

Exploring Novel Phytochemicals as Strategies in the Fight Against Antimicrobial Resistance

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Abstract

Antimicrobial resistance (AMR) is accelerating worldwide and is eroding the effectiveness of frontline antibiotics, driving treatment failure, prolonged illness, higher costs, and avoidable mortality. Medicinal plants have proven to be a potential source of natural new antimicrobials owing to their richness in diverse bioactive compounds called phytochemicals. One appealing thing about these phytochemicals is that they work against multiple targets at once. They break down microbial cell walls, stop biofilm formation, and prevent essential enzymes from working, which may lower the chance of resistance developing. They can also synergize with existing antibiotics. Synthetic antibiotics, however, are not eco-friendly or desirable from the perspective of sustainability, and plant-derived compounds provide an eco-friendly and sustainable strategy to counteract AM. However, key challenges remain, including variable phytochemical composition across plant sources, limited standardization of extraction and susceptibility testing, incomplete mechanistic validation, and gaps in safety, bioavailability, pharmacokinetics, and drug–herb interaction data. Future work should prioritize rigorous chemical profiling and quality control, harmonized *in vitro* assays linked to clinically relevant endpoints, mechanism-led combination studies against multidrug-resistant (MDR) pathogens, and well-designed *in vivo* and clinical evaluations supported by scalable formulation and delivery approaches. Overall, strategically developed phytochemicals, particularly as antibiotic adjuvants could help extend the useful life of current antimicrobials and contribute to integrated AMR mitigation efforts. Drawing on the promise of medicinal plants to battle AMR, this mini-review advocates for interdisciplinary research and policy support to enable the therapeutic potential of phytochemicals to combat this critically important global health issue.

Abstract

Plain language title: Fighting Drug-Resistant Infections Naturally: How Plant-Based Compounds Offer Eco-Friendly and Effective Alternatives to Antibiotics in the Global Effort Against Antimicrobial Resistance.

Plain-language summary

AMR means germs like bacteria and fungi are learning to survive our current medicines, making common infections harder, and sometimes impossible to treat. This mini-review looks at medicinal plants as a promising, eco-friendly source of new treatments. Plants make natural chemicals (“phytochemicals”) that can attack microbes in several ways at once, damaging their protective walls, blocking key enzymes, disrupting biofilms, and even boosting the power of existing antibiotics. The paper highlights well-known

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examples (like ginger, turmeric, cloves, tea tree, and neem) and explains how pairing plant compounds with antibiotics can restore effectiveness against drug-resistant bugs. It also flags real hurdles: plant extracts can vary in strength, large-scale production is hard, and rigorous safety and clinical testing are still needed. The authors suggest combining traditional knowledge with modern biotechnology to standardize, test, and mass-produce the most effective plant compounds. Overall, the message is that plant-based medicines could become an important part of the global toolkit against AMR if we invest in careful research and development.

Keywords

Antimicrobial resistance, medicinal plants, phytochemicals, bioactive compounds, antibiotics

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Introduction

AMR constitutes a growing near-term threat to global health and decades of progress in the prevention and control of infectious diseases. Conventional antimicrobials are falling short because more pathogens are able to adapt to the drugs.¹ Current difficulties encompass the insufficiency of one-drug-one-enzyme methodologies and the intricate progression of antimicrobial resistance.² Moreover, traditional antibiotic formulations exhibit inadequate targeting effects, resulting in insufficient concentrations at infection sites and possible adverse effects.³ Therefore, these concerning data call for urgently needed new therapeutic options, especially those with unique mechanisms of action against resistance. This search for novel antimicrobials is a promising avenue, and medicinal plants provide one source of such avenues. Plants serve as natural sources of bioactive compounds, generating a variety of phytochemicals with proven therapeutic benefits, including antibacterial, antifungal, and antiviral activities. Many plants exhibit considerable antibacterial effectiveness against bacteria and fungi owing to their intrinsic phytochemicals. Examples include ginger, onions, cloves, cinnamon, garlic, and turmeric.⁴ These phytochemicals present varied structures and multitarget antibacterial properties, interfering with vital cellular functions.⁵ Phytochemicals can address significant antimicrobial resistance mechanisms, such as efflux pumps, biofilms, and cell membranes.^{6,7} They offer multiple benefits compared to synthetic antibiotics, including eco-friendliness and diverse mechanisms of action.⁸ Different categories of phytochemicals, such as alkaloids, phenols, coumarins, and terpenes, have shown inhibitory efficacy against drug-resistant infections.⁹ In this mini-review, the potential of phytochemical strategies to address AMR is discussed and future research directions provided.

Literature Search and Evidence Synthesis

Study Design (Narrative Synthesis)

This mini-review used a narrative synthesis approach to summarize evidence on plant-derived phytochemicals/plant extracts as AMR modulators. Studies discussing molecular mechanisms of action, efficacy in bacterial inhibition, and synergistic effects with conventional antibiotics were prioritized.

