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Review article

Active phytoconstituents to tackle the resistance mechanism of MDR and XDR bacteria

Subhasmita Mallik, Jatindra Nath Mohanty*, Subham Jyoti Sahoo

Genetic Engineering and genomic laboratory, Department of Botany, School of Applied Sciences, Centurion University of Technology and Management, Ramachandrapur, Jatni-752050, Odisha, India

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ABSTRACT

Background: The extensive use of antibiotics and the rapid emergence of multiple drug resistance bacteria (MDR) and extensively drug resistant (XDR) are significant global public health issues. Recent findings suggest multiple approaches to tackling these problems, including developing alternative compounds with antimicrobial activities, managing existing antimicrobials, nanotechnology-based drug, genome editing and rapidly detecting AMR pathogens etc. New antibiotics targeting priority superbugs are entering the market or are in clinical development. Continuous identification of effective treatment strategies is crucial due to the potential for resistance development against new antibiotics. Among these strategies, employing alternative compounds such as phytochemicals, either alone or in combination with other antibacterial agents appears to be both effective and safe for combating them. Our aim in this review is to investigate the efficacy of phytochemicals in combating multi-drug resistant (MDR) and extensively drug resistant (XDR) bacteria by analysing their bioactive components, and their impact on various resistance mechanisms.

Introduction

In the 21st century, the worldwide threat of antimicrobial resistance has escalated across humans, animals, and the environment. By 2050, the global economy is forecasted to shrink to $100 trillion due to the anticipated impact of multidrug-resistant bacteria, potentially resulting in around 300 million premature deaths worldwide. Despite its natural occurrence, the significant damage to public health caused by the elevated levels of antimicrobial resistance (AMR) is largely attributed to the high-dose use of antibiotics. The significant health threat posed by 12 families of bacteria, initially highlighted by the world health organization in 2017, remains a critical concern for human well-being. Healthcare workers and physicians are increasingly concerned about the emergence of common pathogens due to the escalation of antimicrobial resistance (AMR) [1].The spread of multidrug-resistant (MDR) bacteria like *Klebsiella pneumonia*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Enterococcus faecalis*, as well as the rise in antimicrobial resistance (AMR) have resulted in prohibited medication alternatives. When bacteria resist at least three different pharmacological classes of antibiotics, it is termed multidrug resistance (MDR). The predominant cause of treatment failures appears to be the emergence of MDR bacterial strains. *Enterobacteria* have emerged as a

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* *Corresponding author:*Jatindra Nath Mohanty
E-mail address: jatindranathmohanty@gmail.com

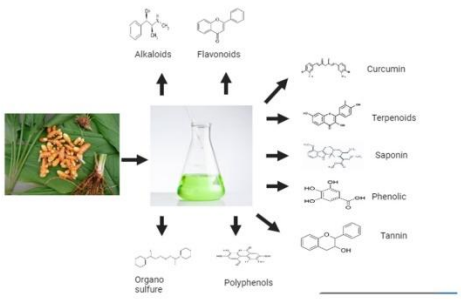
significant public health challenge since the dawn of the twenty-first century. Microorganisms that were previously susceptible to antibiotics, which were effective in combating illnesses created by these bacteria, can develop resistance to these drugs naturally, as initiated by the world health organization [2]. Due to genetic traits, infections within bacterial species can develop resistance to antimicrobial medications. Additionally, these resistant infections can also be accomplished [3]. Acquired resistance to antibiotics is typically gained through various mechanisms, such as plasmids acquiring exogenous genes via integrons and bacteriophages through transduction, conjugation, and transposons (conjugation), as well as through gene mutation. In contrast, native resistance to antibiotics may represent an inherent trait specific to a particular bacterium, determined by its biological characteristics. Hence, mechanisms such as extracellular drug efflux, facilitated by efflux pumps, target alteration, and enzymatic drug degradation, contribute to bacterial resistance development. A highly effective strategy in combating multidrug resistance involves combining the administration of resistance-modifying drugs with effective medication. Antibiotic therapy is inefficient against pathogen infections as a consequence of the virulence factors' expression, including the emergence of biofilms. Once bacterial communities, termed biofilms, reach a critical mass, they prime the development of virulent agents and coordinate changes in gene expression through regular cell-to-cell interactions facilitated by quorum sensing [4]. One of the unique strategies for treating bacterial infections is to interfere with the control of quorum sensing (QS). The rise in efflux pump activity and the decrease in drug accumulation are linked with reduced permeability, alterations in drug targets, or drug inactivation, which typically lead to antibiotic resistance. Horizontal gene transfer, a pivotal force in bacterial evolution, encompasses various mechanisms for acquiring foreign DNA, including transformation, transduction, and conjugation [5,6]. To tackle the rise of resistance and diminish reliance on antibiotics, there's an increasing imperative to innovate and develop new antimicrobial medications. Rural populations persist in using medicinal plants to treat or prevent various illnesses, and their popularity steadily increases. These plant chemicals have significant therapeutic potential in combating resistant microbial strains [7]. Considering these facts, this chapter will highlight the role of active phytoconstituents, alone or combined with antibacterial agents, in combating resistance mechanisms of XDR and MDR bacteria. This information will guide researchers in applying these findings for both therapeutic purposes and early diagnosis of related bacterial infections.

Bio-active Compounds

Plant-derived natural products are now integral to many medications, with numerous plant species serving as sources for therapeutic agents for almost a millennium. The remarkable diversity of medicinal plants found worldwide is staggering. Reports suggest that approximately 70,000 plant species, spanning from low-level lichens to higher trees, have demonstrated potential in treating various illnesses [8]. The world health organisation (WHO) says 21,000 therapeutic plants are utilized for various medical purposes. Remarkably, traditional herbalists in rural areas continue to rely on herbal medicine systems, which are considered among the most extensive in indian medicine. These practitioners treat common ailments using over 2500 different plant species. Ethnomedicinal plants, along with their derived products, alongside fruits and vegetables, offer potent defenses against numerous health issues. The potent antioxidant capabilities, along with numerous other biological functions, originated from medicinal plants, which exhibit an abundance of diverse bioactive compounds such as alkaloids, flavonoids, terpenoids, polyphenols, tannins, steroids, glycosides, chlorophyll, carotenoids, proteins, minerals, vitamins, and essential nutrients. The synergistic action can be enhanced by the emergence of multi-target mechanisms, the presence of compounds that can inhibit bacterial resistance mechanisms, pharmacokinetic or physicochemical effects that improve bioavailability, solubility, and absorption rates, neutralization of adverse effects, and reduce toxicity. Various bioactive compounds found in medicinal plants have demonstrated antibacterial properties in vitro [9] (Figure 1). Biochemical compounds found in the leaves of A. polystachya and M. azedarach include sesquiterpenoids such as 5-dihydroxyguaiane and 6beta,7beta-eooxyguai-4-en-3-one and 6beta,7beta-epoxy-4beta. Prominent substances like limonoids, which include nimono, ohchnolide B, luminol, and ammonium, were found in the phytochemical profile of M. azedarach. The conventional GC/MS analysis conducted on the liquid essential oil (EO) indicated that among the

