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Research Article

Escaping mechanisms of ESKAPE pathogens from antibiotics and their targeting by natural compounds

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ABSTRACT

The microorganisms that have developed resistance to available therapeutic agents are threatening the globe and multidrug resistance among the bacterial pathogens is becoming a major concern of public health worldwide. Bacteria develop protective mechanisms to counteract the deleterious effects of antibiotics, which may eventually result in loss of growth-inhibitory potential of antibiotics. ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* spp.) pathogens display multidrug resistance and virulence through various mechanisms and it is the need of the hour to discover or design new antibiotics against ESKAPE pathogens. In this article, we have discussed the mechanisms acquired by ESKAPE pathogens to counteract the effect of antibiotics and elaborated on recently discovered secondary metabolites derived from bacteria and plant sources that are endowed with good antibacterial activity towards pathogenic bacteria in general, ESKAPE organisms in particular. Abyssomicin C, allicin, anthracimycin, berberine, biochanin A, caffeic acid, daptomycin, kibdelomycin, piperine, platensimycin, plazomicin, taxifolin, teixobactin, and thymol are the major metabolites whose antibacterial potential have been discussed in this article.

1. Introduction

From 1940 to 1965 is the golden era in the field of antibiotics as many antimicrobials were discovered and introduced into modern medicine. The discovery of new antibiotics revolutionized modern medicine as these small molecules have been widely implemented in the treatment of bacterial diseases. Unfortunately, discontinuous or improper, or irregular intake and excessive usage of antibiotics have led to the emergence of antibiotic-resistant microorganisms. Antibiotic resistance is increasing at an alarming pace and has become one of the major health concerns of the globe due to various reasons including the availability of a limited number of antibiotics. According to the antibiotic resistance threats report (2019) of the Centers for Disease Control and Prevention (CDC, United States), 2.8 million people are infected with antibiotic-resistant infection and more than 35,000 people die annually in the United States alone. The existence of drug-resistant pathogens came into recognition only in the last two decades. Lack of development of new antimicrobials is one of the key factors for the crisis in the medical field that has been denoted elsewhere [1]. The Center for Disease Dynamics, Economics, and Policy (CDDEP) have well-documented the global status of antibiotics policy to understand the resistance and need for newer antimicrobials [2]. It is a matter of serious concern that, significant progress has not been made in the discovery and development of new antibiotics in the previous three decades. Many pharmaceutical companies have committed towards the development of drugs for the treatment of non-communicable diseases which are of substantial economic interest [3]. On one hand, pathogens are gaining resistance gradually towards existing therapeutics and on the other hand, a feeble amount of efforts have been made in the discovery of new antibiotics. Therefore, it is the need of the hour to discover new antimicrobials which are potent against a broad spectrum of microorganisms including drug-resistant pathogens.

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Microorganisms develop an adaptive mechanism to survive in the favorable/adverse atmosphere and as a part of this, they subsequently develop several protective mechanisms to reduce their antibiotic susceptibility. This eventually leads to the loss of antibiotic potency and thus, making them ineffective for the treatment of bacterial infections. A group of microorganisms that possess multidrug resistance and virulence include *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* spp. causing nosocomial infections and contributing a lion's share in hospital-acquired infections [4]. Louis B Rice gave the acronym for these pathogens as ESKAPE organisms and the following section discusses about the antibacterial resistance mechanisms of these pathogens [5].

2. ESKAPE pathogens

Hospital-acquired (nosocomial) infections can be caused by various microbes such as bacteria, fungi, viruses, parasites, and other agents. The transmission of these infections could be due to interpersonal communications between patients or with healthcare providers, through contaminated equipment, lack of proper sterilization measures, and many more [6]. Hospital-acquired infections may contribute to lengthier hospital stays, increased treatment-related expenses, and a high mortality rate [7]. The Infectious Diseases Society of America has grouped the bacterial pathogens responsible for hospital-acquired infections and referred to as "ESKAPE" pathogens. *E. faecium, S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa,* and *Enterobacter* spp. are the organisms that are grouped under ESKAPE pathogens and they can escape from the biocidal activity of antibacterial drugs. These organisms display a characteristic of multidrug resistance (MDR) and may pose a potentially fatal condition for immunocompromised individuals or patients with serious illness [6]. The World Health Organization (WHO) has recently included ESKAPE pathogens in the inventory of twelve bacteria which demands the development of new antibiotics urgently [8]. In a critical analysis, the multicriteria decision analysis method was used to prioritize antibiotic-resistant bacteria and classified bacteria into three categories (critical priority, high priority, and medium priority) depending on the need for the development of new antibiotics against antibiotic-resistant bacteria [8]. Among ESKAPE organisms, carbapenem-resistant *A. baumannii* and carbapenem-resistant *P. aeruginosa* were listed under critical priority, and vancomycin-resistant *E. faecium* (VREF) and methicillin/vancomycin resistant *S. aureus* (MRSA/VRSA) were categorised under high priority groups [8]. They also suggested the need for the development of new antibacterial agents against multidrug resistance (MDR)-tuberculosis, Gram-negative bacteria, antibiotic-resistant bacteria responsible for community-acquired infections such as *Salmonella* spp, *Campylobacter* spp, *Neisseria gonorrhoeae*, and *Helicobacter pylori*. The bacteria may develop MDR through various mechanisms including chemical alteration or breakdown of the drug, interference with influx and efflux of antibiotics, modification of drug target, and many more. In the below section, we have briefly discussed major mechanisms of drug resistance shown by ESKAPE organisms to escape from the antibiotics.

3. Major mechanisms of drug resistance acquired by ESKAPE organisms

MDR bacteria have acquired various defense mechanisms to protect

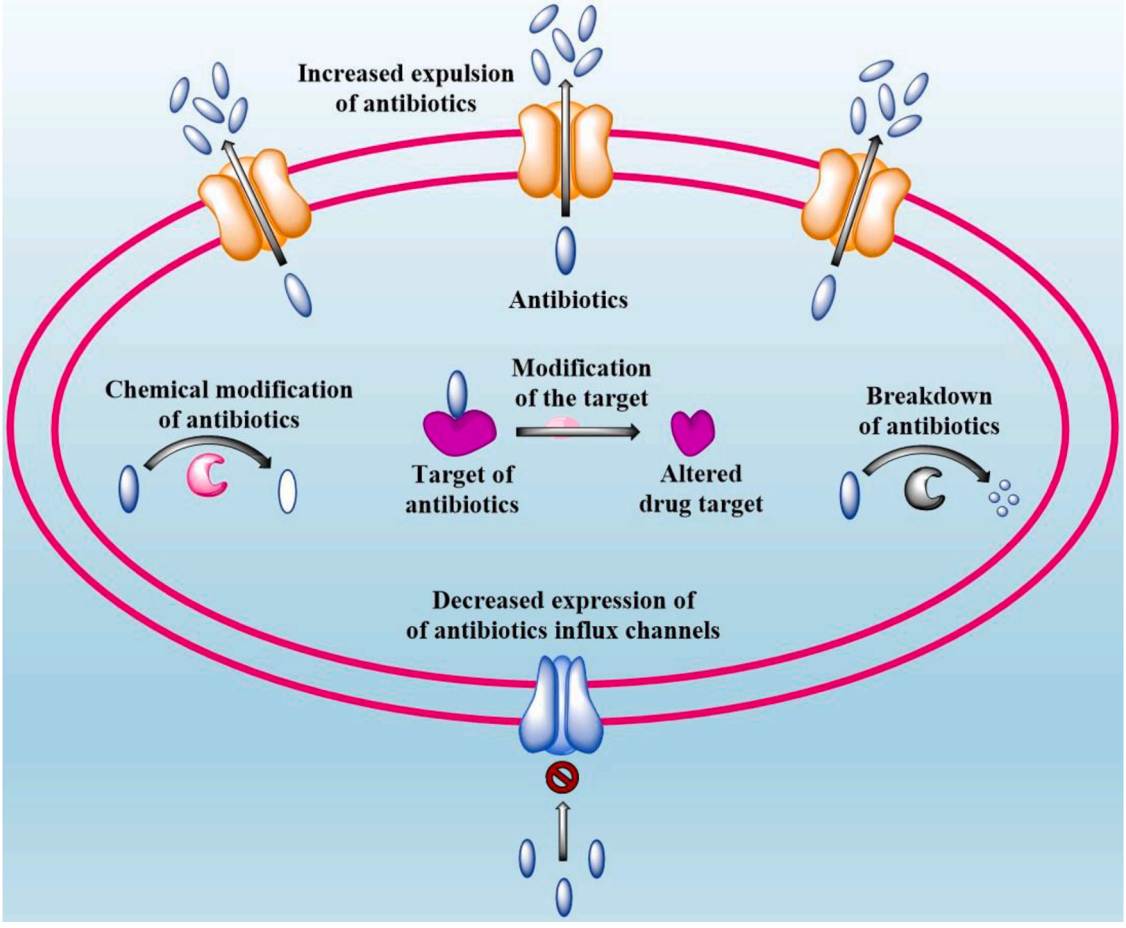

Fig. 1. Bacteria develop resistance against antibiotics through chemical modification or breakdown of the drug, or preventing antibiotic influx, or antibiotic expulsion through efflux pumps or modification of antibiotic targets.

themselves from the bactericidal activity of antibiotics and some of the major drug-resistant mechanisms developed by ESKAPE organisms have been discussed in this section and graphical representation is provided in Fig. 1.

