in medicine throughout many countries such as Afghanistan, Morocco, Egypt, Nepal, and India.[77] Specifically in India its uses include treating kidney stones, aiding in digestion, preventing spasmodic disorders, and treating bronchitis.[77]

3.2.4 Flavonoids—Flavonoids consist of a general skeleton of 15 carbons in a C_6–C_3–C_6 motif arranged as two benzene/phenyl rings and a pyran ring.[78] Isoflavonoids are distinguished by the phenyl group on the C_3 position of the center ring and flavones have this phenyl group on the C_2 position. Biochanin A (**15**) is an isoflavonoid—a phytochemical class often referred to as phytoestrogens—found chiefly in members of the Fabaceae (legume) family. Biochanin A has also been reported to display antidiabetic and anticancer activity.[79, 80] Acacetin (**16**) is a flavone that is derived from apigenin and has been found to inhibit monoamine oxidase A/B.[81] Pachaiappan *et al.* found **15** and **16** to have activity against *P. aeruginosa* with MICs of 0.97 and 3.90 μg/mL, respectively.[82]

Myrsininone A (**17**) and **18** are also both isoflavones, isolated from the fruits of *Ficus auriculata* Lour. from the Moraceae family. Myrsininone A has been reported to have anti-diabetic activity and has been found to inhibit α-glucosidase.[83] Both **17** and **18** displayed potent activity against various bacterial strains with MICs between 1.25 – 10 μM and 10 – 20 μM, respectively.[84] *F. auriculata* is native to Asia and the Himalayan regions. Leaves of this plant have been used as a paste for the treatment of wounds and the fruits have been used for hepatic and neurodegenerative diseases.[85]

While the mechanism of action for the antibacterial activity of many flavonoids remains unknown and many targets and MOAs have been proposed, it has been postulated that they may act through nonspecific action upon the bacterial cell membrane. Flavonoids have been found to permeate the cell membrane,[86] disrupt cellular membrane integrity,[87] and a relationship has been shown between their lipophilicity and antibacterial activity.[88]

3.2.5 Tannins—Corilagin (**19**) is a hydrolysable tannin, a compound class containing a central glucose or polyol moiety, esterified by gallic or ellagic acids. Corilagin is considered an ellagitannin and comprises of a hexahydroxydiphenoyl group that bridges the glucose core which was first isolated by Schmidt *et al.* in 1951 from *Libidibia coriaria* (Jacq.) Schltdl., Fabaceae,[89] a plant used in traditional Mexican medicine.[90] **19** was found to inhibit the hemolysis ability of *S. aureus* at a concentration range of 6 – 10 μg/mL in addition to reducing the expression of accessory gene regulator A at 6 μg/mL, thus disrupting quorum sensing. **19** is also found in multiple species of the genus *Phyllanthus*[91], of which many have use in Ayurvedic medicine.[92] In addition, **19** has displayed anti-tumor, anti-oxidant, anti-inflammatory properties.[91]

3.2.6 Xanthones—Xanthones, such as α-mangostin, are a class of compounds that possess a 9*H*-xanthen-9-one scaffold.[93] Felix *et al.* reported α-mangostin (**20**) isolated from the fruit of *Garcinia mangostana* L., Clusiaceae, to inhibit biofilm attachment and biofilm formation in *S. aureus*[94]. α-Mangostin demonstrated 75% inhibition of attachment at 4 μg/mL and the reported MBIC is 2 μg/mL. At 4 μg/mL this compound also eradicated 96% of established biofilms. Confocal microscopy revealed this compound alters the thickness of the biofilm during formation and after a mature biofilm has formed. Lastly, this study reports in the presence of α-mangostin a decrease in gene expression of *dnaK* which plays a role in biofilm formation, suggesting this may play a part in the mechanism of action.[95] Additional studies show α-mangostin has a wide variety of additional activities such as anti-inflammatory, neuroprotective, and anti-viral.[96–98] *G. mangostana* fruits have historically been used to treat skin infections in southeastern Asian medicine.[99] Ayurvedic medicine primarily used this fruit to treat inflammation, digestive illnesses, and cholera.[99]

3.2.7 Diarylheptanoids—Curcumin (diferuloylmethane) (**21**) is a linear diarylheptanoid in its own group called curcuminoids. Curcuminoids are a class of compounds exhibiting two aromatic rings bridged by a linear seven-carbon chain, of which curcumin's chain exhibits an α,β-unsaturated β-diketone moiety.[100] Under more alkaline conditions and in solid forms the keto-enol tautomer is favored.[100, 101] The derivatives (**22**, **23**) synthesized contain modifications to the methoxy and hydroxy moieties of the phenyl units. Antivirulence activity examined the ability of compounds **21**, **22**, and **23** to inhibit *Streptococcus pneumoniae* and *Vibrio cholerae* sialidase enzymatic activity with a focus on *S. pneumoniae* NanA sialidase, a key component in bacterial interaction with host cells.[102] Compounds **22** and **23** showed an approximate three-fold increase in activity on *S. pneumoniae* NanA sialidase and *V. cholerae* sialidase respectively, compared to curcumin (**21**). Compound **22**, a novel structure, was a competitive inhibitor whereas all others synthesized were non-competitive inhibitors. Curcumin was first isolated from the rhizomes of *Curcuma longa* L., Zingerberaceae (turmeric) by Vogel and Pelletier[103] in 1842.

Turmeric has been used in Vedic culture for around 4000 years as a culinary spice, for cosmetics, and as medicine[104]. Ayurvedic medicinal practices use turmeric to treat respiratory conditions, anorexia, rheumatism, runny nose, cough, sprains, and swelling.[104, 105] It has also been used to as an antibacterial agent for the treatment of burns and cuts in many South Asian countries.[104]

3.2.8 Stilbenes—Salvianolic acid A (**24**) was first isolated from the dried roots of *Salvia miltiorrhiza* Bunge, Lamiaceae in 1984[106] and is classified as a stilbenoid. Although there are various sub-categorizations, stilbenoids have a basic C_6–C_2–C_6 unit in their structure. **24** was reported to have activity against SrtA in Methicillin-resistant *Staphylococcus aureus* (MRSA), a surface protein transpeptidase responsible for bacterial adherence to host cells.[107] Free protein binding assays with SrtA determined a reversible inhibition with an IC_{50} of 5.75 μg/mL, with further binding studies concluding a K_d of 21.53 nM and prediction of the binding pocket using molecular docking studies.[107] *In vivo* studies in a lethal MRSA-induced pneumonia mouse model of infection showed a 100% survival rate when used in the combination of current antibiotic latamoxef.[107] *S. miltiorrhiza* roots

have been used in TCM for more than 2000 years and are recorded in Shennong's herbal classic of *Materia Medica*.[108] Traditional use includes using the dried roots in the form of decoctions or pills either alone or in combination with other herbs to treat coronary heart disease and cerebrovascular diseases.[109]

Hopeaphenol, isohopephenol, and ampelopsin A (**25, 26**, and **27**) are oligomeric stillbenoids isolated from the roots of *Vitis vinifera* L., Vitaceae. Their biosynthesis is derived from the oligomerization of resveratrol, of which dimers through octamers have been found.[110, 111] Besides *V. vinifera*, resveratrol oligomers have been isolated from various other *Vitis* species and plant families such as Cyperaceae, Dipterocarpaceae, Fabiaceae, Gnetaceae, and Paeoniaceae.[112–114] Resveratrol oligomers have been found to interfere with the type III secretion system (T3SS) of various human and plant pathogens.[115, 116] The T3SS system is a needle-like structure in gram negative bacteria that allows the bacteria to penetrate host cell membranes and transfer various substrates.[18] In *Pseudomonas syringae* pv. *Tomato* DC3000, these oligomers exhibit antivirulence through the decreased expression of various *hrp* gene clusters of the T3SS including *hrpA*, *hrpL*, and *hop1,*[116] while resveratrol itself had no effect. Resveratrol can be produced at increasing amounts at sites of plant infection, allowing also for the biosynthesis of oligomers with more potent activity.[110] Various resveratrol oligomers have been shown to have antibacterial, antioxidant, anti-neurodegenerative, anti-tumor, as well as heart and liver protective effects.[111] Many plant foods and medicines contain resveratrol[117] and various oligomers, with TCM preparations displaying numerous decoctions and granules in which resveratrol has been found.[118] These traditional preparations focus on treating lung diseases such as pneumonia, chronic obstructive pulmonary disease, asthma, and idiopathic pulmonary fibrosis and asthma.

