

HARNESSING PHYTOCHEMICALS: MEDICINAL PLANTS AS A FRONTIER AGAINST
MDR PATHOGENS

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Background: The escalating prevalence of multidrug-resistant (MDR) pathogens is fueling a serious healthcare crisis worldwide, undermining the efficacy of conventional antibiotic treatments. The worsening crisis has promoted increased interest in the search for novel antimicrobial agents that are particularly targeted toward bioactive natural products. Medicinal plants, especially key members of traditional medicinal systems adhered to by most cultures on the globe, are rich sources of phytochemicals possessing broad-spectrum antimicrobial properties. **Materials & Methods:** This review extensively discusses the promise of medicinal plants as a strategic choice against MDR bacterial infections. Specific attention is given to important phytochemical groups alkaloids, flavonoids, terpenoids, tannins, and phenolics and their multi-targeting activities such as efflux pump inhibition, membrane disruption, biofilm inhibition, and synergism with traditional antibiotics. **Results:** Plant extracts exhibited significant antimicrobial activity against MDR pathogens, especially when used in combination with antibiotics. Synergistic effects included inhibition of efflux pumps and biofilm disruption. However, variability in efficacy due to extract composition highlights the need for standardization and optimized delivery systems. **Conclusion:** Amid growing antibiotic resistance, medicinal plants emerge as a powerful alternative due to their multi-target action and low risk of resistance. While issues like bioavailability and standardization pose challenges, their potential as adjuvants in combating MDR infections is clear. Advancing their use will require focused efforts on formulation, efficient delivery, and clinical validation.

KEYWORDS: Medicinal plants, Phytochemicals, Multidrug resistance (MDR), Antimicrobial resistance (AMR), Bioactive compounds, Antibiotic alternatives.

1. INTRODUCTION

Antibiotic resistance is a worldwide emergency, with MDR infections accounting for high death tolls and economic losses. Bacterial resistance directly contributed to 1.27 million deaths globally in 2019, as estimated by a seminal study, with 4.95 million deaths linked with antimicrobial-resistant infection.^[1] The World Health Organization (WHO) warned that AMR-associated death will hit 10 million a year by 2050 if there is no quick intervention.^[2] Overuse and misuse of antibiotics, horizontal gene transfer, and the sluggish rate of antibiotic development are the key drivers of MDR. MDR happens when bacteria, fungi, or other microbes become resistant to multiple antibiotics, making standard treatment unsuccessful.^[3] The World Health Organization (WHO) reports that MDR infections kill millions of people each year, with a rising pattern of resistance found in bacteria like *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa*.^[4] The emergence of resistant infections has been accelerated by the overuse of antibiotics in medicine, agriculture, and animal husbandry. The slow

progress of the discovery of new antibiotics, combined with pharmaceutical firms diverting attention from the research of antibiotics because of low returns, has further deepened the crisis.^[5] Confronted with these issues, the quest for new antimicrobials has gained momentum. The global emergence of MDR has underscored the need for new antimicrobial agents. Traditional antibiotics are increasingly becoming ineffective because of bacterial evolution, overuse, and misuse.^[6] The growing failure of traditional antibiotics has forced the discovery of alternative therapeutic agents, and medicinal plants are being seen as good prospects. Medicinal plants, used for centuries in folklore medicine, are presently being under thorough investigation for their ability to fight against MDR infections due to their vast diversity of bioactive compounds.^[7] Compounds of plant origin mostly possess antibacterial, antiviral, antifungal, and antiparasitic activities, which are useful in the creation of novel therapeutics. In light of these difficulties, scientists are looking to natural sources, and more specifically medicinal plants, as substitute or complementary solutions to current antibiotics.^[8] Many plant compounds

have strong antimicrobial activities, and they are able to fight off MDR pathogens using various mechanisms involving the inhibition of biofilm formation, efflux pump inhibition, and membrane disruption. This essay examines the promise of medicinal plants in fighting MDR, their mechanisms of action, scientific advances in recent times, and how they can break the chain of antibiotic resistance.^[9]

