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Mitigating ROS signalling pathway-mediated defence mechanism: a novel approach to counteract bacterial resistance using natural antioxidant-based antibiotics

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Abstract Antibiotic resistance is a critical global health concern and one of the most serious threats to public health worldwide today. In recent decades, resistant pathogenic bacteria have increased significantly, making infections harder to treat. The intrabacterial generation of ROS (reactive oxygen species), especially under antibiotic stress, plays a crucial role in modulating gene networks that drive bacterial resistance. The ROS-responsive regulons and cellular machinery activate defence responses that promote resistance. Recent studies emphasize the pivotal role of ROS-mediated signalling in activating alternative pathways that enhance bacterial survival under antibiotic pressure. As central mediators of stress perception and adaptation, ROS accelerate the evolution of resistance. Amid growing toxicity and reduced efficacy of current antibiotics, natural dual-active compounds such as berberine, caffeic acid, cannabidiol, curcumin, eugenol, luteolin, menadione, quercetin, and ursolic acid offer promising solutions to overcome the limitations of conventional antibiotics. These compounds possess both antibacterial and antioxidant properties, and can scavenge ROS while simultaneously inhibiting bacterial growth, providing a novel therapeutic approach that effectively bypasses ROS-mediated defence mechanisms in pathogens and enhances antimicrobial potential. The objective of this review is to explore recent advances in ROS-mediated signalling pathways that contribute to antibiotic resistance and to propose a novel strategy for overcoming this challenge by targeting ROS-driven defence mechanisms with natural antioxidant-based

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antibacterials. Recent literature has highlighted several promising examples of dual-active antibacterial–antioxidant molecules, offering potential breakthroughs in addressing antibiotic resistance. The dual capacity of these compounds to target pathogens and reduce oxidative stress positions them as promising foundations for next-generation antimicrobial therapies.

Keywords Antibiotic resistance · Antioxidant-based antibiotics · Antibiotic stress · Natural compounds · ROS-mediated defence

Introduction

In the unabating battle for human health, the proliferation of antibiotic-resistant bacteria (ARB) has emerged as an impending catastrophe of unprecedented magnitude, potentially driving mankind toward the brink of an unparalleled healthcare crisis (Salam et al. 2023). Based on the 2019 report by the United States Centres for Disease Control and Prevention, 35,000 people died from drug-resistant bacteria (DRB) infections every year in the United States (Centre for Disease Control and Prevention (U.S.) 2019). European Centre for Disease Prevention and Control stated that infections caused by drug-resistant *Salmonella* spp., *Mycobacterium tuberculosis*, and *Neisseria gonorrhoeae* dramatically increased the expenses of the treatment and threatened lives, health, and safety of people (Antimicrobial resistance in the EU/EEA 2020). Meanwhile, Asia faces greater devastation caused by carbapenem-resistant *Enterobacteriaceae* and carbapenem-resistant *Acinetobacter baumannii* (Mendes et al. 2013). Prolonged antibiotic use can result in allergic reactions, poisoning, coma, shock, and even death (Yang et al. 2022). The emergence of resistant infections has rendered many existing antibacterial drugs less effective or even obsolete, necessitating the development of new antibiotics (Chinemerem Nwobodo et al. 2022). Many antibiotics such as ampicillin, gentamicin, norfloxacin, nitrofurantoin, and polymyxin B, etc. induce ROS in bacteria, which causes substantial cellular damage by modifying the target of the cell structure by oxidizing nucleotide pools, leading to DNA damage, lipid peroxidation, and protein carbonylation (Qi et al. 2023). In bacterial cells, ROS induces significant damage to cellular components, including the cell wall, which plays a crucial role in maintaining cellular integrity and protecting against environmental stress (Kohanski et al. 2010). Cell morphology can be damaged in several ways: (i) disruption of cell wall integrity, which makes bacteria more susceptible to osmotic stress and lysis, as ROS directly oxidize structural proteins, lipids, and peptidoglycan; (ii) degradation of peptidoglycan (essential for cell wall structure, especially in Gram-positive bacteria), as ROS can lead to the breakdown of peptidoglycan by oxidizing critical enzymes like transpeptidases and carboxypeptidases involved in its synthesis; (iii) lipid peroxidation, as ROS can oxidize lipid components of the cell membrane (especially in Gram-negative bacteria), causing changes in membrane fluidity, permeability, and structural stability and disrupting the outer membrane, an additional layer of defence in these bacteria; (iv) formation of pores and leakage produced by ROS in the cell membrane and wall, causing leakage of cellular contents and leading to cell death (Hengge-Aronis 2000; van Duijkeren et al. 2018). Moreover, ROS induces genetic damage in bacterial wall synthesis. ROS can induce mutations in genes coding for enzymes involved in peptidoglycan synthesis and maintenance, weakening cell walls or altering cell wall synthesis pathways, impacting bacterial survival (Imlay 2013). This ROS-mediated damage and mutagenesis can promote adaptive responses for bacterial survival, contributing to the emergence and persistence of antibiotic resistance. Therefore, a thorough understanding of bacterial resistance mechanisms, especially ROS-mediated defence mechanisms is essential for developing effective therapeutic strategies (Kvist et al. 2008).

Antibiotic-induced ROS production acts as a secondary effect, which leads to DNA damage and activates the SOS response, resulting in the upregulation of error-prone DNA polymerase genes involved in DNA repair and mutagenesis (Zhao and Drlica 2014; Maslowska et al. 2019). Antibiotic-resistant bacteria employ complex regulatory mechanisms to modulate ROS signalling pathways (Dawan and Ahn 2022). These strategies include enhancing antioxidant enzyme activity, regulating the production rates of O_2 and H_2O_2-dependent respiratory chains and terminal oxidases, activating the efflux pump, metal homeostasis, and adjusting the sensitivities of signal

transduction pathways (Singh 2003). Bacteria activate these defence mechanisms to mitigate the harmful effects of ROS for their survival against antibiotics. These ROS-mediated defence mechanisms in bacteria play a significant role in the development of resistance to antibiotics such as methicillin, vancomycin, tetracycline, daptomycin, and linezolid, leading to more challenging infections, treatment failures, and increased mortality (Alfei et al. 2024). Therefore, targeting ROS and inhibiting ROS-mediated defence pathways is a critical approach in the development of therapeutic strategies against multidrug-resistant (MDR) bacteria.

Plant-derived antioxidants present a promising avenue for novel antimicrobial therapeutics due to their dual roles in antimicrobial and antioxidant activities (Kumar et al. 2020). Many phytochemicals such as berberine, betulinic acid, cannabinol, curcumin, eugenol, menadione, quercetin, ursolic acid, xanthohumol, etc., have been reported to have dual activities. These compounds exhibit diverse complex chemical structures that make it difficult for bacteria to develop resistance. At the same time, they can disrupt ROS generation, scavenge oxidative stress, and inhibit bacterial defence mechanisms, thereby reducing the likelihood of resistance development. These phytochemicals exert potent antibacterial effects through impairing bacterial cell membrane functions, interrupting nucleic acid synthesis, and inhibiting respiratory metabolism (Naqvi et al. 2019). Moreover, the continuous release and overuse of antibiotics have led to adverse effects on human health and the environment, highlighting the urgency of identifying effective alternatives (Chaturvedi et al. 2021).

Natural antioxidant-based antibacterial agents offer a viable solution, providing therapeutic efficacy while mitigating the side effects associated with conventional antibiotic use and preventing the emergence of antibiotic-resistant bacteria. Hence, this study investigates the role of ROS in bacterial defence mechanisms that drive antibiotic resistance, while also exploring the promising potential of natural antioxidants as innovative antibacterial agents. The aim is to shed light on how these processes contribute to resistance development by unravelling the complex interplay between antibiotic-induced ROS generation and bacterial adaptive responses. This review will also explore the mechanisms by which natural antioxidants can neutralize ROS, offering a cutting-edge approach to combat MDR bacteria. The following section will provide a detailed analysis of ROS dynamics in bacterial resistance and highlight natural antioxidants as a compelling avenue for next-generation antibacterial therapies.

Development of antibiotic resistance: ROS-mediated defence and navigating antibiotic stress

Antibiotic resistance is a growing concern in the healthcare system, posing significant global challenges in managing resistant bacteria (Chinemerem Nwobodo et al. 2022). Bacteria develop antibiotic resistance through genetic alterations, including plasmid conjugation, phage-based transduction, horizontal transformation, activation of mobile genetic elements, and DNA mutagenesis (Dwyer et al. 2009). These changes enable bacterial survival under antibiotic exposure by metabolic pathways and regulatory mechanisms that influence the interplay between multiple gene families. These regulons along with other components of the cellular machinery, may confer resistance against a wide variety of antibiotics, including some that are yet to be discovered. The gene networks are complex, adaptable systems that regulate cellular processes, including antibiotic resistance. These networks maintain essential gene functions despite mutations or environmental stress, often through redundant or compensatory pathways (Dwyer et al. 2009). Recent findings suggest that these networks play a crucial role in the evolution of resistance by activating alternative pathways under antibiotic exposure (Harms et al. 2016). However, detailed mechanistic insights are limited, with much of the current understanding remaining speculative. The signalling pathways within these networks mediate gene expression changes in response to external stimuli like antibiotics. The ROS-mediated signalling pathways play a critical role in the evolution of antibiotic resistance by acting as key mediators in stress perception and cellular responses. The accumulation of ROS in bacterial cells, often due to host immune responses or antimicrobial treatment, can overwhelm their detoxification systems. Oxidative stress in bacteria can originate exogenously from host–pathogen interactions or endogenously through intracellular processes such as aerobic respiration, antibiotic action, and redox reactions (Li et al. 2021).

During aerobic respiration, incomplete reduction of oxygen by flavoenzymes like oxidases and monooxygenases leads to the formation of ROS, including superoxide anions (O_2^-) and hydrogen peroxide (H_2O_2), instead of water (Dwyer et al. 2009).

These ROS cause significant cellular damage by oxidising nucleotide pools, leading to DNA damage, peroxidising lipids, and carbonylating proteins. Such damage can drive mutagenesis and other adaptive responses, contributing to the development and persistence of antibiotic resistance (Kaushik et al. 2022). Moreover, understanding these ROS-driven processes is vital for developing strategies to counteract resistance mechanisms. Several antibiotics cause ROS induction. Antibiotics primarily target bacterial cell walls (e.g., ampicillin), protein synthesis (e.g., kanamycin), DNA replication (e.g., norfloxacin), and others such as nitrofurantoin, β-Lactams, and fluoroquinolones (Alfei et al. 2024). However, studies have shown that antibiotics can also induce ROS production by overstimulating electron flow through the tricarboxylic acid cycle and releasing iron from iron-sulphur clusters, activating Fenton chemistry (Dwyer et al. 2009). Thus, antibiotics with different primary mechanisms of action share a common secondary effect of ROS generation.

In antibiotic-resistant bacteria, the ROS signalling pathways are intricately regulated through a multifaceted approach involving enhancement of antioxidant enzyme activities, modulation of H_2O_2 and O_2^- production rates, and fine-tuning of pathway sensitivities. This precise control enables these bacteria to mitigate antibiotic and ROS damage while activating their defence systems. Furthermore, the crosstalk between ROS and other signalling pathways may enhance adaptive responses to antibiotic exposure (Vaishampayan and Grohmann 2022). The ROS-mediated signalling response and antibiotic-induced stress in bacteria are driven by four core mechanisms i.e. activation of detoxification enzymes, initiation of the SOS response, regulation of metal homeostasis, and the action of efflux pumps (Fig. 1). In addition, two other mechanisms such as modification of the bacterial cell wall and alterations in membrane proteins are indirectly associated with bacterial ROS signalling pathways and contribute to antibiotic resistance.

Activation of detoxification enzymes

In antibiotic-resistant microbes, ROS influence certain gene families like superoxide dismutase, catalase, thioredoxins, haem biosynthesis machinery, glutathione reductases, ferric uptake regulators, and bacterioferritin to mitigate harmful oxidants and convert them to harmless products by neutralising them to prevent oxidative damage (Vaishampayan and Grohmann 2022). The ROS signalling in these resistant bacteria activates important detoxification enzymes, boosting the bacteria's defence against antibiotics. The effects of ROS extend to post-transcriptional and post-translational modifications in bacteria under antibiotic stress. For instance, multidrug resistance in *Enterococcus faecalis* to penicillin and vancomycin is linked with superoxide dismutase and oxidative stress response enzymes (Bizzini et al. 2009). Similarly, it has been observed that oxidative stress-responsive genes and pathways in *Pseudomonas aeruginosa* influence its virulence (Goldová et al. 2011). Martins et al. 2019 identified the upregulation of the catalase gene (*Ctt1*) in *Saccharomyces cerevisiae*, conferring resistance to antifungals fluconazole and miconazole. Sun et al. 2016 reported the role of the catalase gene (KatG) in *Acinetobacter* species, conferring resistance to H_2O_2.

In this perspective, bacterial exposure to antibiotics triggers cellular stress responses that increase ROS production. The elevated ROS level can activate specific redox-sensitive transcription factors (TFs) such as OxyR, PerR, OhrR, and SoxRS, which regulate detoxification genes by binding to their promoter regions and boosting enzyme synthesis. These factors coordinate the expression of genes encoding antioxidant and detoxification enzymes, enabling the bacterial cell to neutralize oxidative stress (Ezraty et al. 2017). For instance, exposure to H_2O_2 activates the OxyR regulon, which in turn regulates the expression of protective genes, including katG and ahpC (Drlica and Zhao 2021). The discovery of the oxidative stress-responsive transcription factor OxyR marked a significant advancement. In *Escherichia coli*, oxidation of Cys199 to sulphonic acid enables disulphide bond formation with Cys208, leading to conformational changes that activate OxyR for DNA binding. Glutaredoxin 1 (Grx1) reduces the Cys199–Cys208 disulphide bond, deactivating OxyR and establishing a negative feedback loop during

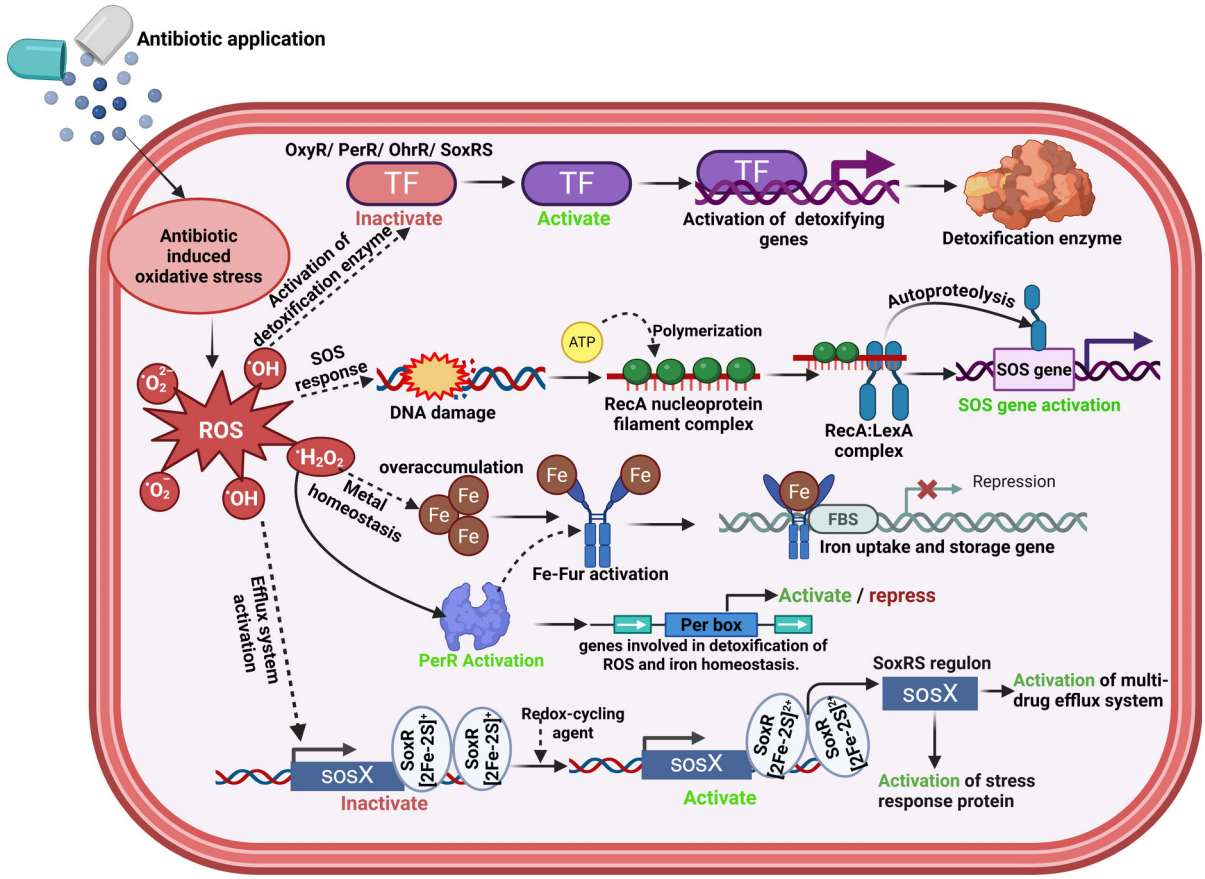


Fig. 1 An illustrative diagram depicting the potential molecular mechanism of the ROS-mediated defence of bacteria contributing to antibiotic resistance. The ROS-mediated response operates through four tightly linked mechanisms: activation of detoxification enzymes, induction of the SOS response, stimulation of multidrug efflux systems, and regulation of metal homeostasis. Upon ROS accumulation, it activates redox-sensitive transcription factors (TFs) such as OxyR, PerR, OhrR, and SoxRS, which further upregulate genes encoding detoxifying enzymes, which are later involved in the ROS-induced stress response. Concurrently, DNA damage and mutagenesis caused by ROS initiate SOS signalling via RecA-mediated autoproteolysis of the LexA repressor, leading to the expression of error-prone translesion synthesis (TLS) DNA polymerases (Pol II, Pol IV, and Pol V). ROS also disrupts metal homeostasis. ROS-induced iron dysregulation further exacerbates oxidative stress, activating Fur and PerR regulatory systems to restore iron homeostasis and regulate detoxification gene expression. Additionally, ROS-induced oxidation of the [2Fe–2S] cluster activates the SoxR/SoxS system, enhancing the expression of efflux pumps and oxidative stress response proteins

oxidative stress (Ezraty et al. 2017). This ROS induction also influences TF binding and serves as a regulatory switch for gene expression (Green et al. 2014).

