Chapter 2
Phytochemicals as Antibacterial Agents: Current Status and Future Perspective

Swagata Nag, Nutan Singh, and Suman Kumaria

Abstract The global emergence of multidrug-resistant (MDR) bacteria has severely compromised the efficacy of current antibacterial drugs and significantly increased the frequency of therapeutic failure. The development of novel and innovative antibacterial drugs with various chemical structures and processes that can combat harmful bacteria is urgently needed. Many studies have recently concentrated on identifying possible answers to these issues. There is a growing interest in medicinal plants for the potential sources of new therapeutic compounds, due to the structural and functional diversity existing in the specialized metabolites found in these plants. So far, many phytochemicals with varied biological activity, such as antibacterial, antifungal, and anti-carcinogenic, have been reported with low toxicity and adverse effects. Anti-quorum sensing (AQS) is a promising strategy for cell–cell communication which plays a vital role in the regulation of various bacterial physiological functions such as pathogenicity, luminescence, mobility, sporulation, etc. A variety of novel plant-based compounds have been discovered with the potential to disrupt bacterial quorum sensing (QS). The present chapter deals with the current developments in the field of plant extracts/phytochemicals, which are being used as the potential antibacterial and antimicrobial agents. Plant-derived molecules, which have antibiofilm or anti-quorum sensing activities, and the various mechanisms involved in their actions are also discussed.

Keywords Alkaloids · Antibacterial · *E. coli* · Flavonoids · *H. pylori* · Medicinal plants · Multidrug resistant · Multidrug-resistant (MDR) bacteria · Methicillin-resistant *S. aureus* · N-acyl-homoserine lactones · Phenolic compounds · Phytochemicals · *S. aureus* · Sulfur-containing phytochemicals · Secondary

S. Nag
Plant Biotechnology Laboratory, Department of Botany, North-Eastern Hill University, Shillong, Meghalaya, India

Siliguri Paramedical College, Jalpaiguri, India

N. Singh · S. Kumaria (✉)
Plant Biotechnology Laboratory, Department of Botany, North-Eastern Hill University, Shillong, Meghalaya, India

T. Saha et al. (eds.), *Alternatives to Antibiotics*,
https://doi.org/10.1007/978-981-19-1854-4_2

metabolites · Tannins · Terpenoids · Quinones · Quorum sensing · Quorum sensing inhibition

Abbreviations

AHL	N-acyl-homoserine lactones
MDR	Multidrug resistant
MRSA	Methicillin-resistant *S. aureus*
SAR	Structure–activity relationship

2.1 Introduction

Infectious diseases are the second greatest cause of death worldwide, after cardiovascular disorders, with 13.3 million people dying each year, being a primary source of morbidity and mortality. Every year, 700,000 people die as a result of bacterial resistance to drugs among the two million people who are sick with several types of bacteria around the world (Adrizain et al. 2018). The number of multidrug-resistant bacterial strains is continuously increasing, as is the advent of bacteria that are less susceptible to antibiotics. The indiscriminate and inappropriate uses of antibiotics have hastened the establishment of drug-resistant bacteria. Furthermore, unsanitary circumstances and improper food handling contribute to the spread of antibiotic resistance. Nosocomial infections with highly resistant bacterial pathogens have developed from a combination of extremely susceptible patients, extensive and sustained antibiotic usage, and cross infection. Hospital-acquired illnesses that are resistant to antibiotics are costly to treat and difficult to eliminate. Drug-resistant bacteria are responsible for up to 60% of hospital-acquired illnesses worldwide. Therefore, a hunt for new antibacterial compounds from a variety of sources, including medicinal plant, has sparked in recent times.

Since the time plants evolved, their important and protective roles have been well known for the mankind. Plants have been known to have anti-infective properties due to the presence of secondary metabolites such as tannins, alkaloids, terpenoids, and flavonoids, since ancient times. An evolving effective demand of natural plant-based products day by day lays an emphasis on the different medicinal plants used traditionally and in modern medicine system. A great majority of modern medicines have their roots in ancient herbal traditions. There are a variety of natural plant compounds with antifungal, antibacterial, and antiprotozoal properties that can be utilized systemically or locally (Dias et al. 2012a, b; Savoia 2012). The remedies obtained from the plants have given an insight for various afflicting human disorders. Plants are known for the production of various chemicals that are diverse in structures and have been adequately well utilized for various purposes. The diverse chemical compounds that have been reported to be useful as raw materials have led

to the discovery of drugs for chronic disorders (Yuan et al. 2016; Dias et al. 2012a, b; Bariş et al. 2006). The increasing demands of plants in the present scenario make the plants more superior to other living organisms present on earth. A majority of medications in clinical use today are derived from naturally occurring compounds, primarily secondary metabolites. Traditional medicine is used by majority of the people worldwide to maintain their health. The earliest records on Indian traditional medicine prescribed the uses of plants in treatment of various ailments with focus on herbal medicines. The demands of herbal-based medicines are at an alarming rate in both developed and underdeveloped countries due to their safety measures and reduced costs (Cragg and Newman 2001). The current chapter discusses recent advances in the field of plant extracts/phytochemicals, which are being investigated as antibacterial and antimicrobial agents. Plant-derived compounds with antibiofilm or anti-quorum sensing properties and the diverse mechanisms behind their actions are also reviewed.

2.2 Secondary Metabolites Acting as Antimicrobial Agent

The secondary metabolites are organic compounds that are indirectly involved in the developmental processes of the plants. Metabolites play an important role in protecting the plants and conferring color, flavor, aroma, texture, and plant defense against various biotic and abiotic agents (Molyneux et al. 2007). The plants with high secondary metabolites such as alkaloids, phenols, tannins, terpenoids, saponins, and flavonoids are reported to have enhanced medicinal properties (Singh and Kumaria 2020a; Edema and Alaga 2012). The growing demands of plant-based metabolites have given insights to the discovery and utilization of the bioactive metabolites in bio-therapeutic uses (Rao and Roja 2002). The research works carried out over the years imply their efficiency and effectiveness against multidrug-resistant bacteria in both planktonic and biofilm forms. However, some phytochemicals show limited solubility in aqueous media, which further limits their medical usefulness. The use of surfactants, nanoparticles, and polymers can serve as an effective delivery vehicle to overcome this constraint.

2.2.1 Phenolic Compounds

Phenolics are diverse groups of plant secondary metabolites that are considered as evolving natural biomolecules due to their known effective bioactive properties. They are aromatic compounds synthesized in plants through shikimate/phenylpropanoid pathway, which leads to the production of phenols and polyphenols (Randhir et al. 2004). Plant phenolics are known to have significant roles in growth, development, and reproduction and also play a defensive role against the various biotic and abiotic stresses such as UV, chitosan, cold, dark, nutrient

deficiency (Lattanzio 2013; Nag and Kumaria 2018; Singh and Kumaria 2020b). Phenolics are reported to participate in defense role against the predators and help in the development of color at different developmental stages of plants (Bravo 1998; Alasalvar et al. 2001). The phenolics are not only predominant in plants but are also reported from the bacteria, fungi, and algae (Harborne 2013). Also, it has been reported that the phenolics exhibit various biological properties such as antimicrobial, antiallergenic, and antioxidant activity (Balachandran et al. 2021). Many different types of phenolic compounds are known to be synthesized in plants and have been reported to be localized in different plant parts and serve as the potential agents for the action of various chronic diseases such as cancer, cardiovascular disease, and diabetes. The phenolics are also know to eliminate the foodborne bacteria and reduce the formation of biofilm. Due to the various useful applications of phenolics, therefore, their interest toward the food industry has increased day by day (Takó et al. 2020; Zambrano et al. 2019; Gyawali and Ibrahim 2014; Del Rio et al. 2013).

The various phenolics such as cinnamic acid, caffeic acid, p-coumaric acid, catechol, ferulic acid, pyrogallol, and eugenol have been reported to be effective against viruses, bacteria, and fungi (Kumar and Pandey 2013). Caffeic acid has been reported to have antimicrobial potential, synergistic effects with antibiotics against *Staphylococcus aureus*, *S. epidermidis*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Pseudomonas mirabilis*, *Escherichia coli*, *P. aeruginosa*, *Bacillus cereus*, and *Mycobacterium luteus* (Santos et al. 2018; Loes et al. 2014; Cushnie and Lamb 2005). Caffeic and p-coumaric acid have been reported to have synergy with the conventional antibiotics such as ampicillin and amikacin and increase their effectiveness against various gram-positive and gram-negative bacterial pathogens (Hemaiswarya and Doble 2010).

