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Success stories of natural product-derived compounds from plants as multidrug resistance modulators in microorganisms

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Microorganisms evolve resistance to antibiotics as a function of evolution. Antibiotics have accelerated bacterial resistance through mutations and acquired resistance through a combination of factors. In some cases, multiple antibiotic-resistant determinants are encoded in these genes, immediately making the recipient organism a "superbug". Current antimicrobials are no longer effective against infections caused by pathogens that have developed antimicrobial resistance (AMR), and the problem has become a crisis. Microorganisms that acquire resistance to chemotherapy (multidrug resistance) are a major obstacle for successful treatments. Pharmaceutical industries should be highly interested in natural product-derived compounds, as they offer new sources of chemical entities for the development of new drugs. Phytochemical research and recent experimental advances are discussed in this review in relation to the antimicrobial efficacy of selected natural product-derived compounds as well as details of synergistic mechanisms and structures. The present review recognizes and amplifies the importance of compounds with natural origins, which can be used to create safer and more effective antimicrobial drugs by combating microorganisms that are resistant to multiple types of drugs.

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1. Introduction

Multidrug-resistant microorganisms (MDRMOs) are progressively being regarded as a major global health challenge.^{1,2} As a result of conventional antibiotic pressure, bacterial efflux pumps were increased, reducing drug concentrations; enzymes were induced to modify and inactivate antibiotic compounds; or the drug target site was elevated, reducing antibiotic potency (Fig. 1).^{3,4}

Infections by pathogenic bacteria, especially those that are multidrug resistant (MDR), are leading to a growing global health crisis. As a result, MDR bacteria can spread rapidly in hospitals and in the community, posing a staggering burden on health care systems both economically and epidemiologically.⁵ In addition, the inability of current clinical technologies to accurately diagnose infections in a timely manner further aggravates the resistance situation.⁶ By 2050, the number of antimicrobial resistance-related deaths could amount to 10 million, which is far more than the number of cancer deaths.² As we approach the postantibiotic era, normal infections and minor injuries will no longer be treatable. However, in contrast

to the rapidly spreading threat of antibiotic resistance, recent decades have seen a dramatic decline in new antibiotic development, with many pharmaceutical companies abandoning antibiotic discovery programs. Due to the subsiding development of antibiotics, alternative therapeutics are needed to treat MDR bacteria, and antimicrobial stewardship necessitates urgent action to stop the evolution of resistance and prevent the emergence of new resistance.

Drug development is aided by natural compounds, especially in regard to the discovery of antimicrobial drugs.^{7–9} Microorganisms have become increasingly resistant and the use of antibiotics is causing numerous side effects, making it essential to develop new and improved antibacterial agents using plant-based derivatives.^{10,11} The purpose of this review is to discuss compounds of natural products and derivatives derived from plants that have been investigated as modulators of MDR by inhibiting or otherwise stopping their activity.

2. Molecular antibiotic resistance mechanisms

By overusing antibiotics, microbes have evolved resistance to many conventional antimicrobials. There are several mechanisms that can lead to drug resistance in microbes, including inactivation or modification of antimicrobial drugs, alteration of drug target sites and expulsion of antimicrobial drugs across

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synthesis. A variety of ribosome-targeting antibiotics have been identified as having antibiotic-resistance mechanisms.^{39–41} How antibiotics become resistant is fairly well understood, as well as their clinical significance. In some cases, ribosome target sites can be mutated or modified to reduce or eliminate the ability to bind antibiotics. A variety of enzymes can degrade, modify, or excrete antibiotics directly from the cell. Thus, the intracellular concentration is reduced from toxic to nontoxic.

2.3. Expellers: pump out antimicrobial agents

2.3.1 Efflux. One possible mechanism for multidrug resistance is the overexpression of efflux pumps. There are currently six family members of bacterial efflux pumps associated with efflux pathways. In one pump, ATP is directly used to drive transport *via* ATP-binding cassettes (ABCs). Five more types of active transporters utilize transmembrane gradients to capture electrochemical energy; these transporters are the major facilitator superfamily (MFS), the multidrug and toxin extrusion (MATE) family, the small multidrug resistance (SMR) family, the resistance-nodulation-cell division (RND) superfamily and the proteobacterial antimicrobial compound efflux (PACE) family.

The association between efflux and drug resistance was first described over 40 years ago. For drug resistance to be effective, there must be an equal or greater amount of efflux than influx. In turn, drug entry is determined by the composition of the cell envelope and the presence of porins or other entry channels. There is no doubt that porin loss can contribute to resistance, and it has been observed to occur during treatment.^{42,43} Additionally, several cases of efflux-mediated resistance have been reported among clinical isolates, some of which involve the overexpression of pumps.

It is essential to have a clear understanding of efflux regulation because the overexpression of efflux proteins is caused by alterations in the regulatory system and transcriptional regulator mutations, including local and global mutations.^{44,45} There can be differences in efflux regulation between species, as well as within species, based on the physiological state of the cell. There are many pumps that are interconnected and regulated by complex circuits. Inhibiting or deleting one pump can lead to the expression of others.^{46–48} This complicates the interpretation of resistant phenotypes caused by efflux pump networks.

2.4. Decreased intracellular concentration

2.4.1 Decreased membrane permeability. Decreasing the degree of membrane permeability may increase the antibiotic resistance. By mediating the transport of molecules, the pores in the outer membrane play a critical role in the resistance and virulence of *Acinetobacter baumannii* (*A. baumannii*) strains. The decrease in membrane pore protein density of *Acinetobacter A. baumannii* was associated with increased carbapenem resistance.^{49,50} As another membrane porin involved in *A. baumannii*, OmpA has been reported to be resistant to aztreonam, chloramphenicol, and nalidixic acid. Studies have shown that OmpA increases virulence, lung infection, sepsis, and mortality.^{51–53}

3. MDR modulators of natural product-derived compounds from plants

Even though bioactive molecules with plant origins are utilized for a variety of purposes, the use of these molecules for fighting MDR bacteria and restoring the effectiveness of antibiotics in clinics has largely been ignored. According to medicinal chemists, natural products are miscellaneous molecules that have evolved to interact with a wide variety of protein targets to accomplish specific goals.^{54–57} Hence, natural sources are considered to be an advantageous source for discovering new antimicrobial molecules. Over half of the drugs approved by the American Food and Drug Administration (FDA) are based on or inspired by natural products.