Data Sources and Search Strategy

A structured literature search was conducted in PubMed, Scopus, and ScienceDirect for articles published between 01 January 2016 and 30 November 2025. Search terms were organized into concept blocks covering: (i) medicinal plants/phytochemicals/plant extracts; (ii) AMR/antibacterial agents/drug-resistant bacteria; and (iii) mechanisms, synergy, or potentiation.

Limits applied were English language and publication dates from 1 January 2016 to 30 November 2025. Reference lists of key included papers were also screened to identify additional relevant records. Database-specific syntax, fields, and controlled vocabulary (eg, MeSH) were applied where available. The search strategy was iteratively refined to optimize sensitivity while retaining relevance, and the final PubMed search string was adapted for Scopus and ScienceDirect.

A sample PubMed search string (used as a template): (“medicinal plants”[MeSH Terms] OR phytochemicals[Title/Abstract] OR “plant extracts”[MeSH Terms]) AND (“anti-bacterial agents”[MeSH Terms] OR “antimicrobial resistance”[MeSH Terms] OR “drug resistance, bacterial”[MeSH Terms]) AND (mechanism OR synergy OR potentiation) AND (“2016/01/01”[Date - Publication] : “2025/11/30”[Date - Publication]). Table 1 summarizes database-specific syntax/fields and limits.

Eligibility Criteria

Eligibility criteria were defined a priori to enhance transparency and reproducibility:

Inclusion Criteria

- (i) Peer-reviewed primary studies and high-quality reviews describing plant-derived extracts and/or phytochemicals with antimicrobial activity and/or AMR-relevant mechanisms (eg, biofilm inhibition, efflux pump inhibition, quorum-sensing interference, membrane disruption, or synergy with antibiotics).
- (ii) Studies reporting activity against clinically relevant pathogens, including drug-resistant or MDR strains, addressing mechanisms that mitigate resistance development, or

Table 1. Summary of Database-specific Syntax/Fields and Limits (PubMed, Scopus, ScienceDirect).

Database	Platform/fields Searched	Limits Applied	Notes	Number of Studies
PubMed	MeSH Terms + Title/Abstract	English; 2016-2025	Search string shown above (MeSH + free text + date filter).	73
Scopus	Title-Abstract-Keywords	English; 2016-2025	PubMed strategy translated to Scopus field tags/syntax; comparable term blocks.	107
ScienceDirect	Title/Abstract/Keywords (where available)	English; 2016-2025	PubMed strategy adapted to ScienceDirect syntax; filters applied where supported.	77

- synergy/potential with antibiotics, biofilm/efflux inhibition, or other AMR-relevant pathways.
- (iii) English-language peer-reviewed publications published between 2016 and 2025.
- (iv) Studies involving clinically relevant bacterial pathogens (including MDR/extensively drug-resistant (XDR) strains) or validated experimental AMR models.

Exclusion Criteria

- (i) Studies focused on non-plant sources (eg, microbial, animal, or marine-derived compounds) or purely synthetic agents without a clear botanical origin.
- (ii) Articles not primarily related to antimicrobial activity/AMR (eg, antioxidant-only studies) or lacking relevance to resistant pathogens/mechanisms.
- (iii) Non-peer-reviewed content (editorials, preprints, commentaries, letters without data, conference abstracts, theses/dissertations) and duplicate records.
- (iv) Non-English articles, publications outside the 2016–2025 window (except where selectively cited as seminal background), or studies with insufficient detail/outcome reporting.
- (v) Duplicates and non-accessible full texts after reasonable attempts.

Study Selection and Screening Outcomes

The database search identified 257 total records (PubMed=73, Scopus=107, and ScienceDirect=77). After removal of duplicates (5), 252 unique articles were screened by title/abstract. Full texts articles were assessed for eligibility. At the full-text stage, 178 articles were excluded, primarily because they: (i) did not evaluate plant-derived phytochemicals/extracts relevant to AMR (33), (ii) were not focused on bacterial AMR outcomes (eg, non-bacterial or non-AMR endpoints) (51), (iii) lacked extractable AMR-relevant outcomes/mechanistic or synergy data (62), (iv) were non-peer-reviewed/grey literature (13), (v) had inaccessible full text (19). A total of 74 studies were included in the final qualitative synthesis.

Study Selection and Data Extraction

Records were removed from duplicated prior to screening. Titles/abstracts were screened for relevance to the eligibility

criteria, followed by full-text assessment of potentially eligible records. From included studies, key data were extracted: plant source/compound class, extraction/compound identification (where available), bacterial species/strain, assay type, outcomes, and proposed mechanisms (eg, efflux pump inhibition, membrane disruption, biofilm inhibition, quorum sensing interference).

For tabulation (Table 2), studies were prioritized when they clearly reported the botanical identity, preparation type (eg, essential oil, crude extract with solvent, purified fraction, or defined phytochemical), and at least one AMR-relevant mechanism. Studies lacking these details were still considered in the narrative synthesis but were not consistently suitable for structured comparison in the table. Findings were synthesized qualitatively and presented thematically, grouping evidence by phytochemical classes and extracts, as well as AMR-relevant mechanisms.

