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Review

Antibacterial plant compounds, extracts and essential oils: An updated review on their effects and putative mechanisms of action

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ABSTRACT

Background: Antibiotic-resistant bacteria pose a global health threat. Traditional antibiotics can lose their effectiveness, and the development of novel effective antimicrobials has become a priority in recent years. In this area, plants represent an invaluable source of antimicrobial compounds with vast therapeutic potential.

Purpose: To review the full possible spectrum of plant antimicrobial agents (plant compounds, extracts and essential oils) discovered from 2016 to 2021 and their potential to decrease bacterial resistance. Their activities against bacteria, with special emphasis on multidrug resistant bacteria, mechanisms of action, possible combinations with traditional antibiotics, roles in current medicine and future perspectives are discussed.

Methods: Studies focusing on the antimicrobial activity of compounds of plant origin and their mechanism of action against bacteria were identified and summarized, including contributions from January 2016 until January 2021. Articles were extracted from the Medline database using PubMed search engine with relevant keywords and operators.

Results: The search yielded 11,689 articles from 149 countries, of which 101 articles were included in this review. Reports from 41 phytochemicals belonging to 20 families were included. Reports from plant extracts and essential oils from 39 plant species belonging to 17 families were also included. Polyphenols and terpenes were the most active phytochemicals studied, either alone or as a part of plant extracts or essential oils. Plasma membrane disruption was the most common mechanism of antimicrobial action. Number and position of phenolic hydroxyl groups, double bonds, delocalized electrons and conjugation with sugars in the case of flavonoids seemed to be crucial for antimicrobial capacity. Combinations of phytochemicals with beta-lactam antibiotics were the most studied, and the inhibition of efflux pumps was the most common synergistic mechanism.

Conclusion: In recent years, terpenes, flavones, flavonols and some alkaloids and phenylpropanoids, either isolated or as a part of extracts, have shown promising antimicrobial activity, being membrane disruption their most common mechanism. However, their utilization as appropriate antimicrobials need to be boosted by means of new omics technologies and network pharmacology to find the most effective combinations among them or in combination with antibiotics.

Introduction

Multidrug-resistant (MDR) bacteria pose a first-rate global health threat. Many of the infections to which we are exposed today are difficult to treat with available antibiotics, which are rapidly losing efficacy due to the emergence of antibiotic-resistant bacteria (Alos, 2015). The discovery of new antibacterial agents capable of dealing with antibiotic-resistant bacteria is a priority in the field of scientific research (Martinez and Baquero, 2014). In this field, certain natural compounds of plant origin have emerged as powerful potential therapeutic tools (Alvarez-Martinez et al., 2020a, 2020b; Kokoska et al., 2019).

Plants produce an invaluable source of secondary metabolites in

Abbreviations: EO, essential oil; MDR, multidrug resistant; MIC, minimum inhibitory concentration; MRSA. methicillin-resistant Staphylococcus aureus, VRE, vancomycin-resistant *enterococci*.

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response to environmental factors such as attack by herbivores, abiotic stress, or interspecific interactions (Yang et al., 2018). Since ancient times, humans have used these secondary metabolites of plants in various fields, including medicine and gastronomy. The vast chemical diversity of plant secondary metabolites and their long history of traditional use make plants very attractive natural reservoirs for research into the discovery of new antimicrobial compounds. Rapid technological advancement and the application of new, increasingly efficient methodologies have allowed the identification and characterization of numerous antibacterial agents in recent years (Katz and Baltz, 2016).

Currently, the best-known and studied mechanisms of action among antimicrobial agents are related with a large variety of bacterial targets and processes, such as the inhibition of protein synthesis, inhibition of metabolic pathways, interference with cell-wall synthesis, inhibition of DNA and RNA synthesis, and lysis of the bacterial membrane, among others. On the other hand, the most common and studied mechanisms of bacterial resistance to antibacterial agents are antibiotic modification by enzymes, antibiotic inactivation and expression of efflux pumps (Chandra et al., 2017; Khameneh et al., 2019). Phytochemicals can act through different mechanisms and target sites compared to traditional antibiotics, hence their combination with conventional antibiotics has been proposed to provide superior efficacy in suppressing the development of resistance (Abreu et al., 2012).

Research into the discovery of antimicrobial phytochemicals, their mechanisms of action, and their inclusion in possible treatments and therapies is progressing rapidly. For this reason, it is necessary to maintain updated information of the advances in this field. There are several reviews about plant-based antimicrobials in the most recent period covering from 2016 to 2021. These are either focused on special group of plant compounds such as flavonoids, only pure compounds and no complex mixtures, or specific type of bacterial resistance (Barbieri et al., 2017; Chandra et al., 2017; Górniak et al., 2018; Li et al., 2019). Nevertheless, none of them includes the full possible spectrum of plant antimicrobial agents and their potential to decrease bacterial resistance. There are no reviews in this period that cover the antibacterial capacity and mechanism of action of pure phytochemicals, plant extracts, essential oils and phytochemicals showing synergistic effects with common antibiotics.

Therefore, the objective of this work was to review the most recent scientific literature published between January 2016 and January 2021 related to the antibacterial activity of compounds of plant origin, with special emphasis on their activity against MDR bacteria and their mechanisms of action. Moreover, this review attempts to provide assessments on the putative mechanism of action of antimicrobial plant compounds in relation to their chemical structure and molecular targets.

Methodology

The articles collected to write this review were extracted from the Medline database using the PubMed search engine. The terms used to perform the searches consisted of keywords including "antibacterial activity", "phytochemical" or "synergy", among others related to the subject of the review. “AND” or “OR” operators were used depending on the combination of terms. For example, "antibacterial activity" AND "plant extract" OR "essential oil". To be eligible for the review, studies had to be published in English, Spanish, German or French between January 2016 and January 2021. Only studies referring to specific antimicrobial agents that included information on their mechanisms of action, quantitative reliable measures of antimicrobial activity and well characterized origin were considered for review.

Phytochemicals with antimicrobial activity: molecular mechanism linked to its chemical structure

Plants have been used for thousands of years by humans to treat various ailments, including bacterial infections. Many ancestral medicinal uses have been scientifically corroborated using modern techniques that have allowed the identification of active compounds and the characterization of their antibacterial mechanism of action.

Some of the compounds of plant origin that have been most studied in recent years are complex plant extracts and essential oils as well as pure compounds such as terpenoids, polyphenols and alkaloids. It should be noted that polyphenols are very chemically diverse and as a group can be subdivided into the following families according to their chemical structures: flavonoids, stilbenes, lignans, tannins and phenolic acids, among others. Fig. 1 shows the number of publications related to antibacterial capacity in the PubMed database for each of the groups of agents of plant origin included in this study.

According to the data displayed in Fig. 1, the antibacterial agents most studied during the established period are plant extracts. The other complex mixture studied, essential oils, rank fifth among the most studied antibacterial agents. Regarding pure compounds, there has been abundant research in recent years on the antibacterial capacity of terpenes, flavonoids and alkaloids, with fewer publications regarding other compound classes. Table 1 lists the phytochemicals studied during the period from 2016 to 2021 with the MIC antimicrobial activity < 1000 μg/ml (Tamokou et al., 2017) and known or proposed mechanisms of action.

Among the compounds included in the table, terpenes were the most abundant antimicrobial compounds, with a presence of 56.8%, followed by polyphenols (including flavonoids, phenolic acids, etc.) with an abundance of 32.4%. These two chemical classes have been associated with very similar mechanisms of action, mainly based on the disruption of the bacterial plasma membrane. If we look at the compounds with exceptionally high antimicrobial activity, i.e., MIC < 10 μg/ml, most of them belong to the flavonoid group. These exceptionally active compounds include chrysoeriol glycosides (3), isorhamnetin glycoside (1), luteolin glycoside (1), hibicuslide C, and propolin D. The chrysoeriol and luteolin glycosides have the sugar moiety attached to the 7-OH of the flavone aglycones chrysoeriol and luteolin respectively, while isorhamnetin glycoside has the sugar moiety attached to the 3-OH of the flavonol aglycone isorhamnetin. These four compounds have shown activity against gram-negative bacteria (*Vibrio cholerae*) and gram-positive bacteria (*Staphylococcus aureus*) through disruption of the plasma membrane and leakage of intracellular content. These compounds have shown levels of activity similar to or even higher than that of ciprofloxacin, which was used as a reference antibiotic (Tagousop et al., 2018). Although little is known about the structure-function relationship of antibacterial phytochemicals, it appears that conjugation with sugar moieties at certain positions of the aromatic ring produces an increase in antibacterial capacity (Mandalari et al., 2007). This high activity could be attributed to a greater affinity for the bacterial membrane or to its ability to modulate its permeability due to the number and position of its hydroxyl and methoxy groups (Fitzgerald et al., 2004).