The necessary starting materials for drug discovery that are used by pharmaceutical companies have always been provided by nature, since these materials have always solved many complex clinical problems. Natural products have been studied extensively as modulators of MDRs. The MDR modulators of natural product-derived compounds from plants are summarized in Table 1 as three major categories: flavonoids, alkaloids and terpenoids.

3.1. Flavonoids

Among the most important classes of phenolic compounds are flavonoids, which are plant secondary metabolites in non-glycosylated (aglycones) or glycosidic states. In addition to the 2-phenylchromane ring system, flavonoids also have different subclasses depending on the substitution at ring B and oxidation status of ring C.^{58,59} There has been considerable evidence that flavonoids possess a variety of pharmacological properties, including anticancer, anti-inflammatory, and antiviral properties.^{60–62} Additionally, flavonoids have been found to exhibit antibacterial properties against many pathogenic microorganisms, such as *Staphylococcus aureus* (*S. aureus*), *Vibrio harveyi*, *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Enterococcus faecalis* (*E. faecalis*).^{63–65} There are over 8000 known flavonoids in plants, making them a potentially valuable resource for new antibiotic discoveries. We reviewed the potential antimicrobial activity of flavonoids against fungal and bacterial infections in Sections 3.1.1–3.1.13, and their structure was shown in Fig. 2.

3.1.1 Isobavachalcone (IBC) and α -mangostin (AMG). Analyses of structure-activity relationships show that prenylation modulates their activity in flavonoids and produces two compounds, isobavachalcone (IBC) and α -mangostin (AMG). Additionally, AMG and IBC are bactericidal against Gram-positive bacteria and restore the susceptibility of colistin against Gram-negative bacteria. AMG and IBC had MIC₅₀ values of 0.5 $\mu\text{g mL}^{-1}$ and MIC₉₀ values of 4–8 $\mu\text{g mL}^{-1}$ against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE), respectively. AMG and IBC are capable of targeting almost all kinds of phospholipids in bacterial membranes and involve faster time-killing



Table 1 Natural product-derived compounds from plants as multidrug resistance modulators in microorganisms^a

Classification	Compound	Source	Antibacterial activity	Mechanism	Reference
Flavonoids	(1) Isobavachalcone (IBC)	Psoralen	MRSA and VRE (MIC ₅₀ : 0.5 µg mL ⁻¹ ; MIC ₉₀ : 4–8 µg mL ⁻¹)	Membrane homeostasis	66
	(2) α-Mangostin (AMG)	—	<i>P. aeruginosa</i> and <i>A. baumannii</i> (MIC: 16–256 µg mL ⁻¹)	Enzyme inhibition and efflux pump inhibition	67
	Quercetin	—	ATCC 25922 (MIC: 1 µg mL ⁻¹)	—	—
	(1) 3,7-Diacylquercetin	Quercetin	<i>E. coli</i> clinical isolates (MIC: 64 µg mL ⁻¹)	Enzymatic inhibition (DNA gyrase and topo IV)	69
	(2) Quercetin 6''-acylgalactoside	—	Multidrug-resistant gram-positive (MIC: 0.13 to 128 µg mL ⁻¹)	—	—
	(3) Quercetin 2'',6''-diacylgalactoside analogues	—	—	—	—
	(1) Procyanidin B3-3-O-gallate	<i>W. uniflora</i>	MRSA	Abnormal cell formation	71
	(2) Rhamnetin 3-O-(6''-galloyl)-β-D-glucopyranoside	—	—	—	—
	(3) Rhamnetin 3-O-α-L-rhamnopyranoside	—	—	—	—
	(4) Quercetin 3-O-(6''-galloyl)-β-D-glucopyranoside	—	—	—	—
Alkaloids	(1) Isobavachalcone;	—	<i>E. coli</i> AG100A and <i>E. aerogenes</i> EA298 isobavachalcone (MIC: 8 µg mL ⁻¹)	Efflux pump components (AcrAB, TolC)	72
	(2) Diospyrone	—	Diospyrone (MIC: 4 µg mL ⁻¹)	—	—
	Lupinifolin	<i>Albizia myriophylla</i>	MDR enterococcal clinical isolates (MIC: 0.5 and 2.0 µg mL ⁻¹)	Membrane permeability and salt tolerance	73
	Phloretin	Apple	<i>E. coli</i> ZJ478 or <i>Salmonella</i> sp. Strain (MIC: 2 µg mL ⁻¹)	Cell membranes	74–76
	Type A procyanidin (TAP)	<i>Cinnamomum zeylanicum</i>	UPEC	Biofilm formation	77
	Artonin I	<i>Morus mesozygia</i> Stapf	MDR bacterial (MIC: 4–8 mg L ⁻¹)	Efflux pump and cell membrane	78
	AFPO	Chalcones	<i>S. aureus</i> 10 strain (MIC: 1024 µg mL ⁻¹)	Internal resistance mechanism	79
	3',4',7-trihydroxyflavone	Kernel	<i>E. coli</i> 06 strain (MIC: 256 µg mL ⁻¹)	—	—
	Epicatechin gallate (ECg)	Green tea	<i>P. stuartii</i> ATCC299645 (MIC: 4 µg mL ⁻¹)	Efflux pumps	80
	—	—	<i>S. aureus</i> BB568, EMRSA-15, EMRSA-16 (MIC: 128 mg L ⁻¹)	Cell membrane	89
Alkaloids	Curcumin	—	<i>A. baumannii</i> (MIC >256 µg mL ⁻¹)	—	65
	Epigallocatechin gallate	Green tea	<i>A. baumannii</i> (MIC >128–1024 µg mL ⁻¹)	—	65
	Eriodictyol	Citrus fruits	<i>S. aureus</i> USA 300 (MIC >512 µg mL ⁻¹)	Inhibitor of SrtA	92
	Rutin	—	<i>K. pneumoniae</i> ATCC700603 (MIC: 1024 µg mL ⁻¹)	Downregulated <i>luxS</i> gene and <i>wabG</i> gene	63
	Baicalcin	—	<i>E. coli</i> ATCC25922 (MIC: 512 µg mL ⁻¹)	Cell wall and Tet K-mediated tetracycline efflux	70
	—	—	MRSA	—	—
	Ursolic acid (UA)	Apple pomace	CRKP (MIC: 0.8 mg mL ⁻¹)	Cell membrane integrity	93
	5-Hydroxy-3,7,4'-trimethoxyflavone	<i>V. gardneriana</i>	MDR bacterial strains <i>S. aureus</i> 358 and <i>E. coli</i> 27 (MIC ≤512 µg mL ⁻¹)	—	94
	Compound 1f (with a 7-phenyl group)	7-Substituted cyclophosphamide (CBBR)	MRSA and VRE (MIC: 1–8 µg mL ⁻¹)	DNA Topo IV ParE subunit	102
	1,4-Naphthoquinones	—	MRSA (MIC: 0.0078 to 0.125 mg mL ⁻¹)	—	103
	Chelerythrine (CHE)	—	CRSM (MIC: 125 mg mL ⁻¹)	Integrity of the cell membrane	105



Table 1 (Contd.)

