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Review

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Antibiotic potentiators as a promising strategy for combating antibiotic resistance

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Antimicrobial resistance (AMR) poses a critical global health challenge. It arises from pathogens' resistance to antibiotics due to misuse, overuse, and insufficient regulation. As new antibiotics emerge slowly, antibiotic potentiators can enhance existing treatments against resistant strains. Challenges such as toxicity and regulatory barriers necessitate further studies to optimize these agents. This review examines the mechanisms, sources, and recent advancements in antibiotic potentiation while highlighting its potential to combat AMR.

Antimicrobial resistance (AMR) is one of the most significant public health concerns of this century, causing approximately 4.95 million deaths globally each year. It is defined as the ability of pathogens to survive exposure to antibiotics that were once effective in killing them. Consequently, treatment becomes ineffective, leading to persistent infections[1,2]. Moreover, the overuse of antimicrobial agents and a lack of regulation in their supply may exacerbate the issue of AMR. Additionally, the use of antimicrobials for purposes such as growth promotion, coupled with increases in population and international travel, has contributed to the global spread of AMR. All these factors have placed immense pressure on bacteria to overcome the effects of antibiotics. This leads to phenotypic and genotypic modifications that enable their survival[3,4]. As a result, they have developed different mechanisms, such as reducing membrane permeability, efflux pump inhibition, modifying the target, and producing antibiotic-modifying enzymes that enhance their antimicrobial activity[5]. This situation is further aggravated by several other factors, including a lack of a proper drug development pipeline.

The development of new antimicrobial drugs is very slow, whereas AMR is steadily increasing[6]. According to the World Health Organization (WHO), the newly developed antimicrobial agents are ineffective against severe bacterial infections. This indicates that sole reliance on novel antimicrobial agents cannot address the situation. Therefore, to overcome this challenge, it is necessary to develop strategies that can modify the resistance to currently ineffective antibiotics[7]. This includes restoring the efficacy of previously effective antibiotics and exploring alternative options for antibiotics. This can be achieved by using a combination of antibiotics, antibiotic potentiator molecules, and stimulating other host processes, such as defense mechanisms against pathogens[7,8]. To achieve this, understanding the mechanisms of action of the molecules in the host as well as in the bacteria is crucial.

Among the aforementioned strategies, antibiotic potentiation is one of the most promising methods. This approach makes antibiotics effective against resistant bacteria. A potentiator is a natural or synthetic compound with minimal or no antimicrobial activity. By combining a potentiator with an ineffective antibiotic molecule, the activity of antibiotics against resistant bacteria is enhanced[9,10]. This is achieved by either reducing or inhibiting the resistance mechanisms utilized by bacteria[11]. Based on their mechanism of action, antibiotic potentiators are classified as direct, indirect, and host-modulating. First, direct antibiotic potentiators target bacterial resistance mechanisms, such as enzyme inhibition and efflux pump inhibition[11,12]. Second, indirect antibiotic potentiators act on other interdependent factors that contribute to resistance. These include various cellular processes and can modify or inhibit the enzymes involved in supporting processes[12–14]. Finally, host-modulating potentiators target different cellular processes, such as the defense mechanism[12,15]. This pattern is observed among various potentiator molecules.

Both natural and synthetic compounds can act as antibiotic potentiators. However, their potential is often undermined or unexplored. Antibiotic potentiators include natural compounds such as alkaloids, phenolic compounds, stilbenes, and terpenes, and synthetic compounds such as synthetic peptidomimetics and nanoparticles[16–18]. Synthetic potentiator molecules are widely used alongside antibiotics in clinical settings and have demonstrated successful results; however, further research is needed on natural potentiator molecules[19]. Many previous studies have explored the capability of these agents as antibiotic potentiators. However, the exact mechanism of action needs to be identified for their safe and effective use. Therefore, this review article discusses the need for antibiotic potentiation, various potentiator molecules, and the potential mechanisms involved.

Global scenario of antibiotic resistance

Increased use and misuse of antibiotics have led to high antibiotic resistance patterns globally. Moreover, estimates suggest that AMR will push about 24 million people into poverty in the coming decade due to productivity losses

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and increased healthcare costs[20,21]. This severity suggests taking effective measures for AMR prevention by considering humans, animals, plants, and the environment as a single, inseparable entity, which is the core idea of One Health[22,23]. Recently, the One Health High-Level Expert Panel suggested that the health of people, animals, and ecosystems should be equally maintained to achieve a stable health status[24]. To achieve this, global communication, collaboration, coordination, and capacity building should be implemented among the various entities.

There are various economic analyses regarding the global antibiotic burden, including the impacts on finances and productivity. However, estimating the precise loss is very difficult[25,26]. The primary reason for this limitation in data stems from irregularities in the diagnosis and medical reports concerning the disease or cause of death. For instance, if a patient dies from sepsis associated with multidrug-resistant bacteria, the cause may be reported as sepsis more often than the involvement of the bacteria[20,27]. This could result in a significant reduction in the number of cases documented as AMR-involved deaths. Additionally, some incidents go unreported due to other underlying health conditions. Moreover, most research occurs in developed countries compared to low or middle-income countries[28,29]. Furthermore, AMR surveillance necessitates microbiologists and well-equipped clinical laboratories, which are scarce in low or middle-income countries[25,26]. Another important limitation is estimating the indirect costs associated with antibiotic resistance, which may include lost wages, decreased productivity, and related job losses. In fact, the impact of psychological changes, pain, and suffering should also be considered, but this is largely absent in most existing research[30]. According to Murray et al.[21], western sub-Saharan Africa had the highest AMR burden in 2019, which should be regarded as a priority considering the earlier-discussed facts highlighting the limitations faced by low or middle-income countries.

Globally, the critical pathogens associated with AMR-based deaths include *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii* and *Pseudomonas aeruginosa*[31,32]. Among these, *E. coli* and *S. aureus* are the major causes of death associated with AMR in high-income countries such as North America, Western Europe, and Australia. In contrast, sub-Saharan Africa has a different pattern. The reason is that many bacteria contributed to the AMR burden, and each accounted for a small share. Additionally, *K. pneumoniae* and *S. pneumoniae* caused comparatively increased death among these bacteria[21]. Similarly, beta-lactams and fluoroquinolones, the first-line antibiotics, have been found to play a significant role in the AMR burden globally[33,34]. Therefore, as stated earlier, collaborative efforts must be developed to address these challenges on a global scale. It is also crucial to support low-income countries. Figure 1 demonstrates an overview of the global antibiotic resistance burden.