numerous chemical components within the tea tree oil sample, β-terpinene, eucalyptol, and α-pinene and terpinene 4-ol were the most abundant, constituting [9.8%, 12.4%, 15.2%, and 35.4%, respectively] [10]. According to phytochemical analysis, several secondary metabolites, including terpenoids, alkaloids, tannin, flavonoids, saponins, and cardiac glycosides, were found in the aqueous and ethanolic extracts of bitter ginger. With an extensive array of abundant bioactive constituents, Tinospora cordifolia emerges as a versatile therapeutic herbal plant. Its efficacy in combating multidrug-resistant pathogens is strongly supported by the presence of flavonoids, terpenoids, carbohydrates, phytosterols, saponins, tannins, proteins, and alkaloids, as evidenced by phytochemical screening [11] (Table 1). When tackling multidrug-resistant strains of *A. baumannii* and *P. aeruginosa*, *Rosmarinus officinalis* essential oil, along with its primary component 1,8-cineole (eucalyptol), has exhibited remarkable antibacterial efficacy. The bioactive compounds of A. indica and T. catappa include vitamins, minerals, and phytochemicals; methanolic extracts of these compounds exhibit greater yields than aqueous ones. Qualitative analysis identified several bioactive chemical components, including tannins, saponins, alkaloids, and flavonoids. These may have medicinal qualities and be utilized as possible sources of pharmaceuticals in herbal medicine. In Thailand and other tropical regions, Eutherine bulbosa is extensively employed in traditional medicine. A crucial aspect is the phytochemical assessment of this plant, revealing the presence of secondary compounds such as tannins, alkaloids, phenols, and flavonoids [12].

Figure 1. Various bioactive compounds found in medicinal plants.



Phytochemicals against MDR Bacteria

Phytochemicals are essential to combating the possibility of bacterial resistance by reducing bacterial pathogenicity. Remarkably, these methods unveil the antibacterial properties of natural phytocompounds by leveraging their chemical structure and traits. Therefore, the development of new and natural antimicrobial medications depends on the procedure of extracting and identifying bioactive substances rich in phenols, flavonoids, terpenoids, alkaloids, and other compounds with antimicrobial characteristics. Because their bioactivity does not encourage resistance, these chemicals have particular therapeutic value [13]. Several studies have been conducted on bioactive compounds and their antibacterial efficacy. Notably, compared to antibiotics, a phytochemical's spectrum of action is wider. Nonetheless, a thorough comprehension of the precise mechanism of action of phytochemicals is necessary since plant metabolites' mechanism of action depends on their chemical composition and characteristics [14]. The use of antibiotherapy has been increasing to fight communicable illnesses due to bacteria's growing multidrug resistance. The unique antibacterial properties of plants are confirming whether they contain bioactive components that can effectively combat various types of multidrug resistance (Table 2). The crude extracts from acacia polyacantha (leaves and bark) generally exhibit moderate to poor antibacterial activity. However, significant efficacy was observed when acacia polycantha leaves were specifically employed against challenging bacterial strains such as *E. aerogenes* ATCC13048, *P. stuartii* NAE16, and *P. aeruginosa* (PA01), the minimum inhibitory concentration (MIC) values were found to be less than 100 µg/mL, indicating a significant improvement in effectiveness [15]. Various phytochemical constituents, including flavonoids, cardiac glycosides, alkaloids, anthraquinones, terpenoids, alkaloids, phenolic compounds, tannins, and saponins, were identified in the plant extracts of R. abyssinicus, D. penninervium, C. englerianum, E. depauperate, L. adonis, C. pustulates, and P. aethiopica. These bioactive compounds exhibit abilities to inhibit bacteria or fungus against the studied pathogens that affect humans and are naturally present in the majority of the extracts. Three species of Meliaceae (Toona ciliata, Aphanamixis polystachya, and Melia azedarach) were efficiently tested. The phytochemicals found in the material included limonoids/terpenoids, flavonoids, stilbenes, phenolic acids, lignans, and lower-molecular-weight phenolic compounds. Extracts from A. rohituka and M. azedarach emerged as promising options for tackling *MRSA* biofilm infections [16].

Tackling strategies of XDR and MDR

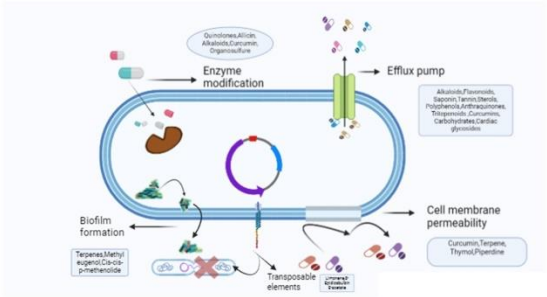
The development of bacterial resistance to conventional antimicrobial treatments is attributed to various processes, including identifying nearly 20,000 resistance genes [11]. Antibiotic resistance in bacteria is known to occur via several different processes. These include actively driving the expelling of the antibiotic from the cell, enzymatically modification, modifying the components of the cell that the antibiotic targets, overexpressing enzymes that the antibiotic inhibits, altering the permeability of bacterial cell membranes, starting alternative metabolic pathways, raising the concentrations of metabolites that oppose the antibiotic, lowering the amount or activity of enzymes that activate the antibiotic's precursor, adjusting regulatory systems that are not directly affected by the antibiotic, or reducing the requirement for products from inhibited metabolic pathway. *ESKAPE* bacteria display three main types of multidrug resistance mechanisms: alteration of the antibiotic binding site, decreased drug accumulation as a consequence of enhanced drug efflux or reduced permeability, and drug inactivation, which is usually facilitated by enzymes and leads to irreversible cleavage [18]. Antibiotics and pathogen-targeted therapies that suppress the formation of biofilms can physically block the host's immune response cells, preventing their ability to combat the pathogen.

i. Efflux pump mechanism:

Antibiotic molecules are expelled from the bacterial cell via essential transporters, specifically bacterial efflux pumps, which are vital in reducing the concentration of regulated antibiotics in drug-resistant strains. The specific resistance mechanisms allow bacteria the opportunity to proliferate, particularly when the efflux system enables their survival at low drug concentrations. The efflux system, in conjunction with the outer membrane barrier, shields cells against a range of chemicals and facilitates the diffusion of genes encoding these systems. Some isolates act as genetic reservoirs, carrying genomes that contain genes encoding diverse efflux pumps [19] (Figure 2). Antibiotic-resistant (MDR) bacteria often use the efflux pump mechanism to reply to drugs. These pumps, which are found in the cytoplasmic membrane, carry proteins and regulate the bacterium's internal environment. The two super-families of bacterial efflux pumps are categorized based on their energy source: (1) secondary transporters and (2) ATP-binding cassette (ABC) multidrug transporters that utilize proton motive force (PMF) as their energy source. Within the secondary transporters, four families are identified: 1) the small multidrug resistance (SMR) family, the multidrug and toxic compound extrusion (MATE); 2) the resistance-nodulation-cell division (RND); 3) the main facilitator superfamily (MFS); multidrug and toxic compound extrusion (MATE); and 4) the multidrug and toxic compound extrusion (MATE). The efflux pump inhibitors (EPI) are a prevalent method for impeding the efflux of medicine from bacterial cells. Efflux pumps are recognized as a rapid and efficient resistance mechanism in bacteria [20]. Antibiotics and EPI molecules can be synergistically utilized to diminish the activity of the bacterial efflux system. These inhibitors function by combating the drug efflux transporters' capacity to function, achieved through powerful binding to the transporters and preventing their driving forces. A transporter protein that exists in the cytoplasmic membrane of gram-negative bacteria is an integral part of a tripartite protein channel that provides efflux pumps in a specific form. The efflux pumps of bacteria belonging to the SMR, ABC, or MFS families are identified by their compactness. They typically consist of a single transporter contained in cytoplasmic membranes [21]. The ability of certain bioactive to combat bacterial infections is associated with their ability to inhibit bacterial cytokinesis and disrupt the formation of Fts Z Z-rings. Some phytochemicals have been reported to reverse antibiotic resistance and act as efflux pump inhibitors (EPI). *P. aeruginosa* was significantly inhibited by the alkaloid compound conessine which was derived from holarrhena antidysenterica, by blocking the bacterial efflux pump. By blocking the efflux pump, the 4-[E-2-(dimethyl carbamoyl) vinyl]-2- methoxyphenyl acetate (E)-methyl 3-{4-[(p-tolyl carbamoyl) methoxy]-3 methoxy phenylyl} acrylate is a derivative of ferulic acid that has antibacterial efficacy against *MRSA*. The challenge against *S. aureus* strains, including *MRSA*, to fluoroquinolones, has emerged due to the increased expression of efflux pumps and rapid mutations in genes encoding target enzymes [22]. When fluoroquinolone antibiotics were combined with piperine, a piperidine alkaloid, they exhibited synergistic effects in lowering the (MIC) values. Piperine is derived from piper longum L. *(*Indian

long pepper) and piper nigrum L. (black pepper). Scutellaria baicalensis, thymus vulgaris L., and scutellaria lateriflora L. are the main sources of baicalein, a flavone compound. Baicalein enhances the efficiency of medications such as tetracycline, β-lactams, and ciprofloxacin against *methicillin-resistant Staphylococcus aureus* by impeding nor A efflux pumps. Furthermore, its inhibition of these efflux pumps leads to a combined effort to combat *Escherichia coli* when combined with tetracycline [23].

Figure 2. Major resistance mechanism of MDR and XDR bacteria towards different class of antibiotics.



ii. Biofilm formation

A newly formed microbial community characterized by the overlapping attachment of microbial cells to inert objects, living cells, or cell aggregation is known as a biofilm. The established microbial community is enveloped by proteins, extracellular polysaccharides, microbial DNA, and other extracellular component. Drugs cannot readily enter the target microbial cells due to antimicrobial resistance, further compounded by the protective barrier of the surrounding matrix. Bacterial resistance mechanisms differ from those of solitary bacterial cells, including their capacity to tolerate specific levels of environmental stress. Microbial biofilms exhibit distinct characteristics in gene expression, protein production, and growth capacity [24]. The essential oil (EO) extracted from Mentha suaveolens ssp. insularis have the phytochemicals cis-cis-p-menthenolide, a compound that plays a vital part in preventing *Chromobacterium violaceum's* signal-mediated quorum sensing (QS) system and biofilm development. This substance is a competitive inhibitor, sharing structural similarities with the natural signal molecule. This might prevent gene expression and promote the creation of biofilms [25].

iii. Quorum-sensing

Bacterial cells communicate intercellularly through quorum sensing, which is facilitated by specialized molecules called autoinducers. The essential elements of quorum sensing mechanisms involve the accumulation, synthesis, and population-wide detection of autoinducers. Gram-positive bacteria utilize oligopeptides as autoinducers, whereas Gram-negative bacteria typically utilize small compounds. As bacterial density rises, these molecules accumulate in the environment. Bacteria monitor this data to detect fluctuations in cell numbers and adjust gene expression accordingly. Anti-quorum sensing compounds synthesized by several plant species have been extensively employed in treating human microbial diseases by combating microbial growth and development. Herbal medicine relies on substances that either eradicate or prevent the growth of microbes to combat bacterial illnesses [26]. The rise of plant-derived compounds to disrupt the quorum sensing system could potentially impact the pathogenicity of bacteria by causing them to become sensitive to and tolerate antibacterial medications. The bacteria's pathogenic virulence factors have exploited the QS system. To address this opportunistic infection, sublethal amounts of L-carvone, a key compound in spearmint EOS, were employed for treatment. garlic extract contains a compound known as ajoene, which is an organosulfur compound with two distinct forms: Z-ajoene and E-ajoene [27]. The QS system has been confirmed to be blocked by ajoene. *Pseudomonas aeruginosa* uses this mechanism to regulate the expression of specific genes that are crucial to its pathogenicity. Anti-quorum sensing characteristics against *Pseudomonas aeruginosa* are demonstrated by caffeine, a xanthine belonging to the alkaloid family. It accomplishes this by interacting with quorum-sensing proteins such as LasR and LasI, reducing the release of virulence components essential to the bacteria's pathogenicity. By reducing the signal-based QS, methyl eugenol, which is found in the essential oils of cumium cymatium, thereby combating biofilm formation and associated virulence in gram-negative bacterial pathogens like *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Escherichia coli*. Multidrug-resistant (MDR) clinical isolates are effectively tackled by essential oils derived from thymus vulgaris, eugenia caryophyllata, and

cinnamomum verum. These oils inhibit both biofilm formation and quorum sensing (QS) activities [28].