3.2.9 Methoxybenzenes—Paeonol (**28**) is a member of the methoxybenzenes and alkyl-phenyl ketones. It has an acetophenone core with a 2-hydroxy,4-methoxy substituted ring. It is isolated from the root bark of *Paeonia suffruticosa* Andrews, Paeoniaceae,[119] but can also be found in other species[120] and even different plant families.[121] **28** was examined for its ability to affect *Salmonella enterica* serovar Typhimurium type III secretion system (T3SS), a multicomponent molecular system that facilitates invasion, intracellular replication, and affect host inflammation encoded by the *Salmonella* pathogenicity island (SPI).[122] **28** significantly reduced host cell injury and reduced cellular invasion by *S. typhimurium* at a concentration of 95 μM as well as increased the survival rate in a *S. typhimurium* infection model with no observed cytotoxicity. From this study, it is proposed that **28** inhibits the expression of key effector proteins of T3SS through the reduction of the transcription level of *hil*A in the SPI-1 regulatory pathway.[122] *P. suffruticosa* commonly referred to as tree peony, has been used in TCM for thousands of years, traditionally prepared by creating slices the root cortex, referred to as "Danpi".[123] Danpi has been used in the form of decoctions, granules, and pills to treat blood stasis through promotion of blood circulation. It is also used to treat amenorrhea and dysmenorrhea, skin sores and bruises.[123]

3.3 Terpenoids

Terpenoids, a class of organic compounds comprised of an isoprene unit, have been used in medicine for thousands of years. Roughly 2000 years ago, the use of *Artemisia*

annua L. for fever reduction was recorded in a text called “52 Prescriptions”, recovered from the Mawangdui Han dynasty tomb.[124] More than a thousand years later, the active compound Artemisinin (a sesquiterpene lactone) was discovered and in 2015, Tu Youyou was awarded the Nobel Prize for her contributions. Terpenoids play broad roles in plant growth and development and plant odors. Another example of is that of paclitaxel, a tetracyclic diterpenoid isolated from the Pacific Yew tree used successfully in the clinic as a chemotherapeutic. Outlined below are terpenoids found within the search criteria as possessing various antibacterial properties.

3.3.1 Diterpenoids—Carnosic acid (**29**) is an abietane diterpenoid found in the aerial parts of *Lepechinia meyenii* (Walp.) Epling, Lamiaceae.[125] Carnosic acid is also found in other members of the Lamiaceae family such as rosemary (*Rosmarinus officinalis* L.) and has been reported to have antioxidant and anti-adipogenic properties.[126] Abietane diterpenoids are characterized by a tricyclic C20 skeleton with an aromatic C ring.[127] The MOA for growth inhibition by carnosic acid is currently unknown but it has been shown that abietane diterpenes interact with the phospholipid bilayer of membranes.[128, 129] *L. meyenii* has historically been used in Peru for a variety of ailments such as bronchitis, heart issues, and wound healing and hair loss.[130] A decoction of the whole plant is typically consumed as a beverage or used in combination with other plant species for bathing.[130] Chabán *et al*. found that carnosic acid displayed antibacterial activity against *Enterococcus faecalis* and methicillin-resistant *Staphylococcus aureus* (MRSA) with MICs of 15.6 and 7.8–15.6 μg/mL, respectively.[125] Derivatives of carnosic acid were also made by the authors and yielded **30** and **31**. The lactone derivative **30** was found to have reduced activity compared to the parent (**29**) but **31**, the C20 methylated derivative, was found to have a greater increase in antibacterial activity than the parent compound. Additionally, this same study found that the hydroxyl group on the C12 of carnosic acid and its derivatives was required for antibiotic activity.

Compound **32** is a diterpene lactone andrographolide isolated from *Helichrysum caespititium* (DC.) Sond., Asteraceae, with antibiofilm properties against *Neisseria gonorrhoeae* [131]. When tested at 60 μg/mL, **32** inhibited biofilm cell attachment by 81%, but only inhibited biofilm formation by 32%. The potential mechanism of action may be a disruption of the EPS cohesiveness. *H. caespititium* has many known uses in traditional medicine across South and Central Africa, individually against respiratory infections, and as a component of traditional medicinal mixtures for various other diseases.[132]

Andrographolide sulfonate (**33**) isolated from *Andrographis paniculata* (Burm.f.) Wall., Acanthaceae, demonstrates antibiofilm activity against MRSA at a test concentration of 25 mg/mL.[133] This concentration is considered very high, but the minimum inhibitory concentration of bacterial growth for this compound is 50 μg/mL. This highlights the potential for derivatives to work as antibiofilm inhibitors. Additionally, this study observed downregulation of genes associated with intracellular adhesion (*icaA, icaD, and PIA*), key to biofilm formation, in the presence of the compound. Andrographolide sulfonates are part of injections based on TCM and are currently approved in China to treat respiratory infections, tonsillitis, and numerous other infections.[134] *A. paniculata* has uses in traditional Chinese medicine to treat snake bites, sore throats, and to treat colds and fevers.[135]

3.3.2 Triterpenoids—Triterpenes are a common natural product found throughout nature that shares the common structural formula $C_{30}H_{48}$. There are over 20,000 natural triterpenes known.[136] An annual review by Connolly and Hill catalogues the latest triterpenes isolated from nature.[137] Pentacyclic triterpenes are a class of triterpenes characterized by their 5-membered rings and include the compounds ursane, lupane, and oleanane.[138]

Starting with various pentacyclic triterpene skeletons, Kazakova *et al.* (2021) synthesized multiple pentacyclic triterpenoid derivatives (**34**–**38**) and studied their efficacy against the ESKAPE pathogens.[139] These derivatives were found to have MICs of 0.15 μM against *S. aureus*. The MOA for growth inhibition by these pentacyclic triterpenoid derivatives is currently unknown. But, pentacyclic triterpenes have been reported to disrupt the bacterial cell membrane and inhibit NADH oxidation in *S. aureus*.[140]

In a separate study by Kazakova *et al.* (2021), the authors tested the antibacterial activity of different oleanolic acid derivatives.[141] **39** is a derivative of oleanolic acid, a compound found in over 1,600 plant species and found in many members of the Oleaceae family.[142] **39** was found to have anti-MRSA activity and also displayed anti-chlamydial activity. The MOA for **39** was not reported, but a previous study has reported that oleanolic acid and related derivatives have been found to deregulate peptidoglycan metabolism in *S. aureus.*[143]

Betulin (**40**) and celastrol (**41**) are two triterpenoids also possessing antivirulence activity. Betulin is a pentacyclic triterpenoid of lupane structure and contains a hydroxy and hydroxymethyl group. It can be found in a wide variety of *Betula* species (Betulaceae family) and is commonly isolated form birch bark which can contain around 20–30% betulin by dry weight.[144] Many pharmacopoeias around the world have traditional medicinal application of plants of *Betula* species.[145] In North America, gray birch bark (*Betula populifolia* Marshall, Betulaceae) was used by the Maliseet and Mi′kmaq to treat infected wounds.[146]

Experiments using *Listeria monocytogenes* show that **40** was able to inhibit listeriolysin O (LLO) hemolysis likely by disrupting LLO oligomerization in concentrations as low as 4.5 μM. Additionally, bacterial burden in livers and kidneys of mice infected with *L. monocytogenes* was significantly reduced when administered at 50 mg/kg.[147]

Celestrol, also known as tripterine, (**41**) is a pentacyclic quinone methide triterpene and is present in high abundances in the roots of *Tripterygium wilfordii* Hook.f., Celastraceae.[148] *T. wilfordii* has been used for more than two thousand years in TCM[149] to treat various inflammatory disorders namely rheumatoid arthritis[150] and has also been shown to possess anticancer properties.[151] In *S. aureus*, celastrol inhibits a virulence factor called carotenoid staphyloxanthin (STX) which is essential for *S. aureus* to disrupt reactive oxygen species produced by host macrophages and neutrophils, thus reducing bacterial clearance by the innate immune system.[152]

Compounds **42**, **43**, **44** are triterpenoid acids, classified by having 30 carbons forming 6 isoprene units in their skeleton. Triterpenoids can be linear or cyclic, with **43** and **44**

showing tetracyclic tirucallane-like structure and **42** with a pentacyclic oleanolic acid-like structure. Isolated from the fruits of *Schinus terebinthifolia* Raddi, Anacardiaceae, these compounds exhibit antivirulence in MRSA through quorum sensing inhibition of the accessory gene regulator (*agr*) system and broader antivirulence effects through targeting the *sae*-two component system.[153] The *agr* signaling system has been found to be crucial for MRSA skin infection and leads to the production of toxins and exoenzymes.[154] Compounds **43** and **44** exhibited the best activity with IC_{50} of the *agr* system ranging between 2–9 μM, decreasing *δ*-toxin, while exhibiting little to no growth inhibition at these concentrations. A traditional medicine in Brazil, its indigenous habitat,[155] various parts of the plant have been used to treat wounds and ulcers of the skin, tumor, arthritis, infections of the urinary and respiratory tracts, and contusions.[155, 156]

