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Role of Plant-Based Antimicrobial Agents in Controlling Multidrug-Resistant Bacteria: A Mini Review

Swechchha Soni and *Sumiran Srivastava

Department of Biochemistry,
Bundelkhand University, JHANSI-284128 (UP) INDIA
*Corresponding Author
E-mail : sumiran.srivastava@gmail.com

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ABSTRACT

The rapid escalation of multidrug-resistant (MDR) bacteria, particularly the virulent "ESKAPE" pathogens, has compromised conventional antibiotic efficacy and necessitated the search for alternative therapeutic strategies. Plant-derived antimicrobial agents have emerged as critical candidates due to their immense chemical diversity and multi-target modes of action, which impose lower selective pressure for resistance compared to synthetic drugs. This review synthesizes current research on medicinal plant extracts.such as those from *Curcuma longa, Allium sativum*, and *Azadirachta indica* and isolated phytochemicals including alkaloids, polyphenols, and terpenoids. These bioactive compounds exert their effects through diverse mechanisms, including the disruption of cell membrane integrity, inhibition of bacterial efflux pumps, interference with quorum sensing pathways, and the degradation of biofilm matrices. Furthermore, their role as antibiotic adjuvants facilitates the restoration of standard drug activity and potential dose reduction against resistant strains. Despite their potential, significant research gaps remain regarding standardized extraction methodologies, clinical validation, and the optimization of bioavailability. Future progress depends on leveraging nanotechnology-based delivery systems and advanced omics technologies to bridge the gap between laboratory findings and effective clinical applications.

Figure : 00 References : 30 Tables : 02

KEY WORDS : Antimicrobial activity, Biofilm inhibition, Efflux pump inhibitors, Multidrug-resistant bacteria, Phytochemicals, Quorum sensing, Secondary metabolite

Introduction

Antimicrobial resistance (AMR) represents one of the most critical challenges to global public health, compromising the efficacy of modern medical treatments and leading to increased morbidity and mortality[3,14]. This phenomenon occurs when microorganisms transform over time and no longer respond to conventional pharmacological agents, rendering standard infections difficult or impossible to treat[3,14]. Driven primarily by the irrational use and over-prescription of antibiotics in human medicine, veterinary settings, and agriculture, AMR was associated with approximately 4.95 million deaths in 2019, with estimates suggesting this could rise to 10 million annual deaths by 2050[12,14]. Beyond clinical impacts, AMR imposes a severe economic burden, with healthcare costs and productivity losses expected to reach trillions of dollars globally[3,18].

The clinical severity of this crisis is underscored by the emergence of multidrug-resistant (MDR) pathogens, defined as bacterial strains resistant to at least one agent in three or more antimicrobial classes[3,11]. Of particular concern are the "ESKAPE" pathogens. *Enterococcus faecium*, *Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp. which are frequently implicated in healthcare-associated infections[14,18,25]. The World Health Organization (WHO) has categorized several of these, such as carbapenem-resistant Gram-negative bacilli, as "critical priority" pathogens that necessitate the urgent development of alternative therapeutic strategies[8,24].

The stagnation of the antibiotic discovery pipeline further complicates the management of MDR infections[2,24]. In the past 50 years, only two new classes of synthetic antibiotics fluoroquinolones and oxazolidinones have been developed, while bacterial resistance mechanisms continue to evolve rapidly[15,24]. These mechanisms include the enzymatic degradation of drugs (such as swech-lactamases), the alteration of antibiotic target sites, and the over expression of energy-

driven efflux pumps that extrude drugs from the cell[11,21,24]. Furthermore, the high doses often required to treat resistant infections can lead to severe host toxicity, such as the nephrotoxicity associated with colistin[2,7].

Medicinal plants have emerged as promising reservoir for novel antimicrobial agents, serving as "natural laboratories" for the production of chemically diverse secondary metabolites[15,25]. Phytochemical classes, including alkaloids, polyphenols, and terpenoids, exhibit broad-spectrum antimicrobial activity through multi-target modes of action[3,15]. Unlike conventional antibiotics, these plant-derived compounds often target non-growth-related processes like quorum sensing and biofilm formation, which reduces the selective pressure for resistance development[15]. Furthermore, these agents can function as antibiotic adjuvants or potentiators, restoring the efficacy of existing drugs by inhibiting bacterial efflux pumps and increasing membrane permeability[15].