Data on the potential toxicity of some of these antimicrobial compounds derive from different assays and models. Nevertheless, the available data leads us to believe that their therapeutic or selectivity index is high. The 3 chrysoeriol glycosides, the isorhamnetin glycoside and the luteolin glycoside were tested for hemolytic activitiy against red blood cells at concentrations up to 256 μg/ml. No hemolytic activities were found in any of the compounds (Tagousop et al., 2018). Hibicuslide C demonstrated weak hemolytic activity against human erythrocytes, showing hemolytic activity of 25% at 80 μg/ml, 1% at 40 μg/ml, and 0% at 20 μg/ml (Hwang et al., 2013). The toxicity of propolin D was tested in vivo in the nematode *Caenorhabditis elegans* and this compound was found to be nontoxic up to concentrations of 200 μg/ml (Lee et al., 2019).

Regarding the most active structural types of Table 1, the phenylpropanoid eugenol and the monoterpenes thymol and limonene showed to be significantly active (Tamokou et al., 2017) with MICs < 10 μg/ml.

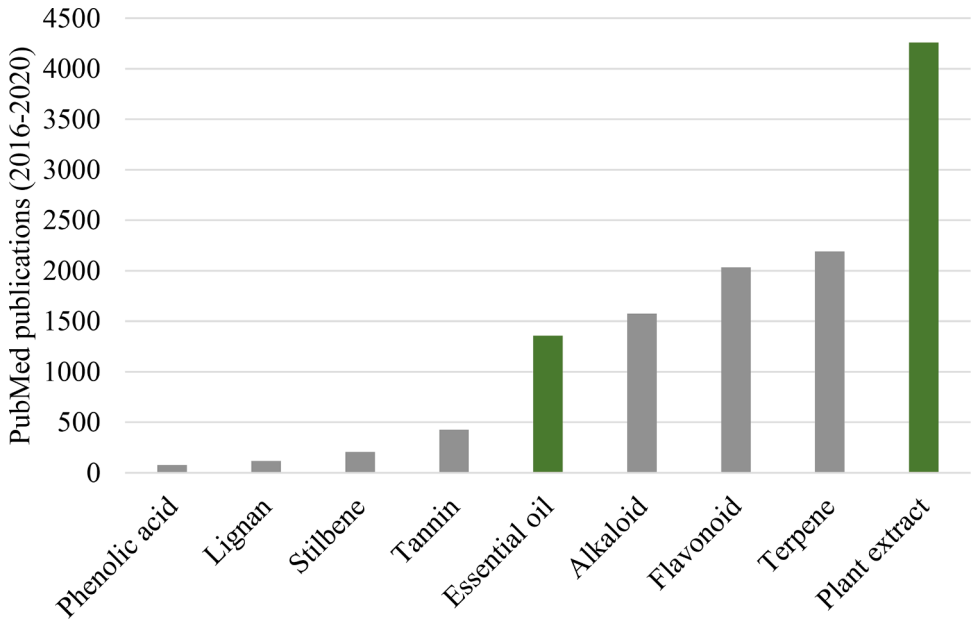


Fig. 1. Publications in PubMed between 2016 and 2020 related to antibacterial activity for each group of compounds of plant origin. PubMed search was performed on 31/12/2020. Keywords used: "antibacterial," "plant compound" (e.g., antibacterial, flavonoid). Gray bars correspond to pure compounds. Green bars correspond to compound mixtures.

The high antimicrobial activity of eugenol and thymol can be attributed to the presence of phenolic hydroxyl groups. The relevance of containing a free phenolic hydroxyl substituent can be seen by comparing the increased antibacterial activity of compounds such as carvacrol to its methyl ether form (Ultee et al., 2002). Furthermore, the relative position of the hydroxyl group is also relevant, since the thymol and carvacrol position isomers have different levels of activity against gram-positive and gram-negative bacteria (Dorman and Deans, 2000). The importance of the phenolic ring was also demonstrated by comparing the high antimicrobial activity of thymol with the weak activity of the related monoterpene derivative *p*-cymene (Saad et al., 2013), which differs from thymol in that the hydroxyl group is absent in the aromatic ring.

Eugenol is considered a safe substance and a safe food additive by the Federal Food, Drug and Cosmetics Administration. However, a case of failure in liver function has been reported in a two-year-old boy who consumed between 5 and 10 ml of clover oil very rich in eugenol (Mohammadi Nejad et al., 2017). (+)-Limonene is considered a safe molecule for human consumption with a reference dose, no-observed-adverse-effect level, and systemic exposure dose of 2.5 mg/kg /d, 250 mg/kg /d, and 1.48 mg/kg/d, respectively. Nevertheless, there are some reports that indicate that it could cause irritation to human skin (Kim et al., 2013). Thymol is generally considered a safe substance for humans. Toxicity studies have been performed on Caco-2 model cells and no cytotoxic effects have been found at concentrations of 0 to 250 μM after 24 and 48 h of exposure (Salehi et al., 2018).

Generally, pure compounds appear to be more effective against gram-positive bacteria such as *S. aureus* than against gram-negative bacteria such as *E. coli*. In Table 1, antibacterial activity against gram-positive bacteria has been reported 59 times, while activity against gram-negative bacteria has been reported 40 times. The mean MIC values of the pure compounds in Table 1 against gram-positive bacteria was 93.88 μg/ml, while the mean against gram-negative bacteria was 101.17 μg/ml.

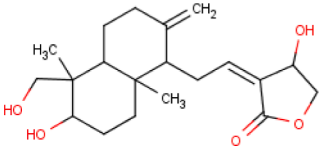
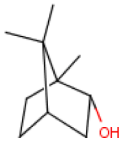
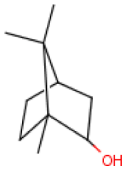
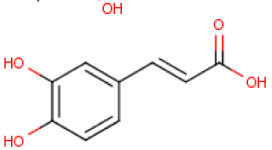
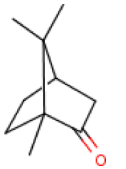
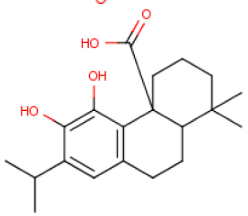
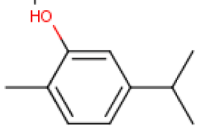
Regarding plants (or their parts) extracts, it is estimated that they are very active if they show MIC values < 100 μg/ml, significantly active if $100 \leq$ MIC ≤ 512 μg/ml, moderately active if $512 <$ MIC ≤ 2048 μg/ml and not active if MIC > 2048 μg/ml (Tamokou et al., 2017). Following this criterion, only plant extracts with MICs < 2048 μg/ml are included in Table 2, which shows the latest antibacterial plant extracts described between 2016 and 2021 in the scientific literature with MICs < 2048 μg/ml and a known mechanism of action.