Oleanolic (**45**) and maslinic acid (**47**) were isolated from the waste of olive oil, *Olea europaea* L., Oleaceae, and two promising C-28 amide derivatives were synthesized: oleanolic acid-HDA (**46**) and maslinic acid-HDA (**48**).[157] These derivatives from oleanolic acid (**45**) and maslinic acid (**47**) demonstrated potential biofilm inhibition properties. At 50 μg/mL oleanolic acid (**45**) did not demonstrate notable destructive activity, but its derivatives **46**, **47**, and **48** were able to remove 99% of the pre-existing biofilm grown on catheters. **46** and **48** were also tested against a continuous biofilm after 4 days, and after 24 hours demonstrated a decrease in biofilm (30% for **46** and 45% for **48**) and a decrease in the thickness (~10 μm). These derivatives potentially penetrate the bacterial cellular membranes causing damage, indicating a potential MOA. Oleanolic acid (**45**) is also reported to have anti-cancer anti-diabetic, hepatoprotective, anti-parasitic, anti-bacterial, and antioxidant activities.[158] Maslinic acid (**47**) also has a range of additional activities including cardio protection, anticancer, antiparasitic, and anti-inflammatory.[159] *O. europaea* can be found in medicinal practices throughout the globe including Japan, the United States, Brazil, and the Mediterranean as a laxative, anti-asthmatic, antibacterial, and anti-inflammatory.[160]

4. Summary Tables Organized by Activity

4.1

Antibacterial

Natural product compounds	Chemical Class	Plant source	Antibacterial activity			Proposed Mechanism	Other biological activity	Refs.
			Bacterial target	Activity (MIC)	Derivative activity (MIC)			
Piperine (**1**) Piperlongumine (**2**)	Amide Alkaloids	*Piper* species	*S. aureus* *P. aeruginosa*	(**1**) 3.9–15.6 μg/mL (**2**) 3.9–31.2 μg/mL	(**1a**–**1e**) 0.15–0.36 μM (*M. tuberculosis*)	–	Anti-tumor, antifungal. analgesic, and antidepressant Host targeted mechanism: Increased mTORC1 signaling leading to increased bacterial clearance by macrophages	30 31

Natural product compounds	Chemical Class	Plant source	Antibacterial activity			Proposed Mechanism	Other biological activity	Refs.
			Bacterial target	Activity (MIC)	Derivative activity (MIC)			
Biochanin A (**15**)	Flavonoids	Fabaceae species	*P. aeruginosa*	0.97 μg/mL	–	–	Antidiabetic, anticancer	82
Acacetin (**16**)	Flavonoids	Fabaceae species	*P. aeruginosa*	3.90 μg/mL	–	–	MAO-A/B inhibitor	82
Flavonoids (Isoflavonoids, flavones) Myrsininone A (**17**) (**18**) (**6**)	Flavonoids (**17**, **18**) Anthraquinone (**6**)	*Ficus auriculata* (Lour.) (**17**) *Ficus auriculata* (Lour.) (**18**) *Stereospermum fimbriatum* (Wall. Ex G. Don) (**6**)	various various MRSA	1.25–10 μM (**17**) 10–20 μM 6.25 μg/mL	-	Potentially through nonspecific action upon the bacterial cell membrane (**17**) Unknown (**18–19**)	α-glucosidase inhibition IC_{50} 50.5 ± 3.7 μM (**17**)	84 49
Carnosic acid and derivatives Carnosic acid (**29**)	Diterpenoids	*Lepechinia meyenii* (Walp.)	*E. faecalis*, various MRSA strains	15.6, 7.8–15.6 μg/mL	Anti-MRSA activity; (**30**), 31.2 μg/mL; (**31**) 3.9 μg/mL	Interaction with bacterial membrane phospholipids	Antioxidant and anti-adipogenic	125
Triterpenic derivatives (**34**–**38**)	Terpenoids	various	*S. aureus*	(**34**–**38**) 0.15 μM	–	Disrupts *S. aureus* cell membrane and inhibits NADH oxidation	–	139
Oleanolic acid derivative (**39**)	Terpenoids	various	*S. aureus*	4 μg/mL (MRSA)	–	Deregulate peptidoglycan metabolism	Anti-chlamydial activity	141

4.2

Antivirulence

Natural product	Compound Class	Plant source	Antibacterial activity			Mechanism	Other biological activity	References
			Bacterial target	Activity	Derivative activity			
Curcumin (**21**) (**22**) (**23**)	Diarylheptanoids		*Streptococcus pneumoniae* Nan A; *V. cholerae*	0.6–5.3 μM (IC_{50})	0.2–1.9 μM (IC_{50})	Sialidase inhibitors	–	161
Ligustchuanes (**3**) (**4**)	Lignans	*Ligusticum striatum* DC.	*Staphylococcus aureus*	(**4**) 3 – 6 μM* (**3**)96 μM*	–	Inhibits α-hemolysin secretion	–	162
Paeonol (**28**)	Methoxybenzenes	*Paeonia* spp., dried root bark	*Salmonella enterica* serovar Typhimirium	95–190 μM*	–	T3SS inhibitor, reduces *SipA* translocation and expression of effector proteins	–	163

Natural product	Compound Class	Plant source	Antibacterial activity			Mechanism	Other biological activity	References
			Bacterial target	Activity	Derivative activity			
Salvianolic acid A (**24**)	Phenolic derivatives	*Salvia miltiorrhiza* Bunge	*Staphylococcus aureus*	5.75 μg/mL (IC_{50})	–	Inhibition of *SrtA* activity	–	164
Resveratrol oligomers (**25**) (**26**) (**27**)	Stilbenes	*Vitis vinifera* L.	*Pseudamonas syringae* pv. Tomato DC3000	25–100 μM*	–	Inhibition of T3SS through downregulation of *hrp* gene expression	–	165
Corilagin (**19**)	Tannins	*Terminalia chebula* Retz.	*S. aureus*	6–10 μg/mL*	–	Quorum sensing inhibitor through *agrA*, Anti-α-hemolysin	Biofilm inhibition, Pigment inhibition. Decreased STX production	166
Betulin (**40**)	Terpenoids	*Betula* spp.	*Listeria monocytogenes*	4.5 – 36 μM*	–	Inhibition of exotoxin, LLO activity	–	147
Celastrol (**41**)	Terpenoids	*Tripterygium* spp.	*S. aureus*	0.44–2.2 μM*	–	Decreased expression of virulence transcriptional regulators SigB, msaB, and stress adaptor yjbH	–	167
Triterpenoid acids (**42**) (**43**) (**44**)	Terpenoids	*Schinus terebinthifolia* Raddi	*S. aureus*	2–70 μM (IC_{50})	–	Quorum sensing inhibitors	Biofilm inhibition	168

*Unspecified IC_{50}, IC_{90}, or activities of multiple assays listed as range

4.3

Antibiofilm

Natural Product Compounds	Natural Product Class	Plant source	Antibacterial activity			Mechanism	Other biological activity
			Bacterial target	Activity	Derivative activity		
Umbelliferone (**13**) Feselol (**14**)	Coumarins	Apiaceae family (**13**) *Ferula narthex* Boiss. (**14**)	*S. epidermidis* *S. aureus*	*S. epidermidis* 200 μg/mL MBIC (**13**)	*S. epidermidis* 174 μg/mL MBIC *S. aureus* 87 μg/mL MBIC (**14**)	Downregulation of genes key for biofilm formation via adhesion (*icaD, aap,* and *pbh*)	Anti-fungal, antioxidant, and antidiabetic activities
Phillygenin (**5**)	Lignans	*Forsythia suspensa* Vahl	*H. pylori*	100–150 μg/mL MBIC	–	–	Antioxidant, protection of HDL and LDL lipid peroxidation, and may also have anti-

