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PLANT-DERIVED ANTIMICROBIALS AS EMERGING THERAPEUTIC ALTERNATIVES AGAINST MULTIDRUG-RESISTANT HUMAN PATHOGENS

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ABSTRACT

The accelerating emergence of antimicrobial resistance (AMR) has severely undermined the efficacy of conventional antibiotics, creating an urgent need for novel therapeutic strategies with broader and more sustainable antimicrobial potential. Medicinal plants offer a chemically diverse reservoir of bioactive metabolites, including alkaloids, flavonoids, terpenoids, tannins, and phenolic acids, that exhibit potent activity against a wide range of emerging and multidrug-resistant (MDR) pathogens. These phytochemicals act through multiple complementary mechanisms such as membrane disruption, efflux pump inhibition, quorum-sensing interference, enzyme suppression, and biofilm degradation, thereby countering bacterial survival strategies that contribute to AMR. Contemporary spectroscopic and chromatographic analyses, supported by metabolomics and network pharmacology, have enhanced the identification and mechanistic understanding of these compounds. Furthermore, several medicinal plants demonstrate additional gastroprotective, anti-inflammatory, and urease-inhibitory activities, making them promising candidates for the management of *Helicobacter pylori*–associated peptic ulcer disease. Synergistic interactions between plant extracts and conventional antibiotics further improve therapeutic efficacy by lowering minimum inhibitory concentrations and restoring antibiotic sensitivity in resistant strains. Despite substantial preclinical evidence, challenges such as poor phytochemical

standardization, variability in plant composition, and limited clinical validation continue to hinder translation into mainstream therapy. Bridging these gaps requires rigorous quality control, advanced analytical profiling, and well-designed clinical studies. Overall, plant-derived antimicrobials hold significant potential as complementary or alternative strategies to address the global AMR crisis and strengthen future infectious disease management.

KEYWORDS: Medicinal plants; Antimicrobial resistance; Phytochemicals; Drug-resistant pathogens; *Helicobacter pylori*; Synergistic therapy; Bioactive metabolites; Natural antimicrobials.

INTRODUCTION

1.1 Global burden of antimicrobial resistance

Antimicrobial resistance has emerged as a critical global health concern, driven by widespread antibiotic misuse and the rapid evolution of drug-resistant pathogens. Studies show that bacterial species such as *Escherichia coli* and *Helicobacter pylori* are increasingly exhibiting multidrug resistance, compromising the effectiveness of conventional therapy and increasing disease burden, particularly in low-resource regions.[1] Factors such as unregulated antibiotic access, poor sanitation, and improper prescribing practices further accelerate resistance development. The growing failure of antibiotics calls for alternative strategies, including plant-derived antimicrobials with multi-target mechanisms that reduce resistance risks.

1.2 Escalating global AMR crisis

Antimicrobial resistance accounted for an estimated 4.71 million deaths in 2021, with 1.14 million directly caused by resistant infections. The burden is highest in low-income regions where healthcare and sanitation are inadequate. The lack of effective antibiotic pipelines and treatment options exacerbates the crisis. These alarming trends underscore the urgent need for alternative antimicrobial sources, including botanicals with novel mechanisms of action.[2,3]

1.3 Medicinal plants as antibacterial agents: A review perspective

Medicinal plants contribute substantially to antimicrobial research due to their phytochemical diversity. Alkaloids, flavonoids, phenolics, and glycosides impart broad-spectrum antibacterial activity. Traditional use and scientific validation demonstrate the efficacy of plant-based remedies against diverse human pathogens. With rising global antimicrobial

resistance and concerns regarding synthetic antibiotics, phytomedicines represent safer, economical, and pharmacologically potent alternatives.[4]

1.4 Herbal drugs as dual antimicrobial and gastroprotective agents

Herbal medicines with antibacterial and antiulcer activities are increasingly explored as alternatives to synthetic therapies, especially due to rising concerns about rebound acidity, nutrient malabsorption, and antibiotic resistance associated with conventional treatments. Many plants traditionally used in gastrointestinal disorders exhibit both antimicrobial potential and acid-neutralizing properties, making them effective in managing infections by drug-resistant pathogens while protecting mucosal integrity. Several botanicals such as *Acacia arabica*, *Terminalia chebula*, and *Aloe barbadensis* demonstrate measurable acid-neutralizing capacity, supporting their relevance in conditions where microbial infection and gastric acidity coexist.[5]