Despite this therapeutic potential, significant research gaps remain. Current studies are limited by a lack of standardization in extraction methodologies and inconsistencies in the concentrations used across different laboratories[10,20]. Furthermore, the vast majority of research is based on *in vitro* evidence, with a significant deficiency in animal models and clinical trials to evaluate the safety, bioavailability, and pharmacokinetics of plant-based antimicrobials in humans[7,11,20].

This mini-review aims to provide a comprehensive analysis of the role of plant-based antimicrobial agents in controlling MDR bacteria. It evaluates the mechanisms of action of key phytochemicals, their effectiveness against high-priority pathogens, and their potential for synergistic use as antibiotic adjuvants[11,15,20]. Finally, the review identifies current challenges and future directions, such as the integration of nanotechnology for enhanced drug delivery, to advance the clinical utility of plant-derived compounds in the fight against antimicrobial resistance[10].

Plant-Based Antimicrobial Agents: Diversity and Phytochemical Characterisation

The therapeutic utility of medicinal plants is derived from their capacity to synthesise a vast library of secondary metabolites (SM), which evolved as chemical defences against microbial predation and environmental stressors[3,27]. These bioactive compounds exhibit immense structural diversity and are distributed unevenly across specific plant anatomical parts, including leaves, roots, bark, seeds, and flowers[11,27]. For instance, antimicrobial constituents are concentrated in the rhizomes of *Curcuma longa* and *Curcuma caesia,* the bulbs of *Allium sativum,* the bark of *Cinnamomum cassia,* and the flower buds of *Syzygium aromaticum*[9,13,23,27]. Systematic research into species such as *Hagenia abyssinica* and *Azadirachta indica* underscores the selection of plant parts is non-trivial, as specific tissues may harbour significantly higher concentrations of active principles[11,30].

The efficacy of these agents is heavily influenced by the extraction methodology and solvent polarity, which determine the profile of the isolated metabolites[13]. Organic solvents, particularly methanol and ethanol, are generally superior to aqueous extraction for recovering moderately polar constituents such as polyphenols and flavonoids[9,30]. Furthermore, sequential extraction techniques using solvents of increasing polarity.ranging from non-polar n-hexane to polar water.allow for the fractionated isolation of bioactive classes according to their solubility profiles[13]. Volatile essential oils, predominantly composed of hydrophobic monoterpenes and sesquiterpenes, represent a distinct class of antimicrobials often isolated *via* distillation or solvent extraction to treat persistent infections[19,27].

Phytochemical classes are broadly categorised into nitrogenous compounds, such as alkaloids, and nitrogen-free metabolites, including phenolics and terpenoids[3,27]. Alkaloids like berberine and sanguinarine are among the most potent agents, frequently acting as efflux pump inhibitors (EPIs) or DNA intercalators[2]. Phenolics, encompassing flavonoids, tannins, and phenolic acids (*e.g.*, gallic acid and quercetin), constitute the largest group of antimicrobial SMs and are ubiquitous in traditional phytotherapies[3,27,29]. Terpenoids and their derivatives exhibit broad-spectrum activity through their lipophilic nature, which facilitates interaction with microbial lipid bilayers[2,10,27]. The synergistic presence of multiple phytochemical classes within a single extract often enhances biological activity and reduces the selective pressure for the development of resistance in multidrug-resistant pathogens[3,15].

Antimicrobial Activity against Multidrug-Resistant Pathogens

The antimicrobial efficacy of plant-based agents is quantitatively evaluated using the diameter of the zone of inhibition (ZOI), minimum inhibitory concentration (MIC), and minimum bactericidal concentration (MBC)[5]. As summarized in Table-1, these metrics reveal a broad spectrum of activity against "ESKAPE" pathogens, with potency varying significantly based on plant species and extraction methods.

