Medicinal Plant Phytochemicals for Combating Antimicrobial Resistance through Molecular and Computational Approaches

Dhithi Mahendra Reddy[1], Shreosee Ghosh[2], Rupak Roy[3]
[1] *National Public School, Koramangala*
[2,3] *SHRM Biotechnologies Pvt. Ltd., Kolkata*

Abstract—**Antimicrobial resistance has narrowed the therapeutic options available for bacterial infections and has increased interest in antibacterial discovery from natural products. Medicinal plants contain chemically diverse compounds that can affect bacterial membranes, metabolic pathways, biofilms, virulence systems and, in some cases, antibiotic susceptibility. This review examines plant-derived phytochemicals as potential antibacterial agents and antibiotic adjuvants, with emphasis on evidence obtained against resistant bacteria. Alkaloids, flavonoids, phenolic compounds, terpenoids, tannins, saponins and organosulfur compounds are considered, while particular attention is given to curcumin, berberine, quercetin, epigallocatechin gallate, thymol and carvacrol. Experimental evidence is discussed alongside molecular docking, molecular dynamics, ADMET prediction and emerging machine-learning approaches. The review also addresses an important limitation in the current literature: activity reported for a phytochemical in one bacterial strain cannot be assumed to translate to other species or to clinically useful exposure. For example, published studies have reported substantial strain-to-strain variation in curcumin susceptibility, while systematic evidence for thymol and carvacrol against Klebsiella pneumoniae shows measurable antibacterial and antibiofilm activity but also wide variation in MIC values. These observations support a more cautious development strategy based on standardized susceptibility testing, mechanism-specific assays, pharmacokinetic studies and testing in clinically relevant MDR isolates. Phytochemicals therefore remain promising sources of antibacterial scaffolds and adjuvants, but their therapeutic value depends on reproducible activity, selectivity and achievable exposure rather than natural origin alone.**

Index Terms—**antimicrobial resistance; multidrug-resistant bacteria; medicinal plants; phytochemicals; antibacterial agents; antibiotic adjuvants; molecular docking; molecular dynamics; ADMET**

I. INTRODUCTION

Antimicrobial resistance (AMR) is no longer restricted to individual hospitals or bacterial species. Resistant pathogens are distributed across community, healthcare and environmental settings, and the loss of susceptibility to multiple antibiotic classes can leave clinicians with few effective options. The World Health Organization's 2024 Bacterial Priority Pathogens List places particular emphasis on resistant Gram-negative pathogens, including carbapenem-resistant Acinetobacter baumannii and resistant Enterobacterales, as well as other organisms such as Pseudomonas aeruginosa and Staphylococcus aureus that continue to create substantial therapeutic challenges [1].

This situation has encouraged renewed investigation of natural products. Plant-derived compounds are especially attractive because plants synthesize chemically diverse metabolites with activities that may not resemble those of conventional antibiotics. Yet the phrase 'natural antibacterial' can conceal major differences in evidence quality. Some studies use crude extracts and diffusion assays, whereas others investigate purified molecules using broth microdilution, biochemical target assays or animal models. Results from these approaches are not interchangeable.

The purpose of this review is therefore not simply to list medicinal plants with reported antibacterial activity. Instead, the discussion focuses on what can reasonably be concluded from the available evidence,

how proposed mechanisms have been investigated, and where computational methods can contribute to the discovery process. The central argument is that phytochemicals are best considered as a source of chemical starting points and possible antibiotic adjuvants until potency, selectivity, pharmacokinetics and in vivo efficacy have been established.

Table 1: Phytochemical Classes and Their Antibacterial Relevance

Class	Representative examples	Typical sources	Antibacterial relevance	Evidence caveat
Alkaloids	Berberine, piperine	Berberis spp.; Piper nigrum	Growth inhibition; cell-envelope and intracellular effects; antibiotic combinations	Activity is compound- and strain-dependent
Flavonoids	Quercetin, catechin, EGCG	Tea, fruits, vegetables	Membrane effects, enzyme modulation, biofilm/virulence effects and possible efflux inhibition	Mechanisms are not equally validated for all compounds
Phenolic compounds	Curcumin, eugenol, resveratrol	Turmeric, clove, grapes/berries	Membrane, oxidative-stress, biofilm and metabolic effects	Potency and exposure can be limiting
Terpenoids	Thymol, carvacrol	Thyme, oregano and other aromatic plants	Membrane permeabilization; effects on biofilms and selected resistance mechanisms	Often higher concentrations are required in vitro
Tannins	Hydrolysable and condensed tannins	Tea, berries, woody plants	Protein/enzyme interactions and membrane-associated effects	Complex extracts make attribution difficult
Saponins	Steroidal and triterpenoid saponins	Legumes and medicinal plants	Membrane interaction and permeabilization	Host-cell membrane effects require attention
Organosulfur compounds	Ajoene and related compounds	Garlic	Antibacterial, antibiofilm and potential antibiotic-adjuvant effects	Chemical stability and formulation can be important