Classification	Compound	Source	Antibacterial activity	Mechanism	Reference
Terpenoids	Berberine hydrochloride (BBH)	Berberine	MDR <i>A. baumannii</i> (MIC: 256 mg L ⁻¹)	AdeB and AdeB transporters	106
	Piperine	White pepper	MDR strains of <i>P. aeruginosa</i> , <i>E. coli</i> (in the presence of 125 mg mL ⁻¹)	—	107
	Squalamine	Dogfish shark squalus acanthias	<i>P. aeruginosa</i> ATCC 27853 (MIC: 8 mg L ⁻¹) <i>E. coli</i> ATCC 25922 (MIC: 4 mg L ⁻¹) <i>S. aureus</i> ATCC 25923 (MIC: 2 mg L ⁻¹) <i>S. aureus</i> ATCC 29213 (MIC: 0.03 µg mL ⁻¹)	Cell membranes	108
	N-tetradecyl derivative (BnL-14)	Quaternary ammonium compounds (QACs)	<i>S. aureus</i> ATCC 29213 clinical/MRSA (MIC: 0.12 µg mL ⁻¹) <i>E. coli</i> clinical (MIC: 0.98 µg mL ⁻¹) <i>Candida albicans</i> arborinine (MIC: 250 µg mL ⁻¹)	Membrane disruption and DNA	110
	Arborinine	<i>R. angustifolia</i>	Arborinine (MIC: 500 µg mL ⁻¹) <i>P. aeruginosa</i> (MIC: 400 mg L ⁻¹)	ICL1 gene	111
	Catharanthine	<i>Catharanthus roseus</i>	—	Efflux pump proteins MexA, MexB and OprM	113
	Chanoclavine	<i>I. muricata</i>	<i>E. coli</i>	Efflux pumps and the cell envelope	115
	Limonene	—	<i>E. coli</i> (MIC: 16 µg mL ⁻¹)	Cell membrane and DNA transcription and translation	118 and 119
	Carvacrol	—	<i>S. aureus</i> (MIC: 256 µg mL ⁻¹)	Efflux pump inhibition	120 and 122
	Thymol	—	—	Efflux pump	121
	Oleanolic acid	—	<i>E. faecalis</i> (MIC: 6.25 mg L ⁻¹) MRSA COL _{oxa} (MIC: 1600 mg L ⁻¹) MRSA-ST1745/ST2071/P4620 (MIC: 31.25 µg mL ⁻¹) MRSA-P4627/P4423/ST3151 (MIC: 15.62 µg mL ⁻¹)	EtBr efflux	123
	Clerodane diterpene 16α-hydroxycyclo-3,13(14)-Z-dien-15,16-olide (CD)	<i>Polyalthia longifolia</i>	—	Cell wall integrity and cell adhesion	124
	Geraniol (Ger)	Geranium oil	<i>C. albicans</i> (MIC: 225 µg mL ⁻¹)	—	125
	Oleanane triterpenoid aegicerin	<i>Clavija procera</i>	MTB (MIC: 1.6-3.12 µg mL ⁻¹)	mRNA expression of qnrB and qnrS	126
	Artesunate (ART)	<i>Artemisia annua</i> L	MDR <i>E. coli</i> isolates	—	127
Conjugates	Glycyrrhizin (GLY)	<i>Glycyrrhiza glabra</i>	MDR9 (MIC: 40 mg mL ⁻¹) B1045 (MIC: 15 mg mL ⁻¹) <i>S. aureus</i> (MIC: 20 µg mL ⁻¹) <i>E. coli</i> (MIC: 20 µg mL ⁻¹)	—	129
	Conjugates	—	—	—	129
1,8-Cineole	1,8-Cineole	Rosemary volatile oil	<i>E. coli</i>	Biofilm biomass disruption	135

^a MRSA, methicillin-resistant *Staphylococcus aureus*; VER, vancomycin-resistant *Enterococcus*; MIC₉₀, lowest drug concentration inhibiting 90% of bacterial or fungi growth; MIC, minimum inhibitory concentration; MDR, multidrug-resistant; UPEC, Uropathogenic *Escherichia coli*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRSM, carbapenem-resistant *Serratia marcescens*.

