Chapter 9
New Insights into and Updates on Antimicrobial Agents

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9.1 Introduction

Worldwide, microorganisms and their contribution towards sustainable development are obliging for advanced research in microbiology and microbial drug discovery (Kuhad 2012; Koehn and Carter 2005). Natural products and their semisynthetic analogous have played a crucial role in the identification and development of antimicrobial drug innovation programme (Wright et al. 2014; Atanasov et al. 2021; Moloney 2016). In spite of the notable impact on wellbeing, nature-derived compounds have achieved specific attention for their potential activities against various pathogens. Undoubtedly, antimicrobial agents have saved the human race from piles of microbial infectious disease burden and remain one of the most significant discoveries in the twenty-first century (Moloney 2016). However, at present, the most crucial health trouble is widely seen due to the rise and spread of antimicrobial resistance among the different microorganisms (bacteria, fungi, virus, and parasites). The mechanisms for survival of the bacterial resistance under various unfavourable and toxic environmental conditions include (i) enzymatic alteration or degradation of drug, (ii) variation or modification in target, and (iii) reduced uptake or increased efflux. These mechanisms when act together are responsible for enhanced resistance (Abreu et al. 2012; Lambert 2005). Efflux-mediated resistance is an important mechanism for bacteria to expel the

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chemotherapeutic agent out of cell to render them ineffective. Inhibition of efflux is regarded as an efficient strategy for the rejuvenation of old antibiotics again to market as finding new antibiotics is a much time-consuming and costly affair. Many microorganisms are the major sources of precious bioactive molecules considered as useful secondary metabolites to stand and fight against various microbial resistant strains (Singh et al. 2017a). Many pure natural isolates along with newly developed scattered synthetic analogues have proved their eligibility as the best alternatives as antimicrobial agents against resistant pathogens (Abdel-Razek et al. 2020; Martelli and Giacomini 2018). Furthermore, natural antimicrobial agents have gained extensive interest among young and established researchers to reinstate the potency of ineffective antibiotics. Thereby, re-evaluation approach of existing drugs with a combination of newer pharmacophore as efflux pump inhibitors (EPIs) is now considered as best alternatives against multidrug resistance strains (P Tegos et al. 2011; Lamut et al. 2019). Many heterocyclic natural alkaloids are now well accepted along with known antibacterial due to their significant role as efflux pump inhibitory activity against many infectious diseases (Y Mahmood et al. 2016). A natural piperidine-type alkaloid, piperine, isolated from *Piper nigrum* and *Piper longum* and berberine, an isoquinoline alkaloid, isolated from roots and rhizomes of *Berberis vulgaris*, *Rhizoma coptidis* and *Cortex phellodendri* were identified as effective natural EPI to overcome the multidrug-resistant pathogens and also can improve the clinical performance of various other antibiotics when co-administered (Jin et al. 2011). Piperine and many of its analogues when co-administered with ciprofloxacin were observed to inhibit the growth of a mutant *S. aureus* strain by reducing MIC values noticeably (Rath et al. 2019). Palmatine, a newer natural alkaloid, acts as EPIs in *P. aeruginosa* by lowering the MIC-MBC level of ciprofloxacin (Aghayan et al. 2017). Reserpine, another plant alkaloid, is a known inhibitor of the Bmr efflux pump of *Bacillus subtilis* used to accelerate the action of tetracycline in *Staphylococcus aureus* strains and also observed reversing NorA-conferred multidrug resistance in *S. aureus* (Shaheen et al. 2019; Rath et al. 2019). Microorganisms are considered as useful drug targets for various widespread diseases. Though the fundamental life path of microorganisms, their responses to antimicrobials and concerned biochemical pathways seem to be quite complex they need to be understood and explored using modern tools of molecular biology.

Foodborne illness due to fungal or bacterial growth is another major issue in recent times. The widespread microorganisms can easily reach food, grow by utilizing nutritious materials and produce metabolites which are the major cause for the spoilage of plentiful food and food products (Pitt and Hocking 2009; Petruzzi et al. 2017). They can survive even in adverse conditions like low temperature, vacuum packing, processing, and modified atmosphere (Carpena et al. 2021). Thereby, considering the food safety and improving shelf life of foods, many significant efforts have been made by food industries and researchers to find existing or new natural antimicrobials as food preservatives (Gutiérrez-del-Río et al. 2018;

Carpena et al. 2021). Plants, bacteria, fungus, and animals are different sources of the production and recognition of antimicrobials. Plants, the major source of natural products, have been largely used in the domain of the antimicrobial drug finding process. The plant extracts, crude drugs and different class of secondary metabolites are now considered as major opportunities to identify newer antimicrobial medicines and food preservatives. Many recently identified extracts/compounds which are showing antimicrobial activity belong to the families of Asphodelaceae, Solanaceae, Rutaceae, Berberidaceae, Anacardiaceae, Rhamnaceae, Euphorbiaceae, Myrtaceae, Zygophyllaceae, Asteraceae, Erythroxylaceae, Lamiaceae, Colchicaceae, Amaryllidaceae, Verbenaceae, Lythraceae, Podocarpaceae, Salicaceae, Apocynaceae, Zingiberaceae, etc. (Singh 2018; VasudhaUdupa et al. 2021; Swain and Rautray 2021) Altogether, several class of compounds such as alkaloids, glycosides, terpenoids, flavonoids, tannins, and phenolic or polyphenolics isolated from natural sources especially plants are now taken in major consideration towards to development of newer antimicrobials (Takó et al. 2020). Natural crude extracts of ginger, mustard, garlic, cinnamon, basil, sage, and other herbal products are typically high in terpenes such as carvacrol, eraniol, linalool, and several other phenolic compounds, which serve as food additives and antimicrobials against broad spectrum of Gram-positive and Gram-negative bacteria (Makroo et al. 2021). Citral, a main component of lemongrass essential oil, has demonstrated important antioxidant and antimicrobial activity against a variety of food pathogens (Moumni et al. 2021). Furthermore, numerous extracts from Chinese chives and cassia have been documented to dramatically reduce the proliferation of *Escherichia coli* and other bacteria during the preparation and storage of foods, juices, and dairy products. Understanding the process of antimicrobial activity of medicinal plant extracts is therefore needed for their optimum use as natural antimicrobial agents to extend shelf life and maintain food safety (Makroo et al. 2021).

9.2 Antimicrobial Agents from Natural Origin

Natural antimicrobial agents are getting major attention of researchers due to their structural diversity, safety, and nontoxic status. Plants, microbes, and fungal sources are considered as best possible alternatives in finding natural preservatives to avoid or control microbial food spoilage (Saeed et al. 2019). Majorly, plants are having rich sources of many bioactive scaffolds bearing secondary metabolites which are now the primary focus of scientists to explore them to any particular target site to prevent/cure ailments.

9.3 Plant-Derived Antimicrobial Agents

Various phenolic compounds, terpenoids, volatile oils, flavonoids, and sulphur-containing compounds have been detected in seeds, herbs, and spices. These bioactive compounds can be present in plant leaves, branches, seeds, roots, flowers, bulbs, and other pieces. Many herbal and medicinal plants have been recognized for centuries for their preservative and antimicrobial effects (Tuyen and Le 2021). The rich sources of essential oils and different classes of secondary metabolites like terpenes, flavones, aromatic and aliphatic compounds bearing functional groups alcohols, esters, ethers, aldehydes, ketones, and lactones in plants can most effectively destroy several bacterial, fungal, or microbial pathogens (Hyldgaard et al. 2012; Orey 2019). Since times of yore, essential oils like peppermint oil, eucalyptus, and lemongrass are mostly used widely in tribal areas as natural antibacterial and antimicrobial agents due to their benefic application for myriad of cleaning and cleansing function (Sarkic and Stappen 2018; Orey 2019; Desam and Al-Rajab 2021). Traditional use of peppermint essential oil for mouthwash, tea tree essential oil as jewellery cleaner, cedarwood oil for flu and cold, and lavender oil as cleaner are most customary treatments usually followed (Chouhan et al. 2017; Sarkic and Stappen 2018; Desam and Al-Rajab 2021). The essential oils like 1,8-cineole, camphor, borneol, α-pinene, oleanolic acid, β-bisabolene, longicyclene, β-pinene, limonene, β-pinene, eugenol, β-isoeugenol, caryophyllene, α-humulene, p-cymene, γ-terpinene, thymol, and methyl chavicol in many plant species are responsible for antimicrobial activity (Chouhan et al. 2017; Martelli and Giacomini 2018; Ju et al. 2020; Orey 2019). Plant-derived antimicrobials like thymol, eugenol, carvone, citral, carvacrol, linalool, etc. were identified active against *L. monocytogenes* in food model systems (Kawacka et al. 2021; Ju et al. 2020). Alongside many naturally isolated flavonoids like quercetin, kaempferol, apigenin, chrysin, epicatechin gallate, naringenin, myricetin, phloretin, genistein, luteolin, etc. are responsible for promising antimicrobial/antibacterial activity (Manzoor et al. 2020). Many of these substances have a protective function and are effective for inactivating or inhibiting a wide variety of microorganisms. Coumarins and its analogues are widely accepted among various classes of natural bioactive agents for the treatment against diverse diseases related to inflammation (Sharma et al. 2019), cancer (Küpeli Akkol et al. 2020), and additionally these are also useful to control, prevent, and destruct various microbial pathogens (Gouda et al. 2020). Cinnamic acids and coumarins are examples of a large class of phenylpropane-derived compounds with the maximum oxidation state (Gupta and Pandey 2020; Sharma et al. 2018). The increase in hydroxylation of phenolic compounds might be a cause of better effectiveness against microbial pathogenic bacteria. It was proved that hydroxylated phenolic catechol and pyrogallol, which are having two and three hydroxyl groups respectively, are found lethal to microorganisms (Lima et al. 2019; Leontopoulos et al. 2017). Phloretin, a natural bioactive flavonoid, isolated from *Malus sylvestris* has shown antimicrobial activity against a variety of microbial pathogens. Withaferin A, isolated from *Withania somnifera,* is a potential drug lead itself considered strong

