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Natural Herbal Drugs in Multidrug-Resistant, Extensively Drug-Resistant and Totally Drug-Resistant Bacterial Infection: A Comprehensive Review on Medicinal Plants

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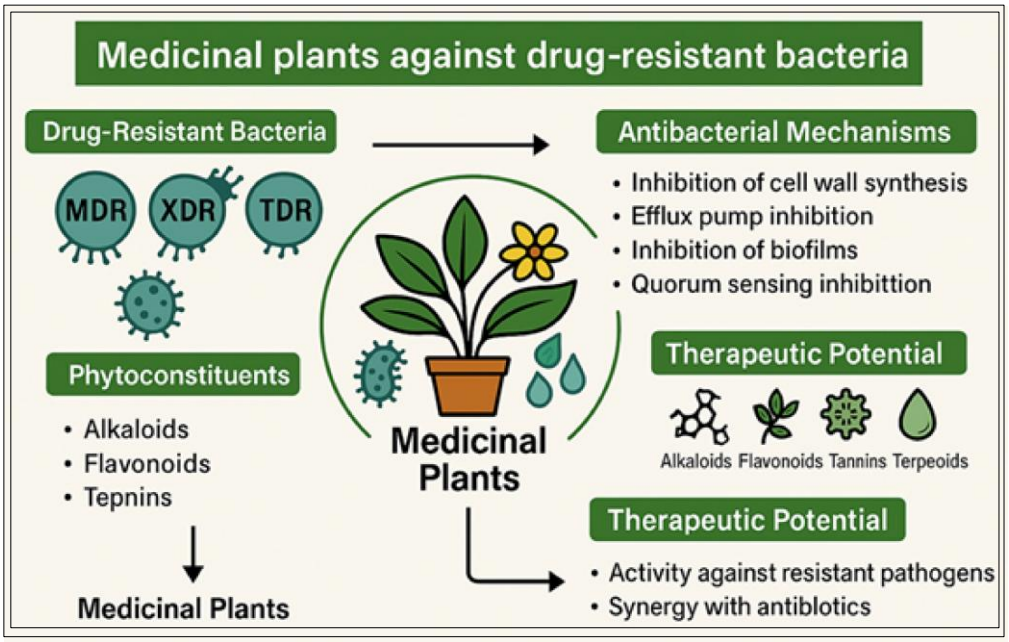

Abstract

The alarming rise of multidrug-resistant (MDR), extensively drug-resistant (XDR) and totally drug-resistant (TDR) bacterial pathogens poses a critical challenge to global public health, rendering many conventional antibiotics increasingly ineffective. The accelerated emergence of these resistance profiles has led to treatment failures; prolonged hospital stays and increased mortality rates. In this dire scenario, medicinal plants represent a promising, cost-effective and sustainable alternative for the discovery of novel antimicrobial agents with unique mechanisms of action. This comprehensive review highlights a diverse array of medicinal plants and their phytoconstituents that exhibit significant antibacterial activity against drug-resistant pathogens. Emphasis is placed on traditional ethnobotanical knowledge, the pharmacological efficacy of plant-based compounds and their molecular mechanisms, such as inhibition of cell wall synthesis, efflux pumps, biofilm formation and quorum sensing. Furthermore, the review explores the synergistic potential of herbal agents with existing antibiotics, current research progress, formulation advancements and the challenges hindering clinical translation. By bridging traditional medicine with modern scientific validation, herbal antimicrobials could contribute substantially to combating the growing threat of antimicrobial resistance (AMR).