II. ANTIBACTERIAL MECHANISMS

The antibacterial behaviour of phytochemicals is often multifactorial. Hydrophobic phenolic compounds such as carvacrol and thymol provide a useful example. Experimental work in *Escherichia*

coli linked their activity to increased membrane permeability and loss of membrane potential, supporting a direct membrane-disruptive mechanism [2]. A later review also summarized evidence for effects on efflux, biofilms, motility and membrane ATPases [3].

Curcumin provides a different example. Reviews have described membrane disruption, interference with virulence and biofilm formation, oxidative stress and antibiotic-potentiating effects [4]. However, activity is not uniform across bacteria. In a study covering more than 100 strains representing 19 species, curcumin showed substantially greater activity against Gram-positive organisms than Gram-negative organisms, and several MDR strains had MICs of at least 2000 µg/mL [5]. This is an important caution against describing curcumin as a broad-spectrum antibacterial agent without specifying the organism and assay conditions.

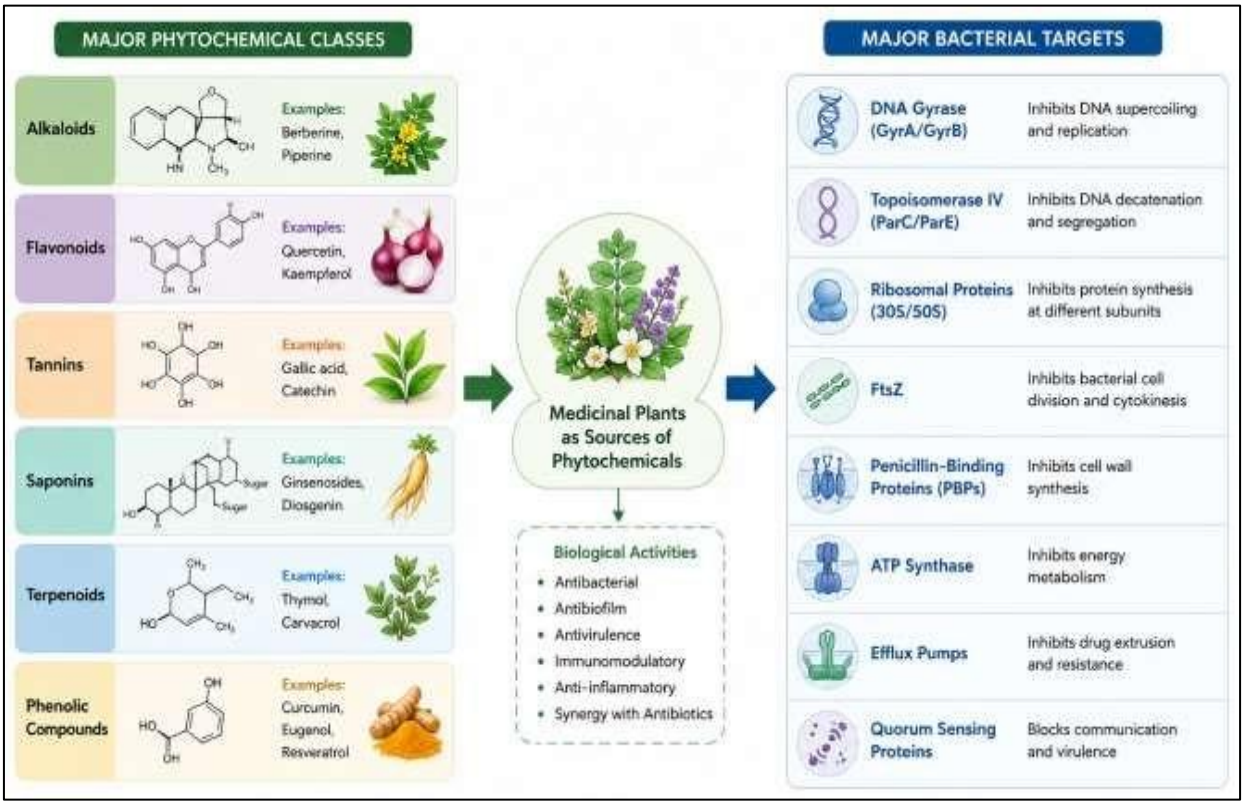

Figure 1. Major Phytochemical classes from medicinal plants, their biological activities, and key bacterial targets involved in antimicrobial action