ROS-mediated Save Our Soul (SOS) response

The SOS response is a critical bacterial stress response mechanism that is primarily activated by DNA damage and mutagenesis, with central regulation by the LexA and RecA proteins. Under non-stress conditions, LexA represses the transcription of SOS genes (Vaishampayan and Grohmann 2022). However, upon DNA damage, RecA binds to single-stranded DNA (ssDNA), forming nucleoprotein filaments. This activated RecA acts as a co-protease that catalyses the autoproteolysis of LexA. This proteolytic event leads to the derepression of over 50 SOS-regulated genes, initiating a comprehensive and dynamic DNA repair process. Initially, the SOS response activates high-fidelity DNA repair pathways, yet sustained activation induces the expression of error-prone translesion synthesis (TLS) DNA polymerases, specifically Pol II, Pol IV, and Pol V. These

TLS polymerases are crucial for bypassing unrepaired DNA lesions that would otherwise stall replication (Dwyer et al. 2009). However, their reduced replication fidelity leads to elevated mutation rates, a phenomenon that can drive the emergence of antibiotic resistance, particularly under prolonged or sub-inhibitory antibiotic exposure (Kaushik et al. 2022). Studies by Händel et al. 2016 demonstrated that RecA, a pivotal factor in the SOS response, plays a crucial role in developing antibiotic resistance in *E. coli.*

Fluoroquinolones are potent inducers of the SOS response due to their direct ability to inflict DNA damage (Baharoglu and Mazel 2011). Non-genotoxic antibiotics, including β-lactams and trimethoprim, can also induce the SOS response through indirect mechanisms, such as ROS generation and activation of two-component signalling systems like DpiAB (Dwyer et al. 2009). The resulting ROS not only sustains the SOS response but also exacerbates DNA damage, creating a feedback loop that drives mutagenesis and promotes resistance development. Beyond its role in DNA repair, the SOS response influences horizontal gene transfer, biofilm formation, and antibiotic resistance (Perez-Capilla et al. 2005). Experimental studies in *E. coli*, *Vibrio cholerae*, *P. aeruginosa*, and *M. tuberculosis* reveal species-specific differences in SOS response induction by various antibiotics (Alfei et al. 2024). For instance, *E. coli* strongly induces the SOS response in response to fluoroquinolones, whereas aminoglycosides do not. Conversely, *V. cholerae* exhibits a broader SOS response to multiple antibiotic classes (Baharoglu and Mazel 2011). The potential to reduce mutation rates and resensitise bacteria to antibiotics lies in targeting the SOS response, particularly through the inhibition of RecA. In *E. coli*, RecA inactivation has been shown to significantly reduce mutation rates and lower the minimum inhibitory concentrations (MICs) for fluoroquinolones, suggesting a promising strategy for mitigating antibiotic resistance (Machuca et al. 2021). Moreover, the combination of RecA inhibition with approaches that elevate ROS production synergistically enhances the efficacy of bactericidal antibiotics, highlighting the importance of concurrently targeting DNA repair mechanisms and oxidative stress responses in antibacterial therapy (Kaushik et al. 2022).

Metal homeostasis

Studies show that metal homeostasis in bacteria is closely linked to their response to ROS, with iron, copper, and manganese playing crucial roles as cofactors for enzymes involved in ROS detoxification. However, iron can also exacerbate oxidative stress by catalysing the formation of harmful hydroxyl radicals through Fenton chemistry. To manage oxidative damage, bacteria regulate metal uptake, storage, and efflux. During oxidative stress, the uptake of iron is reduced, and the upregulation of iron storage proteins such as ferritins occurs to prevent free iron from participating in damaging reactions. In contrast, manganese is accumulated to scavenge ROS directly or replace iron in enzymes, thus protecting against ROS-induced inactivation (Vaishampayan and Grohmann 2022).

Research identified the HssRS/HrtAB haem detoxification system as crucial for bacterial survival in haem-rich environments, such as those encountered in vertebrate hosts (Stauff et al. 2007). The ferric uptake regulator enhances the expression of genes involved in oxidative stress resistance, pH homeostasis, quorum sensing, and other processes in pathogens such as *N. gonorrhoeae* and *E. coli* (Yu and Genco 2012; Carpenter et al. 2009). Studies describe BfrB as the primary iron storage protein in *P. aeruginosa*, which, along with Bfd, facilitates iron mobilization (Punchi Hewage et al. 2020; Yao et al. 2012). The PerR protein senses metal-dependent and H_2O_2-induced oxidative stress in *Bacillus subtilis*, regulating the adaptive response (Duarte and Latour 2010). Similarly, aconitases (AcnA and AcnB) regulate gene expression in response to iron levels and oxidative stress in *E. coli*.

Bacteria utilize regulatory systems such as Fur and PerR to maintain metal homeostasis under oxidative stress. Fur controls the expression of genes involved in iron uptake and metabolism, balancing the need for iron as a cofactor against the risks posed by oxidative damage. Fur functions as a transcriptional repressor by binding to specific DNA sequences known as "Fur boxes" to regulate genes involved in iron acquisition from the environment. Under low iron conditions, Fur dissociates from DNA, which permits the expression of iron acquisition genes to facilitate environmental iron uptake. Conversely, during iron overaccumulation, Fur remains active and represses these genes to maintain metal homeostasis (Troxell and Hassan

2013). Similarly, PerR modulates gene expression in response to oxidative stress. Binding with ferrous iron, PerR regulates oxidative stress defence genes such as katA, ahpCF, and sod, as well as iron homeostasis genes like hemAXCDBL and mrgA (Zhang et al. 2012). Notably, crosstalk between Fur and PerR allows coordinated regulation of iron metabolism and oxidative stress responses. Bacterial metabolism also adapts to counteract ROS damage. The glyoxylate shunt reduces endogenous ROS production, while the pentose phosphate pathway is enhanced to increase NADH levels and replenish antioxidants. Moreover, ketoacids are utilized to neutralize ROS, though this process can lead to the production of toxic by-products. Iron remains essential for bacterial growth, but it also contributes to the generation of ROS. Under iron-limiting conditions, bacteria produce siderophores to enhance iron uptake and combat oxidative stress (Li et al. 2021). Siderophores such as staphyloferrin in *Staphylococcus aureus* and enterobactin in *E. coli* can reduce sensitivity to ROS, likely by neutralizing these reactive species (Peralta et al. 2016).

Oxidative stress can trigger an upregulation of siderophore production, as observed in methicillin-resistant *S. aureus* (MRSA) when exposed to ROS-generating antimicrobial treatments like AGXX® (Vaishampayan and Grohmann 2021). Overall, this intricate regulation of metal homeostasis and metabolic adaptation plays a vital role in bacterial survival under oxidative stress, contributing to their resistance against ROS-generating antimicrobial treatments.

Efflux pump activation

Induced ROS can significantly impact bacterial efflux pumps, which play a crucial role in expelling toxic substances, including antibiotics. Oxidation of key amino acids in efflux pump proteins occurs due to ROS, leading to structural alterations that impair their function. Oxidative stress can also upregulate the expression of efflux pump-associated genes, enhance the removal of ROS-damaged molecules and ultimately reduce oxidative damage (Grant and Hung 2013). The ROS-induced lipid peroxidation may damage the bacterial membrane, and bacteria respond to it by activating efflux pumps (Wang et al. 2017).

Global regulatory systems, such as SoxRS in *E. coli*, are activated by oxidative stress, resulting in increased expression of efflux pumps that aid bacteria in resisting both oxidative stress and antibiotics (Watanabe et al. 2008; Pomposiello et al. 2001). Several antibiotic-resistance genes have been identified in MDR *P. aeruginosa*, including *blaampC* and genes encoding the RND superfamily efflux pumps MexXY, MexAB-OprM, MexCD-OprJ, and MexEF-OprN (Valot et al. 2015; Lorusso et al. 2022). The oxidative stress response in bacteria can protect them from host immune systems and antibiotics, contributing to persistent infections. Persister cells, which exist in a dormant state with low metabolic activity, display high tolerance to antibiotics and possess the ability to recolonize after treatment. These cells are less sensitive to ROS, likely due to the increased activity of efflux pumps that assist in removing ROS-damaged proteins. Moreover, ROS may promote the formation of persister cells by decreasing membrane potential and metabolism. Therefore, monitoring and controlling ROS level is crucial for preventing the formation of persister cells and ensuring the resolution of persistent infections.

Antibiotic resistance and bacterial cell wall modification

Bacteria have evolved a variety of defence mechanisms to counteract antibiotic and ROS-induced damage, which helps preserve cell wall integrity and promotes survival, adaptation, and antibiotic resistance (Fig. 2) (Kohanski et al. 2010). DNA damage induced by ROS triggers the bacterial SOS response, activating repair enzymes and stress-response genes to mitigate such damage; however, this response can also raise mutation rates that potentially alter genes involved in cell wall synthesis (Imlay 2013). To detoxify ROS, bacteria often regulate enzymes like superoxide dismutase and catalase, which indirectly protect the cell wall by limiting intracellular ROS levels. Some bacterial species upregulate stress proteins and repair enzymes in response to ROS-induced stress. Oxidative stress can activate specific sigma factors, enhancing the synthesis of cell wall maintenance proteins and other protective elements (Weinzierl et al. 2002). The bacterial cell wall is crucial for maintaining structural integrity, providing osmotic protection, and acting as a defence barrier. To preserve this structure, bacteria activate several defence mechanisms that enable them to withstand environmental

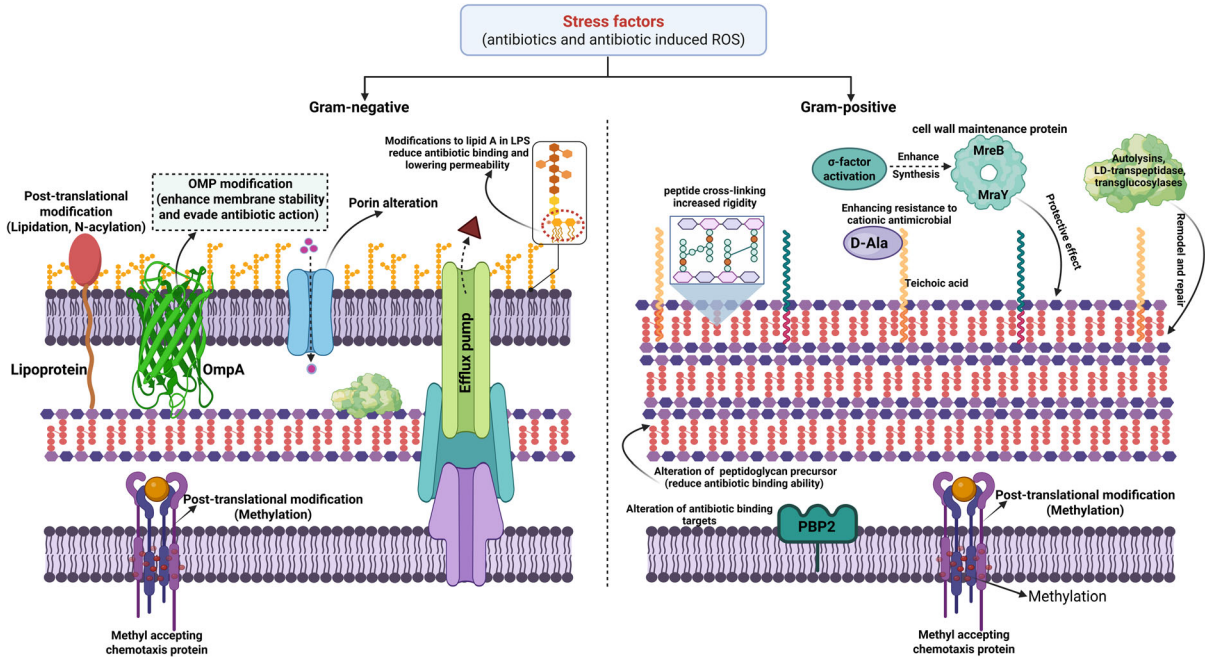


Fig. 2 Detailed scientific illustration demonstrating the strategic remodelling mechanisms of bacterial cell wall and membrane proteins to develop antibiotic resistance. In response to antibiotic pressure and ROS-induced stress, bacteria initiate a robust defence involving multifaceted structural and biochemical adaptations. These include significant alterations of outer membrane proteins (OMPs), porin channel modification, lipopolysaccharide (LPS) restructuring, and extensive post-translational modifications that enhance membrane resilience. Concurrently, cell wall integrity is fortified through the activation of sigma factors, driving the upregulation of genes responsible for peptidoglycan synthesis and repair. This includes enhanced peptide cross-linking, modification of peptidoglycan precursors, and the strategic incorporation of D-alanine into teichoic and lipoteichoic acids, effectively reducing surface charge and increasing resistance to cationic antimicrobial agents. Collectively, these complex and coordinated modifications form a powerful bacterial survival strategy, contributing significantly to the challenge of antibiotic resistance

stresses, including infection-related oxidative damage and structural challenges (Imlay 2013; Fang 2004). Many bacteria reinforce their cell walls during stress; for example, Gram-positive bacteria add peptide cross-links for increased rigidity, while Gram-negative bacteria modify lipopolysaccharides (LPS) in the outer membrane to resist host antimicrobial peptides (Poole 2012). Bacteria may also alter antibiotic targets; for example, MRSA modifies penicillin-binding proteins to evade beta-lactam antibiotics (Wright 2005).

In response to stress, bacteria utilise enzymes such as autolysins, transpeptidases, and transglucosylases to remodel and repair the peptidoglycan layer, adjusting the cell wall structure and repairing damage from external factors. The activity of controlled autolysins cleaves peptidoglycan bonds, allowing for wall remodelling without compromising structural integrity. In addition, LD-transpeptidase modifies peptidoglycan cross-links, enhancing resistance to cell wall-targeting antibiotics, particularly in Gram-positive bacteria (Silhavy et al. 2010). Under stress conditions, bacteria also enhance protection by forming capsules or biofilms around the cell wall, which serve as barriers against ROS, host immune defences, dehydration, and antibiotics. Regulatory pathways, such as the Cpx, Rcs, Psp, and Bae systems in Gram-negative bacteria, detect damage and activate responses for cell wall repair (Poole 2012). In Gram-positive bacteria, teichoic and lipoteichoic acids support cell shape, division, and protection against stress; modifications such as the addition of D-alanine can reduce the negative charge, thereby enhancing resistance to cationic antimicrobials. Glycosylation also assists in evading immune recognition (Silhavy et al. 2010; Peschel 2002). In Gram-negative bacteria, the outer membrane's LPS provides an additional barrier, with structural alterations reducing

permeability to antimicrobials and ROS. Outer membrane proteins (OMPs) also adjust in response to stress to maintain structural integrity (Seaver and Imlay 2001). Modifications to lipid A in LPS can reduce antibiotic binding, lowering permeability and restricting antibiotic entry (Nikaido 2003). Certain bacteria modify their cell wall precursors to prevent antibiotic binding. A notable example is vancomycin-resistant Enterococcus (VRE) exemplifies this, as it alters peptidoglycan precursor structures to reduce vancomycin's binding ability, thereby protecting cell wall synthesis from disruption (Vollmer et al. 2008).

Antibiotic resistance and membrane protein modification

Bacteria can dynamically modify both their cell wall and membrane to adapt to environmental stresses, including immune attacks and antibiotic treatment (Fig. 2). In Gram-negative bacteria, a key survival strategy involves the modification of membrane proteins to reduce antibiotic uptake, which subsequently decreases drug efficacy (Nikaido 2003). For instance, alterations in porins, outer membrane channels that typically allow small molecules, including antibiotics, to enter the cell, enable bacteria to limit the penetration of antibiotics such as beta-lactams and carbapenems. Bacteria can achieve low internal drug concentrations by reducing the size of porins or altering their charge, which limits the penetration of antibiotics (Blair et al. 2015).