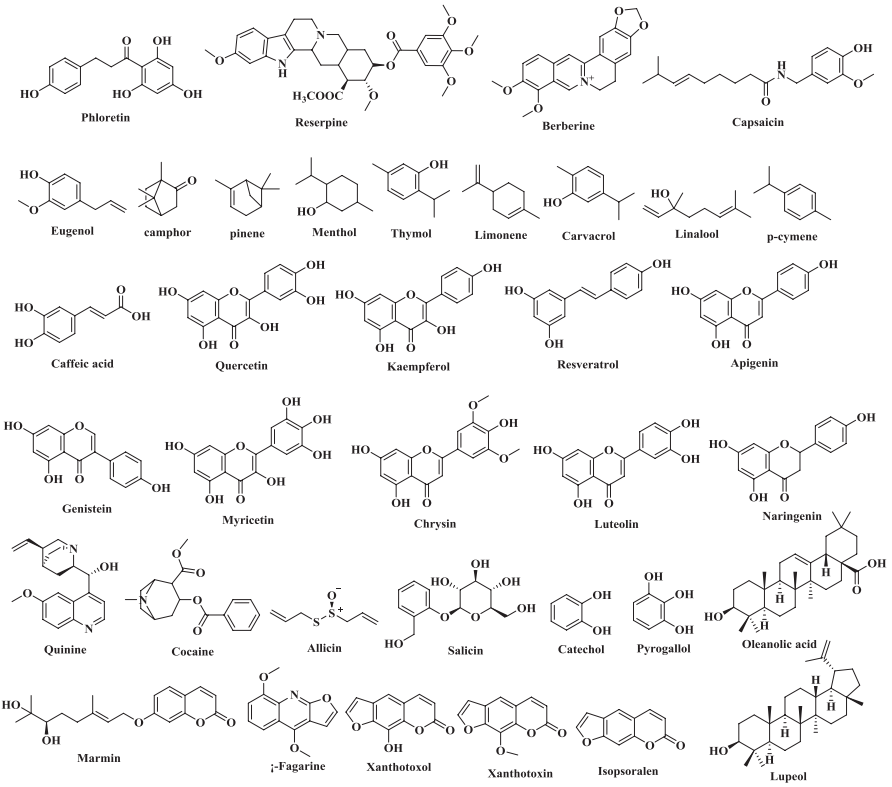

Fig. 9.1 Plant-derived antimicrobial agents

antimicrobial and useful starting material for the development of newer antimicrobials due to the presence of lactone ring and ketone containing unsaturation. Marmin, xanthotoxol, xanthotoxin, lupeol, γ-fragarin, and isopsoralen are class of alkaloids, flavonoids, and terpenoids in *Aegle marmelos* with many reported antimicrobial effects in different in vitro and in vivo assay methods (Reiter et al. 2020). Allicin, a diallylthiosulphinate bioactive defence molecule isolated from *Allium sativum* L., is useful as a broad spectrum antimicrobial agent. However, the instability issue of the molecule retards its effectiveness against microbes in normal or raise in temperature. Allicin's antimicrobial role is largely related to the thiosulphinate functional group (Leontiev et al. 2018) of the molecule. Resveratrol, a naturally occurring phenolic phytoalexin belonging to the stilbene family, has antibacterial activity against diverse Gram-positive and Gram-negative pathogens found in fruit (Dwibedi et al. 2021) (Fig. 9.1).

9.4 Bacterial Origin Antimicrobial Agents

Bacterial infectious diseases are most common in today's time especially in infants and a major cause of paediatric mortality. The antibiotics are the most widely used drugs as powerful therapeutics against various pathogenic bacterial infections (Berkley 2021). Antibacterial drugs, such as ertapenem, erythromycin, gentamycin, tobramycin (*Staphylococcus sp.*), *Aloe vera* (Ghani et al. 2019), retapamulin, periconicins A and ß-resorcyclic acid (*Staphylococcus aureus*), were all identified from natural products and are effective in treating many microbial infections (Suresh and Sona n.d.; Alter and Reich 2021). As a consequence, extensive and injudicious use of antibiotics can be a cause of development for multidrug-resistant microorganisms. The issue of resistance necessitates a renewed attempt to find antibacterial agents from natural sources that are selective against pathogenic bacteria. The 'penicillin' was discovered by Alexander Fleming in 1928. But industrial production of this antibiotic was performed only in 1940 by Howard Florey et Ernst Chain, using *Penicillium chrysogenum* (Gould 2016). Discovery of penicillin made the era of

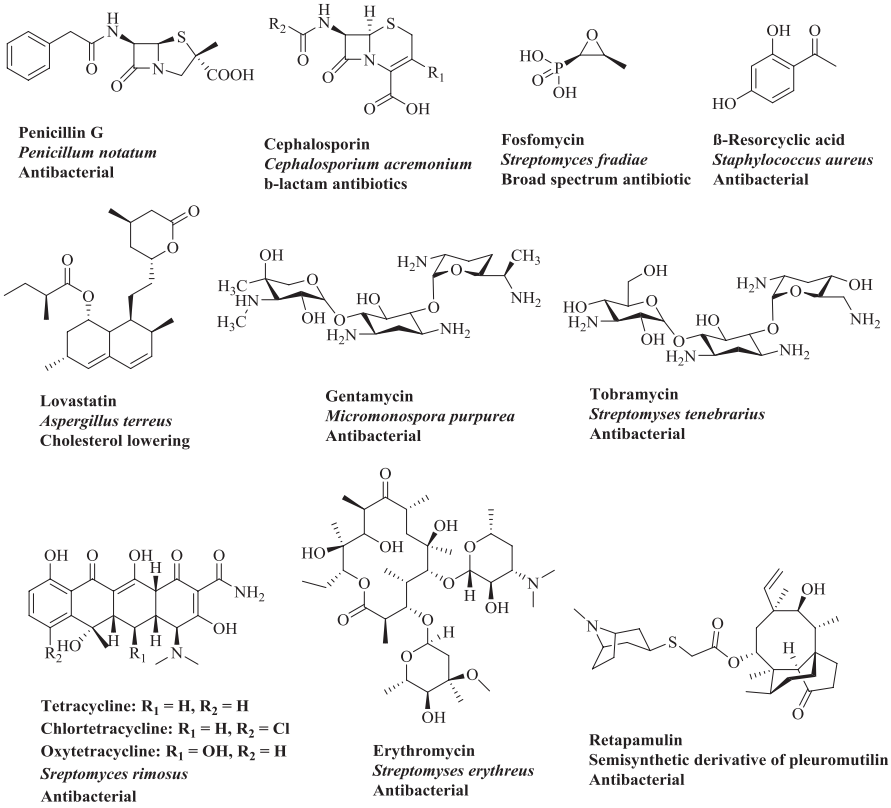

Fig. 9.2 Antimicrobial agents from bacterial source

antibiotics possible, as well as drove the modernization of new methodologies for penicillin discovery (Gould 2016). Many antibiotics used today are derived from microbial classes like β-lactams (penicillin), aminoglycins (gentamicins) and macrolides (erythirosyms), as per instructions (Fig. 9.2). Chlortetracycline, the first antibiotic of tetracycline class, was discovered in 1945 by Benjamin Minge Duggar from Streptomyces (Fig. 9.2). The oxytacycline collaboration between Pfizer and Harvard was called Terramycine (Hochstein et al. 1953; Aminov 2010).