3.1. Chemical modification or breakdown of the drug

Bacteria express some crucial enzymes (such as β-lactamases) which offers them a survival benefit by chemically modifying or destroying the antibiotics. β-lactamases are some of the widely-studied enzymes in relevance to antibiotic resistance and they are characterized by their ability to cleave the amide bond of the four-membered β-lactam ring present in penicillins, cephalosporins, cephamycins, monobactams, and carbapenems [9]. Penicillinase, cephalosporinase, broad-spectrum β-lactamases, metallo-β-lactamases,extended-spectrum β-lactamases (ESBL), and carbapenemases are the major types of lactamases responsible for drug destruction which makes the antibiotic inactive and more than 2600 different β-lactamases have been identified so far [10]. The catalytic activity of some of these enzymes can be inhibited by compounds such as clavulanate, tazobactam, sulbactam, and ticarcillin and therefore administered them to patients along with β-lactam antibiotics [11]. β-lactamases based on molecular structure are classified into four classes according to Ambler scheme such as class A, B, C, and D. Class A family enzymes comprise the largest cluster of β- lactamases known to bear serine residue in their active site and act against various β-lactam antibiotics such as penicillins, early cephalosporins, third-generation oxyimino-cephalosporins, monobactams, cephamycins, and carbapenems [12]. Majority of the *S. aureus* of clinical relevance and few Enterococcus spp. produce *blaZ*–encoded penicillinases that belong to the class A family [13]. CTX-M (Cefotaximase from Munich), PER (Pseudomonas extended resistant), GES (Guiana extended-spectrum β-lactamase), and VEB (Vietnam extended-spectrum β-lactamase) families belong to class A ESBL enzymes and were found to be produced by all Gram-negative ESKAPE pathogens [14]. The majority of the class A ESBL enzymes can be inhibited by clavulanate except TEM-30 (Temoniera), SHV-10 (Sulphydral reagent variable), and TEM-50 [15]. Alarmingly, some strains of *K. pneumoniae* were reported to produce inhibitor-resistant β-lactamases (resistant to many known inhibitors of β-lactamase) such as *Klebsiella pneumoniae* carbapenemase (KPC) enzymes which degrade all β-lactams, including carbapenems [16]. Nevertheless, a combination of imipenem-cilastatin-relebactam or meropenem-vaborbactam was found to be effective against KPC-producing organisms [17]. The Ambler group B constitutes metallo-β–lactamases (MBLs) which contain Zn^{+}ion in their active sites and are prominently found in Gram-negative ESKAPE pathogens [18]. IMP (Imipenemase)- and VIM (Verona integron-encoded MBL)-type MBLs are found to be present in ESKAPE pathogens such as *P. aeruginosa, K. pneumoniae, Enterobacter cloacae* complex isolates, and *Acinetobacter* spp [19,20]. NDM (New Delhi metallo-β–lactamase)-type MBLs are seen in most of the Gram-negative ESKAPE pathogens and they are of particular concern because they are incorporated into the mobile genetic elements that also encode determinants for resistance to other antibiotic classes [21]. The Amber Group C family contains cephalosporinases such as AmpC identified in the *Enterobacter* spp., *P. aeruginosa*, and *Acinetobacter* spp., which act against most narrow- to intermediate-spectrum cephalosporins plus aztreonam. Lastly, the Amber Group D family includes oxacillin-hydrolyzing enzymes which were reported to be present in Acinetobacter spp. and many Enterobacterales species [22]. Similarly, macrolide esterases hydrolyze the lactone ring of macrolides such as azithromycin and erythromycin.

Beside, some bacterial enzymes have the capability of chemically modifying the antibiotics (such as acetylation, phosphorylation, and adenylation) to inactivate them and to acquire antibiotic resistance. The major categories of antibiotic modifying enzymes are aminoglycoside-modifying enzymes (AMEs), rifamycin-modifying enzymes, macrolide phosphotransferases, chloramphenicol acetyltransferases, phosphomycin-modifying enzymes, and flavin-dependent monooxygenases. Rifamycin inhibits prokaryotic transcription by interacting with the β-subunit of the RNA polymerase, whereas rifamycin modifying enzymes modify the hydroxyl group which abolishes the potency of the antibiotic [23].

The aminoglycosides are broad-spectrum antibiotics derived from actinomycetes which inhibit protein synthesis by binding to ribosomal subunits. The resistance against these antibiotics majorly occurs through chemical modification by aminoglycoside-modifying enzymes (AMEs) [24]. The genes coding for these enzymes are generally present in the transmissible elements and have rarely been found in genome of some bacteria. The presence of AME activity in resistant bacterial strains has been documented previously [25–27]. The members of the AME family are classified into aminoglycoside acetyltransferases (AACs), aminoglycoside phosphotransferases (APHs), and aminoglycoside nucleotidyltransferases (ANTs) based on the nature of chemical modifications they catalyze [28]. The chemical modifications catalyzed by these enzymes alter the binding affinity of aminoglycosides to ribosomal subunits. Aminoglycoside acetyltransferases are the largest class of AMEs which are further subdivided into four subclasses and are involved in the acetylation of amino groups present in the aminoglycoside antibiotics. AAC(1) and AAC(3) subclasses are involved in the acetylation of amino groups present in the 1st and 3rd position of the 2-deoxystreptamine moiety of aminoglycosides respectively, whereas AAC(2′) and AAC(6′) subclasses acetylate 2′ and 6′ amino group positions of 2,6-dideoxy-2, 6-diamino-glucose moiety [24]. Recent epidemiological investigations in the United States, Europe, and Asia revealed that AAC(3) and AAC(6′) enzymes are most frequently observed in Gram-negative ESKAPE pathogens which confer resistance against gentamicin, tobramycin, and amikacin [29–31].

APHs are the second largest class of AMEs which are further subdivided into seven subclasses. These enzymes are involved in the phosphorylation of the hydroxyl group present in the aminoglycosides which diminish the binding affinity due to reduced hydrogen bonding interaction between the antibiotic and target. Out of seven subclasses, APH(3′) was reported to be found in *S. aureus* and *Enterococcus* spp. which confer resistance against amikacin [29].

ANTs are the third-largest class of AMEs which are involved in the addition of nucleotide monophosphate to hydroxyl groups of the aminoglycosides at 2″, 3″, 4′, 6, and 9 positions [24]. Out of five subclasses, ANT(2″) and ANT(4′) were reported to be produced by *K. pneumoniae* and *S. aureus* respectively. ANT(2″) confers resistance against 4, 6-di-substituted aminoglycosides whereas ANT(4′) acts against kanamycin A/B/C, gentamicin A, amikacin, tobramycin, and neomycin B/C [32].

3.2. Prevention of antibiotic influx

The bactericidal efficacy of an antibiotic depends on the amount of drug taken into the bacteria and expelled out. Many antibacterial agents use intracellular targets to impart their growth-inhibitory activity and the maximum efficiency is expected only when a sufficient amount of antibiotic molecule reaches the inner compartments of the cell. Many bacteria have evolved with an adaptive mechanism in which they alter the expression levels of channels and efflux pumps. The outer membrane of Gram-negative bacteria has proteins termed porins that are involved in the formation of channels to enable the movement of antibiotics into the cell. *A. baumannii* which displayed the conspicuous loss of outer membrane protein (OMP, 29-kDa) was insensitive to imipenem activity [33]. Experimental evidence was provided to demonstrate the role of the OprD channel in the influx of panipenem/imipenem. OprD is present in the outer membrane of *P. aeruginosa* and a decrease in OprD levels enabled the bacteria to acquire resistance against imipenem [34].