It should be noted that *Bauhinia kockiana* Korth. (*Fabaceae*) ethyl acetate flowers extract; *Cistus salviifolius* L. *(Cistaceae)* leaves aqueous extract; *Cytinus hypocistis* (L.) L. (*Cytinaceae*) and *Cytinus ruber* (Fourr.) Fritsch (*Cytinaceae*) ethanol whole plant extracts; *Punica granatum* L. (*Lythraceae*) aqueous fruit extract and *Syzygium legatii* Burtt Davy & Greenway (*Myrtaceae*) acetone leaves extract showed to be highly active extracts (MIC < 100 μg/ml) according to Tamokou et al. (2017) cut-offs. They were especially effective against methicillin-resistant *S. aureus* (MRSA), MDR *E. coli* and vancomycin-resistant *enterococcus* (VRE). It is also noteworthy that MIC values for these extracts are usually higher than those from pure natural compounds. This is most likely because the extracts are mixtures of various compounds and, in general, not all the compounds included in the mixture have antimicrobial activity. Consequently, higher extract concentrations are required to achieve effective concentrations of the active compounds. Most extracts were obtained using ethanol (5) and water (5), followed by methanol (3) acetone (2) and ethyl acetate (2). The most frequently used plant parts were leaves (6). Whole plant was used twice and bulb, flowers, fruits, valonia (cups of the acorn), stems and beans were used only once.

Much of the antimicrobial activity of plant extracts is attributed to their content of phenolic compounds, mainly flavonoids and their derivatives. This group of polyphenols can interact with lipid bilayers and perturb plasma membrane functionality. This mechanism is shared by almost all the plant extracts described in the table above and shared with most of the compounds already shown in Table 1.

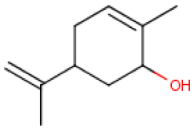
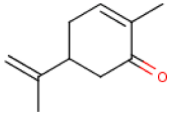
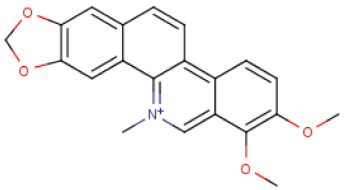
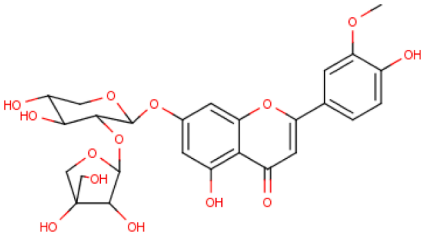
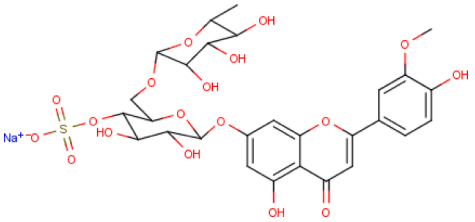
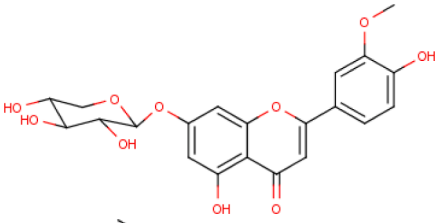
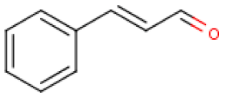
The interaction of polyphenols with bacterial plasma membranes can trigger a myriad of effects that contribute to their antibacterial capacity. There is a large body of evidence suggesting that plant extracts and polyphenols have the ability to disrupt the structure of the bacterial plasma membrane, causing the formation of pores, leakage, altering electrical charge, altering polarity, increasing permeability, modifying fluidity, delocalizing membrane proteins, and other phenomena responsible for antibacterial activity. For example, polyphenols such as galloyl catechins are able to intercalate in membranes, reaching a deep position in the lipid palisade and causing remarkable biophysical changes to its structure. These alterations can prevent the formation of biofilms, reduce the secretion of part of the exoproteome, and disperse

Table 1
Pure compounds with antibacterial activity described between 2016 and 2021. MDR: Multidrug resistant. MRSA: methicillin-resistant *Staphylococcus aureus*. VRE: vancomycin-resistant *enterococci*.

Compound	Structure	Class	Origin	Bacteria	Mechanism	Activity (MIC)	Reference
Andrographolide		Terpene (labdane diterpene)	*Andrographis paniculata* (Burm.f.) Nees (*Acanthaceae*)	*Bacillus subtilis* *Escherichia coli* *Staphylococcus aureus* *Streptococcus pneumoniae*	Protein and DNA synthesis	250 μg/ml 125 μg/ml 100 μg/ml 250 μg/ml	(Banerjee et al., 2017)
(-)-Borneol		Terpene (bicyclic monoterpene)	Purchased from Sigma-Aldrich (St Louis, MO, USA)	*Bacillus cereus* *E. coli* *S. aureus* *Salmonella typhimurium*	Cell membrane rupture	120 μg/ml 250 μg/ml 30 μg/ml 120 μg/ml	(Guimaraes et al., 2019)
(+)-Borneol		Terpene (bicyclic monoterpene)	Purchased from Sigma-Aldrich	*B. cereus* *E. coli* *S. aureus*	Cell membrane rupture	250 μg/ml 250 μg/ml 250 μg/ml	(Guimaraes et al., 2019)
Caffeic acid		Phenylpropanoid (cinnamic acid derivative)	Purchased from Sigma-Aldrich	MRSA	Cell membrane rupture and aerobic metabolism interference	256 μg/ml	(Kepa et al., 2018)
(±)-Camphor		Terpene (bicyclic monoterpene)	Purchased from Sigma-Aldrich	*B. cereus* *E. coli* *S. aureus* *S. typhimurium*	Cell membrane rupture	250 μg/ml 250 μg/ml 15 μg/ml 250 μg/ml	(Guimaraes et al., 2019)
Carnosic acid		Terpene (diterpene)	Purchased from Sigma-Aldrich	MRSA	Unclear, probably cell membrane rupture	12 μg/ml	(Vazquez et al., 2016)
Carvacrol		Terpene (cyclic monoterpene)	Purchased from Sigma-Aldrich	*B. cereus* *E. coli* *S. aureus* *S. typhimurium*	Cell membrane rupture	30 μg/ml 30 μg/ml 15 μg/ml 15 μg/ml	(Guimaraes et al., 2019)

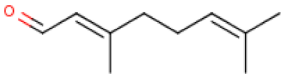
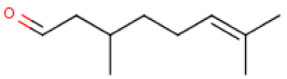
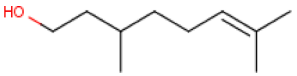
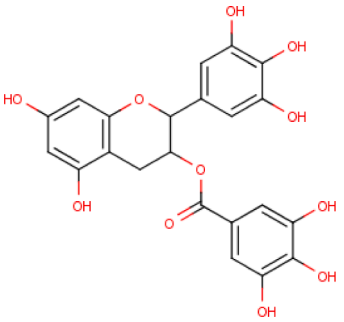
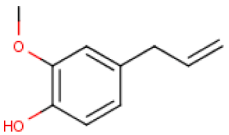
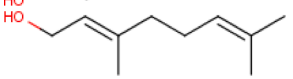
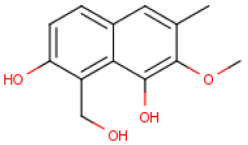
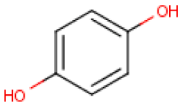
(*continued on next page*)

Table 1 (*continued*)