iv.Cell membrane permeability

Modifying specific ion channels may change the bacterial cell membrane's permeability, affecting antibiotic transport and, consequently, medication efficacy. Antibiotics' ability to enter bacterial cells is regulated by the membrane's permeability. It is thought that modifying the membrane's permeability can either assist or inhibit the diffusion of antibiotics into the cell via modifying the membrane proteins and fatty acid content. The cellular structure is disrupted by hydrophobic phytochemicals' interactions with membrane lipids, which ultimately results in increased membrane permeability. The lack of transparency in bacterial cells causes them to be unable to detect when their own molecules are leaking out. Several investigations confirm phytochemicals' significant ability to target permeability in cell membranes. The essential oils exhibit significant antimicrobial properties against strains of *Staphylococcus* and *E. coli* [29]. The multidrug-resistant (MDR) uropathogenic strain of *Escherichia coli* was carried out by the essential oils extracted from coriandrum sativum, which caused the disruption of its cell membrane permeability. In *MRSA*, catechin disrupts the membrane, leading to the flow of potassium ions and damaging the cell membrane. The research examined the membrane disruption mediated by 3-arylidene flavanone, which causes bacterial cells to accumulate, altering the membrane's integrity and allowing pathogenic strains of *E. faecalis* and *S. aureus*, isolated from clinical samples, to exhibit increased permeability. The alkaloids tetrahydrosecamine (piperidine) and heptanol (indole), extracted from Rhazya stricta decne, exhibited significant antibacterial efficacy against *P. aeruginosa*, *E. coli*, and *MRSA* by rupturing the membrane of the bacterial cell. *Staphylococcus aureus* and *Escherichia coli* have demonstrated susceptibility to the antibacterial effects of curcumin, a compound abundant in curcuma longa L. Its antibacterial action is attributed to its ability to penetrate the lipid bilayer and enhance membrane permeability. Thymol, an essential oil derived from thymus vulgaris L., exhibits antimicrobial efficacy against *Escherichia coli* and *Salmonella typhimurium* that are persistent to tetracycline, *Streptococcus pyogenes* and penicillin-resistant *Staphylococcus aureus* that are resistant to erythromycin. Multiple researches indicate that the rupture of cell membranes is a component of the mechanism of action [30].

1. V. Enzymatic modification

Antibiotic resistance primarily arises from bacterial strategies involving the production of specialized enzymes that either alter the antibiotic's target or degrade the medication. Thus, inhibiting these enzymes' activity can potentially restore resistant bacteria's antibiotic sensitivity. Numerous phytochemicals can inhibit the DNA gyrase enzyme, which is essential for the replication of DNA molecules. This impacts nucleic acid synthesis and has antibacterial properties [31]. Different phytochemicals, like flavonoids, can inhibit the activity of helicases such as *Dna*B and *Rec*BCD, which in turn impedes DNA replication. Allicin, found in allium sativum (garlic), is an organosulfur compound known for its antibacterial properties against *S. epidermidis* and *P. aeruginosa*. Its antibacterial mechanism involves inhibiting protein and DNA synthesis and sulfhydryl-dependent enzymes. *Mycobacterium tuberculosis*, resistant to quinolones has been demonstrated to have its DNA gyrase inhibited by chelinic acid, primarily derived from Terminalia species. Argemone Mexicana L. sanguinaria canadensis L., Chelidonium majus L.and Macleaya cordata (Willd.) R.Br. are some of the plants containing sanguinarine, an alkaloid. Its antibacterial capability depends on the generation of autolytic enzymes, triggering cell lysis. It has shown efficacy against *MRSA* strains and is an inhibitor of transcription and bacterial cell proliferation [32].

Vi. Transposable elements

1. Mobile genetic elements, such as plasmids, enable the horizontal transfer of resistance genes among bacterial pathogens. The generation, transmission, and proliferation of resistant plasmids constitute significant processes that drive global resistance to antibiotics and greatly aid in the emergence of resistance genes. Eliminating R-plasmids could potentially mitigate the transmission of resistance genes among bacteria. Phytochemicals, such as essential oils, are believed to possess antibacterial properties and the ability to reverse resistance by targeting and removing R-plasmids. Hence, there's a promising prospect that integrating bioactive compounds with conventional antibiotics

could diminish the potential of drug resistance emergence. The compound 8-Epidiosbulbin-E-acetate, derived from dioscorea bulbifera, has exceptional effectiveness in reducing antibiotic-resistant R-plasmids found in clinical strains of *P. aeruginosa*, *Shigella sonnei*, *E. faecalis*, and *E. coli*. During a sublethal heat shock, the major component of citrus essential oils, (+)-limonene, was investigated for its bactericidal activity against *E. coli* BJ4 (wild type). The findings revealed a reduction in bacterial resistance and an enhancement in cell wall permeability [33].

2. **Phytochemicals used with other combinational antibacterial agents**

A novel and effective approach for treating multidrug resistance (MDR) involves the synergistic interactions between herbal medications, phytochemicals, and antibiotics, as well as other clinically significant drugs. This approach entails the co-administration of antibiotics and phytochemical compounds to prevent the development of resistance. The ability of rosemary's major constituents, carnosic acid, and carnosol, to enhance antibiotic efficacy against treatment-resistant *S. aureus* strains was investigated. When applied to *S. aureus* strains expressing msr (A), carnosic acid increased the activity of erythromycin eightfold. This potentiating effect may have been caused by the suppression of efflux pumps. The gallic acid extracted from *C. jejuni* displayed significant transcription reduces in CmeABC, acting as a multi-drug efflux mechanism that gives rise to the bacterium's resistance. A year later, further investigators explored the efficiency of tannic acid either by using it itself or in combination with the broad-spectrum antimicrobial norfloxacin against the strain of *S. aureus* [34]. This synergistic anti-*MRSA* effect was primarily due to baicalein suppressing the efflux pump, thereby reducing the efflux of ciprofloxacin [35]. The antibacterial abilities of MNPs [Multi-metallic Nanoparticles] offer significant potential for treating bacterial infections, particularly those caused by multi-drug-resistant strains. MNPs possess distinct physicochemical characteristics that support their antibacterial actions, including their ability to rupture bacterial cell membranes, generate reactive oxygen species, induce protein malfunction, and inflict DNA damage [36].