III. PHYTOCHEMICALS AND MULTIDRUG RESISTANCE

The relationship between phytochemicals and MDR should be considered at the level of resistance mechanism. Potentially useful strategies include increasing membrane permeability, reducing efflux activity, interfering with biofilm development, weakening virulence-associated signalling, or increasing the intracellular activity of an existing antibiotic. Evidence for these effects is growing, but the degree of support differs markedly among compounds.

Polyphenols have recently been reviewed as potential modulators of bacterial efflux systems. Compounds including curcumin, quercetin, luteolin, tannic acid, naringenin, EGCG, ellagic acid and resveratrol have been reported to interfere with efflux activity or its regulation in experimental systems [6]. These findings are mechanistically interesting because efflux contributes to reduced intracellular concentrations of several antibiotic classes. However, demonstrating an effect on an efflux pump in vitro is not equivalent to proving reversal of clinical

resistance.

Combination therapy is another practical direction. A recent study of berberine against 50 clinical MRSA strains reported variable but significant inhibition; synergistic activity with an antibiotic was observed with amikacin in 6 of the 50 isolates [7]. The result is valuable precisely because it demonstrates both potential and variability: a combination that works in one isolate should not be assumed to work across an entire species.

Table 2: Selected Compounds with Evidence-Based Examples

Compound	Study context	Reported observation	Interpretation
Curcumin	>100 strains, 19 species	MDR S. aureus, S. haemolyticus, E. coli and Proteus mirabilis showed MICs ≥2000 µg/mL in the cited study; other species/strains were more susceptible [5]	Curcumin
Thymol	Systematic review of Klebsiella studies	17 studies contributed 60 MIC observations; mean unweighted MIC 475.46 ± 509.95 µg/mL [8]	Antibacterial activity is measurable but highly variable
Carvacrol	Systematic review of Klebsiella studies	10 studies contributed 68 MIC observations; mean unweighted MIC 279.26 ± 434.38 µg/mL [8]	Shows promise, but dispersion of MICs is large
Thymol/carvacrol	Klebsiella systematic review	Antibiofilm effects were reported; most collected combinations were additive or synergistic [8]	Supports further antibiotic-adjuvant research
Berberine	50 clinical MRSA strains	Inhibition was variable; synergy with amikacin occurred in 6/50 isolates [7]	Potential adjunct, but isolate-specific response is important
Carvacrol/thymol	E. coli mechanistic study	Both compounds increased membrane permeability and reduced membrane potential [2]	Provides direct mechanistic evidence for membrane effects

IV. EXPERIMENTAL EVALUATION OF ANTIBACTERIAL ACTIVITY

Agar diffusion remains useful for preliminary screening, particularly when many extracts are being compared. It should not, however, be used as a substitute for quantitative susceptibility testing. Diffusion depends on molecular size, solubility, stability and interaction with the test medium, so a small inhibition zone does not necessarily mean weak biological activity.

For quantitative work, broth microdilution is a reference approach for determining MIC in aerobic bacteria. CLSI M07-Ed12 describes standardized broth macrodilution, broth microdilution and agar dilution procedures, including inoculum preparation, incubation, endpoint determination and quality-control requirements [9]. The current CLSI standard was published in 2024. The same principle should be followed for phytochemicals: solvent controls, growth controls, sterility controls and a reference antibacterial agent should be included, and the phytochemical should be chemically characterized.

MBC, time-kill curves and combination studies add

information that MIC alone cannot provide. When synergy is claimed, checkerboard testing with fractional inhibitory concentration indices and/or time-kill experiments should be used. For compounds with strong colour, precipitation or fluorescence, optical readouts should be checked against appropriate controls.

Mechanism claims require additional experiments. Membrane-active compounds can be examined by membrane-potential and permeability assays; efflux hypotheses can be tested using accumulation or efflux-substrate assays; target-specific hypotheses can be evaluated using purified enzymes, binding assays, gene-expression analysis or genetic perturbation. This hierarchy of evidence helps prevent a docking result from being presented as proof of a molecular mechanism.

V. MOLECULAR DOCKING AND MOLECULAR DYNAMICS

Molecular docking is useful for asking whether a phytochemical can adopt a plausible orientation within a proposed protein pocket. It is particularly useful when a compound library is too large for immediate experimental testing. Nevertheless, docking scores are model-dependent and should not be treated as experimental binding constants.