Another investigation has shown that the caffeic acid has anti-staphylococcal action, with minimum inhibitory concentrations (MICs) ranging from 62.5 to 250 g/mL (Luís et al. 2014). Catechol (two-hydroxyl group) and pyrogallol (three-hydroxyl group) are hydroxylated phenols that show toxic effects on microorganisms. More hydroxylation of catechol results in high toxicity. Mechanisms of phenol toxicity to microbes have been shown through enzyme inhibition processes with the oxidized compounds' interaction with sulfhydryl groups or nonspecific interaction with proteins (Ciocan and Bara 2007).

Catechin is a polyphenol that acts on different bacterial strains by producing the hydrogen peroxide or by modifying the microbial membrane permeability (Kumar et al. 2013). Gallic acid has additionally been proven to have antibacterial activity against *S. aureus*, *S. epidermidis*, *E. coli*, *Shigella flexneri*, *Salmonella* spp., *P. aeruginosa*, and *A. baumannii* with MICs ranging from 630 to 5000 g/mL (Fu et al. 2016). Gallic acid is proven to be more effective against *Campylobacter jejuni* and *Campylobacter coli* with MICs ranging from 15.63 to 250 g/mL, the mechanism being the loss of calcium ions (Sarjit et al. 2015). According to another research, gallic acid–conjugated gold nanoparticles have shown a much better antibacterial activity than gallic acid alone against the foodborne pathogens *Sh. flexneri* and *Plesiomonas shigelloides* (Randhawa et al. 2016).

2.2.2 Quinones

Quinones are aromatic (hexacyclic saturated) di-one or di-ketone compounds, ubiquitous and highly reactive in nature. They are derived from the oxidation of hydroquinones, namely, anthraquinones, benzoquinones, naphthoquinones, and polyquinones. The browning reaction seen in cut vegetables is due to the accumulation of quinones. This also forms the intermediates in the synthesis of melanin and provides basis for the formation of stable free radicals. Quinones are also found accumulating irreversibly with nucleophilic amino acids in protein, which lead to functional loss of the proteins. Quinones have a wide range of antimicrobial effects (Jali 2021; Balachandran et al. 2021; Liu et al. 2017; Jung et al. 2016; Jiang et al. 2007).

2.2.3 Flavonoids and Their Derivatives

Flavonoids are a large, low molecular weight, and structurally diverse group of natural bioactive products. They are hydroxylated diphenylpropanes (C6–C3–C6) in structural skeleton. The reported flavonoids differ in the degree of oxidation, which leads to the diverse flavonoid derivatives (Kumar and Pandey 2013). Diverse group of flavonoids such as flavonols (quercetin, kaempferol, and myricetin), flavanones (naringin), flavones (luteolin), chalcones (licochalcone A, licochalcone E), catechins, anthocyanin, and isoflavonoids (sophoraisoflavone A) have been reported in plants (Farhadi et al. 2019; Patra 2012).

Flavonoids and their derivatives are synthesized in plants in response to different microbial attack. According to the report of Kumar and Pandey (2013), flavonoids have been reported to be effective against the wide array of microorganisms in in vitro studies. Flavonols such as quercetin, myricetin, morin, galangin, entadanin, rutin, piliostigmol, and their derivatives are among the most important class of flavonoids that show potent antibacterial activities (Siriyong et al. 2017; Geoghegan et al. 2010). The catechins present in green tea, epigallocatechin gallate (EGCG), have been found to be active against *B. cereus* in nanomolar concentrations (Friedman et al. 2006). Antibacterial activities of EGCG alone and in combination with various antibiotics have been studied extensively against a variety of bacteria, including multidrug-resistant strains such methicillin-resistant *S. aureus* (MRSA; Steinmann et al. 2013). The addition of long alkyl chains to EGCG dramatically increased its in vitro activity against a variety of bacteria and fungi, particularly *S. aureus* (Matsumoto et al. 2012). Another study demonstrated the action of EGCG on *E. coli*'s outer membrane and reported that the substance interacted with the membrane at many sites (Nakayama et al. 2013). Polyphenon E is prominent in distinguishing at least five distinct catechins, wherein EGCG is the most abundant component reported which is widely used clinically (Clark and You 2006). Another flavanol with antibacterial potential is a flavin, which has been shown to work

against a variety of bacteria, including *A. baumannii*, *B. cereus*, and *Shigella* spp. (Betts et al. 2017; Friedman et al. 2006).

Many studies have shown that flavonoids are responsible for the inhibition of biofilm formation by disrupting the quorum sensing (QS). Flavonoids appear to impair the interaction between acyl-homoserine lactones (signal molecules used by gram-negative bacteria) and their receptors. It has been reported that baicalein inhibits the cytoplasmic membrane-associated receptor TraR (Zeng et al. 2008; Qin et al. 2000). Quercetin is a well-known flavonoid with a wide range of biological activities that include antioxidant, antibacterial, anti-inflammatory, antiviral and anticancer properties (Wang et al. 2016). Quercetin has been demonstrated to suppress *E. coli* growth under in vitro conditions and to have antibacterial effect against *S. aureus* and *K. pneumoniae* (Ohemeng et al. 1993). Mirzoeva et al. (1997) demonstrated that quercetin and other flavonoids reduce the bacterial motility considerably. Quercetin's antibacterial activity was boosted in vitro when it was coupled with different antibiotics (Sakharkar et al. 2009; Hirai et al. 2010) and also had synergistic effects when combined with sulfamethoxazole, rifampicin, and fusidic acid against methicillin-resistant *S. aureus* (MRSA) strains and clinical isolates (Sahyon et al. 2019; Kyaw and Lim 2012). By hindering QS, quercetin was found to have antibiofilm activity against *K. pneumoniae*, *Pseudomonas aeruginosa*, and *Yersinia enterocolitica* (Gopu et al. 2015). A more recent research has revealed that quercetin can boost the antibacterial action of metals, with silver nanoparticles made from polyphenol having more antibacterial activity as compared to quercetin or silver nitrate alone against gram-negative and gram-positive infections (Jain and Mehata 2017).

Kaempferol, another flavonol, is reported to have a wide range of biological and pharmacological properties. It is known to impede the growth and survival of antibiotic-resistant *S. aureus* by inhibiting the activity of the PriA helicase (SaPriA) and bacterial efflux pumps, hence improving antimicrobial effectiveness and blocking the growth and survival of antibiotic-resistant *S. aureus* (Brown et al. 2015; Huang et al. 2015).

2.2.4 Tannins

Tannins are polymer of phenolic substances and are found in almost all the plants. Tannins are divided into condensed and hydrolyzable tannins. Hydrolyzable tannins are gallic acid based and contain multiple esters of D-glucose. The condensed form of tannins is often called proanthocyanidins and is derived from flavonoid monomers. It has been reported that tannins may have formed by condensations of flavan derivatives or by polymerization of quinine (Ciocan and Bara 2007; Karou et al. 2007). Studies have reported that tannins can be toxic to bacteria, yeast, and fungi (Cowan 1999). Punicalagin suppressed violacein synthesis in *Chromobacterium violaceum* and swarming motility in *Sa. typhimurium* SL1344 (Li et al. 2014).

2.2.5 Alkaloids

Alkaloids are the diverse group of chemical organic nitrogen-containing heterocyclic compounds. They are one of the structurally diverse groups of the metabolites effectively used as therapeutically important plant substances. Based on their core chemical structure, alkaloids are grouped into indoles, isoquinolines, piperidine alkaloids, quinolines, etc. The in-depth research on alkaloids from different plants have revealed their potential to acquire the properties of natural antibiotic with a wide antibacterial spectrum with low propensity to make drug resistant. When co-administered with ciprofloxacin, piperine, a piperidine-type alkaloid produced from *Piper nigrum* and *P. longum*, decreased the growth of a mutant *S. aureus* and considerably reduced the MIC values for *S. aureus* (Khan et al. 2006). Piperine and gentamicin co-administration was found to be effective in the treatment of MRSA infections (Khameneh et al. 2015). Tomatidine is a steroidal alkaloid found in solanaceous plants such as tomato, potato, and eggplant that has been shown to have significant antibacterial action against *S. aureus* whether used alone or in combination with aminoglycosides (Jiang et al. 2016).