1.5 WHO priority pathogens and plant-based opportunities

The 2024 WHO Bacterial Priority Pathogen List identifies carbapenem-resistant *Acinetobacter*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and ESBL-producing *Enterobacterales* as critical threats. Natural products from medicinal plants show inhibitory effects against several of these priority pathogens. Due to their structural diversity and multi-target activity, plant-derived compounds offer promising scaffolds for developing next-generation antimicrobials.[6,7]

1.6 *H. pylori* as a global drug-resistant pathogen

H. pylori is a major gastric pathogen linked to gastritis, peptic ulcer disease, and gastric cancer. Increasing resistance to clarithromycin, metronidazole, and levofloxacin has reduced the success of conventional eradication therapies. Treatment failures continue to rise globally, reinforcing the need for plant-based antimicrobials as adjunct or alternative therapies for resistant *H. pylori* infections.[8]

1.7 Limitations of current acid-suppression therapies

Although proton pump inhibitors (PPIs) remain central to peptic ulcer therapy, long-term use causes hypochlorhydria, nutrient deficiencies, and microbiota disruption. Resistance to antibiotic-based therapies has further reduced eradication rates. These limitations highlight the need for safer, plant-based antimicrobial and gastroprotective strategies.[9]

1.8 Urease inhibition as a strategy against resistant *H. pylori*

Urease inhibition has emerged as a targeted therapeutic approach for combating *H. pylori*, especially in the context of increasing antibiotic resistance. Urease enables *H. pylori* to neutralize gastric acid and survive, making it a key virulence factor. Medicinal plants such as *Solanum nigrum*, *Terminalia chebula*, and *Phyllanthus niruri* exhibit strong urease-inhibitory activity, with some extracts showing IC_{50} values superior to thiourea. These phytochemicals disrupt microbial survival mechanisms, highlighting their potential against drug-resistant gastric pathogens.[10]

1.9 Spectroscopic evidence supporting antimicrobial plant potency

Spectroscopic characterization of medicinal plants provides crucial insights into the bioactive compounds responsible for antimicrobial activity. UV/Vis and FTIR spectroscopic analysis reveal that *Terminalia chebula* and *Allium sativum* contain diverse phytochemicals, phenolics, tannins, flavonoids, and organosulfur compounds, contributing to strong antibacterial and antiulcer effects. UV maxima and FTIR functional groups emphasize their rich biochemical profiles and ability to counter multidrug-resistant pathogens.[11]

1.10 Chromatographic profiling and phytochemical standardization

Chromatographic profiling strengthens the scientific basis of plant-based therapeutics. HPTLC and HPLC chromatographic analysis have revealed that plant extracts including *Aloe barbadensis*, *Terminalia chebula*, and *Allium sativum* contain phenolics, flavonoids, tannins, and alkaloids. Chromatographic fingerprints support correlation between specific phytoconstituents and antimicrobial activity, validating the therapeutic potential of these plants against multidrug-resistant pathogens.[12]

1.11 Role of modern analytical and omics tools

Advancements in LC–MS, GC–MS, FTIR, and metabolomics have transformed plant antimicrobial discovery. Metabolomic profiling identifies hundreds of bioactive compounds and correlates metabolite abundance with antimicrobial potency. Network pharmacology and chemometric analyses enable prediction of molecular targets, accelerating the transition of plant metabolites into preclinical development.[13,14]

1.12 Mechanisms of plant phytochemicals against resistant bacteria

Phytochemicals interfere with bacterial survival pathways by disrupting membranes, inhibiting efflux pumps, blocking quorum sensing, and preventing biofilm formation.

Compounds such as alkaloids, flavonoids, and terpenoids modulate microbial signaling and virulence gene expression, thereby weakening multidrug-resistant pathogens and restoring antibiotic susceptibility.[15,16]

1.13 Synergistic interactions: Plants + antibiotics

Plant extracts demonstrate synergistic effects with conventional antibiotics, reducing minimum inhibitory concentrations and reversing resistance. Studies show enhanced antibacterial activity when medicinal plants are combined with β-lactams or fluoroquinolones, especially against MRSA, ESBL-producing *E. coli*, and MDR *Pseudomonas*. Such plant–drug combinations represent a promising approach to revitalize failing antibiotics.[17,18]