A credible docking study should report the protein structure and preparation procedure, ligand protonation and tautomeric state, binding-site definition, software and scoring function, search parameters and validation strategy. Re-docking of a known ligand or comparison with experimentally characterized ligands can provide a basic check on whether the docking protocol reproduces known binding modes.

Molecular dynamics can then be used to test whether a docked pose remains structurally plausible over a defined simulation. RMSD, RMSF, hydrogen-bond occupancy, ligand positional stability and interaction persistence can be

informative. Multiple replicas and appropriate controls are preferable to relying on a single trajectory. Even so, a stable trajectory remains a computational observation and does not establish antibacterial activity.

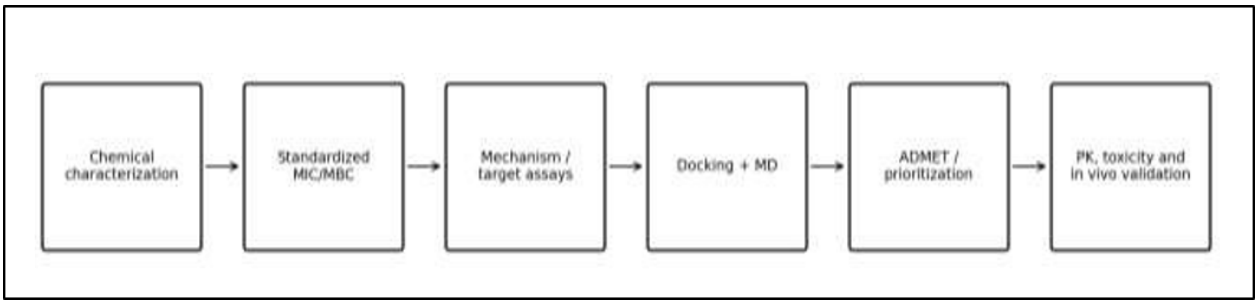

Figure 2. Suggested evidence pathway for moving a phytochemical from chemical characterization to biological and pharmacological validation.

VI. ADMET AND FORMULATION CONSIDERATIONS

Many promising phytochemicals encounter pharmacological problems before reaching clinical development. Curcumin illustrates this issue well: reviews describe hydrophobicity, instability in solution and low bioavailability as major barriers, motivating work on delivery systems and nanoformulations [10]. Similar concerns have been reported for thymol and carvacrol, for which poor bioavailability is an important consideration in therapeutic development [11].

ADMET prediction can therefore be useful for prioritizing compounds, but computational estimates should be followed by experimental measurements of solubility, metabolic stability, permeability, protein binding and cytotoxicity. A compound with a strong docking score but inadequate systemic or local exposure may be a poor therapeutic candidate.

VII. AI AND MACHINE LEARNING

Machine-learning approaches are increasingly used to

connect chemical structure with antibacterial activity and to prioritize compounds for testing. Their usefulness depends heavily on the quality of the training data. MIC values obtained under different media, inoculum densities, incubation conditions and endpoint definitions should not be treated as perfectly interchangeable labels. External validation, careful handling of chemical analogues across train/test sets and transparent reporting are therefore essential.

For phytochemical research, AI/ML is most useful when it narrows a chemically characterized library to a manageable number of candidates. Experimental testing should remain the final arbiter of antibacterial activity and mechanism.

Table 3: Translational Limitations

Issue	Why it matters	What should be done
Strain variability	A compound may be active against one strain but weak against another, as illustrated by curcumin [5].	Use diverse clinical isolates and report resistance phenotypes.
Potency	Some phytochemicals require concentrations that may be difficult to achieve therapeutically.	Compare MIC/MBC with achievable exposure and investigate medicinal-chemistry optimization.
Bioavailability	Poor solubility, instability or rapid metabolism can limit exposure [10, 11].	Perform formulation and pharmacokinetic studies early.
Host toxicity	Membrane-active compounds may also affect mammalian cells.	Measure cytotoxicity and calculate a selectivity index.
Evidence quality	Crude extracts contain multiple constituents and can vary between preparations.	Characterize extracts and, where possible, test purified compounds.
Mechanistic certainty	Docking or network analysis can suggest targets without proving them.	Use biochemical, genetic and cellular validation.
Clinical translation	Most evidence remains in vitro or preclinical.	Progress candidates through PK, toxicology, animal efficacy and appropriately designed clinical studies.

