

Plant-Derived Antimicrobials as Next-Generation Solutions to Multidrug Resistance

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Abstract

The steady rise of multidrug-resistant (MDR) pathogens is reshaping how clinicians, researchers, and policymakers think about infection control. When bacteria acquire the ability to survive exposure to three or more antibiotic classes at once – whether through efflux pumps, enzyme-mediated drug destruction, target modifications, or reduced membrane permeability – treatment options narrow dramatically, hospital stays lengthen, and mortality climbs. Conventional pharmaceutical pipelines have struggled to keep pace with this biological arms race, pushing the scientific community to look beyond synthetic chemistry for novel solutions. Plants have evolved rich arsenals of bioactive secondary metabolites over hundreds of millions of years of co-evolution with microbial pathogens. Alkaloids – such as berberine, flavonoids such as epigallocatechin gallate, terpenoids such as thymol and carvacrol, tannins, saponins, and quinone derivatives – each offers mechanistic approaches that differ fundamentally from those of conventional antibiotics – disrupting microbial membranes, blocking efflux machinery, interfering with quorum-sensing communication, and inhibiting resistance enzymes. When intelligently combined with existing drugs, many of these compounds restore sensitivity in isolates that had previously been classified as untreatable.

Keyword: Plant-derived antimicrobials, multidrug resistance, phytochemicals, *Tecomella undulata*, ESKAPE pathogens, synergistic therapy, nanoformulation, antibiotic resistance

INTRODUCTION

When Alexander Fleming observed that a stray mould was killing the bacterial colonies on his Petri dish in 1928, he could not have anticipated that the era of antibiotics he inaugurated would, within a century, begin to unravel under the weight of microbial adaptation. Today, the World Health Organization categorises antimicrobial resistance among the ten most urgent global health threats, projecting that, without decisive intervention, drug-resistant infections could account for ten million deaths annually by 2050 – surpassing cancer as a cause of mortality [1, 2].

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Multidrug resistance arises when a microorganism acquires non-susceptibility to agents across at least three antimicrobial categories simultaneously, while extensive drug resistance implies sensitivity to only one or two remaining classes [3]. The molecular underpinnings are well characterised: overexpressed efflux transporters actively eject drug molecules before they reach effective concentrations; beta-lactamases and carbapenemases hydrolyse the chemical bonds central to antibiotic activity; mutations in target proteins – penicillin-binding proteins, topoisomerases, ribosomal subunits – abolish drug binding; and alterations in outer-membrane porins curtail drug entry [4]. Genes encoding these traits

move laterally between species through conjugative plasmids, transposons, and integrons, spreading resistance at a pace that evolutionary biology rarely produces by vertical inheritance alone.

Ethnopharmacological scholarship has catalogued thousands of botanical preparations used across traditional medical systems for the management of infectious disease [5]. Modern laboratory science has, in many cases, validated these traditional applications by isolating and characterising the responsible bioactive constituents. What makes plant-derived antimicrobials particularly attractive in the current landscape is not simply that they kill bacteria, but that the mechanisms through which they act – membrane disruption, efflux inhibition, interference with cell-to-cell communication, enzymatic resistance reversal – are largely orthogonal to those exploited by existing drugs [6, 7]. A pathogen that has painstakingly evolved resistance to ciprofloxacin through target mutation has not necessarily made itself resistant to carvacrol-mediated membrane disruption; this mechanistic independence is the conceptual foundation for plant–antibiotic combination therapy.

This review aims to provide B. Pharm students and early-career pharmaceutical researchers with a rigorously evidenced and practically oriented survey of the field. Sections progress from epidemiology through phytochemistry, resistance mechanisms, individual plant evidence profiles, formulation science, and clinical translation barriers – with four original diagrams designed to make the conceptual structure of the field immediately accessible.

EPIDEMIOLOGY OF MULTIDRUG RESISTANCE

Six pathogen groups – collectively acronymised as ESKAPE – sit at the center of the nosocomial MDR crisis: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species. Their designation reflects not just clinical importance but a near-unique capacity to acquire and accumulate resistance genes from environmental reservoirs [8]. The scale of the problem is illustrated starkly by pan-drug-resistant *A. Baumannii* lineages for which no approved antibiotic retains reliable bactericidal activity – a scenario that effectively returns the management of these infections to the pre-antibiotic era.

The drivers of resistance accumulation are intersecting and mutually reinforcing. Inappropriate prescribing practices, prophylactic and sub-therapeutic antibiotic use in livestock agriculture, inadequate hospital infection control, and the near-abandonment of antibiotic research by major pharmaceutical companies between roughly 1990 and 2010 have all accelerated the trajectory [2, 9]. India occupies a particularly complex position in this landscape: the country carries one of the world's highest burdens of drug-resistant tuberculosis, broad over-the-counter antibiotic availability persists in many states, and dense urban populations create ideal conditions for horizontal gene transfer between community and healthcare reservoirs [10]. At the same time, India's traditions of Ayurvedic, Siddha, and Unani medicine offer a uniquely rich empirical starting point for systematic phytochemical exploration (Figure 1).

PHYTOCHEMICAL BASIS OF ANTIMICROBIAL ACTIVITY

Alkaloids

Alkaloids are structurally varied nitrogen-containing ring systems synthesised by a wide swath of vascular plant families as constitutive defences against herbivores and competing microorganisms. Berberine, an isoquinoline alkaloid drawn primarily from *Berberis aristata*, *Hydrastis canadensis*, and *Coptis chinensis*, has attracted particular research attention because it targets both bacterial DNA gyrase and topoisomerase IV through intercalation – enzymes whose equivalent in human cells differ sufficiently that selective toxicity is achievable [11]. What distinguishes berberine from fluoroquinolones, which share the same bacterial targets, is its additional interaction with the NorA efflux pump: berberine is a substrate for NorA, but sub-inhibitory concentrations of berberine-derived compounds can saturate pump capacity, and when combined with dedicated pump inhibitors, even high-level fluoroquinolone-resistant staphylococcal isolates regain sensitivity [7].