Bacteria also modify membrane proteins involved in signalling and environmental interactions to enhance membrane stability and evade antibiotic action (Silhavy et al. 2010; Peschel 2002). These modifications can include the addition of lipid groups (lipoproteins) to anchor proteins, phosphorylation to regulate protein activity, methylation for chemotaxis, and N-acylation to integrate proteins into the lipid bilayer. Understanding the mechanisms of antibiotic resistance, particularly concerning bacterial envelopes and the role of ROS, is essential for developing effective strategies to combat resistant infections. The interaction between these factors highlights both challenges and opportunities in addressing the global health crisis of antibiotic resistance.

Bacteria resistant to conventional antibiotics but sensitive to antioxidant-based approaches

Bacterial antibiotic resistance occurs when bacteria adapt to survive treatments that are meant to kill them, rendering standard therapies ineffective. This growing public health crisis prolongs infections, increases complications, and leads to higher healthcare costs and mortality rates. The challenge of addressing antibiotic resistance necessitates a comprehensive approach that includes responsible antibiotic use, strict infection control measures, the development of new drugs, and ongoing public health surveillance to monitor resistance ends (Ventola 2015; World Health Organization 2014).

One innovative approach to combatting antibiotic resistance involves the use of antioxidant-based antibiotics, designed to disrupt bacterial oxidative stress pathways. Oxidative stress, often triggered by ROS, can be utilized against bacteria, as it disrupts cellular functions and can lead to cell death. Antioxidant-based antibiotics aim to selectively amplify oxidative damage in bacterial cells or inhibit bacterial antioxidant defences, thereby rendering resistant strains more susceptible to treatment. Research indicates that antioxidants can modulate bacterial stress responses and have shown potential to enhance antimicrobial effects against specific resistant strains. However, the efficacy of these compounds varies widely, influenced by bacterial species, resistance mechanisms, and metabolic pathways involved, necessitating targeted studies for each pathogen (Majtan et al. 2014).

Several notable antibiotic-resistant bacteria may be susceptible to antioxidant-based antibiotic treatments. Methicillin-resistant MRSA, which is resistant to multiple β-lactam antibiotics such as methicillin and oxacillin, has shown vulnerability to antioxidant therapies that utilize flavonoids, curcumin, and other polyphenols. These compounds disrupt bacterial membranes and oxidative stress pathways, potentially enhancing antimicrobial effects (Majtan et al. 2014). Vancomycin-resistant *Enterococcus* (VRE) is known for its resistance to vancomycin through target modifications but can regain susceptibility when antioxidants, such as epigallocatechin gallate (derived from green tea), are combined with conventional antibiotics (Ahmad et al. 2023).

Carbapenem-resistant *Enterobacteriaceae* (CRE) produce enzymes that degrade carbapenems, creating significant challenges for treatment. However, antioxidant-based therapies can impair CRE's metabolic defences and oxidative resistance (Centers for Disease Control and Prevention (U.S.) 2019). *Pseudomonas aeruginosa*, notorious for its natural resistance mechanisms such as efflux pumps, biofilm formation, and low membrane permeability, responds positively to treatments that include antioxidant-based inhibitors of pyocyanin or nitric oxide donors. These approaches reduce biofilm formation and virulence, thereby increasing the bacterium's susceptibility to other antibiotics (Abdelraheem et al. 2022).

Escherichia coli strains that produce Extended-Spectrum Beta-Lactamases (ESBLs) to degrade β-lactam antibiotics show sensitivity to antioxidants such as vitamin C and tannins, which reduce oxidative damage and improve antibiotic effectiveness (Munita and Arias 2016). *Acinetobacter baumannii*, an opportunistic pathogen exhibiting high resistance due to modifications in antibiotic targets, efflux mechanisms, and biofilm production, shows decreased virulence and membrane stability in response to plant-derived antioxidants like quercetin and resveratrol (Mumtaz et al. 2023). These antioxidant-based strategies offer promising adjunctive therapies in the fight against antibiotic-resistant infections. A thorough understanding of how antioxidant-based antibiotics affect different bacterial strains is crucial for the development of targeted therapies.

Natural antioxidant as potential antibiotics: targeting ROS-mediated defence to overcome bacterial resistance

The increasing prevalence of antibiotic resistance, along with the systemic toxicity associated with conventional antibiotics, underscores the urgent need for novel antibacterial agents. The preceding discussion highlighted the role of antibiotic-induced ROS generation in facilitating bacterial resistance by activating alternative survival pathways during antibiotic exposure. In this context, plant-derived natural compounds such as baicalein, berberine, betulinic acid, caffeic acid, cannabinol, chelerythrine, curcumin, fangchinoline, piperine, and α-mangostin represent a promising and sustainable approach to counteracting bacterial resistance by modulating ROS-mediated defence pathways. These bioactive compounds exhibit dual functionalities, combining both antimicrobial and antioxidant properties. This combination offers a multifaceted strategy to address the limitations of traditional antibiotics and effectively mitigate the challenge of antimicrobial resistance (Adesanwo et al. 2013; Appendino et al. 2008; Chung et al. 2014; Felix et al. 2022; Jain et al. 2023; Khameneh et al. 2015; Liu et al. 2020; Luis et al. 2014; Mun et al. 2014; Rivero-Cruz et al. 2020; Stasilowicz-Krzemien et al. 2023; Yu et al. 2005).

The precise mechanisms by which plant-derived compounds mitigate bacterial ROS-mediated defences remain incompletely understood. The compounds discussed disrupt bacterial processes by enhancing membrane permeability, leading to cytoplasmic leakage and inhibiting essential functions such as nucleic acid synthesis, cell wall formation, and respiratory metabolism (Pancu et al. 2021). Figure 3 illustrates the probable mechanisms of dual-active phytochemicals in counteracting antibiotic-resistant bacteria. However, these mechanisms remain partially understood and require further elucidation. The inherent structural complexity of these phytochemicals poses a significant challenge for bacterial adaptation, offering a strategic advantage in preventing the development of resistance (Simoes et al. 2009). The following sections will provide a detailed exploration of these dual-active compounds.

Alkaloids

Alkaloids represent one of the major groups of bioactive compounds found in many medicinal and aromatic plants, possessing both antibacterial and antioxidant activities. These organic nitrogenous compounds exhibit substantial structural diversity, which contributes to their potential bioactivity, particularly due to the presence of nitrogen atoms (Martelli and Giacomini 2018). The antibacterial activity of alkaloids is closely tied to their structural diversity, with key mechanisms including the disruption of cell division, respiration, membrane integrity, and virulence gene expression. In addition, alkaloids effectively inhibit bacterial efflux pumps, a crucial resistance mechanism in MDR bacteria (Radulovic et al. 2013).

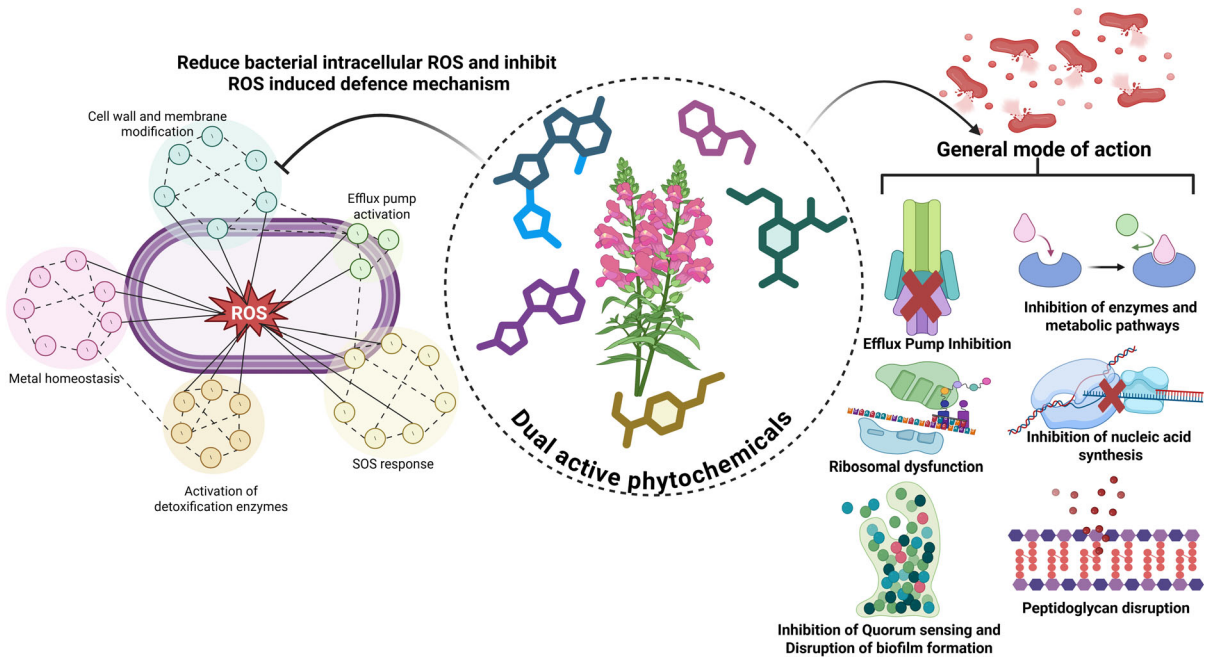


Fig. 3 A visual representation showing a probable antibacterial mechanism of dual-active phytochemicals in combating antibiotic resistance. These compounds act through multifactorial pathways, directly targeting bacterial cells with a general antibacterial mode of action while simultaneously exhibiting antioxidant properties. Their dual functionality provides an added advantage by modulating intracellular ROS and ROS-mediated defence mechanisms in bacteria, thereby enhancing their ability to overcome resistance

Recent studies highlight the multifaceted activity of various alkaloids, positioning them as promising agents for treating infectious diseases and addressing antibiotic resistance. Berberine exhibits significant activity against MRSA with MICs ranging from 32 to 128 µg/mL and shows strong antioxidant effects by effectively scavenging DPPH, NO, and superoxide radicals at 320 µg/mL (Jain et al. 2023; Yu et al. 2005). Chelerythrine similarly inhibits MRSA growth at MICs of 2–4 µg/mL while demonstrating high antioxidant activity in vivo at 100 mg/kg (Wang et al. 2021; Wu et al. 2022). Fangchinoline has demonstrated antibacterial efficacy with MIC of 160 µg/mL alongside 93.3% inhibition of lipid peroxidation at 30 µg/mL (Gülçin 2010; Fu et al. 2017). Harmaline has reported activity against MRSA strain N441 with a MIC of 125 µg/mL and offers free radical scavenging at a concentration of 10 µM (Javeed et al. 2018; Mohtar et al. 2009).

Other alkaloids, for example, piperine and reserpine, have also been reported to be effective against MRSA, with MICs of 100 µg/mL and 1–270 µg/mL, respectively (Khameneh et al. 2015; Sridevi et al. 2017). For ciprofloxacin-resistant *S. aureus*, indirubin exhibits antimicrobial activity with a MIC as low as 12.5 mg/L and also displays significant DPPH and superoxide radical scavenging activity (Ponnusamy et al. 2010; Zhao et al. 2017). Tetrandrine, with a MIC of 80 µg/mL, and tomatidine, with MICs ranging from 0.06 to 1 µg/mL, further demonstrate robust antibacterial and antioxidant properties, particularly against MDR strains (Bhagya and Chandrashekar 2016; Silva-Belan et al. 2015). These antioxidant-rich alkaloidal compounds contribute to mitigating bacterial resistance by alleviating oxidative stress and disrupting essential bacterial defence mechanisms (Gangwar et al. 2023). By netrualizing ROS, these compounds interfere with bacterial survival strategies, including the upregulation of efflux pump activity and the activation of stress response pathways, both of which are crucial for bacterial resilience. This dual functionality not only attenuates ROS-induced cellular damage but also simultaneously impairs bacterial defence mechanisms, thereby enhancing the efficacy of antioxidant-based antibacterials. This presents a potent strategy for counteracting bacterial resistance.

Phenolics

Flavonoids

Flavonoids represent another important class of bioactive compounds with notable antibacterial activity, functioning through diverse mechanisms such as the inhibition of nucleic acid synthesis, disruption of cell wall biosynthesis, modulation of membrane fluidity, suppression of respiratory metabolism, and impairment of critical membrane functions (Naqvi et al. 2019). Their dual function as potent antioxidants and antibacterial agents makes flavonoids compelling candidates for combating MDR bacterial infections. The antioxidant properties of flavonoids arise from their hydroxyl groups and aromatic ring structures, which enable them to neutralize ROS and interfere with oxidative pathways integral to bacterial energy metabolism (Heim et al. 2002). This antioxidant capacity plays a critical role in mitigating ROS-mediated stress responses, such as the SOS response, while inhibiting the activation of efflux pumps and detoxifying enzymes, which are key mechanisms through which bacteria acquire MDR phenotypes (Naqvi et al. 2019).

Several flavonoids have demonstrated potent antibacterial activity against MDR pathogens. For instance, baicalein exhibits effective inhibition of ciprofloxacin-resistant *S. aureus*, with a MIC ranging from 64 to 256 μg/mL. Additionally, baicalein has been reported to enhance the efficacy of linezolid against MRSA biofilms while providing substantial antioxidant benefits (Chan et al. 2011; Liu et al. 2020; Wang et al. 2011). Caffeic acid also shows broad-spectrum MRSA activity, with MIC between 62.5 and 250 μg/mL, along with robust radical scavenging, which aids in oxidative stress reduction (Luis et al. 2014; Rivero-Cruz et al. 2020). Catechin exhibits strong antibacterial activity against MRSA, with a reported MIC of 78.1 μg/mL. In combination with epicatechin gallate, catechin significantly reduces bacterial loads in MRSA-infected models, highlighting a promising synergistic effect (Sinsinwar and Vadivel 2020). Epigallocatechin gallate (EGCG), a major flavonoid compound derived from green tea, further supports these findings, showing potent antibacterial efficacy against various MRSA strains with MIC values ranging from 50 to 180 μg/mL (Cho et al. 2008). This evidence underscores the potential of catechins and their derivatives as effective agents against resistant MRSA infections. Several other flavonoids have demonstrated notable antibacterial activities against drug-resistant *S. aureus* and *M. tuberculosis* strains. Galangin was tested against various penicillin-resistant *S. aureus* strains, showing MIC values ranging from 100 to 300 μg/mL, indicating moderate antibacterial potential (Eumkeb et al. 2010). Glabridin also exhibited promising activity, with MICs between 3.12 and 25 μg/mL against MDR clinical isolates of *S. aureus* (Singh et al. 2015). Similarly, kaempferol was reported to inhibit MRSA with a MIC of 250 μg/mL (Al-Ghanayem et al. 2024). Notably, plumbagin demonstrated strong antimycobacterial activity, with MICs ranging from 0.25 to 4 μg/mL against both MDR and extensively drug-resistant *M. tuberculosis* strains, highlighting its potential as a lead compound against resistant tuberculosis (Dey et al. 2014).

Studies have reported that licochalcones A, C, and E possess a low MIC of 4 μg/mL and enhance the Keap1-Nrf2 pathway while inhibiting NF-κB-mediated inducible nitric oxide synthase (iNOS) expression, effectively combating the MRSA T144 strain (Franceschelli et al. 2011; Mittal and Kakkar 2021; Wu et al. 2019). Strong anti-MRSA activity has been reported for luteolin (MIC at 512 μg/mL), myricetin (MIC at 128 μg/mL), quercetin (MIC at 256 μg/mL), rutin (MIC at 32 μg/mL), and xanthohumol (MIC at 4 μg/mL) (Bogdanova et al. 2018; Xu and Lee 2001; Yang et al. 2008). An interesting study conducted by Pinto et al. 2020 demonstrated that combining oxacillin with myricetin improved survival rates in MRSA-infected *Galleria mellonella* larvae by 20% compared to control groups, highlighting a promising synergistic effect in enhancing host survival. Several studies have also reported the antioxidant potential of these compounds, effectively disrupting oxidative stress through multiple mechanisms (Lang et al. 2024; Qu et al. 2006; Radulovic et al. 2013; Traj et al. 2023; Yamaguchi et al. 2009). This dual action disrupts oxidative stress induction and inhibits bacterial energy metabolism, which not only weakens bacterial defences but also enhances the overall antimicrobial efficacy of these compounds. Given their multifaceted mechanisms, flavonoids represent a promising natural alternative to conventional antibiotics in the fight against MDR bacteria.