2. MECHANISTIC INSIGHTS INTO MULTIDRUG RESISTANCE (MDR)

Microorganisms such as bacteria, fungi, viruses, and parasites describe their resistance to the action of several antimicrobials. This is a serious worldwide health problem that reduces the effectiveness of drugs and makes morbidity and mortality due to infectious diseases higher.^[10] MDR mechanisms can be categorized broadly into intrinsic resistance, which occurs naturally in some microbial species, and acquired resistance, which occurs as a result of genetic modification or horizontal gene transfer. Molecular and biochemical mechanisms of MDR are essential to understand in order to devise new therapeutic approaches to combat drug-resistant infections.^[11] Efflux pumps make a huge contribution to multidrug resistance (MDR) by pumping antibiotics out of microbial cells, reducing their intracellular levels. Such transporters belong to families like ABC (ATP-dependent), RND, and MFS (both proton motive force-dependent). The RND pump AcrAB-TolC of *E. coli* and *P. aeruginosa* pumps out several antibiotics, whereas the MFS pump NorA of *S. aureus* causes resistance to fluoroquinolones. Overexpression of these pumps has been associated with increased resistance and clinical treatment failure.^[12] Pathogens resist antimicrobials in many cases by synthesizing enzymes that degrade or modify drugs. β -lactamases, such as ESBLs and carbapenemases, inactivate β -lactam antibiotics in pathogens such as *A. Baumannii* and *K. pneumoniae*. Aminoglycoside-modifying enzymes (AMEs) modify drugs such as gentamicin through acetylation, phosphorylation, or adenylation. Chloramphenicol acetyltransferase (CAT) inactivates chloramphenicol by acetylation. These genes of resistance tend to disseminate through plasmids and transposons and exacerbate MDR.^[13] Pathogens avoid antimicrobials by changing drug targets, decreasing drug binding. Resistance to fluoroquinolones involves DNA gyrase and topoisomerase IV mutations. Erm-catalyzed 23S rRNA methylation causes macrolide-lincosamide-streptogramin (MLS) resistance. In MRSA, *mecA* encodes PBP2a, a β -lactam-resistant penicillin-binding protein. In *Mycobacterium tuberculosis*, *katG* mutations prevent isoniazid activation.^[14] Pathogens can resist antimicrobials by metabolic adaptations. Sulfonamide and trimethoprim resistance results from mutations in *folP* (DHPS) and *folA* (DHFR), lowering drug binding but maintaining folate production. These adaptations facilitate survival in spite of drug presence.^[15]

2.1 DEVELOPMENT DYNAMICS AND MATURATION OF BIOFILM

Biofilm formation is an essential defense mechanism that plays a major role in multidrug resistance (MDR). These organized microbial populations, within a self-synthesized extracellular polymeric substance (EPS), restrict antibiotic penetration and enhance persistence. *Pseudomonas aeruginosa* is a recognized biofilm-former that exhibits increased resistance because of both its EPS barrier and due to the presence of dormant persister cells. Biofilm formation is a controlled, multi-step procedure that consists of the transition from free-floating (planktonic) cells to a refractory, sessile population. This adaptation increases survival against antimicrobials, immune defenses, and environmental stress, making it difficult to treat and necessitating the use of biofilm-directed therapies.^[16] Motile planktonic microorganisms come into contact with an abiotic or biotic substratum. Transient reversible adhesion takes place through weak physicochemical interactions such as hydrophobic interactions, vander Waals interactions and electrostatic forces. The physicochemical nature of the substratum (e.g., roughness, hydrophilicity/hydrophobicity, and charge) plays a decisive role in determining the probability of microbial adhesion.^[17] With extended contact, microbial cells stabilize adhesion through the production of extracellular polymeric substances (EPS), i.e., lipids, protein, polysaccharides and extracellular DNA (eDNA). Appendages on the surface like fimbriae, pili, flagella, and adhesins enable strong attachment by contacting substratum molecules. Induction of quorum sensing (QS) pathways, controlled by autoinducer molecules (e.g., oligopeptides in Gram-positive bacteria and acyl-homoserine lactones in Gram-negative bacteria), promotes coordinated gene expression to sustain biofilm development.^[18] Adhering cells grow and develop microcolonies by clonal growth and recruitment of other microbial components as shown in **Figure 1**. EPS production increases, covering microbial clusters with a sheltering matrix acting as a scaffolding biofilm for stability. Interspecies and intraspecies communication through QS signaling pathways controls genetic regulation, enabling phenotypic diversity and metabolic specialization among biofilm residents.^[19]