9.5 Fungal-Derived Antimicrobial Agents

Fungi have the ability to produce toxic secondary metabolite mycotoxins which can withstand various harsh/unfavourable conditions at different stages of food chain causing many unavoidable severe health issues and also death in both humans and other animals. Even though fungi are considered as a major cause of food spoilage, still they can have the ability to produce many effective and successful antimicrobials against various ailments. The discovery of first antibiotic Penicillin, a beta-lactum drug that targets the cell wall of bacteria, was derived from the fungus *Penicillium notatum* (Guzmán-Chávez et al. 2018). For many years, *Penicillium notatum* has undergone a program of classical strain improvement (CSI) to improve antibiotics titters. This achievement allowed the lower than normal quantities of BGC-expressed natural products to be generated, resulting in a considerable reduction in the scope of BGC-associated natural product output, or, thus reduced the abundance of a diverse array of these items, which resulted in a significant increase in penicillin enzyme capability alongside the downregulation of a variety of biosynthetic gene clusters (DGCs), resulting in a smaller than usual volume of BGC-encoded DGC-enriched products (NPs). Similarly, edible fungi, such as mushrooms, have possible nutraceutical and inhibitory action against pathogenic microbes (Guzmán-Chávez et al. 2018). From the other side, the fungus *Acremonium fusidioides* (formerly *Fusidium coccineum*) produces steroidal antibiotic fusidine (fusidic acid), the biosynthetic pathway of which is quite close to cholesterol synthesis throughout the human body (Trenin 2013).

Several microbes from the aquatic ecosystem have been shown to secrete secondary metabolites, such as *E. coli*, Proteus genus, and others (Valente et al. 2020). Echinocinocandin, a particular antimycotic, was extracted from *Aspergillus nidulans* using lipo-hexosides as the carbon source (Hu et al. 2020). Interest in the pleuromutilin class has exploded in the modern century, as shown by the production of new human derivatives. Patients with impetigo and untreated superficial lacerations, abrasions, or sutured wounds caused by *Staphylococcus aureus* and *Streptococcus pyogenes* were given Retapamulin, a medicinal antibiotic (Paukner and Riedl 2017).

Trichothecium cinnamon was found to be stable in the organic fraction of the fungus and was also tested for antifungal activity against filamentous fungi. It also reported anti-tumour activity against breast cancer cells, MDA-MB-231 and HeLa, and against MDA- lines B10F and MDA-MB231. (Taware et al. 2015; Silva et al.

2017). Silva et al. isolated and characterized three new isoaigialones, A, B, and C, as well as an aigialone from the endophytic fungus *Phaeoacremonium sp*., and measured them against the phytopathogenic fungi *Cladosporium cladosporioides* and *C. sphaerospermum* (Silva et al. 2017). Curvularine was found in a leaf of the Murraycian tree (*Hyloomsantia myrmexella*) and produced the antifungalecycol products: murolide A, murolide A, and murop acid, along with six previously unknown compounds: mupiranol A, murasin, mursan, and muran-6, all together with the well-known components muracidin, and murin (Mondol et al. 2017). Acetolide compound (2-amino-1-1-acetapregnadicapramide) 3-ben-β-ol-C and ergosylan-7,22(2,5,6), obtained from ethyl acetate extract of *Anvillearcium chasteriinense*, was used to characterize ethyl acetate extract a novel fusario acetohydide (2-AG:ET:1O) while three known compounds (1-acetolan, 8:3β-diol:7, 6:6-d) and epichlororenone (6:3β-dihydroxymide) were used to complete the characterization of the fused amide. Disc diffusion assay was used to monitor the antibacterial and antifungal efficacy of compound fusarithioamide A against various microorganisms. It demonstrated antibacterial activity against *B. cereus*, *S. aureus*, and *E. coli*, with inhibition zone diameters (IZDs) of 19.0, 14.1, and 22.7 mm, and MICs of 3.1, 4.4, and 6.9 g ml1, respectively.

One additional antifungal toxin out of three new examples of triovirabacinolides and three new triovirividines from the endophytic fungus *Penicillium raccum* (Kajula et al. 2016) found in the literature by expounding upon three ways of looking at this genus of fungus was noted for antifungostase and anti-inflammation, the terms described above (Kajula et al. 2016). The recognized compounds of seven different species of fungi ((R)-3-Hydroxybutynonine isolated from the endophyte fungus *Aspergillus* sp.) have bioactive dianospermine as the seventh in their list of isolated bioactive compounds. These secondary metabolites were screened against fungi that are phytopathogenic (*Botrytis cinerea*, *Gibberella saubberti*, *Colletrix gloeoproides*, and *Magnipeniella grossi*). A test was performed against *Phytophthora capsici, Escherichia coli*, *Rhizoctonia solani*. Compounds R-3-hydroxybutanonil were effective against all of the phytopathogenic fungi studied, with the exception of those with a minimum inhibitory concentration (6.25–50 μM) and below MIC level of 6.25 μM, although less active on viruses, antimicrobial compounds less than 25-fold inhibitory concentrations, outosaminic acid had a MIC in the range of 25–100 μM, but was ineffective, or outamin C was active against all pathogenic bacteria, but active down to the low MIC values (of 25-fold) less than 25-to-mM concentrations were ineffective (Xiao et al. 2014). Similarly Trichodermin is a strong antifungal bioactive compound isolated from endophytic fungus *Trichoderma brevicompactum* with EC_{50} of 25 μg/mL fraction possessed significant ability to hinder growth of the plant pathogen *Phenacoccus solani*. Also, it had minimal ability to influence *B. cinerea* at EC_{50} of 25 mg/L (Shentu et al. 2014). A fifth mammalian antifungal that was sourced from *Bignonia magnifica*, evaluated for their anti-pityriasis properties on walnut and mediterrane fungus species *O. fragariaeola*, *O. cinereoxys*, *C. glosum* were also tested. (Silva-Hughes et al. 2015).

It was found that four compounds in Wang's study include cladosin, isocladoside, and 5-hydroxyaspeona. Additionally, Wang et al. (2013) discovered an additional one that foundcladoside, isocladoside, and 5-hydroxyaspeona could be extracted from the endophytic fungus *Cladosioquinidium*. In the presence of this weed, both the synthetic growth inhibitors were found to be effective against *Colletodothis viti* (weed) and the natural relatives (the synthesized and natural kinase inhibitors) (Wang et al. 2013). Altenusin showed activity against clinical strains of *Aspergillus* fungi, and some other *Aspergillus* and *Penicillium* molds. Endophytic *Alternaria alternata* extract shows strong antifungal activity against *Staphylococcus aureus, Escherichia coli* and *Chlamydia trachomatis*. (Johann et al. 2012). Two amides called trimethynilic [also known as tetramic] and tetraethlyinic were obtained from the endophytic (or graminophilic) fungus *Bimucidula* MU34. IC50 μg/mL against plant pathogen, 1.6 mg per gm/ml, 3.2 mg/ml, and 1.6 mg/gm per millilitre of bacteria, which proved to be useful antifungal compounds, in addition to the beneficial for the fungi *Cladosporina*, *Gylezymea*, which has a MIC of 16 mg/mL, and *Gylezymea* which has a MIC of 32 mg/gm and bacteria, that has a 1.5 mg/g 3 g Tiyzin, which can be utilized as anti fungicide (Siriwach et al. 2014). An endophyte-derived phioprothine (an inhibitory one, phorbininophoreinorein compound, used for Giberella root rot), with an IC50 of 15.9 mm was found for *Pestalopsis* sp. a new PC 50-82, also from the root system of an endophytic fungus (Liu et al. 2013).

Chemical investigation of an acetonitrile fraction led to isolation of novel product 2-hydroxyethylol and monoglycolate, along with cytochalasins J and H and 5'-epialtenuene, and the mycotoxins alternariol monomethyl ether, alternariol and cytosporone C from the endophytic fungus *Phomopsis* sp. Furthermore, the antioxidant, anti-inflammatory, antifungal and cytotoxic activities of these compounds, which were isolated from *Phomopsis* sp., *were calculated. C. globosum* and *clostridium extracts* was proven to be strong antimicrobial activity against the human pathogenic bacteria such as *Salmonella* sp., *Staphylococcus* sp. and *Streptococcus* sp. (Chapla et al. 2014). The novel marine bacterium CN-328 grows a novel fungal extract made in coculture was treated with an antifungaliotic, *Potia* sp., as commonly found in this medium. It showed a strong antimicrobial potency (or activity) in the human microdilution assay against methicillin-resistant *Staphylococcus* with a MIC of 37 ng/mL and against vancomyceicm *Antophysomonas endocarditium* with a MIC of 78 ng (Cueto et al. 2001). Strong antimicrobial activity was found in Emerrla red from *Proteus fragilasens*, which had a MIC of 12.5, and bioactive collagen extracts from *S. geliferum* produced excellent antimicrobial activity against S. a that had a MIC of 12 μg (Bugni and Ireland 2004). Periconin-forming diterpenic A and B, which was created by endophytic bacteria *Klebsiella*, *Staphylococcus*, and *Salmonella*, tested in the same range (measured in millilitres per litre), had bacteriocins *Klebsiella*, *Staphylococcus*, and *Salmonell*a typhi with a 3.12–12.5 micomol per litre resulting in measurable bacterization, *Staphylococcus microclo* and *Salmonella* (Kim et al. 2004).

