RSC Advances

REVIEW

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Cite this: *RSC Adv.*, 2022, **12**, 29078

Antimicrobial potentials of natural products against multidrug resistance pathogens: a comprehensive review

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Antibiotic resistance is one of the critical issues, describing a significant social health complication globally. Hence, the discovery of novel antibiotics has acquired an increased attention particularly against drug-resistant pathogens. Natural products have served as potent therapeutics against pathogenic bacteria since the glorious age of antibiotics of the mid 20th century. This review outlines the various mechanistic candidates for dealing with multi-drug resistant pathogens and explores the terrestrial phytochemicals isolated from plants, lichens, insects, animals, fungi, bacteria, mushrooms, and minerals with reported antimicrobial activity, either alone or in combination with conventional antibiotics. Moreover, newly established tools are presented, including prebiotics, probiotics, synbiotics, bacteriophages, nanoparticles, and bacteriocins, supporting the progress of effective antibiotics to address the emergence of antibiotic-resistant infectious bacteria. Therefore, the current article may uncover promising drug candidates that can be used in drug discovery in the future.

Received 5th August 2022
Accepted 3rd October 2022

DOI: 10.1039/d2ra04884a

rsc.li/rsc-advances

1. Introduction

Natural products have provided a major foundation for the development of antibiotics since ancient times (*e.g.*, β-lactams, tetracycline, lincosamides, aminoglycosides, glycopeptides, and macrolides) (Fig. 1). Antibiotics have been shown to act on different targets within bacterial cells, including inhibition of cell wall synthesis (β-lactams: cephalosporins, carbapenems, penicillins, monobactams, glycopeptides), protein synthesis (binding to the 30S ribosomal subunit: tetracyclines, aminoglycosides, or binding to the 50S ribosomal subunit: lincosamides, chloramphenicol, macrolides, streptogramins, oxazolidinones), DNA or RNA synthesis (quinolones: fluoroquinolones, rifampin), metabolic pathways (sulfonamides: trimethoprim), or mycolic acid synthesis (isoniazid) (Fig. 1).[1]

Nowadays, the rise of pathogenic different species resistant to antibiotics is one of the greatest challenges. Infections caused by multidrug-resistant (MDR) bacteria are increasingly common and represent a serious problem for the global public health. It dramatically reduces the probability of effectively treating infections and increases the morbidity and mortality associated with common bacterial diseases.[2] Since the discovery of penicillin in 1928, antimicrobial resistance has been linked to antibiotic use.[3] Besides, bacterial strains resistant to newly developed antibiotics have emerged recurrently.[4] Therefore, antimicrobial resistance presents an ongoing challenge that requires a multifaceted approach. It is alarming since bacterial resistance continues to emerge and the rate at which antibiotics are being developed is decreasing. Antimicrobial resistance is commonly mediated through extra-chromosomal genetic elements acquisition *via* horizontal gene transfer.[5] Low permeability of the outer membrane in Gram-negative bacteria, efflux pumps, production of degrading enzymes, biofilm formation, and modification of targets are examples of mechanisms used by bacteria to resist the toxicity of antibiotics (Table 1).[5]

Among the Gram-positive resistance bacteria species, *Enterococcus faecium*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Enterococcus aecalis* are the most frequent problem.[6] While for Gram-negative resistance bacteria strains, *Klebsiella pneumoniae*, *Escherichia coli*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacteria* sp., have been

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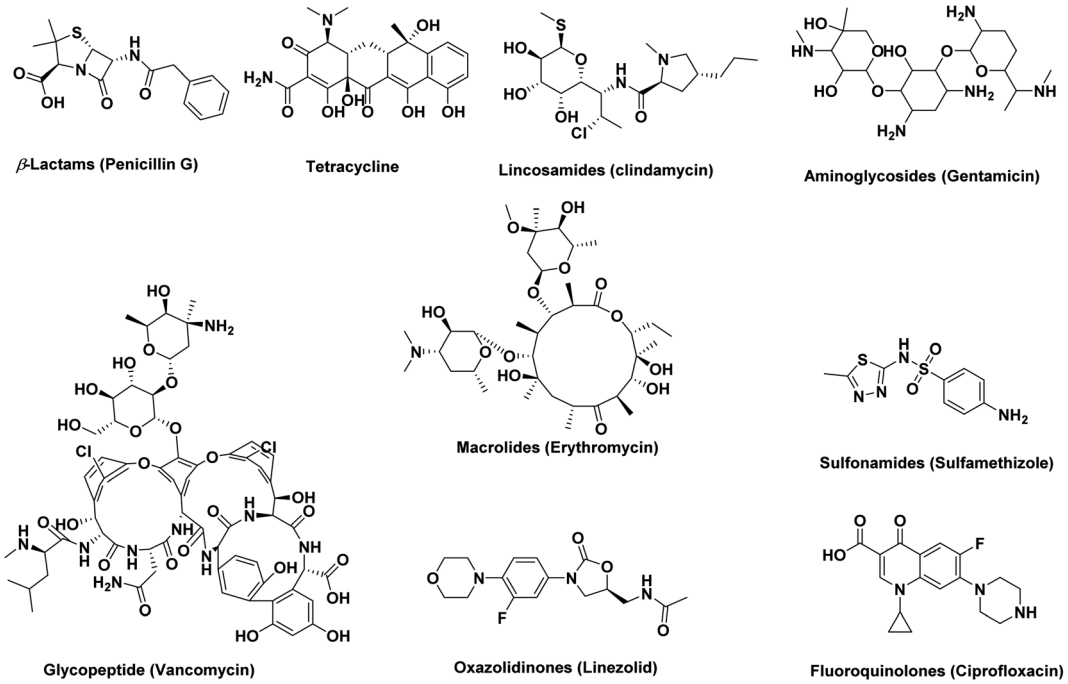

Fig. 1 Examples of naturally occurring antibiotics classes along with three synthetic ones (sulfonamides, oxazolidinones, and fluoroquinolones).

Table 1 Antimicrobial resistance mechanisms against antibiotic different classes

Drug	Drug uptake limitation	Drug target modification	Drug inactivation	Efflux pumps
β-Lactams	+	+	+	+
Carbapenems	+			
Cephalosporins	+			
Glycopeptides	+	+		
Lipopeptides		+		
Aminoglycosides	+	+	+	+
Tetracyclines	+	+	+	+
Chloramphenicol		+	+	+
Lincosamides		+		+
Macrolides		+		+
Oxazolidinones		+		+
Streptogramins				+
Fluoroquinolones		+	+	+
Sulfonamides		+		+
Trimethoprim		+		+

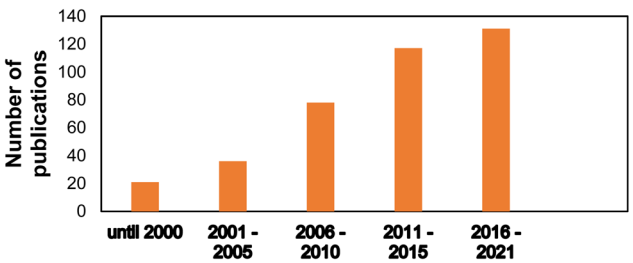

Fig. 2 Distribution of publications covering antimicrobial agents derived from natural products in the last period of research.

mostly common.[6] Globally, excessive use of antibiotics in animal husbandry and aquaculture, use of multiple broad-spectrum agents, and lack of good antimicrobial stewardship can be listed as the factors mostly responsible for the spread of antibiotic resistance species.[7]

The increase in the prevalence of antibiotic-resistant pathogens implies fewer antimicrobial agents to treat infections caused by these bacteria.[8] This raises consequently the need to search for alternative drugs or methods for controlling antibiotic-resistant pathogens.

Natural products and their semisynthetic analogous have participated in a vital part in the description and expansion of antimicrobial drug, especially in the last 20 years.[9] Fig. 2, where diverse terrestrial sources, including plants, fungi, lichen presented more than 80% of reported naturally derived antibiotics, Fig. 3. These products were found to act by different mechanisms controlling multi-resistant pathogens, Fig. 4. Despite the marked impact on safety, nature obtained compounds have attained specialized attention for their potential actions against diverse microorganisms. Many pure natural products along with newly synthetic analogs have confirmed their efficiencies as alternatives as antimicrobial agents against resistant infections.[10] Furthermore, natural antimicrobial agents have built up considerable interest to replace the potency of non-effective antibiotics.

The objective of this review is to list and highlight the potential of terrestrial natural products isolated from plants, lichens, insects, animals, fungi, bacteria, mushrooms, and minerals that have been tested against the most frequent antibiotic-resistant bacteria along with describing the alternative methods that were proposed to control them. Therefore, it

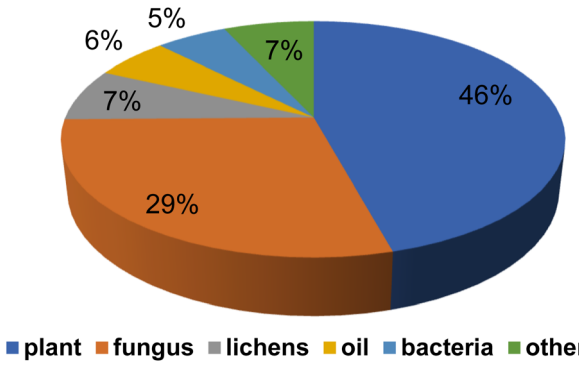

Fig. 3 Natural products against drug resistant bacteria from diverse terrestrial sources.

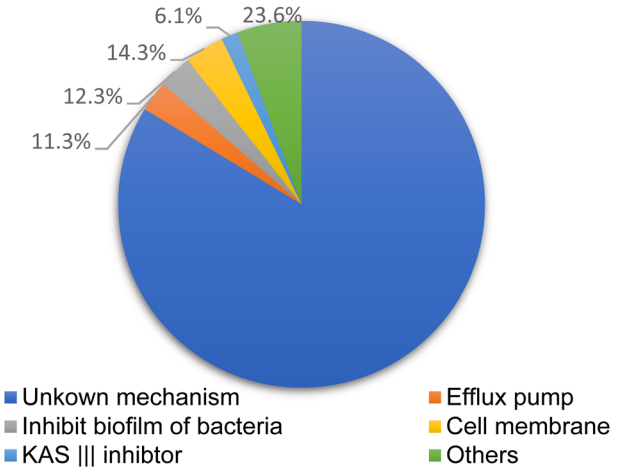

Fig. 4 Methods for controlling multi-resistant pathogens controlling by natural products compounds.

may reveal more drug candidates that can be used in drug industry in the near future.

2. Methods for controlling multi-resistant pathogens

2.1. Elimination of resistant plasmids

The formation, transfer, and transmission of resistant plasmids are important mechanisms that cause extensive antibiotic resistance, which play a major role in the dissemination of resistance genes.[11] Consequently, one of the effective mechanisms for decreasing antibiotic resistance is inhibition of the transfer of resistant plasmids or elimination of those plasmids.

2.2. Effect on the permeability of cell membrane

Since the bacterial cell membrane prevents the transport of antibiotics and consequently affects the drug efficiency, permeability of the cell bacterial membrane could be changed through changing some ion channels. By this method, the permeability of cell membranes to transport antibiotics into bacterial through bacterial cell wall may be effective against MDR pathogens overcoming antibiotic resistance.[12]

2.3. Inhibition on the efflux pump of antibiotic-resistant bacteria

Antibiotics can easily induce the overexpression of bacterial efflux pump to force bacteria pump out more antibacterial drugs to significantly decrease drug concentration at the target site, exacerbating bacterial infection. The efflux system is observed to be present in both Gram-positive and Gram-negative bacteria.[13] For example, methicillin resistant *Staphylococcus aureus* (MRSA) up-regulates the expression of NorA gene to increase drug excretion. NorA efflux pump belongs to MFS family and is first found in clinic to be the important mechanism of bacteria resistant to quinolone and methicillin. Efflux pump inhibitors (EPI) of bacteria could eliminate antibiotic resistance.[13]

2.4. Changes in drug targets

Peptidoglycan is the major component of the cell envelope of most bacteria. In peptidoglycan synthesis, several proteins such as Mur enzymes and PBPs were found to be the targets of antibiotics. However, changes in the structure and quantity of PBPs by bacteria play important roles in bacterial drug resistance.[14] Such changes involved diverse mechanisms especially ribosomal subunits *via* ribosomal mutation and ribosomal subunit methylation, commonly involving the *erm* genes interfering with drugs ability to bind to the ribosome. Additionally, for drugs that target nucleic acid synthesis, resistance is *via* modifications in DNA gyrase or topoisomerase IV. For the drugs that inhibit metabolic pathways, resistance is *via* mutations in enzymes (DHPS—dihydropteroate synthase, DHFR—dihydrofolate reductase) involved in the folate biosynthesis pathway and/or overproduction of resistant DHPS and DHFR enzymes.[1]

2.5. Inhibition on the biofilm formation

Bacterial colonization has been widely reported which is identified as the formation of a biofilm by a bacterial community. For pathogenic organisms, formation of a biofilm protects the bacteria from the host immune system, in addition to provides protection from antimicrobial agents. The thick, sticky consistency of the biofilm matrix which contains polysaccharides, proteins, and DNA from the resident bacteria, makes it difficult for antimicrobial agents to reach the bacteria. In addition, the bacterial cells in the biofilm tend to be sessile (slow metabolism rate, slow cell division), so antimicrobials that target growing, dividing bacterial cells have little effect. An important observation about biofilms is the horizontal transfer of genes facilitated by the proximity of the bacterial cells. This results in sharing of antimicrobial resistance genes among bacterial communities.[1]

2.6. Inhibition drug inactivation

Two main ways by which bacteria can inactivate antibiotics. They are either by actual degradation of the drug or drug

modification through the transfer of a chemical group to the drug chemical structure (*e.g.*, the β-lactamases are a very large group of drug hydrolyzing enzymes, hydrolyzation of tetracycline, *via* the *tetX* gene). Drug inactivation by transfer of a chemical group to the drug most commonly uses transfer of acetyl, phosphoryl, and adenyl groups. There are many transferases have been identified that can be acted on overcoming antibiotic (drugs) resistance.[1]

2.7. Bacteriocins

Bacteriocins are antimicrobial peptides ribosomally synthesized by almost all bacterial species and have a varied mechanism of action and spectrum of activity. Many bacteriocins properties as high stability, low toxicity, and broad spectra of activity, make them good alternative to antibiotics. In addition, some bacteriocins, have a dual mechanism of action, reducing the probability of selecting resistant strains. However, bacteriocin resistance *in vitro* is observed, and easily developed which is mostly associated with physiological adaptation. Topical, intranasal or intravenous are the available therapeutical administration ways for bacteriocin since enzymes present in the gastrointestinal tract inactivate them.[6]

2.8. Essential oils (EOs)

Another alternative tool to control MDR pathogens are essential oils (EOs). EOs have shown antimicrobial activity against MRSA, MDR-*K. oxytoca*, β-lactamases and carbapenemases *E. coli*, erythromycin-resistant Group A *streptococci*, and MDR-*A. baumannii.* EOs when blended with antimicrobial agents, their constituents could unlock the cell membrane channels, opening the passage of antimicrobial agents to reach their internal target sites. This is a great strategy to avoid selection of resistant strains in the future. However, low water-solubility/high vapor pressure are characters that limit the EOs utilization.[6]