Evidence Synthesis and Scientific Discussion

The Urgency of Novel Strategies Against AMR

AMR is becoming an increasing threat to public health worldwide, with current estimates revealing a high burden of mortality and morbidity. In 2019, The Lancet published a thorough investigation that linked antimicrobial resistance to 4.95 million fatalities worldwide, directly attributing 1.27 million deaths to AMR.^{8,38} Recent estimates suggest that AMR causes millions of deaths annually, and if inaction persists, it could potentially lead to up to 10 million AMR deaths annually by 2050.³⁹ It also has significant economic repercussions, with a global economic cost projected to reach several trillion dollars by 2050.⁴⁰ The rise of multi-resistant bacteria in healthcare settings complicates outbreak management due to poor infection control practices and insufficient surveillance.⁴¹ The utilization of antibiotics in healthcare and the emergence of superbugs constitute a global concern, particularly in developing countries, with a pronounced impact in Africa. This results from issues including antibiotic overuse, inadequate healthcare facilities, and poor cleanliness habits.⁴²

The pharmaceutical pipeline for novel antibiotics is insufficient to combat the increasing rates of resistance.⁴³ The shortage results from multiple problems in drug discovery, development, and market uncertainty, prompting numerous pharmaceutical companies to withdraw from the antibacterial sector.⁴⁴ More

Table 2. Some Plants with Proven Antimicrobial Activity.

S/N	Plant	Family	Phytochemicals Present	Preparation/main Compound	Target Bacteria	AMR Mechanism	References
Phenolics/alkaloid-rich extracts							
1	<i>Cicer arietinum</i> (chickpea)	Fabaceae	phytosterols, alkaloids, phenolic compounds, tannins, flavonoids, glycosides, and saponins	Preparation: NR Main compound: NR	<i>Escherichia coli</i> (<i>E. coli</i>), <i>Pseudomonas aeruginosa</i> (<i>P. aeruginosa</i>), <i>Klebsiella pneumoniae</i> (<i>K. pneumoniae</i>), <i>S. aureus</i>	Inhibition of bacterial enzymes (eg, DNA gyrase, topoisomerase, β -lactamases), quorum sensing interference	10
2	<i>Syzygium aromaticum</i> (cloves)	Myrtaceae	saponins, alkaloids, flavonoids, glycosides, tannins, and steroids	Preparation: Essential oil / crude extract (solvent NR) Main compound: Eugenol	<i>S. aureus</i>	Membrane + anti-biofilm	11,12
3	<i>Myristica fragrans</i> (nutmeg)	Myristicaceae	alkaloids, flavonoids, phenols, and glycosides	Preparation: Essential oil / crude extract Main compound: Myristicin	<i>S. aureus</i> , <i>Salmonella typhi</i> (<i>S. typhi</i>)	Disruption of bacterial cell membrane leading to increased antibiotic susceptibility	11,13
4	<i>Auricularia auricular-judae</i> (mushroom)	Auriculariaceae	alkaloids, saponins, tannins, and flavonoids	Preparation: NR Main compound: NR	<i>S. aureus</i> , <i>Bacillus subtilis</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>K. pneumoniae</i> , <i>C. albicans</i> (<i>C. albicans</i>)	Disrupt bacterial cell membrane integrity, increasing permeability and causing leakage of intracellular contents	14,15
5	<i>Moringa oleifera</i> (drumstick tree)	Moringaceae	flavonoids, phenolic acids, alkaloids, glucosinolates, and carotenoids	Preparation: NR Main compound: Benzyl isothiocyanate	<i>Rhizoctonia solani</i> , <i>Fusarium culmorum</i> , <i>Agrobacterium tumefaciens</i> , <i>Erwinia amylovora</i> , and <i>Pectobacterium atrosepticum</i>	Inhibit key bacterial enzymes required for survival and replication of bacterial enzymes and proteins	16,17
6	<i>Curatuma longa</i> (turmeric)	Zingiberaceae	tannins, flavonoids, cardiac glycosides, and alkaloids	Preparation: Purified compound and/or extract (solvent NR) Main compound: Curcumin	<i>E. coli</i> , <i>S. aureus</i>	Efflux/biofilm modulation	18,19
7	<i>Tetraphlura tetraptera</i> (Aridan)	Fabaceae	tannins, flavonoids, and phenols	Preparation: NR Main compound: NR	<i>P. aeruginosa</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>C. albicans</i> , and <i>Proteus mirabilis</i>	Membrane disruption, efflux pump, quorum sensing, and enzyme inhibition	20,21
Terpenoid-containing extracts							
8	<i>Chrysanthemum cinerariaefolium</i> (pyrethrum)	Asteraceae	flavonoids, terpenoids glycosides, cyanides	Preparation: NR Main compound: Pyrethrins	<i>S. aureus</i> and <i>Pseudomonas</i> strains	Membrane disruption, quorum sensing, and efflux pump inhibition	22,23
9	<i>Ciborium inebius</i> (Belgium endive, chicory, coffee chicory)	Asteraceae	sesquiterpene lactones, glycosides, caffeic acid derivatives, flavonoids, alkaloids, steroids, terpenoids	Preparation: NR Main compound: NR	<i>B. subtilis</i> , <i>S. aureus</i> , <i>Rhizobium leguminosarum</i> , <i>V. cholerae</i> , <i>E. coli</i> and <i>Pseudomonas fluorescens</i>	Bacterial cell membrane disruption	24
10	<i>Azadirachta indica</i> (neem)	Meliaceae	alkaloids, flavonoids, saponins, steroids, terpenes, and limonoids	Preparation: Crude extract Main compound: Nimbolide/nimbin	<i>P. aeruginosa</i>	Anti-biofilm	25