S. officinalis aqueous leaf extract was utilized to create biogenic IONPs [Iron oxide nanoparticles] that have the potential to be antibacterial in an environmentally friendly manner. These nanoparticles could potentially be utilized to create surface disinfectants for use in healthcare centre. The combination of biogenic IONPs with tigecycline antibiotics has the potential to decrease the usage of antibiotics, hence lowering the prevalence of multi-drug resistant bacteria and enhancing the treatment of nosocomial infections in healthcare facilities. Due to chitosan's biocompatible characteristics, it has been explored as a potential medication carrier. In this study, crosslinking polyacrylic acid) (PAA) on the surface of chitosan-tripolyphosphate (CSTPP) particles resulted in the formation of cationic CS-PAA nanoparticles. This nano-system exhibited enhanced antibiofilm activity and antibacterial properties against various strains of gram-negative bacteria. The promising results suggest that this unique system could be a potentially useful, safe, and cost-effective approach for combating bacterial infections. Moreover, it could be utilized as an agent for antimicrobial medications to augment their efficacy [37].

Table 1. Active phytochemicals and their effect against the target pathogen.

SPECIES NAME	PARTS USED	Phytochemicals	Targaet pathogen
Anogeissus acuminata	Leaf/Bark	Alkaloids, Tannin, Steroids Glycosides, Saponins Carbohydrates, Flavonoids, Anthraquinone,	*E. faecalis, E. coli S.aureus,A.baumannii, C. freundii, P. vulgaris E.aerogenes, K.oxytoca, K. pneumoniae, P. mirabilis, and P. aeruginosa*
Azadirachta indica L.	Leaf	Glycosides,Steroids,Saponins, Terpenoids, Carbohydrates	E. *faecalis, E. coli S.aureus,A.baumannii, C. freundii, P.vulgaris , K.oxytoca E.aerogene,K.pneumoniae, P. mirabilis,and* P. aeruginosa
Bauhinia variegata L.	Leaf/ Root	Alkaloids, Tannins, Steroids, Saponins, Glycosides, Carbohydrates, Anthraquinone,	*E. faecalis, E. coli S.aureus,A.baumannii, C. freundii, P. vulgaris E.aerogenes, K.oxytoca, K. pneumoniae, P. mirabilis,and P. aeruginosa*
Boerhaavia diffusa L.	Leaf	Alkaloids,Tannins, Flavonoids, Steroids, Anthraquinone	*P. aeruginosa, E. coli K. pneumoniae, S. aureus K. oxytoca, E. aerogenes, C. freundii, E. faecalis, A. baumannii*
Punica granatum L.	Leaf/ Bark/ Fruits	Anthraquinone, Steroids, Flavonoids, Alkaloids, Tannins, Saponins, Terpenoids, Glycosides	*K. pneumoniae, P. mirabilis, E. coli S.aureus, P. aeruginosa E. faecalis, A.baumannii, C. freundii, P. vulgaris E.aerogenes, K.oxytoca,*
Soymida febrifuga Roxb.	Leaf/ Bark	Carbohydrates, Alkaloids, Terpenoids, Steroids, Tannin, Flavonoids, Glycosides, Anthraquinone	*P. aeruginosa E. faecalis, A.baumannii, S.aureus C. freundii, P. vulgaris K. pneumoniae, E. coli P. mirabilis, K.oxytoca C. freundii, P. vulgaris E.aerogenes,*
Terminalia chebula Retz.	Leaf/ Fruits	Anthraquinone, Alkaloids, Terpenoids, Flavonoids, Tannins, Glycosides, Carbohydrates	*A. baumannii, E. faecalis, S. aureus, E. coli, K. oxytoca, P. mirabilis K. pneumoniae, P. aeruginosa*
Tinospora cordifolia	Leaf/ Bark	Glycosides, Steroids, Alkaloids, Saponins, Carbohydrates	*E. faecalis, S. aureus, E. coli, P. aeruginosa K. oxytoca, P. mirabilis K. pneumoniae,*
Tribulus terrestris L.	Leaf/ Bark	Steroids, Terpenoids	*E. faecalis, E. coli S.aureus,A.baumannii, C. freundii, P. vulgaris K.oxytoca, P. mirabilis K. pneumoniae and P. aeruginosa*
Amarantus	Leaves	Terpenes, Flavonoids,	*E.coli, E.aerogenes,*

Hybridus		Anthocyanins	*K.pnemoniae, P.stuartii, E.cloacae,P.aeruginosa*
Vernonia Hymenolepis	Leaves	Flavonoids, Phenols, Alkaloids	*,P.aeruginosa, E.cloacae K.pnemoniae, P.stuartii E.coli, E.aerogenes*
Lactuca sativa	Leaves	Flavonoids, Alkaloids, Phenols	*K.pnemoniae, P.stuartii, E.coli, E.aerogenes P.aeruginosa, E.cloacae*
Lactuca capensis	Leaves	Alkaloids, Phenols, Tannin, Steroids	*E.aerogenes, P.aeruginosa K.pnemoniae, , E.cloacae E.coli, P.stuartii*
Sechium edule	Leaves	Saponins, Flavonoids, Steroids, Phenols, Alkaloids, Terpene	*E.coli,P.stuartii, K.pnemoniae, , E.cloacae E.aerogenes, P.aeruginosa*
Manihot esculinta	Leaves	Alkaloids, Phenols, Tannin, Terpene, Flavonoids, anthraquinone, Saponins	*E.coli,P.stuartii,K.pnemoniae, E.cloacae, E.aerogenes, P.aeruginosa*
Phaseolus Vulgaris	Cloves	Alkaloids, Phenols, Flavonoids, Steroids	*E.cloacae,E.aerugenosa, K.pneumoniae,E.coli, P.stuartii*
Cucurbita pepo	Leaves	Alkaloids, Flavonoids, Phenols, Steroids	*P.stuartii,E.coli ,E.aerugenosa,K.pneumoniae, P.aerugenosa,E.cloacae*
Solanum nigru	Leaves	Alkaloids, Phenols, Steroids, Flavonoids	*K.pneumoniae, P.aerugenosa,E.cloacae P.stuartii,E.coli ,E.aerugenosa*
Capsicum Frutescens	Fruits	Anthraquinones, Terpenes, Phenols,Flavonoids, Alkaloids	*P.stuartii,E.cloacae, E.aerugenosa K.pneumoniae,E.coli*
Alkanna tinctoria	Leaves	Carbohydrates, Flavonoids, Alkaloids	*P. aeruginosa, A. baumannii, MRSA, E. coli*
Allium sativum L. (garlic)	Fruit	Allicin [sulfur-containing Compound]	*P. aeroginosa*
Zanthoxylum Alatum	Leaves, Stem	Fenchol, linalool	*E. coliK. Pneumoniae*
Cinnamomum Tamala	Leaves	Cinnamaldehyde	*MDR-H. pylori*
Cinnamomum Zeylanicum	Leaves	Polyphenol	*S. aureus,P. aeruginosa E. coli,S. enteric*
Myrtus communis L.	Seeds	Fatty acid, Tannin, Gallic acid, Flavonoids, Ellagic acid	*S. aureus, E.coli , S.enteric, P. aeruginosa*
Peganum harmala L.	Seeds	Harman,Harmine, Harmaline, Harmalol, Alkaloids	*MRSA*
Glycyrrhiza glabra L.	Fruit & leaves	Alkaloids, saponin, Tannin, flavonoids, Phenols, Terpenes, Coumarin	*P. aeruginosa*
Ficus sycomorus L.	Leaves	Phenols, Flavonoids	*Resistant S.auerus, A.baumannii*
Syzigium cumin	Leaves	Flavonoids, Alkaloids, Terpenoids	*E.coli, MRAS*
Punica granatum	Peel	Gallic acid ,Ellagic tannin,	P. aeruginosa