Compound	Structure	Class	Origin	Bacteria	Mechanism	Activity (MIC)	Reference
L-Carveol		Terpene (cyclic monoterpene)	Purchased from Sigma-Aldrich	*B. cereus* *E. coli* *S. aureus* *S. typhimurium*	Cell membrane rupture	120 μg/ml 60 μg/ml 15 μg/ml 30 μg/ml	(Guimaraes et al., 2019)
L-Carvone		Terpene (cyclic monoterpene)	Purchased from Sigma-Aldrich	*B. cereus* *E. coli* *S. aureus* *S. typhimurium*	Cell membrane rupture	250 μg/ml 60 μg/ml 30 μg/ml 120 μg/ml	(Guimaraes et al., 2019)
Chelerythrine		Alkaloid (benzophenanthridinic)	*Toddalia asiatica* (L.) Lam. (*Rutaceae*)	*S. aureus* MRSA	Cell wall and membrane rupture and protein biosynthesis inhibition	156 μg/ml 156 μg/ml	(He et al., 2018)
Chrisoeriol-7-*O*-β-D-apiofuranosyl-(1→2)-β-D-xylopyranoside		Flavonoid (flavone glycoside)	*Graptophyllum grandulosum* Turrill (*Acanthaceae*)	*V. cholerae* *S. aureus*	Cell membrane rupture	32 - 64 μg/ml 8 μg/ml	(Tagousop et al., 2018)
Chrysoeriol-7-*O*-α-*L*-rhamnopyranosyl-(1→6)-β-D-(4″-hydrogeno sulfate) glucopyranoside		Flavonoid (flavone glycoside)	*Graptophyllum grandulosum* Turrill (*Acanthaceae*)	*V. cholerae* *S. aureus*	Cell membrane rupture	8 μg/ml 4 μg/ml	(Tagousop et al., 2018)
Chrysoeriol-7-*O*-β-D-xyloside		Flavonoid (flavone glycoside)	*Graptophyllum grandulosum* Turrill (*Acanthaceae*)	*V. cholerae* *S. aureus*	Cell membrane rupture	8 –16 μg/ml 4 μg/ml	(Tagousop et al., 2018)
trans-Cinnamaldehyde		Phenylpropanoid	Purchased from Sigma-Aldrich	MDR *Clostridium difficile*	Cell membrane rupture and intracellular ATP depletion	0.03% (v/v)	(Roshan et al., 2019)

(*continued on next page*)

Table 1 (*continued*)

Compound	Structure	Class	Origin	Bacteria	Mechanism	Activity (MIC)	Reference
Citral		Terpene (linear monoterpene)	Purchased from Sigma-Aldrich	*B. cereus* *E. coli* *S. aureus* *S. typhimurium*	Cell membrane rupture	60 μg/ml 60 μg/ml 60 μg/ml 70 μg/ml	(Guimaraes et al., 2019)
Citronellal		Terpene (linear monoterpene)	Purchased from Sigma-Aldrich	*B. cereus* *E. coli* *S. aureus* *S. typhimurium*	Cell membrane rupture	120 μg/ml 250 μg/ml 250 μg/ml 120 μg/ml	(Guimaraes et al., 2019)
β-Citronellol		Terpene (linear monoterpene)	Purchased from Sigma-Aldrich	*B. cereus* *E. coli* *S. aureus* *S. typhimurium*	Cell membrane rupture	120 μg/ml 250 μg/ml 30 μg/ml 120 μg/ml	(Guimaraes et al., 2019)
Epigallocatechin gallate		Polyphenol (catechin ester)	Purchased from Teavigo, Japan	*Clostridium perfringens*	Inhibition of proteins involved in septum formation, DNA segregation and cell division	250 - 500 μg/ml	(Noor Mohammadi et al., 2019)
Eugenol		Phenylpropanoid	Purchased from Sigma-Aldrich	*B. cereus* *E. coli* *S. aureus* *S. typhimurium*	Cell membrane rupture	70 μg/ml 30 μg/ml 3 μg/ml 70 μg/ml	(Guimaraes et al., 2019)
trans-Geraniol		Terpene (linear monoterpene)	Purchased from Sigma-Aldrich	*B. cereus* *E. coli* *S. aureus* *S. typhimurium*	Cell membrane rupture	70 μg/ml 60 μg/ml 30 μg/ml 30 μg/ml	(Guimaraes et al., 2019)
Hibicuslide C		Naphtol derivative	*Abutilon theophrasti* Medik. (*Malvaceae*)	MDR *P. aeruginosa*	DNA fragmentation	5 - 10 μg/ml	(Lee et al., 2016)
Hydroquinone		Phenol (*p*-diphenol)	*Ainsliaea bonatii* Beauverd (*Asteraceae*)	*S. aureus*	Cell wall and membrane rupture	310 μg/ml	(Ma et al., 2019)

(*continued on next page*)

Table 1 (*continued*)

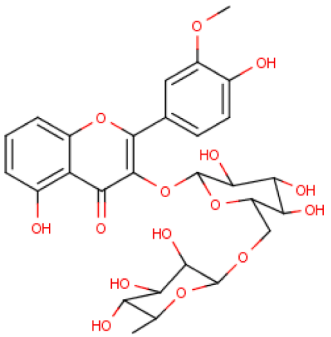
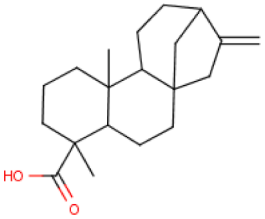
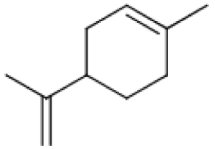
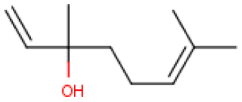
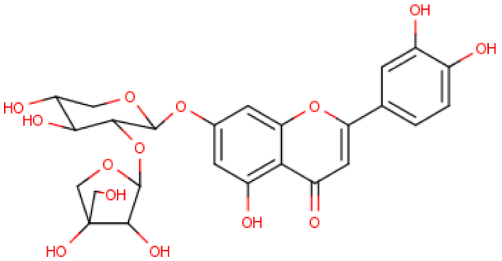
Compound	Structure	Class	Origin	Bacteria	Mechanism	Activity (MIC)	Reference
Isorhamnetin-3-*O*-α-*L*-rhamnopyranosyl-(1→6)-β-*D*-glucopyranoside		Flavonoid (flavonol glycoside)	*Graptophyllum grandulosum* Turrill (*Acanthaceae*)	*V. cholerae* *S. aureus*	Cell membrane rupture	16 −32 μg/ml 8 μg/ml	(Tagousop et al., 2018)
Kaurenoic acid		Terpene (diterpene)	*Mikania glomerata* Spreng. (*Asteraceae*)	*Actinomyces naeslundii* *Porphyromonas gingivalis* *Parvimonas micra* *Prevotella nigrescens*	Cell membrane rupture by insertion into the lipophilic region	25 μg/ml 3.12 μg/ml 3.12 μg/ml 25 μg/ml	(Martins et al., 2018)
(+)-Limonene		Terpene (cyclic monoterpene)	Purchased from Sigma-Aldrich	*B. cereus* *E. coli* *S. aureus* *S. typhimurium*	Cell membrane rupture	250 μg/ml 250 μg/ml 250 μg/ml 60 μg/ml	(Guimaraes et al., 2019)
			Purchased from Tokyo Chemical Industry Co	*Listeria monocytogenes*	Inhibition of expression of respiratory chain complex proteins	0.32 μl/ml	(Han et al., 2019)
Linalool		Terpene (linear monoterpene)	Purchased from Sigma-Aldrich	*B. cereus* *E. coli* *S. aureus* *S. typhimurium*	Cell membrane rupture	250 μg/ml 250 μg/ml 250 μg/ml 250 μg/ml	(Guimaraes et al., 2019)
Luteolin-7-*O*-β-*D*-apiofuranosyl-(1→2)-β-*D*-xylopyranoside		Flavonoid (flavone glycoside)	*Graptophyllum grandulosum* Turrill (*Acanthaceae*)	*V. cholerae* *S. aureus*	Cell membrane rupture	8 −16 μg/ml 4 μg/ml	(Tagousop et al., 2018)

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Table 1 (*continued*)