Natural Product Compounds	Natural Product Class	Plant source	Antibacterial activity			Mechanism	Other biological activity
			Bacterial target	Activity	Derivative activity		
							inflammatory activity
Rhein (**7**) Rhein-8-O-β-D-glucopyranoside (**8**)	Anthraquinones	*Rheum palmatum* L., *Senna tora* (L.) Roxb., *Reynoutria multiflora* (Thunb.) Moldenke and *Aloe vera* (L.) Burm.f.	*S. mutans*	60% inhibition at 10 μg/mL, complete inhibition at 50 μg/mL (**8**) $MBEC_{50}$ of 6.31 μg/mL and $MBEC_{90}$ > 50 μg/mL (**7**)	–	(**7**) may downregulate the expression of *brpA* and *luxS* in *S. mutans*	Moderate bioactivity against human PTP1B (protein tyrosine phosphatase 1B) Promote the metabolic activity and purgative activity of sennoside A Neuroprotection, bacterial growth inhibition, anticancer, anti-inflammatory, antiapoptotic
Emodin (**9**) N'-((4,5-dihydroxy-9,10-dioxo-9,10-dihydroanthracen-2-yl) methylene) benzenesulfonohydrazide (**10**)	Anthraquinones	*Frangula alnus* Mill. (**9**) *Rheum palmatum* L. and *Senna obtusifolia (L.) H.S.Irwin & Barneby* (cassia seed) (**10**)	Methicillin resistant *S. aureus* (**9**) Methicillin sensitive *S. aureus* (**9**) Methicillin resistant *S. aureus* (**10**)	0.05–3.125 μg/mL MBIC 30% Biofilm Eradication at 12.5 μg/mL (**9**) 0.05–3.125 μg/mL MBIC (**9**)	40% biofilm formation inhibition at 4 μg/mL (**10**)	Decrease in *ica* gene expression. (**9**) Dispersion of the biofilm into the planktonic culture (**10**)	antioxidant, anti-inflammatory, antiviral, anti-diabetic, and anticancer activity (**9**)
Chrysophanol (**11**)	Anthraquinones	*Rheum palmatum* L.	*Streptococcus suis*	MBIC: 0.124 μg/mL	–	Lack of interconnection between bacterial cells prevents biofilm formation	Cardioprotective, anticancer, neuroprotective, and anti-inflammation
Hypericin (**12**)	Anthraquinones	*Hypericum perforatum* L.	Methicillin resistant *S. aureus*	60% inhibition at 8 μg/mL	–	Inhibits *sarA* expression in MRSA	Anticancer and antiviral
α-Mangostin (**20**)	Xanthones	*Garcinia mangostana* L.	*S. aureus*	Attachment inhibition 75% at 4 μg/ml Formation inhibition: 2 μg/mL (MBIC) Eradication: 96% at 4 μg/mL		Decrease in gene expression of *dnaK*	anti-inflammatory, neuroprotective, and anti-viral
Andrographolides: diterpene lactone (**32**) sulfonate (**33**)	Terpenoids	*Helichrysum caespititium* (DC.) Sond (**32**) *Andrographis paniculata paniculata* (Burm.f.)	*N. gonorrhoeae* (**32**) *S. aureus*	81% attachment inhibition and 32% formation inhibition at 60 go/mL (**32**) Biofilm		(**32**) Disturbs extracellular polysaccharides cohesiveness (**33**) Down-regulates gene expression of intercellular adhesion genes	

Natural Product Compounds	Natural Product Class	Plant source	Antibacterial activity			Mechanism	Other biological activity
			Bacterial target	Activity	Derivative activity		
		Wall. (**33**)		eradication at 25 mg/ml (**33**)		(*icaA*, *icaD*, and *PIA*)	
Oleanolic acid (**45**) Oleanolic acid – HDA (**46**)	Terpenoids	*Olea europaea* L.	*S. aureus*	(**45**) No eradication at 50 μg/mL	(**46**) 45% eradication at 50 μg/mL	Penetration of bacterial cellular membranes causing damage as well	Anti-cancer anti-diabetic, hepatoprotective, anti-parasitic, anti-bacterial, and antioxidant activities
Maslinic acid (**47**) Maslinic acid – HDA (**48**)	Terpenoids	*Olea europaea* L.	*S. aureus*	(**47**) 20% eradication at 50 μg/mL	(**48**) 30% eradication at 50 μg/mL	Penetration of bacterial cellular membranes causing damage as well	Cardioprotection, anticancer, antiparasitic, and anti-inflammatory

5. Conclusion and Perspectives

Antibiotic resistance (AMR) continues to be a widespread worldwide issue. The recent manifestation of COVID-19 has exacerbated the rise of antibiotic resistance as more individuals are exposed to nosocomial MDR bacterial infections and an increase in patients on antibiotics that developed pneumonia as a co-infection. Some predict that the pace of antibiotic development will not be able to keep up with the pace of bacterial resistance, leading to an antibiotic crisis and potentially the next pandemic. [169] Natural products are an incredible tool in urgent drug discovery efforts and are the basis of the field of antimicrobial development. Alexander Fleming accidentally discovered one of the most famous natural products, penicillin, in the early days of anti-infective research. Selman Waksman, who coined the term “antibiotic”, took an interest in the mechanisms behind penicillin’s activity, the ability of microorganisms to produce antimicrobial agents, and developed the first screening protocols that led to the isolation of 15 antibiotics. Since the 1940’s, the advancement of protocols and technologies available to mine, extract, produce, characterize, and manipulate natural products should have led to additional novel antibiotic development, but there is a stall in novel antibiotic classes brought to the market for clinical use. Furthering the field of natural product research has great potential to fill this gap in medicine.

In this review, we highlight research results from 2018–2022 on plant-derived natural products that demonstrate anti-infective characteristics against pathogenic bacteria, including growth inhibition, antivirulence and antibiofilm activity. Although various structures and natural sources with anti-infective activity were reported, under the inclusion criteria, only three main classes of compounds were discussed in this review, in which a large diversity of phenolic derivatives was observed. Alkaloids, phenolic derivatives, and terpenoids are extremely diverse chemical classes and are among the most abundant types of compounds found in plants. Some novelty arose from the synthesis of derivatives, re-emphasizing complementarity of medicinal chemistry in natural products drug discovery.

A significant portion of the discussed compounds were of known structure, with novel biological activities as antibacterial agents.

6. Potential Clinical Relevance of the Reported Antimicrobial Compounds

Natural product research involves many difficulties in the process from plant collection to isolation and structural identification. In particular, appropriate reporting criteria for plant materials must include adequate documentation of the plant collection (e.g., herbarium vouchers), species authentication, sample preparation, and validation of extraction methodology. Articles in which plant material were not validated or properly reported were not included in this review work. In addition, inconsistencies in the reporting of experimental results creates an issue for data comparability. For experimental design and data interpretation, publications such as the CLSI (Clinical and Laboratory Standards Institute) are an excellent resource for many antibacterial studies but are limited in their scope for biofilm and antivirulence assays. An additional disadvantage is the inconsistent definition of relevant concentrations for all studies (i.e., studies reporting novel compounds with activity in the μg/mL range vs mg/mL). Compounds that require significant starting material may not be great candidates for drug discovery efforts alone but can provide a basis for modification through medicinal chemistry. Further additions and definitions in the field can ensure uniform research and reproducibility, as well as ensuring the reported compounds have the potential to be potent preclinical drug candidates.

Our search criteria were stringent, thus leaving out additional natural products that may have potential in the clinic. An approach not included under the criteria of this review were natural products aided by the delivery of nanoparticles whether *in vivo* or examining *in vitro* cell permeability. Many natural products lack the physiological and chemical properties needed to make a drug with good bioavailability and pharmacokinetic properties. Thus, methods of better delivery could provide an avenue in which natural products with promising *in vitro* biological activity could play a role in antibacterial drug development.

Notably, as of May 2023, there are currently no FDA approved antibacterial drugs that are botanical natural product. Preclinical animal studies for the compounds listed in this review are rare. The following preclinical animal studies were found for piperine and curcumin,[170] and for celastrol. [171] All other compounds listed in this review had no registered preclinical animal studies at the registry databases we searched (https://www.animalstudyregistry.org, https://preclinicaltrials.eu/). We found more success searching for these compounds at the NIH's clinical trial database (https://clinicaltrials.gov/). The compounds found (**1**, **3**, **17**, **22**, **23**, **27**, **28**, **29**, **33**, **39**, **41**, **42**, **44**, **45**, **47**) with active/completed clinical trials, were all unrelated to antimicrobial studies. But, outside of well-studied commonly described natural products (piperine, curcumin, hypericin, salvianolic acid A) there were very few (≤5 clinical trials) for these compounds. Bioavailability and/or pharmacokinetic clinical trials were completed or being conducted for six compounds (**1**, **17**, **23**, **29**, **41**, **42**). The trials examining the pharmacokinetic properties of these compounds are a promising first step. Characterizing the safety profiles of these compounds in human subjects may facilitate future studies examining the antimicrobial properties of these botanical natural products.

While a few studies in this review merely acknowledge the traditional use of these plants in their discussion, over half (28/48) of the reported compounds have a history of traditional uses (compounds **6**–**8**, **17**–**23**, **27**, **30**–**37**, **39**, **40**, **42**–**48**). While not always explicitly stated, many studies on plant-derived bioactive natural products stem are based on plants with strong documentation for traditional medicinal applications in ethnobotanical literature. Herein, many of the studies reviewed sought out unidentified or derivative compounds (**18**, **19**, **39**, **46**, **48)** from traditional medicinal plants, or to further explore the bioactivity of previously identified bioactive compounds (**27**, **33**, **34**, **36**, **39, 42**–**48**). The studies of natural products and their derivatives with bioactivity can contribute to the search for new drug candidates.

Plant-derived natural products can inspire the development of the next generation of antimicrobials. In addition, ethnobotanical knowledge from different countries and cultures or searching historical uses can be a valuable starting point for researchers. In the future, active collaboration is needed not only by natural products and microbiology researchers but also by scientists from the fields of medicinal chemistry and ethnobotany to discover and develop the next generation of anti-infective agents.