The quinolone alkaloid evocarpine, isolated from *Fructus evodiae*, was found to have significant antimicrobial action against MRSA (Pan et al. 2014). The steroidal alkaloid tomatidine was isolated from the tomato plant. It has a high vulnerability to MRSA, according to the findings (Chagnon et al. 2014). Two guanidine alkaloids were found from the *Pterogyne nitens*. These two guanidine alkaloids, galegine and pteridine, possessed high anti-MRSA activity. The presence of a side chain observed in guanidine alkaloids was thought to impart the antibacterial property (Coqueiro et al. 2014). Because of the significant implications and need for conventional therapy following antibiotic failure against MRSA, there has been a huge push to develop novel compounds that can slow the progression of bacterial infections and enhance patient quality of life. Isolation of 6-methoxydihydrosanguinarine (6-MS), 6-acetonylhydrosanguinarine, and dihydrosanguinarine from *Hylomecon hylomeconoides* paved the door for medication sensitivity against MRSA to be regained. These alkaloids prevent MRSA strains with MICs ranging from 1.95 to 250 ug/mL (Choi et al. 2010). Plant alkaloids' capacity to intercalate DNA may explain their ability to inhibit MRSA activity. It has also been proposed that alkaloid components impede or degrade beta-lactamase action (Zoraghi et al. 2011). Plant alkaloids such as berberine (found in *Berberis* sp.) and piperine (found in *Piper* sp.) can interact with the bacterial cytoplasmic membrane, intercalate with DNA, and inhibit efflux pumps in *S. aureus* (Khan et al. 2006; Jennings and Ridler 1983).

Berberine is an isoquinoline-type alkaloid used in the treatment of dental infections. Several investigations utilizing a multispecies biofilm tooth model have showed the efficacy of berberine against oral streptococcal growth and certain endodontic pathogens (Dziedzic et al. 2015; Xie et al. 2012). Berberine has been demonstrated to improve the inhibitory activity of antibiotics against clinical multidrug-resistant isolates of methicillin- resistant *S. aureus* (MRSA) (Chu et al. 2016). Berberine was found to have antibacterial activity against *Streptococcus*

agalactiae by disrupting the membrane and reducing protein and DNA production (Peng et al. 2015). Dusane et al. (2014) studied the effect of reserpine and piperine from *P. nigrum* against *E. coli*, which causes urinary tract infections in humans. Piperine improved the action of the antibiotics azithromycin and ciprofloxacin in dispersing biofilms by increasing their penetration into *E. coli* biofilms.

2.2.6 Terpenoids

Terpenoids are a wide class of chemicals produced by plants that have antibacterial properties. Several terpenes and their derivatives have been demonstrated to be effective defenses against herbivores and infections. Gram-positive bacteria are usually more sensitive to terpenes than gram-negative bacteria. Terpenes' antibacterial action is closely linked to their lipophilic properties. Monoterpenes preferentially affect membrane structures by increasing fluidity and permeability, modifying protein architecture, and causing disruptions along the respiration chain. Togashi et al. (2010) studied the effects of linalool, geraniol, nerolidol, plaunotol, farnesol, geranylgeraniol, and phytol on the growth of *S. aureus*. Among all of the compounds examined, only farnesol and nerolidol, with MBC of 20 and 40 g/mL, demonstrated a significant antibacterial effect. Two diterpenoids, salvipisone and aethiopinone, were extracted from *Salvia sclarea* roots and tested as antibacterial and antibiofilm agents against gram-positive and gram-negative bacteria. These diterpenoids inhibited the growth of *S. aureus*, *S. epidermidis*, and *Enterococcus faecalis* at a concentration of 37.5 g/ml, and *S. aureus* and *S. epidermidis* pre-formed biofilms were disturbed by at least 85% (Rózalski et al. 2007). Chung et al. (2014) extracted and identified three known triterpenoids (amyrin, betulinic acid, and betulinaldehyde) from the bark of *Callicarpa farinosa.* These compounds were found to have antibacterial activity against MRSA and methicillin-sensitive *S. aureus* (MSSA) and could be used to combat antibiotic resistance in *S. aureus*. Dehydroabietic acid, a resin acid, is reported to be another terpene molecule with antibacterial action against *S. aureus*. Broniatowski et al. (2015) investigated the antimicrobial mechanism of two pentacyclic triterpenes, ursolic acid and amyrin, which are natural chemicals with broad antibacterial activity. The other well-known terpenoids are eugenol and cinnamaldehyde, which are found in the essential oils of a variety of plants and have been shown to be effective against a variety of infections. Eugenol has been reported to have a lot of bioactivity against MRSA and MSSA clinical strain biofilms. According to the findings of Yadav et al. (2015), eugenol inhibits biofilm formation, disrupts cell-to-cell communication, eradicates pre-existing biofilms, and kills bacteria in biofilms, and this is true for both MRSA and MSSA. Essential oils including thymol, carvacrol, eugenol, and vanillin demonstrated antibacterial action against *E. coli* O157:H7, *Sa. typhimurium*, and *Listeria monocytogenes* when mixed with soy sauce (Moon and Rhee 2016). Knezevic et al. (2016) tested the antibacterial activity of essential oils from *Eucalyptus*

camaldulensis against multidrug-resistant (MDR) *Acinetobacter baumannii* wound isolates.

2.2.7 Sulfur-Containing Phytochemicals

Organosulfur compounds such as allicin, ajoene, sulfasalazine, and isothiocyanates have been shown to have antibacterial activity against a variety of bacteria, including MDR strains. Park et al. (2013) investigated the antibacterial efficacy of horseradish root isothiocyanates against oral microbes. Dias et al. (2012b) investigated the antibacterial activity of isothiocyanates in the presence of antibiotics such as gentamicin and vancomycin against both gram-positive and gram-negative bacteria. Garlic's main component allicin has been found as having antibacterial activity against a wide range of microorganisms. Allicin was responsive to vancomycin-sensitive and vancomycin-resistant clinical isolates and standard strains of *Enterococcus* species (Jonkers et al. 1999). When compared to diallyl sulfide, allicin had the best anti-*Helicobacter pylori* action against three strains (O'Gara et al. 2000). According to a meta-analysis of clinical data, combining allicin with standard therapy promotes the eradication of *H. pylori* infections (Si et al. 2019). Allicin was proven to be active against *Clostridium difficile* and other commensal gut bacteria in a recent study, and there was no substantial synergy between allicin and conventional antibiotics (Roshan et al. 2017).

A list of plant secondary metabolites such as alkaloids, flavonoids, tannins, terpenes, quinines, resins, coumarins, organosulfur, terpenoids, phenols, lactones, benzoic acid, diarylheptanoid, phenolic acids, polyphenol, iridoid lactone, and sesquiterpene lactone with their reported antibacterial activities is shown in more details in Table 2.1.

2.3 Quorum Sensing (QS)

QS, as a mechanism of bacterial cell-to-cell chemical communication, plays a key role in pathogen biofilm development, antibiotic resistance, survival, proliferation, and toxin synthesis. Targeting quorum sensing has emerged as a viable technique for fighting against bacterial infections since it does not put any selection pressure on pathogens, making it unlikely to develop multidrug resistance. Quorum quenching phytochemicals may be a potential non-antibiotic therapy method for pathogenic bacteria by inhibiting bacterial communication and making them less virulent. Extracts and specific compounds from several fruits, herbs, and spices have been displayed to inhibit QS. Polyphenols, for example, are QS-inhibiting phytochemicals that can impact biofilm development in some bacteria, because their chemical structure is comparable to that of QS signals N-acyl-homoserine lactones (AHL) and/or their capability to degrade signal receptors (LuxR/LasR) (Santos et al. 2021;

Table 2.1 Plant secondary metabolites with their reported antibacterial activities