3.3. Antibiotic expulsion through efflux pumps

Efflux pumps are responsible for the outflux of antibiotics from the bacterial cell and overexpression of various types of efflux pumps is observed in MDR bacteria. Drug expulsion could be either due to increased expression of efflux pump proteins or base substitution mutation in the gene that codes for the efflux pump protein which may result in the replacement of an amino acid that potentiates the activity of the efflux pump [35]. The genes that encode for efflux pumps can be present either in the bacterial genome or mobile genetic elements such as plasmids. Six families of bacterial drug efflux pumps have been described so far, they are ATP-binding cassette (ABC) family, the multidrug and toxin extrusion (MATE) family, major facilitator superfamily (MFS), the resistance-nodulation-cell division (RND) superfamily, the small multidrug resistance (SMR) family, and the proteobacterial antimicrobial compound efflux (PACE) family [36]. For an instance, *P. aeruginosa* strains are relatively less sensitive to tigecycline and the loss of MexXY (OprM) efflux pumps resulted in the increased sensitivity

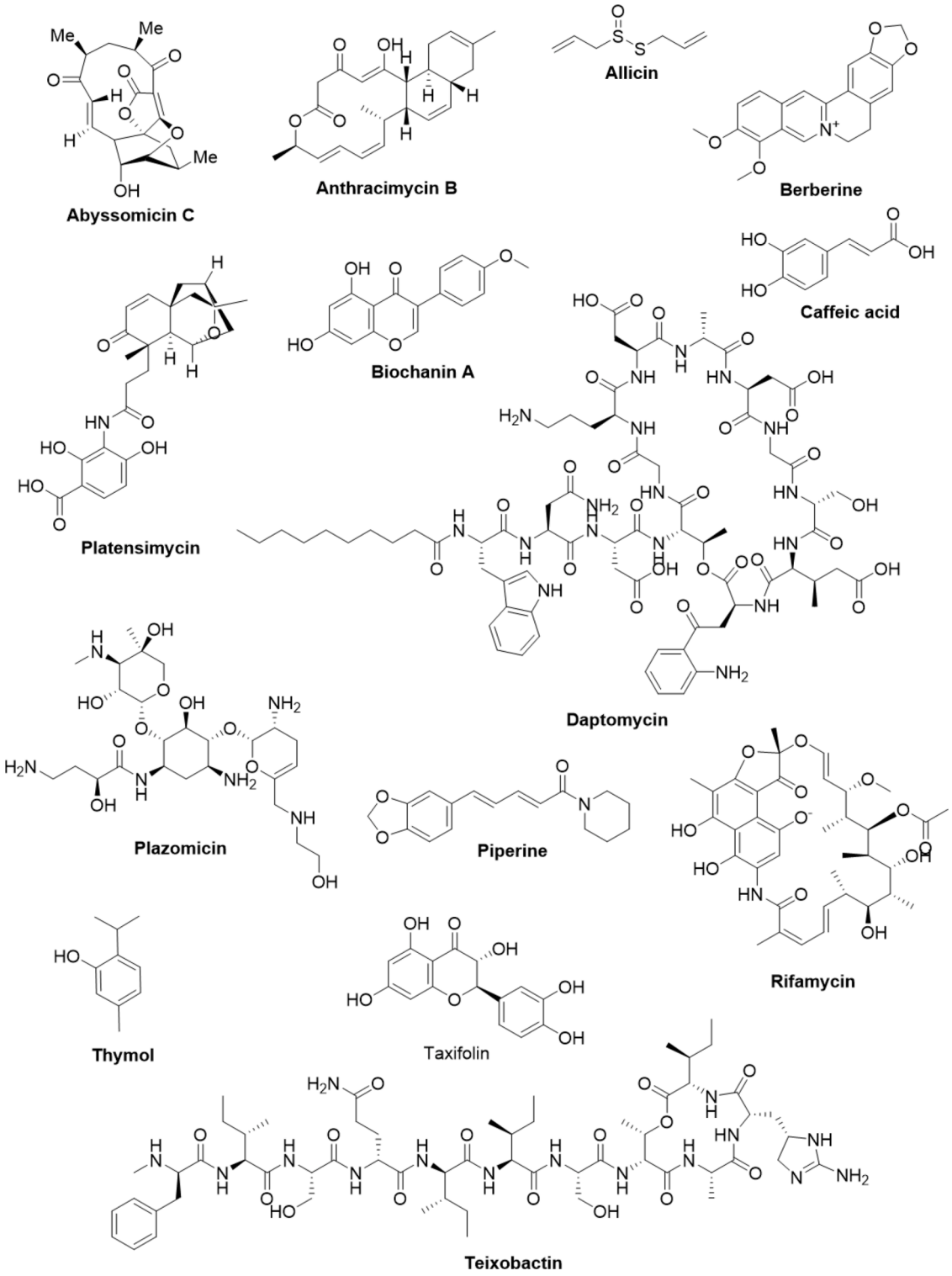

Fig. 2. Chemical structure of secondary metabolites derived from bacteria and plants.

of microbe towards tigecycline [37]. The members of the RND superfamily such as MexAB-OprM, MexCD-OprJ, MexEF-OprN, MexXY, and MuxBC—OpmB are involved in the expulsion of various antibiotics including β-lactams, aminoglycosides, chloramphenicol, fluoroquinolones, macrolides, quinolones, tetracycline, and novobiocin in *P. aeruginosa* [38]. It can be concluded that all resistant bacteria express their own set of efflux pumps to combat the harmful effects of antibiotics on them.

3.4. Modification of antibiotic target

Bacteria protect themselves from the action of antibiotics through modification of the drug target. The modifications include mutations in the gene that encode target protein, chemical alteration of the interaction site, and substitution of the original target [39]. Many antibiotics impart their antibacterial action by targeting ribosomal subunits (the 50S and 30S). Aminoglycoside antibiotics interact with a 16S rRNA of the 30S subunit and hamper the interaction of aminoacyl-tRNA to the anticodon which ultimately results in the abrogation of translation and bactericidal effects. 16S rRNA methyltransferases either methylate N7 of guanine (1405) or N1 of adenine (1408) of 16S rRNA to confer resistance against the majority of aminoglycosides [28]. Some rRNAs (5S and 23S rRNA) and ribosomal proteins of the 50S subunit are targeted by macrolides, ketolides, lincosamides, and streptogramin. Like 16S rRNA methyltransferases, 23S rRNA methyltransferases methylate the antibiotic binding site resulting in the abolishment of antibiotic activity [40]. Similarly, bacterial targets of antibiotics are modified by phosphoethanolamine transferases and peptidoglycan modifying enzymes.

4. Antibacterial agents derived from the Mother Nature

Mother Nature has been serving as an inexhaustible source of bioactive secondary metabolites which are endowed with a wide range of pharmacological activities including antibacterial, anticancer, antifungal, antihypertensive, antidepressants, antiviral, and many more [41–46]. The structural complexity of these compounds makes the synthetic process impractical. Thousands of secondary metabolites have been isolated from bacteria, plants, fungi, endophytes, and marine

Table 1
Secondary metabolites derived from the bacterial origin with antibacterial activity towards ESKAPE pathogens.