The 2022 Report of GLASS by WHO indicated a reduction in the reporting of AMR data following the COVID-19 pandemic[35]. Despite this decline, some antibiotics showed an increase in AMR of up to 15% compared to previous reports. This rise is notably observed among *E. Coli* and *Salmonella* associated with bloodstream infections[35]. Additionally, most countries implemented strict measures to regulate antibiotic use; however, there remains a pressing need for alternative strategies to tackle this issue, as millions of deaths globally are attributable to antibiotic resistance[27,36]. Therefore, preventing AMR globally is a high priority. Rigorously adhering to One Health concepts and managing antibiotic resistance is a monumental task[37,38]. Nevertheless, efforts focusing on vaccines, immunotherapeutics, CRISPR, probiotics, microbial therapies, phage therapy, and fecal transplants are gaining attention. Furthermore, biotic nanoparticles, enzybiotics, antimicrobial peptides, and antibiotic adjuvants and potentiators have also

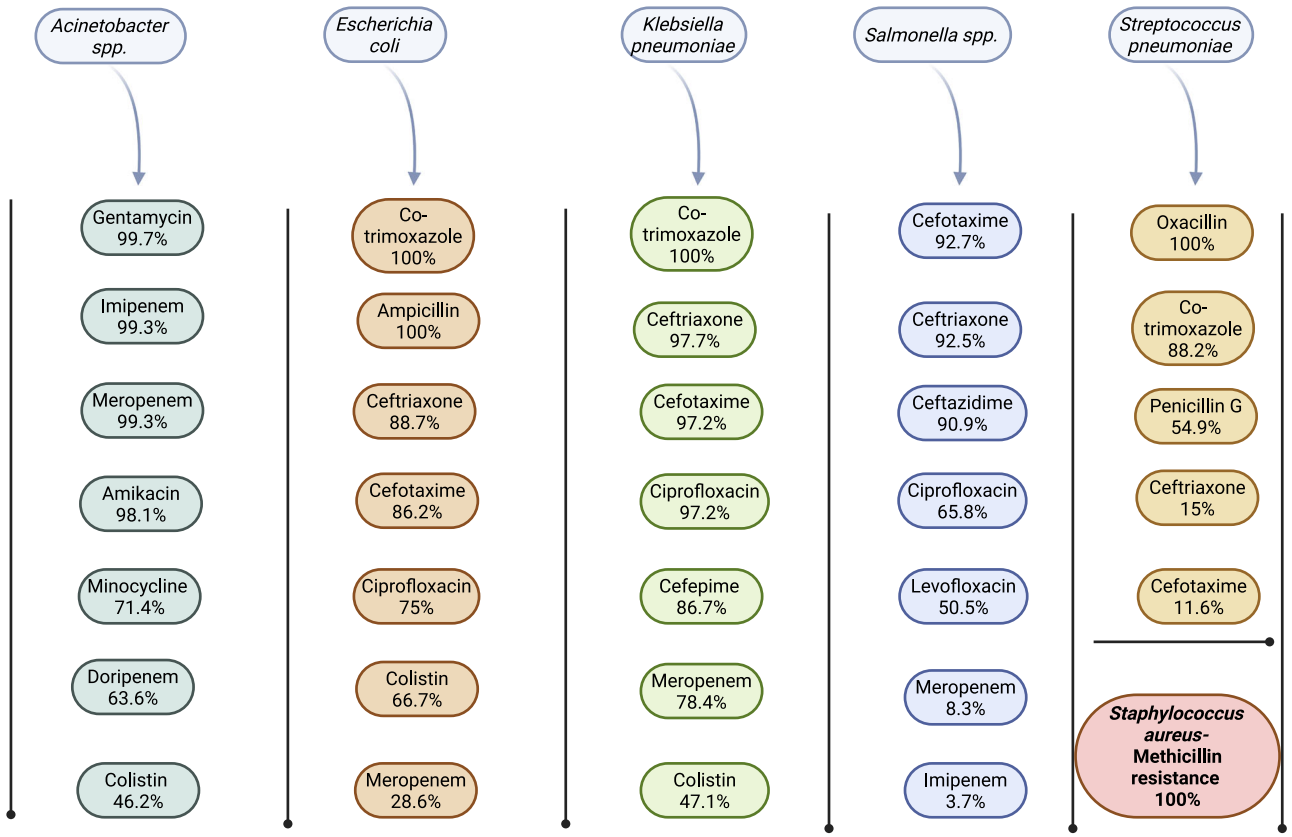

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Fig. 1 | Antibiotic resistance patterns observed among major bacterial species against selected antibiotics, based on the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) report: 2022. The percentage value represents the maximum antibiotic resistance observed from the data, in which antibiotic susceptibility results were compared to the reported number per million of bacteriologically confirmed infections.

received significant consideration[39–44]. Moreover, understanding the mechanisms involved in AMR is crucial. The four primary mechanisms involved include enzymatic degradation, target modification, prevention of drug entry, and efflux pump activation[19,45]. Antibiotic potentiators are a favorable choice as they help overcome antibiotic resistance. Moreover, these potentiators do not exhibit antimicrobial activity themselves, but they enhance the antibacterial efficacy of antibiotics when used in combination[11]. They can also be described as non-antibacterial active molecules that can be employed to increase antibiotic effectiveness[9]. Both natural and synthetic antibiotic potentiators have been evaluated for their contribution to the antibiotic potentiation effect, which will be discussed in subsequent sections. Some of these mechanisms focus on producing reactive oxygen species, glutathione depletion, plasmid curing inhibition, efflux pump inhibition, and resistance enzyme inhibition[46,47]. Greater emphasis should be placed on developing effective bacterial diagnostics alongside innovative drug delivery systems and antibiotic potentiators/ adjuvants[19].

Brief history of antibiotic potentiation

During the 20th century, antibiotic therapy became an inevitable part of animal and human life. Penicillin mass production began in 1942; however, resistance was observed around 1947[48]. Since then, it has reached a level where a patient can die from an infection caused by a *K. pneumoniae* strain, as this strain is resistant to every available antibiotic in the U S[49]. Therefore, the scientific community is curiously exploring alternatives to antibiotics. Some researchers have identified the importance of vaccines in limiting the need for antibiotics[50,51], while others have observed the effects of bacteriophages in treatments[52,53]. Moreover, they have attempted to identify the synergy between antibiotics and both conventional and unconventional agents, including bacteriophages. Scientists named Neter and Clark[54] were among the first to recognize such synergies. Another significant milestone was the use of drug combinations in prescriptions during the 1950s, despite limited knowledge about the mechanisms involved; nonetheless, it helped treat various diseases. This also contributed to advancements such as the use of clavulanic acid with beta-lactams and amoxicillin, leading to increased therapeutic efficiency when used in combination rather than alone[49,55]. Science began considering the combination of chemical entities, which could mark the beginning of the antibiotic potentiation concept. Additionally, WHO promotes combination therapy over monotherapy, especially in cases of severe infectious diseases[14].

Scientists have discovered various synthetic and natural substances in the search for new compounds with antibacterial effects. Several plant-derived antibacterial agents have been part of traditional medicine practices in diverse countries, including India and China[49,56,57]. A recent study on research trends showed an increase in the number of PubMed articles from 2016 to 2020 related to antibiotic-potentiating agents of plant origin. The 2021 study revealed that there were more than 4000 articles discussing this concept, demonstrating the significance of this research area[58]. Most studies identified new agents from plant extracts, including classes such as phenolic acids, lignan, stilbene, tannin, alkaloid, flavonoid, terpene, and more. Additionally, complex mixtures or modified synthetic versions of these compounds are widely studied for their synergistic effects with antibiotics[58–61]. Amid various challenges, including pandemics, relying on the synergistic effects of natural and synthetic compounds with antibiotics could be beneficial in the fight against drug resistance.