Secondary metabolites and plant families	Antibacterial activity	References
Alkaloids		
Amaryllidaceae	*Staphylococcus aureus*	Savoia 2012
Apiaceae	*Enterococcus faecalis*	Basile et al. 2009
Apocynaceae	*Acinetobacter baumannii*	Siriyong et al. 2017
Berberidaceae	*P. aeruginosa*	Boberek et al. 2010
Capparaceae	*Mycobacterium tuberculosis*	Agbafor et al. 2011
Compositae	*Salmonella typhi*	Munyendo et al. 2011
Fabaceae	*Escherichia coli*	Carson and Hammer 2011
Mimosaceae	*Pseudomonas aeruginosa*	Ramawat 2007
Piperaceae	Methicillin-resistant *S. aureus* (MRSA)	Khameneh et al. 2015 Birdi et al. 2012 Hochfellner et al. 2015
Rubiaceae	*Mycobacterium kansasii*	Mariita et al. 2011
Flavonoids		
Adoxaceae	*E. coli* Methicillin-resistant *S. aureus* (MRSA)	Wu et al. 2008 Randhawa et al. 2016
Amaryllidaceae	*Mycobacterium fortuitum*	Munyendo et al. 2011
Apiaceae	*Helicobacter pylori*	Wu et al. 2008
Asphodelaceae	*Mycobacterium fortuitum* Methicillin-resistant *S. aureus* (MRSA)	Randhawa et al. 2016
Asteraceae	*Helicobacter pylori* Methicillin-resistant *S. aureus* (MRSA)	Zhang et al. 2008 Hong et al. 2006 Stermitz et al. 2003
Capparaceae	*E. coli* Methicillin-resistant *S. aureus* (MRSA)	Wu et al. 2008
Fabaceae	*P. aeruginosa*	Agbafor et al. 2011 Gutiérrez et al. 2017 Hong et al. 2006
Labiatae	*S. typhi*	Zhang et al. 2008
Moringaceae	Methicillin-resistant *S. aureus* (MRSA)	Randhawa et al. 2016
Rubiaceae	*S. aureus*	Sibi et al. 2012
Rubiaceae	*Salmonella typhi*	Zhang et al. 2008
Rutaceae	Methicillin-resistant *S. aureus* (MRSA) *E. faecalis*	Munyendo et al. 2011 Sibi et al. 2012
Theaceae	*E. coli*	Gutiérrez et al. 2017 Li et al. 2006

(continued)

Table 2.1 (continued)

Secondary metabolites and plant families	Antibacterial activity	References
Tannins		
Fabaceae	*St. faecalis*	Mariita et al. 2011
Mimosaceae	*Bacillus subtilis*	Sibi et al. 2012
Myrtaceae	*S. aureus*	Abdulhamid et al. 2014
Rubiaceae	*E. coli*	Oboh 2010
Terpenes		
Compositae	*Staphylococcus epidermidis*	Munyendo et al. 2011
Fabaceae	*S. aureus*	Togashi et al. 2010
Labiatae Rutaceae	Methicillin-resistant *S. aureus* (MRSA)	Korir et al. 2012
Lamiaceae	*Pseudomonas aeruginosa E.coli*	Althunibat et al. 2016 Gutiérrez et al. 2017
Myrtaceae	*Streptococcus faecalis* *Staphylococcus epidermidis*	Sibi et al. 2012 Rathinam et al. 2017
Rubiaceae	*Pseudomonas aeruginosa*	Abdulhamid et al. 2014
Quinones		
Boraginaceae	*S. aureus*	Papageorgiou et al. 2008
Plumbaginaceae	*S. epidermidis*	Carson and Hammer 2011 Periasamy et al. 2019
Polygonaceae	*Helicobacter pylori*	Khalil et al. 2019
Resins		
Fabaceae	*Shigella dysenteriae*	Mariita et al. 2011
Labiatae	*P. aeruginosa*	Oboh 2010
Coumarins		
Apiaceae	*Salmonella typhi* *Enterococcus faecalis*	Tan et al. 2017 Basile et al. 2009
Fabaceae	*E. coli*	Mun et al. 2014 Jeong et al. 2009
Lauraceae	*S. aureus*	Ali et al. 2005
Rutaceae	Methicillin-resistant *S. aureus* (MRSA)	Basile et al. 2009
Organosulfur		
Alliaceae	*Acinetobacter baumannii* *P. aeruginosa*	Reiter et al. 2017
Amaryllidaceae	Methicillin-resistant *S. aureus* (MRSA)	Reiter et al. 2017
Brassicaceae	*Helicobacter pylori*	Haristoy et al. 2005
Liliaceae	*Klebsiella pneumoniae*	Reiter et al. 2017
Resedaceae	Methicillin-resistant *S. aureus* (MRSA)	Reiter et al. 2017
Tropaeolaceae	*St. pneumonia*	Reiter et al. 2017

(continued)

Table 2.1 (continued)

Secondary metabolites and plant families	Antibacterial activity	References
Terpenoids		
Lamiaceae	Methicillin-resistant *S. aureus* (MRSA)	Althunibat et al. 2016 Qiu et al. 2010
Lamiaceae	*E. coli*	Althunibat et al. 2016
Myrtaceae	*P. aeruginosa* Methicillin-resistant *S. aureus* (MRSA) *E. coli*	Althunibat et al. 2016 Togashi et al. 2010 Althunibat et al. 2016 Gutiérrez et al. 2017
Rutaceae	*H. pylori*	Ali et al. 2005
Phenols		
Ericaceae	*E. coli*	Gutiérrez et al. 2017
Scrophulariaceae	*E. coli*	Gutiérrez et al. 2017
Vitaceae	*Campylobacter* spp.	Klancnik et al. 2017
Lactones		
Apocynaceae	*M. tuberculosis*	Kumar et al. 2013
Asteraceae	*M. tuberculosis*	Kalani et al. 2019
Benzoic acid		
Scrophulariaceae	*P. aeruginosa*	Gutiérrez et al. 2017
Diarylheptanoid		
Asteraceae	*P. aeruginosa*	Wu et al. 2008
Zingiberaceae	*P. aeruginosa*	Tyagi et al. 2015
Polyphenol		
Myrtaceae	*E. coli*	Gutiérrez et al. 2017
Vitaceae	*E. coli*	Gutiérrez et al. 2017
Diterpenoid		
Acanthaceae	*M. tuberculosis*	Prabu et al. 2015
Euphorbiaceae	*M. tuberculosis*	Jung et al. 2016
Iridoid lactone		
Apocynaceae	*M. tuberculosis*	Kumar et al. 2013
Sesquiterpene lactone		
Asteraceae	*M. tuberculosis*	Kalani et al. 2019

Hossain et al. 2017). Gamma-aminobutyric acid (GABA), which is generated by some plants, promotes lactonase (AttM) degradation of the OHC8HSL AHL signal in *Agrobacterium tumefaciens*, limiting the QS-dependent infection process. The extracts from the Annurca apple having various polyphenols, such as hydroxycinnamic acids, rutin, and epicatechin, revealed anti-quorum sensing (AQS) activity against *Chromobacterium violaceum* (Fratianni et al. 2013). Cinnamaldehyde and its derivatives have an impact on a range of QS-regulated activities, including biofilm formation in *P. aeruginosa* and AI-2-mediated QS in various *Vibrio* species (Brackman et al. 2008; Niu et al. 2006). Garlic extracts have

been shown to suppress QS in *P. aeruginosa*, reducing biofilm formation and thereby aiding the bacteria's clearance (Bjarnsholt et al. 2005). Similarly, vanilla extracts have been reported to hamper with QS in *C. violaceum*, suggesting that eating vanilla-flavored meals may be helpful (Choo et al. 2006). Many plants produce polyphenol chemicals with a gallic acid moiety, such as epigallocatechin gallate, ellagic acid, and tannic acid, which can particularly interfere with AHL-mediated signalling by preventing bacteria-to-bacterium transmission (Hao et al. 2021; Bouyahya et al. 2017; Slobodníková et al. 2016).

It was reported that in case of a clinically import ant strain, i.e., *S. aureus*, baicalein (5,6,7-trihydroxyflavone) was found to lower levels of enterotoxin A (SEA) and hemolysin (hla) (Chen et al. 2016). At sub-inhibitory concentrations (32 and 64 g/ml), baicalein treatment significantly reduced the expression of the quorum sensing regulators agrA, RNAll, and sarA and the expression of the ica gene.

Quercetin, a common flavonoid, interacts to the QS receptor protein LasR and inhibits its capacity to bind promoter regions of DNA, lowering total QS gene production. The presence of two hydroxyl groups in the flavone A ring is required for suppression of QS-related self-regulatory proteins in *P. aeruginosa*, according to structure–activity relationship (SAR) analyses of various flavonoids. Among the plant-derived pigments, zeaxanthin was tested for QS inhibitory action using two *P. aeruginosa* fluorescent monitor strains, lasB-gfp and rhlA-gfp. The levels of gene expression of lasB and rhlA were shown to decrease in a concentration-dependent way (Gökalsın et al. 2017). Quorum sensing is known to influence the expression of numerous virulence factors. Attenuating pathogenicity in bacteria through QS interference is predicted to result in disease control, especially where antibiotics are ineffective owing to the development of multidrug resistance.