Sl. No.	Antibacterial compound	Source	Activity against	Mode of action	Reference
1.	Lysobactin (Depsipeptide)	Several gram-negative gliding bacteria from soil	*S. aureus* (MIC=0.75 μg/mL), MRSA (MIC= 0.39 μg/mL), VRE (MIC= 0.78 μg/mL)	Interfere with peptidoglycan biosynthesis by binding to lipid I, Lipid II, Lipid III cell wall precursors	[164, 165]
2.	Salinamide F (Depsipeptide)	*Streptomyces* sp., strain CNB-091	*E. faecalis* (MIC_{50} =12.5 μg/ml), *S. aureus* (MIC_{50} =100 μg /ml), *H. influenzae*, (MIC_{50} =12.5 μg/ml), *Neisseria gonorrhoeae* (MIC_{50} = 25 μg/ml), *Enterobacter cloacae* (MIC_{50} = 50 μg/ml)	Inhibition of RNA polymerase	[166]
3.	Siamycin-I (Tricyclic peptide)	*Streptomyces* sp.	VRE (MIC = 7.4 μM), *S. aureus* (MIC = 3.7 μM), MRSA (MIC = 7.4 μM), multidrug resistant *S. aureus* (MIC = 14.8 μM)	Interferes in peptidoglycan biosynthesis by binding to lipid II.	[167]
4.	Capistruin (Lasso peptide)	*Burkholderia thailandensis E264*	*E. coli 363* (MIC = 25 μM), *P. aeruginosa* AT27853 (MIC = 50 μM)	Inhibition of RNA polymerase	[168, 169]
5.	Mitomycin C (7-Amino-9alpha-methoxymitosane)	*Streptomyces caespitosus*	*A. baumannii* (MIC = 7 μg/mL)	DNA intercalation	[170, 171]
6.	Marthiapeptide A (Polythiazole cyclic peptide)	*Marinactinospora thermotolerans* SCSIO 00,652	*M. luteus* (2.0 μg/mL) *S. aureus* (8 μg/mL),	ND	[172]
7.	Lobophorin F	*Streptomyces* sp. (SCSIO 01,127)	*S. aureus, E. faecalis* (MIC for both = 8 μg/mL)	ND	[173]
8.	Desotamide (Cyclic hexapeptide)	*Streptomyces scopuliridis* SCSIO ZJ46	*S. pnuemoniae* (MIC = 12.5 μg/mL)„ *S. aureus* (MIC = 16 μg/mL), methicillin-resistant *S. epidermidis* (MIC = 32 μg/mL)	ND	[174]
9.	Abyssomicin C	*Verrucosispora* sp. AB-18–032	MRSA (MIC =4 μg/mL), VRSA (MIC =13 μg/mL)	Inhibition of 4-amino-4-deoxychorismate (ADC) synthase	[50,51]
10.	Ficellomycin	*Streptomyces ficellus*	Multidrug resistant strains of *S. aureus*	Interferes in DNA replication	[175]
11.	Etamycin	*Streptomyces sp*	MRSA (MIC =1–2 mg/L)	Possible role in inhibition of protein synthesis	[176]
12.	Thiomarinol A	*Pseudoalteromonas* sp. SANK 73390	MRSA (MIC = 0.002 - 0.50 μM)	Inhibition of isoleucyl-tRNA synthetase	[177]
13.	Mithramycin	*Streptomyces plicatus, Streptomyces argillaceus*	MRSA and MSSA strains (MIC = 0.125 – 0.25 μg/mL) vancomycin resistant enterococci and vancomycin sensitive enterococci (MIC = 1–16 μg/mL)	Inhibition of transcription	[178]
14.	Marinopyrrole A	*Streptomyces* sp. CNQ-418	*S. aureus* (MIC = 0.5–1 μg/mL), MRSA (MIC = 0.188–0.375 μg/mL), *E. faecalis* (MIC = 1 μg/mL)	ND	[179]
15.	Bottromycin A2 (Macrocyclic peptide)	*Streptomyces* sp. *KM-9459.*	*S. aureus* (MIC = 1 μg/mL), MRSA (MIC = 1 μg/mL), VRE (MIC = 1 μg/mL)	Inhibition of protein synthesis	[180]
16.	Tirandamycin C	*Streptomyces* sp. *307–9*	VREF	Inhibition of RNA polymerase	[181]
17.	Anthracimycin B	*Streptomyces cyaneofuscatus M-169,*	MRSA, MSSA, *E. faecium*	ND	[59]
18.	Fijimycin A (Cyclic depsipeptide)	*Streptomyces* sp. *CNS-575*	MRSA (MIC = 4–16 μg/mL)	ND	[182]
19.	Ecteinamycin	*Actinomadura* sp. *WMMB499*	MRSA (MIC = 0.125 μg/mL), MSSA (MIC = 0.125 μg/mL), *P. aeruginosa* (MIC = 8 μg/mL) *Clostridium difficile* NAP1/B1/027 (MIC = 59 ng/μL)	Acts as an ionophore and is involved in membrane depolarization and dysregulation of potassium cation homeostasis.	[183]
20.	Lajollamycin	*S. nodosus NPS007994,*	*S. pneumoniae* (MIC = 1.5 μg/mL), MRSA (MIC = 5 μg/mL)	ND	[184]

ND: Not determined.

invertebrates and some of them have been approved as therapeutic agents for the treatment of several human ailments [47–49]. Therefore, these biological sources are true treasure houses of secondary metabolites and drugs. In the following sections, we have discussed some of the antibacterial agents derived from bacteria (Fig. 2 and Table 1) and plants (Table 2).

4.1. Abyssomicin C

Abyssomicin C is one of the promising compounds belonging to the family of abyssomicin with antibacterial activity against many Gram-positive bacteria. Abyssomicin C along with its atrop isomer (atrop-abyssomicin C) and other inactive derivatives such as abyssomicins B and D were isolated from an actinomycete strain *Verrucosispora* AB-18-

Table 2
Secondary metabolites derived from plant origin with antibacterial activity towards ESKAPE pathogens.

Sl. No.	Antibacterial compound	Source	Activity against	Mode of action	Reference
1.	Resveratrol	Grapevines (*Vitis vinifera*), Peanuts (*Arachis hypogea*), Japanese knotweed (*Polygonum cuspidatum*)	*S. aureus, E. faecalis, and Streptococcus pyogenes* (MICs = 100–200 μg/mL) *M. smegmatis* (MIC = 64 μg/mL) *H. pylori* (MIC = 25–50 μg/mL) *N. gonorrhoeae* (MIC = 75 μg/mL) *M. tuberculosis* (100 μg/mL)	Partial inhibition of ATP hydrolysis and synthesis functions of ATP synthase complex. Possible role in the inhibition of FtsZ-mediated septum formation and cell division Cell membrane leakage.	[185]
2.	Glabrol	Licorice (*Glycyrrhiza glabra* L.)	MRSA T144 (MIC=2 μg/mL), MSSA 1518 (MIC=1 μg/mL)	Disruption of membrane permeability Dissipation of proton motive force	[186]
3.	Apigenin	Parsley *(Petroselinum crispum)*, Chamomile (*Matricaria chamomilla* L.), Celery (*Apium graveolens* L.), Vine-spinach (*Basella rubra L.*), Artichokes (*Cynara scolymus* L.), and Oregano (*Origanum vulgare* L.),	*A. baumannii* (RSKK 02026 Strain MIC=2 μg/mL, clinical isolate=64 μg/mL) *E. aerogenes* (MIC=64 μg/mL)	Inhibition of D-alanine-D-alanine ligase and DNA gyrase enzyme	[187–189]
4.	Baicalin	Baikal skullcap *(Scutellaria baicalensis),* Blue skullcap *(Scutellaria lateriflora)*	*Staphylococcus saprophyticus, Streptococcus mutans*	Inhibition of biofilm formation, Inhibition of efflux pump	[190]
5.	Carvacrol	Conehead thyme (*Thymus capitatus*) Thyme (*Thymus vulgaris*)	*E. coli* (MIC=8 μg/mL)	Disruption of membrane integrity	[191]
6.	Sanguinarine	Celandine (Chelidonium majus L.) Blood Root (*Sanguinaria canadensis* L.), Fumitory (*Fumaria officinalis* L.) Plume poppy *(Bocconia frutescens* L.)	*S. aureus* (MIC 1.9 mg/L) MRSA (3.12 μg/mL) MRSA (MIC=1.56 μg/mL)	Release of autolytic enzymes and cell lysis. DNA intercalation leads to inhibition of replication and transcription	[192]
7.	Reserpine	Sarpagandha or Indian snake root (*Rauvolfia serpentina* (L.) Benth. ex Kurz)	*Staphylococcus* sp., *Streptococcus* sp. *Micrococcus* sp.	Efflux pump inhibitory activity	[193,194]
8.	Tomatidine	Tomato (*Solanum lycopersicum*)	*S. aureus, L. monocytogenes, Bacillus ssp.*	Inhibition of ATP synthase complex	[195]
9.	Sakuranetin	*Asteraceae species (Polymnia fruticosa, Baccharis retusa), Himalayan cherry (Prunus puddum)*	*H. pylori* (MIC= 87.3 μM)	Inhibition of HpFabZ enzyme	[196]
10.	Curcumin (Diferuloylmethane)	Turmeric (*Curcuma longa*)	*E. faecalis, S. aureus, P. aeruginosa*	Membrane leakage	[197]
11.	Agasyllin	*Finocchiazzo* (*Ferulago campestris*)	*S. Typhi, E. aerogenes, E.cloacae, S. aureus* (MIC=32 μg/mL)	Inhibition of DNA gyrase enzyme	[198,199]
12.	Conessine	Kutaja Kurchi *(Holarrhena antidysenterica),* Kelinda (*Holarrhena mitis*), False rubber tree (*Holarrhena floribunda*)	*P. aeruginosa, Bacillus spp.*	Inhibition of MexAB-OprM efflux pump.	[200–202]
13.	Shikimic acid	All plants	*S. aureus* (2.5 mg/mL)	Alteration of membrane potential and leakage of cellular contents, Inhibition of biofilm formation	[203,204]
14.	Ferulic acid	All plants	*E. coli* (100 μg/mL), *P.aeruginosa* (100 μg/mL), *S. aureus* (1100 μg/mL), *L. monocytogenes* (1250 μg/mL)	Membrane rupture and release of intracellular contents	[205]
15.	Kaempferol	Abudant in Tea (*Camellia sinensis*), Broccoli (*Brassica oleracea*), Apple *(Malus domestica*), Strawberry (*Fragaria x ananassa*).	*S. aureus*	Efflux pump inhibition, Inhibition of PriA helicase enzyme, Inhibition of biofilm formation, Inhibition of Sortase A activity	[206–209]
16.	Kurarinol	Shrubby sophora (*Sophora flavescens*)	*S. aureus* (219 μM), *B. subtilis* (219 μM), *S. typhimurium* (219 μM), *P. vulgaris* (109 μM)	Inhibition of Sortase A enzyme	[210]
17.	Morusin	Mulberry (*Morus alba*)	*S. aureus* (14.9 μmol/L)	Disruption of membrane integrity, Reduction gene expression of acc C, Fab D, Fab F, Fab G, Fab H, Fab I, Fab Z, Pls X, Pls Y, Pls C (phosphatidic acid biosynthesis-associated genes)	[211]
18.	Lonicerin	Japanse honeysuckle (*Lonicera japonica*)	*P. aeruginosa*	Inhibition of biofilm formation, Inhibition of alginate secretion protein (AlgE)	[212]
19.	Plumbagin	*Indian leadwort* (*Plumbago rosea*), *Ceylon leadwort* (*Plumbago zeylanica*)	*S. aureus* (5 μg/mL), MRSA (4–8 μg/mL)	Possible role in the inhibition of DNA gyrase	[213–215]
20.	Naringenin	Present in many citrus fruits such as Grapefruit (*Citrus paradisi*), Sour orange (*Citrus aurantium*), tart cherries (*Prunus cerasus*), tomatoes (*Solanum lycopersicum*), and greek oregano (*Origanum vulgare* L.).	*E. faecalis (256* μg/mL), VERF (512 μg/mL)	Inhibition of β -Ketoacyl acyl carrier protein synthase (KAS) III (through in silico approach)	[140,216]