Non-flavonoid phenolics

In addition to flavonoids, various other plant-derived phenolic compounds possess both antibacterial and antioxidant properties, making them potential candidates for combating MDR bacterial infections (Martelli and Giacomini 2018). The key phenolics, including α-mangostin, anacardic acid, curcumin, eugenol, galbanic acid, gambogic acid, menadione, and methyl gallate, have shown significant antibacterial activity against MDR strains (Table 1). Curcumin demonstrated an inhibitory efficacy with a MIC ranging from 125 to 250 μg/mL against MDR *S. aureus* in vitro. Its combination with light irradiation significantly reduced the bacterial load in vancomycin-resistant *S. aureus*-infected rat models (Akhtar et al. 2021; Rivero-Cruz et al. 2020). Similarly, methyl gallate displayed a MIC of 250 μg/mL against a clinical isolate of MRSA (Chew et al. 2018).

α-Mangostin exhibits potent antibacterial effects against MRSA, with MICs as low as 1.57 μg/mL, and has been shown to increase survival rates in MRSA-infected *G. mellonella* larvae. It also possesses strong antioxidant properties, demonstrated by a FRAP value of 344.60 μM Fe(II)/g and a DPPH IC_{50} of 20.64 μg/mL (Felix et al. 2022; Ghasemzadeh et al. 2018; Iinuma et al. 1996). Anacardic acid, derived from cashew shells, demonstrated antibacterial effects with MICs of 6.25 μg/mL and scavenged 82% of superoxide anions at a concentration of 30 μg/mL (Kubo et al. 2006; Muroi and Kubo 1996). A study reported that eugenol reduced MRSA infections by 88% in rat models (Yadav et al. 2015), with its impressive antioxidant capacity also being documented (Gülçin 2011). Galbanic acid effectively inhibits tetracycline-resistant *S. aureus*, with MICs ranging from 10 to 80 μg/mL (Bazzaz et al. 2010). Methyl gallate was likewise noted to be effective against MRSA, exhibiting a MIC of 250 μg/mL while also demonstrating strong antioxidant activity (Chew et al. 2018; Hsieh et al. 2004). Additionally, resveratrol was found to exhibit a MIC range of 32–128 μg/mL against MDR *Klebsiella pneumoniae* and *E. coli* (Liu et al. 2020).

The antibacterial action of phenolics involves multiple mechanisms, including the disruption of the bacterial cell wall and membrane integrity, leading to increased permeability and cell lysis. These compounds also inhibit crucial bacterial enzymes involved in nucleic acid synthesis, energy production, and protein synthesis, thereby disrupting bacterial metabolic processes (Rempe et al. 2017). Moreover, phenolic compounds induce oxidative stress by generating ROS, which damages bacterial proteins, lipids, and DNA, ultimately leading to cellular dysfunction and death. A study by Hua et al. 2019 showed that gambogic acid reduced bacterial growth by generating ROS, with MICs ranging from 0.5 to 4 μg/mL. However, the antioxidant properties of phenolic compounds can mitigate the ROS-mediated defence mechanisms employed by MDR bacteria. Their ability to chelate metal ions also disrupts bacterial homeostasis, enhancing antimicrobial efficacy (Martelli and Giacomini 2018). These multifaceted mechanisms position phenolic compounds as promising therapeutic agents in the fight against MDR bacterial infections.

Terpenoids

Terpenoids constitute the major compounds found in many natural products. Several terpenoids, such as 18β-glycyrrhetinic acid, α-amyrin, betulinic acid, lupeol, and ursolic acid, act as both antibacterial and antioxidant agents (Ludwiczuk et al. 2017). Some of these compounds are under various stages of preclinical and clinical evaluation for development as antibacterial agents. These compounds primarily function as enzyme inhibitors that are responsible for bacterial survival. Several other mechanisms are involved, including the disruption of bacterial cell membranes, which leads to increased permeability and cell lysis. Terpenoids inhibit key enzymes involved in metabolism and cell wall biosynthesis, interfere with nucleic acid synthesis, and induce oxidative stress by generating ROS, causing damage to proteins, lipids, and DNA (Martelli and Giacomini 2018).

Terpenoids inhibit bacterial efflux pumps, enhancing the accumulation of antimicrobial agents and disrupting biofilms, thus increasing bacterial susceptibility to treatments (Jubair et al. 2021). These multifaceted actions render terpenoids effective against both susceptible and resistant bacterial strains. The 18β-glycyrrhetinic acid exhibited a MIC of 60 μg/mL against the MRSA strain USA400 but showed limited in vivo efficacy over short incubation periods. This compound also reduced lipid peroxidation and enhanced antioxidant status in rats at a dose of 100 mg/kg (Kalaiarasi and Pugalendi 2011; Wang

Table 1 Natural antioxidants showing antibacterial efficacy against MDR bacteria

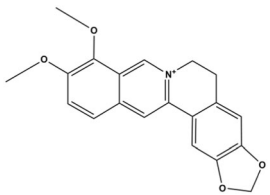
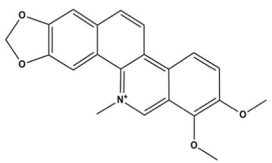
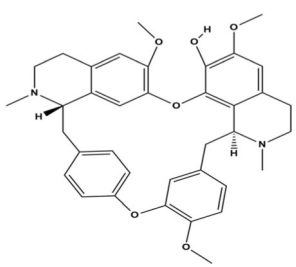
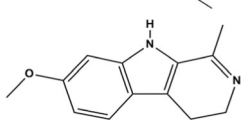
Chemical class	Phytochemical	Compound structure	Antimicrobial activity	Antioxidant activity	Reference
Alkaloid	Berberine		The authors tested the phytochemical against various MRSA strains and found its MIC ranging from 32 to 128 µg/mL	The authors found that berberine exhibited antioxidant activity, with significant increase in DPPH, NO, and superoxide radical scavenging activity at a concentration of 320 µg/mL	Jain et al. (2023) and Yu et al. (2005)
	Chelerythrine		The antimicrobial activity was tested against a range of MRSA strains and extended-spectrum β-lactamases *E. coli*. The phytochemical showed strong antimicrobial activity with MICs of 2–4 µg/mL against MRSA and 16–256 µg/mL against ESBL-producing *E. coli*	Researchers showed the antioxidant capacity of chelerythrine and found that even a small dose of 100 mg/kg was more effective than a higher dose of control sulfasalazine with 500 mg/kg when administered in a mouse model, in vivo	Wang et al. (2021) and Wu et al. (2022)
	Fangchinoline		The authors tested the activity of the phytochemical against MRSA strain 13,366 and found that the inhibitory activity was prominent at 160 µg/mL, showing its efficacy to be better than resistant drugs	The authors reported the antioxidant activity of fangchinoline and found inhibition at 93.3% on lipid peroxidation of linoleic acid emulsion at 30 µg/mL concentration	Gülçin et al. (2010) and Fu et al. (2017)
	Harmaline		The study was reported on MRSA strain N441 and various other strains, which gave a MIC at 125 µg/mL for strain N441 and greater than 250 µg/mL for the other strains of MRSA tested	The antioxidant potential of its derivatives was enumerated by the author and found free radical scavenging activity at 10 µM concentration, and lipid peroxidation in enzymatic Fe^{3+}ADP-NADPH and non-enzymatic Fe^{3+}ADP-DHF oxygen radical generating systems, in a concentration-dependent way	Javeed et al. (2018) and Mohtar et al. (2009)

Table 1 continued

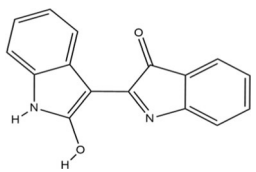
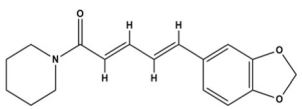
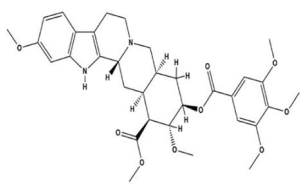
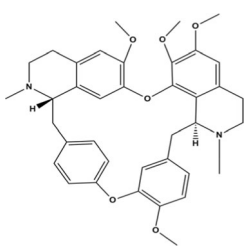
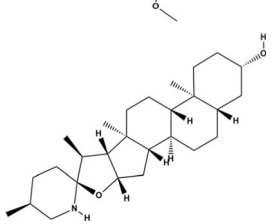
Chemical class	Phytochemical	Compound structure	Antimicrobial activity	Antioxidant activity	Reference
	Indirubin		The authors checked the antimicrobial activity of the phytochemical against two ciprofloxacin-resistant strains of *S. aureus* and found MIC at 12.5 mg/L	The DPPH scavenging activity was reported by the authors to be 22.35% at a concentration of 0.10 mg/mL, and anion superoxide scavenging activity was at 0.74 mg/mL, proving it to be a good antioxidant	Ponussamy et al. (2010) and Zhao et al. (2017)
	Piperine		They tested the growth-inhibitory activity of piperine against MRSA strain ATCC43300 and found it to be active at MIC of 100 μg/mL	The authors performed DPPH radical scavenging activity and found an IC_{50} value of 286.34 μM	Jaisin et al. (2020) and Khameneh et al. (2015)
	Reserpine		The phytochemical was found to be potent against a series of MRSA strains, with MIC reported in the range of 1–270 μg/mL	They showed antioxidant activity of the compound using DPPH assay and found that it had slightly lower antioxidant properties with inhibitions at less than 50% at 200 μg/mL concentration	Begum et al. (2012) and Sridevi et al. (2017)
	Tetrandrine		Tetrandrine was tested for its inhibitory activity against MRSA strain 13,366 and was found to be a good antibacterial agent against drug-resistant *S. aureus,* with MIC reportedly at 80 μg/mL	The authors tested the activity of tetrandrine against superoxide anion radicals and found it to scavenge at a deficient concentration of 0.1 μg/ml	Bhagya and Chandrashekar (2016) and Lamontagne Boulet et al. (2018)
	Tomatidine		Tomatidine exhibited good antibacterial activity with MICs in the range of 0.06–1 μg/mL when tested against resistant strains of *S. aureus*	They tested the antioxidant activity of leaf exact along with the compound using DPPH, ABTS and ORAC assays and found it to have higher activity, displaying DPPH, ABTS, and ORAC values of 0.798, 1.702, and 13.489 mmol TE/GE, respectively	Lamontagne Boulet et al. (2018) and Silva Beltran et al. (2015)

Table 1 continued

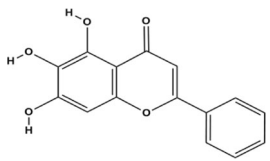
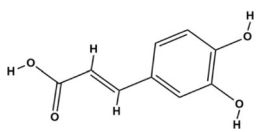
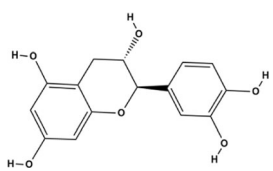
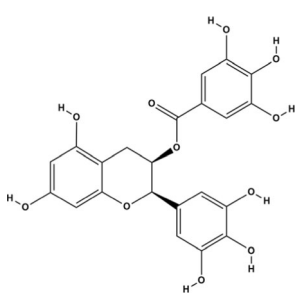
Chemical class	Phytochemical	Compound structure	Antimicrobial activity	Antioxidant activity	Reference
Flavonoids	Baicalein		In an in vitro study, the phytochemical showed effective antibacterial activity against ciprofloxacin-resistant *S. aureus* with MICs ranging from 64 to 256 µg/mL. In an in vivo study, its combination with linezolid enhanced effects against MRSA when used as bacterial implants, making it a promising option for implant-related infections	Baicalein's antioxidant activity showed IC_{50} values of 7.01, 4.58, 25.32, 18.63, 11.74, 4.75, 1.38, 2.18, and 32.50 µg/mL for Fe^{3+}, Cu^{2+} reducing power, hydroxyl, superoxide, lipid peroxidation, DPPH, ABTS, and Fe^{3+}, Cu^{2+} chelating ability, respectively	Chan et al. (2011), Liu et al. (2020) and Wang et al. (2011)
	Caffeic acid		The authors tested caffeic acid against a wide range of MRSA strains and found MICs in the range of 62.5–250 µg/mL, proving to be an effective antimicrobial agent	The authors reported the antioxidant activity using DPPH and ABTS assays and found IC_{50} values of 5.9 µg/mL for DPPH and 9.7 µg/mL for ABTS scavenging activity	Luis et al. (2014) and Rivero-cruz et al. (2020)
	Catechin		Catechin was tested against MRSA strain, which exhibited antibacterial activity with MIC at 78.1 µg/mL. Subsequently, in vivo testing of catechin in combination with epicatechin gallate resulted in a reduced bacterial load in MRSA-infected mice with a great level at MIC of 128 µg/mL	They reported the antioxidant activity of catechin against MRSA strain quantifying ROS generation, SOD and catalase activity and found an increase in ROS generation and a decrease in SOD and catalase activity, leading to oxidative stress in the bacteria	Qin et al. (2013) and Sinsinwar and Vadivel. (2020)
	Epigallocatechin gallate		The phytochemical was tested against various MRSA strains, which exhibited antibacterial activity in the range of MICs 50–180 µg/mL. While in vivo studies on mice reported the activity of the phytochemical in combination with catechin with MIC at 16 mg/L, when this combination was used on MRSA-infected mice, it reduced the bacterial load in the blood of septic mice to a great extent	The authors made nanocomposites with dopamine hydrochloride and the compound and tested its antioxidant activity using DPPH assay and ABTS scavenging assays, and found activity with 70.93% and 56.68% for the DPPH assay and ABTS scavenging assay, respectively	Alavi et al. (2023), Cho et al. (2008) and Qin et al. (2013)

Table 1 continued

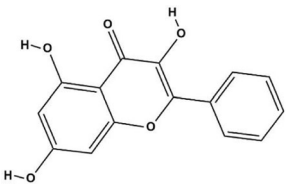
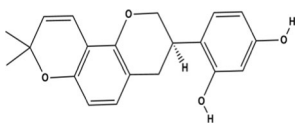
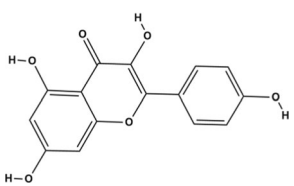
Chemical class	Phytochemical	Compound structure	Antimicrobial activity	Antioxidant activity	Reference
	Galangin		The phytochemical was tested against various penicillin-resistant *S. aureus* strains and reported MICs in the range of 100–300 µg/mL, which acts as a good antibacterial agent	They tested antioxidant activity of galangin using DPPH and ABTS assays and found IC_{50} values of 15.3 µg/mL for DPPH and 26.8 µg/mL for ABTS activity, respectively	Eumkeb et al. (2010) and Rivero-Cruz et al. (2020)
	Glabridin		Glabridin was tested against various strains of MDR clinical isolates of *S. aureus* and antibacterial activity with MICs in the range of 3.12–25 µg/mL	Glabridin's antioxidant activity was tested using DPPH, FRAP, and SOD assays. The results of DPPH assay provided highest inhibition (14.25%). FRAP and SOD assays showed dose-dependent effects, with the increase in the concentration the inhibition raised from 4.09% to 13.93%and 6.17% to 14.81%, respectively	Singh et al. (2015)
	Kaempferol		The authors reported the antibacterial activity using MRSA strain and found MIC at 250 µg/mL. The in vivo studies on mouse wounded with MRSA had a bacterial load of 3.25 ± 1.43 Log_{10} CFU/g compared to control with load of 9.47 ± 1.24 Log_{10} CFU/g, making it a great antibacterial agent against methicillin-resistant *S. aureus*	They showed the antioxidant efficacy of kaempferol and found it to have an antioxidant effect after local application with increased levels of the antioxidant enzymes SOD and catalase	Al-Ghanayem et al. (2024) and Randhawa et al. (2016)

Table 1 continued

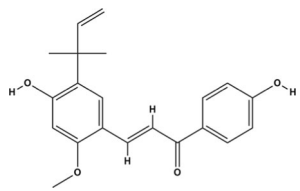
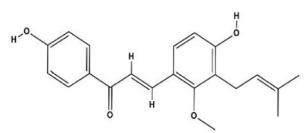
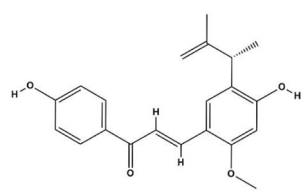
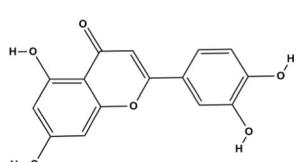
Chemical class	Phytochemical	Compound structure	Antimicrobial activity	Antioxidant activity	Reference
	Licochalcone A		The authors reported the antibacterial activity of the compound against MRSA strain T144 and found MIC at 4 µg/mL	The authors tested Licochalcone A against expression of antioxidant enzyme on mice and found it to inhibit upregulation of antioxidant enzyme expression via the Keap1-Nrf2. Reduced inflammation in collagen antibody-induced arthritic mice was observed at a dose of 25–50 mg/kg	Su et al. (2018) and Wu et al. (2019)
	Licochalcone C		The authors reported the growth-inhibitory activity of Licochalcone C against MRSA strain T144 and found MIC at 4 µg/mL, proving to be good antibacterial agent	They tested antioxidant activity of Licocalchone C and reported that it was responsible for inhibiting iNOS via NF-kB signalling molecule in THP-1 cell line, modulating the antioxidant network activity of SOD, CAT and GPx	Franceschelli et al. (2011) and Wu et al. (2019)
	Licochalcone E		The authors reported the biological activity of the phytochemical against MRSA strain T144 and found MIC at 4 µg/mL, portraying strong antibacterial activity	The authors tested Licochalcone E for its antioxidant activity and reported that it scavenged hydroxyl and hydroperoxyl radicals, carbonate radical anion, and NO_2 radical effectively with little tendency to scavenge the superoxide radical anion	Mittal and Kakkar (2021) and Wu et al. (2019)
	Luteolin		The authors tested the phytochemical against MRSA strain 9,247,922 and found inhibitory activity with MIC at 512 µg/mL	They tested the phytochemical for lipid peroxidation and oxidative stress and reported a remarkable decrease in the exatrcellular H_2O_2 and MDA concentrations at a concentration of 4 µg/mL	Traj et al. (2023) and Xu and Lee (2001)