2.9. Quorum-sensing inhibitors (QSI)

Quorum sensing (QS) is an intercellular bacterial communication used to coordinate group behaviors in a cell density-dependent manner. At high concentrations, pathogens can switch their transcription profiles to an invasive phenotype, including genes related to antibiotic tolerance and virulence determinants, and cause disease.[6] In this way, QS systems constitute important ant virulence targets, as they often regulate the expression of several virulence genes simultaneously. QSI act by inhibiting cell-to-cell communications and, consequently, disease evolution, enabling the host immune system to prevent bacterial colonization and/or to clear an established infection. This antimicrobial control relies on reducing the burden of virulence rather than killing the bacteria.[6] In the last two decades, various QSI from plants, animals, and microorganisms have been characterized and animal and plant infection models have demonstrated their antibacterial efficacy against QS pathogens. QSI could thus serve as a good alternative to treat infections caused by MDR pathogens. However, its application clinically still requires more research.[6]

3. Controlling multi-resistant pathogens using terrestrial/microbiota derived natural products applications

3.1. Oil derived natural products

Most reports regarding the EOs' constituents against MDR bacteria were investigated in *in vitro* studies. Examples include geraniol **1**, which is a monoterpenoid alcohol, that was found to efficiently increased the susceptibility of MDR-*Enterobacter aerogenes*, *E. coli*, *and P. aeruginosa* by becoming a potent EPI.[15,16] Phenol monoterpene, carvacrol **2**, was reported to inhibit biofilm formation of *S. aureus*, and *S. typhimurium*.[17] In other study, researchers observed heat shock protein induction in *E. coli* 0157 : H7 cells treated with carvacrol **2** with flagellin synthesis inhibition, beside to the consequent production of nonmotile cells.[18] Recently, monoterpene linalool **3** reported to exhibit strong antimicrobial activity against resistant *K. pneumoniae* through membrane disruption.[19]

Additionally, farnesol **4**, an isoprenoid natural acyclic sesquiterpene alcohol, showed moderate effects against *Streptococcus mutans* and *Streptococcus sobrinus* biofilm formation.[20] Farnesol **4** also showed antibacterial activity against *S. aureus* and *S. epidermidis* whereby it also inhibited the biofilm development.[21] Two studies conducted by Masako,[22] evidenced that combinations of farnesol **4** with xylitol, which is a natural sugar alcohol, have positive effects against atopic dermatitis caused by *S. aureus* and successfully inhibited the biofilm production of *S. aureus*. Study conducted by Sayout *et al.*, 2020 (ref. 23) evidenced that camphor **5** has been shown to be active against MRSA P637, *Escherichia coli* P1420, *Enterobacter aerogenes* P1260, *Pseudomonas aeruginosa* P1418, *Klebsiella pneumoniae* LA726, *Klebsiel laoxytoca* BU9399, *Salmonella* spp., *Acinetobacter baumanii* PDP533, and *Enterobacter cloacae P*1374.

Other compounds have also been studied (α-pinene **6**, camphene **7**, fenchone **8**, *cis*-verbenol **9**, borneol **10**, and verbenone **11**). These compounds showed a strong antimicrobial activity against most of MDR strains, except camphene **7** which was not active against MRSA, and *Enterobacte rcloacae*, and borneol **10** which was inactive against *Salmonella* spp. Sayout *et al.*, 2020,[23] also conducted that β-pinene **12**, myrcene **13**, Δ^3-carene **14**, *p*-cymene **15**, 1,8-cineole **16**, limonene **17**, γ-terpinene **18**, terpinen-4-ol **19**, and carvone **20** even if are presented in low concentrations, they have interesting antimicrobial activity against MDR bacteria.[24] reported that *Salmonella typhimurium* when exposed to eugenol **21** at 1% and 5% (v/v), developed increased membrane permeability followed by leakage of the cell contents. In contrast,[25] reported the activity of eugenol **21** (5 mM) on *Listeria monocytogenes* cells results in inhibition of the uptake and utilization of glucose. *Salmonella enterica* serovar Thompson cells were treated with a sublethal concentration of thymol **22** (0.01%), which caused overexpression of a group of molecular chaperone proteins (DnaK, GroEL, HtpG, and the Trigger factor Tf) and outer membrane-associated proteins (OmpX and two OmpA proteins), in addition to upregulation of proteins related to citrate metabolism and ATP synthesis.[26] Niu *et al.*[27] observed that cinnamaldehyde

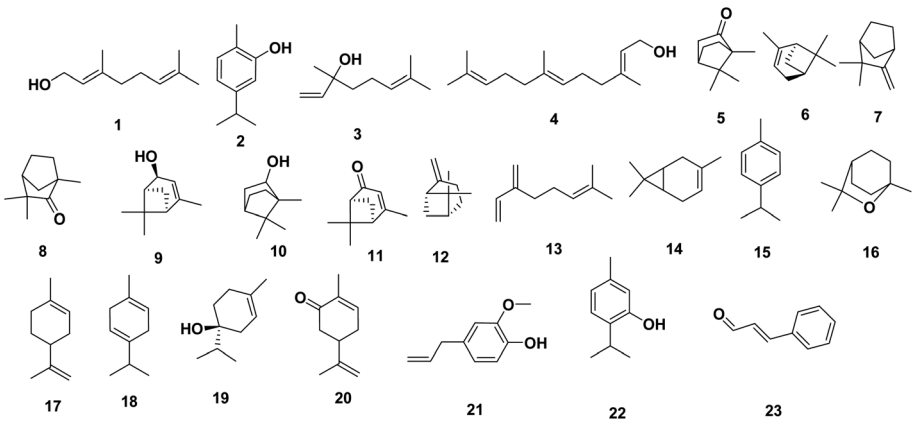

Fig. 5 Oil derived natural products **1–23**.

23 affects transcription of two acyl homoserine lactones (HSLs), 3-oxo-C_6-HSL and 3-oxo-C_{12}-HSL, and the bioluminescence of *V. harveyi*, which is mediated by 3-hydroxy-C_4-HSL and the autoinducer-2 (AI-2). The effect of several terpenes (geraniol **1**, carvacrol **2**, eugenol **21**, and thymol **22**) in combination with penicillin against MRSA ATCC 25923 and an *E. coli* strain was evaluated in a study of Gallucci *et al.*[28] The MICs of carvacrol **2**, eugenol **21**, thymol **22** for the MRSA strain were 15.25, 133.75, and 30.15 mg mL^{-1}, and the MICs of for geraniol **1**, carvacrol **2**, eugenol **21**, and thymol **22** for the *E. coli* strain were 222.25, 7.62, 66.82, and 15.07 mg mL^{-1}, respectively (Fig. 5).

3.2. Plants/endophytes derived natural products

Fig. 6 illustrates the chemical structure for natural derived compounds **24–110** from plants and their associated endophytes. They showed potential antibacterial activity against MDR strain mostly in *in vitro* studies. They may be classified phytochemically into curcuminoids (*e.g.*, curcumin **24**), chalcones and acylphloroglucinols (*e.g.*, humulone **25**, lupulone **26**, xanthohumol **27**, desmethylxanthohumol **28**, cohumulone **29**, colupulone **30**), alkaloids (*e.g.*, compounds **31–68**, **160–162**, and **188–189**), flavonoids and isoflavonoids (*e.g.*, **69–74**, **138**, and **197–200**), quinonoids (*e.g.*, **75–79**), xanthones, terpenoids, and others. In the following section, such bioactive antibacterial compounds shall be discussed in detail.

Curcumin **24**, a natural polyphenolic flavonoid isolated from *Curcuma longa* Linné., showed to have MICs against 10 MDR strains of *S. aureus* ranged from 125 to 250 g mL^{-1}. In the checkerboard test, curcumin **24** markedly reduced the MICs of the antibiotics oxacillin (OXI), ampicillin (AMP), ciprofloxacin (CIP), and norfloxacin (NOR) used against MRSA. The time-kill curves showed that a combined curcumin **24** and OXI treatment reduced the bacterial counts below the lowest detectable limit after 24 h.[29] Bogdanova *et al.*, 2017,[30] reported that the prenylated chalcones and acylphloroglucinols; humulone **25**, lupulone **26**, and xanthohumol **27**, isolated from *Humulus lupulus* L., possessed antimicrobial properties against *Staphylococcus* spp., including methicillin-susceptible and resistant strains, in both planktonic and biofilm-dwelling, with no significant difference between resistant and susceptible strains. Where humulone **25**, lupulone **26**, and xanthohumol **27** lowered the number of bacterial cells released from the biofilm, with the strongest effect seen for lupulone **26**, followed by xanthohumol **27**.

Moreover, lupulone **26**, and xanthohumol **27** were not only able to penetrate the biofilm and reduce the number of bacteria within it, but their higher concentrations (~60 μg mL^{-1} for xanthohumol **27** and ~125 μg mL^{-1} for lupulone **26**) reduced the number of surviving bacterial cells to zero. Asides, humulone **25**, lupulone **26**, and xanthohumol **27**, with desmethylxanthohumol **28**, cohumulone **29**, colupulone **30**, reported as potent antibacterial compounds with MIC < 1 μg mL^{-1}, against MRSA strains, through kill curves, post-antibiotic effects, anti-biofilm assays and synergy studies with antibiotics.[31] Alkaloids **31–34** are β-carboline type, where berberine **31** was reported to have moderate inhibitory activity against MRSA with MIC 125 μg mL^{-1}.[32] Notable efflux inhibitory activity (ranging from two-to eightfold Ethidium Bromide MIC reduction) meanwhile was detected from quinine **32**, piperine **33**, and harmaline **34** using reserpine **35** as the positive control.[33] Canthin-6-one **36**, and 8-hydroxy-canthin-6-one **37** isolated from *A. neapolitanum*, displayed MICs in the range 8–64 μg mL^{-1} against MDR/MRSA strains.[34] Three carbazole alkaloids, Clausamine A, B, F **38–40**, isolated from *Clausena harmandiana*, where clausamine B **39** exhibited significant activity against MRSA SK1 with an MIC value of 0.25 μg mL^{-1} which was higher than that of standard drug, vancomycin (MIC 1 μg mL^{-1}). While clausamine F **40**, and A **38** showed strong activity with MIC 4 and 8 μg mL^{-1}, respectively. Also, clausamine F **40** showed strong antibacterial activity against *S. aureus* TISTR 1466 with MIC 4 μg mL^{-1}.[35]

The carbazole alkaloids, 2,7-dihydroxy-3-formyl1-(3′-methyl-2′-butenyl) carbazole **41**, clausenawalline E **42**, clausenawalline B **43**, were isolated from *Clausena wallichii*, and exhibited significant activity against MRSA SK1 and *S. aureus* TISTR 1466 with MIC 4–16 μg mL^{-1}.[36] Clausenawalline E–K **44–48** isolated also from *Clausena wallichii*, showed weak antibacterial activities with MIC 64–128 μg mL^{-1} against *S. aureus* TISTR 1466 and MRSA SK1, and *E. coli* TISTR 780 and *S. typhimurium* TISTR 292.[36] The antibacterial activity of lysergol **49** and its synergy with the conventional antibiotic nalidixic acid (NA) against

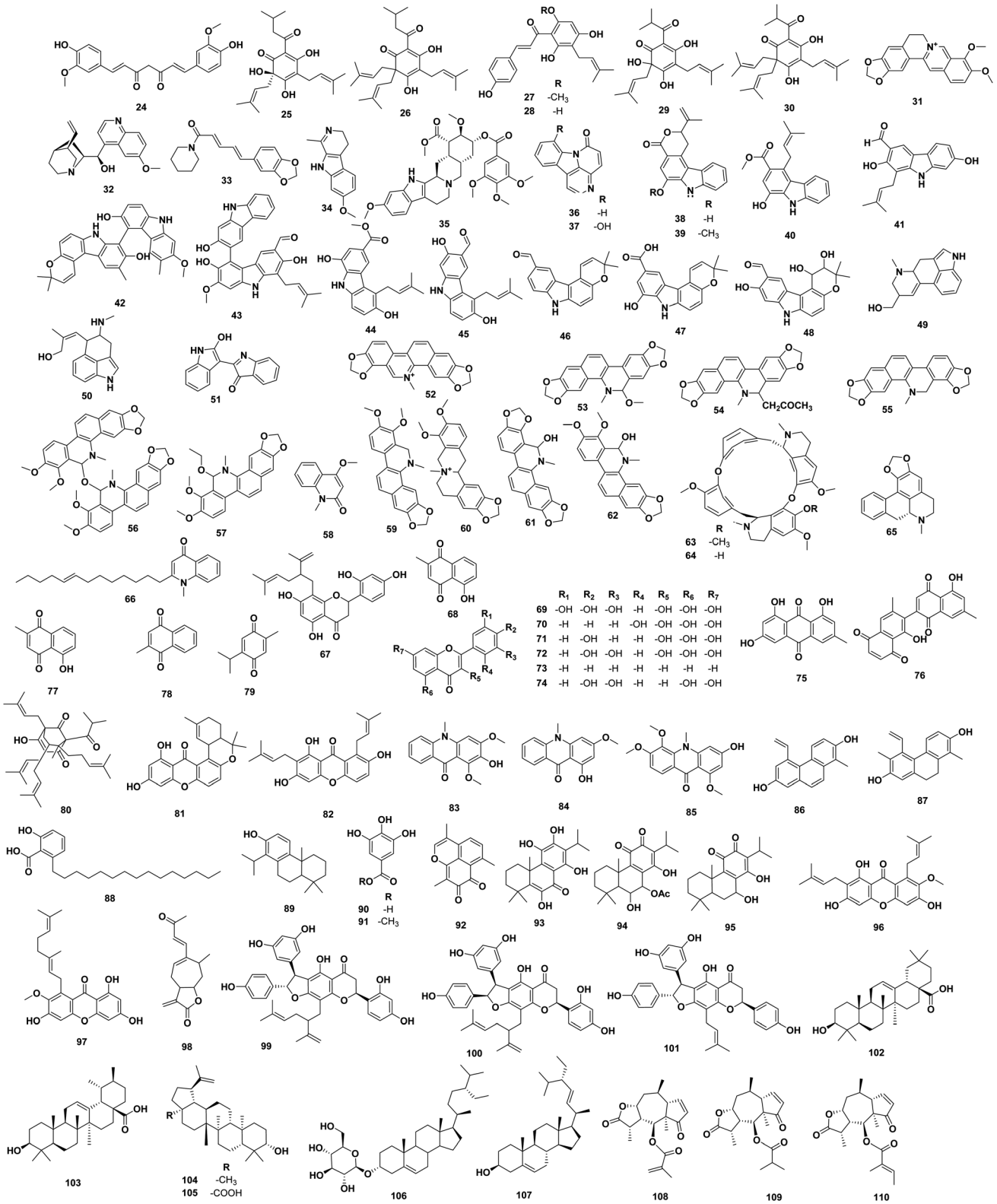

Fig. 6 Plant derived natural products **24–110**.