032. The actinomycete strain was isolated from the sediments of the deep Sea of Japan at a depth of 289 m [50]. Abyssomicin C has been reported to possess antibacterial activity against MRSA and VRSA with MIC values of 4 and 13 μg/mL, respectively [51]. The studies of Freundlich et al. demonstrated the antibacterial activity of Abyssomicin C and atrop-abyssomicin C against *Mycobacterium tuberculosis* H37Rv with MIC values of 3.6 and 7.2 μM, respectively [52]. Abyssomycin C and atrop-abyssomicin C are the first natural compounds reported to inhibit the p-aminobenzoic acid/tetrahydrofolate biosynthesis pathway in Gram-positive bacteria [53,54]. ADC synthase (4-amino-4-deoxy chorismic acid synthase) and ADC lyase (4-amino-4-deoxy chorismic acid lyase) are the two important enzymes involved in the biosynthesis of p-aminobenzoic acid from chorismic acid. ADC synthase has two subunits (namely PabA and PabB) which are involved in the conversion of chorismic acid and glutamine to 4-amino-4-deoxy chorismic acid and glutamate, respectively. ADC lyase converts 4-amino-4-deoxy chorismic acid into p-aminobenzoic acid which further participates in the folate biosynthesis. Abyssomycin C and atrop-abyssomicin C independently inhibit the activity of ADC synthase by covalently binding to the side chain of Cys263 of the PabB subunit of ADC synthase [55]. Monjas et al. synthesized truncated derivatives of abyssomycin C and studied their structure-activity relationship towards ADC synthase and these derivatives were found to have lower antibacterial activity compared to abyssomycin C [56].

4.2. Anthracimycin

Anthracimycin was isolated initially in 2013 from the *Streptomyces* strain CNH365 that was collected from the marine sediments of Santa Barbara, USA. Anthracimycin is a 14-membered macrolide that possesses a rare chemical structure that closely resembles the structure of chlorotonil A (antimalarial agent). In the initial studies, anthracimycin demonstrated potent antibacterial activity against the Gram-positive organisms such as *Bacillus anthracis, S. aureus, Enterococcus faecalis, Streptococcus pneumoniae* with MIC values of 0.031, 0.0625, 0.125, 0.25 μg/mL, respectively [57]. Later, anthracimycin was also demonstrated to possess antibacterial activity against the methicillin-susceptible/resistant *S. aureus* (MSSA/MRSA), and VRSA with MIC values less than 0.25 mg/L. In the *in vivo* studies, anthracimycin protected the mice from MRSA-induced mortality at 1 or 10 mg/kg. They also showed that anthracimycin inhibits the DNA and RNA synthesis in *S. aureus* and the inhibition is independent of DNA intercalation. Using genome mining strategy, Sirota et al., identified that *Nocardiopsis kunsanensis* produces an anthracimycin analog named anthracimycin BII-2619 [58]. Notably, both anthracimycin BII-2619 and anthracimycin displayed antibacterial activity against the MSSA and MRSA with MIC values $\leq$1 μM. In another study, Rodríguez et al., isolated the anthracimycin B along with anthracimycin from actinomycete *Streptomyces cyaneofuscatus* M-169 species obtained from gorgonian coral that was collected from Avilés submarine Canyon at 1500 m depth [59]. The anthracimycin B exhibited potent antibacterial activity against MSSA, MRSA, vancomycin sensitive *E. faecium*, and vancomycin sensitive *E. faecalis*. Interestingly, Davison et al. developed a method for the chemical synthesis of anthracimycin which opened a new avenue for the synthesis of potent anthracimycin analogs [60].

4.3. Daptomycin

Daptomycin is a cyclic lipopeptide antibiotic produced by *Streptomyces roseosporus*. It received FDA approval for the treatment of skin infections and *S. aureus* bacteremia. Daptomycin is the only lipopeptide antibiotic that is in clinical practice and has potent activity against Gram-positive bacterial infections, MRSA, and vancomycin-resistant Enterococci (VRE) [61]. Daptomycin is used as an alternative therapeutic agent to vancomycin for invasive MRSA or MSSA infections in patients who are allergic to β-lactams. It has been considered as a last-resort treatment for heterogeneous vancomycin-intermediate *S. aureus* (hVISA) and vancomycin-intermediate *S. aureus* (VISA) infections [62]. Although the precise mechanism of action of daptomycin is yet to be understood, a model proposes that daptomycin interacts with the plasma membrane resulting in its permeabilization and depolarization caused by a loss of cytoplasmic potassium ions [62]. Although daptomycin resistance is uncommon, failure of treatment up to 33% may be observed in invasive infections including bacteremia or osteomyelitis [63]. In one of the interesting studies, *S. aureus* was demonstrated to release phospholipids in response to daptomycin treatment to sequester the drug and to escape from its bactericidal effects [64]. In a similar study, *E. faecalis* and pathogenic streptococci were demonstrated to nullify the effect of daptomycin by shedding phospholipids [61]. Considering the therapeutic importance of daptomycin, a large number of studies are being carried out to potentiate its bactericidal action in combination with other antibacterial agents.

4.4. Kibdelomycin

Kibdelomycin is a novel class of antibiotics produced by *Kibdelosporangium* sp. (MA7385) [65]. *S. aureus* fitness test strategy was employed for the discovery of kibdelomycin which signifies the importance of a high-throughput chemical genetic approach in the screening of potential natural compounds. The kibdelomycin showed potent antibacterial activity against many Gram-positive organisms such as wild-type *S. aureus*, MRSA, *S. pneumoniae, E. faecalis* with MIC values 2, 0.5, 1, and 2 μg/mL, respectively and *Haemophilus influenzae* (Gram--negative organism) with a MIC value of 2 μg/mL. Kibdelomycin was found to impart their antibacterial activity by interrupting DNA replication through the inhibition of ATPase activity of DNA gyrase and topoisomerase IV of *Escherichia coli* and *S. aureus* [65]. Subsequently, kibdelomycin A, a congener of kibdelomycin was isolated from *Kibdelosporangium* sp. (MA7385) and its derivatives (kibdelomycin C-33 acetate and tetrahydro-bisdechloro derivative of kibdelomycin) were prepared [66]. Kibdelomycin A and its derivatives were reported to have inferior antibacterial activity compared with kibdelomycin against MSSA, MRSA, *S. pneumoniae, E. faecalis, Bacillus subtilis, H. influenzae, E. coli, and Candida albicans* [66]. Kibdelomycin A displayed relatively lesser inhibitory activity compared to kibdelomycin towards DNA gyrase and topoisomerase IV of *S. aureus* whereas both the compounds showed similar inhibitory activity towards DNA gyrase and topoisomerase IV of *E. coli* [66]. Interestingly, co-crystallization studies between kibdelomycin and gyrase B or topoisomerase IV of *S. aureus* revealed that kibdelomycin exhibits a “dual-arm” U-shaped binding mode with both enzymes [67]. Kibdelomycin is a wide-spectrum antibiotic without cross-resistance to known gyrase inhibitors, including clinically effective quinolones. The ‘dual arm’ U-shaped binding interaction of kibdelomycin is unique and not seen in other gyrase inhibitors [67]. This may be the reason to present kibdelomycin as an antibiotic without cross-resistance to other gyrase inhibitors. Beside, kibdelomycin was reported with potent antibacterial activity against *Clostridium difficile*, a causative agent of *C. difficile*-associated diarrhea, especially in elder people [68]. Kibdelomycin acted as a broad range bactericidal agent and found to be effective against the Gram-negative organisms such as *Moraxella catarrhalis* and *A. baumannii* with MIC_{90} values of 0.5 and 0.125 μg/mL, respectively. Taken together, kibdelomycin can be considered as the potential antimicrobial compound against many pathogenic bacteria [69].