Table 1 continued

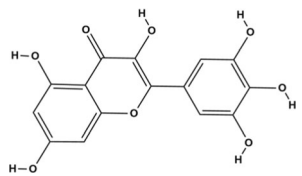
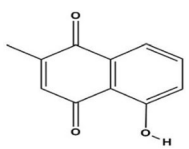
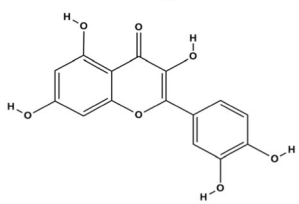
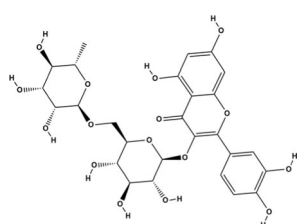
Chemical class	Phytochemical	Compound structure	Antimicrobial activity	Antioxidant activity	Reference
	Myricetin		Myricetin was tested against MRSA strain and it showed inhibitory activity with MIC of 128 µg/mL, MIC of 128 µg/mL against vancomycin-resistant *enterococci* and 32 µg/mL against MDR *B. cepacia*. In vivo evaluations using *G. mellonella* confirmed the efficiency of oxacillin combined with myricetin against MRSA-infected larvae compared to controls, increasing host survival by 20%	The authors reported 71.5% DPPH radical scavenging activity at 1 mg/mL withIC_{50} value of 9 µg/mL	Pinto et al. (2020), Qu et al. (2006) and Xu and Lee (2001)
	Plumbagin		It demonstrated a MIC of 0.25–4 µg/mL against all tested MDR and extensively drug-resistant *M. tuberculosis* strains	Plumbagin exhibited a 41% inhibitory rate in scavenging DPPH radicals	Dey et al. (2014) and Tan et al. (2011)
	Quercetin		They tested quercetin against MRSA strain that exhibits antibacterial activity with MIC of 256 µg/mL. In vivo testing showed an increase in survival rate by 50% in MRSA-infected mouse models when treated with quercetin	They reported the radical scavenging activity of quercetin via DPPH assay	Jing et al. (2022), Wang et al. (2021) and Xu and Lee (2001)
	Rutin		The authors combined rutin with carbon dots and tested them against MRSA strain and found it to be active with MIC of 32 µg/mL	Rutin exhibited strong DPPH radical scavenging activity with a 90.4% inhibition at the concentration of 0.05 mg/ml	Lang et al. (2024) and Yang et al. (2008)

Table 1 continued

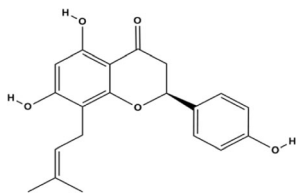
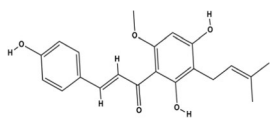
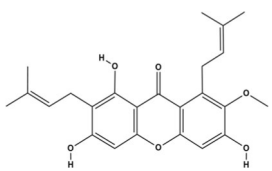
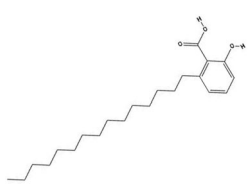
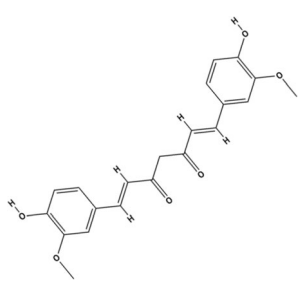
Chemical class	Phytochemical	Compound structure	Antimicrobial activity	Antioxidant activity	Reference
	Sophoraflavanone B		Sophoraflavanone B was tested for its antibacterial efficacy against several MRSA strains and showed MICs between 15.6–31.25 μg/mL	The authors reported moderate antioxidant activities of sophoraflavanone B against Fe^{2+}/cysteine-induced toxicity at a concentration of 0.1 μM, with inhibition of 72.49%	Mun et al. (2014) and Zhu et al. (2018)
	Xanthohumol		The authors reported antibacterial activity with a MIC of 4 μg/mL against MRSA, and MICs of 2 μg/mL against MDR *S. epidermidis* and *S. capitis*, respectively	They showed the activity of the compound using Oxygen radical absorbance capacity (ORAC) and found that the inhibition was 4.2X greater than vitamin C and vitamin E	Bogdanova et al. (2018) and Yamaguchi et al. (2009)
Non-flavonoid phenolics	α-mangostin		The authors reported the antibacterial efficacy of the compound against various MRSA strains, which had a MIC value between 1.57 and 12.5 μg/mL. In vivo study reported an increase in the survival rate by 75% in MRSA-infected *G. mellonella*	The researchers evaluated the antioxidant properties of α-mangostin through FRAP and DPPH assays, finding a FRAP activity level of 344.60 μM Fe (II)/g DM and an IC_{50} value of 20.64 μg/mL in the DPPH assay	Felix et al. (2022), Ghasemzadeh et al. (2018) and Linuma et al. (1996)
	Anacardic acid		The authors demonstrated antibacterial activity of the compound against two strains of MRSA ATCC 33591 and ATCC 33592 and found a MIC of 6.25 μg/mL for each bacterial strain	They demonstrated that anacardic acid effectively inhibited formazan formation, showing an 82% reduction in superoxide anion production at a concentration of 30 μg/ml	Kubo et al. (2006) and Muroi and Kubo (1996)
	Curcumin		The authors evaluated antibacterial efficacy against four MDR *S. aureus* strains, reporting MICs of 125–250 μg/mL. In vivo testing on Vancomycin-resistant *S. aureus*-infected rats, both normal and immunocompromised, showed a reduction in bacterial load with daily curcumin treatment combined with light irradiation	The authors found that curcumin exhibited antioxidant activity, with 28.4% effectiveness against H_2O_2, 56.7% in Fe ion chelation, and 42.7% in superoxide scavenging	Ak and Gülçin (2008), Akhtar et al. (2021) and Mun et al. (2014)

Table 1 continued

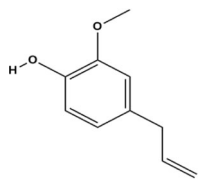
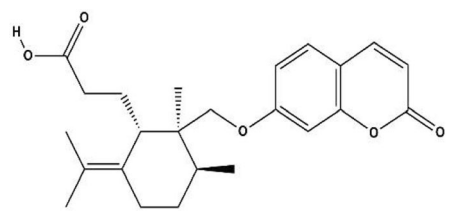
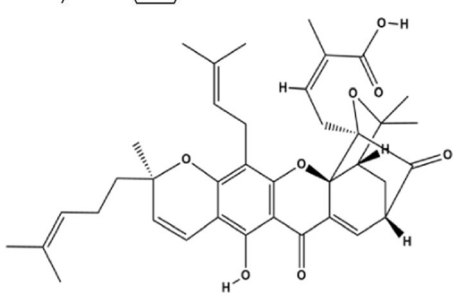
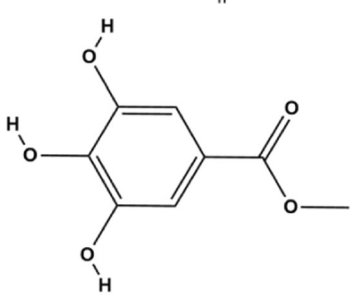
Chemical class	Phytochemical	Compound structure	Antimicrobial activity	Antioxidant activity	Reference
	Eugenol		The study investigated eugenol's antibacterial effects on MRSAand found a MIC value ranging between 0.01% and 0.04%. In vivo results demonstrated that a sub-MIC dose of eugenol inhibited MRSA growth by 88% in an infected rat model	The authors evaluated eugenol's antioxidant properties, finding it capable of scavenging DPPH, ABTS, and DMPD, highlighting its effectiveness as a potent antioxidant agent	Gülçin (2011) and Yadav et al. (2015)
	Galbanic acid		The authors demonstrated the antibacterial activity of galbanic acid against several tetracycline-resistant *S. aureus* strains, with MICs ranging from 80 to 10 µg/mL	The authors evaluated galbanic acid for its antioxidant properties and found it to effectively inhibit DPPH and ABTS free radicals, with IC_{50} values of 180 µg/mL and 60 µg/mL, respectively	Bazzaz et al. (2010) and Sajjadi et al. (2019)
	Gambogic acid		The author demonstrated that gambogic acid exhibited growth-inhibitory effects against multiple MRSA ATCC33591 clinical isolates, with MICs ranging from 0.5 to 4 µg/mL, highlighting its efficacy at low concentrations	The authors demonstrated that gambogic acid exhibits antioxidant activity against glioblastoma cells, leading to increased ROS levels in T98G cells	Hua et al. (2019) and Thida et al. (2016)
	Methyl gallate		The authors showed the antibacterial activity of methyl gallate against MRSA strain ATCC33591 and found MIC at 250 µg/mL	The authors demonstrated that methyl gallate exhibits antioxidant activity in Madin-Darby canine kidney (MDCK) cells by scavenging intracellular ROS, inhibiting lipid peroxidation, and preserving glutathione levels	Chew et al. (2018) and Hsieh et al. (2004)

Table 1 continued

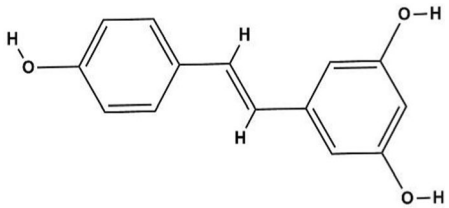
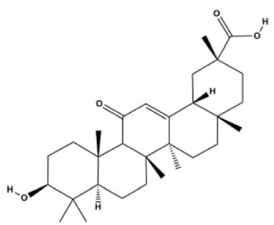
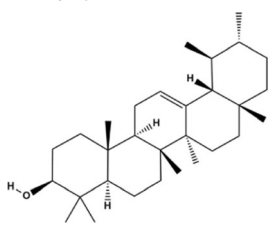
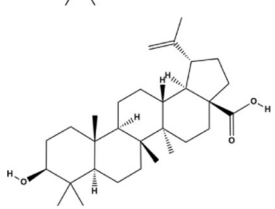
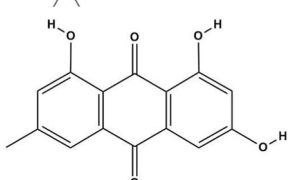
Chemical class	Phytochemical	Compound structure	Antimicrobial activity	Antioxidant activity	Reference
	Resveratrol		The compound had a MIC of 32–128 µg/mL against MDR *K. pneumoniae* and *E. coli*, and increased wound healing by 64.25% by day 14 in rats, with a rapid decrease in *S. aureus* bacterial load compared to controls	Resveratrol showed an EC_{50} of 6.96 µg/mL for radical cation scavenging, 71.8% inhibition of superoxide anion generation, and strong hydrogen peroxide scavenging activity	Gülçin (2010), Liu et al. (2020) and Shevelev et al. (2020)
Terpenoids	18β-Glycyrrhetinic acid		They tested 18β-glycyrrhetinic acid against clinical isolate of MRSA strain USA400 and found MIC to be at 60 µg/mL	The authors evaluated the antioxidant effects of 18β-Glycyrrhetinic acid by giving it orally at 100 mg/kg doses, observing a reduction in lipid peroxidation and an improvement in the rats' antioxidant levels	Kalaiarasi and Pugalendi (2011), Long et al. (2013) and Wang et al. (2015)
	α-Amyrin		They showed the efficacy of the α-amyrin against various MRSA strains and the MICs were between 2 and 64 µg/mL	The authors evaluated the antioxidant activity of a combination of α-amyrin and β-amyrin using the DPPH and ABTS assays, reporting IC_{50} values of 125.55 µg/mL and 155.28 µg/mL for each test, respectively	Chung et al. (2014) and Viet et al. (2021)
	Betulinic acid		The authors reported the antibacterial activity of betulinic acid against various strains of MRSA and the MICs were between 4 and 64 µg/mL	The authors evaluated the antioxidant potential of betulinic acid using the DPPH assay and determined an IC_{50} value of 0.141 mg/mL	Adesanwo et al. (2013) and Chung et al. (2014)
	Emodin		It showed a MIC of 4–16 µg/mL against all tested MDR and extensively drug-resistant *M. tuberculosis* strains	Emodin showed 30% inhibition of induced lipid peroxidation using linoleic acid as a target	Dey et al. (2014) and Vargas et al. (2004)

Table 1 continued

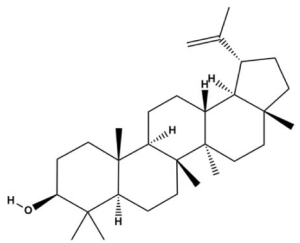
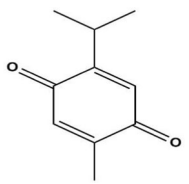
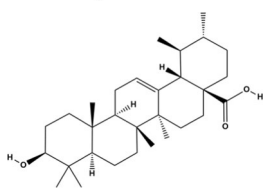
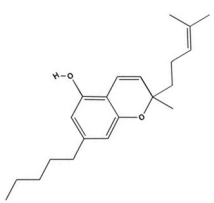
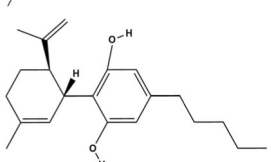
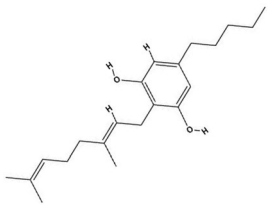
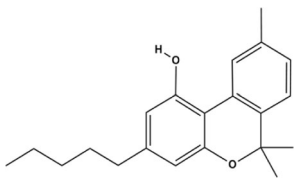
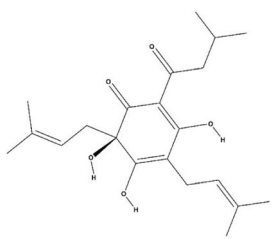
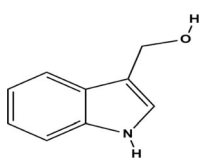
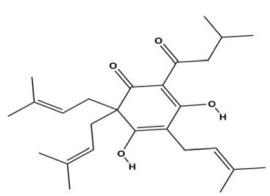
Chemical class	Phytochemical	Compound structure	Antimicrobial activity	Antioxidant activity	Reference
	Lupeol		The authors found that the MIC of lupeol against the MRSA ATCC43300 was greater than 128 µg/mL	Authors reported that the lupeol treatment caused decreases in nitric oxide levels, with a concomitant increase in antioxidant levels, and a decrease in the level of thiobarbituric acid-ROS	Gupta et al. (2012) and Wang et al. (2016)
	Thymoquinone		The compound showed a MIC of 4–16 µg/mL against all tested MDR and extensively drug-resistant *M. tuberculosis strains* in vitro	It exhibited antioxidant activity with an IC_{50} value of 199.33 ± 88.02 using the DPPH assay after applying the vapours of the phytochemical	Dey et al. (2014) and Houdkova et al. (2020)
	Ursolic acid		The authors reported that ursolic acid showed antibacterial activity with MICs of 4–8 µg/mL against various MRSA strains and 0.1 mg/mL against carbapenem-resistant *E. cloacae*	The authors evaluated ursolic acid's antioxidant activity via the DPPH assay, reporting a strong radical scavenging effect with an IC_{50} of 5.97 mg/mL	Do Nascimento et al. (2014) and Kim et al. (2012)
Cannabinoids	Cannabichromene		The authors demonstrated cannabichromene's growth-inhibitory effects against MRSA XU212, with MICs ranging from 1 to 2 µg/mL	The compound was tested for antioxidant activity, revealing an antioxidant profile of 0.71 ± 0.01 µg/g	Appendino et al. (2008) and Stasilowicz-Krzemien et al. (2023)
	Cannabidiol		The authors showed that the MICs of cannabidiol against several clinical isolates of MRSA XU212 strain were from 0.5 to 1 µg/mL	The authors evaluated the antioxidant potential of cannabidiol, reporting an antioxidant profile of 184.51 ± 5.61 µg/g	Appendino et al. (2008) and Stasilowicz-Krzemien et al. (2023)