nalidixic acid-sensitive (NASEC) and nalidixic acid-resistant (NAREC) strains of *Escherichia coli* were evaluated. Lysergol **49** did not possess antibacterial activity of their own, but in combination, it significantly reduced the MIC of NA. Furthermore, lysergol **49** brought down eightfold reductions in the MIC of tetracycline (TET) against MDR clinical isolate of *E. coli*. Additionally, lysergol **49** inhibited ATP-dependent efflux pumps, which was evident by ATPase inhibition and down-

regulation of multidrug ABC transporter ATP-binding protein (yojI) gene.[37] Chanoclavine **50** isolated from *Ipomoea muricata*, showed synergy potential against multidrug-resistant *Escherichia coli* (MDREC). Although chanoclavine **50** did not show antibacterial activity of its own, but in combination, it could reduce MIC of tetracycline (TET) up to 16-folds. Chanoclavine **50** was found to inhibit the efflux pumps which seem to be ATPase-dependent.[38] The EPI properties of indirubin **51** isolated from *Wrightia tinctoria*, were investigated using *S. aureus* SA1199B, and its synergistic effects were tested with ciprofloxacin. Indirubin **51** showed activity against multidrug-resistant *Staphylococcus aureus* (MDRSA) with MIC 12.5 mg L^{-1} for *S. aureus* and 25 mg L^{-1} for *S. epidermidis*. It synergistically potentiated the activity of ciprofloxacin with a fractional inhibitory concentration index (FICI) of 0.45, may be through inhibiting the NorA efflux pump. Indirubin **51** showed to exhibit EPI activity nearly comparable to that of reserpine **35** by 4-fold reduction in ciprofloxacin MIC.[39] The antimicrobial DNA-intercalating alkaloid sanguinarine **52**, demonstrated a strong activity against MDR-Gram-positive and Gram-negative bacteria, with MIC 0.5–128 μg mL^{-1}.[40] 6-Methoxydihydrosanguinarine (6 MS) **53**, 6-acetonylhydrosanguinarine **54**, and dihydrosanguinarine **55** isolated from *Hylomecon hylomeconoides*, showed MIC against MRSA 1.95–250 μg mL^{-1}. Where 6 MS **53** appeared to be the most active with MICs in the range of 1.9 to 3.9 μg mL^{-1}.[41] Alkaloids *bis*-6-(5,6-dihydro-chelerythrinyl)-ether **56**, 6-ethoxy-chelerythrine **57**, 4-methoxy-*N*-methyl-2-quinolone **58**, isolated from *Zanthoxylum monophyllum* exhibited strong activity against MRSA (ATCC 43300). The Compound **58** exhibited significant activity against MRSA with IC_{50} value of 8.0 μM.[42]

Furthermore, dihydrochelerythrine **59**, and *N*-methylcanadine **60**, isolated from the *Zanthoxylum tingoassuiba*, showed potent anti-MRSA ATCC 25923 with MIC values ranging from 85.8 to 171.7 μM and 76.9 to 307.8 μM, respectively. Nevertheless, dihydrochelerythrine **59** displayed better activity than chloramphenicol against *S. aureus* ATCC 25923.[43] It is interesting that the 8-hydroxylated benzo[*c*]phenanthridine derived alkaloids, 6-hydroxy-dihydrosanguinarine **61**, and 6-hydroxy-dihydrochelerythrine **62**, showed potent *in vitro* inhibitory effects on both the methicillin sensibler *Staphylococcus aureus* (MSSA) and MRSA strains. The **61** and **62** minimal inhibitory concentrations/minimal bactericidal concentrations (MICs/MBCs) values against MRSA strains were as low as to be 0.49/1.95 and 0.98/7.81 μg mL^{-1}, respectively, showing that the alkaloid **61** was demonstrated as the most potent. Its 90% MICs (1.95 μg mL^{-1}) against MRSA were comparable to vancomycin (2.34 μg mL^{-1}).[44] The antibacterial activity of two bisbenzylisoquinoline alkaloids, tetrandrine **63** and demethyltetrandrine **64** isolated from *Stephania tetrandra* roots, alone and in combination with the antibiotics ampicillin (AMP), azithromycin (AZM), cefazolin (CFZ) and levofloxacin (LEV) against 10 clinical isolates of staphylococcal chromosomal cassette mec (SCCmec) III type MRSA was studied. The MICs/MBCs ranges alone were 64–128/256–1,024 μg mL^{-1}, for both compounds. Significant synergies against 90% of the isolates were observed for the tetrandrine **63**/CFZ combination, with their MICs being reduced by 75–94% FICIs ranged from 0.188 to 0.625, respectively.[45] Roemerine **65**, is an aporphine alkaloid isolated from *Annona senegalensi*, and is reported to be effective *in vitro* against MDR strains, as it was found to increase cell membrane permeability in a concentration-dependent manner.[46] Evocarpine **66** isolated from Fructus *Euodiae* showed activity against MRSA with MIC 8 μg mL^{-1}, which was equivalent to or lower than the control antibiotics, oxacillin, erythromycin, and tetracycline (MIC ≥ 128 μg mL^{-1}).[47] The anti-MRSA activity of sophoraflavanone G (SFG) **67** and synergism between SFG **67** and antibacterial agents against MRSA were evaluated. The MICs of SFG **67** against 27 strains of MRSA ranged from 3.13 to 6.25 mg mL^{-1}. Synergism between SFG **67** and vancomycin hydrochloride (VCM) or fosfomycin (FOM) was observed (FIC indices were 0.16 and 0.48), while partial synergism was admitted between SFG **67** and other antibacterial agents such as methicillin (DMPPC), cefzonam (CZON), gentamicin (GM), minocycline (MINO) and levofloxacin (LVFX) (the FIC indices were 0.71, 0.73, 0.69, 0.65 and 0.58, respectively).[48] Plumbagin **68** isolated from *Plumbago zeylanica* showed activity against MRSA with MIC range of 4–8 μg mL^{-1}. Where the time-kill study revealed 99% kill of a reference MRSA strain, 8 h after exposure to plumbagin **68**. In the combination MIC study using the reference MRSA strain, plumbagin **68** showed synergistic effect with ciprofloxacin and piperacillin while additive or indifference effect with other commonly used antibiotics. The transmission electron micrograph of the reference MRSA strain treated with plumbagin **68** confirmed cell wall and cytoplasmic changes.[49]

Asides, myricetin **69**, datiscetin **70**, kaempferol **71**, and quercetin **72**, flavone **73**, and luteolin **74** exhibited inhibitory activity against MRSA. Myricetin **69** was also found to inhibit the growth of MDR *Burkholderia cepacia*, vancomycin-resistant enterococci (VRE) and other medically important organisms such as *Klebsiella pneumoniae* and *Staphylococcus epidermidis*. Moreover, myricetin **69** was bactericidal to *B. cepacian*.[50] Five quinonoids, emodin **75**, diospyrin **76**, plumbagin **77**, menadione **78**, and thymoquinone **79** were evaluated against a broad panel of multi-drug and extensively drug resistant tuberculosis (M/XDR-TB) strains, rapid growing *Mycobacteria*, and other bacterial isolates, some of which were producers of β-lactamase, Extended-spectrum β-lactamase (ESBL), AmpC β-lactamase, metallo-betalactamase (MBL) enzymes, as well as their drug-sensitive ATCC counterparts. All the tested quinones exhibited antimycobacterial and broad-spectrum antibacterial activity, particularly against *M. tuberculosis* (lowest MIC 0.25 μg mL^{-1}) and Gram-positive bacteria (lowest MIC < 4 μg mL^{-1}) of clinical origin. Where the order of antitubercular activity of the tested quinonoids was plumbagin **77** > emodin **75** ∼ menadione **78** ∼ thymoquinone **79** > diospyrin **76**, whereas their antibacterial efficacy was plumbagin **77** > menadione **78** ∼ thymoquinone **79** > diospyrin **76** > emodin **75**.[51] Penicillin-resistant (PRSA) and MRSA were reported to be susceptible to hyperforin **80**, isolated from *Hypericum perforatum*.[52] The prenylated xanthones isolated from *Calophyllum* species, calozeyloxanthone **81**, and 6-deoxy-γ-mangostin **82** showed inhibition against *S. aureus*. However, the activity of 6-deoxy-γ-mangostin **82** was not

significant. The MIC of calozeyloxanthone **81** for *S. aureus* (MSSA and MRSA) ranged from 4.1 to 8.1 mg mL^{-1}.[53] Three acridone alkaloids; hydroxy-1, 3-dimethoxy-10-methyl-9-acridone **83**, 1-hydroxy-3-methoxy-10-methyl-9-acridone **84**, and 3-hydroxy-1, 5, 6-trimethoxy-9-acridone **85**, isolated from *Z. leprieurii* stem bark, were tested against pan sensitive (H37rv), isoniazid resistant (TMC 301) and rifampicin resistant (TMC 331) strains of *M. tuberculosis* using micro plate alamar blue assay. The MIC of 3-hydroxy-1, 5, 6-trimethoxy-9-acridone **85** was found to be 5.1, 4.5 and 3.9 μg mL^{-1} on H37rv, TMC 331 and TMC 301 while that hydroxy-1, 3-dimethoxy-10-methyl-9-acridone **83** was found to be 1.5, 8.3 and 3.5 μg mL^{-1} respectively.[54]

Additionally, the phenanthrene derivatives, *i.e.*, dehydroeffusol **86**, and juncusol **87**, were isolated from the common rush, *Juncus effusus* L., reported to enhance the antimicrobial activities in light. The MIC for these compounds against methicillin-resistant and -sensitive *Staphylococcus aureus* was increased up to 16-and two-fold, respectively, by irradiation with ultraviolet A (UVA). Under UVA irradiation, dehydroeffusol **86** strongly inhibited all the restriction enzymes (*Kpn*I, *Xba*I, *Pme*I, *Dra*I, *Pac*I and *Bci*VI) that have at least one 5′-TpA sequence in their recognition sites. Weak inhibitions were found for the restriction enzymes *Eco*RI, *Sac*I, *Bam*HI, *Sal*I, *Pst*I and *Hin*dIII, which do not possess a 5′-TpA sequence at their restriction sites and the restriction site sequences of which consist of all bases, A, T, G and C. Weak or no inhibition was found for *Asc*I and *Sma*I, the restriction site sequences of which are composed of only C and G. These results indicated the necessity of thymine (adenine) for the photosensitized DNA-binding activity of dehydroeffusol **86**. A strong inhibition against *Sph*I, which does not have a 5′-TpA sequence in the restriction sequence, indicates that there are possibly other binding sequence(s) for dehydroeffusol **86**. With juncusol **87** and UVA, strong inhibitions for *Kpn*I and *Bci*VI and trace inhibitions for *Pac*I, *Xba*I, *Pme*I and *Dra*I were found. This result also showed a preference of juncusol **87** for 5′-TpA, but the preference could be more selective than that of dehydroeffusol **86** depending on the surrounding sequences of 5′-TpA in the respective restriction sites. A strong inhibition of *Sph*I by juncusol **87** with UVA also indicated the existence of an unknown binding sequence for this compound. Generally, the DNA-binding activity of juncusol **87** was weaker than that of dehydroeffusol **86**.[55] Growth of two strains of MRSA was inhibited by 6.25 μg mL^{-1} of anacardic acid **88** isolated from the cashew *Anacardium occidentale*, apple, nut, and nutshell oil, and 0.78 μg mL^{-1} of totarol **89** isolated from the bark of *Podocarpus nagi*, and these two compounds were found to be bactericidal. Anacardic acid **88** was founded to be bactericidal against MRSA at any stage of growth.[56] Gallic acid **90**, and methyl gallate **91**, isolated from *Terminalia chebula*, exhibited inhibitory activity against MRSA with MIC 7.9–125 μg mL^{-1}.[57] A highly potent anti-MRSA sesquiterpenoid mansonone F **92** has been isolated from *Ulmus davidiana* var., and showed an MIC range of 0.39–3.13 mg mL^{-1}, compared to that of vancomycin.[58] Coleon U **93**, 7α-acetoxy-6βhydroxyroyleanone **94**, and horminone **95**, are abietanes natural products isolated from *Plectranthus grandidentatus* and showed MIC values ranging 0.98–15.63 mg mL^{-1} for MRSA, and 15.63–31.25 mg mL^{-1} for vancomycin-resistant Enterococcus faecalis (VRE).[59]

Also, one active product, α-mangostin **96**, a xanthone derivative isolated from *Garcinia mangostana*, had MIC of 1.57–12.5 μg mL^{-1} against MRSA. Other related xanthones was rubraxanthone **97**, which was isolated from *Garcinia dioica*, had the highest activity against *Staphylococcal* strains (MIC = 0.31–1.25 μg mL^{-1}), an activity which was greater than that of the antibiotic vancomycin (3.13–6.25 μg mL^{-1}). The anti-MRSA activity of α-mangostin **96** was clearly increased by the presence of vancomycin; this behavior was not observed for rubraxanthone **97**.[60] Xanthatin **98** a sesquiterpene lactone isolated from *Xanthium sibiricum*, is highly species-specific for MRSA and MSSA strains.[61] Alopecurone A-C **99–101**, flavanostilbenes isolated from *Sophora alopecuroades*, inhibited MRSA strains at concentrations of 3.13–6.25 μg mL^{-1}.[62] Oleanolic acid **102**, ursolic acid **103**, lupeol **104**, betulinic acid **105**, β-sitosterol glucoside **106**, and stigmasterol **107**, isolated from *Psychotria sycophylla*, showed MICs varied from 16 to 256 μg mL^{-1} against *Providencia stuartii* PS2636, *S. aureus* MRSA9, *S. aureus* MRSA3, and *Enterobacter aerogenes* EA27. The mechanistic investigations showed interference of **102–107** with bacterial growth kinetic (by extending the lag phase) and inhibition of proton pumps.[63] Sesquiterpene lactones, 6-*O*-methylacrylylplenolin **108**, 6-*O*-isobutyroylplenolin **109**, and 6-*O*-angeloylplenolin **110**, isolated from *Centipeda minima*, had activity against resistance *Bacillus subtilis* and *S. aureus*, where 6-*O*-isobutyroylplenolin **109** being the most active with MIC 300–600 μg mL^{-1} for MRSA.[64]

Other naturally plant-derived products were shown in Fig. 7 illustrating their chemical structures, **111–190.** Guaianolide **111**, secoguaianolide sesquiterpene, isolated from *Artemisia gilvescens* showed good MRSA inhibition activity with MIC 1.95 μg mL^{-1}.[65] Dehydroleucodine **112**, sesquiterpene lactone isolated from *Gynoxys verrucosa*, showed moderate MRSA inhibition activity with MIC_{50} between 49–195 μg mL^{-1}.[66] 8(17),12*E*,14-labdatrien-6,19-olide **113**, labdane diterpenoid isolated from *Salvia leriifolia* showed an MIC 213 μM against MRSA.[67] 8(17),11(*Z*),13(*E*)-trien-15,19-dioic acid **114**, is epimeric cassane-type diterpenoid, isolated from *Caesalpinia decapetala* displayed moderate MRSA inhibiton activity with an MIC 5.99 μg mL^{-1}.[68] (*E*)-8(17),12-labdadiene-15,16-dial **115**, zerumbol **116**, are terpenes isolated from *Zingiber montanum* showed MIC values 32–128 μg mL^{-1}; 0.145–0.291 mM against MDR and MRSA different strains.[69] 16α-hydroxycleroda-3, 13(14)-*Z*-dien-15, 16-olide (CD) **117**, clerodane diterpene isolated from *Polyalthia longifolia*, exhibited significant anti-MRSA activity (15.625–31.25 mg L^{-1}), while time kill assays at graded MICs resulted in 2.78–9.59- and 2.9–6.18-fold reduction in growth of reference strain and clinical isolates of *S. aureus*, respectively. The molecule CD **117** was found to interact synergistically with clinically used antibiotics (FICI $\leq$ 0.5) against all clinical isolates. In infected mice, CD **117** significantly ($p < 0.001$) lowered the systemic microbial load in blood, liver, kidney, lung and spleen tissues and did not exhibit any significant toxicity at 100 mg kg^{-1} body weight.[70] Rel-15,16-epoxy-7α-hydroxypimar-8,14-ene **118**, a diterpenoid isolated from *Plectranthus ernstii*