2.4 Future Prospects

Nature provides a rich supply of bioactive substances that are readily available, inexpensive, and simple to extract with little risk to humans. Phytochemicals have emerged as a possible alternative to conventional antibacterial medicines. A majority of antimicrobial phytochemicals lack thorough structure–activity relationship (SAR) data, which has been done for many classes of microbial antibiotics. The variety in extraction procedures and antibacterial assays utilized is a key barrier for identifying new antibacterial compounds from plants. Depending on their ability to suppress the growth of microorganisms, different phytochemicals have different antimicrobial properties. They come in a variety of forms, each with improved efficacy against a variety of diseases and pathogens. Modern approaches have been employed with traditional ways for extracting phytochemicals to boost yield and productivity. The key barrier in the development of novel phytochemicals has been translating in vitro investigations into in vivo experiments and then into human clinical trials. The challenge is particularly difficult in the case of natural antimicrobial drugs/

antibacterial phytochemicals, because a variety of parameters, such as tissue penetration, maximum plasma concentration, and bioavailability, might affect their activity. For example, phenolic natural compounds are easily glucuronidated by hepatic enzymes, which have a significant impact on tissue penetration and plasma levels. To boost phytochemical antibacterial activity, various nanoformulations can be developed using liposomes, dendrimers, micelles, and polymers. The development of new antimicrobial metabolites from medicinal plants is a promising approach to combating to human diseases' increasing treatment resistance. Scientists have conducted studies on many plant families to identify antibacterial properties of phytochemicals, and experimental investigations to evaluate the biological activities of numerous plants should be conducted in the future. Another appealing application of phytochemicals is their potential in combination with other antibacterial products, which merits more investigation.

2.5 Conclusion

Plant-derived chemicals or herbal medicine offer a significant contribution to primary healthcare and have shown considerable promise in modern phytomedicine for a variety of diseases and ailments in today's world. Scientists have looked to nature for solutions to the fast growth of bacterial resistance to conventional antibiotics. As a source of novel antimicrobials, plants offer a lot of promise. They are commonly available, inexpensive, and almost without negative effects. Numerous investigations have been conducted, and the medicinal potential of plant-derived substances has been established. Thousands of phytochemicals have been discovered all over the world that exhibit antibacterial, antifungal, and antiviral action against a variety of diseases. When used with antibiotics, the MIC values of the antibiotics are reduced, and synergistic effects are observed.

Phytochemicals, in general, damage the bacterial membrane, reduce some virulence factors such as enzymes and toxins, and hinder the production of bacterial biofilms. However, a lot of significant work needs to be done in vitro and in vivo to assure the identification of active and nontoxic antimicrobial phytochemicals. Antibacterial agents with a new mechanistic approach should be sought quickly to tackle the problems of antibiotic resistance.

Acknowledgments None to declare.

Conflict of Interest None to declare.

References

Abdulhamid A, Fakai IM, Sani I, Argungu AU, Bello F (2014) Preliminary phytochemical and antibacterial activity of ethanol and aqueous stem bark extracts of *Psidium guajava*. J Drug Dis Dev 4:95–89

Adrizain R, Suryaningrat F, Alam A, Setiabudi D (2018) Incidence of multidrug-resistant, extensively drug-resistant and pan-drug-resistant bacteria in children hospitalized at Dr. Hasan Sadikin general hospital Bandung Indonesia. Science 125(1):012077)

Agbafor KN, Akubugwo EI, Ogbashi ME, Ajah PM, Ukwandu CC (2011) Chemical and antimicrobial properties of leaf extracts of *Zapoteca portoricensis*. Res J Med Plant 5(5):605–612

Alasalvar C, Grigor JM, Zhang D, Quantick PC, Shahidi F (2001) Comparison of volatiles, phenolics, sugars, antioxidant vitamins, and sensory quality of different colored carrot varieties. J Agric Food Chem 49(3):1410–1416

Ali SM, Khan AA, Ahmed I, Musaddiq M, Ahmed KS, Polasa H, Rao LV, Habibullah CM, Sechi LA, Ahmed N (2005) Antimicrobial activities of eugenol and cinnamaldehyde against the human gastric pathogen *Helicobacter pylori*. Ann Clin Microbiol Antimicrob 4:20

Althunibat OY, Qaralleh H, Al-Dalin SYA, Abboud M, Khleifat K, Majali IS, Aldalin HKH, Rayyan WA, Jaafraa A (2016) Effect of thymol and carvacrol, the major components of *Thymus capitatus* on the growth of *Pseudomonas aeruginosa*. J Pure Appl Microbiol 10:367–374

Balachandran C, Al-Dhabi NA, Duraipandiyan V et al (2021) Bluemomycin, a new naphthoquinone derivative from *Streptomyces* sp. with antimicrobial and cytotoxic properties. Biotechnol Lett 43:1005–1018

Bariş Ö, Güllüce M, Şahin F, Özer H, Kiliç H, Özkan H, Sökmen M, Özbek T (2006) Biological activities of the essential oil and methanol extract of Achillea biebersteinii Afan (Asteraceae). Turk J Biol 30(2):65–73

Basile A, Sorbo S, Spadaro V, Bruno M, Maggio A, Faraone N, Rosselli S (2009) Antimicrobial and antioxidant activities of coumarins from the roots of *Ferulago campestris* (Apiaceae). Molecules 14:939–952

Betts JW, Hornsey MA, Wareham DW, La Ragione RM (2017) In *vitro* and *in vivo* activity of the flavin – epicatechin combinations versus multidrug-resistant *Acinetobacter baumannii*. Infect Dis Ther 6:435–442

Birdi T, D'Souza D, Tolani M, Daswani P, Nair V, Tetali P, Carlos TJ, Honer S (2012) Assessment of the activity of selected Indian medicinal plants against *Mycobacterium tuberculosis*: a preliminary screening using the microplate alamar blue assay. Eur J Med Plants 2:308–323

Bjarnsholt T, Jensen PØ, Rasmussen TB, Christophersen L, Calum H, Hentzer M, Hougen HP, Rygaard J, Moser C, Eberl L, Høiby N (2005) Garlic blocks quorum sensing and promotes rapid clearing of pulmonary Pseudomonas aeruginosa infections. Microbiology 151(12):3873–3880

Boberek JM, Stach J, Good L (2010) Genetic evidence for inhibition of bacterial division protein FtsZ by berberine. PLoS ONE 5:e13745

Bouyahya A, Dakka N, Et-Touys A, Abrini J, Bakri Y (2017) Medicinal plant products targeting quorum sensing for combating bacterial infections. Asian Pac J Trop Med 10(8):729–743

Brackman G, Defoirdt T, Miyamoto C, Bossier P, Van Calenbergh S, Nelis H, Coenye T (2008) Cinnamaldehyde and cinnamaldehyde derivatives reduce virulence in Vibrio spp. by decreasing the DNA-binding activity of the quorum sensing response regulator LuxR. BMC Microbiol 8(1):1–4

Bravo L (1998) Polyphenols: chemistry, dietary sources, metabolism, and nutritional significance. Nutr Rev 56(11):317–333

Broniatowski M, Flasiński M, Wydro P, Fontaine P (2015) Grazing incidence diffraction studies of the interactions between ursane-type antimicrobial triterpenes and bacterial anionic phospholipids. Colloids Surf B: Biointerfaces 128:561–567

Brown AR, Ettefagh KA, Todd D, Cole PS, Egan JM, Foil DH, Graf TN, Schindler BD, Kaatz GW, Cech NB (2015) A mass spectrometry-based assay for improved quantitative measurements of efflux pump inhibition. PLoS One 10(5):e0124814

Carson CF, Hammer KA (2011) Chemistry and bioactivity of essential oils. Lipids essent. Oils Antimicrob Agents 25:203–238

Chagnon F, Guay I, Bonin MA et al (2014) Unraveling the structure activity relationship of tomatidine, a steroid alkaloid with unique antibiotic properties against persistent forms of *Staphylococcus aureus*. Eur J Med Chem 80:605–620

Chen Y, Liu T, Wang K, Hou C, Cai S, Huang Y, Du Z, Huang H, Kong J, Chen Y (2016) Baicalein inhibits Staphylococcus aureus biofilm formation and the quorum sensing system in vitro. PLoS One 11(4):e0153468

Choi JG, Kang OH, Chae HS et al (2010) Antibacterial activity of Hylomeconhylomeconoides against methicillin-resistant *Staphylococcus aureus*. Appl Biochem Biotechnol 160:2467–2474