Piperine, the principal pungency compound of *Piper nigrum* (black pepper), is simultaneously an antimicrobial agent and a clinically useful bioenhancer: in pharmacokinetic studies, it inhibits intestinal and hepatic CYP3A4 and P-glycoprotein, substantially increasing the oral bioavailability of co-administered drugs including several antibiotics. Sanguinarine, isolated from *Sanguinaria canadensis*, shows selective activity against oral biofilm-forming species including *Streptococcus mutans*, and has been evaluated in commercial anti-plaque dental formulations [12].

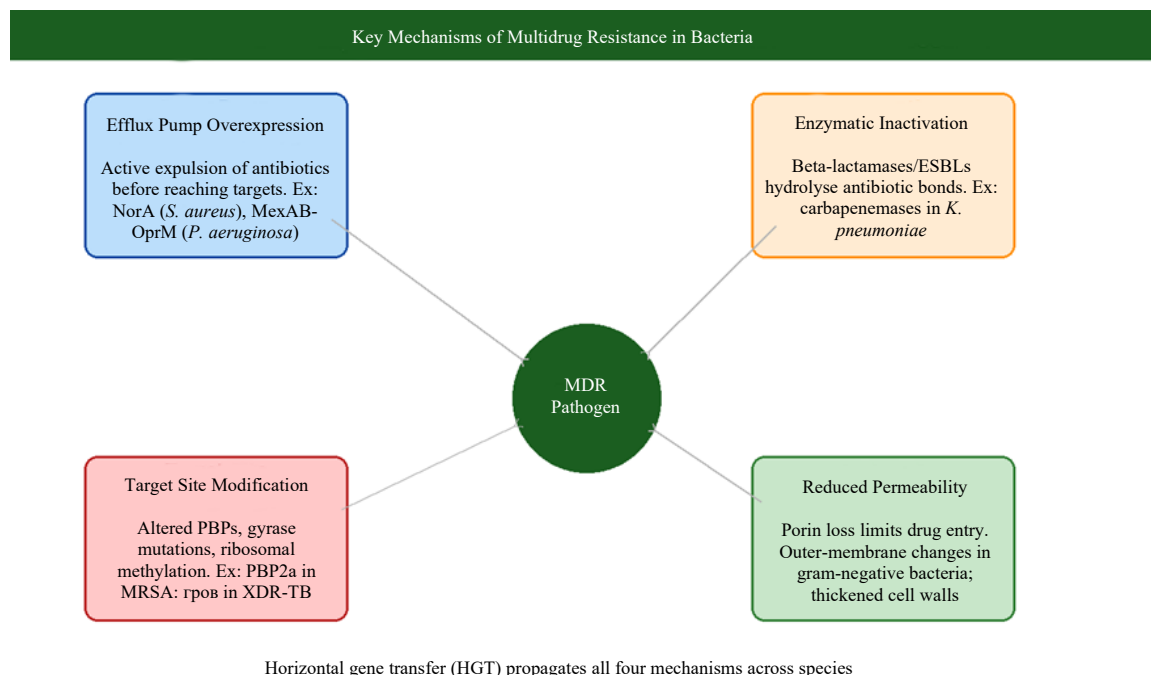


Figure 1. The four principal molecular mechanisms of multidrug resistance in bacteria, with representative examples from clinically significant pathogens. Horizontal gene transfer (HGT) propagates all four mechanisms across taxonomically distant species.

Flavonoids and Polyphenols

Flavonoids represent one of the most structurally diverse families of plant secondary metabolites, encompassing chalcones, flavones, flavonols, isoflavones, and anthocyanidins among their subclasses. Their antimicrobial mechanisms are multifactorial and often context-dependent: at low concentrations, quercetin primarily inhibits DNA gyrase and suppresses biofilm gene expression; at higher concentrations, it disrupts cell membrane integrity directly [11]. Epigallocatechin gallate (EGCG), the predominant catechin of *Camellia sinensis* green tea, has been identified as one of the few natural compounds that inhibits the bacterial FabI enzyme – a critical step in de novo fatty acid biosynthesis – through a mechanism that has no structural counterpart in any currently marketed antibiotic [13]. EGCG also directly interacts with PBP2a, the altered penicillin-binding protein that confers methicillin resistance in MRSA, thereby restoring beta-lactam drug binding and re-sensitising otherwise untreatable isolates to penicillins and cephalosporins. Apigenin has demonstrated competitive inhibitory activity against class A and class D beta-lactamases, while resveratrol from *Polygonum cuspidatum* shows documented synergy with oxacillin against MRSA in time-kill experiments [14].

Terpenoids and Essential Oils

The terpenoid family is the most numerically vast in all-natural product chemistry, with well over 80,000 individual structures catalogued. Their antimicrobial members include monoterpenes, sesquiterpenes, diterpenes, and triterpenes, each with distinct target profiles. Thymol and carvacrol, the principal bioactive monoterpenes of *Thymus vulgaris* and *Origanum vulgare*, respectively, are among the most rigorously studied membrane-active natural compounds. They partition into the phospholipid

bilayer, increasing membrane fluidity and permeability in a concentration-dependent fashion, leading to the dissipation of the proton motive force (PMF) that drives ATP synthesis and active transport [15]. Terpinen-4-ol, the dominant antimicrobial in *Melaleuca alternifolia* (tea tree oil), has completed randomised controlled trials for nasal and skin MRSA decolonization with efficacy broadly comparable to the mupirocin standard of care [16]. Artemisinin from *Artemisia annua*, acting through endoperoxide bridge-mediated generation of carbon-centred radicals that alkylate haem and parasite proteins, remains the most clinically impactful phytochemical in modern medicine – its derivatives forming the backbone of every WHO-recommended combination regimen for falciparum malaria.