(continued)

Table 2. Continued.

S/N	Plant	Family	Phytochemicals Present	Preparation/main Compound	Target Bacteria	AMR Mechanism	References
11	<i>Symplocos racemosa</i> Roxb. (Lodhra)	Symplocaceae	flavonoids, cardiac glycosides, saponins, tannins, triterpenes and phytosterols	Preparation: Ethyl acetate extract + fractions (flavonoids; cardiac glycosides) Main compound: NR	<i>E. coli</i> , Methicillin-resistant <i>S. aureus</i> (MRSA) and <i>Salmonella</i> spp	Anti-biofilm; activity versus drug-resistant isolates; time-kill/PAE assessed	26
12	<i>Melaleuca alternifolia</i> (Tea tree)	Myrtaceae	flavonoids, triterpenoids, polyphenols, and tannins	Preparation: Essential oil Main compound: Terpinen-4-ol	Oral microbes such as <i>Porphyromonas gingivalis</i> , <i>Enterococcus faecalis</i> , and <i>Streptococcus mutans</i> .	Membrane + anti-biofilm	27,28
13	<i>Jasminum agrifolium</i> (lemon-scented jasmine)	Oleaceae	alkaloids, flavonoids, terpenes, phenols, and glucosides	Preparation: NR Main compound: NR	<i>S. aureus</i> , <i>Shigella flexneri</i> , <i>E. coli</i>	Enzyme and protein inhibition	29
14	<i>Artemisia abrotanum</i> (Wormwood)	Asteraceae	tannins, phenols, phenolic acids, terpenoids	Preparation: NR Main compound: NR	<i>Pasteurella multocida</i> , <i>Staphylococcus epidermidis</i> , MRSA, <i>Pasteurella multocida</i> , <i>B. cereus</i> , <i>S. mutans</i> , and <i>Enterococcus faecium</i> .	Block quorum-sensing signaling pathways and interfere with biofilm formation	30,31
15	<i>Ephedra alata</i> (Ephedrites Gopp)	Ephedraceae	alkaloids, flavonoids, tannins, phenolic acid, terpenoids	Preparation: NR Main: Ephedrine-type alkaloids	MRSA, <i>Klebsiella oxytoca</i>	NR	32
16	<i>Orobanchae aegyptiaca</i> (Egyptian broomrape)	Orobanchaceae	flavonoids, saponins, glycosides, alkaloids, tannins and phenols, and terpenoids	Preparation: NR Main compound: NR	<i>S. aureus</i> , <i>C. albicans</i>	NR	33
17	<i>Ocimum basilicum</i> (basil or sweet basil)	Lamiaceae	terpenoids, alkaloids, flavonoids, tannins, saponin glycosides	Preparation: Essential oil / crude extract (solvent NR) Main compound: Linalool/ estragole (chemotype-dependent)	<i>E. coli</i> , <i>E. faecalis</i> , and <i>S. aureus</i>	Membrane + Quorum sensing/biofilm inhibition	34
18	<i>Asteriscus graveolens</i> (fragrant asteriscus)	Asteraceae	alkaloids, flavonoids, tannins, terpenes, coumarins, and cyanogenic compounds	Preparation: NR Main compound: NR	<i>E. coli</i> , <i>S. aureus</i> , <i>B. subtilis</i> , <i>P. aeruginosa</i> , <i>C. albicans</i> , <i>Aspergillus niger</i> , <i>Aspergillus flavus</i> , and <i>Fusarium oxysporum</i>	Disrupting microbial membranes	35
19	<i>Zingiber officinale</i> (ginger)	Zingiberaceae	phenolics, terpenoids, flavonoids, saponins, and alkaloids	Preparation: Crude extract (solvent NR) Main compound: [6]-Gingerol	<i>E. coli</i> , <i>S. aureus</i> , <i>Salmonella enterica</i>	Membrane + anti-biofilm	36
Quinone-containing extracts							
20	<i>Aloe secundiflora</i> (African aloe)	Asphodelaceae	anthraquinones, naphthoquinones, phenols, alkaloids, saponins, tannins, and flavonoids	Preparation: Crude leaf extract (methanol) Main compound: Aloin/ aloe-emodin	<i>C. albicans</i> , <i>S. aureus</i>	NR (mechanism not fully resolved; mixed phytochemicals likely multi-target)	37

Note: NR indicates not reported/ not extractable from the cited article as summarized in this mini-review table.