9.6 Animal Origin Antimicrobial Agents

Studies into the antibiotic resistance of animals (whether terrestrial or marine) have been made considerably less in comparison to their use in plants and microorganisms, as well as in smaller animals, which includes amphibians and molluscs (Wang et al. 2018). Quite a small number of the roughly 7.77 million animal species living in different habitats have been evaluated for their antimicrobial efficacy (Jiravanichpaisal et al. 2007). The incredible competency of complex fauna to thrive in difficult environments provides a road on which to discover their survival causes for decades. Because several groups of animals, such as fish, amphibians, reptiles, and rodents, are exposed to changing habitats, it is believed that they have built-in defence against pathogenic threats. Many animals, for the development of new antimicrobial drugs, are ubiquitous and have a significant and mostly underutilized supply (Wang et al. 2018; Jiravanichpaisal et al. 2007).

A novel cecropins B-derived peptide with potent antimicrobial activity against Grame-negative bacteria such as *Micrococcus luteus*, *Aerococcus viridans*, *Bacillus megaterium*, and *Bacillus subtilis*, as well as low toxicity in human cells (Wang et al. 2018). This particular compound generally found in insects was isolated from the *Musca domestica* (Wang et al. 2018). It is also the duty of them to safeguard the crayfish against in the marine world, diverse fish pathogens. The antimicrobial peptide astacidin was derived from the freshwater crayfish *Pacifastacus leniusculus*, and it has a large spectrum of bactericidal potential against both Gram-positive and Gram-negative bacteria (Jiravanichpaisal et al. 2007; Ennaas et al. 2016). In an In vitro study Ennaas et al. (2016) extracted and characterized Collagencin, a bactericidal peptide with good action against multidrug-resistant *Staphylococcus aureus* (Ennaas et al. 2016). Dermaseptin is a brand-new linear peptide with antimicrobial effects. It was first discovered in amphibian skin secretions. Dermaseptin was produced by Ying et al. (2019), and it demonstrated high antimicrobial potential against planktonic bacteria *M. luteus*, *S. aureus*, *S. epidermidis*, *S. enterica*, *Aeromonas hydrophila*, and *E. coli*, which were extracted from cystic fibrosis (CF) patients (Ying et al. 2019). Squalamine is a compound polycationic aminosterol obtained from the shark *Squalus acanthias*. Squalamine has shown to be successful against multidrug-resistant Gram-negative and Gram-positive bacteria. Squalamine's membranolytic efficacy and outstanding biocompatibility render it one of the most powerful antibiotics against nosocomial pathogens including *Acinetobacter baumannii* (Nicol et al. 2019).

Crocodiles and alligators are recognized for their longest life span, and they experience many infectious agents, toxicants, contaminants, carcinogens, etc., during their lives, but they survive under these circumstances (Leelawongtawon et al. 2010). *Siamese crocodile* (*Crocodylus siamensis*) serum has been purified into different antimicrobial agents and has been shown to be effective against so many pathogenic bacteria, including *S. typhi*, *E. coli*, *S. aureus*, *S. epidermidis*, *K. pneumoniae*, *P. aeruginosa* and *V. cholerae* (Leelawongtawon et al. 2010). Birds, such as crows, chicken, ostrich, vulture, turkeys with antimicrobial peptides that regularly

feed on tainted food. Janecko et al. (2018) reported in their study a strong antimicrobial peptide with MDR activity against *Escherichia coli* and *Klebsiella* sp. isolated from *Corvus corax* in Canada (Janecko et al. 2018). Pancreatic juice, which is present in the intestine of mammals such as rabbits, guinea goats, pigs, dogs, and livestock, was discovered to have antibacterial action against *Micrococcus pyogenes*, *E. coli*, *Shigella* sp., *Salmonella* sp., *K. pneumoniae*, *Staphylococci*, and *Pseudomonus aeruginosa* (Pierzynowski et al. 1993). L-lysophillic peptides have antimicrobial efficacy against Gram-positive and Gram-negative microbes, such as *Streptococcus* and *Pseudomonas* (Szponder et al. 2018) (Table 9.1).

9.7 Mechanism of Antimicrobials

Due to the immense chemical diversity available in bioactive compounds, the mode of action of all these molecules are not well understood (Wink 2015). Numerous studies have shown that different bioactive molecules target different levels of organization, varying through cellular to individual scale and population scale, and also in some instances, including such biofilms (Wink 2015; Singh et al. 2017b; Abushaheen et al. 2020). The complexity of mode of action posed by bioactive natural products appears to become very encouraging in combating the development of multidrug resistance often seen in pathogens responsible for various infectious diseases. At the cellular level, different antimicrobial phytochemicals react with different biomolecules present at the target site and thus alter themselves chemically and physically to the degree whereby they drop their bio functionality whether partially or fully. During these interactions, bioactive natural compounds bind to different biomolecules, including such protein and nucleic acid, through various bond formation. Many of these bioactive components contain very active sites, like C=O and R-S-R′, RCO_3H, double bonds with anion configuration, and triple bonds in their framework, which can form covalent bonds with proteins and sometimes the DNA of microorganisms (Abushaheen et al. 2020; Singh et al. 2017b; Wink 2015). For example, during defined circumstances, the reactive aldehyde group of these molecules may create a Schiff base with amino/imino groups that occur in amino acid residues and protein and DNA nucleotide bases, respectively.

On the one side, a number of bioactive compounds such as polyphenols have the potential to minimize ROS generation via their strong antioxidant potential, whereas on the other hand, some bioactive compounds induce ROS generation. ROS tends to contribute significantly in the inducing of programmed cell death. After which the O_2-generated in mitochondria by aerobic cellular respiration is changed to H_2O_2 by superoxide dismutase, which then in turn reacts with ferrous ions and produces highly reactive OH-radicals. OH-radicals interact wantonly with various macromolecules, such as unsaturated fatty acids, proteins and DNA, and thus induce apoptosis induction (Le et al. 2017; Memar et al. 2018). The mechanism of the antimicrobial

Table 9.1 Antimicrobials from natural sources

S.N.	Sources	Antibiotic compound	Tested system	Biological activity response	References
(A) Plant-derived antimicrobial agents					
1.	Aloe vera (*Aloe barbadensis*)	Latex (Complex mixture)	*Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*)	Inhibition zone on *S. aureus* bacterium (26.33 mm) was larger than *E. coli* (21 mm)	Hilmi et al. (2019)
2.	Apple (*Malus sylvestris*)	Phloretin (Flavonoid derivative)	Oral-toxicity test in Kunming mice	The total bacterial and *Pseudomonas* sp. counts suppressed by 2 and 1.5 logarithms	Wei et al. (2020)
3.	Ashwagandha (*Withania somniferum*)	Withaferin A (Lactone)	*Leishmania donovani*-infected peritoneal macrophages and BALB/c mice	Withaferin-A (1.5 μM) reduce amastigote count in peritoneal macrophages	Chandrasekaran et al. (2017)
4.	Bael tree (*Aegle marmelos*)	Essential oil (Terpenoid)	*S. aureus, C. diphtheriae, B. cereus* and *C. diphtheriae*	Inhibition zone was 21.4 mm, 17.2 mm, lowest MIC was against *B. cereus* and *C. diphtheriae* (MIC = 125 μg/ml)	Mahomoodally et al. (2018)
5.	Barberry (*Berberis vulgaris*)	Berberine (Alkaloid)	Influenza A/FM1/1/47 (H1N1) in vivo and in vitro	Berberine strongly suppressed viral replication in A549 cells and in mouse lungs	Yan et al. (2018)