Comparative analysis highlights exceptional inhibitory activity in certain species. One of the strongest

TABLE -1 : Antimicrobial activity of plant extracts against multidrug-resistant bacteria

Plant Species	Extraction Method	Target MDR Bacteria	ZOI (mm)	MIC	MBC	Reference
Cirsium arvense	Ethanol	*P.aeruginosa*	72	2 µg/mL	4 µg/mL	5
Avena fatua	Ethanol	*P.aeruginosa*	65	1 µg/mL	2 µg/mL	5
Chenopodium murale	Ethanol	*P.aeruginosa*	52	1 µg/mL	2 µg/mL	5
Curcuma caesia	n-hexane (Rhizome)	*A.baumannii*	23	3.12 µg/mL	6.25 µg/mL	13
Curcuma caesia	n-hexane (Leaf)	*S. aureus*	24	3.12 µg/mL	6.25 µg/mL	13
Curcuma caesia	Chloroform (Leaf)	*K.pneumoniae*	32	6.2 µg/mL	12.5 µg/mL	13
Phyllanthus emblica	Ethanol (70%)	*A.baumannii*	Not reported	125 µg/mL	250 µg/mL	16
Nigella sativa	Ethyl Acetate	*S. aureus*	20	5 µg/mL	Not reported	4
Curcuma amada	Methanol	*E.coli*	22	10 µg/mL	Not reported	4
Arnica montana	Ethanol	*A.baumannii*	Not reported	234.4 µg/mL	Not reported	1
Curcuma longa	Methanol	*S. aureus*	18	Not reported	Not reported	20
Curcuma longa	Methanol	*E.coli*	15	Not reported	Not reported	20
Curcuma longa	Methanol	*K.pneumoniae*	16	Not reported	Not reported	20
Opuntia ficus-indica	Aqueous	*P.aeruginosa*	Not reported	0.05 mg/mL	Not reported	20
Azadirachta indica	Ethanol	*E.coli* (MDR)	20	Not reported	Not reported	26
Allium sativum	Ethanol	*S. aureus* (MRSA)	18	Not reported	Not reported	26

Plant Species	Extraction Method	Target MDR Bacteria	ZOI (mm)	MIC	MBC	Reference
Ocimum sanctum	Ethanol	*K.pneumoniae*	14	Not reported	Not reported	26
Roemeria refracta	Alkaloidal ext.	*S. aureus*	Not reported	0.065 µg/mL	Not reported	11
Hagenia abyssinica	Ethanol (Flower)	*E.coli*	5	Not reported	Not reported	30
Hagenia abyssinica	Ethanol (Leaf)	*S. aureus*	3	Not reported	Not reported	30

Note : *Values for ZOI are generally reported at specific extract concentrations (e.g., 75 µg/mL for C. caesia or 20 mg/mL for crude extracts) as per individual study methodologies.*

results recorded involves ethanol extracts of *Cirsium arvense*, which exhibited a ZOI of 72 mm against *Pseudomonas aeruginosa*, outperforming the standard antibiotic ciprofloxacin (66 mm) under identical conditions[5]. Similarly, *Avena fatua* and *Chenopodium murale* demonstrated superior absolute potency, achieving MIC values as low as 1 µg/mL and MBC values of 2 µg/mL against *P. aeruginosa* 5. In the Gram-positive category, alkaloidal extracts from *Roemeria refracta* showed remarkable sensitivity against *Staphylococcus aureus* with an MIC of 0.065 µg/mL[11].

Conversely, some plants demonstrated relatively weak or standalone activity. Extracts from *Hagenia abyssinica* produced minimal ZOI values of only 5 mm against *Escherichia coli* and 3 mm against *S. aureus*[30]. Furthermore, *Linum usitatissimum* (flaxseed) extracts were reported to show no inhibition, and in some instances, actually enhanced bacterial growth, suggesting they are ineffective as standalone treatments[20].

The data in Table 1 also underscore the influence of solvent polarity on antimicrobial outcomes. Research on *Curcuma caesia* indicates that non-polar sequential extracts (n-hexane and chloroform) are significantly more effective than aqueous versions, with MICs as low as 3.12 µg/mL against *Acinetobacter baumannii* and *K. pneumoniae*[13]. Similarly, *Phyllanthus emblica* (amla) required higher concentrations (MIC 125 µg/mL) to inhibit MDR *A. baumannii*, yet it remained effective where standard drugs failed[16]. These findings, systematically detailed in Table-1, emphasize that while many plants possess antimicrobial properties, clinical relevance is highly dependent on achieving specific sub-microgram inhibitory thresholds.