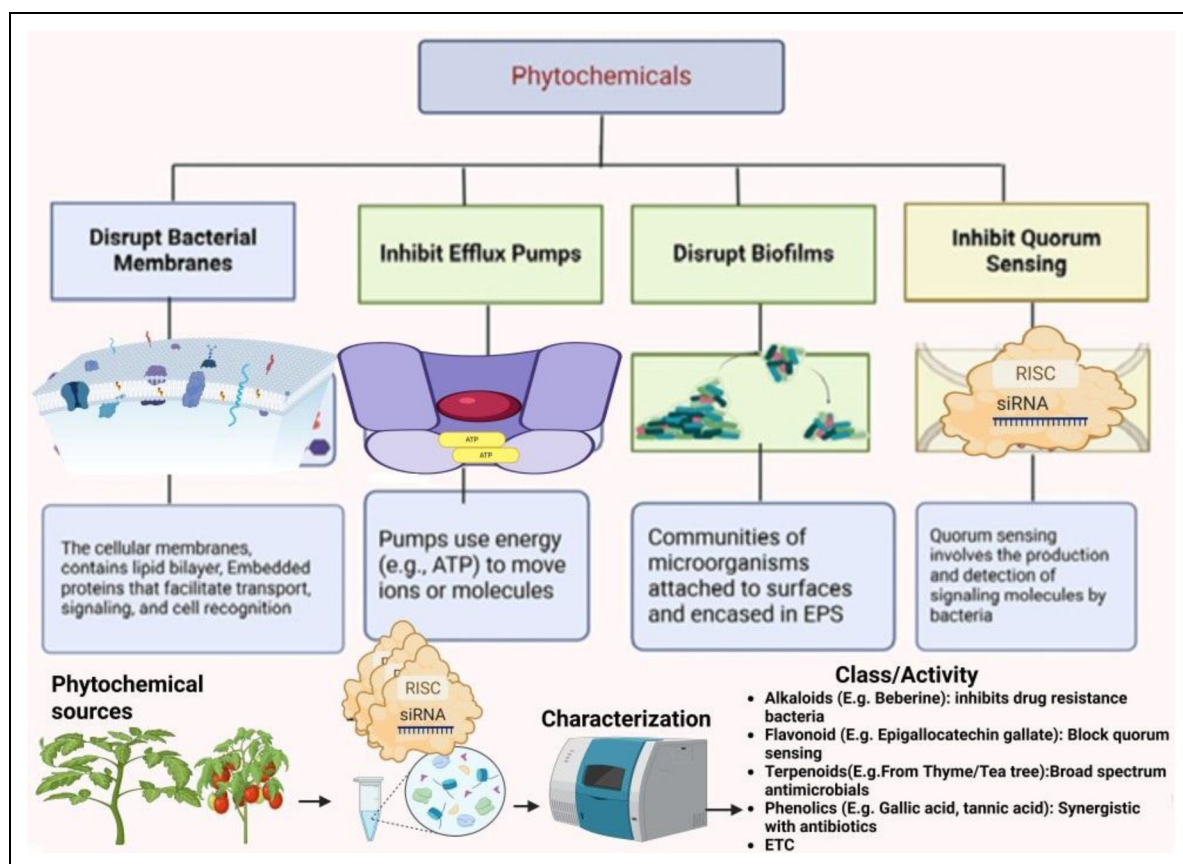


Figure 1. Mechanisms of phytochemicals in combating antimicrobial resistance. EPS means Extracellular Polymeric Substances (Created in BioRender.com).

so, current drug pipelines have not been able to keep up with the fast-increasing resistant pathogens, partly due to the high costs and extended timelines for developing new antibiotics.⁴⁵ In this sense, phytochemicals from medicinal plants are a valuable alternative. These compounds evolved in parallel with the pathogens and have given plants chemical agents that are naturally diverse and perhaps effective against pathogen resistance. Certain phytochemicals can disrupt the microbial cell wall or membrane, or damage vital organelles, which can also lead to cell death.⁸ Global research efforts currently focus on various plants used in traditional medicine, and these natural compounds continue to be an underexplored yet promising source of novel antimicrobials.⁴⁶

Mechanistic Evidence: How Phytochemicals Counter AMR

Recent studies underscore the promise of phytochemicals as a feasible solution to address AM. Phytochemicals have many antibacterial effects on bacterial membranes, efflux pumps, biofilms, and the communication between cells⁴⁷ (Figure 1). Phytochemicals can efficiently suppress MDR bacteria and are less prone to inducing resistance due to their intricate composition.^{8,47} Researchers have investigated diverse sources of phytochemicals, including Himalayan medicinal plants, which

provide a substantial reservoir of antimicrobial substances.⁵ Phytochemicals can break down biofilms at levels below what is needed to inhibit them, without making bacteria resistant or hurting the host microbiota.⁴⁷