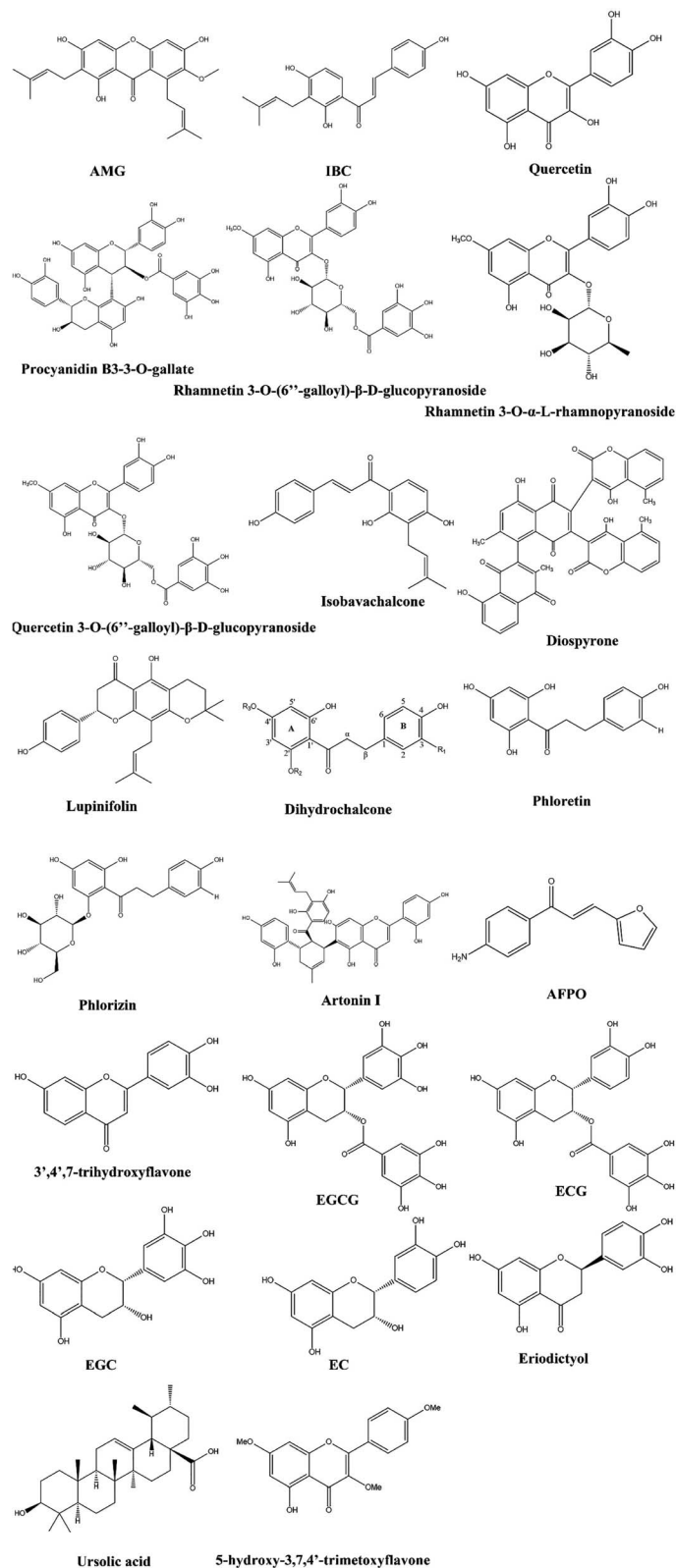


Fig. 2 Structure of flavonoids having MDR modulatory activity.

dynamics than that of nearly all antibiotics currently used in clinics, including vancomycin. Despite their ability to disrupt membranes, these agents are unlikely to develop resistance to

antibiotics, since bacteria are unable to change their membranes without losing functions.⁶⁶ In mice, AMG or IBC single-dose models were constructed for wound infection and



intestinal colonization of *S. aureus*. The results showed that by using AMG and IBC, it may be possible to reduce the number of foodborne bacterial infections and poisonings.

3.1.2 Quercetin. In 2002, Denny *et al.* demonstrated for the first time that quercetin inhibited L1 metallo- β -lactamase.⁶⁷ At high concentrations, quercetin has been found to inhibit Gram-positive and Gram-negative bacterial growth. By inhibiting blaNDM expression, quercetin could potentiate meropenem activity. The combination of quercetin-meropenem induced bacterial death by altering cell morphology and disrupting cell wall/membrane integrity, inhibiting carbapenem hydrolysis in periplasmic spaces and preventing bacterial efflux. Furthermore, quercetin inhibits carbapenemase and efflux pump activity in carbapenem-resistant *E. coli*, *Klebsiella pneumoniae*, *P. aeruginosa* and *A. baumannii*.⁶⁸ Das *et al.* (2019) identified naphthoate synthase (1,4-dihydroxy-2-naphthoyl-CoA synthase, EC: 4.1.1.3.36; DHNS, *EfdHNS*) as an anti-*E. faecalis* target in novel antibacterial drugs. Moreover, quercetin inhibits *EfdHNS* catalytic activity, potentially allowing the use of quercetin for the treatment of MDR *E. faecalis* infections.⁶⁹ According to structure-guided molecular design, quercetin diacylglycoside analogs were optimized, including 3,7-diacylquercetin, quercetin 6''-acylgalactoside, and quercetin 2'',6''-diacylgalactoside analogs, which exhibited four times greater activity against Gram-positive bacteria than that of previous compounds. A possible mechanism of action of this drug is to inhibit bacterial DNA gyrase and topoIV enzymes simultaneously. More importantly, its acute toxicity in mice was very low, as well as realistic *in situ* intestinal absorption in rats.⁷⁰ In another study, quercetin significantly enhanced the tetracycline sensitivity of *E. coli*. According to further studies, the combination therapy causes profound ultrastructural changes in the cells that result in an increase in permeability and a weakening of the cell envelope.⁷¹

3.1.3 The methanolic extract of *W. Uniflora*. Based on phytochemical analysis of the methanolic extract of *W. uniflora* leaves coupled with LC/MS analysis, the following flavonoid analogs (1–4) were isolated: procyanidin B3-3-*O*-gallate (1), rhamnetin 3-*O*-(6''-galloyl)- β -D-glucopyranoside (2), rhamnetin 3-*O*- α -L-rhamnopyranoside (3), and quercetin 3-*O*-(6''-galloyl)- β -D-glucopyranoside (4). In addition to inhibiting MRSA biofilm formation, these compounds also synergize with methicillin. Compounds achieved this synergistic effect by remodeling metabolism, and defects in central carbon metabolism and glutamine biosynthesis led to abnormal MRSA cell formation and a reduction in biofilm formation. Moreover, rhamnetin 3-*O*-(6''-galloyl)- β -D-glucopyranoside (2) and quercetin 3-*O*-(6''-galloyl)- β -D-glucopyranoside (4) showed no significant cytotoxicity.⁷²

3.1.4 Isobavachalcone and diospyrone. Isobavachalcone and diospyrone were evaluated against multidrug-resistant (MDR) Gram-negative bacteria. The results showed that both compounds had intrinsic antibacterial properties against Gram-negative bacteria, and in the presence of an efflux pump inhibitor, their activity was significantly enhanced (MIC values decreased to below 10 $\mu\text{g mL}^{-1}$). A significant increase in activity was also observed for diospyrone, and isobavachalcone was shown to be efficient against strains that have deletions of

major efflux pump components (AcrAB, TolC). As a result of the study, it appears that isobavachalcone and diospyrone could be used as new antimicrobials against MDR bacteria, particularly by combining them with efflux pump inhibitors, which reinforces their activity.⁷³