L.		Ellagic acid	
Croton macrostachyus hochst. ex Delile.	Leaves	Saponins,Sterols, Polyphenol, Triterpene	*MRSA*
Catharanthus roseus (L.) G.Don	Leaves	Polyphenols, Sterols, Flavonoids, Alkaloids, Triterpenes	*MRSA*
Paullinia pinnata L.	Leaves	Polyphenol, Triterpene Saponins, Sterols,	*MRSA*
Anacardium occidentale L.	Leaves	Anthocyanin,Phenol,Tannin, Flavonoids,Alkaloids,Saponin	*E. coli,K. pneumoniae*
Bymbra spicata L.	Arial Parts	Thymol Camphor,Carvacol,	*E.coli*
Lawsonia inermis (henna)	Leaves	Phenolic compounds, Tannins, Steroids, Alkaloids, Terpenoids	*P. aeruginosa ATCC37853, MRSA ATCC43300, K. pneumoniae* ATCC700603
Azadirachta indica (neem)	Leaves	Tannins, Steroids, Saponins, Flavonoids, Alkaloids, terpenoids, phenolic compounds,	*MRSA ATCC43300, P. aeruginosa* ATCC37853, *K. pneumoniae* ATCC700603
Platanus hybrida	Fruits	Phenolic compounds	*P.aeruginosa, K. pneumoniae, E. faecium, E. faecalis*
Tinospora cordifolia	Stem	Alkaloids, Saponins, Proteins, Terpenoids, Phytosterols, Tannins, Flavonoids and Carbohydrates	*S. aureus,A. baumannii, P. aeruginosa,MRSA, K. pneumoniae,E.coli, Enterobacter* spp.

Table 2. Mode of action to tackle the MDR and XDR bacteria with different plant sources.

Plant name	**Bioactive compound**	**Target pathogen**	**Mode of action**
Holarrhena antidysenterica	Conessine [Alkaloids]	*P. aeruginosa*	Efflux pump
Piper nigrum L.	Piperidine [Alkaloid]	*MRSA*	Efflux pump
Rauwolfia serpentina (L.)	Reserpine [Alkaloid]	*Stenotrophomonas maltophilia,*	Efflux pump
Scutellaria baicalensis, Thymus vulgaris L., Scutellaria lateriflora L.	Baicalein [Flavone]	*MRSA*	Efflux pump
Cumium cymatium	Methyl eugenol	*E. coli, Serratia marcescens, Proteus mirabilis, and P. aerugosa*	Biofilm formation
Plectranthus amboinicus	Terpenes	*S. aureus*	Biofilm formation
Mentha suaveolens ssp. Insularis	cis-cis-p-menthenolide	*Chromobacterium violaceum*	Biofilm formation
Coriandrum sativum		*Escherichia coli*	Cell membrane permeability
Rhazya stricta Decne.,	Tetrahydrosecamine (piperidine) and streptanol (indole)[Alkaloids]	*MRSA, E. coli, and P. aeruginosa*	Cell membrane permeability
Curcuma longa L	Curcumin	*Escherichia coli, Staphylococcus aureus*	Cell membrane permeability
Thymus vulgaris L	Thymol	Salmonella typhimurium, Escherichia coli	Cell membrane permeability
Allium sativum	Allicin	*P. aeruginosa,and S. epidermidis*	Enzyme modification

Terminalia species	Quinolones	*Mycobacterium tuberculosis*	Enzyme modification
Chelidonium majus L., Sanguinaria canadensis L., Argemone Mexicana L., and Macleaya cordata (Willd.) R.Br.,	Sanguinarine Alkaloids]	*MRSA*	Enzyme modification
Dioscorea bulbifera	8-Epidiosbulbin-E-acetate	P. aeruginosa, Shigella sonnei, E. faecalis, and E. coli	Mobile genetic elements [plasmids]
Citrus sps.	Limonene	*E. coli BJ4 (wild type).*	Mobile genetic elements
Myristica fragrans	3′,4′,7trihydroxyflavone	*K. pneumoniae, E. coli* , P. stuartii, *E. aerogenes*	Efflux pump
Acacia polyacantha	3-*O*-[*β*-xylopyranosyl-(1□→4)galactopyranosyl]-oleanolic acid , 3-*O*-[*β*-galactopyranosyl-(1□→4)-*β*-D-galactopyranosyl]-oleanolic acid. Epicatechin, Saponin, and quercetin-3-*O*-glucoside	*Escherichia coli, Enterobacter aerogenes Klebsiella pneumoniae, Pseudomonas aeruginosa Providencia stuartii,*	Efflux pump
Bryophyllum Pinnatum	Kaempferol	S. aureus and P. aeruginosa	NorA efflux pump
Olea europaea	Triterpene	*M. tuberculosis, E. faecalis, E. coli, P. aeruginosa, Streptococci*, and *S. pneumoniae*	Efflux pump
Salvia hydrangea	1,8-cineole, camphor, trans-caryophyllene, Spathulenol, *β*-eudesmol, *α*-pinene, caryophyllene oxide,and *β*-pinene	*P. aeruginosa, K. pneumoniae*	Significant inhibitory and lethal effect
Cortex phellodendri and Rhizoma coptidis	Berberine [isoquinoline alkaloids]	*Escherichia coli*	Cell division/ Inhibition of Protein/DNA synthesis
Ipomoea muricata	Chanoclavine[alkaloid]	*E. coli*	ATPase-dependent
Diplotaxis harra	Sulforaphane [Organosulfur]	*E. coli*	ATP synthase inhibitor, Membrane destruction, DNA/protein synthesis inhibitor
Scutellaria Baicalensis	Baicalein [Phenols]	*MRSA*	Efflux pump mechasnism
Alpinia calcarata	Kaempferol [Phenolic compounds]	*MRSA*	Efflux pump mechanism
Vitis vinifera	Resveratrol [Phenolic compounds]	*Campylobacter jejuni*	Efflux pump mechanism
Ferulago Campestris	Aegelinol [Curcumin]	*Salmonella enterica serovar Typhi, Staphylococcus aureus, Enterobacter cloacae, E.aerogenes*	Enzyme modification
Asphodelus Microcarpus	Asphodelin A [Curcumin]	*Pseudomonas aeruginosa, E. coli, S.aureus,*	Enzyme modification
Ferula szowitsiana	Galbanic acid [Curcumin]	*S.aureus*	Efflux pump inhibitor