The biofilm matures architecturally, becoming a sophisticated three-dimensional matrix with water channels that allow for nutrient diffusion and waste efflux. The microbial cells undergo physiological differentiation, such as persister cell formation, efflux pump operation, and metabolic changes, resulting in increased tolerance to disinfectants, standard drugs (antibiotics) and host immune responses.^[20] Biofilm dispersal is caused by environmental cues, such as nutrient starvation, shear stress, QS signaling, and enzymatic degradation of the EPS matrix. Dispersal is either through active motility (e.g., flagellar-dependent swimming, twitching, or gliding motility) or passive detachment. Released planktonic cells have increased

virulence and colonization capacity, sustaining biofilm dissemination into new ecological niches.^[21]

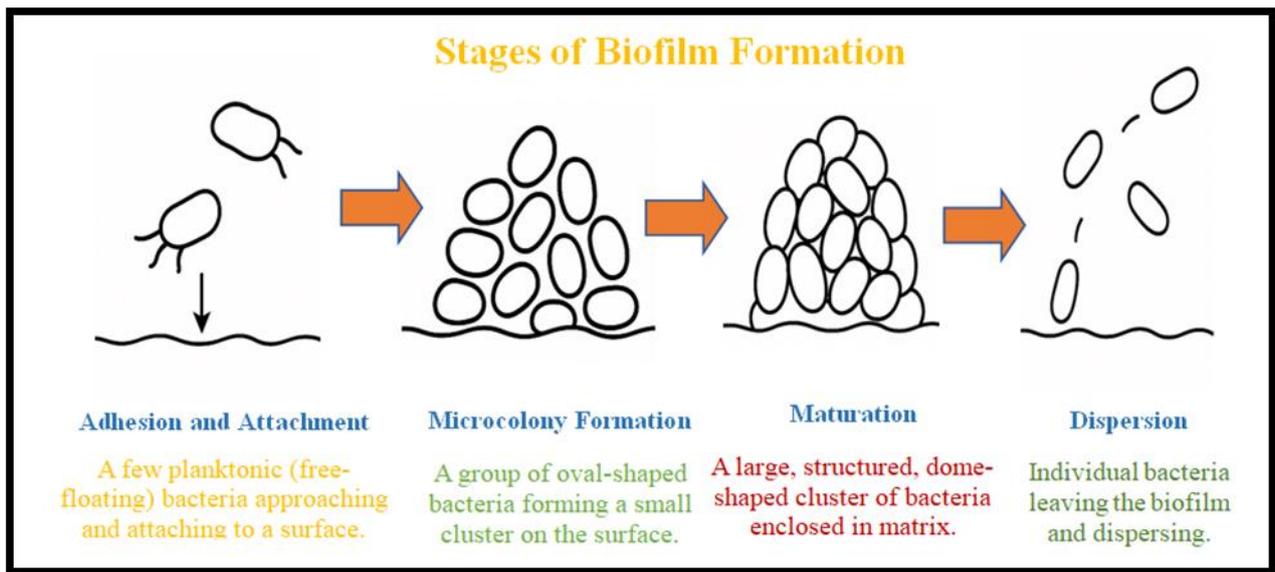


Figure 1: Different stages of biofilm formation.

2.2 HORIZONTAL GENE TRANSFER

Multidrug resistance (MDR) is transferred easily by horizontal gene transfer (HGT) through plasmids, transposons, integrons, and bacteriophage-transduction. For instance, ESBL-producing *E. coli* usually have β -lactamase genes on conjugative plasmids. These processes allow the spread of resistance genes in clinical and environmental environments, highlighting the need for stringent antibiotic stewardship and monitoring.^[22] MDR is caused by multiple mechanisms, such as efflux pumps, enzymatic inactivation of drugs, target alteration, decreased permeability, metabolic bypassing, biofilm formation, and HGT. The control of MDR demands a holistic solution: careful use of antibiotics, creation of new antimicrobials, efflux pump inhibitors, biofilm breakers, and therapeutic alternatives such as phage therapy. Collaborative actions among health providers, investigators, and public health officials are critical to

contain the transmission of resistant pathogens and protect available treatment approaches.^[23]

3. MEDICINAL PLANT RESOURCES AND THEIR THERAPEUTIC UTILIZATION

Medicinal plants possess bioactive phytochemicals with therapeutic activity and have been utilised in traditional systems such as Ayurveda, TCM, and Unani for centuries. Important phytochemicals including flavonoids, alkaloids, polyphenols and terpenoids possess anti-inflammatory, antimicrobial, antioxidant, and various pharmacological activities. Pharmacognosy, the scientific study of medicinal plants, plays a crucial role in drug discovery. Himachal Pradesh, having a variant climate and high biodiversity, contains a variety of medicinal plants that form the backbone of traditional medicine systems.^[24] Several medicinal plants having therapeutic properties have been discussed in **Table 1**.