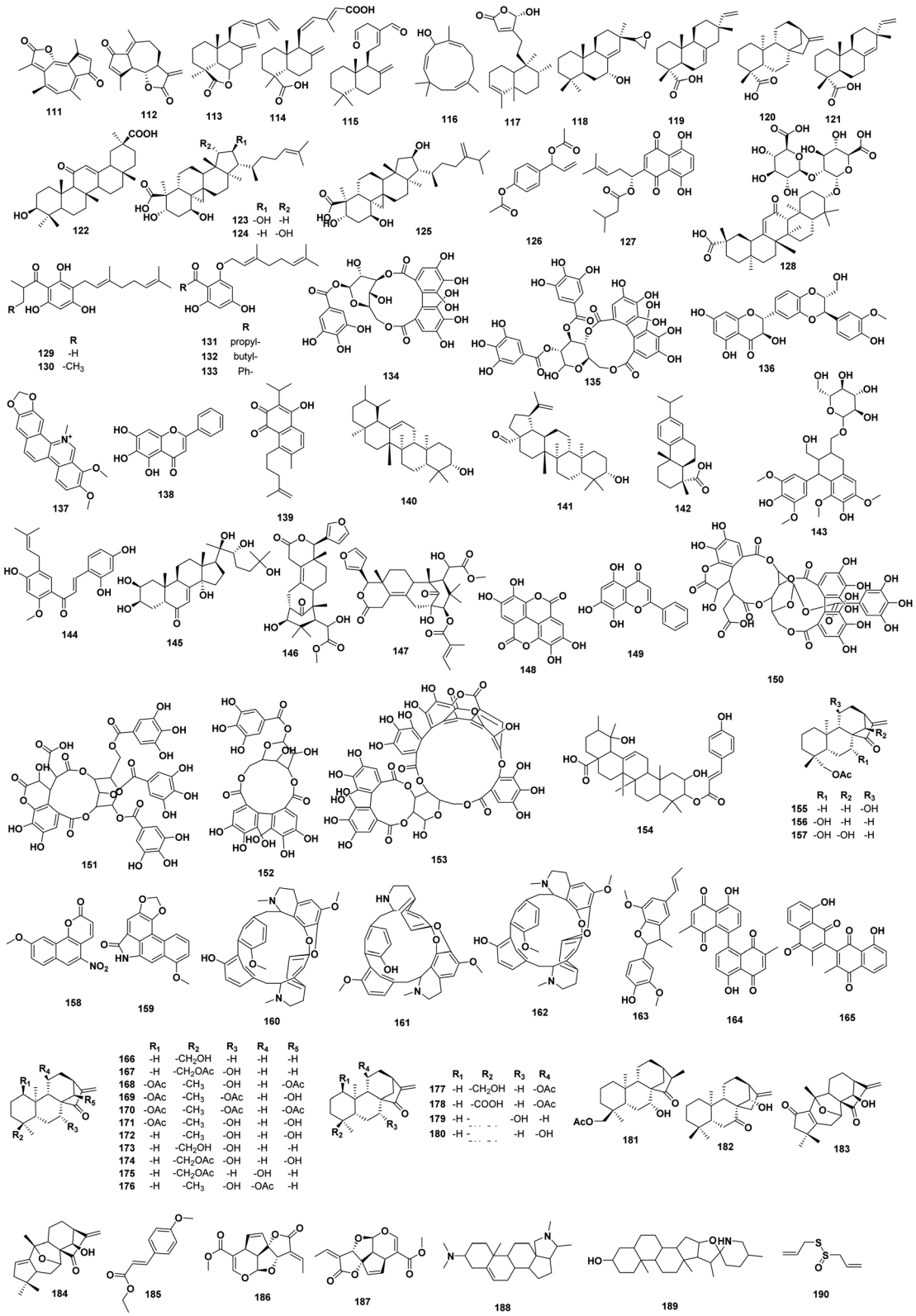

Fig. 7 Plant derived natural products **111–190**.

exhibited moderate anti-MRSA activity with MIC of 32 μg mL^{-1}.[71] The diterpene isopimaric acid **119**, isolated from *Pinus nigra* exhibited anti-staphylococcal activity against a range of MDR and MRSA strains of *S. aureus* with MIC of 32–64 μg mL^{-1}.[72] *ent*-kaurenoic acid **120**, and *ent*-pimaradienoic acid **121**, diterpenoid isolated from *V. arenaria* exhibited activity against

MDR and MRSA strains of *S. aureus*.[73] 18β-glycyrrhetinic acid **122**, isolated from *Glycyrrhiza glabra*, enhanced the bactericidal activity of the aminoglycoside's tobramycin, gentamicin, amikacin, and of polymyxin B against two MRSA strains, reducing the MIC of these antibiotics 32–64-fold with FICI of 0.12–0.13. In an air-exposed airway epithelial cell culture, 18β-glycyrrhetinic acid **122** enhanced the bactericidal activity of tobramycin and polymyxin B against the MRSA strain. Consequently, the potential of 18β-glycyrrhetinic acid **122** to synergise with certain types of antibiotics to eliminate strains of MRSA.[74]

16R-hydroxymollic **123**, 15R-hydroxymollic **124**, and 7α,16αdihydroxy-1,23-dideoxyjessic acid **125**, were isolated from *Acalypha communis*, showed better antimicrobial activity against vancomycin-resistant enterococci than penicillin G (MIC 128 μg mL^{-1}). In addition, 16R-hydroxymollic **123** was also found active against MRSA, with a MIC 64 μg mL^{-1} 15R-hydroxymollic **124** and penicillin G were found to be equipotent against MRSA (MIC of 128 μg mL^{-1}).[75] 1′-Acetoxychavicol **126**, isolated from *Alpinia galanga* exhibited anti-plasmid activity against *Salmonella typhi*, *Escherichia coli* and vancomycin resistant *Enterococcus faecalis* with an efficiency of 92%, 82% and 8% respectively at 400 μg mL^{-1} SIC. 1′-Acetoxychavicol **126** demonstrated the ability to cure plasmid encoded antibiotic resistance in various MDR bacterial strains of clinical isolates such as *Enterococcus faecalis*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Bacillus cereus* with curing efficiency of 66%, 75%, 70%, 32% and 6% respectively at SIC of 400–800 μg mL^{-1}.[76]

In addition, isovalerylshikonin (IVS) **127**, was isolated from *Arnebia euchroma*, exhibited marginal antibacterial activity against MRSA RN4220, with MIC 16 μg mL^{-1}. In addition, a synergistic effect between IVS **127** and streptomycin (STM) was detected by the microdilution antimicrobial chequerboard assay, with MIC reduction for STM up to 16-fold against strain RN4220. IVS **127** also significantly inhibited bacterial efflux and expression of msrA mRNA *in vitro*. A murine peritonitis/sepsis model was employed to test the *in vivo* synergistic activity of IVS **127** and STM. IVS **127** synergistically decreased bacterial counts with STM in peritoneal, spleen and liver tissue and increased mouse survival with STM in 7 days. The acute toxicity of IVS **127** was tested and the 50% lethal dose (LD_{50}) of IVS **127** with a single exposure was 2.584 g kg^{-1} in mice. Overall, IVS **127**, a low-toxicity RMA, exhibited synergistic antibacterial activities *in vitro* and *in vivo* against MRSA. The effects were mediated by suppression of msrA mRNA expression and reduced bacterial efflux. In addition, these data support that IVS **127** is a potential resistance-modifying agent (RMA) against microbial resistance caused by the MsrA efflux pump.[77] Glycyrrhizic acid **128**, at the subinhibitory concentration of 2.4 mM was found to reduce the MIC of gentamicin in intrinsically resistant *E. faecium* strains down to 6.25 % of MIC of gentamicin alone, whereas relatively low concentrations of glycyrrhizic acid **128** (18 μM) resulted in increased susceptibilities for some *E. faecium* isolates to gentamicin.[78] 3-geranyl-1-(2-methylpropanoyl)-phloroglucinol **129**; 3-geranyl-1-(2-methylbutanoyl) phloroglucinol **130**; 2-geranyloxy-1-(2-methylpropanoyl)-phloroglucinol **131**; 2-geranyloxy-1-(2 methylbutanoyl)-phloroglucinol **132**; 2-geranyloxy-4,6-dihydroxybenzophenone **133**, isolated from *Hypericum densiflorum*, *H. ellipticum*, *H. prolificum*, and *H. punctatum*, were tested for their ability to attenuate biofilm production by *S.* species. The MBIC values of the *Hypericum* metabolites ranged from 1.95–7.81 μg mL^{-1} 3-Geranyl-1-(2-methylbutanoyl)-phloroglucinol **130**, displayed the most potent biofilm inhibition against *S. aureus* and *S. epidermidis* at an MBIC of 1.95 μg mL^{-1}. Compounds **129–131** also inhibited biofilm formation at concentrations below their respective MIC and MBC values against some test strains. Compounds **129–131** consistently demonstrated MBIC values at or below their respective MIC values.[79] Corilagin **134**, and tellimagrandin I **135**, are polyphenols isolated from *Arctostaphylos uvaursi* and *Rosa canina*, respectively, which reported to reduce MIC of β-lactams in MRSA. Another study investigated the effect of **134–135** on the penicillin binding protein 2′ (2a) (PBP2′ (PBP2a)) which mainly confers the resistance to β-lactam antibiotics in MRSA. These compounds when added to the culture medium were found to decrease production of the PBP2′ (PBP2a) slightly. Using Bocillin Fl, a fluorescent-labeled benzyl penicillin, it was found that PBP2′ (PBP2a) in MRSA cells that were grown in medium containing corilagin **134** or tellimagrandin I **135** almost completely lost the ability to bind Bocillin Fl. The binding activity of PBP2 and PBP3 were also reduced to some extent by these compounds. These results suggested that inactivation of PBPs, especially of PBP2′ (PBP2a), by corilagin **134** or tellimagrandin I **135** are the major reason for the remarkable reduction in the resistance level of β-lactams in MRSA.[14]

Silybin **136**, is a flavonolignan isolated from milk thistle seed, and showed to disrupt the MRSA41577 resistance to ciprofloxacin through reducing the expression of the quinolone resistance protein NorA (norA) and quaternary ammonium resistance proteins A/B (qacA/B) efflux genes in MRSA.[80] Chelerythrine **137**, isolated from *Toddalia asiatica* showed strong antibacterial activities against MRSA, and extended spectrum β-lactamase *S. aureus* (ESBLs-SA) with MIC 0.156 mg mL^{-1}, which attributed to **137** destruction of the channels across the bacterial cell membranes, causing protein leakage to the outside of the cell, and to its inhibition on protein biosynthesis.[12] In *S. aureus*, von Willebrand factor-binding protein (vWbp) is one of the key virulence determinants because it mediates not only the activation of thrombin to convert fibrinogen to fibrin, thereby enabling *S. aureus* to escape from the host immune clearance, but also the adhesion of *S. aureus* to host cells. Thus, vWbp is regarded as a promising druggable target to treat *S. aureus*-associated infections. Baicalein **138**, isolated from *Scutellaria baicalensis*, can effectively block the coagulase activity of vWbp without inhibiting the growth of the bacteria. Molecular dynamics simulations and mutagenesis assays revealed that the Asp-75 and Lys-80 residues are necessary for baicalein **138** binding to vWbp. Importantly, baicalein **138** treatment attenuates the virulence of *S. aureus* and protects mice from *S. aureus*-induced lethal pneumonia. In addition, baicalein **138** can improve the therapeutic effect of penicillin G by 75% *in vivo*.[81] Moreover, baicalein **138**, at 16 μg mL^{-1} could synergistically restore the antibacterial actions of ciprofloxacin against the

NorA efflux pump overexpressed SA-1199B, but not with the poor NorA substrate, pefloxacin. In addition, synergistic effects were observed when baicalein **138** was combined with ciprofloxacin against 12 out of 20 clinical ciprofloxacin resistant strains. For MRSA PK studies, baicalein **138** alone could inhibit the enzymatic activity of MRSA PK in a dose-dependent manner.[82] Abietane diterpenoid salvipisone **139**, demonstrated a very interesting activity when its effect on 24 h-old *staphylococcal* biofilm cells viability was examined. It limited the survival of biofilms formed by *S. aureus* as well as by *S. epidermidis*, putting this compound to the list of potential antibiofilm agents, better than most of known antibiotics.[83] The pentacyclic triterpenoids were isolated from *Callicarpa farinosa*: α-amyrin **140**, and betulinaldehyde **141**, exhibited antimicrobial activities against MRSA and MSSA, with MIC ranging from 2 to 512 μg mL^{-1}. From the genome-wide transcriptomic analysis to elucidate the antimicrobial effects of these compounds, multiple novel cellular targets in cell division, two-component system, ABC transporters, fatty acid biosynthesis, peptidoglycan biosynthesis, aminoacyl-tRNA synthetases, ribosomes and β-lactam resistance pathways are affected, resulting in destabilization of the bacterial cell membrane, halt in protein synthesis, and inhibition of cell growth that eventually led to cell death.[84]

Dehydroabietic acid (DA) **142**, isolated from *Pinus elliottii*, showed the MIC and minimum bactericidal concentration varied between 6.25 and 50, and between 6.25 and 100 μg mL^{-1}, respectively, against MRSA. The time-kill assay conducted with DA **142** at 6.25 μg mL^{-1} evidenced bactericidal activity against *S. epidermidis* 14990 within 24 h.[85] (+)-Lyoniresinol-3α-*O*-β-D-glucopyranoside **143**, isolated from *Lycium chinense*, exhibited potent anti-MRSA activity with MIC 2.5–5 14 μg mL^{-1}.[86] 7,9,2′,4′-Tetrahydroxy-8-isopentenyl-5-methoxychalcone (THIPMC) **144**, isolated from *Sophora flavescens*, was found to be active against MRSA and VRE, either alone or in combination with ampicillin (AM) or gentamicin (GM). The MIC 1–8 μg mL^{-1} for THIPMC **144**, from 128–1024 μg mL^{-1} for AM, and from 128–512 μg mL^{-1} for GM, respectively. The combinations of THIPMC **144** plus AM or GM yielded FICI ranging from 0.188 to 0.375 μg mL^{-1}, thereby indicating a synergistic effect.[87] 20-Hydroxyecdysone (20E) **145**, isolated from *Achyranthes japonica*, was found to be active MRSA, either alone or in combination with ampicillin (AM) or gentamicin (GM). These results investigated the antibacterial activity of 20E **145**, which exhibited poor antibacterial activity (MIC = 250–500 μg ML^{-1}) against all the bacterial strains tested. But the combined activity of ampicillin (AM), gentamicin (GE) plus 20E **145** against MRSA resulted in FICs ranging from 4.00 to 0.031 μg mL^{-1}, respectively. Meanwhile, the FIC index ranged from 0.16–4.50, indicating a marked synergistic relationship between AM, GE and 20E **145** against MRSA with enterotoxin gene *in vitro*.[88] The seeds of *Swietenia mahagoni* afforded two limonoids, swietenolide **146**, and 2-hydroxy-3-*O*-tigloylswietenolide **147**, showed MDR against haemolytic *S. aureus*, *S. aureus*, *S. pneumoniae*, *Haemophilus influenzae*, *E. coli*, *Klebsiella pneumoniae*, *Salmonella typhi*, and *Salmonella paratyphi*. compound **147** displayed overall more potent activity than compound **146**.[89] Ellagic acid **148** from *Rosa rugosa*; norwogonin **149** from *Scutellaria baicalensis*; and chebulagic acid **150**, chebulinic acid **151**, corilagin **152**, and terchebulin **153** from *Terminalia chebula*, had MDR activities. The most potent compound was norwogonin **149** with MIC 128 μg mL^{-1}, and MBC 256 μg mL^{-1} against clinically relevant strains of *A. baumannii*.[90] 3β-*O*-*p*-coumaroyltormentic acid **154**, isolated from *Planchonia careya*, showed weakly selective for VRE compared with eukaryotic cells, with MIC 59.4 μg mL^{-1} and IC_{50} of 72.0 μg mL^{-1} for MA104 cells.[91] Ent-18-acetoxy-11α-hydroxykaur-16-en-15-one **155**, ent-18-acetoxy-7β-hydroxykaur-16-en-15-one **156**, ent-18-acetoxy-7β,14α-dihydroxykaur-16-en-15-one **157**, isolated from *Croton tonkinensis*, exhibited MICs 32, 500, and 125 μg mL^{-1}, respectively, against MRSA strains.[92] 9-Methoxy-tariacuripyrone **158**; and aristololactam I **159**; isolated from *Aristolochia brevipes*, demonstrated very good antituberculous activity against sensitive, mono-resistant, and clinically strains, MDR, with MIC 25–50 μg mL^{-1}, except for *M. tuberculosis* H37RvIr, for MIC 12.5 μg mL^{-1} for **158**. Aristololactam I **159** demonstrated the greatest inhibitory activity against all strains assayed, with MIC 12.5–25.0 μg mL^{-1}.[93] Tiliacorinine **160**, 2′-nortiliacorinine **161**, and tiliacorine **162**, isolated from *Tiliacora triandra*, were tested against 59 clinical isolates of MDR *M. tuberculosis* (MDR-MTB). The alkaloids **160–162** showed MIC 0.7–6.2 μg mL^{-1}, but they exhibited the MIC 3.1 μg mL^{-1} against most MDR-MTB isolates.[94]