4.5. Platensimycin

Platensimycin and platencin are produced by *Streptomyces platensis* that represents a unique structural class of non-toxic natural antibiotics [70]. Platensimycin has been identified as an effective inhibitor of bacterial fatty acid synthases by selectively targeting β-ketoacyl-(acyl-carrier-protein (ACP)) synthase I/II [71]. The discovery of

platensimycin has provided a new direction to the discovery of antibiotics with structural diversity. MRSA biofilms in wounds are difficult to treat with conventional antibiotics. Platensimycin and sulfur-Michael derivatives suppressed the biofilm formation by *S. aureus* beyond 95% at 2 μg/mL [72]. Notably topical application of ointments having platensimycin was successful in treating MRSA infections in a BABL/c mouse burn wound model [72]. However, its clinical development was hindered due to its poor solubility and pharmacokinetic properties. To overcome these shortcomings, several efforts have been made including the preparation of platensimycin nanoformulations. In one such study, platensimycin-loaded nanoparticles substantially decreased residual bacteria relative to free platensimycin in the MRSA-infected macrophage cell model [73]. Notably, encapsulation of platensimycin with liposomes or micelles significantly enhanced its pharmacokinetic properties in Sprague–Dawley rats with an increase in the survival rate of MRSA-infected C57BL/6J mice [73]. These studies suggest that pitfalls of platensimycin may be overcome either through its chemical modifications or the utilization of better delivery systems.

4.6. Plazomicin

Plazomicin [6′-(hydroxylethyl)-1-(haba)-sisomicin] is a next-generation semisynthetic aminoglycoside antibiotic that originated from sisomicin which was isolated from *Micromonopora inyoensis* [74]. Plazomicin obtained approval from the US Food and Drug Administration for the treatment of complicated urinary tract infections caused by Gram-negative aerobic bacteria. Importantly, plazomicin is a relatively efficacious aminoglycoside towards carbapenem-resistant Enterobacteriaceae and ESBL-producing Enterobacteriaceae [75,76]. The positively charged plazomicin belongs to the class of aminoglycosides. These classes of antibiotics penetrate the periplasm of bacteria by interacting with the negatively charged cell membrane [77,78]. Further with the help of oxygen-nitrogen dependant electron chain machinery, they enter the aerobic bacteria [77]. The plazomicin is an inhibitor of protein synthesis and showed synergistic activity in combination with the cefepime, doripenem, imipenem, or piperacillin-tazobactam against *P. aeruginosa.* In addition, it also displayed synergistic antibacterial activity in combination with daptomycin or ceftobiprole against MRSA, hVISA, VISA, and VRSA [79]. The studies of Thwaites et al. showed that plazomicin displayed potent bactericidal activity against MDR *E. coli*, *K. pneumoniae*, and *Enterobacter* spp. with a minimum bactericidal concentration ($MBC_{50/90}$) of 0.5/ 4 μg/mL respectively [80].

4.7. Teixobactin

Teixobactin is a new class of undecapeptide-containing antibiotic recently isolated using iChip (isolation Chip) technology from the uncultured bacteria *Eleftheria terrae,* which belongs to the new genus aquabacteria [81]. The iChip technology employs simultaneous isolation and growth of uncultured bacteria in its natural environment by providing suitable nutrients and growth factors [82]. Teixobactin exhibited excellent antibacterial activity against antibiotic-resistant microorganisms such as *E. faecalis, E. faecium,* MRSA, and many other Gram-positive organisms. The observed antibacterial effect of teixobactin was due to the inhibition of cell wall synthesis by interacting with lipid II (precursor of peptidoglycan) and lipid III (precursor of teichoic acid). The interaction of teixobactin with these precursors interferes with the precursor recycling and synthesis of peptidoglycans and teichoic acid [81]. Interestingly, teixobactin showed no hemolytic activity in human red blood cells and no toxicity against NIH/3T3 and HepG2 cells at 100 μg/mL. Subsequently, after the discovery of this antibiotic, many synthetic routes for the preparation of teixobactin and its analogs were developed using solid and solution phase peptide synthesis [83–86].

Structurally, teixobactin contains four D-amino acids (D-phenylalanine [N-Me-D-Phe], D-glutamine, D-allo-isoleucine, D-threonine), and one rare amino acid (L-allo-enduracididine) out of 11 residues. In the initial approaches of preparation of teixobactin analogs, L-allo-enduracididine was replaced with various acidic, basic, and neutral amino acids followed by evaluation of their antibacterial potency against MRSA [87–89]. The analogs in which L-allo-enduracididine is substituted with Ile, Leu, Val, and Met were found to have equal or higher antibacterial efficacy than teixobactin suggesting that L-allo-enduracididine is not critical for the antibacterial activity of teixobactin [90,91]. The replacement of N-Me-D-Phe with N-benzyl, N-decyl, N, N-dodecyl, N-decanoyl, N-morpholine, and tetramethyl-N-guanidinylated groups resulted in inactive compounds [92]. On the other hand, 4-phenyl and 4-chlorophenyl analogs of teixobactin were found to be more potent and Phe (4-benzoyl)1-teixobactin was almost three-fold more effective than the teixobactin. These studies suggest that the phenyl moiety of teixobactin plays a key role in imparting antibacterial activity. Concerning this, Zong et al. proposed a hydrophobic interaction between lipid II of the cell wall of the bacteria and the N-terminal of teixobactin analogs [93]. Recently, Gunjal et al. comprehensively reviewed different aspects of teixobactin including its antibiotic potential, the effect of replacement of amino acids on antibacterial activity, synthetic efforts for its preparation, and structural-activity-relationships [90]. Unconventionally and unlike other antibiotics, teixobactin targets lipids for bactericidal activity (rather than proteins) which minimizes the risk of development of drug resistance by mutations of drug targets.

5. Antibacterials from plant origin

5.1. Allicin

Allicin (diallylthiosulfinate) is an organosulfur compound present in the garlic (Allium sativum L.) which is endowed with good antibacterial activity against MRSA, *Pseudomonas syringae, Salmonella typhimurium*, and *Vibrio cholerae* [94]. Allicin is synthesized from the non-protein amino acid named alliin by the enzyme alliinase in the garlic [95]. Allicin is a volatile compound and it was used to treat some infections of the respiratory system in the pre-antibiotic era. The antimicrobial effect of the allicin is imparted through its inhibitory activity towards the thiol group-containing enzymes such as alcohol dehydrogenase, thioredoxin reductase, and RNA polymerase [96]. The electrophilic sulfur center of the allicin readily oxidizes thiol groups of the target enzymes to form S-allylmercapto adduct and thereby leads to inactivation of these enzymes. Allicin has also been shown to partially inhibit the synthesis of DNA and proteins. The possible reason for translation inhibition is due to the reaction of allicin with thiol groups of elongating amino acid chains on ribosomes [97]. Some investigations have revealed that allicin augments the antibacterial activity of some of the antibiotics such as cefoperazone, tobramycin, and ciprofloxacin, against *P. aeruginosa* [98]. Despite being a good antibacterial agent, it is unstable at room temperature and antimicrobial activity is lost within minutes upon heating to >80 °C. The thiosulfinate analogs of allicin such as dimethyl-, diethyl-, diallyl-, dipropyl-, and dibenzyl-thiosulfinates were reported to have variable antibacterial activity against *E. coli* K12, *Pseudomonas fluorescens,* and *P. syringae* pv. phaseolicola 4612, *Micrococcus luteus,* and were found to be much more thermally stable than allicin [99].