Tannins and Saponins

Tannins exert antimicrobial effects chiefly through their high affinity for proteins: by precipitating bacterial surface-associated and periplasmic proteins, they disrupt structural integrity and key enzymatic functions at the cell envelope [14]. Ellagitannins from *Punica granatum* pericarp have been evaluated in checkerboard assays against MRSA with FICI values consistent with synergy when combined with oxacillin; punicalagins additionally inhibit two-component signalling systems that coordinate virulence gene expression. Saponins, by contrast, work primarily through their surfactant geometry – the hydrophilic sugar head groups and hydrophobic aglycone tail create structures that intercalate into and disrupt phospholipid membranes with selectivity shaped by membrane sterol composition, explaining why saponins from plant sources display differential activity against cholesterol-rich mammalian cells versus ergosterol- or hopanoid-containing microbial membranes (Figure 2).

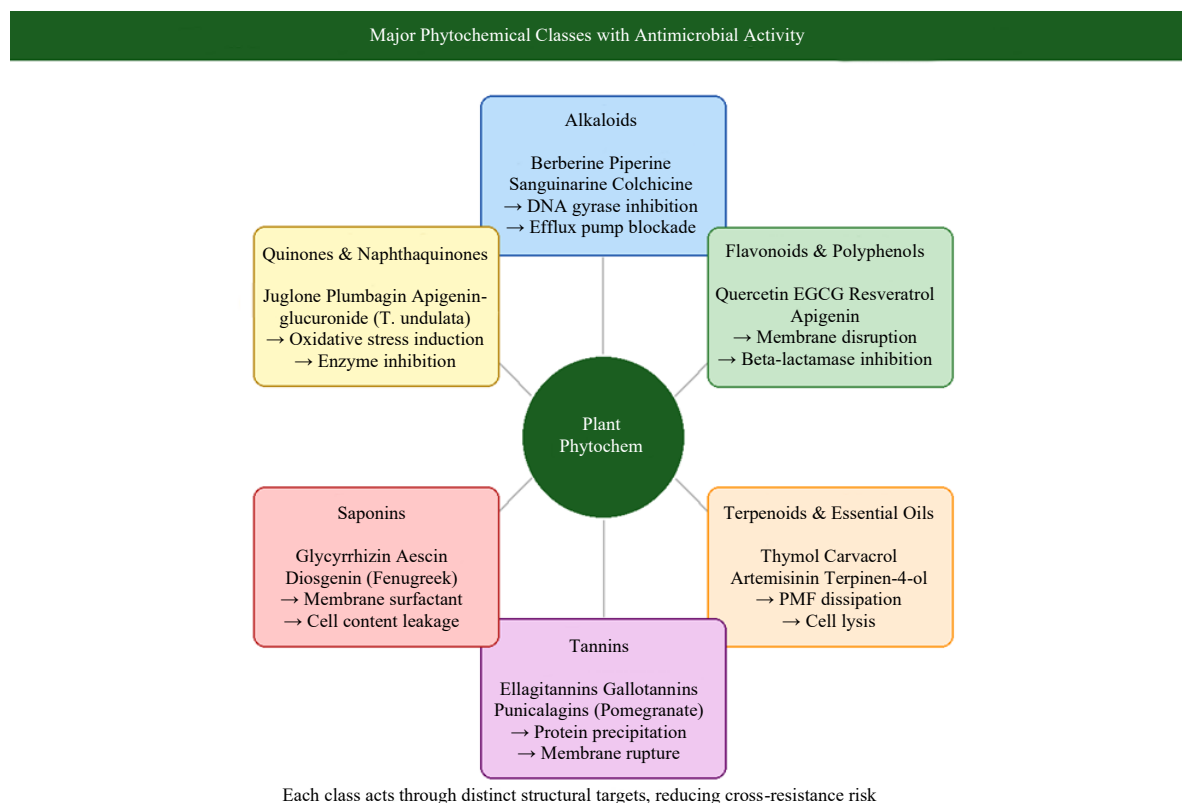


Figure 2. Radial overview of the six major phytochemical classes with documented antimicrobial activity, with representative compounds and primary mechanisms of action for each class.

MECHANISMS BY WHICH PLANT COMPOUNDS OVERCOME ANTIMICROBIAL RESISTANCE

Efflux Pump Inhibition

Efflux pumps represent perhaps the most therapeutically reversible of the major resistance mechanisms, because their inhibition requires no new antibiotic activity – only the restoration of

intracellular drug concentrations that the pump has been reducing. Several plant-derived compounds act as efflux pump inhibitors (EPIs) at concentrations well below their MICs, making combination therapy feasible without adding significant toxicity.

Reserpine from *Rauvolfia serpentina* is the most widely used reference EPI in experimental work on gram-positive systems, reducing the MIC of ciprofloxacin against norA-overexpressing staphylococci by four- to sixteen-fold [4, 7]. Phenolic acids from *Rosmarinus officinalis* inhibit the RND-family MexAB-OprM and MexCD-OprJ pumps in *Pseudomonas aeruginosa*, reducing tobramycin MICs in pump-overexpressing clinical isolates. The practical appeal of this strategy is that EPIs do not need to reach the intracellular space to be effective – they act at the membrane and can, therefore, function even in low-permeability organisms where antibiotic penetration is inherently limited.

Beta-Lactamase Inhibition

Enzymatic beta-lactam hydrolysis is the single most clinically prevalent resistance mechanism in gram-negative bacteria, and the pharmaceutical industry's solution – co-formulation with mechanism-based beta-lactamase inhibitors – such as clavulanic acid and tazobactam – demonstrates both the tractability of this approach and its limitations: serine-based inhibitors are themselves vulnerable to newer class D and metallo-beta-lactamases. Plant-derived compounds offer structurally distinct inhibition profiles: apigenin shows competitive inhibition kinetics against TEM-1 and SHV-1 beta-lactamases with K_i values in the low micromolar range; galangin from *Alpinia galanga* demonstrates inhibitory potency against multiple beta-lactamase classes; and luteolin reduces the expression of blaZ (the principal penicillinase gene in *S. aureus*) at the transcriptional level – a regulatory rather than direct enzymatic inhibition [14].