3.1.5 Lupinifolin. Lupinifolin, a prenylated flavonoid extracted from *Albizia myriophylla Benth.*, was shown to exhibit a potent antimicrobial effect on enterococci. The bacterial membrane is damaged by lupinifolin, which inhibits *S. aureus* and *Streptococcus mutans* growth. Significantly reducing the salt tolerance of lupinifolin-disrupted bacterial cell membranes can also cause the membranes to lose their ability to osmoregulate effectively or to exclude toxic materials, eventually causing arterial cell death. As lupinifolin penetrated and passed through the cell wall of *S. mutans*, lupinifolin was observed in the cytoplasm of lupinifolin-treated cells. By doing so, lupinifolin disrupts the integrity of the cytoplasmic membrane, resulting in the death of the bacteria. Research on lupinifolin's antibacterial activity against a variety of MDR enterococci clinical isolates has furthered our understanding of its properties and mechanisms.⁷⁴ In light of this, lupinifolin could play a critical role in fighting MDR enterococcal infections. There is potential for this compound to be developed into a new potent therapeutic agent.

3.1.6 Dihydrochalcone. Apples contain a specific group of flavonoids called dihydrochalcones, which possess a chemical structure of C6–C3–C6, and there is no direct link between the A-ring and B-ring; instead, a flexible C3 chain connects them. It was found that dihydrochalcones exhibited excellent antibacterial properties against both Gram-positive and Gram-negative bacteria. The glycosylation of the A-ring at the 2'-position, as well as the hydroxyl group at the 3-position of the B-ring, was important for the antibacterial activity of dihydrochalcones. A positive correlation might exist between dihydrochalcone hydrophobicity and its antibacterial properties. Dihydrochalcones act mainly by damaging cell membranes in antibacterial mechanisms.⁷⁵ Despite this, strain type also influenced antibacterial mechanisms. The most abundant dihydrochalcone compound in apple is phlorizin, which accounts for 60–90% of the overall flavonoids. Gram-positive bacteria were inhibited by phloretin, which exhibited the highest levels of antimicrobial activity, especially *S. aureus* ATCC 6538, *L. monocytogenes* ATCC 13932, methicillin-resistant *S. aureus* clinical strains and *S. typhimurium* ATCC 13311. Considering that C20 contains a free hydroxyl group, it can be assumed that glycosyl molecules, or their absence, play an important role in interactions with other biological molecules, and C20, C30, and C50 glycosylated structures demonstrate dramatic decreases in antimicrobial activity. In addition, this compound's antimicrobial activity can be understood through the analysis of cytosolic enzymes from *S. aureus*. Essentially, phloretin inhibits *S. aureus* energetic metabolism by lowering lactate dehydrogenase (LDH) and isocitrate dehydrogenase (IDH) enzyme activity. It significantly inhibits catalase activity and determines the use of biological fuels (sugars, fatty acids, amino acids) by bacteria and its ability to deal with oxidative damage.⁷⁶ Phloretin restored polymyxin E's sensitivity to *E. coli*



had a strong interaction during fluorescence quenching experiments. In subsequent mechanistic studies, eriodictyol was shown to interact with the R197 amino acid residue of SrtA. Moreover, eriodictyol inhibited adhesion-dependent invasion of A549 cells by *S. aureus* and was effective in treating mouse pneumonia.⁹³

3.1.13 Other flavonoids. Rutin, a flavonoid, induces luxS and wabG gene expression to inhibit *K. pneumoniae* in biofilm cells. A positive correlation was observed between biofilm biomass and the type III fimbriae biosynthesis gene mrkA.⁶³

Through its direct binding to the peptidoglycan in the cell wall, baicalein can work synergistically with tetracycline to compromise the integrity of the cell wall. In addition to inhibiting Tet K-mediated tetracycline efflux, baicalein inhibits Tet M and other pumps that are responsible for methicillin-resistant *S. aureus* (MRSA) growth.⁷¹

An antimicrobial agent found in apple pomace, ursolic acid (UA), exhibits antimicrobial properties against some microorganisms. UA was found to be effective against *Klebsiella pneumoniae* (CRKP) at an MIC of 0.8 mg mL⁻¹. The drug disrupted CRKP's cell membrane integrity, inhibited biofilm formation, and inactivated cells that were encased in biofilms.⁹⁴

The compound 5-hydroxy-3,7,4'-trimethoxyflavone, which has a chemical formula of C₁₈H₁₆O₆, was isolated from the leaves of *V. gardneriana*. In combination with norfloxacin and gentamicin, this flavone exhibits antimicrobial activity against the

MDR bacteria *S. aureus* 358 and *E. coli* 27. Hence, this natural compound contributes to the control of resistant bacteria by increasing antibiotic activity.⁹⁵

3.2. Alkaloids

Compared to synthetic antibacterial agents, alkaloids have fewer side effects, a higher efficacy and superior antibacterial properties against both resistance acquired pathogens and nonresistance acquired pathogens.^{96,97} In addition, alkaloids combined with antibiotics increased their efficacy, reduced side effects, and increased their concentration.^{98–100} In addition to inhibiting protein synthesis and efflux pumps, alkaloids inhibit the formation of biofilms, inhibit drug deactivating enzymes, and destroy cell membranes and cell walls.^{101,102} Using this natural gift to its full potential requires advanced studies. A variety of advanced methods, such as virtual screening, molecular modeling, and biological studies, can be used to alter the properties of these substances. This new era of antimicrobial agents may arise through the development of these alkaloids (Fig. 3).