1.14 Integrating herbal therapies to address AMR challenges

Rising antibiotic resistance complicates the management of *H. pylori*-associated ulcers. Medicinal plants such as *Glycyrrhiza glabra*, *Moringa oleifera*, *Azadirachta indica*, and *Curcuma longa* exhibit antibacterial, urease-inhibitory, and gastroprotective properties. Integrating standardized herbal agents with modern therapies may improve treatment outcomes, reduce drug resistance, and offer safer long-term management.[19]

1.15 Translational gaps and future directions

Despite promising laboratory data, clinical translation of plant-based antimicrobials remains limited due to variability in phytochemical composition, inadequate toxicity data, and lack of large, controlled clinical trials. Strengthening extraction standardization, quality control, and human clinical validation is essential for integrating phytochemicals into mainstream antimicrobial strategies.[20,21]

Table 1: Global burden of antimicrobial resistance (Latest WHO/Lancet data 2021–2024).

Indicator	Statistics	Source	Reference(s)
Total deaths associated with AMR	4.71 million (2021)	Lancet Report	[2]
Deaths directly caused by AMR	1.14 million	Lancet Report	[2]
Highest AMR burden regions	Sub-Saharan Africa, South Asia	WHO Fact Sheet	[3]
Common resistant pathogens	*E. coli*, *K. pneumoniae*, *S. aureus*, *P. aeruginosa*	WHO PPL	[6]
Major drivers of AMR	Misuse, poor sanitation, weak stewardship	WHO Fact Sheet	[3]

Table 2: WHO priority pathogens (2024) & plant-based evidence.

WHO Group	Pathogen	Threat Level	Plant Extracts Showing Activity	Reference(s)
Critical	*A. baumannii* (CRAB)	Critical	*Azadirachta indica*, *Curcuma longa*	[6,7]
Critical	*P. aeruginosa* (CRPA)	Critical	*Moringa oleifera*, *Glycyrrhiza glabra*	[6,7]
Critical	ESBL-*Enterobacterales*	Critical	*Allium sativum*, *Ocimum sanctum*	[6,7]
High	MRSA (*S. aureus*)	High	*Zingiber officinale*, *Terminalia chebula*	[7]
Medium	*Streptococcus pneumoniae*	Medium	*P. emblica*, *W. somnifera*	[7]

Table 3: Major phytochemical classes and their antimicrobial mechanisms.

Phytochemical	Antimicrobial Mechanism	Examples	Reference(s)
Alkaloids	DNA intercalation, membrane disruption	Berberine, Piperine	[15]
Flavonoids	Efflux pump inhibition, ROS generation	Quercetin, Kaempferol	[24]
Tannins	Protein precipitation, cell wall disruption	Ellagitannins	[15]
Terpenoids	Membrane permeabilization	Thymol, Carvacrol	[20]
Phenolic acids	Enzyme inhibition, anti-biofilm activity	Gallic acid, Caffeic acid	[16]

Table 4: Synergy between plant extracts and antibiotics against MDR pathogens.

Combination	Target Pathogen	Synergistic Effect	Reference(s)
Allium sativum + Ciprofloxacin	MDR *E. coli*	Reduced MIC	[22]
Moringa oleifera + Amoxicillin	MDR *H. pylori*	Enhanced inhibition	[18]
Zingiber officinale + Clarithromycin	*H. pylori* clinical isolates	Synergistic killing	[18]
Ocimum sanctum + Tetracycline	MRSA	Biofilm disruption	[22]
Curcuma longa + Levofloxacin	MDR *P. aeruginosa*	Increased membrane damage	[22]

Table 5: Modern analytical tools used in plant antimicrobial research.

Technique	Application	Output	Reference(s)
UV–Vis	Phenolic quantification	λmax, absorbance	[11]
FTIR	Functional groups identification	Peak signatures	[11]
LC–MS/MS	Metabolite profiling	Fragmentation patterns	[14]
HPTLC	Fingerprinting & quantification	Rf values	[12]
Metabolomics	Activity-marker correlation	Heatmaps, clusters	[13]

Table 6: Key challenges in translating plant antimicrobials into clinical use.