Biofilm Disruption

Bacteria within biofilms can tolerate antibiotic concentrations 100- to 1,000-fold above the MICs of their planktonic counterparts, a tolerance mediated by multiple factors: slowed growth rates, extracellular matrix as a physical diffusion barrier, persister cell subpopulations, and quorum sensing-coordinated expression of resistance genes [17].

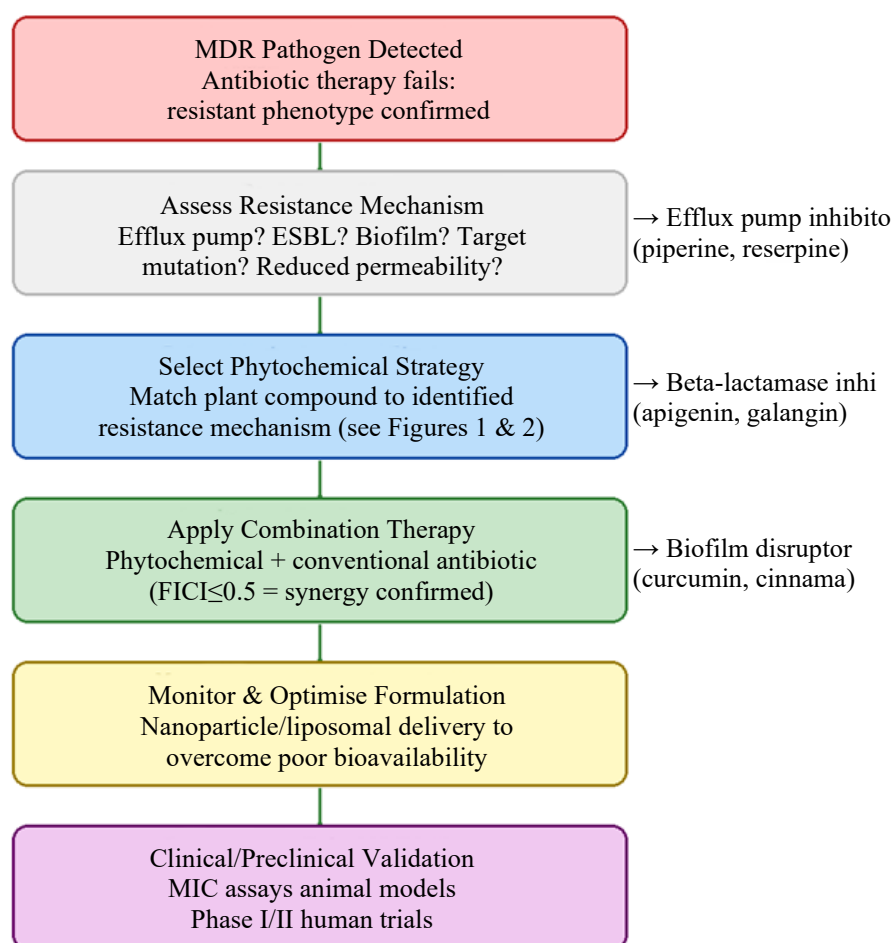
Curcumin from *Curcuma longa* disrupts biofilm formation in both *S. aureus* and *P. aeruginosa* at concentrations far below its bactericidal MIC, principally by targeting the agr (accessory gene regulator) quorum sensing system that governs virulence and biofilm maturation. Cinnamaldehyde from cinnamon bark disrupts the AI-2 type quorum sensing circuitry in *E. coli* and *Salmonella* through competitive binding at LsrK, the kinase responsible for phosphorylating the autoinducer. Eugenol from *Syzygium aromaticum* (cloves) has shown dose-dependent disruption of mature *Candida albicans* biofilms in vitro models, with microscopy confirming disintegration of the hyphal architecture [18].

Membrane Disruption and Permeabilization

Membrane-targeting compounds are, in pharmacological terms, some of the hardest to develop resistance against, precisely because the lipid bilayer is both the most fundamental structural feature of the cell and one of the least amenable to modification without catastrophic disruption of core cellular functions [15]. Plant defensins – small cationic peptides expressed at wound sites and in seeds – adopt amphipathic beta-sheet structures that interact electrostatically with the anionic bacterial surface before inserting into the bilayer to form transmembrane pores.

The terpenoids thymol and carvacrol embed in the hydrophobic core of the bilayer, uncoupling proton gradients across the membrane and depleting the PMF on which gram-negative bacteria depend for nutrient import, active antibiotic expulsion, and flagellar rotation. Resistance to membrane-active agents typically requires global membrane composition remodelling – a high-fitness-cost adaptation that involves dozens of genes and is rarely achievable in a single step (Figure 3).

Flowchart: Phytochemical Strategies Against MDR Pathogens



Iterative optimisation may cycle back from clinical stage to formulation.

Figure 3. Decision flowchart illustrating the clinical and research pathway from MDR pathogen identification through phytochemical strategy selection, combination therapy, formulation optimization, and clinical validation.

EVIDENCE-BASED REVIEW OF KEY MEDICINAL PLANTS

Allium sativum (Garlic)

Among medicinal plants with a documented antimicrobial history, garlic stands out for the chemical elegance of its principal active compound. Allicin (diallyl thiosulfinate) does not exist as a preformed compound in the intact clove – it is generated instantaneously when tissue disruption brings alliin into contact with the enzyme alliinase, a defensive chemistry that also explains why the pharmacological potency of garlic preparations drops sharply with processing. Allicin's antimicrobial mechanism centres on its reactivity with free thiol groups: it rapidly forms mixed disulfides with cysteine residues in essential bacterial enzymes including alcohol dehydrogenase, coenzyme A, and thioredoxin reductase, inactivating them irreversibly [19]. Documented *in vitro* targets include MRSA, *Helicobacter pylori*, *M. tuberculosis*, *Candida albicans*, and multiple Enterobacteriaceae; a randomised clinical study found that adjunctive garlic supplementation meaningfully reduced eradication failure rates when added to standard triple therapy for *H. pylori* [20].