3.2.1 Cycloberberine (CBBR). A novel family of MRSA agents has been identified using cycloberberine (CBBR) scaffolds that were constructed from Chinese natural alkaline berberine (BBR). Based on the structure-activity relationship (SAR), this compound series was significantly more potent against both reference strains and MDR clinical isolates by substituting at C8 or C13 (Fig. 4A). CBBR 7-monosubstitution was the focus of the initial SAR study. After attaching aliphatic chains or rings to the C7 position, compounds **1a–e** (Fig. 4B) (with MIC values between 2 and 64 µg mL⁻¹) display moderate antimicrobial activity against all tested strains, which is better than CBBR. Furthermore, measurements were performed on compounds **1f–j** (Fig. 4B) with different substituted benzene groups, and compound **1f** showed promising activity against both MRSA and vancomycin-resistant *Enterococcus* (VRE) strains. In contrast to vancomycin, compound **1f** with a 7-phenyl group shows higher activity against MRSA and VRE, with MIC values of 1–8 µg mL⁻¹. Based on its rapid bactericidal action against MRSA, **1f** might target the DNA ParE subunits of Topo IV bacteria, suggesting that antibacterial drugs currently used have a different mode of action. Compared with SAR results at the C8 or C13 positions, a phenyl ring at the C7 position may enhance the antimicrobial spectrum. Further studies indicated that antimicrobial activity was dependent on the methylenedioxy ring.¹⁰³

3.2.2 1,4-Naphthoquinones. It was demonstrated that 1,4-naphthoquinones inhibit bacterial growth. In both Gram-positive and Gram-negative bacteria, bacteriostatic and bactericidal effects are observed with 1,4-naphthoquinone and plumbagin. In clinical strains of methicillin-sensitive *S. aureus* and MRSA, 1,4-naphthoquinone showed synergistic interactions with imipenem, cefuroxime, and cefotaxime. In MRSA cultured with ATCC, 1,4-naphthoquinone and cefotaxime have synergism. Combining 1,4-naphthoquinone with imipenem produced only an additive effect, while 1,4-naphthoquinone and cefuroxime had an antagonistic effect. While 1,4-

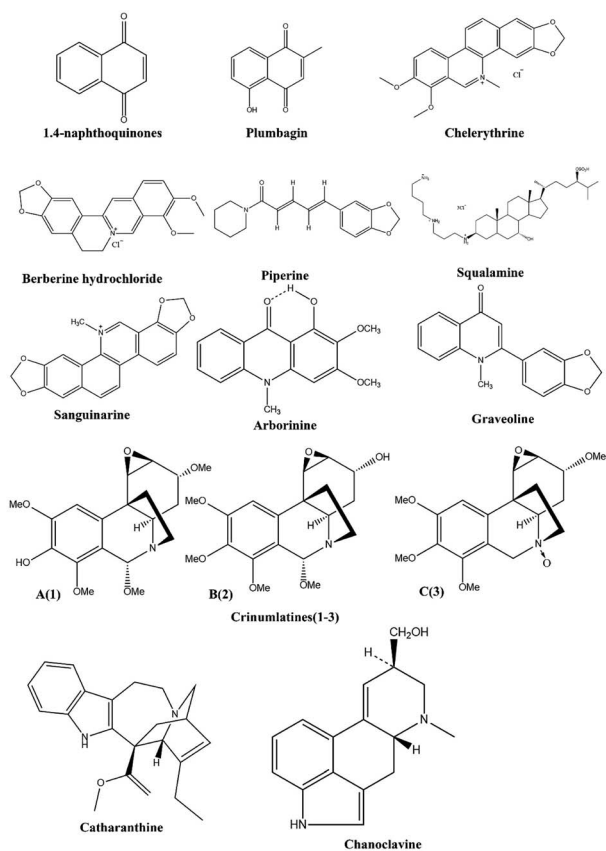


Fig. 3 Structure of alkaloids having MDR modulatory activity.

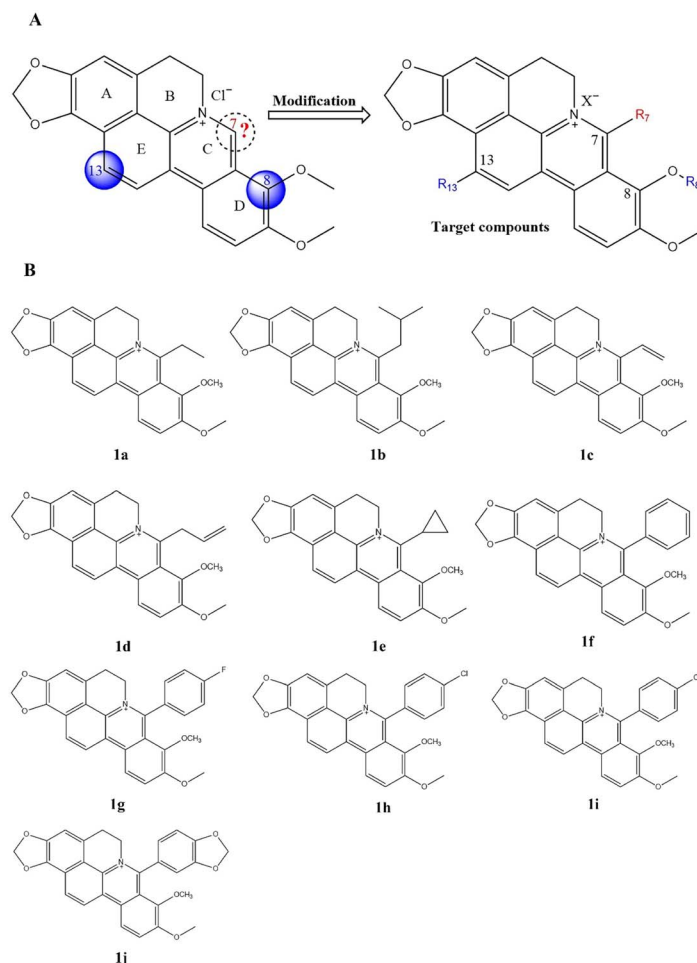


Fig. 4 (A) The chemical structure of CBBR and the structure modification strategy. (B.) the structure of the target compounds 1a–j.

naphthoquinone on its own is not as effective as common antibiotics, it synergizes with imipenem, cefuroxime, and cefotaxime in the treatment of MRSA, and it may be used as an adjunctive antibiotic to treat multidrug resistant bacteria.¹⁰⁴

3.2.3 Chelerythrine (CHE). The natural product chelerythrine (CHE) is a benzophenanthridine alkaloid with antimicrobial potential. In the case of methicillin-resistant *Staphylococcus aureus* and *E. coli* producing extended-spectrum β -lactamases, CHE greatly improved the antibacterial efficacy of the antibiotics.¹⁰⁵ CHE had an MIC of 125 mg mL⁻¹ against CRSM, inhibited growth and destroyed the integrity of the cell membrane, and clearly altered the morphology of the cell. Biofilm components are produced by sub-MIC CHEs, which showed robust inhibitory effects against CRSM biofilm formation. In addition, according to CLSM- and FESEM-mediated evaluation of biofilm damage and biofilm persistence, biofilms can be compromised by CHE at high concentrations and remove previously formed biofilms.¹⁰⁶