Choo JH, Rukayadi Y, Hwang JK (2006) Inhibition of bacterial quorum sensing by vanilla extract. Lett Appl Microbiol 42(6):637–641

Chu M, Zhang MB, Liu YC, Kang JR, Chu ZY, Yin KL, Ding LY, Ding R, Xiao RX, Yin YN, Liu XY (2016) Role of berberine in the treatment of methicillin-resistant *Staphylococcus aureus* infections. Sci Rep 22:1–9

Chung PY, Chung LY, Navaratnam P (2014) Potential targets by pentacyclic triterpenoids from Callicarpa farinosa against methicillin-resistant and sensitive *Staphylococcus aureus*. Fitoterapia 94:48–54

Ciocan ID, Băra I (2007) Plant products as antimicrobial agents. Analele Ştiinţifice ale Universităţii „Alexandru Ioan Cuza", Secţiunea Genetică şi Biologie Moleculară, TOM VIII

Clark J, You M (2006) Chemoprevention of lung cancer by tea. Mol Nutr Food Res 50(2):144–151

Coqueiro A, Regasini L, Stapleton P et al (2014) *In vitro* antibacterial activity of prenylated guanidine alkaloids from Pterogyne nitens and synthetic analogues. J Nat Prod 77:1972–1975

Cowan MM (1999) Plant products as antimicrobial agents. Clin Microbiol Rev 12(4):564–582

Cragg GM, Newman DJ (2001) Natural product drug discovery in the next millennium. Pharm Biol 39(sup1):8–17

Cushnie TPT, Lamb AJ (2005) Antimicrobial activity of flavonoids. Int J Antimicrob Agents 5: 343–356

Del Rio D, Rodriguez-Mateos A, Spencer JP, Tognolini M, Borges G, Crozier A (2013) Dietary (poly) phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. Antioxid Redox Signal 18(14):1818–1892

Dias DA, Urban S, Roessner U (2012a) A historical overview of natural products in drug discovery. Meta 2(2):303–336

Dias C, Aires AN, Bennett RAS, Rosa EJ, Saavedra M (2012b) First study on antimicrobial activity and synergy between isothiocyanates and antibiotics against selected Gram-negative and Gram-positive pathogenic bacteria from clinical and animal source. Med Chem 8(3):474–480

Dusane DH, Hosseinidoust Z, Asadishad B, Tufenkji N (2014) Alkaloids modulate motility, biofilm formation and antibiotic susceptibility of uropathogenic *Escherichia coli*. PLoS One 9(11): e112093

Dziedzic A, Wojtyczka RD, Kubina R (2015) Inhibition of oral Streptococci growth induced by the complementary action of berberine chloride and antibacterial compounds. Molecules 20(8): 13705–13724

Edema MO, Alaga TO (2012) Comparative evaluation of bioactive compounds in Hibiscus sabdariffa and Syzygium samarangense juice extracts. Afr Crop Sci J 20(3):179–188

Farhadi F, Khameneh B, Iranshahi M, Iranshahy M (2019) Antibacterial activity of flavonoids and their structure–activity relationship: an update review. Phytother Res 33(1):13–40

Fratianni F, Nazzaro F, Marandino A, Fusco MD, Coppola R, De Feo V, De Martino L (2013) Biochemical composition, antimicrobial activities, and anti–quorum-sensing activities of ethanol and ethyl acetate extracts from Hypericum connatum Lam. (Guttiferae). J Med Food 16 (5):454–459

Friedman M, Henika PR, Levin CE, Mandrell RE, Kozukue N (2006) Antimicrobial activities of tea catechins and theaflavins and tea extracts against Bacillus cereus. J Food Prot 69(2):354–361

Fu L, Lu W, Zhou X (2016) Phenolic compounds and in vitro antibacterial and antioxidant activities of three tropic fruits: persimmon, guava, and sweetsop. BioMed Res Int

Geoghegan F, Wong RWK, Rabie ABM (2010) Inhibitory effect of quercetin on periodontal pathogens in vitro. Phytother Res 24(6):817–820

Gökalsın B, Aksoydan B, Erman B, Sesal NC (2017) Reducing virulence and biofilm of Pseudomonas aeruginosa by potential quorum sensing inhibitor carotenoid: zeaxanthin. Microb Ecol 74 (2):466–473

Gopu V, Meena CK, Shetty PH (2015) Quercetin influences quorum sensing in food borne bacteria: in-*vitro* and *in-silico* evidence. PLoS One 10(8):e0134684

Gutiérrez S, Morán A, Martínez-Blanco H, Ferrero MA, Rodríguez-Aparicio LB (2017) The usefulness of non-toxic plant metabolites in the control of bacterial proliferation. Probiot Antimicrob Prot 9:323–333

Gyawali R, Ibrahim SA (2014) Natural products as antimicrobial agents. Food Control 46:412–429

Hao S, Yang D, Zhao L, Shi F, Ye G, Fu H, Lin J, Guo H, He R, Li J, Chen H (2021) EGCG-mediated potential inhibition of biofilm development and quorum sensing in Pseudomonas aeruginosa. Int J Mol Sci 22(9):4946

Harborne JB (2013) The flavonoids: advances in research since 1980

Haristoy X, Fahey JW, Scholtus I, Lozniewski A (2005) Evaluation of the antimicrobial effects of several isothiocyanates on *Helicobacter pylori*. Planta Med 71:326–330

Hemaiswarya S, Doble M (2010) Synergistic interaction of phenylpropanoids with antibiotics against bacteria. J Med Microbiol 59(12):1469–1476

Hirai I, Okuno M, Katsuma R, Arita N, Tachibana M, Yamamoto Y (2010) Characterisation of anti-*Staphylococcus aureus* activity of quercetin. Int J Food Sci Technol 45(6):1250–1254

Hochfellner C, Evangelopoulos D, Zloh M, Wube A, Guzman JD, McHugh TD, Kunert O, Bhakta S, Bucar F (2015) Antagonistic effects of indoloquinazoline alkaloids on antimycobacterial activity of evocarpine. J Appl Microbiol 118:864–872

Hong H, Landauer MR, Foriska MA, Ledney GD (2006) Antibacterial activity of the soy isoflavone genistein. J Basic Microbiol 46:329–335

Hossain MA, Lee SJ, Park NH, Mechesso AF, Birhanu BT, Kang J, Reza MA, Suh JW, Park SC (2017) Impact of phenolic compounds in the acyl homoserine lactone-mediated quorum sensing regulatory pathways. Sci Rep 7(1):1–6

Huang YH, Huang CC, Chen CC, Yang KJ, Huang CY (2015) Inhibition of *Staphylococcus aureus* PriA helicase by flavonol kaempferol. Protein J 34(3):169–172

Jain S, Mehata MS (2017) Medicinal plant leaf extract and pure flavonoid mediated green synthesis of silver nanoparticles and their enhanced antibacterial property. Sci Rep 7(1):1–3

Jali BR (2021) A mini-review: quinones and their derivatives for selective and specific detection of specific cations. Biointerf Res Appl Chem 11:11679–11699

Jennings BR, Ridler PJ (1983) Interaction of chromosomal stains with DNA. Biophys Struct Mech 10(1):71–79

Jeong KW, Lee JY, Kang DI, Lee JU, Shin SY, Kim Y (2009) Screening of flavonoids as candidate antibiotics against *Enterococcus faecalis*. J Nat Prod 72:719–724

Jiang JG, Huang XJ, Chen J, Lin QS (2007) Comparison of the sedative and hypnotic effects of flavonoids, saponins and polysaccharides extracted from Semen *Ziziphus jujuba*. Nat Prod Res 21:310–320

Jiang QW, Chen MW, Cheng KJ, Yu PZ, Wei X, Shi Z (2016) Therapeutic potential of steroidal alkaloids in cancer and other diseases. Med Res Rev 36(1):119–143

Jonkers D, van den Broek E, van Dooren I, Thijs C, Dorant E, Hageman G et al (1999) Antibacterial effect of garlic and omeprazole on *Helicobacter pylori*. J Antimicrob Chemother 43:837–839

Jung HA, Ali MY, Jung HJ, Jeon HO, Chung HY, Choi JS (2016) Inhibitory activities of major anthraquinones and other constituents from *Cassia obtusifolia* against beta-secretase and cholinesterases. J Ethnopharmacol 191:152–160

Kalani K, Chaturvedi V, Trivedi P, Tondon S, Srivastava SK (2019) Dihydroartemisinin and its analogs: a new class of antitubercular agents. Curr Top Med Chem 19:594–599