Mechanisms of antibiotic potentiation

There are different mechanisms by which a bacterial community acquires antibiotic resistance; these can originate from intrinsic factors or from the acquisition of mobile genetic elements through processes such as horizontal gene transfer[62,63]. The four main mechanisms of antibiotic resistance are depicted in Fig. 2. In the first category, enzymatic inactivation, the antibiotic molecules are enzymatically modified by the bacteria, rendering them inactive. Methods such as phosphorylation, acetylation, and adenylation are employed to achieve this modification. The second category is increased efflux pump-mediated resistance, with tetracycline resistance through the major facilitator superfamily as a classic example. The third mechanism involves decreased drug uptake due to changes in membrane permeability, caused by alterations in the characteristics of the porin channel. Finally, the fourth mechanism entails target modification, which can occur through mutations, enzymatic alterations, and replacement[19,64,65].

Overcoming these mechanisms presents a potential solution to the issues related to antibiotic resistance. Antibiotic potentiation can focus on tackling these mechanisms of resistance, which are discussed in detail below.

Inhibition of antibiotic-inactivating enzymes

Enzymatic activation of antibiotic molecules is one of the significant ways that bacteria achieve resistance, as discussed previously[9]. Therefore, serious efforts are being made to overcome this using antibiotic potentiators. The β-lactamase inhibitors still represent a major category of antibiotic potentiators that have been widely used to combat antibiotic resistance effects. One way they act is by serving as a substrate and forming acyl enzymes. These acyl enzymes are highly sterically unstable, resulting in unfavorable interactions. One example of this is the synthetic compound avibactam, which is used with ceftazidime[66]. In the second type, the enzyme is permanently inactivated by certain chemical reactions. Clavulanic acid, used with amoxicillin, is an example[67]. Liu et al.[68] focused on aminoglycoside 3'-phosphotransferase, a major enzyme linked with resistance. The synthetic compound was created by the covalent linkage of 3-hydroxyl neamine and adenosine, which inhibits this enzyme. Another important enzyme associated with aminoglycoside resistance in bacteria is N-acetyltransferase. Some synthetic compounds are designed where acetyl-CoA is added to antibiotics as a bisubstrate analog to inhibit N-acetyltransferases such as *AAC(6')Ii* and *AAC(3)-I 9*[69]. Additionally, some studies focus on both the aforementioned enzymes using bovine antimicrobial peptides[70] and a compound, Aronorosin, derived from the fungus *Gymnascella aurantiaca* against methicillin-resistant *S. aureus* (MRSA)[71]. Similarly, a compound derived from *Streptomyces*, venturucidin, was found to interfere with ATP-Synthase and exhibited synergistic activities with gentamicin against *Klebsiella, Pseudomonas*, vancomycin-resistant *Enterococcus* (VRE), and *E. coli*[72]. An enzyme, 6-*o*-adenyl transferase, linked to streptomycin resistance, was inhibited using a synthetic compound called streptidine, which acts as a decoy acceptor in *E. coli*[73]. Moreover, certain natural inhibitors of enzyme activity can effectively target enzymes that modify antibiotics. One such example is the copper leaf plant (*Acalypha wilkesiana*), a tropical plant previously used against various diseases, including malaria[74]. The antibacterial fraction of the ethyl extract interferes with PBP2a synthesis, a major transpeptidase in MRSA. Furthermore, this compound exhibited a synergistic effect with ampicillin against MRSA. Similar potentiation against MRSA was observed when using compounds like luteolin and apigenin along with antibiotics such as amoxicillin, affecting the mecA gene coding for PBP2[75]. Plant extracts are used against Extended Spectrum β-lactamases producing *E. coli* (ESBL) by targeting the enzymes involved in resistance. For example, a compound from the plant, *Sephora alopecuraides*, demonstrates synergistic action with cephalosporins against ESBL *E. coli*[76]. Thus, studies using synthetic and natural compounds that affect the enzymes involved in antibiotic resistance may be a promising choice for antibiotic potentiators.

Inhibiting efflux pumps

Efflux pumps play an important role in transporting substrates involved in various functions from bacterial cells to the outside, and they participate significantly in the development of antibiotic resistance[38,77]. There are five superfamilies of proteins associated with these efflux pumps. In gram-positive bacteria, there are the ATP-Binding Cassette superfamily (ABC), Major Facilitator superfamily (MFS), Multidrug and Toxic Extrusion superfamily (MATE), and Small Multidrug Resistance family (SMR). In gram-negative bacteria, there is a Resistance-Nodulation-Division family (RND), along with ABC and MFS[77]. This represents one of the most critical intrinsic factors, rather than mobile genetic elements, associated with antibiotic resistance, usually resulting from their overexpression. Therefore,