Keywords: *Multidrug Resistance (MDR); Extensively Drug-Resistant (XDR); Totally Drug-Resistant (TDR); Antimicrobial Resistance (AMR); Natural Antibiotics; Ethnopharmacology; Bioactive Compounds; Mechanism Of Action; Synergistic Therapy.*

1. INTRODUCTION

The rapid emergence and global spread of bacterial strains resistant to multiple antibiotics represent one of the most pressing threats to modern medicine. Multidrug-resistant (MDR), extensively drug-resistant (XDR) and totally drug-resistant (TDR) pathogens have been implicated in the increasing rates of treatment failure, prolonged hospital stays, heightened morbidity and mortality and escalating healthcare

costs worldwide (Ventola, 2015; Prestinaci et al., 2015). According to the World Health Organization (WHO), antimicrobial resistance (AMR) is now considered one of the top ten global public health threats facing humanity (WHO, 2023). The misuse, overuse and inappropriate prescription of antibiotics in both human medicine and agriculture have significantly accelerated the development of resistance mechanisms in bacterial populations. Pathogens such as Mycobacterium tuberculosis, Klebsiella pneumoniae, Escherichia coli and Staphylococcus aureus have evolved resistance to nearly all known classes of antibiotics, including last-resort drugs like carbapenems and colistin (Tacconelli et al., 2018; CDC, 2022). Without immediate and coordinated global action, we risk entering a "post-antibiotic era" where common infections and minor injuries could once again become fatal.

In light of the dwindling efficacy of conventional antibiotics and the slow pace of novel antibiotic development, attention has increasingly turned to alternative sources of antimicrobial agents. Medicinal plants, long used in traditional systems of medicine such as Ayurveda, Traditional Chinese Medicine and African ethnomedicine, offer a rich repository of bioactive compounds with potent antibacterial properties (Newman & Cragg, 2020). These phytochemicals—such as alkaloids, flavonoids, terpenoids and phenolics—exhibit diverse mechanisms of action, including disruption of bacterial cell walls, inhibition of protein synthesis, efflux pump blockade and interference with quorum sensing and biofilm formation (Gakuya et al., 2020; Rather et al., 2021). This review aims to provide a comprehensive evaluation of medicinal plants and their phytoconstituents with demonstrated antimicrobial efficacy against MDR, XDR and TDR bacterial pathogens. It also highlights the potential of these natural agents as viable alternatives or adjuncts to conventional antibiotics and discusses their mechanisms of action, therapeutic potential, limitations and future research prospects.

2. Present Scenario of Antibiotic Resistance

The global healthcare landscape is increasingly burdened by the proliferation of antibiotic-resistant bacterial strains, posing a formidable threat to public health and medical progress. Antimicrobial resistance (AMR) has escalated due to a complex interplay of biological, social and economic factors, leading to the emergence of organisms that are increasingly difficult or impossible to treat with existing antibiotics (CDC, 2022; WHO, 2023).

Classification of Resistant Bacteria

- **Multidrug-Resistant (MDR) Bacteria:** Defined as bacterial strains resistant to at least one agent in three or more classes of antimicrobial drugs (Magiorakos et al., 2012).
- **Extensively Drug-Resistant (XDR) Bacteria:** Resistant to nearly all antimicrobial classes, retaining susceptibility to only one or two categories.
- **Totally Drug-Resistant (TDR) Bacteria:** Exhibit resistance to all available antibiotics, rendering treatment virtually impossible (Udwadia et al., 2012; World Bank, 2023).

These classifications help clinicians and public health authorities prioritize infections and develop effective containment strategies.

Urgent and Critical Threat Pathogens

The World Health Organization (WHO) and Centres for Disease Control and Prevention (CDC) have identified several high-priority drug-resistant pathogens, including:

- Mycobacterium tuberculosis (including MDR-TB and XDR-TB),
- Pseudomonas aeruginosa,
- Acinetobacter baumannii,
- Klebsiella pneumoniae (notably carbapenem-resistant strains),
- Methicillin-resistant Staphylococcus aureus (MRSA),
- Extended-spectrum β-lactamase (ESBL)-producing Escherichia coli (Tacconelli et al., 2018; CDC, 2022; WHO, 2023)

Contributing Factors to Resistance

Several factors contribute to the acceleration of antimicrobial resistance:

- **Over-Prescription of Antibiotics:** The unnecessary use of antibiotics, especially for bacterial infections, continues to fuel resistance. Studies estimate that over 30% of antibiotic prescriptions in outpatient settings are unnecessary (Fleming-Dutra et al., 2016).