Table 1: Various medicinal plants exhibiting Pharmacological potential.

S.No.	Medicinal plant	Common Name	Medicinal uses	References
1.	<i>Picrorhiza kurroa</i>	Kutki	Hepatoprotective, anti-inflammatory, antioxidant, immunomodulatory	Raut et al., 2023 ^[25]
2.	<i>Aconitum heterophyllum</i>	Atees	Antipyretic, anti-inflammatory, digestive stimulant	Talreja & Tiwari, 2023 ^[26]
3.	<i>Viola odorata</i>	Banafsha	Expectorant, anti-inflammatory, antipyretic	Bashir et al., 2021 ^[27]
4.	<i>Nardostachys jatamansi</i>	Jatam	Neuroprotective, anti-anxiety, memory-enhancing, anti-inflammatory	Kumar & Behera, 2023 ^[28]
5.	<i>Saussurea costus</i>	Kuth	anti-inflammatory, digestive Antibacterial stimulant.	Elnour & Abdurahman, 2024 ^[29]
6.	<i>Withania somnifera</i>	Ashwagandha	Adaptogenic, anti-stress, immune-boosting, anti-inflammatory.	Mikulska et al., 2023 ^[30]
7.	<i>Swertia chirayita</i>	Chirayata	Antimalarial, hepatoprotective, antimicrobial, anti-inflammatory	Kumar & Van Staden, 2016 ^[31]
8.	<i>Bacopa monnieri</i>	Brahmi	Cognitive-enhancing, adaptogenic,	Choudhary et al.,

			neuroprotective	2021 ^[32]
9.	<i>Commiphora wightii</i>	Guggul	Anti-inflammatory, lipid-lowering, analgesic	Kunnumakkar et al., 2018 ^[33]
10.	<i>Tinospora cordifolia</i>	Giloy	Immunomodulatory, anti-inflammatory, antipyretic	Gupta et al., 2024 ^[34]

4. PLANT-DERIVED STRATEGIES TO TREAT MULTIDRUG RESISTANCE

Multi-drug resistance (MDR) is a tremendous challenge in the therapeutic management of bacterial infections, fungal infections, and cancer. The capacity of pathogenic organisms and cancer cells to resist pharmacological

actions by efflux pumps, biofilm formation, enzymatic hydrolysis, and mutations requires new therapeutic modalities. Medicinal plants offer a good hope for resolving MDR because they contain varied bio-active molecules that act on resistance mechanisms as illustrated in **Figure 2**.