S.N.	Sources	Antibiotic compound	Tested system	Biological activity response	References
6.	Brazilian pepper tree (*Schinus terebinthifolius*)	Terebinthone (Terpenoids)	*Candida albicans*; *Candida krusei*; *Candida glabrata*; and *Candida tropicalis*	There were no significant differences regarding the different strains of *Candida* tested	Torres et al. (2016)
7.	Buchu (*Agathosma betulina*)	Essential oil (Terpenoid)	*Trichophyton rubrum* and *Trichophyton mentagrophytes*	Fungal growth index of 2.3% against *Trichophyton rubrum*	Fajinmi et al. (2019)
8.	Cascara sagrada (*Rhamnus purshiana*)	Tannins (Polyphenols)	*Staphylococcus aureus*, *Bacillus subtilis* and *Streptococcus mutans*	Biofilm formation up to 99.9% and reduced planktonic cell growth up to 10 log units relative to untreated controls	Campbell et al. (2019)
9.	Cashew (*Anacardium pulsatilla*)	Anacardic acid (Polyphenols)	*E. multilocularis*, *E. granulosuss*	Anacardic acid exerted a better efficacy against both pathogen in vitro, and in vivo compared to positive control	Yuan et al. (2019)
10.	Castor bean (*Ricinus communis*)	Volatile organic compounds (VOCs)	Plant-parasitic nematode *Meloidogyne incognit*a	Immobility (>97.3%) and death (>96.9%) of M. *incognita*	Pedroso et al. (2019)
11.	Chamomile (*Matricaria chamomilla*)	Anthemic acid (Phenolic acid)	*M. tuberculosis*, *S. typhimurium*, *S. aureus*	— —	Khameneh et al. (2019)

(continued)

Table 9.1 (continued)

S.N.	Sources	Antibiotic compound	Tested system	Biological activity response	References
12.	Chapparal (*Larrea tridentata*)	Nordihydroguaiaretic acid (Lignan)	Larvae of *Haemonchus contortus*	The effective concentration of the *L. tridentata* extract for 50% larvae mortality (EC_{50}) was 36 mg/mL	García et al. (2018)
13.	Chili peppers, Paprika (*Capsicum annuum*)	Capsaicin (Terpenoid)	Clinical MRSA strains	MIC values ranging from 8 to 256 mg/L against effluxing MRSA strains SA1199B (NorA), XU212 (TetK) and RN4220 (MsrA)	Oyedemi et al. (2019)
14.	Clove (*Syzygium aromaticum*)	Eugenol (Terpenoid)	Several proinflammatory biomarkers VCAM-1, IP-10, I-TAC, MIG	Eugenol significantly inhibited VCAM-1 and collagen III at both protein and gene expression levels	Han and Parker (2017)
15.	Coca (*Erythroxylum coca*)	Cocaine (Alkaloid)	Gram-negative and Gram-positive cocci	__ __	Tsuchiya (2017)
16.	Coriander, Cilantro (*Coriandrum sativum*)	Essential oil (Terpenoid)	*Staphylococcus aureus*	Essential oils have excellent activity against both growing and stationary phase *S. aureus*	Xiao et al. (2020)

S.N.	Sources	Antibiotic compound	Tested system	Biological activity response	References
17.	Eucalyptus (*Eucalyptus globulus*)	Tannin (Polyphenol)	Various Gram-negative and Gram-positive bacteria	*E. camaldulensis* is active against many Gram-positive (0.07–1.1%) and Gram-negative bacteria (0.01–3.2%)	Sabo and Knezevic (2019)
18.	Fava bean (*Vicia faba*)	Fabatin (Thionin)	Food spoilage caused by pathogenic and nonpathogenic bacteria	__ __	Kraszewska et al. (2016)
19.	Garlic (*Allium sativum*)	Allicin, Ajoene (Sulphoxide)	Inhibits DNA gyrase activity in *E. coli*	Cys_{433} in DNA gyrase subunit A (GyrA) was 6% oxidized in untreated bacteria. After allicin treatment the degree of Cys_{433} oxidation increased to 55% in susceptible Pf0–1 but only to 10% in tolerant PfAR-1.	Reiter et al. (2020)
20.	Glory lily (*Gloriosa superba*)	Colchicine (Alkaloid)	MRSA, *S. pyogenes*, and DR extended-spectrum beta-lactamase (ESBL)	The results suggest that the nanoemulsion of colchicine effective against DR bacteria, and acts by inhibiting the drug efflux mechanism of DR strains.	Krishnamoorthy et al. (2018)

(continued)

Table 9.1 (continued)

S.N.	Sources	Antibiotic compound	Tested system	Biological activity response	References
21.	Goldenseal (*Hydrastis Canadensis*)	Berberine, Hydrastine (Alkaloids)	Bacteria, *Giardia* duodenale, Trypanosomes	__ __	Mandal et al. (2020)
22.	Green tea (*Camellia sinensis*)	Catechin (Alavonoid)	*Shigella*, Vibrio, *S. mutans*, Viruses	Catechins, especially epigallocatechin-3-gallate (EGCG), have antiviral effects against diverse viruses and microbes	Xu et al. (2017)
23.	Hemp (*Cannabis sativa*)	ß-Resercyclic acid (Organic acid)	*Staphylococcus aureus* (MRSA)	__ __	Karas et al. (2020)
24.	Henna (*Lawsonia inermi*)	Gallic acid (Phenolic acid)	*S. aureus*	__ __	Karas et al. (2020)
25.	Hops (*Humulus lupulus*)	Lupulone, Humulone (Phenolic acids)	*Bacteroides fragilis* or *Clostridium perfringens*	MIC and MBC values ranging from 15–107 µg/mL	Cermak et al. (2017)
26.	Lantana (*Lantana camara*)	Squalene, β-ionone, Caryophyllene oxide, β-caryophyllene	*Leishmania amazonensis*; *Leishmania mexicana*	IC_{50} value ranging from 12.02 ± 0.36 µM	Delgado-Altamirano et al. (2019)
27.	Lavender-cotton (*Santolina chamaecyparissus*)	Essential oil (Terpenoid)	Nine strains of bacteria and fungi	IC_{50} value ranging from 0.10/0.30 µl/ml for lavender	Mesic et al. (2021)
28.	Onion (*Allium cepa*)	Allicin (Sulphoxide)	*S. aureus*, *Candida albicans*	__ __	Fuchs et al. (2018)
29.	Oregon grape (*Mahonia aquifolia*)	Berberine (Alkaloid)	*Plasmodium falciparum*, *Trypanosoma cruzi*	__ __	Karas et al. (2020)
30.	Periwinkle (*Vinca minor*)	Reserpine (Alkaloid)	*S. aureus*, *Candida*	__ __	Fuchs et al. (2018)

S.N.	Sources	Antibiotic compound	Tested system	Biological activity response	References
31.	Peppermint (*Mentha piperita*)	Menthol (Terpenoid)	ATCC 25922, ATCC 27853, ATCC 14452, ATCC 29213, ATCC 6633, *S. typhimurium*, *B. cereus*	MIC ranging from 0.062% to 0.5% (v/v)	Marwa et al. (2017)
32.	Quinine (*Cinchona sp.*)	Quinine (Alkaloid)	(MDR) Gram-negative bacteria in vitro and in vivo	Significant improvement in the inactivation of MDR *P. aeruginosa* and *A. baumannii* (planktonic cells and biofilms) when aBL was illuminated during Q-HCL exposure	Leanse et al. (2020)
33.	Chandra (*Rauvolfia serpentina*)	Reserpine (Alkaloid)	*Pseudomonas aeruginosa* PAO1 biofilms	Reserpine reduced biofilm formation, cell motility, virulence factor production, and QS-controlled gene expression	Parai et al. (2018)
34.	Rosemary (*Rosmarinus officinalis*)	Essential oil (Terpenoid)	*Candida* sp. and *Streptococcus pneumoniae*	The results showed that the essential oil from *Rosmarinus officinalis* was the most active on all the tested microorganisms	Akroum (2020)

(continued)

Table 9.1 (continued)

S.N.	Sources	Antibiotic compound	Tested system	Biological activity response	References
35.	Tarragon (*Artemisia dracunculus*)	Caffeic acids (Terpenoid)	Nine strains of bacteria, both gram-negative and Gram-positive	MIC ranging from 0.09 mg/mL to 47 mg/mL	Majdan et al. (2020)
36.	Thyme (*Thymus vulgaris*)	Caffeic acids (Terpenoid), thymol (phenolic alcohol)	ATCC 25922, ATCC 25923	The highest inhibition zone was obtained by Tv extracts at 20 µL loading (22 mm)	Akin and Saki (2019)
37.	Tree bard (*Podocarpus nagi*)	Totarol (Flavonol)	*P. acnes*, other gram-positive bacteria	__ __	Hou et al. (2020)
38.	Tua-Tua (*Jatropha gossyphiifolia*)	__ __	Different strains of bacteria and fungi	The seeds and fruits can be used against influenza and as a sedative, analgesic or anti-diarrheal agents	Wu et al. (2019)
39.	Turmeric (*Curcuma longa*)	Curcumin (Terpenoids)	*Escherichia coli* O157:H7 and *Listeria innocua*	Enhancement in antimicrobial activity reduced the time required for the inactivation of 5 log CFU mL^{-1} of *E. coli* O157:H7 from 10 min to 2 min of treatment	de Oliveira et al. (2018)
40.	Willow (*Salix alba*)	Salicin (Phenolic glucoside)	Human peripheral leucocyte cells and human hepatoma cell line HepG2	The results using trypan blue staining test showed viability decreases (viability less than 70%) for concentrations of SA extract equal and higher to 200 µg/ml.	Maistro et al. (2019)