• **Antibiotic Use in Livestock:** The routine administration of antibiotics in agriculture for growth promotion and prophylaxis contributes to the selection of resistant strains, which can be transmitted to humans via the food chain or environment (Van Boeckel et al., 2019).
• **Hospital-Acquired Infections (HAIs):** Nosocomial infections, particularly in intensive care units (ICUs), often involve MDR pathogens due to invasive procedures, immunocompromised patients and high antibiotic exposure.
• **Stagnation in Antibiotic Discovery:** There is a critical lack of novel antibiotic classes in the pharmaceutical pipeline, with most recent antibiotics being derivatives of existing drugs (Theuretzbacher et al., 2020). The high cost and low return on investment have deterred industry innovation.
Collectively, these factors underscore the urgent need for alternative therapies and global stewardship efforts to control the spread of resistance.

3. Common Resistant Bacterial Diseases and Causative Agents
Antibiotic resistance has significantly affected the management of common bacterial infections globally. Diseases such as tuberculosis, pneumonia, urinary tract infections (UTIs), wound infections and gastrointestinal disorders are now frequently associated with multidrug-resistant (MDR), extensively drug-resistant (XDR) and even totally drug-resistant (TDR) bacterial strains (Tacconelli et al., 2018). The emergence of resistant strains like ESBL-producing E. coli, carbapenem-resistant Klebsiella pneumoniae and MRSA has rendered many conventional antibiotics ineffective (CDC, 2022; WHO, 2023). Medicinal plants such as Curcuma longa, Azadirachta indica, Ocimum sanctum, Allium sativum and Tinospora cordifolia have demonstrated significant antibacterial activity and are being explored as alternatives or adjuncts to synthetic antimicrobials (Gupta et al., 2020; Hemaiswarya et al., 2008).

Table 1. Common Drug-Resistant Diseases, Causative Agents, Resistance Category and Potential Herbal Remedies.

Disease	Causative Agent(s)	Resistance Category	Example Herbal Remedies
Tuberculosis	Mycobacterium tuberculosis	MDR, XDR, TDR	Curcuma longa, Tinospora cordifolia
Pneumonia	Streptococcus pneumoniae, K. pneumoniae	MDR, XDR	Nigella sativa, Allium sativum
Urinary Tract Infection (UTI)	E. coli, Proteus spp., K. pneumoniae	ESBL, MDR	Ocimum sanctum, Vaccinium macrocarpon (cranberry)
Wound Infections	MRSA, Acinetobacter baumannii	MDR, XDR	Azadirachta indica, Melaleuca alternifolia
Gastrointestinal Infections	Salmonella spp., Shigella spp., E. coli	MDR	Zingiber officinale, Berberis aristata
Meningitis	Neisseria meningitidis, S. pneumoniae	MDR	Withania somnifera, Ocimum sanctum
Typhoid Fever	Salmonella typhi	MDR, XDR	Emblica officinalis, Terminalia chebula
Skin and Soft Tissue Infections	Staphylococcus aureus, Pseudomonas aeruginosa	MDR, XDR	Aloe vera, Calendula officinalis

Several medicinal plants have demonstrated promising antimicrobial activity against drug-resistant pathogens. For example, Curcuma longa (curcumin) exhibits significant inhibition of MDR M. tuberculosis, while Azadirachta indica (neem) and Allium sativum (garlic) show efficacy against MRSA and Acinetobacter spp. (Gupta et al., 2020; Kuete & Efferth, 2012). These natural alternatives offer new hope in the treatment of resistant infections and should be further explored for potential clinical use.