(−)-Licarin A (LA) **163**, was isolated from *Aristolochia taliscana* and the antitubercular activity of LA **163** was tested in a TB murine model inducing disease with *M. tuberculosis* H37Rv or MDR. In animals infected with drug sensitive or MDR strains, LA **163** produced a significant decrease of pulmonary bacillary burdens at day 30 of treatment, and a significant pneumonia reduction at days 30 and 60 of treatment.[95] Maritinone **164**, and 3,3′-biplumbagin **165**, showed the strongest activity against both MTB/H37Rv strains (MIC 1.56–3.33 μg mL^{-1}). The bioactivity of maritinone **164** and 3,3′-biplumbagin **165** were 32 times more potent than rifampicin against the pan-resistant strain, and both dimers showed to be non-toxic against PBMC and Vero cells, with selectivity index (SI) of maritinone **164** and 3,3′-biplumbagin **165** on Vero cells was 74.34 and 194.11 against sensitive and pan-resistant MTB strains, respectively.[96] Ent-18-hydroxykaur-16-en-15-one **166**, ent-18-acetoxy-7α-hydroxykaur-16-en-15-one **167**, ent-1β,14β-diacetoxy-7α-hydroxykaur-16-en-15-one **168**, ent-1β,7α-diacetoxy-14β-hydroxykaur-16-en-15-one **169**, ent-1β,7α,14β-triacetoxykaur-16-en-15-one **170**, ent-1β-acetoxy-7α,14 β-dihydroxykaur-16-en-15-one **171**, ent-7α,14β-dihydroxykaur-16-en-15-one **172**, ent-7α,18-dihydroxykaur-16-en-15-one **173**, ent-18-acetoxy-7α,14β-dihydroxykaur-16-en-15-one **174**, ent-18-acetoxy-11β-hydroxykaur-16-en-15-one **175**, ent-11β-acetoxy-7α-hydroxykaur-16-en-15-one **176**, ent-11β-acetoxykaur-16-en-18-ol **177**, ent-11β-acetoxykaur-16-en-18-oic acid **178**, ent-18-acetoxy-7α-hydroxykaur-16-ene **179**, ent-18-acetoxy-11α-hydroxykaur-16-ene **180**, ent-16(*S*)-18-acetoxy-7α-hydroxykaur-15-one **181**, 14α-hydroxykaur-16-en-7-one **182**, 7α,10α-epoxy-14β-hydroxygrayanane-1(5),16(17)-dien-2,15-dione **183**, and 7α,10α-epoxy-14β-hydroxygrayanane-1(2),16(17)-dien-15-one **184**, are diterpenoids isolated from *Croton tonkinensis*. All diterpenoids showed high to moderate activity

against *Mycobacterium*. The highest antituberculosis activity was observed for ent-1β,7α,14β-triacetoxykaur-16-en-15-one **170**, with MIC 0.78,1.56 and 3.12–12.5 μg mL^{-1} against H37Ra, H37Rv and all other resistant strains of *M. tuberculosis* examined.[97] Ethyl *p*-methoxycinnamate (EPMC) **185**, isolated from *Kaempferia galanga*, was shown to inhibit *M. tuberculosis* H37Ra, H37Rv, drug susceptible and MDR clinical isolates (MIC 0.242–0.485 mM).[98] Plumericin **186**, showed better activity against pan sensitive as well as four MDR strains of *M. tuberculosis* with MIC values of 2.1 ± 0.12, 1.3 ± 0.15, 2.0 ± 0.07, 1.5 ± 0.13, and 2.0 ± 0.14 μg mL^{-1} and MBC 3.6 ± 0.22, 2.5 ± 0.18, 3.8 ± 0.27, 2.9 ± 0.20, and 3.7 ± 0.32 μg mL^{-1} than isoplumericin **187**, respectively, isolated from *Plumeria bicolor*. Interestingly, both compounds showed an advantage over rifampicin (80 times) and isoniazid (8 times) by being highly active against the MDR strains.[99]

Conessine **188**, isolated from *Holarrhena antidysenterica*, combined with various antibiotics for synergistic activity determination against resistance *P. aeruginosa* PAO1 strain K767 (wild-type), K1455 (MexAB-OprM overexpressed), and K1523 (MexB deletion). H33342 accumulation assay was used to evaluate efflux pump inhibition while NPN uptake assay was assessed membrane permeabilization. Conessine **188** significantly reduced MICs of all antibiotics by at least 8-fold in MexAB-OprM overexpressed strain. With erythromycin, novobiocin, and rifampicin, MICs were 4-8-fold < MICs of the wild-type strain. Loss of MexAB-OprM due to deletion of mexB affected susceptibility to almost all antibiotics, except novobiocin. Synergistic activities between other antibiotics (except novobiocin) and conessine **188** observed in MexB deletion strain suggested that conessine **188** might inhibit other efflux systems present in *P. aeruginosa*. Inhibition of H33342 efflux in the tested strains clearly demonstrated that conessine **188** inhibited MexAB-OprM pump. In contrast, the mode of action as a membrane permeabilizer was not observed after treatment with conessine **188** as evidenced by no accumulation of 1-*N*-phenylnaphthylamine. These results suggested that conessine **188** could be applied as a novel efflux pump inhibitor to restore antibiotic activity by inhibiting efflux pump systems in *P. aeruginosa*. The findings speculated that conessine **188** may also have a potential to be active against homologous resistance–nodulation–division (RND) family in other Gram-negative pathogens.[100] Tomatidine (TO) **189**, a steroidal alkaloid from solanaceous plants, possesses potent antibacterial activity against *S. aureus* small-colony variants (SCVs). Using genomic analysis of *in vitro*-generated TO-resistant *S. aureus* strains to identify mutations in genes involved in resistance, identified the bacterial ATP synthase as the cellular target.[101]

The growth of the majority of *Pseudomonas*, *Streptococcus*, and *Staphylococcus* isolates was completely inhibited by 64 μg mL^{-1} allicin **190**. *S. pyogenes* SNo 67467, *S. pneumoniae* SNo 68668, and *S. aureus* ATCC 43300 were completely inhibited by 32 μg mL^{-1} allicin **190** and all *A. baumannii* isolates were completely inhibited by 16 μg mL^{-1}. *K. pneumoniae* isolates were slightly more resistant, with a MIC of 128 μg mL^{-1}. *P. aeruginosa* DSM2659 showed high resistance to allicin **190** (MIC 512 μg mL^{-1}) compared to *P. aeruginosa* PAO1 SBUG8 and PAO25 (MIC 64 μg mL^{-1}). MDR and non-MDR *S. pneumoniae* strains tested were equally susceptible to allicin **190** and showed MICs 32–64 μg mL^{-1} allicin **190** and MBCs from 64 to 128 μg mL^{-1} allicin **190**, respectively. In comparison to conventional antibiotics, the MICs, and MBCs for allicin **190** were generally higher. Thus, except for the MDR strains, the clinical isolates of *S. pneumoniae* were susceptible to all tested antibiotics at <1 μg mL^{-1}. The MDR *S. pneumoniae* isolates were resistant to erythromycin and clindamycin (MICs > 256 μg mL^{-1}) and for these MDR strains, allicin **190**, including in absolute μM terms, compared favorably with those antibiotics.[102]

Fig. 8 illustrates the chemical structure for plants natural derived compounds **191–265**. The isoflavone biochanin A **191**, exhibited ethidium bromide (EtBr) efflux pump inhibiting activity in *Mycobacterium smegmatis* mc^2155 comparable to that of verapamil. The stilbene resveratrol **192**, and formononetin **193**, were less active.[103] 4′,6′-Dihydroxy-3′,5′-dimethyl-2′-methoxychalcone **194**, 3,5,4′-trimethoxy-*trans*-stilbene **195**, isolated from *Dalea versicolor*, were very weakly active alone (MICs of 250 and 500 μg mL^{-1}, respectively), but they caused complete growth inhibition at very low concentrations (~3.3 μg mL^{-1}) in combination with a subinhibitory concentration of berberine **31** against NorA mutant *S. aureus*.[104] 4-((*E*)-5-(3,3-dimethyl-2-oxiranyl)-3-methyl-2-pentenyl)-oxy-7H-furo(3,2)-chromen-7-one **196**, isolated from grape fruit oil, enhanced the susceptibility of test MRSA strains to ethidium bromide and norfloxacin.[105] Sophoraflavanone B (SPF-B) **197**, a prenylated flavonoid, isolated from *Desmodium caudatum*, showed MIC against MRSA 15.6–31.25 μg mL^{-1}. The optical density at 600 nm of MRSA suspensions treated with a combination of detergent and SPF-B **197** reduced the MRSA by 63–73%. In the SPF-B **197** and PGN combination assay, direct binding of SPF-B **197** with PGN from *S. aureus* was evident.[106] Naringenin **198**, eriodictyol **199**, and taxifolin **200**, are good candidate for β-Ketoacyl acyl carrier protein synthase (KAS) III inhibitors, which is a key catalyst in bacterial fatty acid biosynthesis, and showed good binding affinities, and docked well with efKAS III, with MIC 128–512 μg mL^{-1}.[107] Galbanic acid **201**, a sesquiterpene coumarin isolated from *Ferula szowitsiana* roots, was investigated for its antimicrobial activity as well as ethidium bromide, in six MDR clinical isolates of *S. aureus*. Galbanic acid **201** had inhibitory effect on none of the isolated bacteria tested (up to 800 μg mL^{-1}). The MIC range of ciprofloxacin, tetracycline, and ethidium bromide, against all tested *S. aureus* were 10–80, 10–80 and 4–16 μg mL^{-1}, respectively. These were reduced to ≤2.5–5, 2.5–5 and 0.5–2 μg mL^{-1} in the presence of galbanic acid **201** (300 μg mL^{-1}) or verapamil (100 μg mL^{-1}). The rate of ethidium bromide (2 μg mL^{-1}) accumulation in clinical isolates was enhanced with galbanic acid **201** (300 μg mL^{-1}). There is also a decrease in loss of ethidium bromide from bacteria in the presence of galbanic acid **201**, like verapamil (100 μg mL^{-1}).[108] α-Mangostin (AMG) **202**, and isobavachalcone (IBC) **203**, under 8 μg mL^{-1} dramatically restored the activity of colistin against MDR *E. coli* B2 isolate, with the decreased concentration of colistin from 8 to 0.0625 μg mL^{-1}. The MIC_{50} and MIC_{90} against MRSA and VRE were 0.5 and 4–8 μg mL^{-1} for AMG **202** and IBC **203**, respectively. Both AMG **202** and IBC **203** display similar efficiency to vancomycin. These

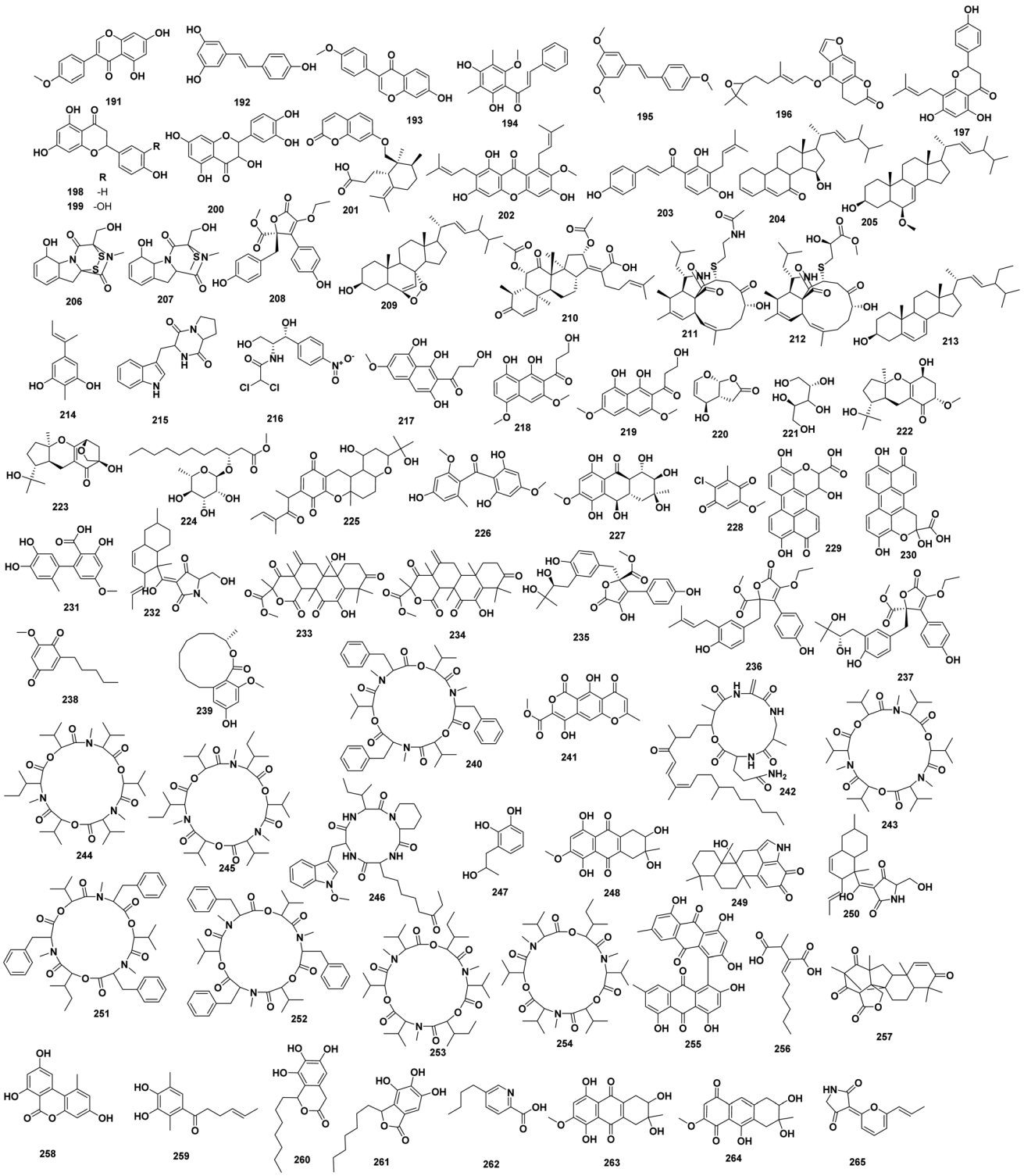

Fig. 8 Plants/endophytes derived natural products **191–265**.