Molecular and Cellular Mechanisms of Action

Plant-based antimicrobial agents employ multi-target mechanisms that significantly diminish the probability of resistance development compared to conventional synthetic monotherapies[15]. As systematically presented in Table 2, a primary mode of action is the disruption of bacterial cell membrane integrity. Lipophilic terpenoids and essential oil components, such as thymol, carvacrol, and eugenol, interact with microbial lipid bilayers, causing membrane depolarization, loss of ion homeostasis, and the leakage of vital intracellular components including ATP and proteins[10,22]. Similarly, indole alkaloids isolated from *Rhazya stricta* and polyphenolic compounds from *Phyllanthus emblica* increase membrane permeability in MRSA and Gram-negative rods, facilitating the entry of standard antibiotics[3,10,16].

Efflux pump inhibition (EPI) represents another critical mechanism for controlling multidrug-resistant (MDR) bacteria[24]. Phytochemicals such as resveratrol, curcumin, and piperine act as potent EPIs by downregulating resistance-associated genes, such as adeJ in *Acinetobacter baumannii* and MexAB-OprM in *Pseudomonas aeruginosa,* or by interfering with pump proteins to prevent the extrusion of antibiotics[6,10,20,24]. This restores therapeutic concentrations of drugs within the bacterial cell[20,22].

Interference with quorum sensing (QS) and biofilm formation further distinguishes these natural agents as "antipathogenic" therapies[7,15,22]. Quorum-quenching (QQ) compounds, including naringenin and

TABLE-2. Molecular mechanisms of action of plant-derived antimicrobial agents against MDR bacteria

Plant Compound/ Extract	Target Mechanism	Specific Molecular Action	Target Pathogen(s)	Reference
Thymol / Carvacrol	C Disruption	Membrane depolarization, increased permeability, and leakage of ATP and proteins.	*S. aureus, E. coli, P. aeruginosa*	10, 11
Resveratrol	Efflux Pump Inhibition (EPI)	Downregulation of *adeJ* gene (AdeABC pump) and inhibition of CmeABC efflux systems.	*A. baumannii, C. jejuni*	2, 6
Curcumin	Multi-target (QS & EPI)	Inhibition of Mex AB-Opr M and Nor A pumps; reduction of virulence factors (prodigiosin) via QS interference.	*P. aeruginosa, S. aureus, S. marcescens*	3, 15, 24
Quercetin	EPI & Biofilm Inhibition	High affinity binding to *AdeJ* and Acr B proteins; interference with rhl transcription to reduce EPS synthesis.	*A. baumannii, K. pneumoniae, P. aeruginosa*	6, 10
Hamamelitannin	Quorum Sensing Inhibition	Antagonism of the Tra P receptor and downregulation of regulator involved in QS and motility.	*S. aureus* (MRSA)	10, 15
Allicin (Garlic)	Enzyme Inhibition	Inhibition of DNA gyrase, preventing the synthesis of RNA, DNA, and proteins.	*General MDR bacteria*	22
Conessine	Efflux Pump Inhibition	Restored levofloxacin activity by blocking Mex AB-Opr M, Mex CD-Opr J, and Mex EF-Opr N pumps.	*P. aeruginosa*	11