5.2. Berberine

Berberine is a phytogenous isoquinoline alkaloid present in the plants that belong to the family of Berberidaceae, Papaveraceae, and Ranunculaceae [100]. The antibacterial property of berberine is extensively reported in the literature and its age-old usage in traditional Chinese and Ayurvedic medicinal systems against bacterial infections is well-documented. The antibacterial activity of berberine is mediated through diverse mode-of-actions such as intercalation of DNA, inhibition of enzymes (such as RNA polymerase, gyrase, and topoisomerase IV), and blockage of cell division [101]. The antibacterial activity of

berberine and in combination with the antibiotics such as ampicillin and oxacillin against the clinical isolates of MRSA was studied and berberine inhibited the growth of MRSA with MIC values ranging from 32 to 128 μg/mL [102]. It has also been identified that berberine decreases the MRSA adhesion and intracellular invasion to the cultured monolayers of human gingival fibroblasts. The antibacterial activity of berberine alone and in combination with ampicillin or oxacillin resulted in additive and synergistic effects against MRSA isolates respectively [102]. In another study, berberine (30–45 μg/mL) induced antibacterial activity and inhibited the biofilm formation in *Staphylococcus epidermidis* [103]. Berberine also inhibited the biofilm formation in other organisms such as *C. albicans, S. typhimurium*, and *S. aureus* [104–106]. Chu et al. provided the mechanistic insight for the inhibition of biofilm formation in MRSA by berberine. It was revealed that berberine inhibits biofilm formation in a dose-dependent manner (1 to 64 μg/mL) by disrupting the aggregation of phenol-soluble modulins (PSMs) into amyloid fibrils [107]. PSMs are a family of amphipathic, α-helical peptides present in staphylococci and have drawn attention due to their involvement in the virulence of *S. aureus*. PSMs are involved in biofilm development which is thought to have a prominent role in staphylococcal colonization [108]. Berberine displayed a synergistic antibacterial effect with azithromycin against the clinical isolates of *P. aeruginosa* [109]. The combination of berberine and azithromycin significantly reduced the production of virulence factors such as alginate, LasA protease, LasB protease, pyoverdin, pyocyanin, chitinase, and extracellular DNA. In addition, the combination also inhibits the expression of quorum sensing-related genes such as lasI, lasR, rhlI, and rhlR. Recently, Li et al., demonstrated that berberine exhibit the synergistic effect with sodium new houttuyfonate against the MRSA and VISA, and the effect is likely to be mediated through interruption of the cell membrane [110]. Overall, these reports suggest that berberine has the potential to be developed as a drug that can be administered along with other clinically approved antibacterials.

5.3. Biochanin A

Biochanin A (5,7-dihydroxy-4′-methoxy isoflavone) is majorly present in the soybean, chickpea, peanuts, Indian rosewood, etc. It was initially isolated from red clover (*Trifolium pretense* L.), which belongs to the Fabaceae family [111]. Biochanin A showed a synergistic effect in combination with ciprofloxacin against clinical isolates of *S. aureus* and also reduced the NorA gene expression in MRSA indicating that biochanin A may suppress the efflux of antibiotics [112,113]. In an interesting study, Lechner et al. examined the antibacterial effect of several plant phenolic compounds (such as baicalein, baicalin, biochanin A, daidzein, formononetin, genistein, luteolin, myricetin, resveratrol, chlorpromazine, reserpine, and verapamil) through ethidium bromide efflux assay in *Mycobacterium smegmatis*. Out of all these compounds, only biochanin A potentiated the effects of ethidium bromide and demonstrated efflux inhibition comparable to standard efflux pump inhibitors [114]. Biochanin A displayed the selective growth inhibitory effect towards *Clostridium* spp. over *Bifidobacterium* spp. [115]. The antibacterial activity of biochanin A was reported against pathogenic organisms such as *Leishmania chagasi* (EC_{50}= 18.96 μg/mL), and *Chlamydia pneumoniae* (IC_{50} =12 μM) [116,117]. An inclusion complex of biochanin A with (2-hydroxypropyl)-β-cyclodextrin was prepared to enhance its aqueous solubility and its antibacterial examination against *E. coli* and *K. pneumoniae* did not display significant activity over pure biochanin A [118]. Recently, the pharmacological effects of biochanin A have been thoroughly reviewed by Sarfraz et al. [111]. Only a limited number of studies have reported the antimicrobial activity towards ESKAPE organisms. Many more studies are essential to comprehensively demonstrate the mode-of-action of this compound.

5.4. Caffeic acid and its derivatives

Caffeic acid is a phenolic compound present in many plant commodities such as olives, cinnamon, nutmeg, blueberries, apple, star anise, etc. [119]. Chemically, caffeic acid is a 3, 4-dihydroxy cinnamic acid-containing phenylpropanoid with hydroxyl groups at the third and fourth position of the aromatic ring [120]. The plant system contains monomeric, dimeric, and trimeric forms of caffeic acid such as organic acid esters, sugar esters, amides, glycosides, etc. The caffeic acid is endowed with diverse pharmacological properties such as antibacterial, antiviral, anti-inflammatory, antioxidant, antiatherosclerotic, immune-stimulatory, antidiabetic, cardioprotective, antiproliferative, hepatoprotective, anticancer, and many other activities. The poor aqueous solubility and lack of stability are the major limitations of caffeic acid and some of its derivatives. They get degraded rapidly *in vitro* and *in vivo* setup and hence attempts were made to encapsulate caffeic acid and its derivatives into nanoparticles to increase the water solubility. Caffeic acid imparted growth inhibitory activity against *S. aureus* and the observed antibacterial activity of caffeic acid is due to the presence of hydroxyl groups in the phenolic ring [121]. The different derivatives of caffeic acid amides showed considerable antibacterial activity against *B. subtilis* with MIC values ranging between 1.18 and 15.5 μg/mL. The caffeic acid conjugated with chitosan exhibited a synergistic antibacterial effect in combination with antibiotics such as tetracycline, erythromycin, and lincomycin against *S. aureus, S. epidermidis, P. aeruginosa, Propionibacterium acnes* [122]. The observed growth inhibitory effects of the conjugates could be due to the alteration of bacterial membrane permeability. Caffeic acid-coated polymeric fibrous materials such as poly(3-hydroxybutyrate) and poly(ethylene glycol) showed antibacterial activity against *S. aureus* and *E. coli* and they were proposed to be useful in controlling wound infections [123]. To address the solubility and stability issues of caffeic acid, several nano-formulations of caffeic acid were made and their antibacterial activity was studied. The caffeic acid immobilized on zinc oxide nanoparticles showed strong antimicrobial activity against *S. aureus*, MRSA, and *E. coli* [124]. The encapsulation of caffeic acid with cyclodextrins improved the solubility of caffeic acid and was found to have enhanced antibacterial activity against the *K. pneumoniae* and *S. aureus* [125].

The caffeic acid phenethyl ester (CAPE) exhibited antibacterial activity against both Gram-positive and Gram-negative organisms such as *S. aureus, Streptococcus mutans, Streptococcus mitis, Bacillus megaterium, B. subtilis, Lactobacillus acidophilus,* etc. [126]. In another study, CAPE displayed remarkable antimicrobial activity against common oral cariogenic bacteria (*S. mutans, Streptococcus sobrinus, Actinomyces viscosus, and L. acidophilus*) [127]. Additionally, CAPE inhibited the formation of *S. mutans* biofilms and their metabolic activity in mature biofilms. CAPE has been reported to induce antibacterial effects through various mechanisms including permeabilization of the cell membrane, alteration of membrane transport, membrane depolarization, and inhibition of bacterial RNA polymerase [128]. The caffeic acid entrapped in silica gel matrix presented good antibacterial activity against *E. faecalis* and *E. coli.* In view of all these studies, caffeic acid and its derivatives are emerging as potential antibacterial agents against a wide variety of bacteria.

Chlorogenic acid is one of the naturally occurring derivatives of caffeic acid seen in coffee, tea, apples, pears, carrots, tomatoes, sweet potatoes, grapes, etc. Chlorogenic acid is a major constituent of some traditional Chinese medicine preparations and it is endowed with many medicinal properties including antibacterial activity against many Gram-positive and Gram-negative organisms [129,130]. A significant synergetic bactericidal and antibiofilm effect was produced against *S. aureus* by the combination of ultrasound and chlorogenic acid treatment which was mediated through increasing the cell membrane permeability, release of ATP, and nucleic acids, and decreasing the exopolysaccharide contents in the biofilm [131]. Similarly, chlorogenic acid presented strong bactericidal and antibiofilm activity in the clinical

isolates of *Stenotrophomonas maltophilia* including the trimethoprim/sulfamethoxazole resistant strain [132]. The antimicrobial roles of caffeic acid, its combinational uses, and synthetic strategies have been thoroughly reviewed recently [119]. These reports suggest that the caffeic acid derivatives or structural analogs could serve as potent chemicals against bacteria with pathological relevance.

5.5. Piperine

Piperine is one of the primary alkaloids present in the black pepper (*Piper nigrum* L.) and long pepper (*Piper longum* L.). The piperine was first isolated by Hans Christian Ørsted in 1819 from the extracts of pepper as a yellow crystalline compound. The IUPAC name of piperine is 1-(5-[1,3-benzodioxol5-yl]-1-oxo-2,4-pentadienyl)piperidine and it is present in four isomeric forms such as piperine, isopiperine, chavicine, and isochavicine [133]. Some of the piperine analogs were reported as the inhibitors of NorA efflux pumps in *S. aureus* [134]. Multidrug efflux pumps are the leading player for bacterial antibiotic resistance due to their involvement in the expulsion of antibiotics out of the cell. NorA multidrug-resistant efflux pump contributes to the reduced susceptibility of *S. aureus* to antibiotics [135]. Notably, inhibition of efflux pumps using natural and synthetic compounds has emerged as an important strategy to counteract bacterial multidrug resistance [136]. Piperine potentiated the effect of ciprofloxacin against *S. aureus* which resulted in a two-fold reduction of the MIC value of ciprofloxacin [137]. The nanoliposomes with co-loaded piperine and gentamicin displayed good antibacterial activity with almost a 32-fold reduction of MIC value compared to free gentamycin against the MRSA [138] and these activities are proposed to be imparted through the inhibition of efflux pumps [134]. These reports emphasize the efflux pump inhibitory activity of piperine and the need for its evaluation with other antibiotics against drug-resistant organisms.