results indicate that AMG **202** and IBC **203** are potent antibiotic candidates to combat MDR bacteria, practically against Gram-positive pathogens.[109]

(22*E*,24*R*)-6β-methoxyergosta-7,22-diene-3β,5α-diol **204**, (22*E*,24*R*)-6β-methoxyergosta-7,22-diene-3β,5α-diol **205**, isolated from a pathogenic fungus, *Microdochium majus* strain 99 049, from wheat, showed moderate to weak anti-MRSA activity (MIC 25, 100 μg mL^{-1}, respectively).[110] The antimicrobial epidithiodioxopiperazine, gliotoxin **206**, and bisdethiobis(methylthio)gliotxin **207**, were isolated from the endophytic fungus *Hypocrea virens*, from *Premna serratifolia*, showed MIC 32–35 μg mL^{-1} against MRSA.[111] Terrenolide S **208**, isolated

from the endophytic fungus *Aspergillus terreus* isolated from the roots of *Carthamus lanatus*, displayed a potent activity towards MRSA with IC_{50} 2.29 μM.[112] (22E, 24R)5, 8-epidioxy-5α,8α-ergosta-6,22E-dien-3β-ol **209**, isolated from Chinese mangrove *Ceriops tagal* endophytic *Cytospora* sp., showed weak anti-MRSA with MIC 233 μM.[113] Helvolic acid **210**, isolated from endophytic fungus *Xylaria* sp. from *Anoectochilus setaceus*, showed potent anti-MRSA with MIC 4 μM.[114] Cyschalasin A & B **211–212**, isolated from the endophytic fungus *Aspergillus micronesiensis*, showed anti-MRSA with MIC 17.5, and 10.6 μM, respectively.[115] (22*E*,24*R*)-stigmasta-5,7,22-trien-3β-ol **213**, isolated from the endophytic fungus *Aspergillus terreus*, derived from *Carthamus lanatus*, exhibited potent antibacterial activity MRSA with IC_{50} 0.96 μg mL^{-1}.[116] Aspergillusphenol A **214**, isolated from the endophytic fungus *Rhytidhysteron* sp. BZM-9, showed moderate antimicrobial activity to MRSA with a MIC value of 6.25 μg mL^{-1}.[117] Cyclo-(tryptophanyl-prolyl) **215**, and chloramphenicol **216**, isolated from *Universiti Kebangsaan* 25, from *Zingiber spectabile*, showed anti-MRSA with a MIC 16, 8 μg mL^{-1}, respectively.[118] 3-Hydroxy-1-(1,3,8-trihydroxy-6-methoxynaphthalen-2-yl) propan-1-one **217**; 3-hydroxy-1-(1,8-dihydroxy-3,5-dimethoxynaphthalen-2-yl) propan-1-one **218**, and 3-hydroxy-1-(1,8-dihydroxy-3,6-dimethoxynaphthalen-2-yl) propan-1-one **219**, were isolated from the *Phomopsis fukushii*, an endophyte of plant *Paris polyphylla*, showed anti-MRSA activity with MIC 4, 4, and 8 mg mL^{-1}, respectively.[119] Oxysporone **220**, and xylitol **221**, isolated from the endophytic fungus *Pestalotia* sp. from *Heritiera fomes*, were tested against various strains of MRSA, *i.e.*, XU212, ATCC 25923, SA-1199B, EMRSA-15, MRSA340702, and showed MIC 128, 128, 64, 64, and 128 μM, respectively, for xylitol **221**, and 128, 64, 32, 32, and 64 μM, respectively, for oxysporone **220**.[120] Guignardone I **222**, and guignardone B **223**, isolated from the endophytic fungus A1 of the mangrove plant *Scyphiphora hydrophyllacea* exhibited zone of inhibition of 9.0 mm and 8.0 mm, respectively, against MRSA at 65 μM.[121] A new fatty acid glycoside, (*R*)-3-hydroxy undecanoic acid methylester-3-*O*-α-L-rhamnopyranoside **224**, was isolated from the *Guignardia* sp. from same plant, and zone of inhibition was found to be 10.7 mm against MRSA.[122] 2,3-Didehydro-19α-hydroxy-14-epicochlioquinone B **225**, griseophenone C **226**, and tetrahydrobostrycin **227**, were isolated from the endophytic *Nigrospora* sp. MA75 from the mangrove plant *Pongamia pinnata* that exhibited anti-MRSA activity with MIC values of 16.5, 1.6, and 5.9 μM, respectively.[123] 2-Chloro-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione **228**, isolated from the endophytic fungus *Xylaria cubensis* PSU-MA34, from mangrove *Bruguiera parviflora* exhibited anti-MRSA with MIC 128 μg mL^{-1}.[124] Xanalteric acid I **229**, xanalteric acid II **230**, and altenusin **231**, isolated from the endophytic *Alternaria* sp., from mangrove *Sonneratia alba*, exhibited anti-MRSA with MIC values of 125, 250, and 31.25 μg mL^{-1}, respectively.[125]

A bioactive compound, equisetin **232**, was isolated from endophytic *Fusarium* sp., and exhibited anti-MRSA activity with MIC 16 μg mL^{-1}.[126] Terretonin **233**, terretonin A **234**, butyrolactone VI **235**, aspernolide F **236**, and aspernolide G **237**, were isolated from the endophytic fungus *Aspergillus terreus* from the roots of *Carthamus lanatus*. All compounds exhibited anti-MRSA activity with IC_{50} 0.94 to <20 mg mL^{-1}.[127] Primin **238**, isolated from endophytic fungus *Botryosphaeria mamane* PSU-M76, isolated from *Garcinia mangostana* leaves, exhibited anti-MRSA with MIC 8 mg mL^{-1}.[128] (3*S*)-lasiodiplodin **239**, isolated from endophytic PSU-M35 and PSU-M11 were isolated from *Garcinia mangostana* leaves, exhibited anti-MRSA with MIC 128 mg mL^{-1}.[129] Beauvericin **240**, isolated from endophytic fungus *Fusarium oxysporum*, isolated from *Cinnamomum kanehirae*, exhibited potent anti-MRSA with MIC 3.125 μg mL^{-1}.[130] An endophytic fungus *Fusarium tricinctum* isolated from *Aristolochia paucinervis* when cocultured with *B. subtilis* on solid rice medium increased the secondary metabolite production by 78-fold, *i.e.*, increase in concentration of lateropyrone **241**, lipopeptide fusaristatin A **242**, and three cyclic depsipeptides of the enniatin type (enniatin B **243**, enniatin B1 **244**, enniatin A1 **245**). The antibacterial activity of this compounds was tested against various pathogenic microbes including MDR *S. aureus* (*S. aureus* 25 697 strain) and showed MIC 2–64 μg mL^{-1}. The highest antimicrobial activity was shown by lateropyrone **241** with MIC 2–4 μg mL^{-1}, followed by enniatin A1 **245** with MIC 4–8 μg mL^{-1} and enniatin B1 **244** that showed activity at MIC of 8 μg mL^{-1}.[131] Apicidin **246**, was isolated from the endophytic fungi *Fusarium* sp. from the plant *Anemopsis californica*. Antiquorum sensing inhibition of apicidin **246** was tested against MRSA. Apicidin **246** showed anti-MRSA by targeting AgrA plasmid.[132] 3-(2-Hydroxypropyl)-benzene-1,2-diol **247**, and desoxybostrycin **248**, were isolated from the PSU-N24, an endophyte of *Garcinia nigrolineata*. At 128 μg mL^{-1}, the two compounds exhibited anti-MRSA activity.[133] Mycoleptodiscin B **249**, isolated from *Mycoleptodiscus* sp. isolated from *Calamus thwaitesii*, showed anti-MRSA activity with MIC 32 μg mL^{-1}.[134]

Trichosetin **250**, beauvericin A **251**, beauvericin **252**, enniatin I **253**, and enniatin H **254**, isolated from endophytic fungi *Fusarium* sp. TP-G1 isolated from the roots of *Dendrobium officinale* Kimura, showed anti-MRSA with MIC 2, 2, 8, 16, and 32, respectively.[135] Skyrin **255** isolated from the *Talaromyces wortmannii*, an endophyte of aloe vera exhibited anti-MRSA activity with MIC 4 μg mL^{-1}.[136] Piliformic acid **256**, was isolated from the *Xylaria cubensis* BCRC 09F 0035, an endophyte of *Litsea akoensis*, and exhibited MIC 200 μg mL^{-1} against MRSA.[137] Andiconin C **257**, isolated from the *Aspergillus* sp. TJ23, an endophyte of *Hypericum perforatum*, exhibited anti-MRSA with MIC > 100 μg mL^{-1}.[138] Alternariol **258**, isolated from the endophytic fungus *Alternaria alternata* resident of plant *Grewia asiatica*, exhibited anti-MRSA with MIC 8 μg mL^{-1}.[139] 2-Deoxysohirnone C **259**, isolated from the *Penicillium* sp. GD6, an endophyte of *Bruguiera gymnorrhiza* showed anti-MRSA with MIC 80 μg mL^{-1}.[140] Cytosporone D **260**, and cytosporone E **261**, were isolated from the *Cytospora* sp. CR200, an endophyte collected from *Conocarpus erectus*, and exhibited moderate anti-MRSA with MIC 8–64 μg mL^{-1}.[141] Fusaric acid **262**, was isolated from the endophytic fungi *Fusarium* Sp. DZ-27, isolated from the mangrove plant *Kandelia candel*, showed Antimycobacterial activity against clinical MDR *M. tuberculosis* strains, and clinical extensively drug-resistant *M. avium*-intracellular strains with MIC 10–60 μg mL^{-1}.[142] 4-Deoxybostrycin **263**, and nigrosporin **264**, isolated from the endophytic fungus *Nigrospora* sp.,

showed antimycobacterial activity against clinical MDR *M. tuberculosis* strain (K2903531), clinical MDR *M. tuberculosis* strains (0 907 961), clinical drug-resistant *M. tuberculosis* strain (K0903557), and clinical extensively drug-resistant (XDR) *M. avium*-intracellular strain (K0803182), with MIC values in the range of 5 to >60 μg mL^{-1} and 15 to >60 μg mL^{-1}, respectively.[143] Vermelhotin **265**, was isolated from endophytic fungus MEXU 26343, collected from the plant *Hintonia latiflora*,[144] exhibited antimycobacterial against clinical strains of MDR-TB with MIC 1.5–12.5 g mL^{-1}.[145]

Fig. 9 illustrates the chemical structure for natural derived compounds **266–307.** 8-*O*-methylepiaustdiol **266**, stemphyperylenol **267**, skyrin **268**, secalonic acid **269**, and norlichexanthone **270**, isolated from endophytic fungus *Talaromyces* sp. ZH-154, was isolated from *Kandelia candel* stem bark, exhibited antimicrobial activity against MDR *P. aeruginosa* with MIC 25.0, 12.5, 12.5, 12.5, and 25.0 μg mL^{-1}, respectively.[146] Neosartorin **271**, derived from the endophytic fungi *Aspergillus fumigatiaffinis*, exhibited antimicrobial activity against resistant *E. faecalis* with MIC 16–32 μg mL^{-1}.[147] The polyketide setosol **272**, isolated from the endophytic fungi *Preussia isomera*, resident of the stem of *Panax notoginseng*, exhibited antibacterial activity with MIC 25 μg mL^{-1} against MDR-resistant *E. faecalis*, MRSA, and MDR *E. faecium*.[148] Equisetin **273**, isolated from the endophyte *Chaetomium globosum* XL-1198, isolated from *Salvia miltiorrhiza*, exhibited antibacterial activity against MDR *S. epidermidis*, MDR *E. faecalis*, MRSA, and MDR *E. faecium* with MIC 3.13–6.25 μg mL^{-1}.[149] 2′-acetyl-4′,4-dimethoxybiphenyl-2-carbaldehyde **274**, was isolated from the endophyte *Pestalotiopsis zonata* resident of the plant *Cyrtotachys lakka*, exhibited weak anti-MRSA and vancomycin-resistant *E. faecium* with MIC values of 0.84 and 0.87 μm mL^{-1} respectively.[150] Alterporriol N **275**, Alterporriol D **276**, were isolated from endophytic *Stemphylium globuliferuman* isolated from *Mentha pulegium* and showed anti-MRSA with MICs of 62.5, 31.25 μg mL^{-1}, respectively.[151] Indolyl-3-carboxylic acid **277**, 5-acyl-2-methylpyrrole **278**, isolated from the endophyte S20 of *Cephalotaxus hainanensis* Li. showed anti-MRSA with diameters of inhibition zones 8, 10 mm/10 μg mL^{-1}, respectively, impregnated on sterile filter paper discs (6 mm diameter).[152,153]

Xiamycin A **279**, indosespene **280**, were produced by endophytic *Streptomyces* sp. HKI0595, isolated from mangrove tree *Kandelia candel*, showed anti-MRSA and vancomycin-resistant *E. faecalis*.[154] Violaceol I **281**, and Violaceol II **282**, isolated from endophytic fungus *Trichoderma polyalthiae* extracted from culture broth media, showed anti-MRSA, with MIC values <9.765–156.25, <9.765–312.5 μg mL^{-1}, respectively.[155] In agar diffusion assays run on bacterial lawns, guanacastepene **283**, isolated from endophytic fungus CR115, *Daphnopsis americana*, shows anti-MRSA and vancomycin-resistant *E. faecalis*. Against MRSA 100 μg of guanacastepene **283** or vancomycin produce 11-, and 17 mm zones of growth inhibition, respectively. While vancomycin is ineffective against VREF, guanacastepene **283** produced a 9 mm zone of growth inhibition.[156] (2*R*,3*S*)-7-ethyl-

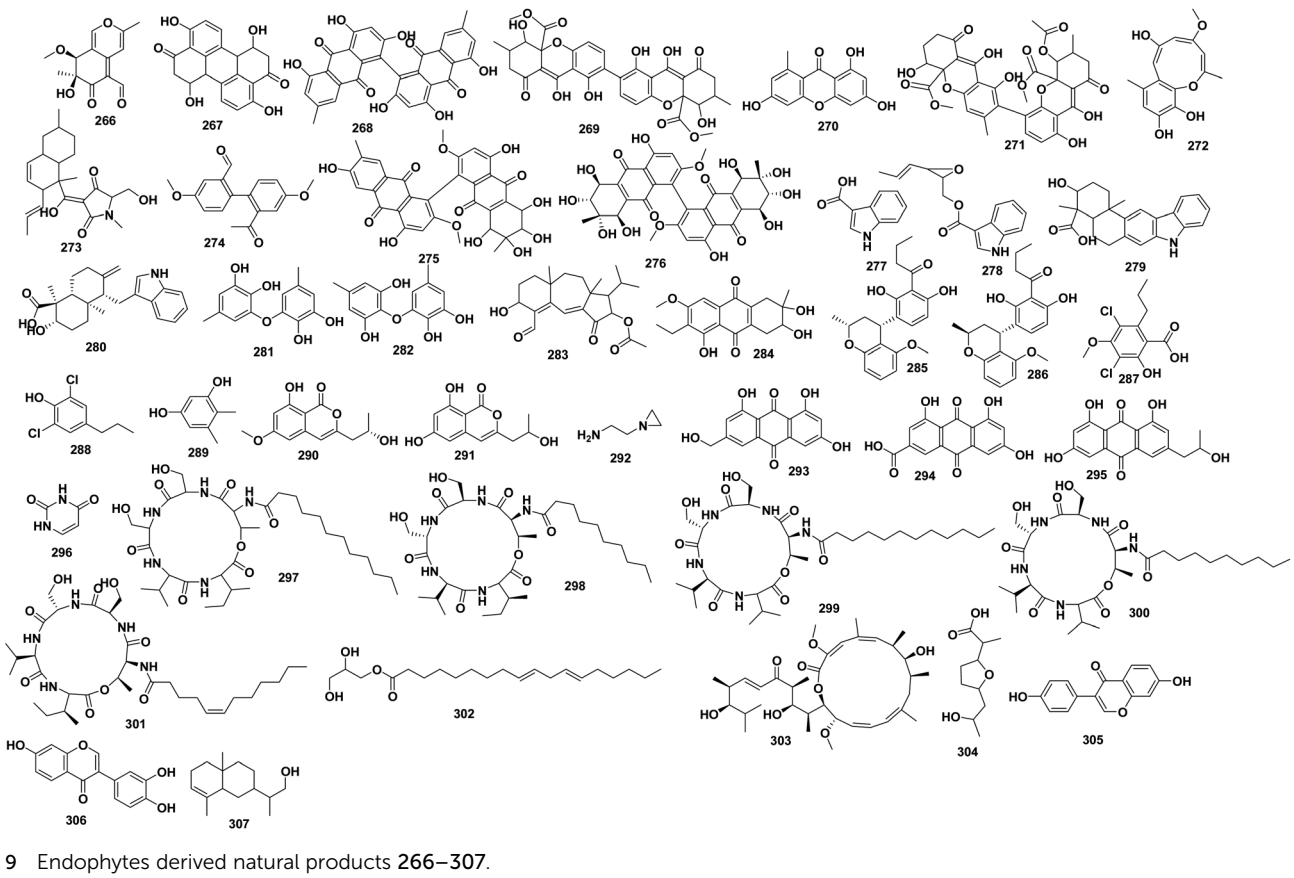

Fig. 9 Endophytes derived natural products **266–307**.