In contrast to traditional antibiotics, phytochemicals have a variety of mechanisms by which they combat AM. Some target microbial enzymes and proteins essential for the pathogen's survival, while others target molecules involved in quorum sensing, a crucial communication step for the development of biofilms and virulence in bacteria.⁴⁸ Studies have shown potent antimicrobial activity of certain phytochemical classes, namely alkaloids, flavonoids, terpenoids, and phenolics. For instance, the alkaloid berberine isolated from plants, like *Berberis*, has been shown to inhibit, among other bacteria, drug-resistant bacteria.⁴⁹ Essential oils and extracts from plants like thyme and tea tree contain terpenoids and phenolics, which are abundant antimicrobials with broad-spectrum antimicrobial activity against MDR pathogens.⁵⁰

Conventional antibiotics can in some cases also act synergistically with phytochemicals, either to increase antibacterial effectiveness or to revert resistance. Compounds from plants, like phenolic acids and essential oil components, have been shown to work as efflux pump inhibitors and antibiotic enhancers.⁵⁰

Gallic acid and tannic acid can enhance the efficacy of some antibiotics by up to four times. According to Cheema et al,⁵¹ phytochemicals like niaziridin and chanaoclavine can lower the lowest concentration of antibiotics needed to kill bacteria that are resistant to them by as much as 16 times. This collaborative strategy not only improves the effectiveness of current medications but also reduces the development of antibiotic resistance. Thus, investigating plant extracts and natural chemicals with conventional antibiotics offers a promising path for the development of novel antimicrobial medicines.⁵² More so, recent researches have shown that combining antibiotics with curcumin from turmeric or epigallocatechin gallate (EGCG) from green tea, make these antibiotics work better against MDR pathogens.^{49,53} This synergistic approach promises to reduce the dosages of effective antibiotics and decrease the probability of resistance to development.

Evidence-Weighted Comparison of Phytochemical Classes and Adjuvant Potential

Across the literature, the strongest and most reproducible “antibiotic-adjuvant” signals are reported for phenolics/polyphenols (especially flavonoids), terpenoids/essential-oil phenolics (notably carvacrol and thymol), and selected alkaloids (particularly berberine). These classes recur across multiple resistant phenotypes and often converge on shared resistance liabilities such as membrane permeability, efflux, and biofilm/quorum-sensing-linked tolerance.⁵⁴

Phenolics/polyphenols: The evidence base is strong because many phenolics show (a) direct growth inhibition and (b) resistance-modifying activity such as efflux suppression and biofilm attenuation, which can reduce antibiotic minimum inhibitory concentrations (MICs) *in vitro*. Flavonoid-type compounds (like quercetin-like scaffolds) are repeatedly implicated as efflux-associated sensitizers in resistant *Staphylococcus* models, supporting their prioritization as adjuvant leads.⁵⁵

Terpenoids/essential-oil phenolics: Terpenoids (especially carvacrol and thymol) stand out for consistent reports of synergy/additivity with conventional antibiotics and for resistance-modulating effects linked to membrane perturbation and efflux-related mechanisms.^{56,57} A systematic study also supports terpenes as frequent efflux pump inhibitors, highlighting that this mechanism can enhance antibiotic activity against resistant bacteria, and thus providing a plausible basis for terpene–antibiotic synergy reported across multiple assays/strains.⁵⁴

Alkaloids: Among alkaloids, berberine has comparatively strong support as an antibiotic adjuvant across multiple antibiotic classes, with proposed mechanisms including efflux inhibition, biofilm disruption, and broader resistance-modifying effects.⁵⁸ Newer studies also show that berberine-derived analogues can be optimized for synergy against drug-resistant Gram-negative pathogens by targeting efflux-related machinery.^{7,59} A recent *in vitro* synergy work suggests that volatile phytochemicals can meaningfully potentiate antibiotics. In this study, carvacrol and thymol displayed synergy in binary combinations

with tetracycline and chloramphenicol against *Staphylococcus aureus* (*S. aureus*) (fractional inhibitory concentration index, FICI range 0.28–0.50 in the study).⁶⁰ Beyond parent compounds, optimized phytochemical scaffolds can be designed for adjuvant use. For instance, a novel berberine analogue (2d) was recently reported as a synergistic antibacterial candidate against drug-resistant *Acinetobacter baumannii*, linked to inhibition of drug efflux and iron acquisition via targeting the *Acinetobacter* drug efflux B (AdeB) transporter.⁶¹