VII. FUTURE DIRECTIONS

The next stage of phytochemical antibacterial research should be more selective rather than simply broader. Instead of screening hundreds of crude extracts and reporting inhibition zones, studies can focus on chemically defined compounds, standardized susceptibility testing and clinically relevant MDR isolates. Compounds with reproducible activity can then be evaluated in antibiotic combinations, with attention to whether the interaction is additive, synergistic or merely coincidental.

A second priority is mechanism. Where an efflux pump, membrane process, enzyme or virulence pathway is proposed, the evidence should progress from computational prediction to a direct assay. This approach would reduce the large gap between the number of phytochemicals reported as 'promising' and the much smaller number that have convincing target-level and pharmacological evidence.

Finally, development decisions should include exposure and safety early. A phytochemical that cannot reach its effective concentration in the relevant tissue, or that produces host toxicity near its antibacterial concentration, is unlikely to become a useful drug without substantial optimization. Delivery systems, structural analogues and antibiotic-adjuvant strategies may offer more realistic development paths than attempting to develop every phytochemical as a stand-alone antibiotic.

VIII. CONCLUSION

Plant-derived phytochemicals remain valuable sources of antibacterial chemistry, particularly for membrane-active compounds, biofilm modulators and potential antibiotic adjuvants. The literature supports biological activity for several classes, but it also shows substantial variation between organisms, strains and experimental systems. Curcumin provides a clear example of why broad antibacterial claims should be tempered by strain-specific data, while the literature on thymol and carvacrol illustrates both measurable antibacterial activity and wide variation in potency.

The most defensible role for phytochemicals at present is therefore as a reservoir of candidate scaffolds and resistance-modifying agents rather than as established replacements for antibiotics. Progress will depend on standardized microbiology, direct mechanism studies, rigorous computational validation, pharmacokinetic and toxicity assessment, and testing in clinically relevant MDR models.

REFERENCES

[1] World Health Organization. WHO bacterial priority pathogens list, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. Geneva: WHO; 2024.

[2] Xu J, Zhou F, Ji BP, Pei RS, Xu N. The antibacterial mechanism of carvacrol and thymol against Escherichia coli. Lett Appl Microbiol. 2008;47(3):174–179. doi:10.1111/j.1472-765X.2008.02407.x.

[3] Marchese A, Arciola CR, Barbieri R, et al. Update on monoterpenes as antimicrobial agents: a particular focus on carvacrol and thymol. Materials. 2017;10(8):947. doi:10.3390/ma10080947.

[4] Tyagi P, Singh M, Kumari H, Kumari A, Mukhopadhyay K. Bactericidal activity of curcumin I is associated with damaging of bacterial membrane. PLoS One. 2015;10(3):e0121313. doi:10.1371/journal.pone.0121313.

[5] Moglad E, et al. Curcumin, a natural antimicrobial agent with strain-specific activity. Pharmaceuticals. 2020;13(12):451. doi:10.3390/ph13120451.

[6] [Recent review] The impact of plant-derived polyphenols on combating efflux-mediated antibiotic resistance. 2025. PubMed PMID: 40362268.

[7] Advancements in MRSA treatment: the role of berberine in enhancing antibiotic therapy. 2025. PubMed PMID: 39731013.

[8] Farhadi K, et al. Thymol and carvacrol against Klebsiella: anti-bacterial, anti-biofilm, and synergistic activities—a systematic review. Front Pharmacol. 2024;15:1487083. doi:10.3389/fphar.2024.1487083.

[9] Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. 12th ed. CLSI standard M07. Wayne, PA: CLSI; 2024.

[10] Antimicrobial Activity of Curcumin in Nanoformulations: A Comprehensive Review. Int J Mol Sci. 2021;22(13):7130. doi:10.3390/ijms22137130.

[11] Carvacrol and Thymol Hybrids: Potential Anticancer and Antibacterial Therapeutics. Molecules. 2024;29(10):2277. doi:10.3390/molecules29102277.

[12] A Comprehensive Review of Antimicrobial Agents Against Clinically Important Bacterial Pathogens: Prospects for Phytochemicals. 2024. PubMed PMID: 39496516.

[13] Volatile phenolics: a comprehensive review of the anti-infective properties of an important class of essential oil constituents. Phytochemistry. 2021;190:112864. doi:10.1016/j.phytochem.2021.112864.

[14] Natural compounds: a promising therapeutic option for managing colistin-resistant bacteria and improving colistin activity. 2026. Microb Pathog. doi:10.1007/s11033-026-11562-y.