Challenge	Description	Reference(s)
Chemical variability	Seasonal/geographic extraction differences	[20]
Limited clinical evidence	Few large-scale human trials	[21]
Standardization issues	Quality control & reproducibility	[21]

Toxicity gaps	Need for long-term safety data	[20]
Regulatory hurdles	Complex approval pathways	[3]

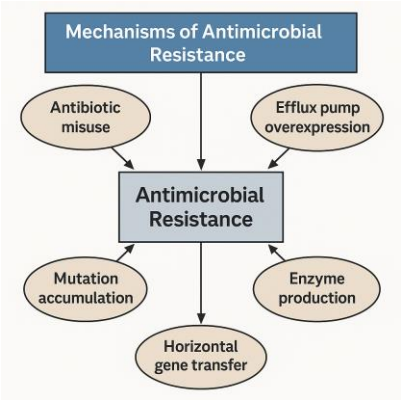

Figure 1: Key mechanisms driving antimicrobial resistance.

Antimicrobial resistance develops through multiple interconnected mechanisms that enable bacteria to survive antibiotic exposure. Frequent antibiotic misuse accelerates mutation accumulation, generating resistant variants within microbial populations. Biofilm formation further protects pathogens by limiting antibiotic penetration and fostering persistent infection niches. Many resistant strains also overexpress efflux pumps that actively expel antimicrobial agents, reducing intracellular drug concentration. In addition, bacteria release enzymes such as β-lactamases that degrade antibiotics before they reach their targets. Finally, horizontal gene transfer through plasmids, transposons, and bacteriophages facilitates the rapid dissemination of resistance traits across species, amplifying the global AMR crisis (Figure 1).

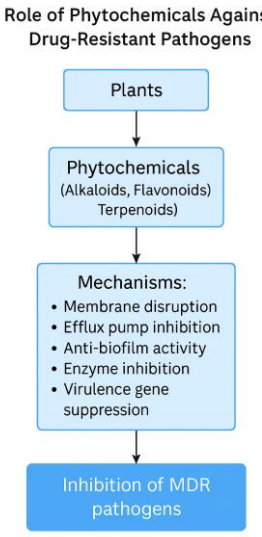

Figure 2: Schematic representation of how plant-derived phytochemicals act against drug-resistant pathogens.

Phytochemicals derived from medicinal plants play a significant role in combating drug-resistant pathogens through diverse, multi-target mechanisms. Compounds such as alkaloids, flavonoids, and terpenoids disrupt bacterial cell membranes, leading to leakage of essential intracellular components. Many phytochemicals inhibit efflux pumps, preventing bacteria from expelling antibiotics and thereby restoring drug susceptibility. Others block quorum sensing and biofilm formation, weakening microbial communication and colonization. Enzyme inhibition, particularly of resistance-related proteins, further reduces bacterial survival. Additionally, suppression of virulence gene expression diminishes pathogenicity. Collectively, these mechanisms position plant-derived phytochemicals as promising alternatives against emerging multidrug-resistant infections (Figure 2).

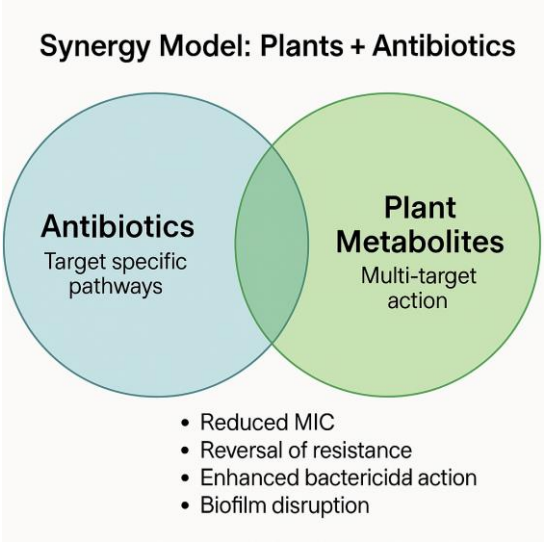

Figure 3: Venn diagram illustrating the synergistic interaction between antibiotics and plant metabolites.

Plant-derived metabolites frequently exhibit synergistic interactions with conventional antibiotics, offering a promising strategy to overcome multidrug resistance. When combined, antibiotics provide targeted microbial killing, while phytochemicals exert multi-site actions such as membrane disruption, efflux pump inhibition, and anti-biofilm activity. This synergy enhances drug penetration, reduces minimum inhibitory concentrations, and restores the potency of antibiotics that have become less effective against resistant strains. Additionally, plant metabolites can suppress resistance mechanisms and virulence pathways, further improving treatment outcomes. Such combined therapy not only increases bactericidal activity but also helps delay the emergence of new resistance patterns, strengthening antimicrobial effectiveness [Figure 3].