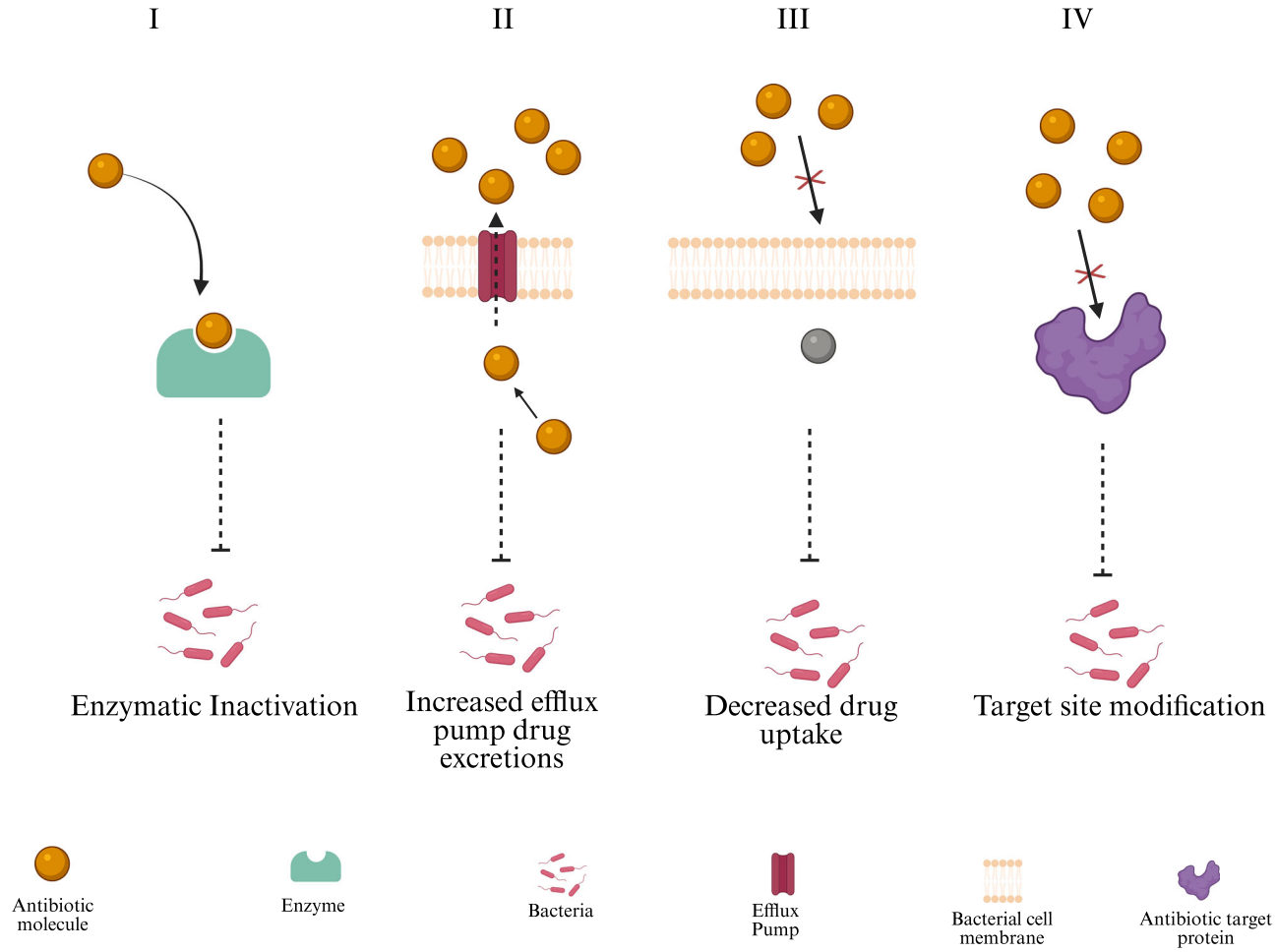

Fig. 2 | Major mechanisms of antibiotic resistance among bacterial pathogens. The resistance can be from enzymatic inactivation, increased drug efflux, decreased intake, or due to target site modification.

compounds that influence the functions of these efflux pumps may be a promising target for antibiotic potentiation.

There are many antibiotic potentiators used against the efflux pump of antibiotic resistance in bacteria. Synthetic compounds such as Verampil affect MATE pumps in *Mycobacterium tuberculosis*, resulting in an antibiotic-potentiating effect with Bedaquiline and Ofloxacin[78]. They bind with the pumps directly or indirectly. Similarly, Vargiu et al.[79] found a synthetic compound, 1-(1-naphthyl methyl)-piperazine, inhibiting the ABC superfamily of various bacteria such as *A. baumannii, E. coli, Enterobacter aerogens*, and *K. pneumoniae when used* with various antibiotics such as oxacillin, rifampicin, clarithromycin, fluoroquinolones, clindamycin, and doxycycline. Some quinoline and chalcone derivatives inhibit the RND of *E. aerogens* and *S. aureus*, respectively, when used with Norfloxacin[80]. Additional studies focus on heterocyclic carboxamides such as TXA00182, an effective efflux pump inhibitor when used with monobactam, fluoroquinolones, sulfonamides, and tetracycline[81]. The efflux pumps can also be disrupted by decoupling available energy. A synthetic compound called carbonyl cyanide-m-chlorophenyl hydrazone (CCCP) was found to act as a decoupler that disrupts the proton motive force of the pump, resulting in an antibiotic-potentiating effect with tetracycline against *Helicobacter pylori and Klebsiella*, alleviating gastrointestinal tract-associated diseases[82,83].

There are a large number of natural compounds effective against efflux pump-mediated antibiotic resistance. The plant alkaloid reserpine is isolated from *Rauwolfia serpentina*. This alkaloid affects the MFS and RND pumps in *Bacillus subtilis* and *S. aureus* with tetracycline and norfloxacin, respectively[84]. Plant-derived flavonoids such as baicalein, genistein, orobol, and biochanin A show potentiating effects by disrupting NorA pumps in *S. aureus*[85,86]. Polyphenol compounds isolated from *Camellia sinensis* include gallates such as epicatechin gallate and epigallocatechin gallate. Gibbons et al.[87] found that these compounds had a synergistic effect with tetracycline, erythromycin, and ciprofloxacin against *Staphylococcus* and *Campylobacter* by influencing the function of NorA and Tet (K) efflux pumps. The antibiotic-potentiating ability of ciprofloxacin against various organisms has been demonstrated by various scientists, most of whom targeted the efflux pumps. Some compounds that showed synergistic effects along with ciprofloxacin include Indirubin, Capsaicin, Silybin, and Kaempferol[88–91]. Most of the studies explored the effect of these compounds in inhibiting the overexpression of efflux pumps to generate antibiotic-potentiating effects. Moreover, rather than relying on mobile genetic elements that are unpredictable, this type of intrinsic target may be more effective in overcoming antibiotic resistance despite limitations such as toxicity[9].

Changes in the bacterial cell membrane permeability

Based on the various classes of antibiotics, there are distinct mechanisms of action. However, the initial step towards their action is penetration through the cell membrane in most cases[92]. From previous discussions, it is clear that one intrinsic method of antibiotic resistance is the decreased permeability of the cell membrane. Therefore, potentiating agents that alter the permeability of the bacterial membrane offer a significant mechanism for synergy. WD 40

is a macromolecular potentiator found to be effective in producing synergy, alongside Rifampin, which increases membrane permeability[93]. Most polymyxins and their derivatives induce changes in the outer membrane of bacteria by displacing cations such as Mg^{2+} and Ca^{2+} [19]. Additionally, various lysine-based peptidomimetics enhance the activity of rifampicin, clarithromycin, and azithromycin against different bacteria by disrupting membrane permeability[17]. Moreover, certain phytochemicals such as gallic acid and thymol produce synergy with antibiotics such as azithromycin, erythromycin, novobiocin, trimethoprim, and many others by causing membrane destabilization[94]. Extracts from numerous plants such as *Albizia lebbeck, Baillonella toxisperma, Nauclea pobeguinii, and Aframomum sulcatum* have shown potentiating effects with amoxicillin, ampicillin, ceftriaxone, and norfloxacin by inducing changes in cell permeability[95]. Similar effects were also observed with various other plant extracts and essential oils. However, most of the mechanisms by which these compounds alter cell membrane permeability are still under investigation. Even so, some combinations of synergy yield promising results in the fight against antibiotic resistance.

Fighting plasmid-mediated resistance

Plasmids are mobile genetic elements that enable bacteria to achieve MDR through horizontal gene transfer. This is one of the major mechanisms by which resistance is spread among bacterial communities. Various compounds exhibit antibacterial effects through the inactivation of plasmids. For example, compounds such as rottlerin,1'acetoxychavicol acetate, and plumbagin have proven effective against plasmid-mediated antibiotic resistance in many bacteria, including *Salmonella, Shigella, Bacillus, and Escherichia*[96–98]. Additionally, a compound called 8-epidiosbulbin E acetate, obtained from the plant *Dioscorea bulbifera*, is used as a plasmid-curing agent. This agent has cured the AMR plasmids from major pathogens, including *E. faecalis, Escherichia*, and *Shigella*. Notably, these pathogens were isolated from clinical infections[97]. This plasmid curing resulted in a decrease in the Minimal Inhibitory Concentration (MIC), enhancing the effectiveness of antibiotics against these clinical isolates. The aforementioned researchers demonstrated a significant effect of phytochemicals in combating plasmid-mediated resistance. However, further exploration of the mechanisms of action is still required to utilize them as promising potentiators.