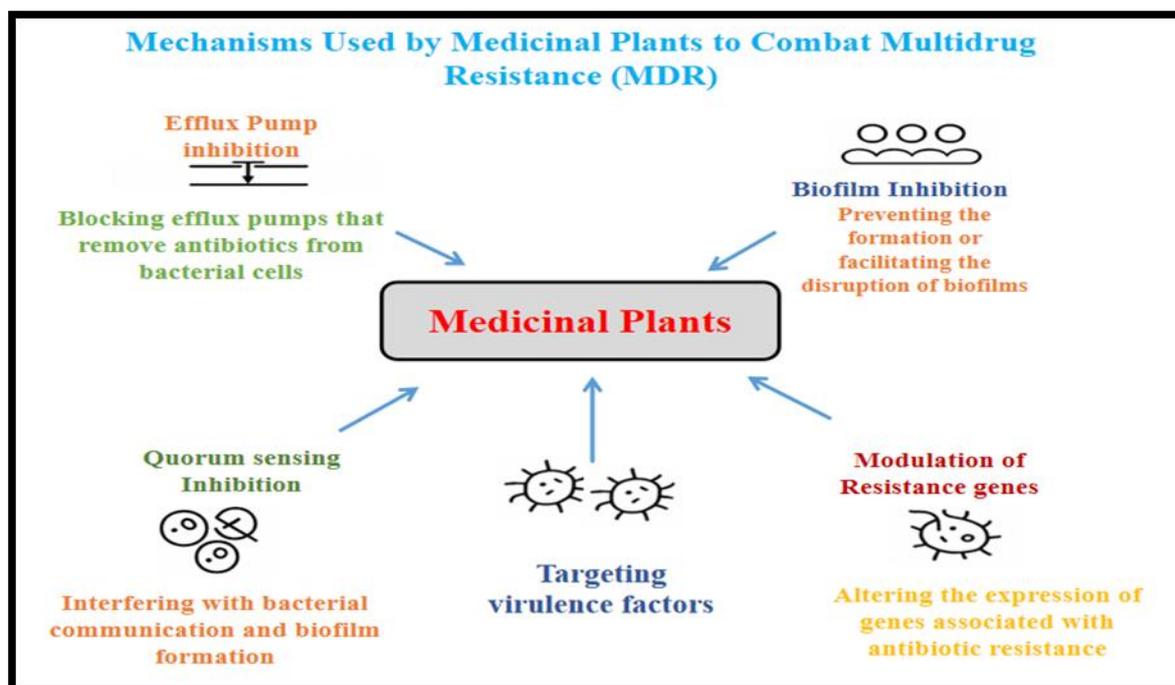


Figure 2: Mechanism of action of Medicinal plants in combating MDR.

- **Modulation of Efflux Pump**

Efflux pumps, such as the ATP-binding cassette (ABC) and resistance-nodulation-division (RND) transporters, play a critical role in expelling drugs from cells, thereby reducing intracellular drug concentrations. Phytochemicals, including alkaloids, flavonoids, and terpenoids, have been shown to inhibit efflux pumps, restoring drug efficacy. Resveratrol (from *Vitis vinifera*) inhibits bacterial efflux pumps, preventing antibiotic expulsion. Berberine (from *Berberis* species) acts as a potent efflux pump inhibitor, enhancing antimicrobial activity. Curcumin (from *Curcuma longa*) modulates efflux pump expression in chemoresistant cancer cells.^[35]

- **Destabilization of Cell Structures**

Cell membrane integrity is essential for pathogen survival. Most plant-derived compounds have antimicrobial activity through increased membrane permeability or lipid bilayer disruption. Thymol and carvacrol from (*Thymus vulgaris* and *Origanum vulgare*) respectively share lipophilic nature, incorporating into microbial membranes and inducing structural changes.

Saponins from (*Glycyrrhiza glabra* and *Panax ginseng*) interfere with membrane integrity, increasing antibiotic penetration.^[36]

- **Impairment of Biofilm Initiation and Maturation**

Biofilms, multicellular microbial communities trapped in extracellular polymeric substances, impart enhanced resistance to antimicrobial compounds. Numerous phytochemicals have antibiofilm activity, inhibiting biofilm growth or disorganizing established biofilms. Quercetin from (*Allium cepa* and *Malus domestica*) prevents biofilm formation by interfering in quorum sensing signaling. Allicin from (*Allium sativum*) disorganizes biofilms in *Pseudomonas aeruginosa*, rendering the bacteria more susceptible to antibiotics.^[37] Efflux pumps like the resistance-nodulation-division (RND) and ATP-binding cassette (ABC) transporters are responsible for drug expulsion from cells, decreasing intracellular drug levels. Phytochemicals like alkaloids, flavonoids, and terpenoids have been found to inhibit efflux pumps, reversing drug efficacy. Resveratrol (from *Vitis vinifera*) inhibits bacterial efflux pumps, halting

antibiotic expulsion. Berberine (from *Berberis* species) inhibits efflux pumps as an effective efflux pump inhibitor, increasing antimicrobial activity. Curcumin (from *Curcuma longa*) regulates efflux pump expression in chemoresistant cancer cells.^[38]

- **Modulation of Resistance-Linked Enzymes Genetic Routes**

Bacteria and cancer cells often employ enzymatic degradation of drugs or genetic mutations to resist treatment. Certain plant-derived compounds inhibit these resistance mechanisms. Epigallocatechin gallate (EGCG) from (*Camellia sinensis*) inhibits β -lactamase enzymes, preventing antibiotic degradation. Baicalein from (*Scutellaria baicalensis*) down regulates resistance genes, restoring drug efficacy.^[39]