3.2.4 Berberine hydrochloride (BBH). Berberine hydrochloride (BBH) is the most common form of berberine. An *in vitro* study was conducted to determine the synergistic effects of BBH with antibiotics against MDR *A. baumannii*. There was weak antimicrobial activity for BBH alone against MDR *A.*

baumannii (MIC of 256 mg L⁻¹). A dramatic increase in susceptibility to antimicrobials when fractional inhibitory concentration index values <0.5 was achieved, even reversing the resistance of MDR strains. According to an *in vivo* study, BBH with sulbactam had greater antimicrobial effectiveness than that of monotherapy in neutropenic murine thigh infections. According to the antibiotic-sensitizing mechanism, boosting the expression of AdeB and binding to AdeB transporters resulted in a lower uptake of BBH, resulting in fewer antibiotics being extruded by the AdeABC pump. As a result of knockout of the *adeB* gene, BBH was more readily taken up by MDR strains, and resistance to antibiotics as well as synergistic effects between antibiotics and BBH were lessened. As a result, BBH effectively resensitizes this MDR pathogen to antibiotics that have become almost ineffective due to antibiotic resistance.¹⁰⁷ Due to this, BBH may work synergistically with antibiotics and have antibiotic-sensitizing activity against MDR *A. baumannii*.

3.2.5 Piperine. The growth of *V. cholerae*, an active ingredient of white pepper, with 200 and 300 μ g mL⁻¹ piperine was inhibited regardless of biotypes or serogroups. Piperine (in the presence of 200 μ g mL⁻¹) also showed growth inhibitory activity against MDR Gram-negative bacteria, including toxigenic *Vibrio*



cholerae, *Pseudomonas aeruginosa* and enterohemorrhagic/enteroaggregative *E. coli* O104 German outbreak strains.¹⁰⁸

3.2.6 Squalamine. Squalamine, a natural aminosterol, has been demonstrated to possess antibacterial properties against several drug-resistant bacteria and molds. A squalamine's positively charged amino group interacts with a Gram-negative bacteria's lipopolysaccharide's negatively charged phosphate groups. As a result of its depolarizing effect, it causes cell death in Gram-positive bacteria, similar to colistin (polymyxin drug). Colistin displaces the divalent cations (Ca^{2+} and Mg^{2+}) after forming a bond with LPS's phosphate groups.¹⁰⁹

3.2.7 Other alkaloids. *Chelerythrine*, an isoquinoline alkaloid, inhibits cellular division and nucleic acid synthesis. A protein called FtsZ, which contributes to Z ring formation during cell division, is tampered with by isoquinoline, inhibiting cellular division.¹¹⁰ The mechanism of action of quaternary ammonium compounds (QACs) targets the bacterial membrane, making them effective antimicrobial agents. For N-benzylimidazole, the synthesis of QACs based on imidazole derivatives, the activity varied in the range of the lowest inhibitory concentration (MICs) to 7 ng mL^{-1} . A bacterial biofilm-fighting compound, *n*-tetradecyl derivative (BnI-14), was also found to bind to DNA, implying interference with bacterial growth.¹¹¹ In Gram-positive and Gram-negative bacteria, sanguinarine inhibits cytokinesis by disrupting Z-ring assembly through binding to FtsZ and affecting the bundling of protofilaments.

Arborinine and graveoline exhibit inhibitory activity against *C. albicans* at 250 and 500 $\mu\text{g/mL}$, respectively. MIC/MFC indicated that these alkaloids played a bactericidal role. Analysis of gene and protein expression revealed effective effects for both compounds on ICL1 gene and protein expression. Hence, arborinine and graveoline appear to be promising inhibitors of ICL1 in *C. albicans* glyoxylate cycles.¹¹² A phytochemical investigation of the 90% ethanol aqueous extract of the bulbs of *Crinum latifolium* led to the isolation of three new crinane-type alkaloids, designated crinumlatines A-C (1–3). Compounds 1–3 exhibited some antimicrobial activity against the tested Gram-negative bacteria with minimum inhibitory concentration values less than $50 \text{ } \mu\text{g mL}^{-1}$.¹¹³

Catharanthine was deduced first through *in silico* inhibition of efflux pump proteins MexA, MexB and OprM. Catharanthine-induced efflux pump inhibition may be useful for lowering antibiotic doses, reducing drug resistance, and increasing the efficacy of old antibiotics against multidrug-resistant bacteria.¹¹⁴

Plants selected for anti-mastitis protection contain higher concentrations of phytochemicals, with alkaloids of *A. sativum* and *B. persicum* showing significant antibacterial activity compared to that of the other selections. Additionally, ATCC strains show greater inhibition of phytochemicals of tested plant species compared to that of MDR bacterial strains.¹¹⁵

We can see that chanoclavine may make it easier to repurpose antibiotics that have become nonfunctional because of acquired bacterial resistance. By inhibiting efflux pumps, weakening the cell envelope, and increasing cell growth, the

molecule synergizes with conventional antibiotics to target bacterial cell membranes or cell walls.¹¹⁶

3.3. Terpenoids

Terpenoids, which are abundant in nature and produced in response to microbial attack, have huge potential as antimicrobial agents through a variety of mechanisms, such as disruption of membranes, anti-quorum sensing, inhibition of protein synthesis and ATP.^{92,117,118} Combinations of terpenoids and antimicrobials, such as combination therapy, have increased the effectiveness of treatment against multidrug resistant microorganisms by showing synergy (Fig. 5).