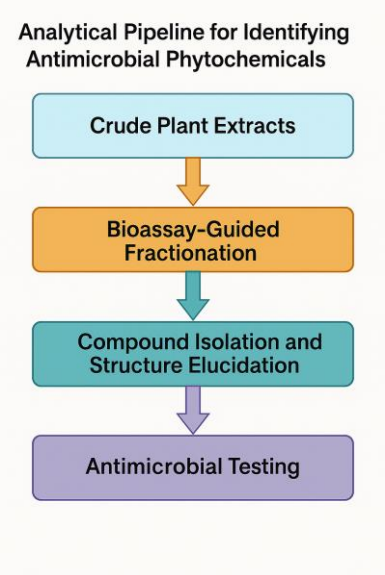

Figure 4: Analytical workflow outlining the sequential steps for identifying antimicrobial phytochemicals.

The analytical pipeline for identifying antimicrobial phytochemicals involves a systematic sequence of processes aimed at isolating and characterizing bioactive compounds from medicinal plants. It begins with extraction of crude plant materials, followed by bioassay-guided fractionation to pinpoint fractions exhibiting significant antimicrobial activity. These active fractions undergo compound isolation and structural elucidation using advanced techniques such as HPTLC, LC–MS/MS, FTIR, and NMR. Once isolated, individual compounds are subjected to antimicrobial assays including MIC, MBC, and biofilm inhibition tests. This integrated workflow enables reliable identification of potent phytochemicals and facilitates their development into novel antimicrobial agents (Figure 4).

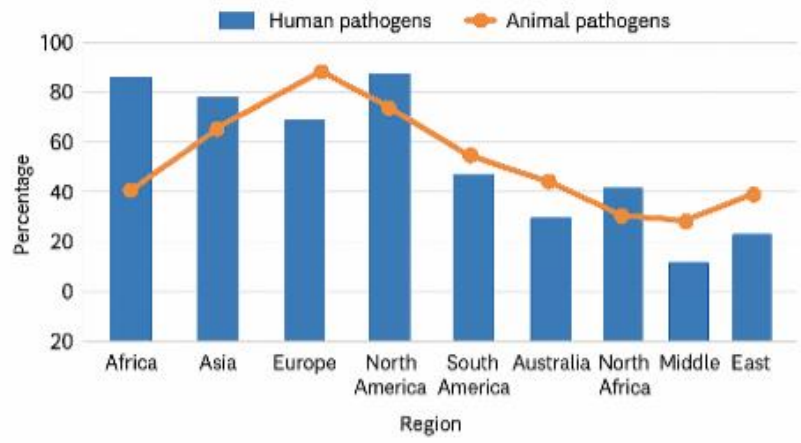

Figure 5: Percentage of medicinal plants exhibiting antimicrobial activity against human and animal pathogens across different global regions.

The distribution of medicinal plants with antimicrobial activity varies significantly across global regions, reflecting differences in biodiversity, traditional medicinal practices, and ethnobotanical knowledge. As shown in Figure 5, Asia demonstrates the highest proportion of plants with documented activity against human and animal pathogens, likely due to its rich flora and long-standing herbal traditions. Regions such as South America and the Middle East also show considerable antimicrobial potential. In contrast, Africa and North Africa display comparatively lower percentages, which may relate to under documentation rather than actual scarcity. Understanding these regional variations helps guide bioprospecting efforts for novel plant-based antimicrobials.