Most phytochemical–antibiotic evidence remains *in vitro*, and findings can vary with method and conditions. Reported MICs/synergy depend on factors such as inoculum size, media composition, solvent/vehicle effects, strain background, and whether assays test planktonic versus biofilm growth.⁶² In addition, synergy metrics are not always comparable across studies, and *in vitro* potency does not necessarily predict clinical efficacy because pharmacokinetics, tissue penetration, metabolism, protein binding, and host-pathogen interactions are not captured. Therefore, claims of translational potential are presented cautiously and framed as priorities for standardized testing and *in vivo* validation.⁶³

Effective Plants and key Bioactives: Curated Mechanistic Evidence

Numerous plants demonstrate significant antibacterial efficacy against bacteria and fungi due to the phytochemicals inherent in them. Examples are clove, ginger, cinnamon, turmeric, and Mentha, which have demonstrated effectiveness in eliminating bacteria.⁴ Conventional medicinal flora from several cultures have been recognized as possible sources of innovative antimicrobial compounds.⁶⁴ These natural chemicals provide benefits, including reduced adverse effects relative to synthetic medications and efficacy against drug-resistant infections.⁶⁵ Given the ongoing issues of antibiotic resistance, plant-derived antimicrobials offer interesting alternatives for future therapeutic advancements. Table 2 synthesizes representative plants/extracts for which the included peer-reviewed studies reported extractable AMR-relevant mechanistic evidence. To maintain comparability and keep the mini-review focused, the table is restricted to 20 plants with sufficiently detailed reporting; therefore, it should be interpreted as a curated subset rather than an exhaustive catalogue of all medicinal plants with antimicrobial claims. Across the included references, repeatedly cited plants included *Syzygium aromaticum* (clove; cited in two studies^{11,12}), *Myristica fragrans* (nutmeg; cited in two studies^{11,13}), *Auricularia auricular-judae* (mushroom; cited in two studies^{14,15}), *Melaleuca alternifolia* (tea tree; cited in two studies^{27,28}), *Tetrapleura tetraptera* (Aridan; cited in two studies^{20,21}), *Moringa oleifera* (cited in two studies^{16,17}), *Artemisia absinthium* (wormwood; cited in two studies^{30,31}), *Curcuma longa* (turmeric; cited in two studies^{18,19}). Mechanistically, the most recurrent AMR-relevant themes across effective plants included: (i) membrane perturbation by essential oils/phenylpropanoids (eg, eugenol, terpinen-4-ol)^{11,12,27,28}; (ii) antibiofilm activity and disruption of biofilm-associated tolerance^{26–28}; and (iii) resistance-modifying actions that can

potentiate antibiotics (eg, efflux/biofilm modulation reported for curcumin).^{18,19} Collectively, these mechanisms explain how phytochemicals can suppress resistance phenotypes and potentiate existing antibiotics. However, demonstrating mechanistic promise is only the first step as translation requires a reliable and scalable supply of bioactive compounds. The next section therefore considers sustainability and sourcing constraints that shape feasibility for clinical and industrial deployment.

Challenges and Translational Barriers

While the use of phytochemicals for combating AMR appears promising, it also presents various challenges. The first challenge is the variability in phytochemical content, which can vary not only with plant species and geographical origin but also with extraction methods. In large-scale applications, standardizing these extracts with consistent potency is crucial but challenging.⁶⁶ There is also concern about biosafety and toxicity. Traditional use of medicinal plants necessitates rigorous clinical trials for safety and efficacy, particularly at the doses necessary for antimicrobial efficacy. As potential drugs, these compounds require toxicity screening and pharmacokinetic studies to ensure their toxicity at higher doses or over extended periods.⁶⁷

One other challenge is the isolation and production of specific phytochemicals. Scalability also hinders the complex and expensive process of extracting pure bioactive compounds from plants.⁴⁶ The laborious extraction procedures and variable yields from plant sources could curtail mass production, and without improvements in biotechnology, the demand for clinical application would remain unmet.⁶⁸ Sustainability is central to phytochemical-based AMR interventions because variability in plant material, harvesting pressure, and supply chains can directly affect compound quality, availability, and cost. While sustainable sourcing reduces ecological and supply-chain risk, it does not by itself ensure reproducible efficacy. Standardization of composition, scalable production, and quality control are also required, issues that are increasingly addressed through biotechnology and biomanufacturing approaches. Biotechnology can improve consistency and scalability (such as controlled cultivation, metabolic engineering, or bioprocessing), while also highlighting the technical barriers that still limit clinical translation.

Limitations of This Mini-review

This mini-review synthesizes recent literature on plant-derived phytochemicals and AMR, but several limitations should be considered when interpreting the conclusions.

- (i) The search strategy was not conducted as a full systematic review; therefore, study selection may be susceptible to publication and selection bias.
- (ii) Only English-language articles (2016-2025) from selected databases were included, so relevant evidence in other languages, older foundational work, or grey literature may have been missed.