5.6. Taxifolin

Taxifolin is chemically known as 3,5,7,3,4-pentahydroxy flavanone or dihydroquercetin, a polyphenolic flavonoid, which is majorly present in plants such as *Silybum marianum, Allium cepa, Pseudotsuga taxifolia,* and *Pinus pinaster*. Taxifolin possesses diverse medicinal properties such as anti-inflammatory, anticancer, antiangiogenic, hepatoprotective, etc. Taxifolin was found to have antibacterial activity against *S. sobrinus*, a pathogen responsible for dental caries, with an IC_{50} value of 21.8 ± 1.7 μg/mL [139]. It also showed good inhibition towards glucosyltransferase derived from *S. sobrinus* with an IC_{50} value of 53.0 ± 0.7 μg/mL [139]. The inhibition of glucosyltransferase is one of the strategies in the prevention of dental caries and this report suggests that taxifolin can be developed as a potent agent for preventing dental caries. Taxifolin inhibited the growth of *E. faecalis* and VREF with MIC values of 128 and 512 μg/mL, respectively [140]. Based on the docking studies, the authors demonstrated that β-ketoacyl acyl carrier protein synthase III, a key enzyme in bacterial fatty acid biosynthesis, is the potential target of taxifolin with a binding affinity of 6.76×10^7 M^{-1} [140]. In another study, the antibacterial activity of taxifolin was evaluated at 0.5, 1.0, 2.0, and 5.0% concentrations against *E. coli, S. epidermidis, P. aeruginosa*, and *M. luteus* and out of which *S. epidermidis* displayed high sensitivity to taxifolin at 5% concentration [141]. DNA gyrase and aminoacyl-tRNA synthetases are the bacterial enzymes crucial for DNA replication and protein synthesis, respectively. Eight flavonoids were investigated for their inhibitory activity towards DNA gyrase and isoleucyl-tRNA synthetase on a molecular docking platform and taxifolin was identified as a lead inhibitor [142]. They also reported that taxifolin interacts with a good number of amino acids at the active sites of DNA gyrase and aminoacyl-tRNA synthetase of *M. tuberculosis* based on the in silico molecular docking and dynamics simulation approach. Additionally, taxifolin displayed antimycobacterial activity against *M. tuberculosis* with a MIC value of ≤ 12.5 μg/mL [142]. In a recent investigation, taxifolin was reported as the inhibitor of sortase A of MRSA, an enzyme essential for bacterial colonization in the host tissues [143]. Taxifolin is also believed to be effective against many Gram-positive organisms which demand further investigation [143].

5.7. Thymol

Thymol (also known as 2-isopropyl-5-methylphenol) is a primary monoterpene present in the essential oils of plants belonging to the genera of Thymus, Ocimum, Origanum, Satureja, Thymbra, and Monarda. The usage of essential oils of these plants as a flavoring and preservative agent is an age-old practice in the food industry. The FDA has listed the thymol and other components present in these essential oils as 'generally recognized as safe' (GRAS) for their supplementation in food products [144]. Many studies reported the antibacterial activity of essential oils that are rich in thymol against various Gram-positive and Gram-negative organisms. Thymol presented antibacterial activity against clinical isolates and standard cultures of MRSA and *S. epidermidis* and the results showed that all isolates were susceptible to thymol with MIC values ranging from 0.03 to 0.06% (v/v) [145]. Thymol displayed antibacterial activity against *S. aureus* and *E. coli* with a MIC of 0.31 and 5.0 mg/mL respectively and mode-of-action analysis revealed that thymol influences the permeability of the lipid membrane of the bacteria which results in leakage of cellular contents [146]. Xu et al. showed that thymol induces bactericidal activity against *E. coli* through the permeabilization and depolarization of the bacterial cytoplasmic membrane. They showed the potential use of flow cytometry as a tool for the investigation of the mode of antibacterial action of essential oil components [147]. The chemical derivatives of thymol were examined for antibacterial effect against *S. mutans, S. aureus, B. subtilis, S. epidermidis*, and *E. coli*. Thymyl acetate (2-isopropyl-5-methylphenyl acetate), thymyl propionate (2-isopropyl-5-methylphenyl propionate), and thymyl isobutyrate (2-isopropyl-5-methylphenyl isobutyrate) displayed consistent activity against all the Gram-positive strains [148]. The effect of thymol against *Salmonella* spp. biofilm on polypropylene was examined. Thymol suppressed bacterial counts about 1–2 log during biofilm formation, reduction of about 1–5 log in the established biofilms [149]. These results suggest the antibiofilm potential of thymol against *Salmonella* spp. which can be examined in other bacterial systems. In another study, thymol imparted antibacterial activity towards *S. aureus, S. epidermidis, B. cereus, E. coli, P. aeruginosa, E. feacalis, Vibrio parahaemolyticus, Vibrio alginolyticus,* and *Salmonella enteritidis* with MIC values ranging between 32 and 64 μg/mL [150]. Additionally, thymol reduced the MIC values of tetracycline and benzalkonium chloride towards these microorganisms. Thymol induced the intracellular accumulation of ethidium bromide in a dosage-dependent manner indicating that thymol may sensitize bacteria to antibiotics through the inhibition of efflux pumps [150]. Marchese et al. thoroughly reviewed the antibacterial and antifungal effects of thymol and its derivatives [144]. Taken together, thymol or its derivatives may be developed as antibacterials towards drug-sensitive/-resistant microbes.

6. Conclusion and future perspectives

ESKAPE organisms are posing a life-threatening condition in the global context and the discovery of new potent antibiotics against these organisms is the need of the hour. ESKAPE organisms are heterogenous at the genetic level, but share common resistance mechanisms such as the chemical modification or breakdown of the drug, prevention of antibiotic influx, antibiotic expulsion through efflux pumps, modification of antibiotic target, etc. It is a global challenge for the discovery of novel potent bactericidal agents with favorable toxicity profiles. Many pathogenic bacteria are developing various strategies to counteract the bactericidal effect of most effective antibiotics through different mechanisms which pose an alarm for the need for newer antibiotics. It is important to note that, a large number of secondary metabolites have

been isolated from bacteria, fungi, plants, and marine invertebrates and have been developed as potent drugs against various human ailments [151–155]. Over 13,000 natural compounds have been isolated from bacterial sources indicating that these microorganisms remain as a treasure house of bioactive compounds [156,157]. Beside, about 70% of these natural compounds have been extracted from actinomycetes (a group of Gram-positive mycelial bacteria) and merely 1% of actinomycetes have been cultured so far indicating the abundance of hidden bioactive compounds in the bacterial kingdom. It is highly essential to speed up the discovery of bioactive compounds from unexplored bacterial and plant sources [158–161]. Antibiotic discovery faces several constraints. Since from 1960s, very few classes of antibiotics were discovered such as quinolones, lincosamides, oxazolidinones, and cyclic lipopeptides which still have a major share in the world's global antibiotic market [162]. Beside, novel antibiotics that were discovered later on were all majorly derived from established antibiotic classes and they are used as last-resort antibiotics which further discouraged the investment in antibiotic drug discovery research by many pharmaceutical industries [163]. In addition, the expensive operational cost of clinical trials poses a significant constraint in the R & D of antimicrobial drug design. Despite these constraints, several alternate strategies are employed in the current antibiotic research to counter the antimicrobial resistance of ESKAPE organisms. Combinatorial drug therapy is one such strategy where adjuvants are used along with the antibiotics to improve the patient response. To combat against the threatening antimicrobial resistance of ESKAPE organisms, other various novel strategies utilized nowadays are repurposing of drugs, monoclonal antibody therapy, vaccine development, bacteriophage therapy, etc. Along with these various strategies, concerted efforts are needed in the global and regional platforms in policymaking, funding, guidelines for appropriate use of antibiotics, diagnostics and treatment, and employment strategies applied against ESKAPE pathogens to keep the antimicrobial resistance mechanisms of these organisms under surveillance and control.

Declaration of Competing Interest

I, Prof Rangappa on behalf of all the co-authors declare that there is no conflict of interest associated with this study. I also declare that the funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. I also declare that the manuscript has been solely submitted to Biotechnology Reports and it is not under consideration in any other journal for publication.

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