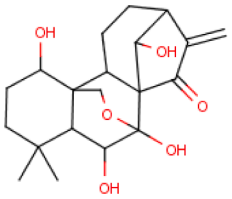
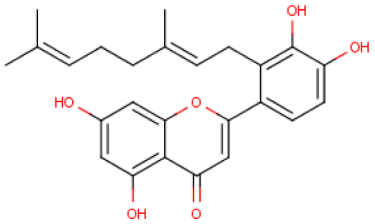
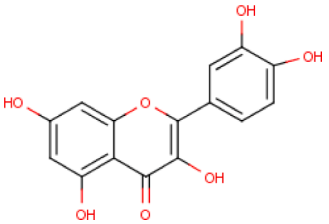
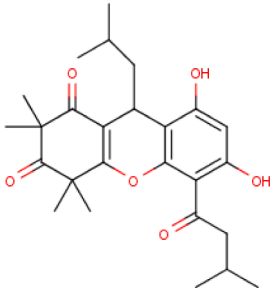
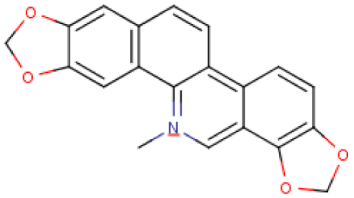
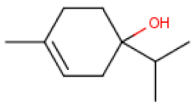
Compound	Structure	Class	Origin	Bacteria	Mechanism	Activity (MIC)	Reference
Oridonin		Terpene (diterpene)	*Rabdosia rubescens* (Hemsl.) H.Hara (*Lamiaceae*)	MRSA	Cell membrane and cell wall permeability increase, disturbance in protein and DNA metabolism	64 μg/ml	(Yuan et al., 2019)
Propolin D		Flavonoid (geranyl flavone)	*Macaranga tanarius* (L.) Müll.Arg. (*Euphorbiaceae*)	*S. aureus* MRSA *Staphylococcus epidermidis*	Cell wall disruption and reduction in fimbriae production	10 μg/ml 10 μg/ml 10 μg/ml	(Lee et al., 2019)
Quercetin		Flavonoid (flavonol)	*Trianthema decandra* L. (*Aizoaceae*)	*Pseudomonas aeruginosa*	Inhibition of FabZ enzyme	39.05 μg/ml	(Geethalakshmi et al., 2018)
Rhodomyrtosone B		Acylphloroglucinol	*Rhodomyrtus tomentosa* (Aiton) Hassk. (*Myrtaceae*)	MRSA	Cell membrane rupture	0.62 −1.25 μg/ml	(Zhao et al., 2019)
Sanguinarine		Alkaloid (benzophenanthridinic)	Purchased from Sigma-Aldrich	MRSA	Cell membrane rupture	6.3 μg/ml	(Khin et al., 2018)
Terpinen-4-ol		Terpene (cyclic monoterpene)	*Cinnamomum camphora* (L.) J.Presl (*Lauraceae*)	*Streptococcus agalactiae*	Damage in cell structure integrity, disturbance in protein and DNA synthesis	98 μg/ml	(Zhang et al., 2018)

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Table 1 (*continued*)

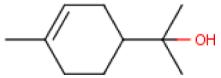
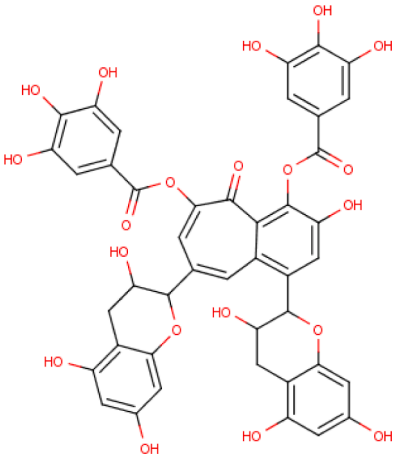
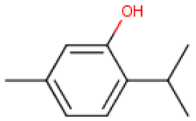
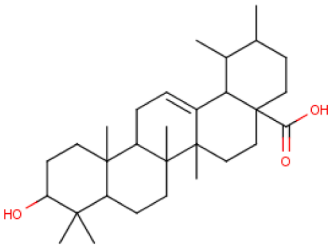
Compound	Structure	Class	Origin	Bacteria	Mechanism	Activity (MIC)	Reference
Terpineol		Terpene (cyclic monoterpene)	Purchased from Sigma-Aldrich	*B. cereus* *E. coli* *S. aureus* *S. typhimurium*	Cell membrane rupture	120 μg/ml 60 μg/ml 30 μg/ml 120 μg/ml	(Guimaraes et al., 2019)
Theaflavin-3,3′-digallate		Polyphenol (flavan-3-ols)	Purchased from Phyto-Lab GmbH & Co, Germany	*C. perfringens*	Reduction in biosynthetic and metabolic activities	125 - 250 μg/ml	(Noor Mohammadi et al., 2019)
Thymol		Terpene (cyclic monoterpene)	Purchased from Sigma-Aldrich	*B. cereus* *E. coli* *S. aureus* *S. typhimurium* VRE	Cell membrane rupture	7 μg/ml 7 μg/ml 7 μg/ml 3 μg/ml 2.5 μg/ml	(Guimaraes et al., 2019) (Zhang et al., 2018)
Ursolic acid		Terpene (triterpene)	Purchased from Sigma-Aldrich	MRSA	Cell membrane rupture, disruption of protein biosynthesis and metabolic pathways	64 μg/ml	(Wang et al., 2016)

Table 2
Plant extracts with antibacterial activity described between 2016 and 2021. MDR: Multidrug resistant. MRSA: methicillin-resistant *Staphylococcus aureus*. VRE: vancomycin-resistant *enterococci*.

Plant	Part used	Solvent	Bacteria	Mechanism	Activity (MIC)	Reference
Acacia nilotica (L.) Delile (*Fabaceae*)	Leaves	Ethanol	MDR *S. typhimurium*	Cell membrane rupture	1560 μg/ml	(Sadiq et al., 2017)
Allium sativum L. (*Amaryllidaceae*)	Bulb	Water	MDR *Clostridium difficile*	Cell membrane rupture and intracellular ATP depletion	0.8% (v/v) (unknown w/v %)	(Roshan et al., 2019)
Bauhinia kockiana Korth. (*Fabaceae*)	Flowers	Ethyl acetate	MRSA	Cell membrane rupture	62.5 μg/ml	(Chew et al., 2018)
Cistus salviifolius L. (*Cistaceae*)	Leaves	Water	*Staphylococcus aureus*	Cell membrane rupture	80.70 μg/ml	(Alvarez-Martinez et al., 2021)
			MRSA		51.21 μg/ml	
Cytinus hypocistis (L.) L. (*Cytinaceae*)	Whole plant	Ethanol	*S. aureus*	Cell membrane rupture and repression of the ica operon inhibiting biofilm formation	125 μg/ml	(Maisetta et al., 2019)
			Staphylococcus epidermidis		250 μg/ml	
			VRE		31.25 μg/ml	
		Water	*S. aureus*		500 μg/ml	
			S. epidermidis		500 μg/ml	
			VRE		125 μg/ml	
Cytinus ruber (Fourr.) Fritsch (*Cytinaceae*)	Whole plant	Ethanol	*S. aureus*	Cell membrane rupture and repression of the ica operon inhibiting biofilm formation	125 μg/ml	(Maisetta et al., 2019)
			S. epidermidis		250 μg/ml	
			VRE		31.25 μg/ml	
		Water	*S. aureus*		250 μg/ml	
			S. epidermidis		250 μg/ml	
			VRE		125 μg/ml	
Phaseolus vulgaris L. (*Fabaceae*)	Leaves	Methanol	*E. coli*	Cell membrane rupture	256 μg/ml	(Nayim et al., 2018)
Punica granatum L. (*Lythraceae*)	Fruit	Water	*S. aureus*	Cell membrane rupture	51.67 μg/ml	(Alvarez-Martinez et al., 2021)
			MRSA		72.89 μg/ml	
Quercus variabilis Blume (*Fagaceae*)	Valonia (cups of the acorn)	Ethanol	*S. aureus*	Cell membrane rupture and metabolism disruption	625 μg/ml	(Zhou et al., 2019)
Smilax china L. (*Smilacaceae*)	Stems	Ethanol and ethyl acetate	*E. coli*	Cell membrane rupture	195.31 μg/ml	(Xu et al., 2019)
			S. typhimurium		781.25 μg/ml	
			S. aureus		195.31 μg/ml	
			Listeria monocytogenes		781.25 μg/ml	
			Bacillus subtilis		781.25 μg/ml	
Syzygium legatii Burtt Davy & Greenway (*Myrtaceae*)	Leaves	Acetone	MDR *E. coli*	Prevent bacterial adhesion	50 μg/ml	(Famuyide et al., 2019)
Theobroma cacao L. (*Malvaceae*)	Beans	Methanol	*E. coli*	Cell membrane rupture	64 μg/ml	(Nayim et al., 2018)
			Klebsiella pneumoniae		64 μg/ml	
	Leaves	Methanol	*Enterobacter aerogenes*		256 μg/ml	
			K. pneumoniae		256 μg/ml	
Triumfetta welwitschia Mast. (*Malvaceae*)	Leaves	Acetone	*Pseudomonas aeruginosa*	Cell membrane rupture	100 μg/ml	(Mombeshora and Mukanganyama, 2019)