Table 1 continued

Chemical class	Phytochemical	Compound structure	Antimicrobial activity	Antioxidant activity	Reference
	Cannabigerol		The antibacterial activity of the cannabigerol of MRSA XU212 strain was reported to be with MICs in the range of 1–2 µg/mL. In vivo testing on MRSA-infected murine model showed the inhibition of biofilms at MIC of 2 µg/mL	The authors documented the antioxidant profile of cannabigerol, reporting a value of 6.10 ± 0.21 µg/g	Appendino et al. (2008) and Stasilowicz-Krzemien et al. (2023)
	Cannabinol		The antibacterial activity of the cannabinol against MRSA strain XU212 reported MIC of 1 µg/ml	The authors documented the antioxidant profile of cannabinol and reported a value of 0.51 ± 0.01 µg/g	Appendino et al. (2008) and Stasilowicz-Krzemien et al. (2023)
Miscellaneous	Humulone		The authors reported antibacterial activity with a MIC of 15 µg/mL against MRSA, and MICs of 30 and 15 µg/mL against MDR *S. epidermidis* and *S. capitis*, respectively	They performed ORAC assay and determined an ORAC value of 1.2 TE for humulone	Bogdanova et al. (2018) and Yamaguchi et al. (2009)
	Indole-3-carbinol		They showed the antibacterial activity of various MDR strains of *S. aureus* with MICs in the range of 400–800 µg/mL	The authors evaluated the antioxidant activity of Indole-3-carbinol against lipid peroxidation induced by CCl_4 in mice, finding it to be a natural antioxidant with an IC_{50} value ranging from 35 to 40 µM	Monte et al. (2014) and Shertzer et al. (1988)
	Lupulone		The authors reported antibacterial activity with a MIC of 0.5 µg/mL against MRSA, and MICs of 4 and 0.5 µg/mL against MDR *S. epidermidis* and *S. capitis*, respectively, and in vivo studies showed a significant reduction in bacterial load in MRSA-infected wounds	Lupulone demonstrated 1.9X higher TE activity than Vitamin C and Vitamin E in the ORAC assay	Bogdanova et al. (2018), Sleha et al. (2021) and Yamaguchi et al. (2009)

et al. 2015). Similarly, α-amyrin and betulinic acid demonstrated broad antibacterial efficacy against MRSA strains, with MICs ranging from 2 to 64 μg/mL and 4 to 64 μg/mL, respectively (Chung et al. 2014). Ursolic acid exhibited a MIC range of 4–8 μg/mL against MRSA strains and 0.1 mg/mL against carbapenem-resistant *Enterobacter cloacae* (Kim et al. 2012) The antioxidant activity of these terpenoids has been reported by several studies (Adesanwo et al. 2013; do Nascimento et al. 2014; Viet et al. 2021). A study by Refaat et al. (2022) reported a moderate antibacterial activity of lupeol against MRSA with a MIC greater than 128 μg/mL. Emodin and thymoquinone exhibited strong antibacterial efficacy against MDR and extensively drug-resistant *M. tuberculosis*, with MICs ranging from 4 to 16 μg/mL, along with significant antioxidant activity (Dey et al. 2014; Houdkova et al. 2020; Vargas et al. 2004). These dual-active terpenoid compounds are capable of neutralizing ROS, which reduces oxidative damage to bacterial proteins, lipids, and DNA, thus promoting bacterial resistance. Terpenoids also inhibit ROS-induced defence mechanisms, including stress pathways and efflux pumps, which increases bacterial susceptibility to antibiotics. Terpenoids enhance antibiotic efficacy by reducing oxidative damage and inhibiting biofilm formation, ultimately boosting antimicrobial activity (Dias et al. 2023; Pancu et al. 2021).

Cannabinoids

Cannabinoids are bioactive compounds mainly derived from *Cannabis sativa*, demonstrating significant antibacterial activity, particularly against gram-positive pathogens such as *S. aureus* and *Streptococcus pneumoniae* (Karas et al. 2020). Their antibacterial action is attributed to several mechanisms, including disruption of bacterial cell membranes, inhibition of biofilm formation, interference with metabolic pathways, specifically those involved in respiration and nutrient uptake, and potential inhibition of bacterial efflux pumps, which may enhance the intracellular retention of antibiotics. Recent evidence suggests that cannabinoids may also disrupt bacterial signalling and cell division, although these pathways remain under investigation (Ribeiro et al. 2024). Notable cannabinoids such as cannabidiol (CBD), cannabigerol (CBG), cannabichromene (CBC), and cannabinol (CBN) have exhibited efficacy against MDR strains, including MRSA, indicating their potential as adjuncts in the treatment of antimicrobial-resistant infections. A study demonstrated that CBC possesses significant antibacterial activity against MRSA clinical isolates, such as strain XU212, with a MIC in the range of 1–2 μL (Appendino et al. 2008). This notable efficacy suggests that CBC may serve as a valuable antimicrobial agent, especially given the challenges of treating MRSA infections. CBD shows even greater antibacterial potency, with MIC range of 0.5–1 μg/mL against MRSA, highlighting its potential as a powerful antimicrobial compound. CBG also demonstrates antibacterial activity along with biofilm inhibition capability, displaying a MIC range of 1–2 μg/mL against MRSA isolates. Biofilms pose a considerable challenge in chronic infections due to their resistance to conventional antibiotics. Hence, the biofilm-disrupting capacity of CBG highlights its potential utility against persistent bacterial infections. Finally, CBN has been found to be effective against MRSA, with MIC of 1 μg/mL.

The antioxidant activity of these cannabinoids has also been reported by Stasilowicz-Krzemien et al. (2023), supporting their therapeutic utility as dual-active compounds for mitigating ROS-induced defence systems in bacteria (Pagano et al. 2023). Cannabinoids disrupt biofilm formation by altering the redox environment within these protective bacterial structures, increasing bacterial vulnerability to both antibiotics and immune responses (Sionov and Steinberg 2022). Further research is required to elucidate their molecular targets and to optimize therapeutic applications fully. This multifaceted action underscores the potential of cannabinoids in enhancing antibiotic effectiveness against MDR bacteria.

Others

Humulone, an organic acid predominantly found in mature hop resin, exhibits both antibacterial and antioxidant properties. The effectiveness of humulone against MRSA, as well as MDR strains of *Staphylococcus epidermidis* and *Staphylococcus capitis*, has been reported, with MICs of 15 μg/mL, 30 μg/mL, and 15 μg/mL, respectively (Bogdanova et al. 2018).

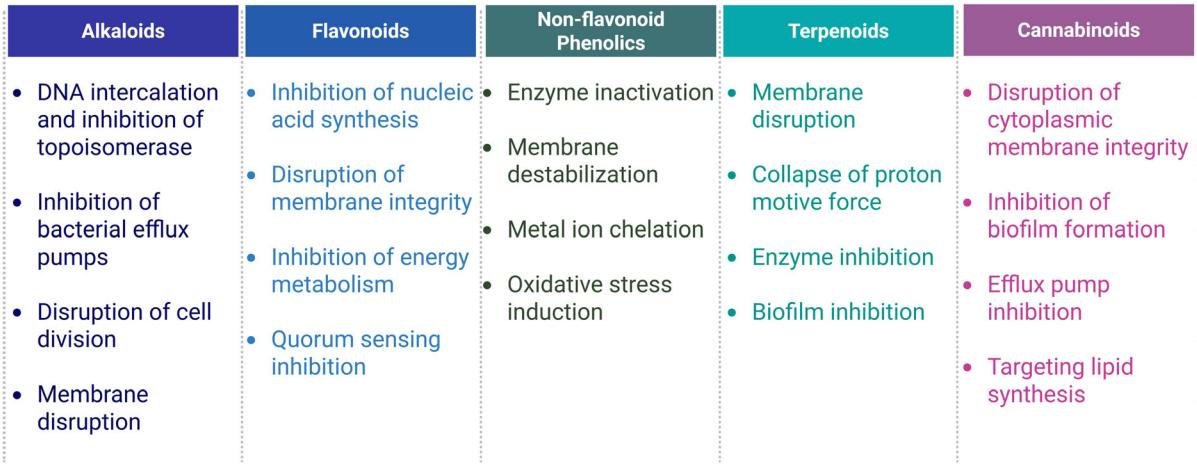


Fig. 4 Overview of the principal antibacterial mechanisms exhibited by major phytochemical classes: alkaloids, flavonoids, non-flavonoid phenolics, terpenoids, and cannabinoids based on evidence from reported literature

Similarly, lupulone, a beta-acid also found in hops, showed even greater efficacy against MRSA, *S. epidermidis*, and *S. capitis*, achieving MICs of 0.5 µg/mL, 4 µg/mL, and 0.5 µg/mL, respectively. In addition, Yamaguchi et al. 2009 documented the notable antioxidant activity of these hop-derived compounds, highlighting their high oxygen radical absorbance capacity. Indole-3-carbinol, primarily sourced from cruciferous vegetables, is recognized for its antioxidant properties (Shertzer et al. 1988). Although its antibacterial effect is more moderate, it demonstrated efficacy against various MRSA strains, with MICs ranging from 400 to 800 µg/mL (Monte et al. 2014). Together, these findings underscore the potential of humulone, lupulone, and indole-3-carbinol as dual-active agents capable of inhibiting microbial growth while preventing ROS-induced signalling in bacteria. These compounds represent promising candidates for treating infections associated with antibiotic-resistant bacteria. Figure 4 depicts an overview of the key antibacterial mechanisms of major phytochemical classes described in this review based on previous evidence. A large number of natural antioxidant compounds have demonstrated effectiveness against MDR bacteria, and these compounds are summarized in Table 1.

Conclusion

The evolution of antibiotic resistance is a complex process driven by intricate gene networks and the dynamic interplay between genetic variation, molecular mechanisms, and ecological factors. A key element in this process is the role of ROS, which act as signalling molecules that activate multiple pathways to enhance bacterial resilience to antibiotic stress. The continued rise of single and MDR bacterial strains, particularly those that are methicillin, vancomycin, tetracycline, and carbapenem-resistant, poses a significant global health threat. This situation emphasizes the urgent need for the development of novel antimicrobial agents.

Oxidative stress, driven by ROS, plays a crucial role in the selection of resistant bacterial strains, though the exact involvement of oxidative stress in antibiotic-induced cell death remains a topic of debate. This scenario highlights the need for innovative therapies that combine antibacterial and antioxidant properties within a single structure. Natural products such as alkaloids, flavonoids, phenolics, and terpenoids exemplify this approach due to their direct antibacterial activity, strong antioxidant effects, antibiofilm activity, and ability to synergize with antibiotics. These properties could prove valuable not only in combating bacterial infections but also in reducing virulence and preventing oxidative damage in various industries, including medical, food, and cosmetics.

The development of synthetic molecular hybrids that combine antioxidant and antibacterial properties offers a promising strategy for future drug design. These dual-active molecules have the potential to enhance efficacy, introduce new mechanisms of action, and help suppress resistance by maintaining a single pharmacokinetic profile. This approach provides a key solution in the fight against drug-resistant pathogens. Synthetic antibiotics offer rapid therapeutic effects; however, they are increasingly associated with severe side effects, such as gastrotoxicity and nephrotoxicity, as well as the acceleration of resistance. In contrast, natural antioxidants, including baicalein, berberine, betulinic acid, caffeic acid, cannabinol, chelerythrine, curcumin, fangchinoline, piperine, α-mangostin, 18β-glycyrrhetinic acid, α-amyrin, lupeol, and ursolic acid, exhibit significant antibacterial potential without promoting resistance. These compounds are positioned as promising candidates for future antimicrobial therapies. While their antibacterial action may be slower, their prolonged, non-toxic effects and low propensity for resistance make them strong alternatives. Continued research into the antibacterial properties of isolated natural antioxidants will be essential for optimising their use and reducing reliance on conventional synthetic antibiotics. Notably, most existing research has focused on the antibacterial efficacy of these compounds against MRSA. To fully comprehend their therapeutic potential, further studies are needed to elucidate their activity against other resistant pathogens.

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Declarations

Conflict of interest The authors declare no conflict of interest.

References

Abdelraheem WM, Refaie MMM, Yousef RKM et al (2022) Assessment of antibacterial and anti-biofilm effects of vitamin C against *Pseudomonas aeruginosa* clinical isolates. Front Microbiol. https://doi.org/10.3389/fmicb.2022.847449

Adesanwo JK, Makinde OO, Obafemi CA (2013) Phytochemical analysis and antioxidant activity of methanol extract and betulinic acid isolated from the roots of *Tetracera potatoria*. J Pharm Res 6:903–907. https://doi.org/10.1016/j.jopr.2013.09.003

Ahmad ZA, Ahmed MB, AL-Ashou WMO, (2023) Antibacterial effect of green tea extract epigallocatechin gallate against *Enterococcus faecalis* as intracanal medicament (an *in vitro* study). Iraqi Dent J. https://doi.org/10.46466/idj.v45i1.277

Ak T, Gülçin İ (2008) Antioxidant and radical scavenging properties of curcumin. Chem Biol Interact 174:27–37. https://doi.org/10.1016/j.cbi.2008.05.003

Akhtar F, Khan AU, Misba L et al (2021) Antimicrobial and antibiofilm photodynamic therapy against vancomycin resistant *Staphylococcus aureus* (VRSA) induced infection *in vitro* and *in vivo*. Eur J Pharm Biopharm 160:65–76. https://doi.org/10.1016/j.ejpb.2021.01.012

Alavi M, Hamblin MR, Aghaie E et al (2023) Antibacterial and antioxidant activity of catechin, gallic acid, and epigallocatechin-3-gallate: focus on nanoformulations. Cell Mol Biomed Rep 3:62–72. https://doi.org/10.55705/cmbr.2022.353962.1052

Alfei S, Schito GC, Schito AM, Zuccari G (2024) Reactive oxygen species (ROS)-mediated antibacterial oxidative therapies: available methods to generate ROS and a novel option proposal. Int J Mol Sci 25:7182. https://doi.org/10.3390/ijms25137182

Al-Ghanayem AA, Alhussaini MS, Asad M, Joseph B (2024) Kaempferol promotes wound-healing in diabetic rats

through antibacterial and antioxidant effects, devoid of proliferative action. Biosci J 40:e40015. https://doi.org/10.14393/BJ-v40n0a2024-68974

Ali Raza Naqvi S, Nadeem S, Komal S et al (2019) Antioxidants: natural antibiotics. Antioxid. https://doi.org/10.5772/intechopen.84864

Antimicrobial resistance in the EU/EEA (EARS-Net) (2020) Annual Epidemiological Report for 2020. Accessed 16 Dec 2024

Appendino G, Gibbons S, Giana A et al (2008) Antibacterial cannabinoids from *Cannabis sativa*: a structure−activity study. J Nat Prod 71:1427–1430. https://doi.org/10.1021/np8002673

Baharoglu Z, Mazel D (2011) *Vibrio cholerae* triggers SOS and mutagenesis in response to a wide range of antibiotics: a route towards multiresistance. Antimicrob Agents Chemother 55:2438–2441. https://doi.org/10.1128/aac.01549-10

Bazzaz BSF, Memariani Z, Khashiarmanesh Z et al (2010) Effect of galbanic acid, a sesquiterpene coumarin from *Ferula szowitsiana*, as an inhibitor of efflux mechanism in resistant clinical isolates of *Staphylococcus aureus*. Braz J Microbiol 41:574–580. https://doi.org/10.1590/S1517-83822010000300006

Begum S, Naqvi SQZ, Ahmed A et al (2012) Antimycobacterial and antioxidant activities of reserpine and its derivatives. Nat Prod Res 26:2084–2088. https://doi.org/10.1080/14786419.2011.625502

Bhagya N, Chandrashekar KR (2016) Tetrandrine: a molecule of wide bioactivity. Phytochem 125:5–13. https://doi.org/10.1016/j.phytochem.2016.02.005

Bizzini A, Zhao C, Auffray Y, Hartke A (2009) The *Enterococcus faecalis* superoxide dismutase is essential for its tolerance to vancomycin and penicillin. J Antimicrob Chemother 64:1196–1202. https://doi.org/10.1093/jac/dkp369

Blair JMA, Bavro VN, Ricci V et al (2015) AcrB drug-binding pocket substitution confers clinically relevant resistance and altered substrate specificity. Proc Natl Acad Sci 112:3511–3516. https://doi.org/10.1073/pnas.1419939112

Bogdanova K, Röderova M, Kolar M et al (2018) Antibiofilm activity of bioactive hop compounds humulone, lupulone and xanthohumol toward susceptible and resistant staphylococci. Res Microbiol 169:127–134. https://doi.org/10.1016/j.resmic.2017.12.005

Carpenter BM, Whitmire JM, Merrell DS (2009) This is not your mother's repressor: the complex role of fur in pathogenesis. Infect Immun 77:2590–2601. https://doi.org/10.1128/iai.00116-09

Centers for Disease Control and Prevention (U.S.) (2019) Antibiotic resistance threats in the United States. Centers for Disease Control and Prevention (U.S.)