Inhibiting biofilms

Bacterial biofilms consist of groups of bacteria that attach to biotic or abiotic surfaces to form a community. This formation aids in better protection, stability adaptation, and communication for their survival. They are among the primary concerns for nosocomial infections and are prioritized for mitigation, as they contribute to the increase in AMR[27]. Various natural compounds, such as curcumin, piperine, plumbagin, thymol, quercetin, and sinapic acids, have been shown to affect *Pseudomonas* biofilm formation. These compounds potentiate antibacterial agents such as amikacin, paromomycin, streptomycin, neomycin, ceftazidime, and norfloxacin[99]. Among these, sinapic acid exhibited the highest antibiofilm activity and significant synergy with amikacin. Furthermore, the antibiotic tolerance of biofilms, especially due to reduced antibiotic penetration, can be addressed by the potentiators that modify cell membrane permeability, as discussed in the previous section. Additionally, previous literature has identified various mechanisms of action for the aforementioned compounds, which disrupt membranes and nucleic acid synthesis, ultimately reducing extracellular polymeric substance secretion and the formation of biofilms[100]. Moreover, 2-amino imidazole compounds such as oroidin and mauritiamine may serve as promising potentiating agents against a wide range of *Enterobacteriaceae* by affecting cell signaling and transcription in bacteria[101]. Therefore, there are still vast opportunities to explore the role of various natural and synthetic compounds in antibiotic potentiation against biofilms. Figure 3 summarizes all the major mechanisms of antibiotic potentiation discussed.

Natural agents for antibiotic potentiation

Plants possess intrinsic mechanisms to defend themselves against microbial threats, a feature that can be utilized to combat AMR. Natural plant-derived compounds such as gallic acid and tannic acid have demonstrated efficacy as potentiators of antibiotics, including novobiocin, rifampicin, and clorobiocin[102]. Phenolic compounds, a class of secondary plant metabolites, are particularly notable for their antimicrobial properties. Specific phenolic compounds, such as catechol and acetaldehydes, have shown strong synergistic effects when combined with ciprofloxacin against *E. coli* and *Pseudomonas*[103]. These compounds can potentiate the activity of existing antibiotics by enhancing their efficacy against a broad spectrum of pathogens. Moreover, given the large diversity of phenolic compounds under investigation and the possibilities yet to be discovered, their potential in combating AMR remains vast and unexplored.

Phenolic compounds are universally distributed in the plant kingdom and are particularly abundant in fruits, seeds, and leaves. These compounds are characterized by the presence of an aromatic ring that bears one or more hydroxyl groups. Interestingly, the number of hydroxyl groups varies among different phenolic structures. Furthermore, these phenolic compounds can be classified into two broad categories: flavonoids and non-flavonoids[96]. The non-flavonoids include phenolic acids, aldehydes, acetophenones, phenylacetic acids, cinnamic acids, coumarins, biflavonyls, benzophenones, xanthones, stilbenes, and tannins[104].

Flavonoids are low molecular weight phenolic compounds predominantly found in plants. These compounds contribute to plant protection against biotic and abiotic stressors[105]. They serve various roles as signaling molecules, detoxifying agents, and UV filters within plants[106]. Additionally, they exhibit antibacterial properties often by modulating the activity of toll-like receptors (TLR)[107]. For instance, kaempferol, a member of the flavonoid class, has been shown to disrupt quorum sensing (QS) in bacteria. QS is a bacterial communication system essential for biofilm formation, and inhibiting this system can enhance the effectiveness of antibacterial agents[108]. Furthermore, baicalein, another flavonoid, exerts anti-QS activity against *P. aeruginosa* by inhibiting QS gene expression and the synthesis of acyl-homoserine lactones (AHLs), which are signaling molecules integral to bacterial communication[109]. Moreover, baicalein enhances the antibacterial potency of antibiotics such as levofloxacin, ampicillin/clavulanic acid, and ceftazidime[110]. Similarly, the flavonoid 3,4,7-trihydroxyflavone has demonstrated synergy with PaβN, an efflux pump inhibitor, suggesting its potential as a substrate for efflux pumps in multidrug-resistant (MDR) *E. coli* and *Providencia. stuartii*[111]. Of interest is isoquercitrin, another flavonoid that induces oxidative stress and bacterial apoptosis by promoting DNA fragmentation and caspase activation, thus enhancing antibacterial activity[112,113].

Stilbenes are plant metabolites found in fruits such as grapes, berries, and tree nuts. They exhibit antibacterial properties against Gram-positive bacteria like *B. subtilis* and *S. aureus*[114]. These compounds contain an aromatic ring with a phenolic group and can exist in *cis* and *trans* isomers due to the presence of a double bond adjacent to the phenolic group. Moreover, they reduce the virulence of *S. aureus* by hemolysis[115]. Stilbenes, such as resveratrol found in red wine, possess anti-inflammatory and antibacterial properties[58,116,117]. Furthermore, resveratrol has been shown to potentiate the effects of antibiotics such as gentamicin, kanamycin, neomycin, and streptomycin against *S. aureus*[118]. Pterostilbene is another stilbene found in berries and grapes that enhances the efficacy of vancomycin against *S. aureus*[119,120]. Additionally, piceatannol, a stilbene compound that augments the activity of ciprofloxacin against *S. aureus*[121].

Terpenes along with their oxygenated derivatives known as terpenoids are hydrocarbons derived from isoprene monomer units. The chemical structure of terpenoids can be altered by modifications to their functional groups, resulting in a diverse range of compounds[122]. Among these, sesquiterpene farnesol, which is present in many essential oils, has demonstrated the ability to potentiate the activity of beta-lactam antibiotics against *Burkholderia pseudomallei*. Specifically, farnesol reduces the MIC of amoxicillin and ampicillin, thereby enhancing their efficacy against this

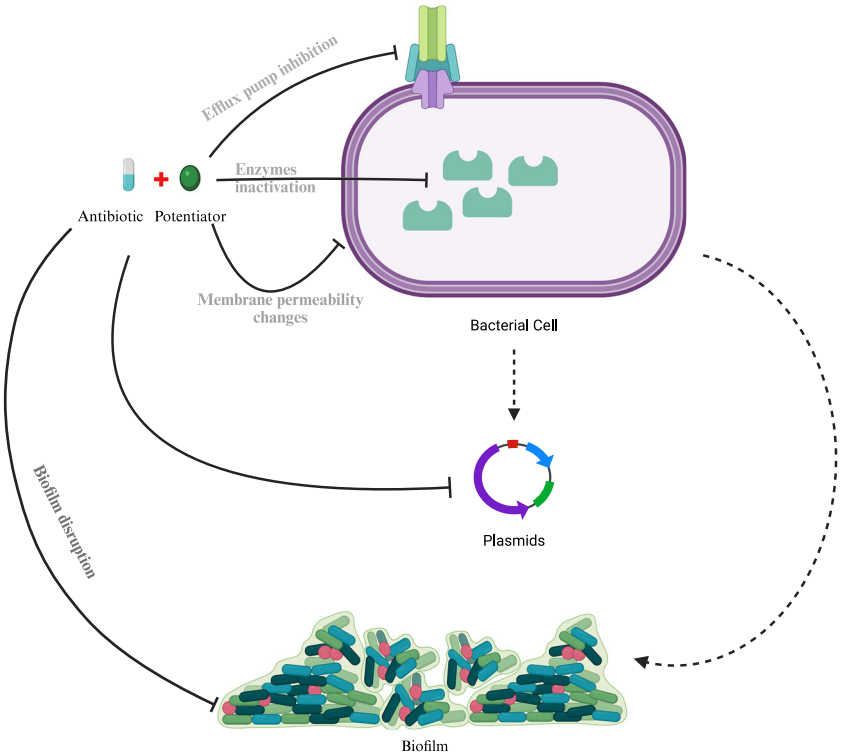

Fig. 3 | Major mechanisms of action associated with antibiotic potentiation. The antibiotic and potentiator can inhibit efflux pumps, inactivate bacterial enzymes, alter bacterial cell membrane permeability, or disrupt community formation.