the biosynthetic machinery of the cell wall responsible for resistance to beta-lactam antibiotics (Palacios et al., 2014). The polyphenols extracted from sugar beet molasses can cause great damage to the bacterial cytoplasmic membrane, causing leakage and separation of the membrane and the cell wall. The antimicrobial mechanisms of the polyphenols that interact with membranes seem to revolve around the disruption of the plasma membrane by the accumulation of hydroxyl groups. This accumulation alters the hydrophobicity and surface charge of the membrane, triggering lipid segregation, local ruptures, pore formation and leakage, among other disruptive effects (Borges et al., 2013; Chen et al., 2017; Taguri et al., 2004).

In general, although lower antimicrobial potency is observed in plant extracts than in pure compounds, some plant extracts are very powerful. This is probably due to the synergy among the components of plant extracts, as this has already been reviewed not only for antimicrobial activity (Alvarez-Martinez et al., 2020a, 2020b; Tomas-Menor et al., 2015) but also for other relevant biological activities, such as anticancer activity (Herranz-Lopez et al., 2018) and improvement of metabolic diseases (Barrajón-Catalán et al., 2014; Herranz-Lopez et al., 2012; Olivares-Vicente et al., 2019).

Another group of plant agents that have been extensively studied are essential oils (EOs). Table 3 lists the essential oils studied during the period from 2016 to 2021 and their proposed mechanism of action.

The main antimicrobial action mechanism found in the EOs presented in Table 3 is related to the permeability increase and subsequent disruption of the plasma membrane. The antimicrobial activity of EOs is largely attributed to their terpene content. Although the mechanism of action of terpene is usually related to its interaction with membranes, the specific mechanisms remain poorly understood (Saad et al., 2013). The proposed specific molecular mechanisms of action of different terpenes are varied and depend fundamentally on their chemical structure. Certain terpenes, such as carvacrol, which have a phenolic OH group, can cross the bacterial plasma membrane, and can bind molecules such as ATP or monovalent cations such as K^+ and transport them out of the bacterial cell, seriously affecting the membrane potential and homeostasis (Hemaiswarya and Doble, 2009; Yang et al., 2015). Furthermore, the hydroxyl group is capable of binding and inhibiting proteins such as ATPase (Gill and Holley, 2006). Other terpenes, such as thymol, are capable of incorporating into the polar-head group region of the lipid bilayer, affecting the structural integrity and fluidity of the membrane (Di Pasqua et al., 2007). In addition, thymol has shown the ability to bind to membrane and periplasmic space proteins through hydrogen

Table 3
Essential oils with antibacterial activity described between 2016 and 2021. All the essential oils present in the table were obtained by hydrodistillation. MRSA: methicillin-resistant *Staphylococcus aureus*. VRE: vancomycin-resistant *enterococci*.

Plant	Bacteria	Mechanism	Activity (MIC)	Reference
Cuminum cyminum L. (*Apiaceae*)	MRSA *E. coli* Ciprofloxacin-resistant *E. coli*	Cell membrane rupture	580 μg/ml 290 μg/ml 290 μg/ml	(Owen et al., 2019)
Eucalyptus globulus Labill. (*Myrtaceae*)	*Lactobacillus spp* *Streptococcus mutans*	Cell membrane rupture and cell leakage	16 - 64 μl/ml (14,544 - 58,176 μg/ml) 64 μl/ml (58,176 μg/ml)	(Tardugno et al., 2018)
Eugenia caryophyllata Thunb. (*Myrtaceae*)	*Aeromonas hydrophyla* *Aeromonas salminicida*	Cell membrane rupture and disruption of DNA-related processes	190 - 1560 μg/ml 10 - 380 μg/ml	(Kot et al., 2019)
	Lactobacillus spp	Cell membrane rupture and cell leakage	4 - 16 μl/ml (4160 – 16,640 μg/ml)	(Tardugno et al., 2018)
	S. mutans		16 - 32 μl/ml (16,640 - 33,280 μg/ml)	
Lavandula × *intermedia* Emeric ex Loisel. (*Lamiaceae*)	*Lactobacillus spp* *S. mutans*	Cell membrane rupture and cell leakage	16 μl/ml (14,320 μg/ml) 16 μl/ml (14,320 μg/ml)	(Tardugno et al., 2018)
Leptospermum scoparium J.R.Forst. & G. Forst. (*Myrtaceae*)	*Lactobacillus spp* *S. mutans*	Cell membrane rupture and cell leakage	16 μl/ml (14,560 μg/ml) 32 μl/ml (29,120 μg/ml)	(Tardugno et al., 2018)
Melaleuca alternifolia (Maiden & Betche) Cheel (*Myrtaceae*)	*A. hydrophyla* *A. salminicida*	Cell membrane rupture and disruption of DNA-related processes	780 μg/ml 780 μg/ml	(Kot et al., 2019)
	Lactobacillus spp	Cell membrane rupture and cell leakage	16 - 32 μl/ml (14,368 – 28,736 μg/ml)	(Tardugno et al., 2018)
	S. mutans		32 μl/ml (28,736 μg/ml)	
Mentha arvensis L. (*Lamiaceae*)	*Lactobacillus spp*	Cell membrane rupture and cell leakage	4 - 16 μl/ml (3572 - 14,288 μg/ml)	(Tardugno et al., 2018)
	S. mutans		8 - 16 μl/ml (7144 - 14,288 μg/ml)	
Mentha × *piperita* L. (*Lamiaceae*)	*Lactobacillus spp*	Cell membrane rupture and cell leakage	1 - 16 μl/ml (898 - 14,368 μg/ml)	(Tardugno et al., 2018)
	S. mutans		4 - 16 μl/ml (3592 - 14,368 μg/ml)	
Myrtus communis L. (*Myrtaceae*)	*Lactobacillus spp*	Cell membrane rupture and cell leakage	1 - 2 μl/ml (912 - 1824 μg/ml)	(Tardugno et al., 2018)
	S. mutans		2 - 4 μl/ml (1824 - 3648 μg/ml)	
Origanum vulgare L. (*Lamiaceae*)	Fluoroquinolone-resistant *pneumococcus*	Cell wall and membrane rupture	1.25 - 5 μl/ml (1150 - 4600 μg/ml)	(Ghafari et al., 2018)
	Staphylococcus aureus MRSA VRE Ciprofloxacin-resistant *E. coli*	Cell membrane rupture	290 μg/ml 580 μg/ml 580 μg/ml 290 μg/ml	(Owen et al., 2019)
Pimenta dioica (L.) Merr. (*Myrtaceae*)	*Acinetobacter baumanii* MRSA *Psuedomonas aeruginosa*	Cell membrane rupture and leakage of *K*+ from cytosol	500 μg/ml 500 μg/ml 500 μg/ml	(Lorenzo-Leal et al., 2019)
Rosmarinus officinalis L. (*Lamiaceae*)	*A. baumanii*	Cell membrane rupture and leakage of *K*+ from cytosol	500 μg/ml	(Lorenzo-Leal et al., 2019)
	Lactobacillus spp	Cell membrane rupture and cell leakage	1 μl/ml (906 μg/ml)	(Tardugno et al., 2018)
	S. mutans		1 - 32 μl/ml (906 - 28,992 μg/ml)	
Salvia officinalis L. (*Lamiaceae*)	*Lactobacillus spp*	Cell membrane rupture and cell leakage	4 - 64 μl/ml (3648 - 58,358 μg/ml)	(Tardugno et al., 2018)
	S. mutans		16 μl/ml (14,592 μg/ml)	
Solidago canadensis L. (*Asteraceae*)	*Pseudomonas fluorescens*	Cell wall rupture	Inhibition zone 10–13 mm	(Elshafie et al., 2019)
Thymus capitatus (L.) Hoffmanns. & Link (*Lamiaceae*)	*Lactobacillus spp*	Cell membrane rupture and cell leakage	4 μl/ml (3800 μg/ml)	(Tardugno et al., 2018)
	S. mutans		8 - 16 μl/ml (7600 - 15,200 μg/ml)	
Thymus daenensis Celak. (*Lamiaceae*)	Fluoroquinolone-resistant *pneumococcus*	Cell wall and membrane rupture	0.625 - 2.5 μl/ml (587 - 2348 μg/ml)	(Ghafari et al., 2018)
Thymus vulgaris L. (*Lamiaceae*)	*A. hydrophyla* *A. salminicida*	Cell membrane rupture and disruption of DNA-related processes	390 - 1560 μg/ml 90 - 780 μg/ml	(Kot et al., 2019)
	Lactobacillus spp	Cell membrane rupture and cell leakage	4 μl/ml (3668 μg/ml)	(Tardugno et al., 2018)
	S. mutans		8 - 16 μl/ml (7336 - 14,672 μg/ml)	