4. Conventional Treatments and Their Limitations

The treatment of drug-resistant bacterial infections increasingly relies on last-resort antibiotics such as carbapenems (e.g., Imipenem, Meropenem), Polymyxins (e.g., Colistin) and Fluoroquinolones (e.g., Ciprofloxacin, Levofloxacin). These antibiotics are typically reserved for severe infections where first- and second-line agents have failed (Boucher et al., 2009; Tacconelli et al., 2018). However, the emergence of resistance even to these critical antibiotics is alarming. For example, resistance to colistin—once considered a final-line drug—has been reported in Klebsiella pneumoniae, E. coli and Acinetobacter baumannii via the plasmid-mediated mcr-1 gene (Liu et al., 2016; Wang et al., 2020). Similarly, carbapenem-resistant Enterobacteriaceae (CRE) have been declared an urgent public health threat by both the WHO and CDC (CDC, 2022; WHO, 2023). Apart from resistance, adverse effects limit the use of these antibiotics. Polymyxins can cause nephrotoxicity and neurotoxicity, fluoroquinolones are linked to gastrointestinal upset, hepatotoxicity and tendinopathy and carbapenems may induce seizures and hypersensitivity reactions (Falagas & Kasiakou, 2006; LiverTox, 2021). Moreover, the high cost and limited availability of these drugs, especially in low- and middle-income countries (LMICs), restrict effective treatment (Laxminarayan et al., 2013). Resistance may even emerge during therapy, rendering treatment ineffective in real time and leading to clinical failure (Doi et al., 2020). This growing crisis underscores the urgent need to explore alternative antimicrobial strategies, including plant-derived Phyto therapeutics with novel modes of action.

5. Medicinal Plants with Antibacterial Activity

Numerous medicinal plants exhibit potent activity against multidrug-resistant (MDR), extensively drug-resistant (XDR) and totally drug-resistant (TDR) bacterial pathogens. Their bioactive compounds act through diverse mechanisms such as disrupting bacterial membranes, inhibiting enzyme systems and modulating quorum sensing. Recent in vitro, in silico and nanotechnology-enhanced studies provide compelling evidence for their antimicrobial prowess.

Highlighted herbal candidates and their efficacy:

- **Azadirachta indica (Neem):** Active compounds like nimbidin, azadirachtin and nimbolide exhibit strong antibacterial activity against MRSA, E. coli and P. aeruginosa by disrupting cell membranes, inhibiting enzymes and interfering with DNA replication (Mudenda et al., 2023; Ghosh et al., 2024).
- **Allium sativum (Garlic):** Contains allicin, ajoene and sulphides that demonstrate bactericidal effects against MDR S. aureus (including MRSA), Salmonella, P. aeruginosa and E. coli by modifying protein thiols and inhibiting penicillin-binding proteins (Merrell, 2022; Ghosh et al., 2024).
- **Curcuma longa (Turmeric):** Curcumin, especially in nanoparticle formulations (e.g., SMA-CUR nanomicelles, ZnO nanoparticle-enhanced extracts), effectively inhibits MRSA, K. pneumoniae, A. baumannii and reduces biofilms and efflux-pump gene expression (Pourasgar et al., 2024; Aldayel, 2023; Stagno et al., 2023).
- **Ocimum sanctum (Tulsi):** Eugenol and ursolic acid show broad-spectrum activity against E. coli, S. aureus and Pseudomonas spp., though recent quantifications are ongoing.
- **Andrographis paniculata:** Andrographolide has demonstrated in vitro activity against MDR M. tuberculosis (Gupta et al., 2020).
- **Phyllanthus niruri:** Phyllanthin is effective against ESBL-producing E. coli and Shigella spp. (Hemaiswarya et al., 2008).
- **Lawsonia inermis (Henna):** Lawsone has demonstrated activity versus MDR Acinetobacter spp. and MRSA (Ahmad & Aqil, 2007).
- **Terminalia chebula:** Chebulagic acid exhibits broad-spectrum antimicrobial activity, including resistant strains (Kuete & Efferth, 2012).

Table 2. Medicinal Plants vs. Drug-Resistant Pathogens.

Plant	Active Compound (s)	Target Pathogens
Azadirachta indica (Neem)	Nimbidin, Azadirachtin, Nimbolide	MRSA, E. coli, P. aeruginosa
Allium sativum (Garlic)	Allicin, Ajoene, Sulfides	MDR S. aureus, Salmonella, P. aeruginosa, E. coli

Curcuma longa (Turmeric)	Curcumin	MRSA, K. pneumoniae, A. baumannii
Ocimum sanctum (Tulsi)	Eugenol, Ursolic acid	E. coli, S. aureus, Pseudomonas spp.
Andrographis paniculata	Andrographolide	MDR M. tuberculosis
Phyllanthus niruri	Phyllanthin	ESBL E. coli, Shigella spp.
Lawsonia inermis (Henna)	Lawsone	MDR Acinetobacter, MRSA
Terminalia chebula	Chebulagic acid	Broad-spectrum resistant strains

Research Insights

• **Neem:** Narrative and systematic reviews confirm that neem's photocidal agents (nimbidin, azadirachtin, nimbolide) disrupt bacterial membranes and cellular functions (Mudenda et al., 2023; Ghosh et al., 2024).