Prangos hulusii	Osthole [Curcumin]	*Klebsiella pneumoniae, B.subtilis,S.aureus*	Enzyme modification
Thymus capitatus	Carvacrol,[Terpene]	Pseudomonas aeruginosa, E.aerogenes S.aureus, E.coli,	Cell membrane permeability
Artocarpus heterophyllus	lauric acid,palmitic acid, oleic acid,and myristic acid,	*S. aureus*	Cell membrane permeability
Rhazya stricta Decne.	Alkaloids	*K. pneumoniae, VRE, MRSA, E. coli*	Cell membrane permeability
Holarrhena Antidysenterica	Conessine alkaloid	*P. aeruginosa*	Efflux pump inhibition
Coula edulis Baill.	Cardiac glycosides, Alkaloids, Saponins, Flavonoids,	*K.pneumoniae, E.coli*	Efflux pump inhibition
Mangifera indica L	Coumarin,Polyphenols, Tanatechin,Carotenoid	*E.coli,P.aeruginosa, Klebsiella spp.*	Efflux pump inhibition
Citrus sinensis	Carbohydrates, Catechin, Polyphenols	*E. coli*	Efflux pump inhibition

Conclusion with future remarks

To sum up, new strategies are needed to fight bacteria that are extensively drug-resistant (XDR) and multi-drug resistant (MDR) due to the growing threat of antimicrobial resistance (AMR). When used alone or in conjunction with antibacterial drugs, phytochemicals and other non-traditional substances show great promise in circumventing resistance mechanisms. The effectiveness of active phytoconstituents in managing and treating this resistant mechanism has been emphasized in this review. Forward-looking, it is imperative that research and development in a number of critical sectors continue. Given that medicinal plants include bioactive molecules with strong antibacterial qualities, it is imperative to step up efforts to find and describe these chemicals. Examining how phytochemicals work in concert with currently available antibiotics can improve treatment outcomes and reduce the emergence of resistance. Progression in diagnostic technology aimed at promptly identifying AMR pathogens would enable prompt and efficient treatment. Lastly, creating immune response-modulating host-directed medicines can improve the body's capacity to fend against infections. By combining these methods, we may create more manageable and preventative plans for bacterial illnesses, which will ultimately lessen the impact of AMR on the world at large.

Conflict of interest

None declared.

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References

1- Zeb S, Mushtaq M, Ahmad M, Saleem W, Rabaan AA, Naqvi BSZ et al., Self-Medication as an Important Risk Factor for Antibiotic Resistance: A Multi-Institutional Survey among Students. Antibiotics. 2022;11(7):842. doi:10.3390/antibiotics11070842

2- Mancuso G, Midiri A, Gerace E, Biondo C. Bacterial Antibiotic Resistance: The Most Critical Pathogens. *Pathogens*. 2021;10(10):1310. doi:10.3390/pathogens10101310

3- Christaki E, Marcou M, Tofarides A. Antimicrobial Resistance in Bacteria: Mechanisms, Evolution, and Persistence. *Journal of Molecular Evolution*. 2019;88(1):26-40. doi:10.1007/s00239-019-09914-3

4- LaSarre B, Federle MJ. Exploiting Quorum Sensing To Confuse Bacterial Pathogens. *Microbiology and Molecular Biology Reviews*. 2013;77(1):73-111. doi:10.1128/mmbr.00046-12

5- Munita JM, Arias CA. Mechanisms of Antibiotic Resistance. Virulence Mechanisms of Bacterial Pathogens. 2016:481-511.

doi:https://doi.org/10.1128/9781555819286.ch17

6- Górniak I, Bartoszewski R, Króliczewski J. Comprehensive review of antimicrobial activities of plant flavonoids. *Phytochemistry Reviews*. 2018;18(1):241-272. doi:10.1007/s11101-018-9591-z

7- Shankar SR, Rangarajan R, Sarada D, Kumar CS. Evaluation of Antibacterial Activity and Phytochemical Screening of Wrightia tinctoria L. *Pharmacognosy Journal*. 2010;2(14):19-22. doi:10.1016/s0975-3575(10)80066-5

8- Kuruppu A, Paranagama P, Goonasekara C. Medicinal plants commonly used against cancer in traditional medicine formulae in Sri Lanka. *Saudi Pharma J* . 2019;565-73. doi:https://doi.org/10.1016/j.biotechadv.2015.08.001

9- Cowan MM. Plant products as antimicrobial agents. Clinical Microbiology Reviews. 1999;12(4):564-582. doi:10.1128/cmr.12.4.564

10- Oliva A, Costantini S, De AngelisM, Garzoli S, Božović M, Mascellino M et al., High Potency of Melaleuca alternifolia Essential Oil against Multi-Drug Resistant Gram-Negative Bacteria and Methicillin-Resistant Staphylococcus aureus. Molecules. 2018;23(10):2584. doi:10.3390/molecules23102584

11- Ezhilarasu K. The antibacterial effect of Tinospora cordifolia (Guduchi) and its role in combating antimicrobial resistance. *Medeniyet Medical Journal.* 2023;38(3):149-158. doi:10.4274/mmj.galenos.2023.84579

12- Raksamat W, Kimkong I. Phytochemical Constituents and Potential of Different Extracts from Eleutherine bulbosa on Skin Infectious Treatment : Anti-fungal, Anti-bacterial, Anti-inflammatory and Cytotoxic Activities. Chiang Mai Journal of Science. 2024;51(1):1-13. doi:10.12982/cmjs.2024.002

13- Bazzaz BSF, Khameneh B, Zahedian MR, Hosseinzadeh H. In vitro evaluation of antibacterial activity of verbascoside, lemon verbena extract and caffeine in combination with gentamicin against drug-resistant Staphylococcus aureus and Escherichia coli clinical isolates. DOAJ (DOAJ: Directory of Open Access Journals). April 2018. doi:10.22038/ajp.2018.15338.1607

14- Simões M, Bennett RN, Rosa E a. S. Understanding antimicrobial activities of phytochemicals against multidrug resistant bacteria and biofilms. Natural Product Reports. 2009;26(6):746. doi:10.1039/b821648g.