Karou SD, Nadembega WM, Ilboudo DP, Ouermi D, Gbeassor M, De Souza C, Simpore J (2007) *Sida acuta Burm*. f.: a medicinal plant with numerous potencies. Afr J Biotechnol 6:25

Khalil AAK, Park WS, Lee J, Kim HJ, Akter KM, Goo YM, Bae JY, Chun MS, Kim JH, Ahn MJ (2019) A new anti-Helicobacter pylori juglone from *Reynoutria japonica*. Arch Pharm Res 42: 505–511

Khameneh B, Iranshahy M, Ghandadi M, Ghoochi AD, Fazly BBS, Iranshahi M (2015) Investigation of the antibacterial activity and efflux pump inhibitory effect of co-loaded piperine and gentamicin nanoliposomes in methicillin-resistant *Staphylococcus aureus*. Drug Dev Ind Pharm 41:989–994

Khan IA, Mirza ZM, Kumar A, Verma V, Qazi GN (2006) Piperine, a phytochemical potentiator of ciprofloxacin against *Staphylococcus aureus*. Antimicrob Agents Chemother 50(2):810–812

Klancnik A, Sikic PM, Trost K, Tusek ZM, Mozetic VB, Smole MS (2017) Anti-campylobacter activity of resveratrol and an extract from waste pinot noir grape skins and seeds, and resistance of camp. Jejuni planktonic and biofilm cells, mediated via the CmeABC efflux pump. J Appl Microbiol 122:65–77

Knezevic P, Aleksic V, Simin N, Svircev E, Petrovic A, Mimica-Dukic N (2016) Antimicrobial activity of *Eucalyptus camaldulensis* essential oils and their interactions with conventional antimicrobial agents against multi-drug resistant *Acinetobacter baumannii*. J Ethnopharmacol 178:125–136

Korir RK, Mutai C, Kiiyukia C, Bii C (2012) Antimicrobial activity and safety of two medicinal plants traditionally used in Bomet district of Kenya Res. J Med Plant 6:370–382

Kumar S, Pandey AK (2013) Chemistry and biological activities of flavonoids: an overview. Sci World J

Kumar P, Singh A, Sharma U, Singh D, Dobhal MP, Singh S (2013) Anti-mycobacterial activity of plumericin and isoplumericin against MDR *Mycobacterium tuberculosis*. Pulm Pharmacol Ther 26:332–335

Kyaw BM, Lim CS (2012) Bactericidal antibiotic-phytochemical combinations against methicillin resistant *Staphylococcus aureus*. Braz J Microbiol 43:938–945

Lattanzio V (2013) Phenolic compounds: introduction 50. Nat Prod:1543–1580

Li BH, Zhang R, Du YT, Sun YH, Tian WX (2006) Inactivation mechanism of the beta-ketoacyl-[acyl carrier protein] reductase of bacterial type-II fatty acid synthase by epigallocatechin gallate. Biochem Cell Biol 84:755–762

Li G, Yan C, Xu Y, Feng Y, Wu Q, Lv X, Yang B, Wang X, Xia X (2014) Punicalagin inhibits Salmonella virulence factors and has anti-quorum-sensing potential. Appl Environ Microbiol 80(19):6204–6211

Liu LQ, Tan XY, Zhao CX, Wu HJ, Liu P (2017) Impact of compatibility ratios of rhubarb-gardenia herbal pair and extraction techniques on anthraquinone dissolution. Chin Tradit Herb Drug 48: 283–287

Loes AN, Ruyle L, Arvizu M, Gresko KE, Wilson AL, Deutch CE (2014) Inhibition of urease activity in the urinary tract pathogen *Staphylococcus saprophyticus*. Lett Appl Microbiol 1:31–41

Luís Â, Silva F, Sousa S, Duarte AP, Domingues F (2014) Antistaphylococcal and biofilm inhibitory activities of gallic, caffeic, and chlorogenic acids. Biofouling 30(1):69–79

Mariita RM, Ogol CKPO, Oguge NO, Okemo PO (2011) Methanol extract of three medicinal plants from Samburu in northern Kenya show significant antimycobacterial, antibacterial and antifungal properties. Res J Med Plant 5:54–64

Matsumoto Y, Kaihatsu K, Nishino K, Ogawa M, Kato N, Yamaguchi A (2012) Antibacterial and antifungal activities of new acylated derivatives of epigallocatechin gallate. Front Microbiol 3:53

Mirzoeva OK, Grishanin RN, Calder PC (1997) Antimicrobial action of propolis and some of its components: the effects on growth, membrane potential and motility of bacteria. Microbiol Res 152(3):239–246

Molyneux RJ, Lee ST, Gardner DR, Panter KE, James LF (2007) Phytochemicals: the good, the bad and the ugly? Phytochemistry 68(22-24):2973–2985

Moon H, Rhee MS (2016) Synergism between carvacrol or thymol increases the antimicrobial efficacy of soy sauce with no sensory impact. Int J Food Microbiol 217:35–41

Mun SH, Joung DK, Kim SB, Park SJ, Seo YS, Gong R, Choi JG, Shin DW, Rho JR, Kang OH (2014) The mechanism of antimicrobial activity of sophoraflavanone B against methicillin-resistant *Staphylococcus aureus*. Foodborne Pathog Dis 11:234–239

Munyendo WLL, Orwa JA, Rukunga GM, Bii CC (2011) Bacteriostatic and bactericidal activities of *Aspilia mossambicensis*, *Ocimum gratissimum* and *Toddalia asiatica* extracts on selected pathogenic bacteria. Res J Med Plant 5(6):717–727

Nag S, Kumaria S (2018) *In silico* characterization and transcriptional modulation of phenylalanine ammonia lyase (PAL) by abiotic stresses in the medicinal orchid *Vanda coerulea* Griff. ex Lindl. Phytochemistry 156:176–183

Nakayama M, Shimatani K, Ozawa T, Shigemune N, Tsugukuni T, Tomiyama D et al (2013) A study of the antibacterial mechanism of catechins: Isolation and identification of *Escherichia coli* cell surface proteins that interact with epigallocatechin gallate. Food Control 33(2):433–439

Niu C, Afre S, Gilbert ES (2006) Subinhibitory concentrations of cinnamaldehyde interfere with quorum sensing. Lett Appl Microbiol 43(5):489–494

O'Gara EA, Hill DJ, Maslin DJ (2000) Activities of garlic oil, garlic powder, and their diallyl constituents against *Helicobacter pylori*. Appl Environ Microbiol 66:2269–2273

Oboh G (2010) Antioxidant and antimicrobial properties of ethanolic extract of *Ocimum gratissimum* leaves. J Pharmacol Toxicol 5:396–402

Ohemeng KA, Schwender CF, Fu KP, Barrett JF (1993) DNA gyrase inhibitory and antibacterial activity of some flavones. Bioorg Med Chem Lett 3(2):225–230

Pan X, Bligh SWA, Smith E (2014) Quinolone alkaloids from fructus evodiae show activity against methicillin-resistant *Staphylococcus aureus*. Phytother Res 28:305–307

Papageorgiou VP, Assimopoulou AN, Ballis AC (2008) Alkannins and shikonins: a new class of wound healing agents. Curr Med Chem 15:3248–3267

Park HW, Choi KD, Shin IS (2013) Antimicrobial activity of isothiocyanates (ITCs) extracted from horseradish (Armoracia rusticana) root against oral microorganisms. Biocontrol Sci 18(3): 163–168

Patra AK (2012) An overview of antimicrobial properties of different classes of phytochemicals. In: Dietary phytochemicals and microbes, pp 1–32

Peng L, Kang S, Yin Z, Jia R, Song X, Li L, Li Z, Zou Y, Liang X, Li L, He C (2015) Antibacterial activity and mechanism of berberine against *Streptococcus agalactiae*. Int J Clin Exp Pathol 8(5):5217

Periasamy H, Iswarya S, Pavithra N, Senthilnathan S, Gnanamani A (2019) *In vitro* antibacterial activity of plumbagin isolated from *Plumbago zeylanica* L. against methicillin-resistant Staphylococcus aureus. Lett Appl Microbiol 69:41–49

Prabu A, Hassan S, Prabuseenivasan SAS, Hanna LE, Kumar V (2015) Andrographolide: a potent antituberculosis compound that targets aminoglycoside 20-N-acetyltransferase in *Mycobacterium tuberculosis*. J Mol Graph Model 61:133–140