- (iii) The included evidence is heterogeneous (different plant parts, extraction methods, phytochemical purity, and assay conditions), limiting direct comparability and preventing quantitative synthesis.
- (iv) Many reports do not fully characterize active constituents or confirm mechanistic targets, making it difficult to attribute activity to specific compounds or pathways (eg, efflux inhibition vs membrane disruption).
- (v) To keep the mini-review focused and comparable, Table 2 summarizes only plants with sufficiently detailed and extractable reporting (preparation type/solvent and quantitative potency and/or synergy/mechanistic outcomes). Consequently, the tabulated set (20 plants) is a curated subset and likely underrepresents the broader medicinal plant literature on antimicrobial activity.
- (vi) Most efficacy data are preclinical (*in vitro/in vivo*) with limited clinical validation; safety, pharmacokinetics, dosing, and potential drug-herb interactions remain insufficiently characterized for many candidates.

Future Directions and Opportunities

Addressing the potential of phytochemicals in combating AMR requires a multifaceted approach. Integrating modern science with traditional medicinal knowledge is a promising approach. Plant-based treatments have an effective history treating various diseases and are common in indigenous and traditional practices.^{69,70} Researchers could document and validate these practices scientifically to discover new antimicrobial candidates. Again, biotechnological advances can also boost the production of phytochemicals. To get around the problems that come with natural harvesting, synthetic biology and metabolic engineering can make it possible to copy phytochemical biosynthesis on a large scale in microbial or plant cell cultures.⁴⁶ Moreover, the genetic engineering of plants to overproduce certain desired compounds could provide a cost-effective way of obtaining enough quantities of phytochemicals.⁷¹ A typical case study is semi-synthetic artemisinin wherein a genetically modified *Saccharomyces cerevisiae* can provide substantial quantities of artemisinic acid (a direct precursor), facilitating commercial fermentation and subsequent chemical transformation into artemisinin.⁷² Despite this promise, translation remains constrained by production and downstream-processing costs, scale-up ineptitudes, and the need to meet stringent regulatory expectations for quality and lot-to-lot consistency. These challenges are heightened for botanicals/complex mixtures where batch variability in chemical composition can arise from plant genetics, geography, seasonality, and processing conditions.⁷³

Future work should prioritize standardized phytochemical profiling, harmonized susceptibility testing, rigorous mechanistic validation, and well-designed *in vivo*/clinical studies to better define efficacy, safety, dosing, and the potential role of these agents as adjuncts to existing antimicrobials. Taken together,

mechanistic plausibility, sustainable supply, and manufacturable standardization form a connected pathway from discovery to application. In the concluding section, we summarize priorities for advancing phytochemicals as AMR countermeasures.

Conclusion

Medicinal plants can serve as a window into innovative antibiotics and a sustainable, nature-based mechanism to realize a pressing public health priority globally, as conventional antibiotics lose their effectiveness. The scientific community has a unique opportunity, by investing in these resources, to capitalize on phytochemicals' potential and reconstitute the future landscape of antimicrobial therapeutics. Phytochemicals from medicinal plants offer scientifically compelling routes to complement existing antimicrobials because many act on multiple bacterial targets and can function as antibiotic adjuvants by weakening resistance-associated phenotypes (such as membrane tolerance, efflux, quorum sensing, and biofilm formation). These multi-target effects support the central implication of this review: phytochemical scaffolds are most promising when positioned not only as stand-alone antimicrobials, but as resistance-modifying partners designed to restore or enhance antibiotic activity. Despite this promises, several gaps limit translation. The current evidence base is dominated by *in vitro* MIC/synergy studies with heterogeneous methods, limited chemical standardization, and incomplete mechanism validation. Safety, pharmacokinetics/bioavailability, potential drug-herb interactions, and clinically relevant dosing windows remain insufficiently defined for many extracts and lead compounds.

Policymakers and funding agencies need to increase their support for phytochemical research, a largely underfunded and underexplored field, both now and in the future. Through supportive collaboration between scientists and traditional knowledge keepers and investment in developing biotechnological solutions, we aim to tap into the therapeutic value of medicinal plants to combat a vital segment of the world's most critical public health challenge.

Intensified research into medicinal plants and phytochemicals should be set in motion to combat AM. The combination of interdisciplinary research in the fields of microbiology, chemistry, pharmacology, and biotechnology may help overcome the gap between phytochemical discoveries and clinical applications.

We suggest the following practical next steps:

- (i) Prioritizing a shortlist of high-evidence compound classes (phenolics/flavonoids, terpenoids, and selected alkaloids) using transparent criteria.
- (ii) Standardizing phytochemical profiling and assay workflows, and confirming mechanisms with target-linked readouts (efflux, biofilm, membrane integrity).
- (iii) Advancing the most consistent synergistic pairs into *in vivo* infection models with exposure-response analysis.
- (iv) Developing scalable, quality-controlled production routes (cultivation, bioprocessing, or metabolic engineering) to ensure reproducible composition.

Collectively, these steps provide a clear, testable pathway to determine which phytochemicals can credibly progress from promising *in vitro* signals to clinically meaningful AMR solutions.

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Availability of Data and Material

All used data is fully presented in the manuscript.

Figures Declaration

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