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Biographies

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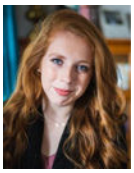

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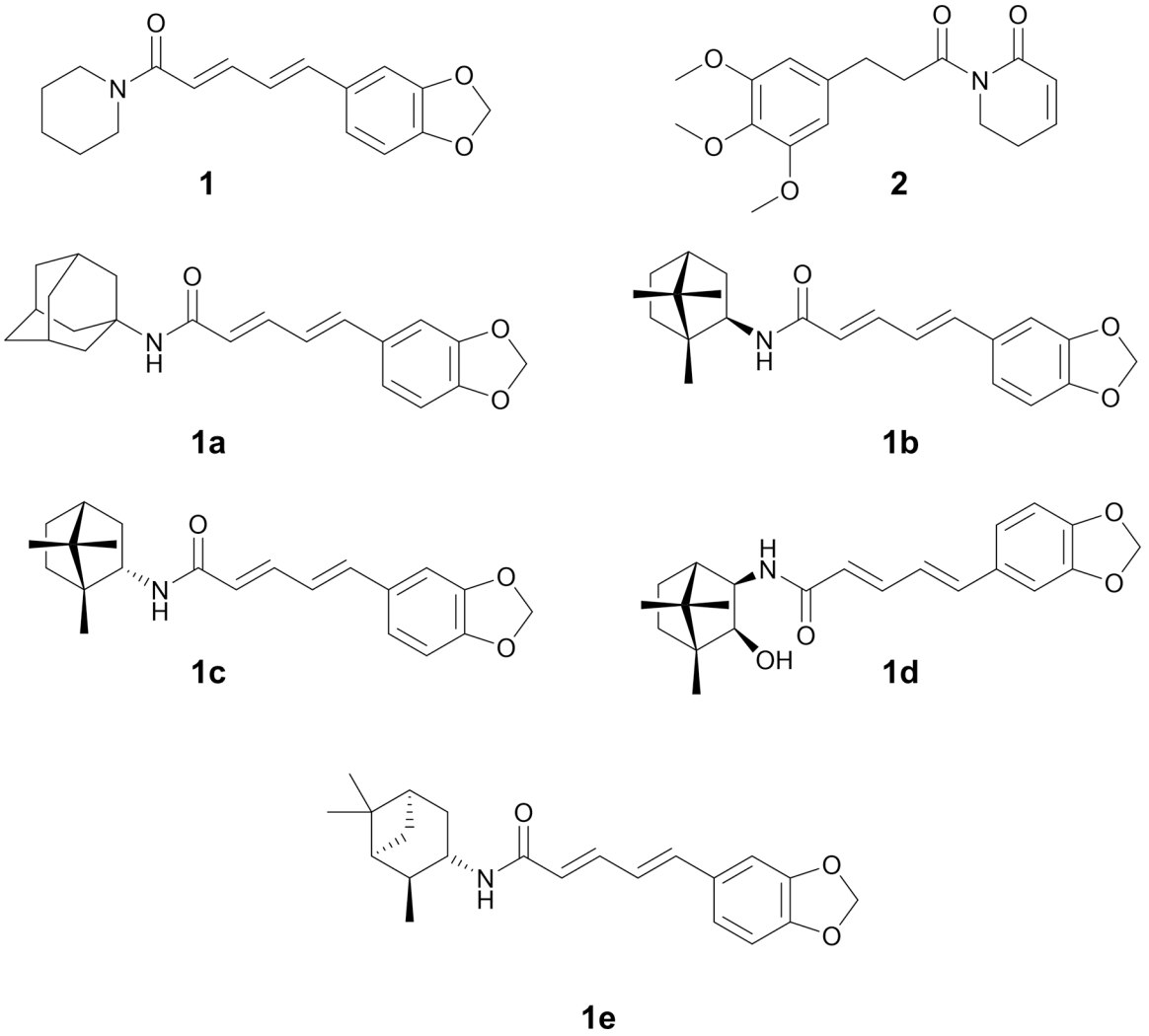