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pathogen. It has shown an 8-fold reduction in MIC of amoxicillin and a 3-fold reduction in the case of ampicillin. Moreover, they have shown antibacterial activity against *S. aureus* and *S. mutans*[123]. The combination of another terpene, carvacrol, and oxacillin shows synergy against MRSA[124]. Apart from this, terpenes such as carvacrol and thymol exhibit synergistic effects with antibiotics like oxacillin and tetracycline, respectively, in combating *S. aureus* and *E. coli*[125]. Moreover, Eugenol is another terpene that has been shown to increase the antibacterial activity of antibiotics like cefotaxime and ciprofloxacin against *E. coli* and *K. pneumoniae*[126]. Furthermore, pinene, disrupts bacterial cell membranes by facilitating the influx of antibiotics such as gentamicin, ciprofloxacin, and amikacin, thus potentiating their antimicrobial effects[127].

Alkaloids are a diverse group of nitrogen-containing compounds characterized by their ring structures[128]. The presence of a nitrogen atom allows alkaloids to form hydrogen bonds with various biomolecules enhancing their biological activities[129]. They are widely distributed in plants including seeds, leaves, barks, fruits, and roots. Alkaloids are soluble in water at acidic pH and in organic solvents at basic pH making them versatile in different environments. Furthermore, they are widely distributed across several plant families including *Amaryllidaceae, Burseraceae, Capparaceae, Mimosaeae, Vitaceae, and Tiliaceae*[130]. Additionally, they exhibit significant antibacterial activity, particularly against multi-drug resistant (MDR) pathogens such as *E. coli*, *Salmonella*, and *S. aureus*[16]. The main mechanism of action for alkaloids in combating antibiotic resistance is through the inhibition of efflux pumps. Other compounds like squalamine and tomatidine have been shown to alter cell membrane permeability[131,132]. Piperine, an alkaloid, when given along with ciprofloxacin potentiates the activity of the antibiotic against *S. aureus* by inhibiting efflux pumps[133]. Similarly, combinations of tomatidine with antibiotics like ampicillin, cefepime, gentamicin, and ciprofloxacin have been shown to potentiate antibiotic efficacy against pathogens such as *P. aeruginosa*, *S. aureus*, and *E. faecalis*.

Microbial and fungal metabolites are known for their diverse biological activities, including antimicrobial, anti-inflammatory, and anticancer properties. Compounds like EA-371α and EA-371δ are fermentation products derived from microbes. They exhibit synergistic effects when combined with levofloxacin against *P. aeruginosa*. This potentiation is associated with their ability to inhibit efflux pumps[134]. Another interesting compound, aranorosin, isolated from *Macella aurantiaca* FKI-6588, shows synergy with aminoglycosides. The possible mechanism involves its inhibition of resistance-related enzymes like β-lactamase[71]. Additionally, depolymerase-Dpo71, a bacteriophage-encoded enzyme from *A. baumannii* phage, enhances the sensitivity of *A. baumannii* to colistin. Although the exact mechanism behind this synergy remains unclear, it may involve destabilization of the bacterial outer membrane through the depolymerase action[135].

Synthetic agents for antibiotic potentiation

In the fight against MDR pathogens, drug combinations such as antibiotics and β-lactamase inhibitors are some of the effective strategies. Synthetic peptides and peptidomimetics, which resemble natural antimicrobial peptides in their physical, chemical, and biological properties, have gained attention as potential antibiotic potentiators. These include peptoids, AApeptides, peptides with non-natural amino acids, and stapled peptides[136]. For example, polymyxin B nonapeptide, which is free of fatty acid chains, has demonstrated synergy with antibiotics like rifampicin, clarithromycin, and mupirocin. They act against *E. coli*, *A. baumannii*, and *K. pneumoniae*[137]. Furthermore, studies have shown that this potentiation is due to the perturbation of the bacterial outer membrane and the upregulation of stress response sensors[138]. Scientists have found that short peptides such as S, S1-Nal, and S1-Nal-Nal enhance the activity of vancomycin against *E. faecium*, *A. baumannii*, and *E. coli*. They can alter the membrane permeability to the antibiotic[139]. Additionally, another peptidomimetic, dUSTBP, potentiates novobiocin and rifampicin against *A. baumannii* and *E. coli*. It acts by modifying the outer membrane permeability and thus facilitating antibiotic uptake[140]. Moreover, CEP-136, which is a peptidomimetic, also modifies membrane permeability and helps to increase the effectiveness of clarithromycin and azithromycin against pathogens like *E. coli*, *A. baumannii*, and *K. pneumoniae*[17].

Nanoparticles are solid particles with distinct properties compared to their metal counterparts, ranging in size from 10 to 1000 nm, and they have emerged as promising drug delivery systems with significant antibacterial activity[141,142]. Their antibacterial properties are attributed to several mechanisms, including gene expression modulation, metabolic pathway alteration, membrane structure modification, reactive oxygen species (ROS) generation, and enzyme inhibition[143]. For instance, silver nanoparticles (AgNP) have been shown to reduce the minimum inhibitory concentration (MIC) of amikacin against MDR pathogens such as *K. pneumoniae*, *P. aeruginosa*, and *E. coli*[144]. Moreover, zinc oxide nanoparticles exhibit synergistic effects with a broad range of antibiotics, including chloramphenicol, amikacin, tetracycline, and ampicillin. They are effective against both Gram-positive and Gram-negative pathogens like *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *S. typhimurium*, *B. cereus*, *B. subtilis*, and *S. aureus*[145]. Recent studies have also explored the use of gold (AuNP) and copper nanoparticles (CuNP) as antibiotic potentiators. For example, CuNP derived from ginger and garlic showed synergistic effects with doxycycline against *E. coli* and *P. aeruginosa*[146]. AuNP has been found to enhance the activity of ciprofloxacin and cefotaxime against *Salmonella* species by promoting ROS production[60].

Acids and their derivatives such as phthalic acid, succinic acid, and carboxylic acid have shown potential as antibiotic potentiators against MDR pathogens. Alkyl and amino-substituted phthalic acids, for example, possess β-lactamase inhibiting properties. Additionally, 3-amino phthalic acid has been shown to enhance the effectiveness of carbapenem antibiotics against *P. aeruginosa*. Similarly, substituted succinic acid reverses *P. aeruginosa* resistance to imipenem. Another example is cyclopropane, a carboxylic acid derivative that, when combined with colistin, potentiates the antibiotic against both gram-positive and gram-negative bacteria[147–149].