3.3.1 Limonene. The antibacterial activity of limonene-containing essential oils has been demonstrated against resistant strains of *S. aureus*, *Salmonella enterica*, and *Listeria monocytogenes*. The mechanism may be due to the lipophilic properties of limonene. Limonene may cross the cell wall and alter the permeability of bacterial cell membranes.¹¹⁹ When *E.*

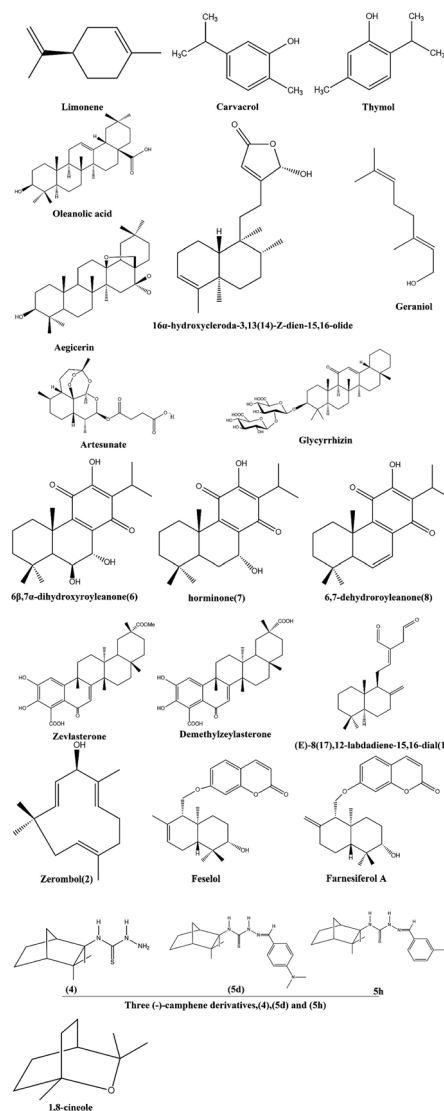


Fig. 5 Structure of terpenoids having MDR modulatory activity.

3.3.11 Conjugates. By computing docking scores for outlandish conjugates of SMZ and monoterpenes, effective agents against DHPs of five bacterial species can be identified. The docking scores for the monoterpenes or SMZ conjugates against five bacterial DHPs were also higher than those for monoterpenes or SMZ alone. In addition, conjugates have been shown to be safer antibacterial agents when both toxicity and LD50 values are taken into consideration. Conjugate 5 (SMZ + thymol) with docking scores greater than $-10.0 \text{ kcal mol}^{-1}$ was the most effective and safest antibacterial agent, while SMZ had docking scores of -8.46 and a high LD50 value of 3500 mg kg^{-1} .¹³⁰

3.3.12 Farnesol. By inhibiting biofilm resistance, farnesol, a QSM secreted by *C. albicans*, affects the formation of biofilms. *C. albicans* has been shown to be inhibited not only on its ERG genes but also on its MDR1 gene, an important multidrug resistance gene.¹³¹ In addition to its many other effects on eukaryotic and prokaryotic cells, FAR also alters ABC efflux transporters, resulting in changes in resistance to azoles in *C. albicans* isolates.¹³² However, this effect is dependent on FAR concentrations.

3.3.13 Zeylasterone and demethylzeylasterone (6-oxophenolic triterpenoids). Zeylasterone and demethylzeylasterone (6-oxophenolic triterpenoids) obtained from the roots of *Maytenus blepharodes* showed potent activity against *Staphylococcus aureus*. Compared to demethylzeylasterone, zeylasterone showed superior activity against microbial cytoplasmic membranes, causing them to rupture. Ethyl acetate extracts from *Croton macrostachys* were tested for their antibacterial properties against *S. aureus* and antifungal properties against *Candida*.¹³³ Five compounds were obtained, including two were lupane triterpenoids and three clerodane diterpenoids, with betulin and 12-oxo-hardwickic acid showing the greatest activity. It was found that lupeol isolated from the aerial parts of *brillantaisia lamium* and *trichodesma amplexicaule* inhibited bacterial and fungal growth significantly by causing membrane damage as a possible mechanism of action.

3.3.14 Other terpenoids. Bioassay-directed isolation of secondary metabolites from the rhizomes of *Zingiber montanum* (*E*)-8(17),12-labdadiene-15,16-dial (1), zerombol (2) demonstrated antibacterial activity (MIC values $32\text{--}128 \text{ g mL}^{-1}$) against a series of clinical isolates of MDR and MRSA.¹³⁴

Fesolol and farnesiferol A are sesquiterpene coumarins that are obtained by extracting aerial parts of *Ferula vesceritensis* (Apiaceae) in dichloromethane, which is associated with a model of the recombinant nucleotide binding site of *Cryptosporidium parvum*'s enteropathogenic efflux pump.¹³⁵

For the first time, the antibiofilm activity of 1,8-cineole against *E. coli* producing MDR ESBLs was demonstrated.¹³⁶ There is no doubt that the compound is capable of causing substantial bacterial death in biofilm-attached as well as biofilm-released cells. The (–)-camphene derivatives tested in the present study, particularly (4) (5d) and (5 h), were shown to be promising anti-TB molecule scaffolds due to the low MIC values in acidic pH against the reference strain H37Rv and MDR *M. tuberculosis* clinical isolates, their low cytotoxicity and the synergism observed with PZA.¹³⁷

All bacteria tested were inhibited by the highest polar fraction of *Cistus ladaniferus* essential oil, which contained mono- and sesquiterpene alcohols with MIC values ranging from 0.05 to 0.8 mg mL^{-1} .¹³⁸ There was high activity of this fraction against the MDR strain *Enterobacter aerogenes* EA289, and its mechanism involves a distortion of the cell wall with detachment of the outer cytoplasmic membrane.

In vitro antibacterial activity of the essential oil of *E. camaldulensis* against multidrug resistant *A. baumannii* wound isolates, demonstrating the plant's traditional use for wounds. As constituents of the *E. camaldulensis* oil, polar terpene compounds and spathulenol may contribute to the observed antibacterial activity.¹³⁹ Additionally, synergistic interactions of the antibiotics ciprofloxacin, gentamicin and polymyxin B with *E. camaldulensis* essential oils were detected in this study for the first time against MDR *A. baumannii* isolates.

4. Conclusion and perspectives

In contemporary society, antibiotics have become an important part of everyday life; the wonders of antibiotics reveal how useful nature can be. Multidrug resistance (MDR) as well as cross-resistance to other drugs have become global concerns due to inappropriate use and overprescription of medications. In response to this emerging problem, we are entering an era of responsibility. Novel solutions are urgently needed to address this significant issue. Natural products are currently being investigated for their antimicrobial properties. Based on the current literature, it appears that there is an urgent need to coordinate efforts for meaningful research and for finding novel alternatives that utilize natural products.

The present study presents a wealth of information regarding the phytocomplexes and mode of action of purified antimicrobials that are isolated and purified from potential medicinal plants. Additionally, these components can be used to design new nutraceuticals or other drugs that are effective. New therapeutics will, however, be discovered by exploring the additional bioactivity of the corresponding species and genus.

Conflicts of interest

There are no conflicts to declare.

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