Figure 1.
Amide alkaloids and derivatives with antimicrobial activity

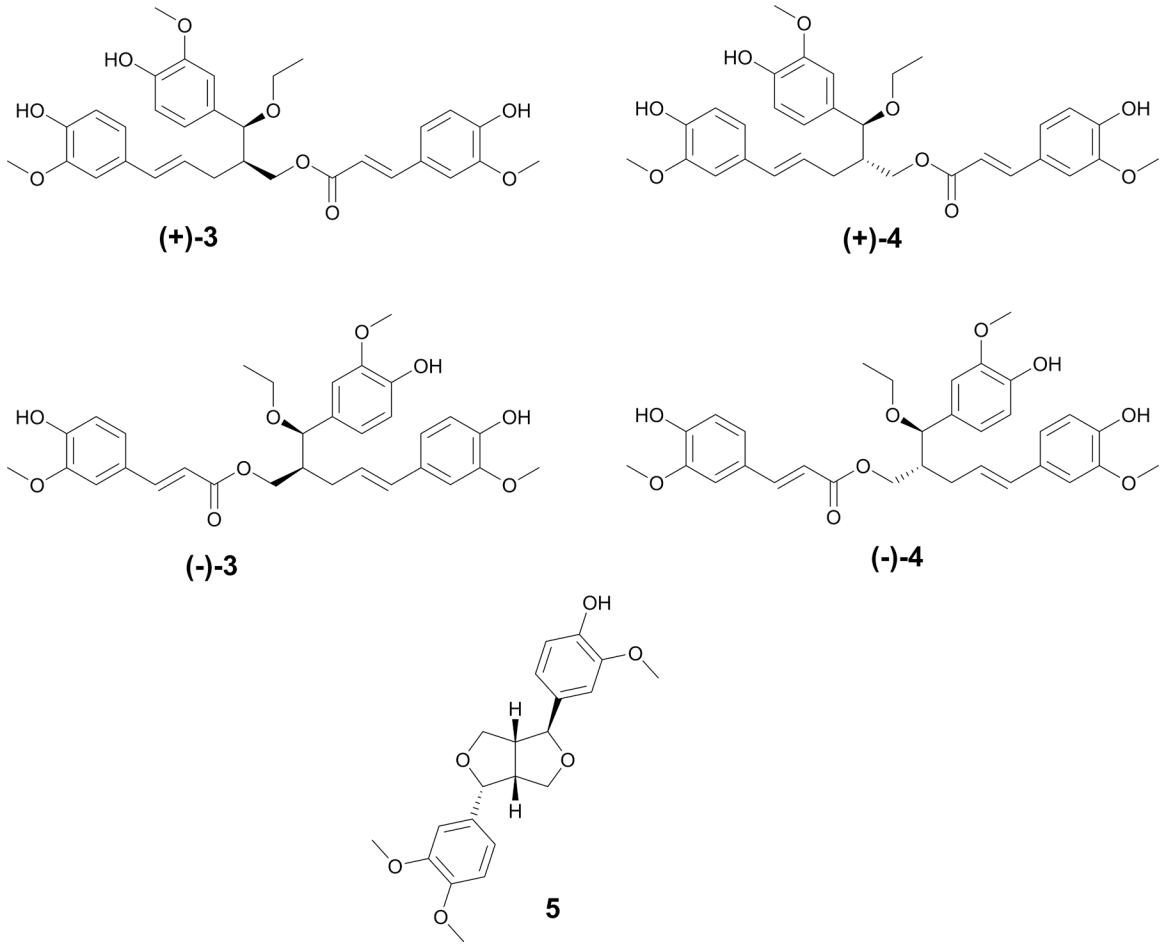

Figure 2.
Lignans with antimicrobial activity

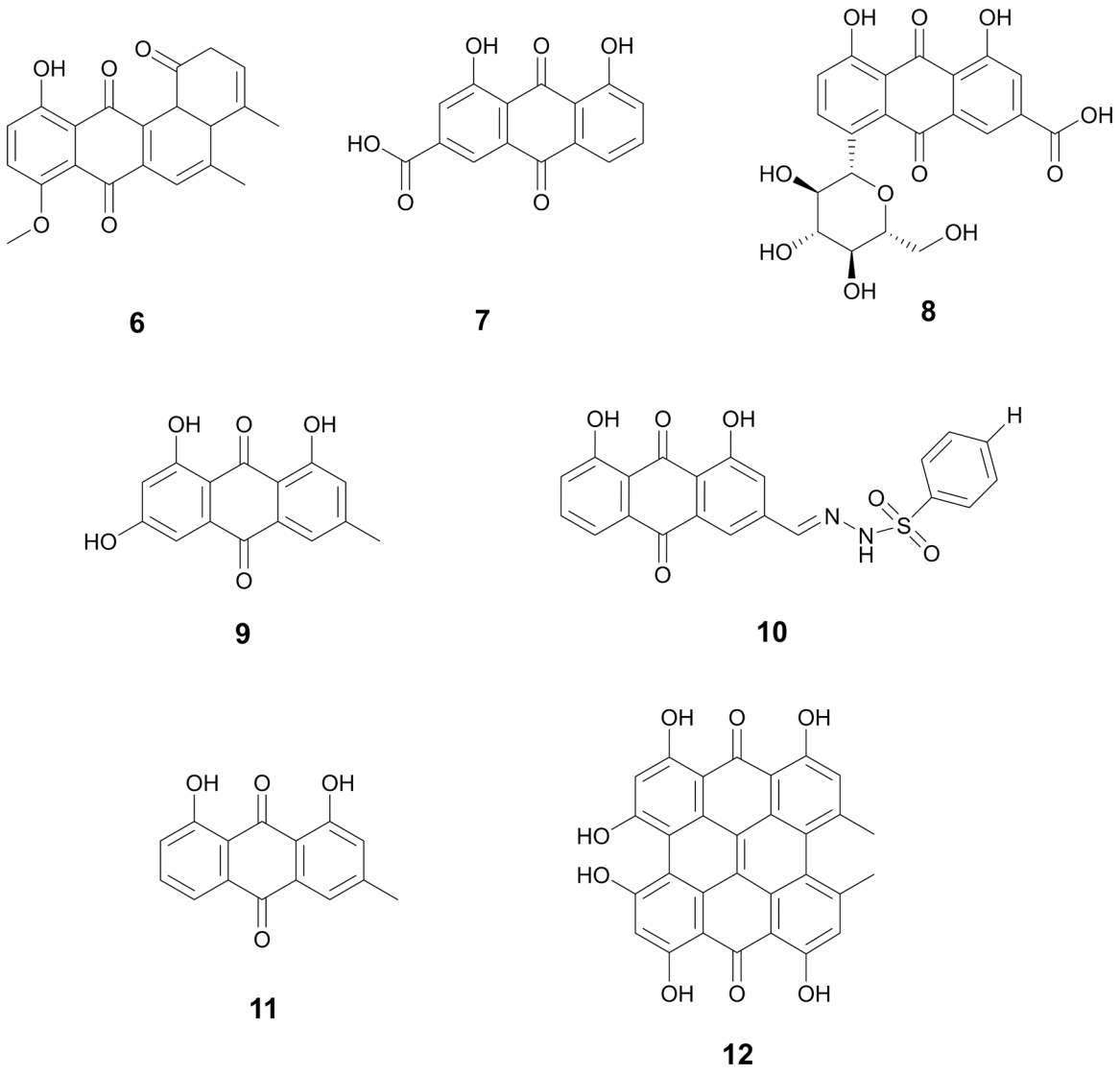

Figure 3.
Anthraquinones and derivatives with antimicrobial activity

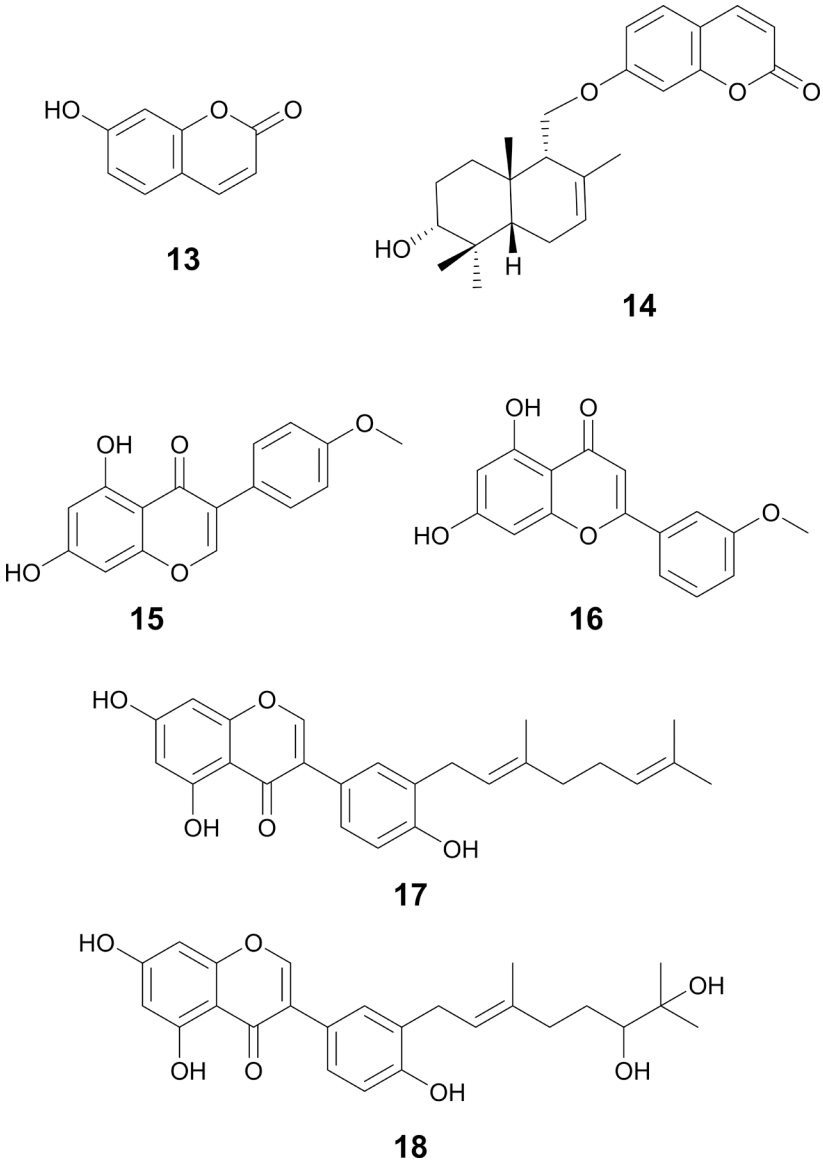

Figure 4.
Coumarins, flavonoids and derivatives with antimicrobial activity

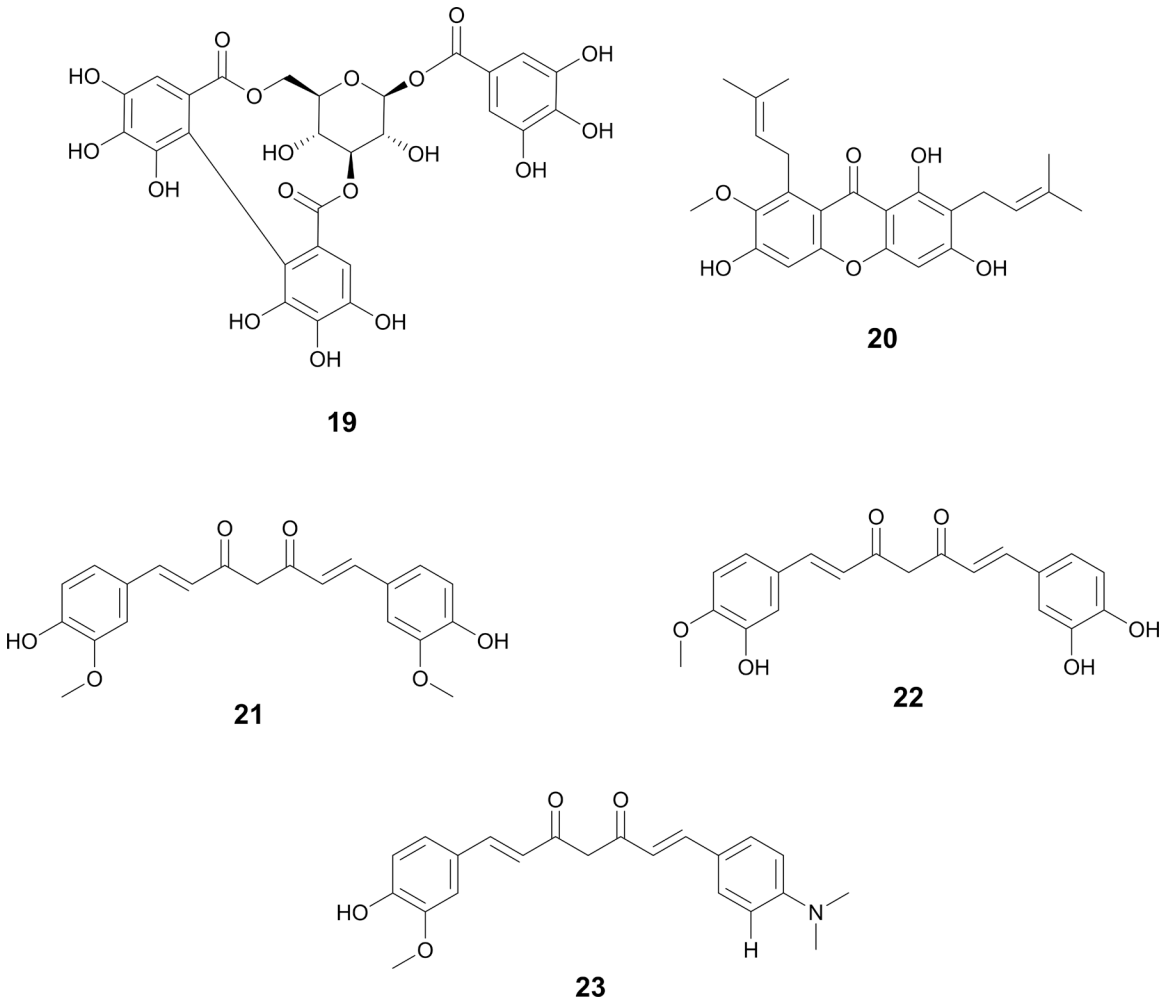

Figure 5.
Tannins, xanthones, diarylheptanoids and derivatives with antimicrobial activity