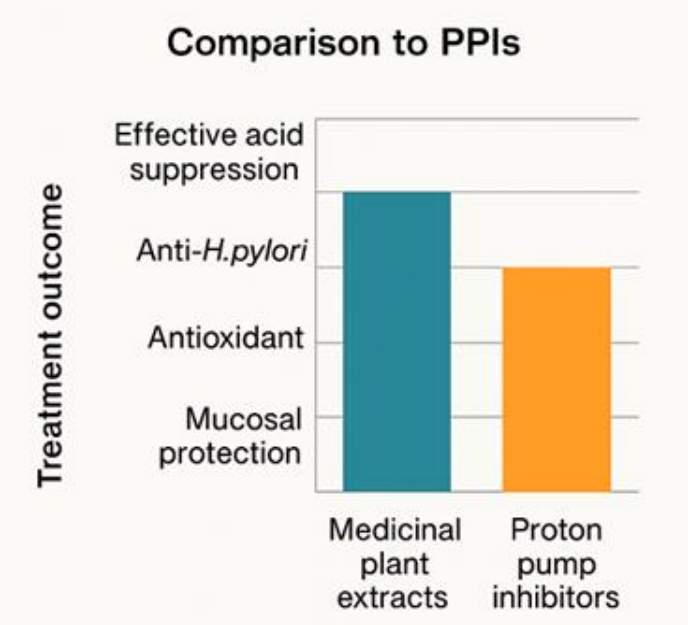

Figure 6: Comparative effectiveness of medicinal plant extracts and proton pump inhibitors (PPIs) across key therapeutic outcomes.

Medicinal plant extracts demonstrate broader therapeutic potential than proton pump inhibitors (PPIs), offering both antimicrobial and gastroprotective benefits. While PPIs primarily provide effective acid suppression, their prolonged use is associated with nutrient malabsorption, dysbiosis, and reduced gastric defence. In contrast, plant extracts exhibit multifaceted actions, including anti-*H. pylori* activity, antioxidant effects, mucosal healing, and modulation of inflammation. These combined effects address both the infection and gastric injury simultaneously. Additionally, phytochemicals can inhibit urease, disrupt biofilms, and reduce bacterial virulence, mechanisms absent in PPIs. Thus, plant-based therapies represent a more holistic approach to managing acid-related and infectious conditions (Figure 6).

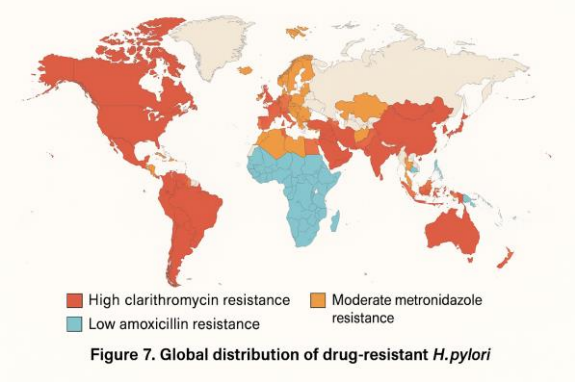

Figure 7: Global distribution of drug-resistant *H. pylori.*

The global distribution of drug-resistant *Helicobacter pylori* varies markedly across regions, reflecting differences in antibiotic usage, healthcare access, and surveillance programs. As illustrated in Figure 7, clarithromycin resistance is highest in several Asian and European countries, where macrolide overuse has accelerated resistance development. Metronidazole resistance shows a moderate yet widespread pattern, particularly in developing regions where the drug is frequently used for parasitic infections. In contrast, amoxicillin resistance remains comparatively low worldwide. These regional disparities highlight the urgent need for localized treatment guidelines, targeted surveillance, and exploration of plant-based therapeutics to improve eradication outcomes.

CONCLUSION

Medicinal plants represent a promising and scientifically substantiated resource for combating antimicrobial resistance, offering multi-target mechanisms that address critical limitations of conventional antibiotics. Their diverse phytochemical compositions enable simultaneous inhibition of biofilms, efflux pumps, virulence factors, and resistance enzymes, providing broad-spectrum activity against emerging and multidrug-resistant pathogens. Additional properties, such as antioxidant, anti-inflammatory, and anti-*H. pylori* effects, further enhance their therapeutic relevance, particularly in conditions where microbial infection and mucosal injury coexist. While in vitro and in vivo findings are compelling, large-scale clinical validation and improved phytochemical standardization are essential to facilitate their integration into evidence-based practice. Advancements in metabolomics, chromatographic fingerprinting, and network pharmacology are expected to accelerate this translational progress. In summary, leveraging medicinal plants alongside modern antimicrobial strategies offers a sustainable and impactful approach to mitigating the global AMR crisis and strengthening infection management.

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Disclaimer: This review is based on published scientific literature and does not involve any new human or animal studies conducted by the authors. The interpretations and conclusions presented herein are solely intended for academic and informational purposes. The authors declare no conflict of interest and the article was drafted by taking assistance of artificial intelligence (ChatGpt).

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