bonding and hydrophobic interactions, slowing down the bacterial response to its antibacterial activity (Di Pasqua et al., 2010). Terpenes such as cinnamaldehyde have shown the ability to modify the lipid profile of the bacterial plasma membrane, inducing an increase in the presence of saturated fatty acids resulting in an increase in rigidity, probably triggered in response to the fluidifying action of the terpene (Di Pasqua et al., 2006). This phenomenon triggers membrane depolarization, loss of membrane integrity, reduced respiratory activity, and coagulation of cytoplasmic material (Bouhdid et al., 2010; Hyldgaard et al., 2012).

Synergy with antibiotics

Finding novel effective antibacterial compounds against MDR bacteria is a global health priority. Certain phytochemicals have been shown to have the ability to inactivate or weaken antibiotic resistance mechanisms by sensitizing bacteria to the action of antibiotics. This ability results in a synergistic action between certain phytochemicals

and antibiotics whose efficacy would be very low in the absence of phytochemicals. Some of phytochemicals are not active when used alone and only show relevant activity when they are administered together with an antibiotic. Other compounds show synergistic activity by other mechanisms, in addition to their own antimicrobial activity due to pleiotropic effects. Table 4 describes the latest plant agents with synergistic mechanisms with clinical antibiotics.

As shown in Table 4, the phytochemicals that have synergistic activity with antibiotics belong to various groups, and all of them have previously presented antimicrobial activity on their own. The most abundant agents in Table 4 are plant extracts and pure polyphenols. As the extracts are complex mixtures containing different compounds, the current studies are deficient in identifying which compound/s is/are responsible for the synergic interaction with the antibiotic/s, and new studies solving this drawback should be addressed in the future. The antibiotics used for these synergy studies are varied, as up to 17 different antibiotics belonging to 10 different chemical families have been used. The family of antibiotics with the greatest presence in synergistic trials are beta-lactams, such as penicillin, oxacillin or cefoxitin. Quinolones also have several representatives in the table, such as ciprofloxacin, levofloxacin or norfloxacin. Finally, the most common mechanisms of synergistic action are the inhibition of efflux pumps, followed by the inhibition of beta-lactamases and the permeabilization of membranes.

Recent studies suggest that plant extracts exert different antimicrobial activities against specific bacterial strains based on their antibiotic resistance profile (Atef et al., 2019). For example, the extract of *C. salviifolius* has shown greater potency against strains of *S. aureus* resistant to beta-lactam antibiotics, while the extract of *P. granatum* has shown greater potency against strains sensitive to quinolones and oxacillin (Alvarez-Martinez et al., 2021). This increased activity of the *C. salviifolius* extract against antibiotic-resistant strains, such as MRSA, can be attributed to the presence of flavonoids with certain elements in their chemical structure, such as -COOH and -OH groups in the *ortho* and *para* positions or an -O–CH_3 group in the *meta* position of the benzene ring (Friedman, 2015). The increased activity of the *C. salviifolius* extract may also be due to the existence of synergy between different classes of polyphenols, such as flavonoids and hydrolysable tannins (Tomas-Menor et al., 2015). This knowledge opens the door to the design of therapies based on phytochemicals applied in a personalized way based on the antibiotic resistance profile shown by the bacteria causing the infection.

New technologies for the discovery and novel application routes for plant antimicrobials

The latest technologies allow the efficient identification and characterization of new antimicrobial agents. The development of omics techniques, computational techniques and other new approaches beyond the classical ligand-target paradigm, such as network pharmacology and systems biology, has promoted the discovery and clarification of the mechanism of action of many plant compounds with remarkable antimicrobial potential (Chandran et al., 2017; Rempe et al., 2017; Santos et al., 2016; Yuan et al., 2017). In addition, advances in administration and vehicle techniques allow the revaluation of already discovered compounds, granting them a new, innovative and efficient application form.

Techniques such as transcriptomics, proteomics and metabolomics are essential when determining the molecular mechanisms of action of phytochemicals. Due to the union of these new technologies, it has been possible to determine the antimicrobial action mechanisms of *Diospyros kaki* L.f. (*Ebenaceae*) (persimmon) tannins and ursolic acid against MRSA, revealing multifactorial activity and pleiotropic effects at various levels (Liu et al., 2020; Wang et al., 2016).

Advances in bioinformatics and the increasing computers' computational capacity allow *in silico* tests or simulations capable of yielding highly valuable results. Molecular docking assays make it possible to predict the binding affinity of thousands of compounds against specific targets, allowing extensive libraries to be screened and the most promising compounds to be selected to progress to the next phases of research (Alvarez-Martinez et al., 2020a). Molecular docking tests have been carried out using the phytochemicals present in various plant species against key MRSA targets, such as PBP2a or PBP4a, or *P. aeruginosa*, such as FabZ, allowing the selection of the phytochemicals with the highest inhibitory activity and the best pharmacological properties (Geethalakshmi et al., 2018; Kuok et al., 2017). Another application of bioinformatics for the discovery of new antimicrobial phytochemicals lies in the prediction of the plants most likely to produce antimicrobials by using phylogenetic analysis (Prasad et al., 2019).

Due to synthetic chemistry and knowledge of the structures of natural antimicrobial compounds such as flavonoids, their antimicrobial capacity has been significantly increased through the chemical synthesis of tricyclic flavonoids. These synthetic flavonoids show MIC and MBC values as low as 0.24 μg/ml against *S. aureus* or 3.9 μg/ml against *E. coli* and are more potent than their natural predecessors (Babii et al., 2016). In addition, these synthetic flavonoids have shown antibiofilm capacity and low cell toxicity, making them good candidates for the development of new antimicrobial agents (Babii et al., 2018). Another example of the use of structural knowledge of natural components is the study of the main active molecules of the *Annona emarginata* (Schltdl.) H.Rainer (*Annonaceae*) extract. The *A. emarginata* flower extract demonstrated good antibacterial activity against MRSA with MIC up to 16 μg/ml. From this extract, bioassay-guided fractions were made to isolate the compound (*R*)−2-(4-methylcyclohex-3-en-1-yl) propan-2-yl(*E*)−3-(4-hydroxyphenyl) acrylate, which demonstrated increased antibacterial activity. Furthermore, thanks to the knowledge about chemical synthesis and structure-activity relationship, four new compounds with antimicrobial potential were created from the information obtained (Dolab et al., 2018).