Chan BCL, Ip M, Lau CBS et al (2011) Synergistic effects of baicalein with ciprofloxacin against NorA over-expressed methicillin-resistant *Staphylococcus aureus* (MRSA) and inhibition of MRSA pyruvate kinase. J Ethnopharmacol 137:767–773. https://doi.org/10.1016/j.jep.2011.06.039

Chaturvedi P, Shukla P, Giri BS et al (2021) Prevalence and hazardous impact of pharmaceutical and personal care products and antibiotics in environment: a review on emerging contaminants. Environ Res 194:110664. https://doi.org/10.1016/j.envres.2020.110664

Chew YL, Mahadi AM, Wong KM, Goh JK (2018) Anti-methicillin-resistance Staphylococcus aureus (MRSA) compounds from Bauhinia kockiana Korth. And their mechanism of antibacterial activity. BMC Complement Altern Med 18:70. https://doi.org/10.1186/s12906-018-2137-5

Chinemerem Nwobodo D, Ugwu MC, Oliseloke Anie C et al (2022) Antibiotic resistance: the challenges and some emerging strategies for tackling a global menace. J Clin Lab Anal 36:e24655. https://doi.org/10.1002/jcla.24655

Cho Y-S, Schiller NL, Oh K-H (2008) Antibacterial effects of green tea polyphenols on clinical isolates of Methicillin-Resistant *Staphylococcus aureus*. Curr Microbiol 57:542–546. https://doi.org/10.1007/s00284-008-9239-0

Chung PY, Chung LY, Navaratnam P (2014) Potential targets by pentacyclic triterpenoids from *Callicarpa farinosa* against methicillin-resistant and sensitive *Staphylococcus aureus*. Fitoter 94:48–54. https://doi.org/10.1016/j.fitote.2014.01.026

Dawan J, Ahn J (2022) Bacterial stress responses as potential targets in overcoming antibiotic resistance. Microorg 10:1385. https://doi.org/10.3390/microorganisms10071385

Dey D, Ray R, Hazra B (2014) Antitubercular and antibacterial activity of quinonoid natural products against multi-drug resistant clinical isolates. Phytother Res 28:1014–1021. https://doi.org/10.1002/ptr.5090

Dias PMS, Portela JC, Gondim JEF et al (2023) Soil attributes and their interrelationships with resistance to root penetration and water infiltration in areas with different land uses in the Apodi Plateau, semiarid region of Brazil. Agricu 13:1921. https://doi.org/10.3390/agriculture13101921

Do Nascimento PGG, Lemos TLG, Bizerra AMC et al (2014) Antibacterial and antioxidant activities of Ursolic acid and derivatives. Mol 19:1317–1327. https://doi.org/10.3390/molecules19011317

Drlica K, Zhao X (2021) Bacterial death from treatment with fluoroquinolones and other lethal stressors. Expert Rev Anti-Infect Ther 19:601–618. https://doi.org/10.1080/14787210.2021.1840353

Duarte V, Latour J-M (2010) PerR vs OhrR: selective peroxide sensing in *Bacillus subtilis*. Mol Biosyst 6(2):316–323

Dwyer DJ, Kohanski MA, Collins JJ (2009) Role of reactive oxygen species in antibiotic action and resistance. Curr Opin Microbiol 12:482–489. https://doi.org/10.1016/j.mib.2009.06.018

Eumkeb G, Sakdarat S, Siriwong S (2010) Reversing β-lactam antibiotic resistance of *Staphylococcus aureus* with galangin from *Alpinia officinarum* Hance and synergism with ceftazidime. Phytomedicine 18:40–45. https://doi.org/10.1016/j.phymed.2010.09.003

Ezraty B, Gennaris A, Barras F, Collet J-F (2017) Oxidative stress, protein damage and repair in bacteria. Nat Rev Microbiol 15:385–396. https://doi.org/10.1038/nrmicro.2017.26

Fang FC (2004) Antimicrobial reactive oxygen and nitrogen species: concepts and controversies. Nat Rev Microbiol 2:820–832. https://doi.org/10.1038/nrmicro1004

Felix L, Mishra B, Khader R et al (2022) *In vitro* and *in vivo* bactericidal and antibiofilm efficacy of alpha mangostin against *Staphylococcus aureus* persister cells. Front Cell Infect Microbiol. https://doi.org/10.3389/fcimb.2022.898794

Franceschelli S, Pesce M, Vinciguerra I et al (2011) Licocalchone-C extracted from *Glycyrrhiza glabra* inhibits lipopolysaccharide-interferon-γ inflammation by improving antioxidant conditions and regulating inducible nitric oxide synthase expression. Mol 16:5720–5734. https://doi.org/10.3390/molecules16075720

Fu S, Yang H, Tu J et al (2017) Separation and activity against drug-resistant bacteria of tetrandrine and fangchinoline in lipophilic akaloids from *Stephania teandra*. Der Chemica Sinica 8:298–304

Gangwar B, Kumar S, Darokar MP, et al (2023) Antioxidant phytochemicals as novel therapeutic strategies against drug-resistant bacteria. In: Importance of oxidative stress and antioxidant system in health and disease. IntechOpen

Ghasemzadeh A, Jaafar HZE, Baghdadi A, Tayebi-Meigooni A (2018) Alpha-mangostin-rich extracts from mangosteen pericarp: optimization of green extraction protocol and evaluation of biological activity. Mol 23:1852. https://doi.org/10.3390/molecules23081852

Goldová J, Ulrych A, Hercík K et al (2011) A eukaryotic-type signalling system of *Pseudomonas aeruginosa* contributes to oxidative stress resistance, intracellular survival and virulence. BMC Genomics 12:437. https://doi.org/10.1186/1471-2164-12-437

Grant SS, Hung DT (2013) Persistent bacterial infections, antibiotic tolerance, and the oxidative stress response. Virulence 4:273–283. https://doi.org/10.4161/viru.23987

Green J, Rolfe MD, Smith LJ (2014) Transcriptional regulation of bacterial virulence gene expression by molecular oxygen and nitric oxide. Virulence 5:794–809. https://doi.org/10.4161/viru.27794

Gülçin İ (2010) Antioxidant properties of resveratrol: a structure–activity insight. Innov Food Sci Emerg Technol 11:210–218. https://doi.org/10.1016/j.ifset.2009.07.002

Gülçin İ (2011) Antioxidant activity of eugenol: a structure-activity relationship study. J Med Food 14:975–985. https://doi.org/10.1089/jmf.2010.0197

Gupta R, Sharma AK, Sharma MC et al (2012) Evaluation of antidiabetic and antioxidant potential of lupeol in experimental hyperglycaemia. Nat Prod Res 26:1125–1129. https://doi.org/10.1080/14786419.2011.560845

Händel N, Hoeksema M, Freijo Mata M et al (2016) Effects of stress, reactive oxygen species, and the SOS response on de novo acquisition of antibiotic resistance in *Escherichia coli*. Antimicrob Agents Chemother 60:1319–1327. https://doi.org/10.1128/aac.02684-15

Harms A, Maisonneuve E, Gerdes K (2016) Mechanisms of bacterial persistence during stress and antibiotic exposure. Sci 354:aaf4268. https://doi.org/10.1126/science.aaf4268

Heim KE, Tagliaferro AR, Bobilya DJ (2002) Flavonoid antioxidants: chemistry, metabolism and structure-activity relationships. J Nutr Biochem 13:572–584. https://doi.org/10.1016/S0955-2863(02)00208-5

Hengge-Aronis R (2000) The general stress response in *Escherichia coli*. Bacterial stress responses pp 161–178

Houdkova M, Albarico G, Doskocil I et al (2020) Vapors of volatile plant-derived products significantly affect the results of antimicrobial, antioxidative and cytotoxicity microplate-based assays. Mol 25:6004. https://doi.org/10.3390/molecules25246004

Hsieh T-J, Liu T-Z, Chia Y-C et al (2004) Protective effect of methyl gallate from *Toona sinensis* (*Meliaceae*) against hydrogen peroxide-induced oxidative stress and DNA damage in MDCK cells. Food Chem Toxicol 42:843–850. https://doi.org/10.1016/j.fct.2004.01.008

Hua X, Jia Y, Yang Q et al (2019) Transcriptional analysis of the effects of gambogic acid and neogambogic acid on methicillin-resistant *Staphylococcus aureus*. Front Pharmacol. https://doi.org/10.3389/fphar.2019.00986

Iinuma M, Tosa H, Tanaka T et al (1996) Antibacterial activity of xanthones from Guttiferaeous plants against Methicillin-resistant *Staphylococcus aureus*. J Pharm Pharmacol 48:861–865. https://doi.org/10.1111/j.2042-7158.1996.tb03988.x

Imlay JA (2013) The molecular mechanisms and physiological consequences of oxidative stress: lessons from a model bacterium. Nat Rev Microbiol 11:443–454. https://doi.org/10.1038/nrmicro3032

Jain S, Tripathi S, Tripathi PK (2023) Antioxidant and anti-arthritic potential of berberine: *in vitro* and *in vivo* studies. Chin Herb Med 15:549–555. https://doi.org/10.1016/j.chmed.2023.02.007

Jaisin Y, Ratanachamnong P, Wongsawatkul O et al (2020) Antioxidant and anti-inflammatory effects of piperine on UV-B-irradiated human HaCaT keratinocyte cells. Life Sci 263:118607. https://doi.org/10.1016/j.lfs.2020.118607

Javeed M, Rasul A, Hussain G et al (2018) Harmine and its derivatives: biological activities and therapeutic potential in human diseases. Bangladesh J Pharmacol 13:203–213

Jing S, Kong X, Wang L et al (2022) Quercetin reduces the virulence of *S. aureus* by targeting ClpP to protect mice from MRSA-induced lethal pneumonia. Microbiol Spectr 10:e02340-21. https://doi.org/10.1128/spectrum.02340-21

Jubair N, Rajagopal M, Chinnappan S et al (2021) Review on the antibacterial mechanism of plant-derived compounds against multidrug-resistant bacteria (MDR). Evid Based Complement Alternat Med 2021:3663315. https://doi.org/10.1155/2021/3663315

Kalaiarasi P, Pugalendi KV (2011) Protective effect of 18β-glycyrrhetinic acid on lipid peroxidation and antioxidant enzymes in experimental diabetes. J Pharm Res 4(1):107–111

Karas JA, Wong LJM, Paulin OKA et al (2020) The antimicrobial activity of cannabinoids. Antibiot 9:406. https://doi.org/10.3390/antibiotics9070406

Kaushik V, Tiwari M, Tiwari V (2022) Interaction of RecA mediated SOS response with bacterial persistence, biofilm formation, and host response. Int J Biol Macromol 217:931–943. https://doi.org/10.1016/j.ijbiomac.2022.07.176

Khameneh B, Iranshahy M, Ghandadi M et al (2015) Investigation of the antibacterial activity and efflux pump inhibitory effect of co-loaded piperine and gentamicin nanoliposomes in methicillin-resistant *Staphylococcus aureus*. Drug Dev Ind Pharm 41:989–994. https://doi.org/10.3109/03639045.2014.920025

Kim S-G, Kim M-J, Jin D-C et al (2012) Antimicrobial effect of ursolic acid and oleanolic acid against methicillin-resistant *Staphylococcus aureus*. Korean J Microbiol 48:212–215. https://doi.org/10.7845/kjm.2012.029

Kohanski MA, Dwyer DJ, Collins JJ (2010) How antibiotics kill bacteria: from targets to networks. Nat Rev Microbiol 8:423–435. https://doi.org/10.1038/nrmicro2333

Kubo I, Masuoka N, Ha TJ, Tsujimoto K (2006) Antioxidant activity of anacardic acids. Food Chem 99:555–562. https://doi.org/10.1016/j.foodchem.2005.08.023

Kumar S, Abedin MdM, Singh AK, Das S (2020) Role of Phenolic Compounds in Plant-Defensive Mechanisms. In: Lone R, Shuab R, Kamili AN (eds) Plant phenolics in sustainable agriculture, vol 1. Springer, Singapore, pp 517–532

Kvist M, Hancock V, Klemm P (2008) Inactivation of efflux pumps abolishes bacterial biofilm formation. Appl Environ Microbiol 74:7376–7382. https://doi.org/10.1128/AEM.01310-08

Lamontagne Boulet M, Isabelle C, Guay I et al (2018) Tomatidine is a lead antibiotic molecule that targets *Staphylococcus aureus* ATP synthase subunit C. Antimicrob Agents Chemother. https://doi.org/10.1128/aac.02197-17

Lang F, Zhao Q, Sun Z et al (2024) Rutin-loaded carbon dots for management of methicillin-resistant *Staphylococcus aureus* lung infection. ACS Appl Nano Mater 7:10902–10910. https://doi.org/10.1021/acsanm.3c05774

Li H, Zhou X, Huang Y et al (2021) Reactive oxygen species in pathogen clearance: the killing mechanisms, the adaption response, and the side effects. Front Microbiol. https://doi.org/10.3389/fmicb.2020.622534

Liu L, Yu J, Shen X et al (2020) Resveratrol enhances the antimicrobial effect of polymyxin B on *Klebsiella pneumoniae* and *Escherichia coli* isolates with polymyxin B resistance. BMC Microbiol 20:306. https://doi.org/10.1186/s12866-020-01995-1

Long DR, Mead J, Hendricks JM et al (2013) 18β-glycyrrhetinic acid inhibits methicillin-resistant *Staphylococcus aureus* survival and attenuates virulence gene expression. Antimicrob Agents Chemother 57:241–247. https://doi.org/10.1128/aac.01023-12

Lorusso AB, Carrara JA, Barroso CDN et al (2022) Role of efflux pumps on antimicrobial resistance in *Pseudomonas aeruginosa*. Int J Mol Sci 23:15779. https://doi.org/10.3390/ijms232415779

Ludwiczuk A, Skalicka-Woźniak K, Georgiev MI (2017) Chapter 11: Terpenoids. In: Badal S, Delgoda R (eds) Pharmacognosy. Academic Press, Boston, pp 233–266

Luís Â, Silva F, Sousa S et al (2014) Antistaphylococcal and biofilm inhibitory activities of gallic, caffeic, and chlorogenic acids. Biofouling 30:69–79. https://doi.org/10.1080/08927014.2013.845878

Machuca J, Recacha E, Gallego-Mesa B et al (2021) Effect of RecA inactivation on quinolone susceptibility and the evolution of resistance in clinical isolates of *Escherichia coli*. J Antimicrob Chemother 76:338–344. https://doi.org/10.1093/jac/dkaa448

Majtan J, Bohova J, Horniackova M et al (2014) Anti-biofilm effects of honey against wound pathogens *Proteus mirabilis* and *Enterobacter cloacae*. Phytother Res 28:69–75. https://doi.org/10.1002/ptr.4957

Martelli G, Giacomini D (2018) Antibacterial and antioxidant activities for natural and synthetic dual-active compounds. Eur J Med Chem 158:91–105. https://doi.org/10.1016/j.ejmech.2018.09.009

Martins D, Nguyen D, English AM (2019) *Ctt1* catalase activity potentiates antifungal azoles in the emerging opportunistic pathogen *Saccharomyces cerevisiae*. Sci Rep 9:9185. https://doi.org/10.1038/s41598-019-45070-w

Maslowska KH, Makiela-Dzbenska K, Fijalkowska IJ (2019) The SOS system: a complex and tightly regulated response to DNA damage. Environ Mol Mutagen 60:368–384. https://doi.org/10.1002/em.22267

Mendes RE, Mendoza M, Banga Singh KK et al (2013) Regional resistance surveillance program results for 12 Asia-Pacific nations (2011). Antimicrob Agents Chemother 57:5721–5726. https://doi.org/10.1128/aac.01121-13

Mittal A, Kakkar R (2021) The antioxidant potential of retrochalcones isolated from liquorice root: a comparative DFT study. Phytochem 192:112964. https://doi.org/10.1016/j.phytochem.2021.112964

Mohtar M, Johari SA, Li AR et al (2009) Inhibitory and resistance-modifying potential of plant-based alkaloids against methicillin-resistant *Staphylococcus aureus* (MRSA). Curr Microbiol 59:181–186. https://doi.org/10.1007/s00284-009-9416-9

Monte J, Abreu AC, Borges A et al (2014) Antimicrobial activity of selected phytochemicals against *Escherichia coli* and *Staphylococcus aureus* and their biofilms. Pathog 3:473–498. https://doi.org/10.3390/pathogens3020473

Mumtaz L, Farid A, Yousef Alomar S et al (2023) Assesment of polyphenolic compounds against biofilms produced by clinical *Acinetobacter baumannii* strains using *in silico* and *in vitro* models. Saudi J Biol Sci 30:103743. https://doi.org/10.1016/j.sjbs.2023.103743

Mun S-H, Joung D-K, Kim S-B et al (2014) The mechanism of antimicrobial activity of Sophoraflavanone B against methicillin-resistant *Staphylococcus aureus*. Foodborne Pathog Dis 11:234–239. https://doi.org/10.1089/fpd.2013.1627

Munita JM, Arias CA (2016) Mechanisms of antibiotic resistance. Microbiol Spectr. https://doi.org/10.1128/microbiolspec.vmbf-0016-2015

Muroi H, Kubo I (1996) Antibacterial activity of anacardic acid and totarol, alone and in combination with methicillin, against methicillin-resistant *Staphylococcus aureus*. J Appl Bacteriol 80:387–394. https://doi.org/10.1111/j.1365-2672.1996.tb03233.x