S.N.	Sources	Antibiotic compound	Tested system	Biological activity response	References
(B) Bacterial-derived antimicrobial agents					
1.	*Streptomyces antibioticus*	Actinomycin	Antibacterial activities against *Sarcinalutea*, *Bacillus mycoides*, *Bacillus subtilis*, *E. coli*, *Aerobacter aerogenes* and *Brucella abortus*	Transcription inhibitor which preventing RNA polymerase elongation	Genilloud (2014)
2.	*Streptomyces lavendulae*	Streptothricin	Various Gram-positive and Gram-negative bacteria	A protein synthesis inhibitor with miscoding activity	Mander and Liu (2010)
3.	*Streptomyces erythraeus*	Erythromycin	*Streptococcus*, *Staphylococcus*, *Haemophilus* and *Corynebacterium*	Inhibits protein synthesis by binding to the 23S rRNA molecule of the bacterial ribosome and hence blocking the exit of the growing peptide chain	Majer et al. (1977)
4.	*Streptomyces aureofaciens*	Tetracycline	*E. coli*, *Haemophilus influenzae*, *M. tuberculosis*, *Pseudomonas aeruginosa*	Inhibits protein synthesis by binding to the 30S ribosomal subunit in the mRNA translation complex	Nelson and Levy (2011)

(continued)

Table 9.1 (continued)

S.N.	Sources	Antibiotic compound	Tested system	Biological activity response	References
5.	*Micromonospora*	Aminoglycosides	Aerobic, Gram-negative bacteria and *M. tuberculosis*	Binding specifically to the 30S ribosome of the bacteria, preventing attachment of the aminoacyltRNA to the RNA-ribosome complex	Mingeot-Leclercq et al. (1999)
6.	*Streptomyces lincolnensis*	Lincomycin	Gram-positive bacteria	Inhibits protein synthesis	Spížek and Řezanka (2004)
7.	*Amycolatopsis orientalis*	Vancomycin	Gram-positive bacteria particularly methicillin-resistant *Staphylococci*	Inhibition of peptidoglycan synthesis	Levine (2006)
8.	*Bacillus* sp.	Mersacidin	MRSA	— —	Kruszewska et al. (2004)
9.	*Bacillus amyloliquefaciens*	Surfactin, Iturin, Fengycin, Plipastatin, Bacitracin, Amylolysin	*M. luteus*, *Micrococcus roseus*, *Bacillus anthracis*, *Bacillus mycoides*, *Corynebacterium pseudodiphthericum*, *S. aureus*, *L. monocytogenes*, *B. cereus*, *Serratia marcescens*, and *Pasteurella haemolytica*, *Proteus vulgaris*	Inhibitory activity	Benitez et al. (2010); Awais et al. (2007)
10.	*Amycolatopsis rifamycinica*	Rifamycin	*Mycobacterium intracellulare* and *Mycobacterium avium*	Inhibition of bacterial DNA-dependent RNA synthesis	Lin et al. (2017)

S.N.	Sources	Antibiotic compound	Tested system	Biological activity response	References
11.	*Dactylosporangium aurantiacum*	Tiacumicins	Gram-positive bacteria	__ __	Hochlowski et al. (1987)
12.	*Streptomyces roseosporus*	Daptomycin	MRSA	__ __	Baltz (2009)
13.	*Streptomyces tenebrarius*	Tobramycin	Gram-positive *Staphylococcus aureus* and various Gram-negative bacteria.	<0.25 μg/mL - 92 μg/mL and 0.5 μg/mL - >512 μg/mL	Meylan et al. (2017)
14.	*Streptomyces cattleya*	Thienamycin	Have a high specificity for PBP2 of gram-positive and Gram-negative microorganisms	Hydrolysis by metallo β-lactamases and other β-lactamases	Bennett et al. (2014)
15.	*Streptomyces clavuligerus*	Clavulanic acid	Three mammalian species, hamsters, rats and cotton-top tamarin monkeys in a series of behavioural assays	Enhance the activity of antibiotics by blocking bacterial beta-lactamases	Kim et al. (2009)
16.	*Burkholderia pseudomallei*	Malleobactin A	*B. pseudomallei*	MICs in the range 0.004–0.016 μg/mL	Mima et al. (2011)
17.	*Burkholderia cepacia*	Burkholderic acid	MRSA	MIC of 0.125–0.5% (v/v)	Vasireddy et al. (2018)
18.	*Janthinobacterium lividum*	Janthinocin A	Gram positive bacteria in vitro and in vivo	__ __	Johnson et al. (1990)

(continued)

Table 9.1 (continued)

S.N.	Sources	Antibiotic compound	Tested system	Biological activity response	References
19.	*Janthinobacteriumag aricidamnosum*	Jagaricin	*Candida albicans*	Jagaricin shows haemolytic effects, at which the growth of prevalent phytopathogenic fungi is inhibited	Fischer et al. (2019)
20.	*Pseudomonas syringae*	Pseudomycins	*Candida albicans*	— —	Kumari Chikkode Narayana et al. (2017)
21.	*Pseudomonas viridiflava*	Ecomycins	*Cryptococcus neoformans* and *C. Albicans*	— —	Kumari Chikkode Narayana et al. (2017)
(C) Fungal-derived antimicrobial agents					
1.	Penicillin	*Penicillium notatum*	Mainly against gram-positive bacteria	Cell wall of bacteria	Guzmán-Chávez et al. (2018)
2.	Fusidic acid	*Acremonium fusidioides*	Methicillin-resistant *S. aureus* and Vancomycin-resistant *Enterococcus faecium*	Sterol biosynthesis	Trenin (2013)
3.	Griseofulvin	*Penicillium griseofulvum*	Mainly against different species of ringworm	Griseofulvin binds to tubulin, interfering with microtubule function thus inhibiting mitosis	Valente et al. (2020)

S.N.	Sources	Antibiotic compound	Tested system	Biological activity response	References
4.	Echinocandin B	*Aspergillus nidulans*	Antifungal drug	Inhibits the synthesis of glucan, a major component of the fungal cell wall, via noncompetitive inhibition	Hu et al. (2020)
5.	Retapamulin	*Pleurotusmutilus* sp.	Gram-positive and fastidious Gram-negative pathogens as well as against mycoplasmas	Inhibit bacterial translation	Paukner and Riedl (2017)
6.	Cephalosporin	*Cephalosporium acremonium*	Gram-positive cocci, *Citrobacter*, *Enterobacter*, *Haemophilus influenzae*	Inhibit synthesis of the bacterial cell wall, causing cell lysis	Hu and Zhu (2016)
7.	*Trichothecium* sp.	Trichothecin	*S. cerevisiae*, *C. albidus* var diffluens (NCIM 3371), *C. albidus* var *diffluens* (NCIM 3372), *F. oxysporum*, *P. expansum*, *T. viride*, *P. varioti* and *A. niger*	MIC of 6.0, 20.0, 12.0, 10.0, 30.0, 40.0, 20.0 and 12.0 μg/mL respectively	Taware et al. (2015)
8.	*Phaeoacremonium* sp.	Isoaigialone B and C, aigialone	*C. cladosporioides* and *C. sphaerospermum*	7 exhibited antifungal activity, with a detection limit of 5 μg nystatin, positive control, showing a detection limit of 1 μg	Silva et al. (2017)
9.	*Curvularia* sp., strain M12	Murranolide A, Murranopyrone, Curvularin, Pyrenolide A, Modiolide A	*Phytophthora capsici*	IC_{50}: 50–100 μg/mL	Mondol et al. (2017)

(continued)

Table 9.1 (continued)