- **Immunomodulatory Response**

Immunomodulatory phytochemicals augment host defense mechanisms, inhibiting pathogen survival and cancer development. Echinacea species augment macrophage activation and cytokine release. *Astragalus membranaceus* activates natural killer (NK) cell function and augments immune surveillance.^[40]

- **Synergistic Interactions with Conventional Drugs**

Phytochemicals are usually synergistic with antibiotics and chemotherapy, raising drug activity and inhibiting resistance development. Piperine from *Piper nigrum* enhances drug bioavailability by preventing hepatic metabolism. Curcumin augments cytotoxic activities of chemotherapeutic agents on resistant cancer cells.^[41]

5. PLANT-BASED BIOACTIVES AS SUBSTITUTES FOR ANTIBIOTICS

Increased emergence of antibiotic-resistant bacteria, caused mainly due to excessive use and misuse of antibiotics, has been a great concern to global health. Subsequently, plant-derived bioactive molecules have been identified as potential alternatives based on their immunomodulatory, antimicrobial and anti-inflammatory activities.^[6] Plants are known to synthesize a wide variety of secondary metabolites like tannins, flavonoids, alkaloids and volatile oils with broad-spectrum antimicrobial properties and synergism against multiple microbial targets, making resistance unlikely.^[42] Compared to synthetic antibiotics that tend to have side effects and interfere with gut microbiota, plant extracts are typically more biocompatible and provide other health benefits such as promoting immunity and lowering inflammation.^[43] For instance, flavonoids such as quercetin interfere with bacterial metabolism, tannins prevent adhesion, alkaloids such as berberine interfere with DNA replication, and essential oils interfere with microbial membranes.^[44] In addition, the application of plant antimicrobials is an environmentally friendly strategy that avoids pharmaceutical contamination and diminishes antibiotic consumption in animal production and husbandry.^[45] Consequently, medicinal plants pose a

multi-dimensional and sustainable solution to the escalating challenge of antibiotic resistance.

6. CHALLENGES & FUTURE ASPECTS

The clinical application of plant extracts against multidrug-resistant (MDR) bacteria faces challenges due to phytochemical variability influenced by species, geography, cultivation, and extraction methods, resulting in inconsistent antimicrobial efficacy. Limited mechanistic insights and poor pharmacokinetic properties such as low bioavailability, solubility, stability, and rapid metabolism reduce in vivo therapeutic potential. Resistance development risk persists, necessitating combination therapies to prevent MDR emergence. Regulatory hurdles stem from inadequate standardized testing protocols, difficulties in large-scale extraction, and scarce in vivo and clinical data, while pharmaceutical industries favor synthetic drugs for their characterized pharmacodynamics and streamlined approval. Advancements in metabolomics, high-throughput screening, and bioinformatics facilitate identification of potent bioactives, whereas synthetic biology and metabolic engineering improve phytochemical biosynthesis and stability through genetic modifications. Nanotechnology-based delivery systems (liposomes, polymeric nanoparticles, metal carriers) enhance solubility, targeted delivery, and sustained release, reducing toxicity. Integration of plant-derived antimicrobials with conventional antibiotics shows promise in synergistically overcoming MDR pathogens, highlighting the need for multidisciplinary approaches combining phytochemical characterization, novel drug delivery, and rigorous clinical validation.^[6]

7. CONCLUSION

Traditional antibiotics have been the cornerstone of infection treatment for centuries, but the emergence of multidrug-resistant (MDR) pathogens has weakened their performance, making alternative treatments necessary. Plant-derived extracts provide a promising alternative because of their varied bioactive compounds, multi-targeting mechanisms, and reduced risk of resistance development. In contrast to antibiotics with selective inhibition of specific bacterial processes, plant phytochemicals synergistically inhibit several processes such as efflux pump inhibition and biofilm disruption and thus increase their antimicrobial efficacy. In spite of these advantages, difficulties in standardization, bioavailability, mass production, and regulatory approval restrict their use for direct replacement of antibiotics. Nevertheless, adding plant extracts as adjuvants or in combination therapy is a sustainable approach for the control of MDR infections. Future work should aim for biotechnological optimization, novel delivery systems, and clinical proof of principle to exploit the therapeutic benefits of plant antimicrobials and decrease dependence on traditional antibiotics.

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