Nikaido H (2003) Molecular basis of bacterial outer membrane permeability revisited. Microbiol Mol Biol Rev 67:593–656. https://doi.org/10.1128/mmbr.67.4.593-656.2003

oxell B, Hassan HM (2013) Transcriptional regulation by Ferric Uptake Regulator (Fur) in pathogenic bacteria. Front Cell Infect Microbiol 3:59. https://doi.org/10.3389/fcimb.2013.00059

Pagano C, Savarese B, Coppola L et al (2023) Cannabinoids in the modulation of oxidative signaling. Int J Mol Sci 24:2513. https://doi.org/10.3390/ijms24032513

Pancu DF, Scurtu A, Macasoi IG et al (2021) Antibiotics: conventional therapy and natural compounds with

antibacterial activity—a pharmaco-toxicological screening. Antibiot 10:401. https://doi.org/10.3390/antibiotics10040401

Peralta DR, Adler C, Corbalán NS et al (2016) Enterobactin as part of the oxidative stress response repertoire. PLoS ONE 11:e0157799. https://doi.org/10.1371/journal.pone.0157799

Pérez-Capilla T, Baquero M-R, Gómez-Gómez J-M et al (2005) SOS-independent induction of *dinB* transcription by β-lactam-mediated inhibition of cell wall synthesis in *Escherichia coli*. J Bacteriol 187:1515–1518. https://doi.org/10.1128/jb.187.4.1515-1518.2005

Peschel A (2002) How do bacteria resist human antimicrobial peptides? Trends Microbiol 10:179–186. https://doi.org/10.1016/S0966-842X(02)02333-8

Pinto HB, Brust FR, Macedo AJ, Trentin DS (2020) The antivirulence compound myricetin possesses remarkable synergistic effect with antibacterials upon multidrug resistant *Staphylococcus aureus*. Microb Pathog 149:104571. https://doi.org/10.1016/j.micpath.2020.104571

Pomposiello PJ, Bennik MHJ, Demple B (2001) Genome-wide transcriptional profiling of the *Escherichia coli* responses to superoxide stress and sodium salicylate. J Bacteriol 183:3890–3902. https://doi.org/10.1128/jb.183.13.3890-3902.2001

Ponnusamy K, Ramasamy M, Savarimuthu I, Paulraj MG (2010) Indirubin potentiates ciprofloxacin activity in the NorA efflux pump of *Staphylococcus aureus*. Scand J Infect Dis 42:500–505. https://doi.org/10.3109/00365541003713630

Poole K (2012) Stress responses as determinants of antimicrobial resistance in Gram-negative bacteria. Trends Microbiol 20:227–234. https://doi.org/10.1016/j.tim.2012.02.004

Punchi Hewage AND, Fontenot L, Guidry J et al (2020) Mobilization of iron stored in bacterioferritin is required for metabolic homeostasis in *Pseudomonas aeruginosa*. Pathog 9:980. https://doi.org/10.3390/pathogens9120980

Qi W, Jonker MJ, Leeuw W et al (2023) Reactive oxygen species accelerate de novo acquisition of antibiotic resistance in *E. coli*. Iscience. https://doi.org/10.1016/j.isci.2023.108373

Qin R, Xiao K, Li B et al (2013) The combination of catechin and epicatechin gallate from *Fructus Crataegi* potentiates β-lactam antibiotics against methicillin-resistant *Staphylococcus aureus* (MRSA) *in vitro* and *in vivo*. Int J Mol Sci 14:1802–1821. https://doi.org/10.3390/ijms14011802

Qu G-Z, Si C-L, Wang M-H (2006) Antioxidant constituents from *Leonurus japonicus*. Nat Prod Sci 12:197–200

Radulovic NS, Blagojevic PD, Stojanovic-Radic ZZ, Stojanovic NM (2013) Antimicrobial plant metabolites: structural diversity and mechanism of action. Curr Med Chem 20:932–952. https://doi.org/10.2174/092986713805219136

Randhawa HK, Hundal KK, Ahirrao PN et al (2016) Efflux pump inhibitory activity of flavonoids isolated from *Alpinia calcarata* against methicillin-resistant *Staphylococcus aureus*. Biol 71:484–493. https://doi.org/10.1515/biolog-2016-0073

Rempe CS, Burris KP, Lenaghan SC, Stewart CN (2017) The potential of systems biology to discover antibacterial mechanisms of plant phenolics. Front Microbiol. https://doi.org/10.3389/fmicb.2017.00422

Ribeiro A, Alsayyed R, Oliveira D et al (2024) Cannabinoids from *C. sativa* L.: systematic review on potential pharmacological effects against infectious diseases downstream and multidrug-resistant pathogens. Future Pharmacol 4:590–625. https://doi.org/10.3390/futurepharmacol4030033

Rivero-Cruz JF, Granados-Pineda J, Pedraza-Chaverri J et al (2020) Phytochemical constituents, antioxidant, cytotoxic, and antimicrobial activities of the ethanolic extract of Mexican brown propolis. Antioxid 9:70. https://doi.org/10.3390/antiox9010070

Sajjadi M, Karimi E, Oskoueian E et al (2019) Galbanic acid: Induced antiproliferation in estrogen receptor-negative breast cancer cells and enhanced cellular redox state in the human dermal fibroblasts. J Biochem Mol Toxicol 33:e22402. https://doi.org/10.1002/jbt.22402

Salam MA, Al-Amin MY, Salam MT et al (2023) Antimicrobial resistance: a growing serious threat for global public health. Healthc 11:1946. https://doi.org/10.3390/healthcare11131946

Seaver LC, Imlay JA (2001) Alkyl hydroperoxide reductase is the primary scavenger of endogenous hydrogen peroxide in *Escherichia coli*. J Bacteriol 183:7173–7181. https://doi.org/10.1128/jb.183.24.7173-7181.2001

Shertzer HG, Berger ML, Wilson Tabor M (1988) Intervention in free radical mediated hepatotoxicity and lipid peroxidation by indole-3-carbinol. Biochem Pharmacol 37:333–338. https://doi.org/10.1016/0006-2952(88)90737-X

Shevelev AB, La Porta N, Isakova EP et al (2020) In vivo antimicrobial and wound-healing activity of Resveratrol, Dihydroquercetin, and Dihydromyricetin against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*. Pathog 9:296. https://doi.org/10.3390/pathogens9040296

Silhavy TJ, Kahne D, Walker S (2010) The bacterial cell envelope. Cold Spring Harb Perspect Biol 2:a000414. https://doi.org/10.1101/cshperspect.a000414

Silva-Beltrán NP, Ruiz-Cruz S, Cira-Chávez LA et al (2015) Total phenolic, flavonoid, tomatine, and tomatidine contents and antioxidant and antimicrobial activities of extracts of tomato plant. Int J Anal Chem 2015:284071. https://doi.org/10.1155/2015/284071

Simões M, Bennett RN, Rosa EAS (2009) Understanding antimicrobial activities of phytochemicals against multidrug resistant bacteria and biofilms. Nat Prod Rep 26:746–757. https://doi.org/10.1039/B821648G

Singh V, Pal A, Darokar MP (2015) A polyphenolic flavonoid glabridin: oxidative stress response in multidrug-resistant *Staphylococcus aureus*. Free Radic Biol Med 87:48–57. https://doi.org/10.1016/j.freeradbiomed.2015.06.016

Singh DP (2003) stress Physiology. New Age International

Sinsinwar S, Vadivel V (2020) Catechin isolated from cashew nut shell exhibits antibacterial activity against clinical isolates of MRSA through ROS-mediated oxidative stress. Appl Microbiol Biotechnol 104:8279–8297. https://doi.org/10.1007/s00253-020-10853-z

Sionov RV, Steinberg D (2022) Anti-microbial activity of phytocannabinoids and endocannabinoids in the light of their physiological and pathophysiological roles. Biomed 10:631. https://doi.org/10.3390/biomedicines10030631

Sleha R, Radochova V, Malis J et al (2021) Strong antimicrobial and healing effects of Beta-acids from hops in Methicillin-resistant *Staphylococcus aureus*-infected external wounds in vivo. Antibiot 10:708. https://doi.org/10.3390/antibiotics10060708

Sridevi D, Shankar C, Prakash P et al (2017) Inhibitory effects of reserpine against efflux pump activity of antibiotic resistance bacteria. Chem. Biol. Let. 4(2):69–72

Stasiłowicz-Krzemień A, Sip S, Szulc P, Cielecka-Piontek J (2023) Determining antioxidant activity of Cannabis leaves extracts from different varieties—unveiling nature's treasure trove. Antioxid 12:1390. https://doi.org/10.3390/antiox12071390

Stauff DL, Torres VJ, Skaar EP (2007) Signaling and DNA-binding activities of the *Staphylococcus aureus* HssR-HssS two-component system required for heme sensing. J Biol Chem 282:26111–26121. https://doi.org/10.1074/jbc.M703797200

Su X, Li T, Liu Z et al (2018) Licochalcone A activates Keap1-Nrf2 signaling to suppress arthritis via phosphorylation of p62 at serine 349. Free Radic Biol Med 115:471–483. https://doi.org/10.1016/j.freeradbiomed.2017.12.004

Sun D, Crowell SA, Harding CM et al (2016) Katg and kate confer Acinetobacter resistance to hydrogen peroxide but sensitize bacteria to killing by phagocytic respiratory burst. Life Sci 148:31–40. https://doi.org/10.1016/j.lfs.2016.02.015

Tan M, Liu Y, Luo X et al (2011) Antioxidant Activities of Plumbagin and Its Cu (II) Complex. Bioinorg Chem Appl 2011:898726. https://doi.org/10.1155/2011/898726

Thida M, Kim DW, Tran TTT et al (2016) Gambogic acid induces apoptotic cell death in T98G glioma cells. Bioorg Med Chem Lett 26:1097–1101. https://doi.org/10.1016/j.bmcl.2015.11.043

Tráj P, Sebők C, Mackei M et al (2023) Luteolin: a phytochemical to mitigate *S. Typhimurium* flagellin-induced inflammation in a chicken *in vitro* hepatic model. Anim 13:1410. https://doi.org/10.3390/ani13081410

Vaishampayan A, Grohmann E (2022) Antimicrobials functioning through ROS-mediated mechanisms: current insights. Microorg 10:61. https://doi.org/10.3390/microorganisms10010061

Valot B, Guyeux C, Rolland JY et al (2015) What it takes to be a *Pseudomonas aeruginosa*? The core genome of the opportunistic pathogen updated. PLoS ONE 10:e0126468. https://doi.org/10.1371/journal.pone.0126468

van Duijkeren E, Schink A-K, Roberts MC et al (2018) Mechanisms of bacterial resistance to antimicrobial agents. Microbiol Spec. https://doi.org/10.1128/microbiolspec.arba-0019-2017

Vargas F, Díaz Y, Carbonell K (2004) Antioxidant and scavenging activity of emodin, aloe-emodin, and rhein on free-radical and reactive oxygen species. Pharm Biol 42:342–348. https://doi.org/10.1080/13880200490519613

Ventola CL (2015) The antibiotic resistance crisis. Pharm Ther 40:277–283

Viet TD, Xuan TD, Anh LH (2021) A-amyrin and β-amyrin isolated from *celastrus hindsii* leaves and their antioxidant, anti-xanthine oxidase, and anti-tyrosinase potentials. Mol 26:7248. https://doi.org/10.3390/molecules26237248

Vollmer W, Joris B, Charlier P, Foster S (2008) Bacterial peptidoglycan (murein) hydrolases. FEMS Microbiol Rev 32:259–286. https://doi.org/10.1111/j.1574-6976.2007.00099.x

Wang X, Li X, Li H (2011) Reassessment of antioxidant activity of Baicalein *in vitro*. Asian J Pharm Biol Res (AJPBR) 1:186–194

Wang L, Yang R, Yuan B et al (2015) The antiviral and antimicrobial activities of licorice, a widely-used Chinese herb. Acta Pharm Sin B 5:310–315. https://doi.org/10.1016/j.apsb.2015.05.005

Wang C-M, Chen H-T, Wu Z-Y et al (2016) Antibacterial and synergistic activity of pentacyclic triterpenoids isolated from *Alstonia scholaris*. Mol 21:139. https://doi.org/10.3390/molecules21020139

Wang T, El Meouche I, Dunlop MJ (2017) Bacterial persistence induced by salicylate via reactive oxygen species. Sci Rep 7:43839. https://doi.org/10.1038/srep43839

Wang M, Ma B, Ni Y et al (2021) Restoration of the antibiotic susceptibility of Methicillin-resistant *Staphylococcus aureus* and extended-spectrum β-lactamases *Escherichia coli* through combination with chelerythrine. Microb Drug Resist 27:337–341. https://doi.org/10.1089/mdr.2020.0044

Watanabe S, Kita A, Kobayashi K et al (2008) Crystal structure of the [2Fe–2S] oxidative-stress sensor SoxR bound to DNA. Proc Natl Acad Sci USA 105:4121–4126. https://doi.org/10.1073/pnas.0709188105

Weinzierl G, Leveleki L, Hassel A et al (2002) Regulation of cell separation in the dimorphic fungus *Ustilago maydis*. Mol Microbiol 45:219–231. https://doi.org/10.1046/j.1365-2958.2002.03010.x

World Health Organization (2014) Antimicrobial resistance: global report on surveillance. World Health Organization, Geneva

Wright GD (2005) Bacterial resistance to antibiotics: enzymatic degradation and modification. Adv Drug Deliv Rev 57:1451–1470. https://doi.org/10.1016/j.addr.2005.04.002

Wu S-C, Yang Z-Q, Liu F et al (2019) Antibacterial effect and mode of action of flavonoids from licorice against Methicillin-resistant *Staphylococcus aureus*. Front Microbiol. https://doi.org/10.3389/fmicb.2019.02489

Wu J-S, Liu H-J, Han S-J et al (2022) Chelerythrine ameliorates acetic acid-induced ulcerative colitis via suppression of inflammation and oxidation. Nat Prod Commun 17:1934578X221132417. https://doi.org/10.1177/1934578X221132417

Xu H-X, Lee SF (2001) Activity of plant flavonoids against antibiotic-resistant bacteria. Phytother Res 15:39–43. https://doi.org/10.1002/1099-1573(200102)15:1%3c39::AID-PTR684%3e3.0.CO;2-R

Yadav MK, Chae S-W, Im GJ et al (2015) Eugenol: a phytocompound effective against methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* clinical strain biofilms. PLoS ONE 10:e0119564. https://doi.org/10.1371/journal.pone.0119564

Yamaguchi N, Satoh-Yamaguchi K, Ono M (2009) *In vitro* evaluation of antibacterial, anticollagenase, and

antioxidant activities of hop components (*Humulus lupulus*) addressing acne vulgaris. Phytomedicine 16:369–376. https://doi.org/10.1016/j.phymed.2008.12.021

Yang J, Guo J, Yuan J (2008) *In vitro* antioxidant properties of rutin. LWT Food Sci Technol 41:1060–1066. https://doi.org/10.1016/j.lwt.2007.06.010

Yang Y, Geng X, Liu X et al (2022) Antibiotic use in China's public healthcare institutions during the COVID-19 pandemic: an analysis of nationwide procurement data, 2018–2020. Front Pharmacol. https://doi.org/10.3389/fphar.2022.813213

Yao H, Wang Y, Lovell S et al (2012) The structure of the BfrB–Bfd complex reveals protein–protein interactions enabling iron release from bacterioferritin. J Am Chem Soc 134:13470–13481. https://doi.org/10.1021/ja305180n

Yu C, Genco CA (2012) Fur-mediated activation of gene transcription in the human pathogen *Neisseria gonorrhoeae*. J Bacteriol 194:1730–1742. https://doi.org/10.1128/jb.06176-11

Yu H-H, Kim K-J, Cha J-D et al (2005) Antimicrobial activity of berberine alone and in combination with ampicillin or oxacillin against methicillin-resistant *Staphylococcus aureus*. J Med Food 8:454–461. https://doi.org/10.1089/jmf.2005.8.454

Zhang T, Ding Y, Li T et al (2012) A fur-like protein PerR regulates two oxidative stress response related operons dpr and metQIN in *Streptococcus suis*. BMC Microbiol 12:85. https://doi.org/10.1186/1471-2180-12-85

Zhao X, Drlica K (2014) Reactive oxygen species and the bacterial response to lethal stress. Curr Opin Microbiol 21:1–6. https://doi.org/10.1016/j.mib.2014.06.008

Zhao G, Li T, Qu X et al (2017) Optimization of ultrasound-assisted extraction of indigo and indirubin from *Isatis indigotica* Fort. and their antioxidant capacities. Food Sci Biotechnol 26:1313–1323. https://doi.org/10.1007/s10068-017-0112-4

Zhu H, Yang Y, Feng Z et al (2018) Sophoflavanones A and B, two novel prenylated flavanones from the roots of *Sophora flavescens*. Bioorg Chem 79:122–125. https://doi.org/10.1016/j.bioorg.2018.04.019