1,2,3,4-tetrahydro-2,3,8-trihydroxy-6-methoxy-3-methyl-9,10-anthracenedione **284**, isolated from the mangrove-derived fungus *Phomopsis* sp. PSU-MA214, showed anti-MRSA-SK1.[157] Nodulisporin H **285**, and 8-*O*-methylnodulisporin F **286**, isolated from the mangrove-derived fungus *Daldinia eschscholtzii* HJ004, showed a moderate anti-MRSA with MIC 6.25–12.5 μg mL^{-1}.[158]

Differanisole A **287**, 2,6-dichloro-4-propylphenol **288**, and 4,5-dimethylresorcinol **289**, isolated from endophytic fungus *Chaetomium* sp. HQ-1, exhibited moderate anti-MRSA, with MIC 16–128 μg mL^{-1}.[159] Diaporthin **290**, and orthosporin **291**, isolated from endophytic fungus *Diaporthe terebinthifolii*, showed anti-MRSA.[160] Aziridine, 1-(2-aminoethyl)-**292**, isolated from endophytic fungus *Cochliobolus* sp. APS1, from *Andrographis paniculate*, showed MIC 15.62 to 250 μg mL^{-1} against MRSA and VRSA.[161] ω-Hydroxyemodin **293**, emodic acid **294**, (+)-2′*S*-isorhodoptilometrin **295**, isolated from endophytic fungus *Penicillium restrictum* was isolated from the stems of a milk thistle plant. These compounds were quorum sensing inhibitors in a clinical isolate of MRSA, with IC_{50} 8–120 μM.[162] Pyrimidine-2,4-dion **296**, isolated from endophytic fungus *Bacillus* sp. RD26, isolated from *Phyllanthus amarus*, showed anti-MRSA, with MIC 64 μg mL^{-1}.[163] Stephensiolides I, D, G, C, F **297–301**, isolated from endophytic fungus *Lecanicillium* sp. from *Sandwithia guyanensis* plant. Stephensiolides I **297** showed a strong anti-MRSA with MIC ≤ 4 μg mL^{-1}, while stephensiolides G **299** exhibited activity with MIC ≤ 16 μg mL^{-1}, D **298** and F **301** were found to be less active with MIC ≤ 32 μg mL^{-1}, and C **299** showed a moderate MIC of ≥128 μg mL^{-1}.[164] 1-Monolinolein **302**, bafilomycin D **303**, nonactic acid **304**, daidzein **305**, 3′-hydroxydaidzein **306**, isolated from endophytic *actinomycete* strain YBQ59 was isolated from *Cinnamomum cassia*, exhibited anti-MRSA ATCC 33591 and methicillin-resistant *Staphylococcus epidermidis* ATCC 35984 (MRSE) among which **302** revealed the strongest effects with MIC 8.5 and 14.6 μg mL^{-1}, respectively. However, **303** showed high potential effect against MRSA (MIC of 11.1 μg mL^{-1}) but less effect against MRSE (MIC of 30.3 μg mL^{-1}).[165] Eutyscoparin G **307**, isolated from endophytic fungus *Eutypella scoparia* SCBG-8, displayed anti-MRSA with MIC 6.3 μg mL^{-1}.[117]

The novel homicorcin peptide **308**, isolated from plant endophyte *S.s hominis* strain MBL_AB63, displayed anti-MRSA.[166] Actinomycin D **309** peptide, produced by plant endophyte *S. smyrnaeus* UKAQ_23, showed anti-MRSA ATCC 33591 (MIC of 2.5 μg mL^{-1}), and MDR *M. tuberculosis* MDRP (IC_{50} of 10 μg mL^{-1}).[167] Munumbicin peptide named munumbicins C **310**, produced by plant endophyte *Streptomyces* NRRL 30562, showed activity against drug-resistant *M. tuberculosis* MDR-P (IC_{50} > 125 μg mL^{-1}) and vancomycin-resistant ciprofloxacin-sensitive *Enterococcus faecalis* ATCC 51299 (MIC of 16 μg mL^{-1}).[168] Munumbicins E-4 peptide **311**, was produced by endophytic *Streptomyces* NRRL 30562, isolated from *Kennedia nigricans*, showed anti-MRSA 43000 (MIC of 16 μg mL^{-1}).[169] Kakadumycin A **312**, peptide produced by *Streptomyces* NRRL 30566, an endophyte of the plant *Grevillea pteridifolia*, showed activity against MRSA ATCC 33591 (MIC of 0.5 μg mL^{-1}).[170]

3.3. Lichens/endo-lichens derived natural products

Fig. 10 illustrates the chemical structure for natural derived compounds **313–341.** Most reports on the activity of the following isolated compounds against MDR bacteria relate to *in vitro* studies. (+)-Usnic acid **313,** isolated from *Usnea steineri*,

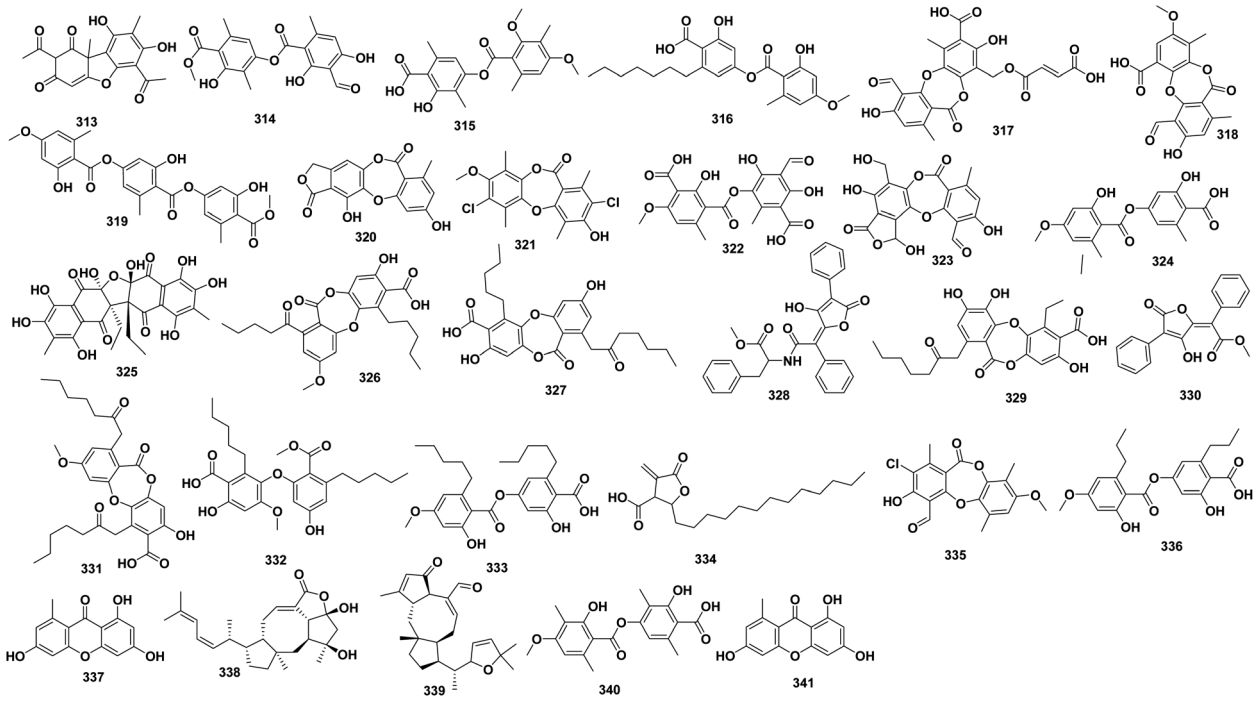

Fig. 10 Lichens/endo-lichens derived natural products **313–341**.

exhibited strong activity against resistance strains of *S. epidermidis* (MIC 3.12 μg mL^{-1}), *S. aureus* and *S. haemolyticus* (MIC 12.5 μg mL^{-1}).[171,172] Atranorin **314**, diffractaic acid **315**, sphaerophorin **316**, fumarprotocetraric acid **317**, psoromic acid **318**, tenuiorin **319**, variolaric acid **320**, and vicanicin **321**, isolated from lichens, collected in several Southern regions of Chile (including Antarctica), showed anti-MRSA with MIC 8–1024 μg mL^{-1}.[172,173] Thamnolic acid **322**, isolated from *Usnea florida* showed activity against the drug-resistant *M. tuberculosis* H37Rv strain with MIC 250 μg mL^{-1}.[174] Salazinic acid **323** was isolated from *Usnea hirta*, showed anti-MRSA with MIC 7.8 μg mL^{-1}.[175] Evernic acid **324** (*Evernia prunastri*), hybocarpone **325** (*Lecanora conizaeoides*), lobaric acid **326** (*Sterocaulon dactylophyllum*), physodic acid **327** (*H. physodes*), rhizocarpic acid **328** (*Psilolechia lucida*), 3-hydroxyphysodic acid **329** (*H. physodes*), vulpinic acid **330** (*Letharia vulpina*), showed anti-MRSA with MIC 4–128 μg mL^{-1}.[176,177] Collatolic acid **331** from *Lecanora atra*, epiphorellic acid **332** from *Cornicularia epiphorella*, perlatolic acid **333** from *Stereocaulon* sp., protolichesterinic acid **334** from *Cornicularia aculeata*, showed anti-MRSA with MIC 4–128 μg mL^{-1}.[178] Pannarin **335** from *Psoroma. dimorphum*, showed anti-MRSA with MIC 4–8 μg mL^{-1}.[179] Divaricatic acid **336** was isolated from *Evernia mesomorpha*, showed anti-MRSA with MIC 7 μg mL^{-1}.[180] Norlichexanthone **337**, isolated from *Everniastrum* sp., showed anti-MRSA with IC_{50} 5.4 μg mL^{-1}.[181] Ophiobolin P& T **338–339**, isolated from endo-lichen fungus *Ulocladium* sp. (CHMCC5507), from *Everniastrum* sp. lichen, showed anti-MRSA with IC_{50} 25.1, 12.7 μg mL^{-1}, respectively.[182] Barbatic acid **340**, from *Cladia aggregate*, showed anti-MRSA with MIC 100 μg mL^{-1}.[183] Norlichexanthone **341**, isolated from endo-lichen fungus *Ulocladium* sp., isolated from *Everniastrum* sp., showed anti-MRSA with IC_{50} 20.95 μg mL^{-1}.[181]

3.4. Insects/animal/and their associated symbiont organism derived natural products

Fig. 11 illustrates insects/animal/and their associated symbiont organism derived natural products. Most reports on the activity of the following isolated compounds against MDR bacteria relate to *in vitro* studies. Hexanedioic acid **342**, Lauric acid **343**, glycerol monolaurate **344**, isolated from the edible *Hermetia illucens* larvae, showed anti-MRSA with MIC 137.369 μg mL^{-1}.[184,185] The prenylflavanones propolin H **345**, propolin G **346**, propolin D **347**, and propolin C **348**, isolated from Pacific propolis from bees' nest, showed anti-MRSA, where propolin D **347** and C **348** were the most active with MIC 8–16, 8–32 μg mL^{-1}, respectively.[186] Also, the propolins D **347**, C **348**, F **349** and G **346** from Taiwanese green propolis was obtained and showed antibacterial activity with MIC less than 2 μg mL^{-1} and MBC of 4 μg mL^{-1} against MRSA.[187]

Roseoflavin **350** was isolated from *Streptomyces davaonensis* YH01, which was isolated from the body surface of the queen of *Odontotermes formosanus*, and showed potential against nine kinds of MRSA strains, with inhibition zones in the ranges of 12.7–19.7 mm under a concentration of 15 μg/6 mm discs and 18.3–22.7 mm under a concentration of 30 μg/6 mm discs.[188] Actinomycin D and Actinomycin X2, isolated from endophytic *Gordonia* in the intestinal tract of *Periplaneta americana*, have anti-MRSA (ATCC 43300), with MIC 0.25 μg mL^{-1}.[189] 4-Methoxy-2*H*-pyran-2-one **351**, 4-methoxy-6-pentyl-2*H*-pyran-2-one **352**, 6-(1-hydroxypentyl)-4-methoxy-pyran-2-one **353**, 6-[8-propyloxiran-1-yl]-4-methoxypyran-2-one **354**, pestalotin **355**, 5,6-dihydro-4-methoxy-6-(pentanoyloxy)-2*H*-pyran-2-one **356**, and cyclo-(L-Pro-L-Val) **357**, isolated from *Chrysosporium multifidum* fungus isolated from *Hermetia illucens* gut, showed moderate anti-MRSA, where compound **354** showed the greatest activity (IC_{50} = 11.4 ± 0.7 μg mL^{-1} and MIC 62.5 μg mL^{-1}) against MRSA.[190]

A number of peptides were also reported to eradicate resistant bacterial strains. For instance, a small, <500 Da factor, isolated from the blowfly, *Lucilia sericata*, or Maggot, showed potent, thermally stable, protease resistant antibacterial activity against MRSA.[191] Mastoparan-1 peptide, isolated from *Polybia paulista* (Neotropical social wasp), had MIC 0.001–0.019 μM against MRSA.[192] Mauriporin, isolated from *Androctonus mauritanicus* (Fat tailed scorpion), had MIC 5–10 μM against MRSA.[193] Pro10-1D (derived from *protaetiamycine*), isolated from *Protaetia brevitarsis* (White-spotted flower chafer beetle) had MIC 4 μM against MDR.[194] A3 peptide, is modified version for AamAP1 which is a novel HDP that belongs to the venom of the North African scorpion *Androctonus amoeruxi*. A3 with