A key element in designing antimicrobial therapies is the format and route of administration of the antimicrobial agent. As occurred with previous periods, most of the studies developed between 2016 and 2021 have used traditional routes of administration, mainly by dissolving the compounds in the right vehicle. However, new routes have been studied in recent years. At present, the possible application of natural antimicrobials in the gaseous state is being investigated, taking advantage of the volatility of certain compounds such as EOs. These volatile agents could be used to treat respiratory tract infections (Acs et al., 2018) or used as biopesticides (Rienth et al., 2019). Another novel method of administering antimicrobial phytochemicals, such as polyphenols, is their inclusion in reversible hydrogels (Hu et al., 2018) or in bioadhesives suitable for wound closure (Guo et al., 2018). Administration of nanoencapsulated phytochemicals (Cui et al., 2016; Lin et al., 2018) or phytochemicals in conjunction with nanoparticles (Majoumouo et al., 2019; Tiwari et al., 2020) has proven to be a promising strategy due to the enhancement of the antimicrobial activity of phytochemicals or the improvement of their physicochemical properties.

Conclusions and future prospects

The advent of new high-throughput molecular screening techniques and new discoveries in the field of proteomics, metabolomics, genomics and network pharmacology have allowed rapid advancement in the field of plant-based antimicrobials. In recent years, numerous antimicrobial phytochemicals have been discovered or better characterized. In most cases, their mechanisms of action have also been clarified.

Among the most active phytochemicals studied, polyphenols and terpenes stand out, either alone or as part of plant extracts or essential oils. The most common mechanisms of antimicrobial action are those related to the disruption of plasma membranes. The specific mechanisms of the polyphenols and terpenes that produce membrane alterations appear to be related to the alteration of the membrane potential produced by ion transport and binding to other molecules such as

Table 4
Plant origin compounds with antibacterial synergic activity with antibiotics described between 2016 and 2021. MDR: Multidrug resistant. MRSA: methicillin-resistant *Staphylococcus aureus*.

Plant extract	Plant part / solvent used	Synergy with	Bacteria	Mechanism	Reference
Anthocleista schweinfurthii Gilg (*Gentianaceae*)	Fruits / Methanol	Chloramphenicol	MDR *Enterobacter aerogenes* MDR *Klebsiella pneumoniae* MDR *Providencia stuartii* MDR *Pseudomonas aeruginosa*	Efflux pump inhibition	(Djeussi et al., 2016)
Daphne genkwa Siebold & Zucc. (*Thymelaeaceae*)	Not disclosed. Purchased from Runxue Biological Company (Xi'an, China)	Gentamicin Oxacillin	MRSA	PBP2a and PBP4 inhibition	(Kuok et al., 2017)
*Melissa officinalis*L. (*Lamiaceae*)	Not disclosed. Purchased from Ruikang Biological Company (Shanxi, China)	Gentamicin Oxacillin	MRSA	PBP2a and PBP4 inhibition	(Kuok et al., 2017)
Punica granatum L. (*Lythraceae*)	Leaves / Acetone and water	Amoxicillin Cefotaxime	Penicillin-resistant *E. coli* Penicillin-resistant *Staphylococcus aureus* MDR *E. coli* MRSA	Cell membrane rupture, inhibition of penicillinase activity and biofilm inhibition	(Trabelsi et al., 2020)
Smilax china L. (*Smilacaceae*)	Stems / Ethanol, water and ethyl acetate	Penicillin Streptomycin Penicillin Streptomycin	*E. coli* *S. aureus*	Cell membrane rupture and cell wall composition alteration	(Xu et al., 2019)
Valeriana officinalis L. (*Caprifoliaceae*)	Not disclosed. Purchased from Ruikang Biological Company (Shanxi, China)	Gentamicin Oxacillin	MRSA	PBP2a and PBP4 inhibition	(Kuok et al., 2017)
Zehneria scabra Sond. (*Cucurbitaceae*)	Whole plant / Methanol	Chloramphenicol Streptomycin	MDR *E. aerogenes* MDR *K. pneumoniae* MDR *E. aerogenes* MDR *P. aeruginosa*	Efflux pump inhibition	(Djeussi et al., 2016)
Essential oil	**Plant part / method used**	**Synergy with**	**Bacteria**	**Mechanism**	**Reference**
Origanum vulgare L. (*Lamiaceae*)	Leaves / Hydrodistillation	Ciprofloxacin	MDR *Streptococcus pneumoniae*	Efflux pump inhibition	(Ghafari et al., 2018)
Thymus daenensis Celak. (*Lamiaceae*)	Leaves / Hydrodistillation	Ciprofloxacin	MDR *S. pneumoniae*	Efflux pump inhibition	(Ghafari et al., 2018)
Compound	**Type**	**Synergy with**	**Bacteria**	**Mechanism**	**Reference**
Caffeic acid	Phenylpropanoid (cinnamic acid derivative)	Ciprofloxacin Gentamicin Tetracycline	MDR *K. pneumoniae*	Efflux pump inhibition	(Dey et al., 2016)
		Cefoxitin Clindamycin Erythromycin	MRSA	Cell membrane rupture	(Kepa et al., 2018)
Carnosic acid	Terpene (diterpene)	Gentamicin		Efflux pump inhibition	(Vazquez et al., 2016)
Conessine	Steroid alkaloid	Cefotaxime Erythromycin Levofloxacin Novobiocin Rifampicin Tetracycline	MDR *P. aeruginosa*	Efflux pump inhibition	(Siriyong et al., 2017)
Epigallocatechin gallate	Polyphenol (catechin ester)	Ciprofloxacin Gentamicin Tetracycline	MDR *K. pneumoniae*	Efflux pump and biofilm inhibition	(Dey et al., 2016)
Hibicuslide C	Naphtol derivative	Norfloxacin	MDR *P. aeruginosa*	Biofilm inhibition	(Lee et al., 2016)
Kaempferol	Flavonoid (flavonol)	Penicillin	MDR *S. epidermidis*	Inhibition of peptidoglycan synthesis, β-lactamase activity, decrease in fatty acids and increase of cytoplasmic membrane permeability	(Siriwong et al., 2016)
Lectin from *Alpinia purpurata* (Vieill.) K.Schum. (*Zingiberaceae*)	Protein	Oxacillin Ceftazidime	Oxacillin-resistant *S. aureus* MDR *P. aeruginosa*	Pore formation and protein leakage Alteration of membrane permeability and nutrient uptake	(Ferreira et al., 2018)
Quercetin	Flavonoid (flavonol)	Amoxicillin	MDR *Staphylococcus epidermidis*	Inhibition of peptidoglycan synthesis, β-lactamase activity, decrease in fatty acids and increase of cytoplasmic membrane permeability	(Siriwong et al., 2016)
Rutin	Flavonol glycoside	Florfenicol	MDR *Aeromonas hydrophila*	Biofilm inhibition	(Deepika et al., 2019)

membrane proteins. There are also compounds that can insert into the lipid bilayer or bind to it with great affinity, causing structural changes that lead to increased permeability, resulting in leakage or alteration of bacterial homeostasis. The presence of hydroxyl groups in certain positions of phenolic rings, double bonds, and delocalized electrons and conjugation with sugars in the case of flavonoids are common elements in the compounds with the highest antimicrobial capacity. Regarding the synergy with traditional antibiotics, the most studied combination was that of phytochemicals with beta-lactam antibiotics. The most common mechanisms of synergistic action are the inhibition of efflux pumps, followed by the inhibition of beta-lactamases and the permeabilization of membranes.

One of the pending challenges for many phytochemicals is to find effective routes and forms of administration able to release the active antimicrobial compound at the target site in systemic infections. Another challenge still unsolved is the need to determine the compounds responsible for the antimicrobial activity in complex mixtures, such as extracts and essential oils, and their potential pharmacological interactions. The development of current and new technologies will facilitate the substantial discovery of antibacterial phytochemicals in the near future, as well as the elucidation of complete multifactorial mechanisms of action beyond the classical ligand-target paradigm. For this purpose, the use of modern technologies, antimicrobial tests with internationally recognized standardized protocols and the use of plant material with their corresponding quality controls are essential.

Declaration of Competing Interest

We confirm that there are no known conflicts of interest associated with this publication.

CRediT author statement

Who wrote the paper draft? Who corrected the draft? Who supervised the experimentators? Who performed the experiments? All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

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