15- Kebede T, Gadisa E, Tufa A. Antimicrobial activities evaluation and phytochemical screening of some selected medicinal plants: A possible alternative in the treatment of multidrug-resistant microbes. PLoS ONE. 2021;16(3):e0249253. doi:10.1371/journal.pone.0249253

16- Zhang L, Ismail MM, Rocchetti G, Fayek NM, Lucini L, Saber FR. The Untargeted Phytochemical Profile of Three Meliaceae Species Related to In Vitro Cytotoxicity and Anti-Virulence Activity against MRSA Isolates. Molecules. 2022;27(2):435. doi:10.3390/molecules27020435

17- Van Hoek AH a. M, Mevius D, Guerra B, Mullany P, Roberts AP, Aarts HJM. Acquired Antibiotic Resistance Genes: An Overview. Frontiers in Microbiology. 2011;2. doi:10.3389/fmicb.2011.00203

18- Yuan L, Zhai YJ, Wu H, et al. Identification and prevalence of RND family multidrug efflux pump oqxAB genes in Enterococci isolates from swine manure in China. Journal of

Medical Microbiology. 2018;67(6):733-739. doi:10.1099/jmm.0.000736

19- Du D, Wang-KanX, Neuberger A, Van VeenHW, Pos KM, Piddock LJV, Luisi BF. Multidrug efflux pumps: structure, function and regulation. Nature Reviews Microbiology. 2018;16(9):523-539. doi:10.1038/s41579-018-0048-6

20- Kongkham B, Prabakaran D, Puttaswamy H. Opportunities and challenges in managing antibiotic resistance in bacteria using plant secondary metabolites. Fitoterapia. 2020;147:104762. doi:10.1016/j.fitote.2020.104762

21- Gade ND, Qazi MS. Fluoroquinolone Therapy in Staphylococcus aureus Infections: Where Do We Stand? Journal of Laboratory Physicians. 2013;5(02):109-112. doi:10.4103/0974-2727.119862

22- Chan BC, Ip M, Lau CB, Lui S, Jolivalt C, Ganem-ElbazC et al., Synergistic effects of baicalein with ciprofloxacin against NorA over-expressed methicillin-resistant Staphylococcus aureus (MRSA) and inhibition of MRSA pyruvate kinase. Journal of Ethnopharmacology. 2011;137(1):767-773. doi:10.1016/j.jep.2011.06.039

23- Oliveira D, Borges A, Simões M. Staphylococcus aureus Toxins and Their Molecular Activity in Infectious Diseases. Toxins. 2018;10(6):252. doi:10.3390/toxins10060252

24- PoliJ-P, Guinoiseau E, De Rocca SerraD, Sutour S, Paoli M, Tomi F et al., Anti-Quorum Sensing Activity of 12 Essential Oils on chromobacterium violaceum and Specific Action of cis-cis-p-Menthenolide from Corsican Mentha suaveolens ssp. Insularis. Molecules. 2018;23(9):2125. doi:10.3390/molecules23092125

25- Hentzer M, Givskov M. Pharmacological inhibition of quorum sensing for the treatment of chronic bacterial infections. Journal of Clinical Investigation. 2003;112(9):1300-1307. doi:10.1172/jci20074

26- Abreu A, Borges A, Simoes L, Saavedra M, Simoes M. Antibacterial Activity of Phenyl Isothiocyanate on Escherichia coli and Staphylococcus aureus. Medicinal Chemistry. 2013;9(5):756-761. doi:10.2174/1573406411309050016

27- He N, Wang P, Wang P, Ma C, Kang W. Antibacterial mechanism of chelerythrine isolated from root of Toddalia asiatica (Linn) Lam. BMC Complementary and Alternative Medicine. 2018;18(1). doi:10.1186/s12906-018-2317-3

28- Budzyńska A, Różalski M, Karolczak W, Szakiel MW, Sadowska B, Różalska B. Synthetic 3-Arylidenefl avanones as Inhibitors of the Initial Stages of Biofilm Formation by Staphylococcus aureus and Enterococcus faecalis. Zeitschrift Für Naturforschung C. 2011;66(3-4):104-114. doi:10.1515/znc-2011-3-40

29- Xiao G, Li J, Sun Z. The Combination of Antibiotic and Non-Antibiotic Compounds Improves Antibiotic Efficacy against Multidrug-Resistant Bacteria. International Journal of Molecular Sciences. 2023;24(20):15493. doi:10.3390/ijms242015493

30- Xu H. Flavones inhibit the hexameric replicative helicase RepA. Nucleic Acids Research. 2001;29(24):5058-5066. doi:10.1093/nar/29.24.5058

31- Si H, Hu J, Liu Z, Zeng ZL. Antibacterial effect of oregano essential oil alone and in combination with antibiotics against extended-spectrum β-lactamase-producingEscherichia

coli: Table 1. FEMS Immunology & Medical Microbiology. 2008;53(2):190-194. doi:10.1111/j.1574-695x.2008.00414.x

32- Dzotam JK, Simo IK, Bitchagno G, et al. In vitro antibacterial and antibiotic modifying activity of crude extract, fractions and 3′,4′,7-trihydroxyflavone from Myristica fragrans Houtt against MDR Gram-negative enteric bacteria. BMC Complementary and Alternative Medicine. 2018;18(1). doi:10.1186/s12906-018-2084-1 Fujita M, Shiota S, Kuroda T, et al. Remarkable Synergies between Baicalein and Tetracycline, and Baicalein and β-Lactams against Methicillin-Resistant Staphylococcus aureus. Microbiology and Immunology. 2005;49(4):391-396. doi:10.1111/j.1348-0421.2005.tb03732.x

33- Amin MU, Khurram M, Khan T, et al. Effects of Luteolin and Quercetin in Combination with Some Conventional Antibiotics against Methicillin-Resistant Staphylococcus aureus. International Journal of Molecular Sciences. 2016;17(11):1947. doi:10.3390/ijms17111947.

34- Yassin MT, Al-Otibi FO, Al–Askar AA. Green synthesis, characterization and antimicrobial activity of iron oxide nanoparticles with tigecycline against multidrug resistant bacterial strains. Journal of King Saud University - Science. 2024;36(4):103131. doi:10.1016/j.jksus.2024.103131.

35- Al-Fawares O, Alshweiat A, Al-Khresieh RO, Alzarieni KZ, Rashaid AHB. A significant antibiofilm and antimicrobial activity of chitosan-polyacrylic acid nanoparticles against pathogenic bacteria. Saudi Pharmaceutical Journal. 2023;32(1):101918. doi:10.1016/j.jsps.2023.101918.

Mallik S, Mohanty J, Sahoo SJ. Active phytoconstituents to tackle the resistance mechanism of MDR and XDR bacteria: A critical review. Microbes Infect Dis 2025; 6(3): 4005-4019.