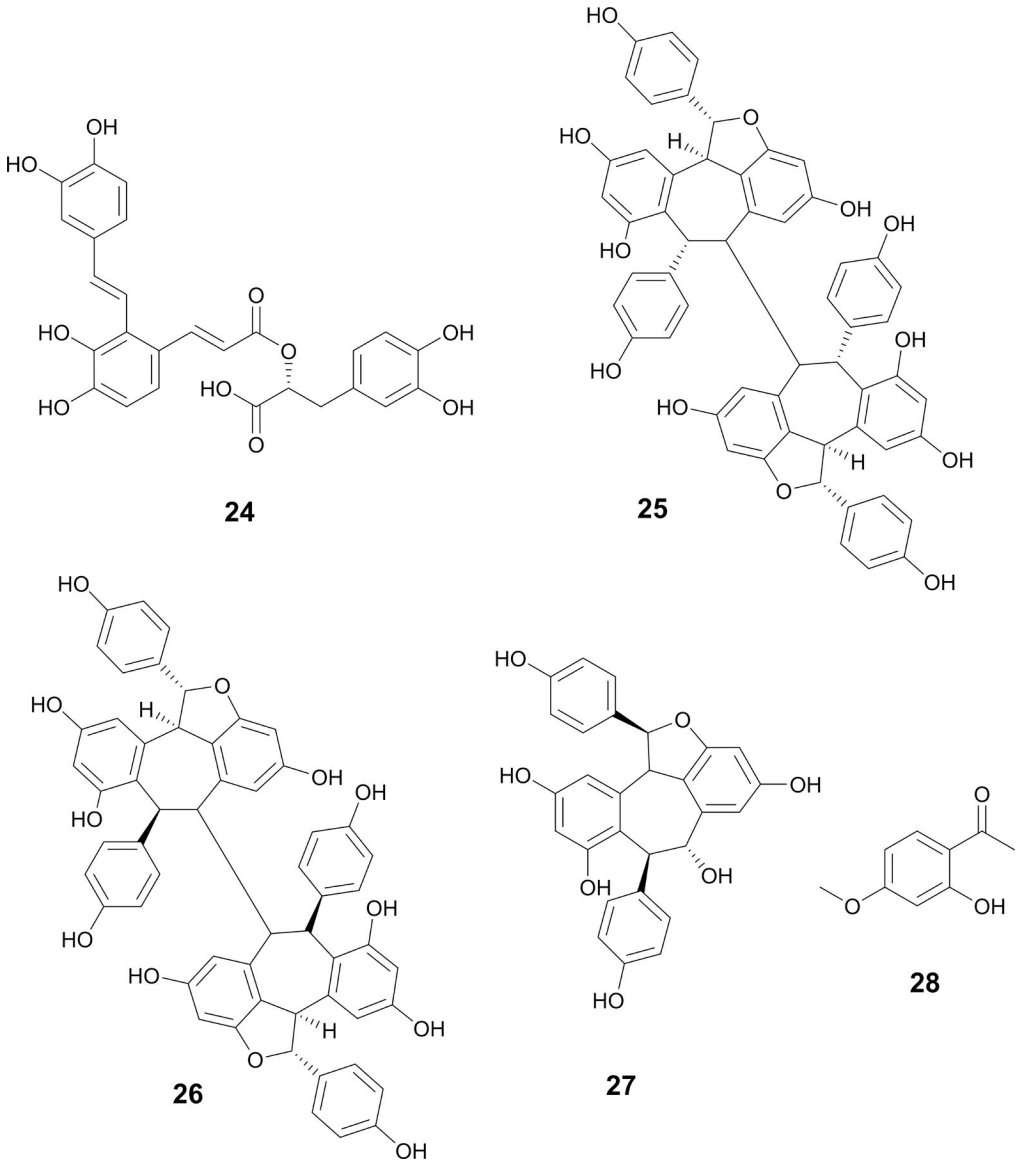

Figure 6.
Stilbenes and methoxybenzenes with antimicrobial activity

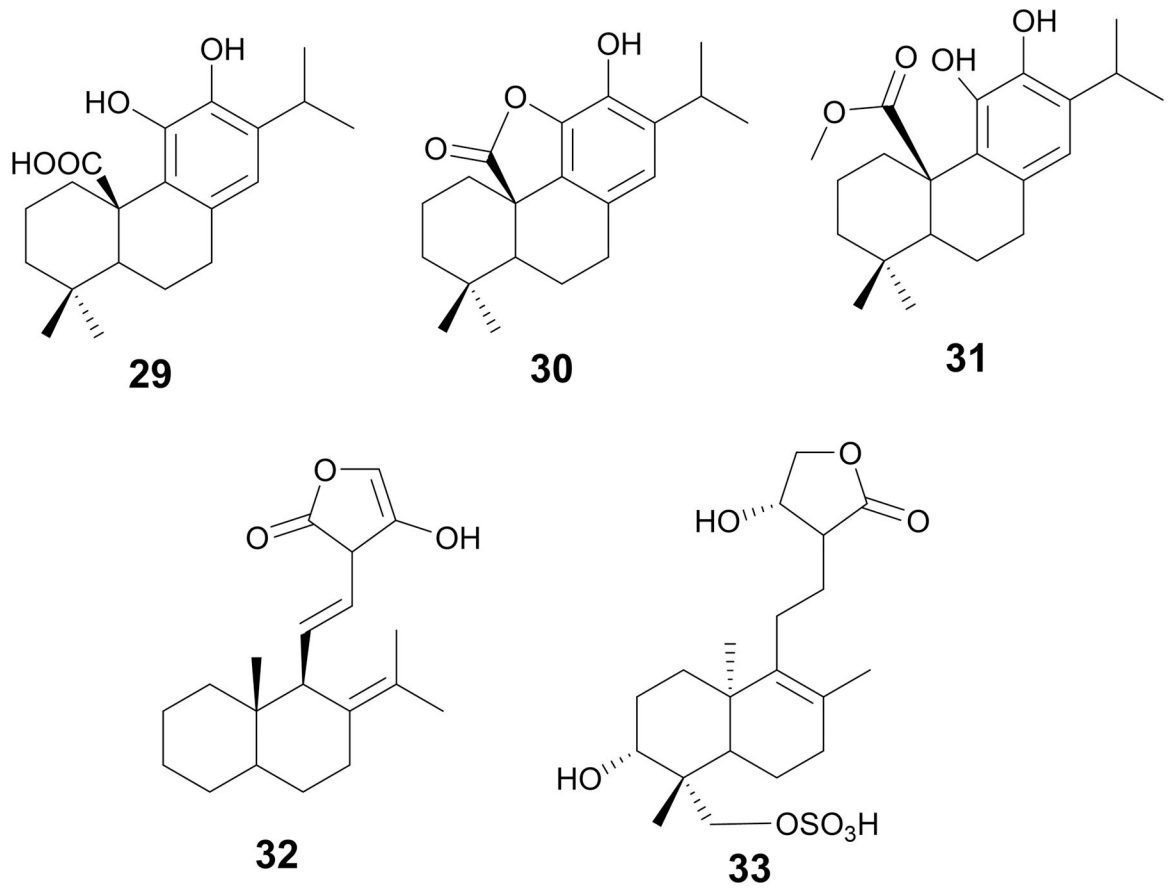

Figure 7.
Diterpenes and derivatives with antimicrobial activity

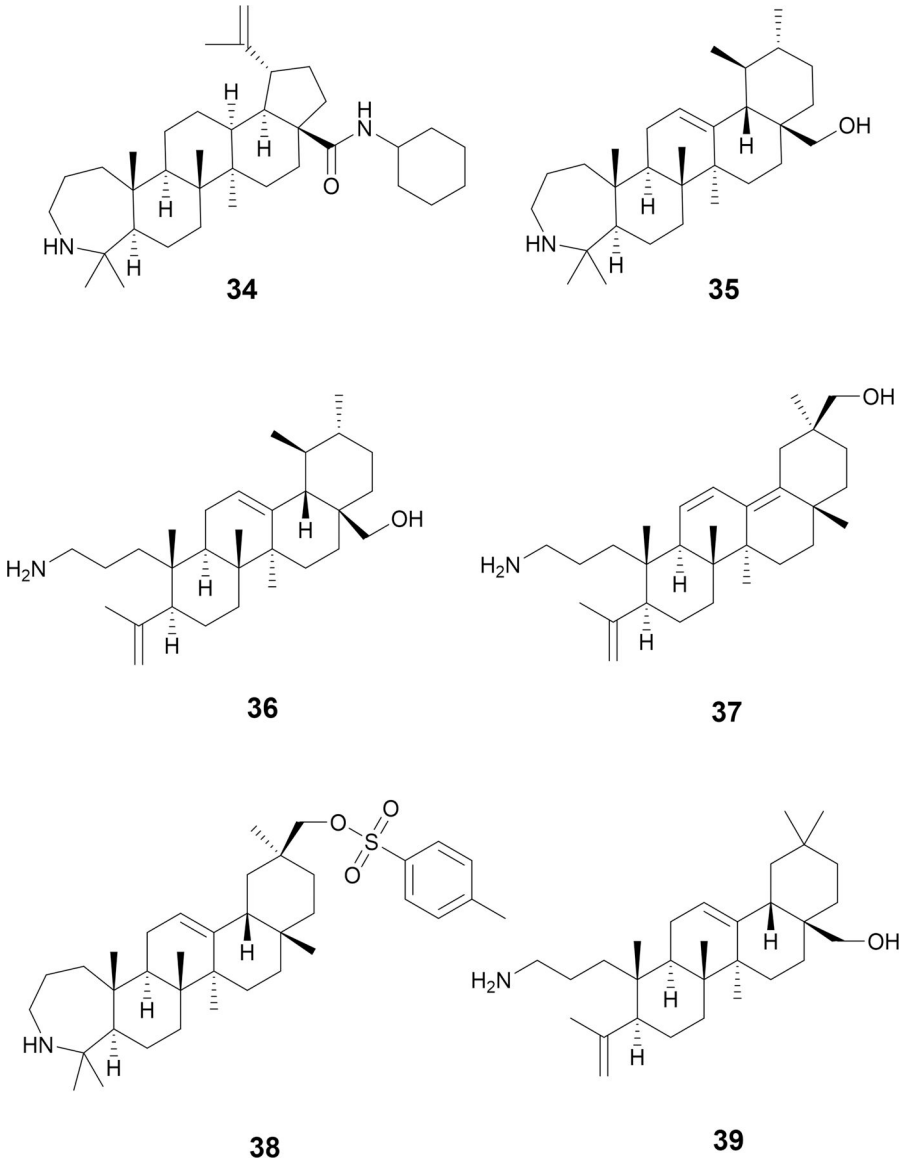