• **Curcumin:** SMA-CUR nanomicelles and ZnO nanoparticle-enhanced extracts significantly boost antimicrobial activity against MDR pathogens, reduce biofilm formation and efflux-pump gene expression (Stagno et al., 2023; Aldayel, 2023; Pourasgar et al., 2024).

These plant-derived compounds exhibit significant promise as alternative or adjunctive agents against resistant bacterial infections. Continued research into synergistic combinations, optimized delivery systems, safety profiles and clinical trials is essential for translating in vitro and nanotechnology-enabled success into clinical reality.

6. Mechanisms of Action of Herbal Compounds

Phytochemicals derived from medicinal plants combat drug-resistant bacteria through multiple, often synergistic mechanisms, enhancing their therapeutic potential and reducing the likelihood of resistance development:

1. Cell Wall/Membrane Disruption

Terpenoids and phenolics—such as curcumin, totarol and eugenol—intercalate into bacterial membranes, increasing permeability and causing lysis. Curcumin-ZnO nanoparticles dramatically enhance membrane disruption and ROS production, leading to biofilm reduction and bacterial death (Magdy et al., 2023; Stagno et al., 2023).

2. Protein Synthesis Inhibition

Flavonoids and tannins (e.g., luteolin, quercetin, biochanin A) interfere with ribosomal subunits or aminoacyl-tRNA synthetases, halting bacterial protein translation, as demonstrated in E. coli and P. aeruginosa (Eshra et al., 2020).

3. Efflux Pump Inhibition

Polyphenols like curcumin, quercetin and epigallocatechin-3-gallate inhibit efflux systems (e.g., NorA, AcrAB-TolC), restoring antibiotic efficacy and often exhibiting synergy with antibiotics (Joshi et al., 2018).

4. Biofilm Inhibition

Compounds such as curcumin, thymol, cinnamaldehyde and eugenol prevent biofilm formation, reduce extracellular polymeric matrix and disrupt motility. Eugenol nano emulsions particularly inhibit Listeria biofilms and bacterial communication (Balasubramaniam et al., 2023; Stagno et al., 2023).

5. Quorum Sensing Inhibition

Phytochemicals like Furanones, Curcumin, Eugenol and Carvacrol disrupt bacterial quorum sensing, reducing virulence factor expression and biofilm maturation in P. aeruginosa and other species (Nguyen et al., 2024; Balasubramanian et al., 2023).

6. ROS Generation

Phenolic compounds including eugenol, curcumin and thymol, especially when nano formulated (e.g., curcumin–ZnO), induce high intracellular ROS, overwhelm antioxidant defenses and trigger bacterial apoptosis (Magdy et al., 2023; Stagno et al., 2023).

Table 3. Mechanisms of Action of Key Phytochemicals.

Phytochemical	**Mechanism (s)**	**Example of Source**
Curcumin	Membrane disruption, ROS, efflux pump blockade, biofilm & quorum sensing inhibition	Curcuma longa

Eugenol	Membrane damage, ROS, antibiofilm, quorum sensing inhibition	Ocimum spp. / clove oil
Luteolin, Quercetin	Protein synthesis inhibition, efflux pump blocking	Flavonoids (Joshi et al.)
Biochanin A	Efflux pump inhibition	Isoflavones
Totarol	Cell wall interference, FtsZ inhibition, efflux pump activity	Totarol reviews

Herbal compounds deliver a multi-pronged attack on resistant bacteria by combining structural disruption, functional enzyme inhibition, virulence attenuation and oxidative stress. When used alongside antibiotics, they may restore drug sensitivity and reduce effective dosages. However, further rigorous in vivo studies and clinical trials are essential to convert promising laboratory findings into viable therapeutics.