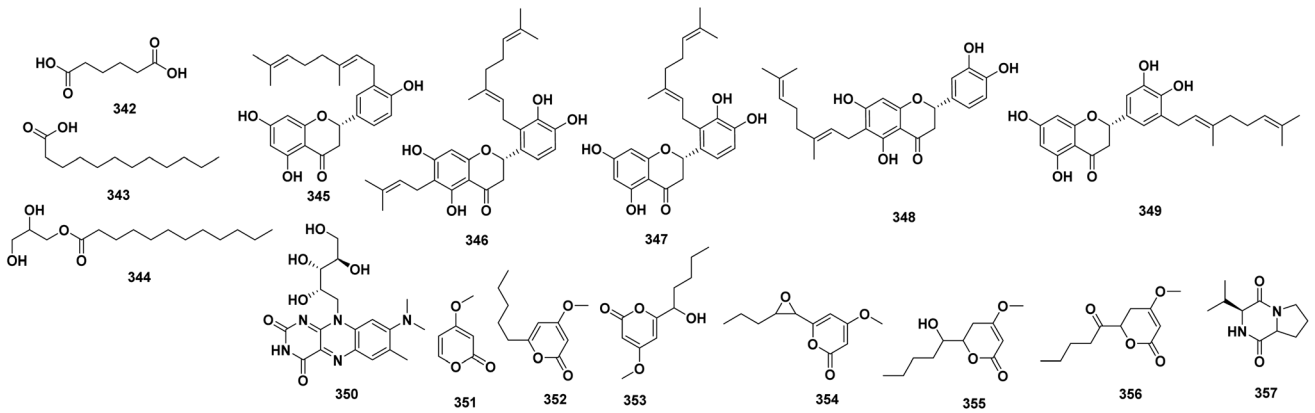

Fig. 11 Selected insects/animal/and their associated symbiont organism derived natural products.

conventional antibiotics caused a synergistic antimicrobial behavior that resulted in decreasing the MIC value for A3 peptide as low as 0.125 μM against MDR.[195] DLP4 peptide, isolated from *Hermetia illucens* larvae, had antibacterial activity against MRSA.[196] Lycotoxins I, was identified from venom of the wolf spider *Lycosa carolinensis*, had anti-MRSA USA300.[197,198] Arenicin-3, isolated from *Arenicola marina* (sandworm), had considerable antimicrobial activity even against XDR (extensive drug resistance) and MDR strains as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *E. coli and Klebsiella pneumoniae*.[199] Maculatin 1.3 peptide, isolated from frog *Litoria eucnemis*, showed anti-MRSA in a concentration dependent manner.[198,200] IP, isolated from the hard tick *Ixodes persulcatus*, has MIC 0.625–2.5 μg mL^{-1} for MRSA.[201]

3.5. Bacteria, fungi, higher fungi (mushrooms) derived natural products

Fig. 12 illustrates selected bacteria, fungi, higher fungi (mushrooms) derived natural products. Most reports on the activity of the following isolated compounds against MDR bacteria relate to *in vitro* studies. Mollicellin S **358**, mollicellin T **359**, and mollicellin U **360**, mollicellin D **361** and mollicellin H **362**, isolated from *Chaetomium brasiliense* SD-596 fungus, exhibited significant anti-MRSA, with MIC 6.25–12.5 μg mL^{-1}.[202] Fusidic acid **363**, the steroid-like topical antibiotics which was isolated from *Fusidium coccineum* or *Acremonium fusidioides* fungus, showed activity against MRSA.[203] Pleuromutilin **364** isolated from *Pleurotus mutilis* fungus, showed activity against MRSA.[204] Osmundalactone **365**, 5-hydroxy-hex-2-en-4-olide **366**, spiromentins C **367**, isolated from *Tapinella atrotomentosa* mushroom. These compounds proved to possess significant antibacterial activity against multi-resistant *Acinetobacter baumannii* and extended-spectrum β-lactamase (ESBL)-producing *E. coli*.[205] CoQ0 **368**, isolated from *Antrodia cinnamomea* fungus, showed strong MRSA growth inhibition with MIC 7.81 μg mL^{-1}. CoQ0 **368** was found to eradicate biofilm MRSA efficiently and reduce the biofilm thickness. The compound **368** has also bactericidal activity against MRSA by inhibiting DNA polymerase and topoisomerases. The proteomic assay showed that CoQ0 **380** also reduced the ribosomal proteins.[206] Rubellins B **369**, C **370**, D **371**, and E **372** and caeruleoramularin **373**, isolated from fungus *Ramularia collo-cygni*, showed activities against Gram-negative bacteria, including MDR strains, such as *S. aureus* (SG) 511, *S. aureus* 134/94 (MRSA), *B. subtilis* (ATCC) 6633, *Mycobacterium vaccae* (IMET) 10 670, or *Enterococcus faecalis* 1528 (VRE).[207] Viriditoxin **374** which is xanthoradones relative structure, produced by *Penicillium radicum* FKI-3765-2, exhibit anti-MRSA by inhibiting FtsZ, the bacterial tubulin homolog which is crucial in septum formation.[208]

Moreover, the peptide antibiotics tripropeptins A, B, C, D, and Z were isolated from cultured cells and broth of *Lysobacter* sp. Tripropeptins are active against Gram-positive bacteria including MRSA *in vitro*.[209] Also, serrawettin W1, cyclodepsipeptide isolated from Gram-negative bacterium *Serratia marcescens*, inhibited the growth of nine different MRSA isolates.[210] In addition, plectasin peptide, isolated from a fungus *Pseudoplectania nigrella*, showed especially activity against resistance strains of *S. pneumoniae*, *S. aureus*, *S. epidermidis*, and *S. pyogenes* with MIC 32–64, 32, 8, and 0.125 μg mL^{-1}, respectively.[211]

3.6. Minerals

Nanomedicine is a budding branch of medicine that uses advancement in nanotechnology for the prevention and treatment of infectious disease. The advancement in nanotechnology has become an effective approach for the fabrication of metallic/salt bulk materials in nanosized particles for the

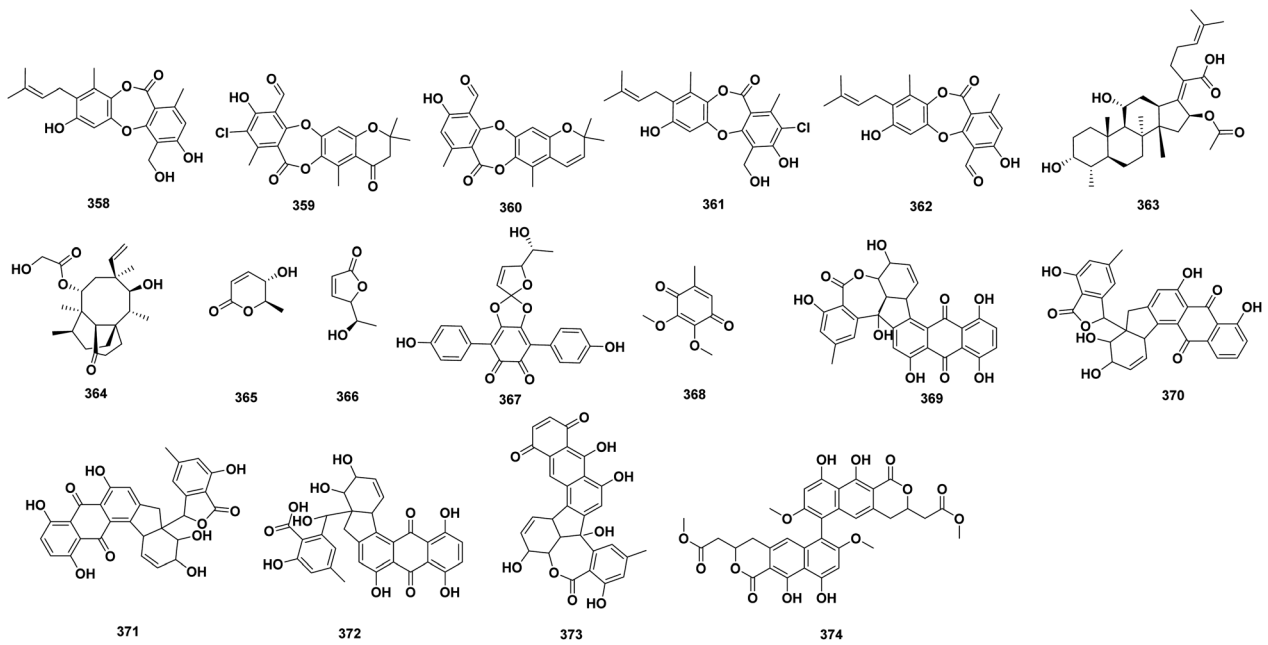

Fig. 12 Selected bacteria, fungi, higher fungi (mushrooms) derived natural products.

treatment against drug-resistant microbes. There are many metallic/salt nanoparticles that have efficient activity against MDR microbes with different mechanism as titanium,[212] zinc,[213–215] copper,[216] gold,[217,218] silver **398**,[218,219] iron **399**,[215] sulphur,[220] *etc.* These nanoparticles (NPs) have developed antibacterial activities against MDR microorganisms *via* adhesion to the bacterial cell membrane, followed by cell penetration, causing various structural disruptions and dysfunction through reactive oxygen species (ROS) generation which induced oxidative stress and inhibition the formation of polymeric matrix from substrate in the form of biofilm.

4. Alternative branches research on developing new drugs for multi-drugs resistance pathogens

In addition to natural products, several remedies have been investigated as prebiotics, probiotics, synbiotics, bacteriophages, nanoparticles, bacteriocins, antimicrobial peptides, innate defense regulator peptides, peptidomimetics, vaccines and immune stimulation *etc.*, each one providing its own benefits and limitations. Prebiotics which are nondigestible compounds that are selectively fermented by commensal microbiota in the human gut and hold an appropriate growth habitat for commensals and raise diversification within the microbiome, with improving human health.[221] Sources of prebiotics include fructose, glucose, xylo-oligosaccharide, lactulose, and inulin.[222] The metabolism of prebiotics by commensal organisms provides metabolic outputs as the short-chain fatty acids (SCFAs) propionate, butyrate, and acetate. SCFAs improve the barrier function of the gut through various mechanisms, incorporating the arrangement of energy for enterocytes; upregulation of tight junctures between cells of the epithelial layer promotion of mucus manufacture; and management of regulatory T-cells and T-helper 17 cell function to reduce inflammation.[223] Through these processes, prebiotics support to both build up the population of commensal organisms and reduce colonization by enteric organisms. Probiotics vary from prebiotics in that probiotics are living bacteria or fungi that are directly employed and provide a health benefit to the host. Like prebiotics, probiotics expend their effect through the manufacture of SCFAs from metabolic precursors, leading to the same downstream effects of immune modulation and raised mucosal barrier function.[223] Probiotics may have the extra effect of making their own antimicrobial compounds, as well as physically covering the epithelial niche and inhibiting the qualification for other pathogens to colonize the enteric microbiome.[223] Whereas prebiotics produce an indirect effect on the microbiome through metabolic routes and expansion of commensal organisms, probiotics expend a further direct effect. Other than commercialized crops, probiotics are naturally developing in fermented foods such as yogurt, cheese, kimchi, and sauerkraut.[224] While synbiotics are the mix of both prebiotic and probiotic.[223] As such, their technique of action incorporates both the indirect effect of the metabolic precursor (prebiotics) on SCFA, and the direct modulation of organisms (probiotics) within the enteric microbial community. Synbiotics are generally applicable over the counter in a mixture of both probiotic strains and prebiotic fibers. Probiotic strains usually covered in synbiotics include *Bifidobacterium* species, *Lactobacilli*, and *S. boulardii*; the prebiotic it is added to an oligosaccharide such as fructose-oligosaccharide or inulin.[225] The service of microbiome manipulation with prebiotics, probiotics, and synbiotics is in its infancy related with alternative methods. A survey of the present experimental literature can give no direct conclusions concerning the effectiveness of these measures; however, as the field increases in both the recognition of the microbiome and our ability to handle it, prebiotics, probiotics, and synbiotics are expected to participate a distinguished role. For today, these supplements look safe and are well accepted in most communities. Further analysis may accurately determine their role as an option method for fighting antimicrobial resistance. These nutritionally based remedies should continue to be utilized in partnership with other demonstrated techniques, such as antibiotic management and progress in hygiene and sterilization practices, to aid in the reduction of colonization with MDROs.[225]

Nano-formulation of natural products provided many benefits, such as targeted drug delivery, raised component solubility, diminished dose, enhanced absorption, diminished metabolism, and enhanced bioavailability.[226] It serves in increasing stability and achieving rigor targeting, with raising the efficiency of phytoconstituent. This can be carried out by encapsulation of natural products in a convenient carrier system such as nanoparticles, liposomes, and nano-emulsions, which can transform an inadequately available herbal drug into a successfully bioavailable drug candidate. Despite numerous advantages, the harmful effects of nano-formulation are connected to their minor sizes and inherent toxicity to the surface. This can be overcome by the development of natural products nano-formulation.[226]

Undoubtedly, bacteriophages presented great diversification and have great capacity for progress as antimicrobial therapy. Bacteriophages are a virus affected bacterium. Their potential in managing MDR pathogens is owing to their specificity and efficiency in generating harmful effects in the host bacterium by cell lysis. Phage therapy employing has been introduced *via* intravenous, and oral passages, and for vaccine issue. Some advantages of using phage therapy cover lower developmental costs, 100% bactericidal nature, high specificity, and the demand of only a single dose at the infection site. The disadvantage for phage therapy was the genetic material in temperate phage could raise the virulence of species of bacteria through transduction of virulence genes.[6] To ensure the maximum effectiveness of clinical phage therapy, fast-track investigation requires to be performed on pathogenic bacteria, followed by isolation, identification, and evaluation against individual phage strains. Looking at the narrow armamentarium of antibiotics useable and a deficiency in management of newer ones, phages are a nature's gift, which is safe and efficient method as an option remedy. To reduce individual limitations of a therapy, a combination therapy approach is developed. The prospects of phage preparations to be handled in combination with antibiotics, probiotics, and vaccines against resistant pathogenic bacteria can serve reduce illnesses significantly.[6]

5. Conclusion

The research aimed to unravel novel natural antibiotics therapy against MDR bacterial strains which has been recognized of high priority, particularly in the last 20 years. Following the clear knowledge of resistance mechanism, various approaches have been followed. Various phytochemical classes were successfully isolated and investigated as antibacterial candidates from plants and their associated endophytes. Natural antimicrobial agents are characterized by their structural diversity, safety, and nontoxic quality. Examples include many bioactive scaffolding's secondary metabolites as phenolic compounds, terpenoids, volatile or EOs oils, flavonoids, and sulfur-containing compounds, peptides, and polyketides. Consequently, bioactive moieties with diverse chemical designs and modes of action are promising therapeutic manifestos for the introduction of novel bioactive compounds. However, further investigations are needed to assimilate mechanisms as well as the pharmacokinetic, and pharmacodynamics aspects of the bioactive compounds. Hence, nowadays several other alternatives were developed, including the use of prebiotics, probiotics, synbiotics, bacteriophages, bacteriocins, antimicrobial peptides, innate defense regulating peptides, peptidomimetics, and others.

Unfortunately, a decrease in the developmental rate of antimicrobial agents has appeared in limited approval of novel antimicrobial drugs. Hence, building up of the microbial resistance to existing drugs could not be counterbalanced and following decrease in treatment opportunities. Several reasons account for this failure in developmental rate, including covering monetary issues, trouble in arranging clinical trials, and interruptions in investigating the treatment for acute infections, in addition to exorbitant enrolment of drug approval, despite of the several measures taken by the FDA to encourage the development of antimicrobial medications so that medical practitioners have access to a better number of treatment choices.

Author contributions

U. R. A., A. H. E., N. H. S., and A. Z. conceived and designed the work. A. H. E., N. H. S., K. M. A., N. G. S., M. B. E., Y. H. M., A. N. A, H. H. H., E. A. T. collected the data. A. H. E. wrote the manuscript. All authors contributed to & revised the article and approved the submitted version.

Conflicts of interest

The authors declare no conflict of interest.

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