Curcuma longa (Turmeric)

Curcumin is one of the most cited natural compounds in biomedical literature, yet it is also one of the most pharmacokinetically challenging – its poor aqueous solubility, rapid hepatic conjugation, and

renal clearance conspire to keep systemic free-curcumin concentrations low after oral dosing [21]. The mechanistic evidence for its antimicrobial properties, however, is genuinely broad: curcumin intercalates into bacterial DNA, disrupts membrane organization in *S. aureus* at low concentrations, inhibits the agr quorum sensing system that governs virulence gene expression in staphylococci, and under photodynamic activation generates singlet oxygen capable of sterilising wound surfaces [22]. Checkerboard assays reveal synergistic FICI values when curcumin is combined with ampicillin or norfloxacin against resistant isolates, and sub-inhibitory curcumin concentrations reduce the expression of efflux pump genes in fluoroquinolone-resistant *Salmonella typhi*. Phospholipid complexes and PLGA nanoparticles have both been shown to improve oral bioavailability approximately five-fold in rodent pharmacokinetic studies, providing a credible route to therapeutic systemic concentrations [21].

***Azadirachta indica* (Neem)**

Azadirachta indica has earned a near-ubiquitous presence in Indian households as a multipurpose therapeutic, with Ayurvedic texts cataloguing uses spanning skin infections, oral disease, fever, intestinal worms, and wound care [19]. Its antimicrobial chemistry is dominated by limonoid terpenoids – azadirachtin, nimbin, nimbolide, and gedunin – which act through multiple pathways including disruption of bacterial cell wall biosynthesis, inhibition of respiratory enzymes, and direct membrane permeabilization. Nimbolide has drawn interest for its antifungal potency against *Candida* species at concentrations that do not significantly affect mammalian cell viability in short-term cytotoxicity assays. Bark extracts have shown in vitro activity against drug-resistant *M. tuberculosis*, and the immunomodulatory polysaccharide fraction of neem leaf activates macrophage respiratory burst – a host-directed mechanism that operates entirely independently of direct antimicrobial action.

***Ocimum tenuiflorum* (Holy Basil/Tulsi)**

Ocimum tenuiflorum occupies a distinctive place among Indian medicinal plants in that it bridges pharmacological and spiritual significance, appearing in both classical Ayurvedic texts as a Rasayana herb and in modern phytochemical catalogues as a source of eugenol, beta-caryophyllene, linalool, rosmarinic acid, and ursolic acid [15]. Eugenol achieves bactericidal concentrations against *E. coli* O157: H7 and *Listeria monocytogenes* at approximately 0.05–0.1% (v/v), acting primarily by disrupting membrane architecture and inhibiting membrane-bound ATPase activity, which impairs both ATP production and active drug efflux. The immunoadaptogenic properties of ursolic acid and rosmarinic acid – reducing corticosterone-mediated immune suppression and enhancing natural killer cell activity – add a host-directed dimension that may enhance clearance of intracellular pathogens [23].

***Tinospora cordifolia* (Guduchi)**

Guduchi is perhaps the single most immunologically active medicinal plant in the Ayurvedic pharmacopoeia, classified as a tridoshic rasayana – a rejuvenating herb balancing all three constitutional humors. Its alkaloids berberine and palmatine contribute direct antimicrobial activity, while the polysaccharide fraction is the principal driver of its immunomodulatory effects: oral administration of *T. cordifolia* polysaccharides in experimental models consistently increases macrophage phagocytic index, nitric oxide production, and TNF-alpha secretion – effects that translate into enhanced bacterial clearance independent of any direct antibiotic mechanism [5]. This host-directed pharmacology is conceptually invulnerable to pathogen-level resistance acquisition, since the therapeutic target is the immune cell rather than the bacterium – a property that deserves far more attention in the MDR context than it currently receives.

***Berberis aristata* (Indian Barberry)**

As the primary commercial source of berberine alkaloid in South Asian herbal practice, *Berberis aristata* has a validated therapeutic history extending from infectious diarrhoea to ocular infections and chronic skin conditions. Clinical evaluations of berberine-containing preparations for *Vibrio cholerae* and enterotoxigenic *E. coli* diarrhoea have demonstrated reductions in stool frequency and volume relative to oral rehydration therapy alone [11]. The combination of berberine with the NorA inhibitor

reserpine in MRSA infections has been extensively modelled, with consistently synergistic FICI values below 0.5 reported across multiple independent research groups using diverse MRSA clinical isolates – this is one of the most reproducible phytochemical synergy results in the literature and has been proposed as a proof-of-concept system for rational phytochemical combination therapy.

***Camellia sinensis* (Green Tea)**

Green tea is, by volume, one of the most widely consumed plant-derived preparations in the world – a fact that lends its constituents an unusual degree of implicit human safety data. The catechin EGCG is present at approximately 100–200 mg per standard cup and achieves transiently significant concentrations in the gastrointestinal tract post-ingestion. Its dual mechanism of FabI inhibition and PBP2a binding makes it arguably the most mechanistically versatile plant antimicrobial compound yet characterised: two entirely distinct bacterial targets, neither shared with any approved antibiotic class [13]. In practical terms, the interaction with PBP2a is perhaps more clinically significant – MRSA accounts for a disproportionate fraction of healthcare-associated mortality, and a compound that restores oxacillin activity against MRSA isolates without requiring any new antibiotic synthesis represents a pharmacologically efficient and economically attractive therapeutic direction.

***Tecomella undulata* (Desert Teak / Rohida)**

Tecomella undulata (Sm.) Seem. Is a xerophytic deciduous tree of the family Bignoniaceae native to the arid belt extending from Rajasthan and Gujarat through Sindh, Balochistan, Afghanistan, and into Iran and Oman. In the Thar Desert, it is revered as the state tree of Rajasthan and occupies a central place in local ethnomedicine, though its timber value has driven population declines severe enough to warrant endangered status under Indian conservation law [24, 25].