Due to the recent approval of platinum-containing compounds as anticancer agents, there is a rising interest in the use of metals against MDR pathogens[150]. Metallopolymers, which are synthetic molecules composed of metals and polymers, have shown promise in this regard[151]. A recent study suggested that combinations of metallopolymers with ineffective antibiotics exhibit synergy against MDR pathogens like *E. coli* and *P. aeruginosa*. For example, the combination of cobaltocenium-based polymers with ceftazidime, rifampicin, and minocycline resulted in a significant reduction in antibiotic resistance. These reductions were about 2-fold, 18-fold, and 16-fold against *E. coli*, respectively. The potentiation mechanism involves inhibition of β-lactamase hydrolysis by ceftazidime, alteration of outer membrane permeability by rifampicin, and membrane perturbation by minocycline[150]. Another cobaltocenium polymer exhibits synergy with different beta-lactam antibiotics through the formation of ionic complexes[152]. Additionally, synthetic amphiphiles, which alter membrane permeability, have shown potential as antibiotic potentiators. Furthermore, the combinations of benzyl hydrophile with norfloxacin and tetracycline demonstrate synergistic effects against *E. coli* and *S. aureus*[153]. These findings highlight the diverse strategies employed to overcome MDR pathogens, underscoring the importance of combining natural and synthetic antibiotic potentiators in the fight against antimicrobial resistance. Various natural and synthetic antibiotic potentiators are discussed in Table 1.

Limitations and future perspectives

The use of an antibiotic potentiator in combination with antibiotics is still in the development stage. Candidates, such as SPR741 and pentamidine, are in clinical trials[12]. Moreover, since these involve the combination of two drugs, the potential side effects of drug-drug interactions remain unknown. For these reasons, a study on the pharmacokinetic and pharmacodynamic effects of the combination is needed[154]. Additionally, further studies should explore any off-target effects of the antibiotic potentiators that target cell membranes and efflux pumps[12].

Additional limitations include toxicity, developed resistance, and the effect of the potentiator compound on the host cell. First, since most of the compounds are novel, their complete characteristics are not yet known, creating a need to understand their toxicology. Moreover, the combination of an antibiotic and its potentiator may produce some toxic byproducts. Combinations require optimal dispersion of the two compounds to achieve maximum efficacy; thus, any variation in dispersion at the target site can reduce the effectiveness of the combination[155]. Second, there is a chance that bacteria may develop resistance against the combination. Bacteria can develop chromosomal or acquired resistance to the new agents. For example, there have been reports of TEM-1 and SHV-2 ESBLs showing resistance to clavulanic acid[156]. Third, these compounds may impact the host cell, including its cellular metabolism. Therefore, more in vivo studies are needed to establish the effects on the host cell[12]. In addition, regulatory approval for clinical trials is challenging, as potentiators often lack inherent antibacterial activity[157]. Efforts should be taken to overcome these challenges in order to address AMR, as the combination of antibiotics and the antibiotic potentiator molecule can significantly contribute to combating AMR.

New and advanced technologies for antibiotic potentiation

Advancements in technology have significantly accelerated research on antibiotic potentiation. One important advancement is improved nanotechnology[158]. This cutting-edge technology will likely play a pivotal role in antibiotic potentiation research. For example, Khan et al.[159] showed improved drug delivery and significant antibacterial activity with chitosan nanoparticles, a natural polymer typically found in the exoskeleton of crustaceans, such as shrimp. Anionic polysaccharides like alginates and various proteins, including albumin and ferritin, have also been identified as effective nanoparticles that can deliver either single or combinations of antimicrobial agents[160,161]. One key mechanism of action of this nanoparticle drug delivery system is its production of various reactive oxygen species (ROS), which may lead to a reduction in ATP levels and DNA damage. For instance, various metal-based nanoparticles, such as Zn and Ag, produce ROS by causing initial membrane damage[162,163]. Additionally, natural products with antibacterial properties are nanosized and used in drug delivery. For example, in wound healing, curcumin has been employed as a nano-drug delivery system and has proven to be highly effective[164]. Moreover, *A. vera* extracts and eucalyptol have also demonstrated effectiveness in drug delivery as nanoemulsions[165,166]. Most of these advanced technologies focus on ROS production as mentioned previously. Lv et al.[167] identified the significance of heat shock and its role in antibiotic potentiation, particularly regarding aminoglycosides against *E. coli*, *A. baumannii*, and *K. pneumoniae*. CRISPR-based gene editing is gaining widespread acceptance, and various genomic approaches have demonstrated significant antibiotic potentiation effects. Otoupal et al.[168] studied the synergistic interactions between different drugs and gene knockout models of an *E. coli* strain. The gene knockouts primarily targeted non-essential gene expressions based on CRISPR and found significant synergy with various combinations of antibiotics and knockouts. Another study identified the involvement of a transcriptional regulator, *ampR*, in β-lactamase overexpression. When this pathway was inhibited with an antibiotic potentiator, antibiotic resistance decreased, making the targeted *P. aeruginosa* population susceptible to the β-lactam antibiotic, Ceftazidime[169]. Furthermore, RecA is a critical factor in antibiotic resistance as it is involved in SOS-mediated DNA repair. Scientists have identified certain inhibitors, such as phthalocyanine tetra sulfonic acid, which inhibit RecA and enhance the effects of antibiotics on both gram-positive and gram-negative bacteria[170]. Therefore, genomic approaches in identifying potentiating targets are significant.

Additionally, proteomics approaches, along with transcriptomics and metabolomics, have significant possibilities in this research area[171]. For example, the cell membrane remodeling of *K. pneumoniae* was studied using techniques such as tandem mass tag (TMT) labeling, which is a chemical labeling technique used in mass spectrometry to identify relative protein abundance, and liquid chromatography mass spectrometry (LC-MS) metabolomics, which helps to separate, identify, and quantify metabolites. These techniques revealed possible mechanisms of polymyxin resistance[172]. Another study screened certain natural compounds showing anti-bacterial activity based on a chemical motif structure using the proteomics

Table 1 | Shows major natural and synthetic antibiotic potentiators against various bacterial isolates and the antibiotic used for synergy