Qin Y, Luo ZQ, Smyth AJ, Gao P, von Bodman SB, Farrand SK (2000) Quorum-sensing signal binding results in dimerization of TraR and its release from membranes into the cytoplasm. EMBO J 19:5212–5221

Qiu J, Feng H, Lu J, Xiang H, Wang D, Dong J, Wang J, Wang X, Liu J, Deng X (2010) Eugenol reduces the expression of virulence-related exoproteins in *Staphylococcus aureus*. Appl Environ Microbiol 76:5846–5851

Ramawat KG (2007) Secondary plant products in nature. In: Merillon KG (ed) Biotechnology: secondary metabolites; plants and microbes. Science Publishers, New York, pp 21–57

Randhawa HK, Hundal KK, Ahirrao PN, Jachak SM, Nandanwar HS (2016) Efflux pump inhibitory activity of flavonoids isolated from *Alpinia calcarata* against methicillin-resistant *Staphylococcus aureus*. Biologia 71:484–493

Randhir R, Lin YT, Shetty K, Lin YT (2004) Phenolics, their antioxidant and antimicrobial activity in dark germinated fenugreek sprouts in response to peptide and phytochemical elicitors. Asia Pac J Clin Nutr 13(3)

Rao PS, Roja G (2002) Anticancer compound from tissue culture of medicinal plants. I. Herbs Spices Med Plants 7:71–102

Rathinam P, Kumar VHS, Viswanathan P (2017) Eugenol exhibits anti-virulence properties by competitively binding to quorum sensing receptors. J Bioadhesion Biofilm Res 33:624–639

Reiter J, Levina N, Van der Linden M, Gruhlke M, Martin C, Slusarenko AJ (2017) Diallylthiosulfinate (Allicin), a volatile antimicrobial from garlic (*Allium sativum*), kills human lung pathogenic bacteria, including MDR strains, as a vapor. Molecules 22(10):1711

Roshan N, Riley TV, Hammer KA (2017) Antimicrobial activity of natural products against Clostridium difficile in vitro. J Appl Microbiol 123:92–103

Rózalski M, Walencka E, Rózalska B, Wysokinska H (2007) Antimicrobial activity of diterpenoids from hairy roots of *Salvia sclarea* L.: salvipisone as a potential anti-biofilm agent active against antibiotic resistant *Staphylococci*. Phytomedicine 14(1):31–35

Sahyon HA, Ramadan EN, Mashaly MM (2019) Synergistic effect of quercetin in combination with sulfamethoxazole as new antibacterial agent: *in vitro* and *in vivo* study. Pharm Chem J 53(9): 803–813

Sakharkar MK, Jayaraman P, Soe WM, Chow VT, Sing LC, Sakharkar KR (2009) In vitro combinations of antibiotics and phytochemicals against *Pseudomonas aeruginosa*. J Microbiol Immunol Infect 42(5):364–370

Santos C, Goufo P, Fonseca J, Pereira JL, Ferreira L, Coutinho J, Trindade H (2018) Effect of lignocellulosic and phenolic compounds on ammonia, nitric oxide and greenhouse gas emissions during composting. J Clean Prod 171:548–556

Santos CA, Lima EM, de Melo Franco BD, Pinto UM (2021) Exploring phenolic compounds as quorum sensing inhibitors in foodborne bacteria. Front Microbiol 12:735931

Sarjit A, Wang Y, Dykes GA (2015) Antimicrobial activity of gallic acid against thermophilic Campylobacter is strain specific and associated with a loss of calciumions. Food Microbiol 46:227–233

Savoia D (2012) Plant-derived antimicrobial compounds: alternatives to antibiotics. Future Microbiol 7(8):979–990

Si XB, Zhang XM, Wang S, Lan Y, Zhang S, Huo LY (2019) Allicin as add-on therapy for *Helicobacter pylori* infection: a systematic review and meta-analysis. World J Gastroenterol 25: 6025–6040

Sibi G, Chatly P, Adhikari S, Ravikumar KR (2012) Phytoconstituents and their influence on antimicrobial properties of *Morinda citrifolis* L. Res J Med Plant 6:441–448

Singh N, Kumaria S (2020a) A combinational phytomolecular-mediated assessment in micropropagated plantlets of *Coelogyne ovalis* Lindl.: a horticultural and medicinal Orchid. Proc Natl Acad Sci 90(2):455–466

Singh N, Kumaria S (2020b) Molecular cloning and characterization of chalcone synthase gene from *Coelogyne ovalis* Lindl. and its stress-dependent expression. Gene 762:145104

Siriyong T, Srimanote P, Chusri S, Yingyongnarongkul BE, Suaisom C, Tipmanee V, Voravuthikunchai SP (2017) Conessine as a novel inhibitor of multidrug efflux pump systems in *Pseudomonas aeruginosa*. BMC Complement Altern Med 17:405

Slobodníková L, Fialová S, Rendeková K, Kováč J, Mučaji P (2016) Antibiofilm activity of plant polyphenols. Molecules 21(12):1717

Steinmann J, Buer J, Pietschmann T, Steinmann E (2013) Antiinfective properties of epigallocatechin 3 gallate (EGCG), a component of green tea. Br J Pharmacol 168(5):1059–1073

Stermitz FR, Cashman KK, Halligan KM, Morel C, Tegos GP, Lewis K (2003) Polyacylated neohesperidosides from *Geranium caespitosum*: bacterial multidrug resistance pump inhibitors. Bioorg Med Chem Lett 13:1915–1918

Tan N, Bilgin M, Tan E, Miski M (2017) Antibacterial activities of prenylated coumarins from the roots of *Prangoshulusii*. Molecules 22:1098

Takó M, Kerekes EB, Zambrano C, Kotogán A, Papp T, Krisch J, Vágvölgyi C (2020) Plant phenolics and phenolic-enriched extracts as antimicrobial agents against food-contaminating microorganisms. Antioxidants 9(2):165

Togashi N, Hamashima H, Shiraishi A, Inoue Y, Takano A (2010) Antibacterial activities against *Staphylococcus aureus* of terpene alcohols with aliphatic carbon chains. J Essent Oil Res 22(3): 263–269

Tyagi P, Singh M, Kumari H, Kumari A, Mukhopadhy K (2015) Bactericidal activity of Curcumin I is associated with damaging of bacterial membrane. PLoS ONE 10:e0121313

Wang W, Sun C, Mao L, Ma P, Liu F, Yang J, Gao Y (2016) The biological activities, chemical stability, metabolism and delivery systems of quercetin: a review. Trends Food Sci Technol 56: 21–38

Wu D, Kong Y, Han C, ChenJ HL, Jiang H, Shen X (2008) D-Alanine: D-alanine ligase as a new target for the flavonoids quercetin and apigenin. Int J Antimicrob Agents 32:421–426

Xie Q, Johnson BR, Wenckus CS, Fayad MI, Wu CD (2012) Efficacy of berberine, an antimicrobial plant alkaloid, as an endodontic irrigant against a mixed-culture biofilm in an *in vitro* tooth model. J Endod 38(8):1114–1117

Yadav MK, Chae SW, Im GJ, Chung JW, Song JJ (2015) Eugenol: a phytocompound effective against methicillin-resistant and methicillin-sensitive Staphylococcus aureus clinical strain biofilms. PLoS One 10(3):e0119564

Yuan H, Ma Q, Ye L, Piao G (2016) The traditional medicine and modern medicine from natural products. Molecules 21(5):559

Zambrano C, Kerekes EB, Kotogán A, Papp T, Vágvölgyi C, Krisch J, Takó M (2019) Antimicrobial activity of grape, apple and pitahaya residue extracts after carbohydrase treatment against food-related bacteria. LWT Food Sci Technol 100:416–425

Zeng Z, Qian L, Cao L, Tan H, Huang Y, Xue X et al (2008) Virtual screening for novel quorum sensing inhibitors to eradicate biofilm formation of *Pseudomonas aeruginosa*. Appl Microbiol Biotechnol 79:119–126

Zhang L, Kong Y, Wu D, Zhang H, Wu J, Chen J, Ding J, Hu L, Jiang H, Shen X (2008) Three flavonoids targeting the ß-hydroxyacyl-acyl carrier protein dehydratase from *Helicobacter pylori*: crystal structure characterization with enzymatic inhibition assay. Protein Sci 17: 1971–1978

Zoraghi R, Worrall L, See RH et al (2011) Methicillin-resistant *Staphylococcus aureus* (MRSA) pyruvate kinase as a target for bis-indole alkaloids with antibacterial activities. J Biol Chem 286: 44716–44725