Phytochemical characterization has revealed a structurally varied secondary metabolite profile that includes: flavonoid glucosides and glucuronides (apigenin-7-O-glucuronide, isoquercitrin, quercitrin, and luteolin derivatives); naphthaquinone derivatives with known antimicrobial and cytotoxic activity; iridoid glucosides and secoiridoids; triterpenoids and phytosterols (beta-sitosterol, ursolic acid); and nitrogen-containing alkaloids confirmed by GC-MS analysis [26, 27]. The richness of this profile is consistent with the ecological pressures of semi-arid environments [28], where plant–pathogen competition is intense and chemical defences are correspondingly complex.

Antibacterial data generated by Khosravi and colleagues using the microdilution method found that hydroalcoholic bark extracts inhibited growth of *E. coli*, *S. aureus*, *P. aeruginosa*, and *Shigella dysenteriae* at MIC values ranging from 1.87 to 3.75 mg/mL [28]. Methanolic bark extracts have been reported to achieve MICs as low as 0.1 mg/mL against *E. coli* and 1–2 mg/mL against *K. Pneumoniae* and *P. aeruginosa*. Antifungal disc diffusion assays by Bhardwaj recorded inhibition zone diameters of 27.66 ± 1.52 mm against *Candida albicans*, 18.66 ± 1.52 mm against *Fusarium oxysporum*, and 18.66 ± 0.57 mm against *Penicillium funiculosum*—values that compare favorably with fluconazole controls in the same assay [27].

Traditional uses of *T. undulata* span treatment of leucorrhea, urinary tract infections, syphilis, gonorrhea, hepatitis, jaundice, and wound healing, with the Ayurvedic formulation Rohitakarishtha – prepared from the stem bark – prescribed for liver and spleen diseases and oedema [25, 26]. Recent laboratory investigations have identified anti-HIV activity in bark extracts [26], and endophytic bacteria isolated from *T. undulata* tissues – notably a *Bacillus* sp. EBS9 strain – have been shown to exhibit quorum quenching activity through lactonase-type enzymes, an indirect antimicrobial mechanism that may contribute to the host plant's resistance to phytopathogenic bacteria [29, 30].

The endangered status of *T. undulata* means that wild-harvest-dependent pharmaceutical development is neither sustainable nor legally straightforward. Fortunately, validated plant tissue culture protocols – including axillary bud proliferation and adventitious shoot induction from nodal explants – have been established and published, demonstrating that large-scale in vitro propagation is

technically feasible [25]. Integrating these micropropagation approaches into any pharmaceutical supply chain is an ethical necessity rather than an optional enhancement – and, practically, the only route to assured and scalable phytochemical yields from this species (Figure 4).

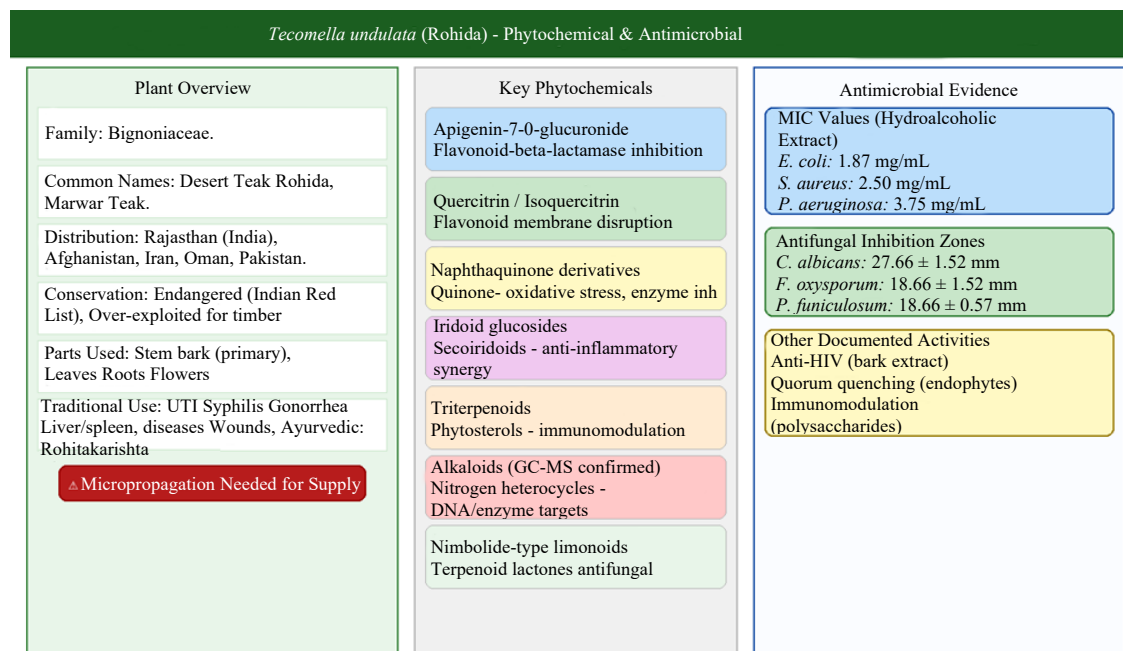


Figure 4. Comprehensive profile of *Tecomella undulata* (Desert Teak/Rohida): Plant taxonomy and conservation status (left), key phytochemical constituents (center), and quantitative antimicrobial evidence from published laboratory studies (right).

SYNERGISTIC COMBINATIONS: PHYTOCHEMICALS AND CONVENTIONAL ANTIBIOTICS

The concept of therapeutic synergy – where the combined effect of two agents exceeds the sum of their individual effects – is operationalised in antimicrobial science through the FICI. When two drugs are tested in checkerboard dilution arrays and the resulting FICI is 0.5 or below, the combination is classified as synergistic; values above 4.0 indicate antagonism [6]. Several phytochemical-antibiotic pairings reliably achieve synergistic FICI values against MDR clinical isolates that are unresponsive to either agent alone.