2. DISCUSSION

Plant-derived antimicrobials present a promising strategy against drug-resistant bacteria due to their ability to act through multiple pathways, significantly reducing the likelihood of resistance emergence. By targeting various mechanisms—such as cell wall disruption, protein synthesis inhibition, efflux pump modulation and oxidative stress induction—these compounds provide robust and adaptable antibacterial defence (Hoerauf, 2024; Woo et al., 2023). A key advantage of phytochemicals is their synergy with conventional antibiotics. Studies reveal that combining plant extracts—like those from Senna alata, Ricinus communis and Lannea barteri—can dramatically reduce minimum inhibitory concentrations when used alongside standard antibiotics, even against MDR strains (Donkor et al., 2023; Bonincontro et al., 2023). This synergistic potential opens pathways to dose reduction, side-effect mitigation and prolonged antibiotic efficacy.

Despite encouraging in vitro and in vivo data, clinical translation remains limited. Major barriers include poor standardization due to variability in raw materials and extraction methods, insufficient clinical trials and complex regulatory hurdles (Paul & Kumar, 2023; Hoerauf, 2024). Fragmented global guidelines further complicate herbal drug approval, resulting in slow progress. On the technological front, advanced formulation techniques such as nanocarriers, phytosomes, liposomes and nanoemulsions have shown potential to enhance phytochemical bioavailability, stability and targeted delivery. However, these innovations come with increased manufacturing complexity and cost, demanding rigorous quality control and regulatory validation against defined standards.

To overcome these challenges and expedite the clinical uptake of plant-based antimicrobials, several measures are essential:

- Standardized Cultivation: Implementing Good Agricultural and Collection Practices (GACP) to ensure consistent phytochemical profiles.
- Robust Quality Control: Employing DNA barcoding, chromatographic fingerprinting and validated analytical tools as recommended by WHO and global pharmacopoeias (Paul & Kumar, 2023).
- Clinical Trial Innovation: Using adaptive and seamless master protocol designs to streamline evaluation while ensuring statistical rigor.
- Regulatory Harmonization: Collaborating across jurisdictions to establish unified frameworks for herbal drug assessment.

3. CONCLUSION

Medicinal plants represent a valuable and largely untapped resource in the global fight against multidrug-resistant (MDR), extensively drug-resistant (XDR)and totally drug-resistant (TDR) bacterial infections. Their ability to exert multitarget antimicrobial actions—including disruption of bacterial membranes, inhibition of efflux pumps, biofilm suppression and interference with quorum sensing—offers a significant advantage over conventional antibiotics, which often rely on a single mode of action and are thus more prone to resistance development. In addition to their pharmacological versatility, plant-derived compounds tend to exhibit lower toxicity, greater biocompatibility and improved patient tolerability, particularly when derived from traditionally used medicinal species. Their synergistic potential with existing antibiotics also opens avenues for dose-sparing strategies, reduced adverse effects and restoration of antibiotic sensitivity in resistant pathogens. Despite these advantages, the full therapeutic potential of herbal antimicrobials remains underutilized due to several challenges. These include inconsistent

phytochemical profiles, limited knowledge of molecular mechanisms, lack of rigorous toxicological assessments and the paucity of well-designed clinical trials. Moreover, regulatory uncertainty and the absence of standardized guidelines for herbal drug development further hinder their acceptance in mainstream medicine.

Moving forward, a multidisciplinary approach is essential. This includes:

- Isolation and structural characterization of active phytoconstituents.
- Mechanistic studies using omics, molecular docking and systems biology.
- Formulation advancements (e.g., nanotechnology, phytosomes) to enhance bioavailability.
- Comprehensive toxicity profiling in preclinical models.
- Clinical validation through well-structured, multi-center trials.

With scientific rigor and regulatory harmonization, medicinal plants could transition from traditional use to evidence-based, clinically integrated antimicrobial alternatives or adjunct therapies, offering hope in an era of growing antibiotic resistance.

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