S.N.	Sources	Antibiotic compound	Tested system	Biological activity response	References
10.	*Fusarium chlamydosporium*	Fusarithioamide A	*C. albicans*	MIC 2.6 µg/mL	Ibrahim et al. (2016)
11.	*Penicillium raciborski*	Outovirin C	*F. oxysporum*, *B. cinerea*, and *V. dahlia*	Compound active against *B. cinerea* (57% inhibition) and slightly less effective against *V. dahliae* (45% inhibition)	Kajula et al. (2016)
12.	*Aspergillus sp.* KJ-9	Fonsecinone A	*G. saubinetti*, *M. grisea*, *B. cinerea*, *C. gloeosporioides* and *A. solani*	MIC range of 6.25–50 µM	Xiao et al. (2014)
13.	*Trichoderma brevicompactum* 0248	Trichodermin	*R. solani*, *B. cinereal*, *C. lindemuthianum*	EC_{50} of 0.25, 2.02 and 25.60 µg/mL respectively	Shentu et al. (2014)
14.	*Biscogniauxia mediterraneaOhu* 19B	5-methylmellein	*C. acutatum*, *C. fragariae*, *C. gloeosporioides*, *F. oxysporum*, *B. cinerea*, *P. obscurans*, and *P. viticola*	__ __	Silva-Hughes et al. (2015)
15.	*Cladosporium cladosporioides*	Cladosporin, Isocladosporin	*C. acutatum*, *C. fragariae*, *C. gloeosporioides* and *P. viticola*	At 30 µM compound exhibited 92.7, 90.1, 95.4, and 79.9% growth inhibition	Wang et al. (2013)
16.	*Alternaria sp*. UFMGCB 55	Altenusin	Eleven strain of *P. brasiliensis*	MIC values ranging between 1.9 and 31.2 µg/mL	Johann et al. (2012)
17.	*Bipolaris sp*. MU34	Bipolamide B	*C. cladosporioides*, *C. cucumerinum*, *S. cerevisiae*, *A. niger* and *R. oryzae*	MIC values of 16, 32, 32, 64 and 64 µg/mL, respectively	Siriwach et al. (2014)
18.	*Pestalotiopsis fici*	Ficipyrone A	*G. zeae*	IC_{50} 15.9 µM	Liu et al. (2013)

S.N.	Sources	Antibiotic compound	Tested system	Biological activity response	References
19.	*Phomopsis sp.*	Cytochalasin H	*C. cladosporioides* and *C. sphaerosphermum*	MIC 10.0 and 25.0 µg, respectively	Chapla et al. (2014)
20.	*Pestalotiopsis sp.* when cocultured with marine bacterium, strain CNJ-328	Pestalone	Methicillin-resistant *S. aureus* and vancomycin-resistant *Enterococcus faecium*	MIC = 37 ng/mL and 78 ng/mL	Cueto et al. (2001)
21.	*Emericella variecolor*	Varixanthone	*E. coli*	MIC values of 12.5 µg mL^{-1}	Bugni and Ireland (2004)
22.	*Periconia sp.*	Periconicins A and B	*Bacillus subtilis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Salmonella typhimurium*	MIC in the range of 3.12–12.5 µg/mL	Kim et al. (2004)
(D)animal origin antimicrobial agents					
1.	*Musca domestica*	Cecropins	*M. luteus*, *Aerococcus viridians*, *Bacillus megaterium*, *B. subtilis*	Cecropin DH has potential as a therapeutic agent for both antibacterial and anti-inflammatory applications	Wang et al. (2018)
2.	Crayfish	Astacidin	Gram-positive and Gram-negative bacteria	Bactericidal activities	Jiravanichpaisal et al. (2007)
3.	*Larimichthys crocea*	Collagencin	*S. aureus*	The peptide completely inhibited the growth of *S. aureus* at 1.88 mM and non-toxic at 470 µM	Ennaas et al. (2016)

(continued)

Table 9.1 (continued)

S.N.	Sources	Antibiotic compound	Tested system	Biological activity response	References
4.	*Phyllomedusa distincta*	Dermaseptin	*M. luteus*, *S. aureus*, *S. epidermidis*, *S. enterica*, *Aeromonashydrophila* and *E. coli*	Rapidly killed planktonic bacteria isolated from cystic fibrosis (CF) patient	Ying et al. (2019)
5.	*Squalus acanthias*	Squalamine	Anti-persister activity against *Acinetobacterbaumannii*	Squalamine at 100 mg/L (below its haemolytic concentration) was able to kill dormant cells	Nicol et al. (2019)
6.	*Crocodylus siamensis*	Antimicrobial peptides	ATCC-registered strains of nine bacterial species and two fungal species	MIC was in the range of 25.00–100.00 mg/ml	Leelawongtawon et al. (2010)
7.	*Corvus corax*	Peptides	*Escherichia coli* and *Klebsiella*spp	Specific target site not determined	Janecko et al. (2018)
8.	Pancreatic juice of rabbit, Guinea pig, rats, pig, sheep and cattle	Heat-stable proteinaceous substance with molecular weight of <4000	*Micrococcus pyogenes*, *E. coli*, *Shigella sp.*, *Salmonella sp.*, *K. pneumoniae*, *Staphylococci* and *Pseudomonus aeruginosa*	The antibacterial activity remained unchanged after heating to 65 degrees C and upon dilution to 1:10	Pierzynowski et al. (1993)
9.	Rabbit granulocytes	Antimicrobial peptides	Gram-positive and Gram-negative bacteria	These peptides exhibit microbicidal activity due to increased acidity and ionic strength	Szponder et al. (2018)

agent is primarily due to two pathways, namely chemical interaction with the synthesis or function of essential bacterial components and/or circumvention of traditional antibacterial resistance mechanisms. Multiple targets for antimicrobial agents include microbial protein biosynthesis; microbial cell-wall biosynthesis; microbial cell membrane destruction; microbial DNA replication and repair; and metabolic pathway inhibition. Cell wall is an ultra-dynamic structure in some microbes, such as fungi and bacteria, which protects the body from environmental osmotic shocks which are also essential for the distinctive phenotypes of different species. Any alteration triggered by an antimicrobial triggering an organizational or functional disruption of the cell wall will lead to the death of the microorganism (Timofeeva and Kleshcheva 2011; Le et al. 2017; Memar et al. 2018) (Fig. 9.3).

In the case of microbial antibiotics such as penicillin which inhibit cell synthesis, the mechanism of cell wall disintegration is well understood. Two types of family enzymes, including transglycosylases and transpeptidases, have critical roles in the creation of this sheet, while their functionality has been defined previously. Bifunctional enzymes containing both the transpeptidase and transglycosylase

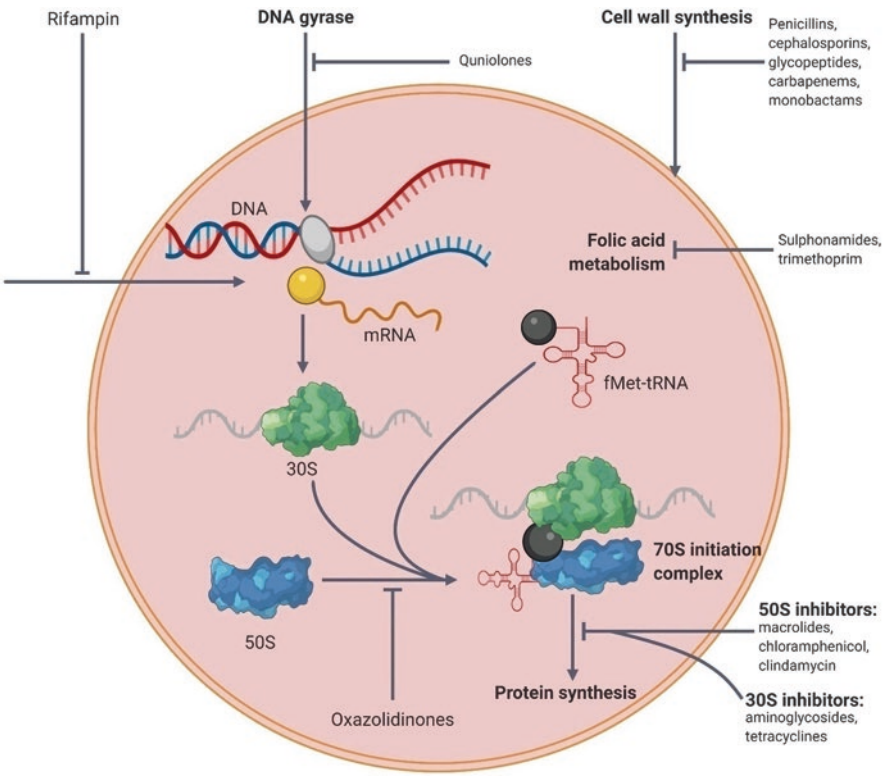

Fig. 9.3 Antimicrobial drug target; in microbes, there can be five major antimicrobial drugs targets: cell-wall synthesis, DNA gyrase, metabolic enzymes, RNA polymerase directed by DNA, and protein synthesis

domains are appropriate targets for bactericidal antibiotics such as penicillins and cephalosporins (Memar et al. 2018; Le et al. 2017; Timofeeva and Kleshcheva 2011). The glycopeptide antibiotics group, like vancomycin, has often been identified to attack the peptidoglycan layer in some other way inside the cell-wall assembly. These antibiotics are capable of binding to the peptide substrate of the peptidoglycan layer, thus preventing enzyme reactions from occurring. However, the net result is very similar, reducing peptidoglycan cross-linkage and thereby weakening the cell wall (Wink 2015; Singh et al. 2017b).