Class	Compound	Antibiotic	Bacteria	Possible mechanism	References
Flavonoids	Baicalein	Tetracycline	MRSA	Efflux pump inhibition	183
	daidzein	Carbenicillin Levofloxacin	*P. aeruginosa* *E. coli*	Efflux pump inhibition	184
	Quercetin	Amoxicillin, Ampicillin, Ceftriaxone	MRSA	Cell membrane damage	185
	Quercetin	Tetracycline	*E. coli*	Cell membrane damage	186
	Kaempferide	Colistin, Amoxicillin	*P. aeruginosa* *E. coli*, *K. pneumoniae*	Cell membrane damage	187,188
	Daidzein	Gentamicin	*A. baumannii*	Efflux pump inhibition	189
	Myricetin	Chloramphenicol, Ciprofloxacin	*S. aureus*, *P. aeruginosa*	Change in capsule structure, Efflux pump inhibition	189
	Morin	Tetracycline, Vancomycin	*S. aureus*	Biofilm inhibition	190
	3,4,7-trihydroxy flavone	Chloramphenicol	*E. coli, P. stuartii*	Efflux pump inhibition	111
	Genistein, orobol and biochanin A	Norfloxacin	*S. aureus, B. megaterium*	Efflux pump inhibition	191
Stilbenes	Resveratrol	Gentamicin, Kanamycin, Neomycin, Streptomycin	*S. aureus*	ATP synthase inhibitor	118
	Pterostilbene	Vancomycin	*S. aureus*	Cell membrane changes	120
	Piceatannol	Ciprofloxacin	*S. aureus*	dissipating the bacterial proton motive force	121
Terpenes and terpenoids	Sesquiterpene farnesol	Amoxicillin, Ampicillin	*B. pseudomallei*	Inhibition of β- lactamase enzyme	123
	Pinene	Gentamicin, Ciprofloxacin, Amikacin	*S. aureus*	Cell membrane damage	127
	borneol	Ciprofloxacin, Gentamicin	*S. aureus*	Cell membrane alteration	127
	Thymol	Tetracycline, Colistin	*E. coli*	Change in membrane permeability	126
	Eugenol	Cefotaxime, Ciprofloxacin	*E. coli, K. penumoniae*	Cell membrane damage	125
	carvacrol	Xxacillin	MRSA	Cell membrane damage	124
Alkaloids	Piperine	Ciprofloxacin	*S. aurues*	Efflux pump inhibition	37
	Berberine	Vancomycin Gentamicin	*C. difficile* *P. aeruginosa*	Efflux pump inhibition	192,193
	Salosodine	Gentamicin, Ampicillin	*S. aureus*, P. aeruginosa	Alteration in cell membrane permeability	194
	Sanguinarine	Streptomycin Ciprofloxacin Nitroxoline	*A. baumannii*, MRSA, VRE, *E. coli, B. cereus, E. faecalis, L. monocytogenes*,	Alteration in cell membrane permeability	195,196
	Tomatidine	Gentamicin, Cefepime Ampicillin and Ciprofloxacin	*P. aeruginosa*, *S. aureus*, and *Enterococcus faecalis*	Alteration in cell membrane permeability	131
	Chanoclavine	Tetracycline	*E. coli*	Alteration in ATPase	197
	Capsaicin	Ciprofloxacin	*S. aureus*	Efflux pump inhibition	90
Microbial and fungal derivatives	*EA-371α, EA-371δ*	Levofloxacin	*P. aeruginosa*	Efflux pump inhibition	134
	Aranorosin	Aminoglycoside	MRSA	Inhibiting enzymes	71
	Depolymerase Dpo71	Colistin	*A. baumannii*,	Cell membrane changes	172
Peptide and peptidomimetics	Polymyxin B nano peptide	Rifampicin, Clarithromycin, Mupirocin	*E. coli*	outer membrane perturbation	137
	S, S1-Nal, and S1-Nal-Nal	Vancomycin	*E. faecium, A. baumannii, and E. coli*	Alteration in cell membrane permeability	139
	dUSTBP	Novobiocin, Rifampicin	*A. baumannii, and E. coli*	Alteration in cell membrane permeability	140
	C-terminally encoded peptide (*CEP-136)*	Clarithromycin, Azithromycin	*E. coli, A. baumannii and K. pnemuoniae*	Alteration in cell membrane permeability	17

Table 1 (continued) | Shows major natural and synthetic antibiotic potentiators against various bacterial isolates and the antibiotic used for synergy

Class	Compound	Antibiotic	Bacteria	Possible mechanism	References
Nanoparticles	AgNP*	Amikacin	*K. penumoniae, P. aeruginosa, E. coli*	Inhibiting enzymes, Cell membrane changes, ROS production	144
	Zinc Oxide nanoparticle	Chloramphenicol, Amikacin, Tetracycline, Ampicillin	*E. coli, P. aeruginosa, K. penumoniae, S. typhimurium B. cereus, B. subtilis, S. aureus*	Inhibiting enzymes, Cell membrane changes, ROS production	145
	CuNP*	Doxycycline	*E. coli and P. aeruginosa*	Inhibiting enzymes, Cell membrane changes, ROS production	146
	AuNP*	Cefotaxime and Ciprofloxacin	*Salmonella species*	ROS production	198
Acid and its derivatives	3-amino phthalic acid	Carbapenem	*P. aeruginosa*	Cell membrane changes	148
	succinic acid	Imipenem	*P. aeruginosa*	ROS production	147
	cyclopropane	Colistin	*E. coli, Salmonella enterica serovar Typhimurium, K. pneumoniae, S. aureus, methicillin-resistant*, MRSA	Intracellular target engagement	149
Synthetic amphiphiles	benzyl hydrophile	Norfloxacin, Tetracycline	*E. coli and S. aureus*	change the membrane permeability	153
Metallopolymers	Cobaltocenium	Ceftazidime, Rifampicin, and Minocycline	*P. aeruginosa*	inhibition of β-lactamase hydrolysis, Alteration in cell membrane permeability, membrane perturbation	150
	cobaltocenium	beta lactam antibiotics	MRSA	ionic complexes	152

**AgNP* Silver nanoparticles, *CuNP* Copper nano particles, *AuNP* Gold nanoparticles.

approach[173]. All the "omics" techniques provide a solid scientific foundation to pursue newer ideas regarding antibiotic potentiators or new targets.

Finally, machine learning and artificial intelligence are effective in medical research, including drug discovery[174]. Olcay et al.[175] showed that a machine learning model called a hyperparameter-optimized light gradient-boosted machine classifier achieved an accuracy of 76.92% in predicting synergy between antimicrobial agents. This technology could save thousands of dollars per laboratory experiment. Moreover, machine learning-based screening has identified potentiators of β-lactams and other antibiotics against a wide variety of bacteria[176–178]. Artificial intelligence to predict drug targets is also a promising tool. Recently, new antibiotics were predicted against *A. baumanii* infections using a synergism prediction of demethoxycurcumin and colistin with a quantitative structure-activity relationship (QSAR) screening model[179]. Molecular docking is a very promising strategy in this aspect as it helps identify ligand-protein docking and predict the best interactions among the interacting compounds[180–182]. Overall, cutting-edge technologies have the potential to accelerate therapeutic drug discovery research, including antibiotic potentiators.

Conclusion

The rise in antibiotic resistance is a significant global issue that must be addressed urgently. Efforts should treat human and animal health as a single entity because antibiotic resistance has co-evolved alongside the introduction of newer antibiotics. New strategies to combat antibiotic resistance need to be implemented. Antibiotic potentiation presents a promising approach. A wide variety of natural and synthetic agents are effective in this area, including their action on biofilms. Additionally, most natural compounds have limited side effects and align with the concept of One Health. Meanwhile, technological advancements are facilitating the identification of new drug targets more efficiently and quickly. The capacity to identify new compounds that are safe and also produce synergistic effects with existing antibiotics against major bacterial pathogens will aid in controlling global antibiotic resistance and its associated increasing death toll.

Data availability

No datasets were generated or analysed during the current study.

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Author contributions

M.S.M. conceptualized and provided the funding. J.J., S.B., S.M., and M.S.M. wrote the article. J.J. and M.S.M. illustrated the figures, while SB created them using BioRender. S.M. and M.S.M. reviewed the paper. All authors have read and approved the paper.

Competing interests

The authors declare no competing interests.

Additional information

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