Plant Compound/ Extract	Target Mechanism	Specific Molecular Action	Target Pathogen(s)	Reference
Naringenin	Quorum Sensing Inhibition	Downregulation of las and rhl family genes, reducing AHL-mediated virulence.	*P. aeruginosa*	10, 15
Baicalein	Efflux Pump Inhibition	Restoration of tetracycline and lactam activity by blocking Nor A and other MDR pumps.	*MRSA, E. coli, Salmonella enteridis*	2, 11
Luteolin	EPS & Gene Inhibition	Reduction of polysaccharide and eDNA synthesis; down regulation of oqx A RND pump gene.	*E. coli, Enterobacter cloacae*	6, 10
Andrographolide	Quorum Quencing	Downregulation of las R gene expression, attenuating protease activity and swarming motility.	*P. aeruginosa*	15
Gallotannin (PGG)	Metal Chelation	Sequestration of iron from the extracellular matrix, destabilizing the biofilm structure.	*E. coli*	10

hamamelitannin, disrupt intercellular communication by inhibiting signal synthesis (e.g., AHLs in Gram-negatives) or by antagonizing QS receptors[10,15]. This process suppresses virulence factors like pyocyanin production and swarming motility without imposing lethal selective pressure[15,28]. Furthermore, flavonoids like luteolin and quercetin inhibit the synthesis of extracellular polymeric substances (EPS), thereby destabilizing the biofilm matrix and rendering protected microbial communities vulnerable to standard pharmacological treatments[7,10,17].

Comparative Insights and Critical Synthesis of Findings

Comparative analysis identifies *Cirsium arvense* as exhibiting the largest zone of inhibition (72 mm) against *P. aeruginosa*, yet this does not universally translate to the lowest minimum inhibitory concentrations across all pathogens[5]. Instead, species such as *Avena fatua* and *Chenopodium murale* demonstrate superior absolute potency with MICs as low as 1 µg/mL against the same resistant strains[5]. This highlights a significant contradiction in reporting metrics; large inhibition zones frequently reflect high agar diffusion rates rather than intrinsic bactericidal efficacy, necessitating standardized MIC and MBC evaluations for clinical relevance[5,13].

Regarding extraction, a consistent pattern confirms the superiority of organic solvents particularly methanol, ethanol, and chloroform over aqueous methods for isolating bioactive phenolics and flavonoids[9,13,30]. In species like *Curcuma caesia*, non-polar sequential extraction using n-hexane and chloroform yields significantly more potent antimicrobial activity against MRSA and *K. pneumoniae* than aqueous fractions, which often show negligible effects[13]. Essential oils also consistently outperform crude extracts due to their concentrated volatile terpenes like carvacrol and

thymol, which facilitate immediate membrane disruption[19].

Critical synthesis of spectrum activity reveals that while plant extracts are often described as broad-spectrum, their standalone efficacy is structurally biased toward Gram-positive pathogens due to the lack of an outer membrane barrier[11,22,25]. However, structure-activity relationship (SAR) analysis suggests that while individual compounds may vary, those containing catechol or gallol motifs exhibit the highest synergy rates (80.9%) and up to an 8-fold reduction in antibiotic MICs[17,26]. Paradoxically, species such as *Linum usitatissimum* exhibit concentration-dependent contradictions where sub-optimal levels may enhance rather than inhibit bacterial growth, underscoring the critical need for precise standardization to avoid unintended growth promotion in MDR isolates[20].

Conclusion

Plant-derived antimicrobial agents, specifically alkaloids, phenolics, and terpenoids, demonstrate significant potential in controlling multidrug-resistant (MDR) pathogens through multi-target mechanisms[3,24,25,27]. Key findings highlight their ability to disrupt cell membrane integrity, inhibit biofilm maturation, and deactivate energy-driven efflux pumps[3,10,22,24]. These secondary metabolites are critical because they function as potent antibiotic adjuvants, restoring the efficacy of conventional drugs and allowing for dose reductions that mitigate host toxicity[14,20,26].

Despite these promising findings, several research gaps limit the clinical translation of phytochemicals. Current literature is characterized by a lack of standardized extraction methodologies and a significant deficiency in human clinical trials to validate safety and efficacy[12,20,30]. Furthermore, the poor aqueous solubility and rapid metabolism of many bioactive compounds remain substantial hurdles[7,11,15]. Future directions must prioritize the development of nanotechnology-based delivery systems to enhance bioavailability and stability[15,18]. Additionally, the integration of artificial intelligence and advanced omics technologies will be essential for the high-throughput discovery and molecular characterization of next-generation plant-based therapies[14,15]. Addressing these challenges is vital to successfully integrating medicinal plant compounds into the global strategy against antimicrobial resistance.

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