Figure 8.
Pentacyclic triterpenes with antibacterial activity

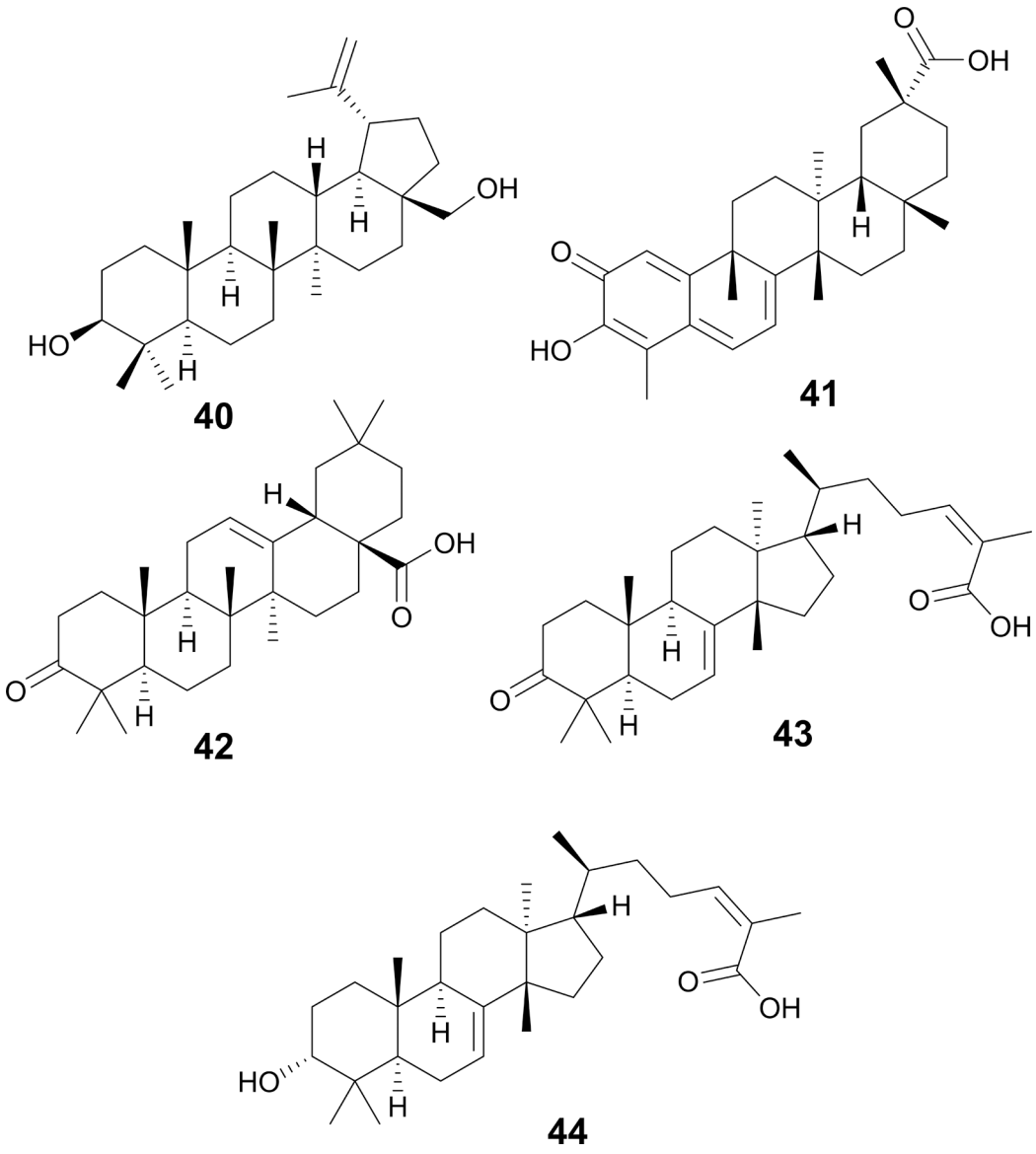

Figure 9.
Triterpenoids with antivirulence activity

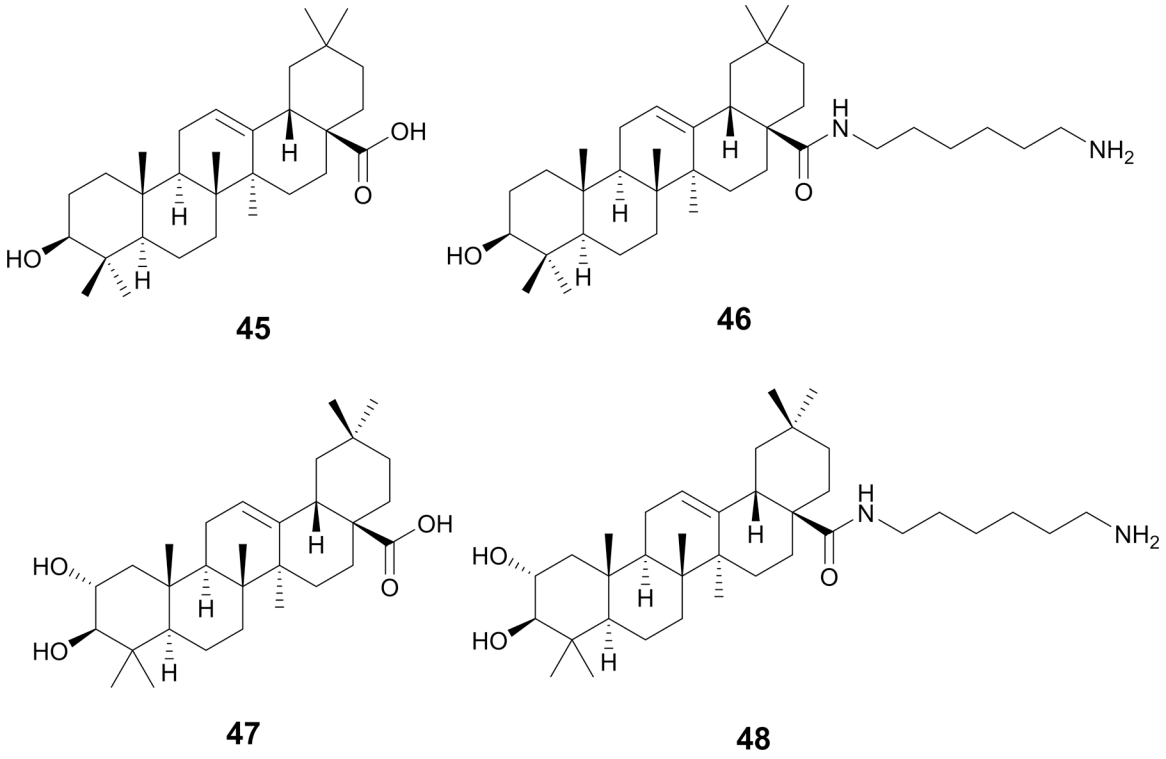

Figure 10.
Triterpenoids with antibiofilm activity