The EGCG–oxacillin pairing against MRSA is among the most extensively replicated findings in phytochemical antimicrobial research [13]. The mechanistic basis is well understood: EGCG binds PBP2a with an affinity that reduces the protein’s effective resistance to beta-lactam binding, allowing oxacillin to exert bactericidal activity at concentrations that would be clinically achievable. Curcumin combined with ciprofloxacin shows enhanced killing of fluoroquinolone-resistant *Salmonella typhi* at FICI values of approximately 0.25 in published studies, with transcriptomic data suggesting that curcumin suppresses the *acrB* efflux pump gene that drives fluoroquinolone resistance in this species [22].

The idea of phytosynergy – where combinations of phytochemicals within a crude plant extract produce greater activity than isolated individual compounds – is supported by multiple comparative bioassay studies finding that crude extracts outperform their most abundant purified constituents at equivalent concentrations [15]. This finding has practical implications for formulation strategy: standardised full-spectrum extracts that preserve the minor-constituent matrix may outperform single-compound preparations in clinical application, though they are harder to characterise analytically and to approve through conventional regulatory routes. Resolving this tension – between the pharmacological advantage of chemical complexity and the regulatory preference for defined single-entity drugs – is one of the central challenges of plant-derived antimicrobial development.

NANOFORMULATION STRATEGIES TO ENHANCE PHYTOCHEMICAL DELIVERY

Bioavailability remains the most practically significant obstacle between promising in vitro data and clinical utility for phytochemicals. Curcumin, quercetin, resveratrol, and most essential oil monoterpenes share profiles of low aqueous solubility, rapid intestinal and hepatic biotransformation, and short plasma half-lives that limit systemic exposure after oral administration [21]. Nanoparticulate drug delivery systems address these limitations by protecting drug cargo within colloidal carriers, reducing first-pass metabolism exposure, extending circulation time, and in some designs, targeting drug release to specific tissue compartments. Chitosan nanoparticles are of particular relevance to antimicrobial drug delivery because the polymer matrix itself disrupts bacterial membranes through electrostatic interaction with anionic surface lipopolysaccharides – an inherent synergy between carrier and cargo [18].

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have been used to encapsulate thymol, eugenol, and carvacrol for both food preservation and pharmaceutical applications, with studies consistently reporting lower effective concentrations against target organisms compared with unformulated essential oil components. PLGA nanoparticle encapsulation of curcumin has achieved approximately five-fold improvement in oral bioavailability relative to free curcumin in rat pharmacokinetic studies [21]. Green-synthesis silver nanoparticles – where plant extracts (including those of neem, tulsi, and, increasingly, *T. undulata*) serve as both reducing and stabilising agents – combine the intrinsic antimicrobial activity of the nanoparticle surface with residual phytochemical activity, producing composite systems with documented activity against MDR *Acinetobacter baumannii* and *Klebsiella pneumoniae* [23].

CHALLENGES AND LIMITATIONS IN CLINICAL TRANSLATION

The gap between rigorous in vitro activity and validated clinical efficacy is wide in phytomedicine – wider, arguably, than in conventional pharmaceutical development – because multiple compounding uncertainties accumulate at each stage of translation [5]. The most foundational of these is standardization: the secondary metabolite profile of a medicinal plant extract shifts with every change in growing conditions, harvest timing, extraction parameters, and storage duration. Without robust phytochemical standardization backed by validated quantitative analytical methods for all relevant active markers, inter-study comparisons are unreliable and dose-response relationships cannot be established with confidence.

The pharmacokinetic attrition of potent phytochemicals between the intestinal lumen and the infected tissue site is a related and compounding problem. Plasma protein binding, partitioning into adipose tissue, and biotransformation to metabolites that may lack or differ in antimicrobial activity all reduce effective tissue concentrations below what in vitro MIC data would predict from a given dose [23]. Systematic pharmacokinetic characterization – covering absorption, distribution, metabolism, and excretion (ADME) – has been completed for only a minority of phytochemicals with compelling antimicrobial profiles. Without these data, rational clinical dosing is not achievable.

The regulatory environment adds further complexity. In India, the intersection of CDSCO oversight for new drug applications and Ministry of AYUSH jurisdiction over traditional formulations creates potential ambiguity for botanical drug candidates that do not fit neatly into either category [10]. Internationally, the FDA's botanical drug guidance and the EMA's herbal medicinal product pathway provide frameworks, but neither was designed with primary antimicrobial indications in mind, and global harmonization remains incomplete. Navigating this landscape requires strategic regulatory expertise that academic research groups rarely possess and that commercial partners have been slow to develop for botanical drug candidates.

FUTURE DIRECTIONS

Computational approaches are rapidly changing the economics of phytochemical lead identification. Machine learning models trained on structural databases can now predict MIC values, efflux pump

substrate likelihood, and beta-lactamase inhibitory activity from molecular descriptors with accuracy that warrants experimental follow-up for top-scoring candidates [23]. Molecular docking of phytochemical libraries against validated resistance protein crystal structures – NorA, TEM-1 beta-lactamase, AcrB – has already identified several plant compounds whose experimental evaluation was directly guided by computational prediction. This ligand-based prioritization strategy has the potential to collapse years of bioassay screening into weeks of computational filtering.

Host-directed therapy using plant immunomodulators represents an underexplored but conceptually compelling research direction, particularly for intracellular pathogens where achieving therapeutic drug concentrations within phagocytic cells is pharmacokinetically difficult [5]. If an immunostimulant – such as *T. cordifolia* polysaccharide – can reliably upregulate macrophage killing capacity, then the clinical outcome in an infection with an intracellular MDR organism might be improved without directly challenging the resistance mechanisms at all – a strategy that, by definition, pathogens cannot develop resistance to in any conventional sense.