The cell membrane is an essential element of the lipid bilayers that includes integrated extrinsic and intrinsic proteins that serve the roles of enzymes, signalling protein and transport proteins. Owing to their lipophilic nature or bonding to some particular membrane part, numerous bioactive compounds can trigger membrane degradation, leading to loss of membrane stability and functionality (Ibrahim et al. 2000; Chongsiriwatana et al. 2008). Multiple antibiotics including polymyxins may bound to the lipid a constituent of lipopolysaccharide and thus cause substantial modifications through phospholipid interchange, which might lead in osmotic disturbance and, eventually, lead to microbial death. In the case of microbial biosynthesis, there seem to be a significant number of molecular steps involved in the initiation, elongation and termination of microbial ribosome protein assembly. Inhibiting protein synthesis by targeting ribosomal subunits is also an efficient way to fight microbial infections. Significant groups of antibiotics, such as macrolides, tetracycline's, aminoglycosides and oxazolidinones, demonstrate antimicrobial activity through this particular mechanism (Chongsiriwatana et al. 2008; Ibrahim et al. 2000).

9.8 Current Antimicrobial Therapy and Drug Resistant

Microorganisms had evolved on universe more than four billion years ago. During that period, a wide variety of naturally occurring antibiotics are encountered, including those created by other bacteria, such as *Penicillium notatum*, which produces penicillin (Yim et al. 2017). In order to sustain, microbes have established a seemingly inexhaustible repertoire of antibiotic resistance mechanisms (Mulani et al. 2019). This is not shocking that they rapidly became immune to all the antimicrobial agents which have been produced throughout the last five decades. For this reason, there is a lot of variability in antimicrobial responses; even the best of antibiotics have differing effects on the level of resistance. Mode of operation, if an antimicrobial compound is a dose or time-dependent killing agent, effectiveness against pathogenic bacteria, and the magnitude and duration of the available serum concentration are all variables that affect whether resistance arises (Petchiappan and Chatterji 2017). For example, the resistance of β-lactam within streptococci class a still has not been established. But at the other hand, certain antimicrobial agents,

like rifampicin, are easily selected for resistance. Antimicrobials that target single enzymes, such as rifampicin, are thought to be the most resistant to resistance production, while agents like penicillin, which irreversibly inactivates several targets, may build resistance more steadily. Because pathogens have been exposed to natural antibiotics such as ß-lactams and macrolides in the environment, it is rational to believe that susceptibility determinants to natural products have formed and spread horizontally. While it was anticipated that resistance to synthetic antimicrobial agents such as fluoroquinolones and linezolid will be sluggish to develop, resistance to synthetic agents developed rather rapidly. It seems that if an antibacterial agent is widely employed in the human community, tolerance can develop rapidly, at least in some microbe populations (Buehrle et al. 2017; Laws et al. 2019).

The development and dissemination of resistant pathogens is a significant concern as the main trigger of antimicrobial drug resistance (Juárez-Verdayes et al. 2012; Iino et al. 2012). The pathways entail modification of drug targets or enzymatic inactivation of antimicrobial agents like ß-lactams, macrolides, tetracyclines and fluoroquinolones. Many antibiotics were discovered to be efflux pump substrates, resulting in medication extrusion from cells. Problem becomes more serious due to intensive use of antibiotics which result in clonal selection of efflux pump overexpressing strains for which chemotherapeutic agents are good substrate. Moreover, hyper expression of naturally occurring multidrug efflux transporters plays an ubiquitous type of resistant element which could use chemical energy (e.g. ATP, Na + or H+ gradients) to expel a set of dissimilar molecules or antibiotics from the cytoplasm through an antiport mechanism (Campion et al. 2004; Stavri et al. 2007; Abdali et al. 2017). Protein architecture has distinguished between five families, i.e. Multidrug, Multid, MATE, ABC, the resistance-family, and the main facilitator superfamily. Secondaryly these have been studied at present in significant amounts including NorA, NorB, MdeA, and LmrP pump. NorA among these has been found overexpressed in nearly half of resistant clinical isolates as compared to other efflux pumps (Abdali et al. 2017; Jang 2016). As a consequence of the intense battle against MDR pathogens, efflux pump inhibitors (EPIs) are potentially effective as adjunctive therapies with an antibiotic to obstruct the activity of such efflux proteins and could be a better approach to improve antibacterial potency at low concentration and help in decreased virulence of bacterial infection (Patkari and Mehra 2013; German et al. 2008). Capsaicin is shown to alter fluoroquinolone pump tolerance in clinical isolates of *Staphylococcus aureus*. Similarly, polystyryladines, for example, dihydropanamidic polyamine esters with amino acid esters, have recently been discovered as antibacterial agents against NorA-overexp bacterium strains. It's worth exploring whether these drug-intermediate infections can even be treated with non-EPIs, which could have new therapeutic benefit for obsolete antibiotics (Fig. 9.4).

Ampuse from available drugs may come from the organism's intrinsic properties, or due to genetic transformation. Resistance is likely to occur in the commensal microflora as well, and the more likely it is (Buehrle et al. 2017; Laws et al. 2019).

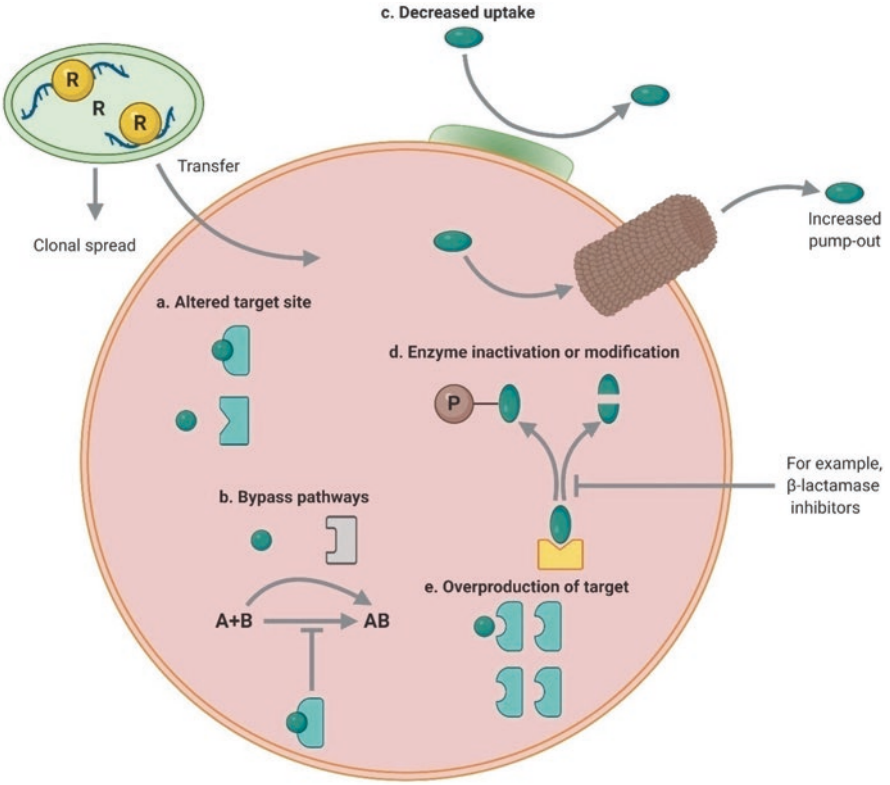

Fig. 9.4 Mechanisms of genetic resistance to antimicrobial agent

9.9 Future Opportunities

There have been a change in the way the drugs/lead molecules used in experimental trials to clinical studies, as researchers began to use advancement in the techniques of synthesizing them from the results of in vitro study. Bioavailability is a challenge because certain bacteria can not only move through the skin but also because of tissue penetration, so when using bioactive products is mixed with the natural antimicrobials. According to that theory, phenolic compounds are said to profoundly influence the body's ability to enter both the liver and the blood. A significant challenge to effective therapy of pathogenic microorganisms has been the emergence of antibiotic-resistant microorganisms. As of now, there is an urgent need to establish a new drug resistance strategy. Bioactive moieties with different chemical structures and modes of action are promising therapeutic platforms for the discovery of novel bioactive compounds in the years to come. However, more study should be done to properly completely comprehend mechanisms as well as the pharmacokinetic and pharmacodynamics characteristics of the bioactive compounds. Although conducting more research on combinations of antibiotics to improve their duration of action

would further the duration of these compounds, This class of multidrug-resistant bacteria is a true to life origins, so more research on them must also be performed to reduce resistance in normal flora. Currently, checks are needed to ensure the efficacy of any pathogens that are still in the sample. Since many antibiotics in modern treatments lack specificity, this could yield medications that are less effective when combined with the conventional antimicrobials that can mitigate environmental pathogens that do not have established resistance to these days. If these potential advantages are combined, then a more compliant patient-friendly and cost-conscious approach to antibiotic therapy is taken, such resistance could be prevented, longer durations of use could be achieved, and so less resistance to medications could be developed.

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