For endangered species, like *T. undulata*, synthetic biology pathways that enable heterologous biosynthesis of the most valuable compounds in microbial expression systems represent both a conservation strategy and a route to unlimited scalable supply [25]. The precedent set by artemisinin acid production in engineered *Saccharomyces cerevisiae* suggests that the naphthaquinone and iridoid pathways of *T. undulata* could, with sufficient investment in biosynthetic pathway elucidation and metabolic engineering, eventually be reconstructed in fermentation-compatible hosts – removing the ecological constraint entirely while preserving and even expanding access to the plant's medicinal chemistry.

CONCLUSION

Antibiotic resistance is not a future problem waiting to arrive – it is a present clinical reality that is already limiting therapeutic options for patients on every continent. The organisms responsible are not new, but their capacity to accumulate resistance mechanisms and share them laterally has outstripped the rate at which the pharmaceutical industry has been producing genuinely novel antibiotic scaffolds [1, 2]. In this environment, the pharmacological biodiversity of the plant kingdom – representing hundreds of millions of years of evolutionary optimization against microbial threats – is not merely academically interesting; it is a strategically important resource that medicine has a pragmatic obligation to evaluate rigorously.

The evidence surveyed in this review supports a graduated optimism. The mechanistic basis for activity is established across multiple phytochemical classes. The synergistic interaction of plant compounds with existing antibiotics has been demonstrated in reproducible, independently verified experimental systems. Nanoformulation strategies exist and are advancing that can address the bioavailability limitations that have historically prevented phytochemicals from reaching effective tissue concentrations. The challenges of standardization, pharmacokinetic characterization, toxicological profiling, and regulatory navigation are significant but are tractable problems, not fundamental impossibilities.

For students of pharmacy, this field offers something increasingly rare in a mature scientific discipline: genuine open frontier. The phytochemical space is vast, the resistance crisis is urgent, and the methodological toolkit – computational, nanotechnological, synthetic-biological – is now powerful enough to address questions that were inaccessible a decade ago. *Tecomella undulata*, sitting at the intersection of traditional Rajasthani ethnomedicine, emerging pharmacological data, conservation biology, and novel biosynthetic potential, exemplifies the kind of under-characterised botanical resource that rewards exactly this kind of systematic scientific attention [25, 26]. The botanical pharmacopoeia is not a competitor to modern medicine – it is one of its most underutilised assets (Table 1).

Table 1. Summary of key medicinal plants, active compounds, target organisms, and antimicrobial mechanisms.

Plant (common name)	Active compound(s)	Target organisms	Mechanism & citation
<i>Allium sativum</i> (Garlic)	Allicin, diallyl disulfide	MRSA, <i>H. pylori</i> , <i>Candida</i> spp.	Thiol enzyme inhibition; membrane disruption (Cowan, 1999).
<i>Curcuma longa</i> (Turmeric)	Curcumin, bisdemethoxycurcumin	MRSA, <i>M. tuberculosis</i> , <i>Candida</i> spp.	DNA intercalation; quorum sensing inhibition (Moghadamtousi et al., 2014).
<i>Thymus vulgaris</i> (Thyme)	Thymol, carvacrol	<i>S. aureus</i> , <i>E. coli</i> , <i>Candida</i> spp.	Membrane permeabilization; PMF dissipation (Burt, 2004).
<i>Azadirachta indica</i> (Neem)	Azadirachtin, nimbolide, quercetin	<i>S. aureus</i> , <i>E. coli</i> , <i>M. tuberculosis</i>	Cell wall disruption; enzyme inhibition (Cowan, 1999).
<i>Ocimum tenuiflorum</i> (Tulsi)	Eugenol, linalool, rosmarinic acid	MRSA, <i>E. coli</i> O157:H7, <i>Candida</i> spp.	Membrane disruption; ATPase inhibition (Burt, 2004).
<i>Berberis aristata</i> (Indian Barberry)	Berberine, palmatine, berbamine	MRSA, Leishmania spp., <i>M. tuberculosis</i>	DNA gyrase inhibition; efflux pump inhibition (Stavri et al., 2007).
<i>Camellia sinensis</i> (Green Tea)	EGCG, epicatechin gallate	MRSA, <i>M. tuberculosis</i> , <i>Candida</i> spp.	FabI inhibition; PBP2a inhibition (Sudano Roccaro et al., 2004).
<i>Tecomella undulata</i> (Desert Teak)	Apigenin-7-O-glucuronide, quercitrin, naphthaquinones, alkaloids	<i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>C. albicans</i>	Membrane disruption; enzyme inhibition (Khosravi et al., 2020; Bhardwaj, 2018).

List of Abbreviations

The following abbreviations are used throughout this review. Each term is defined in full at its first occurrence in the text.

Abbreviation	Full form
ACT	Artemisinin-Based Combination Therapy.
AMR	Antimicrobial Resistance.
ATP	Adenosine Triphosphate.
ATPase	Adenosine Triphosphatase (enzyme).
AYUSH	Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homeopathy (Ministry of India).
CRE	Carbapenem-Resistant Enterobacteriaceae.
CDSCO	Central Drugs Standard Control Organisation (India).
EGCG	Epigallocatechin Gallate.
EPI	Efflux Pump Inhibitor.
ESBL	Extended-Spectrum Beta-Lactamase.
ESKAPE	Enterococcus faecium, <i>S. aureus</i> , <i>K. pneumoniae</i> , <i>A. baumannii</i> , <i>P. aeruginosa</i> , Enterobacter spp.
FabI	Enoyl-ACP Reductase (bacterial fatty acid synthesis enzyme).
FICI	Fractional Inhibitory Concentration Index.
GC-MS	Gas Chromatography–Mass Spectrometry.
MDR	Multidrug Resistance / Multidrug Resistant.
MIC	Minimum Inhibitory Concentration.
MRSA	Methicillin-Resistant <i>Staphylococcus aureus</i> .
NLC	Nanostructured Lipid Carrier.
NorA	Chromosomally Encoded Efflux Pump in <i>S. aureus</i> .
PBP2a	Penicillin-Binding Protein 2a (methicillin resistance determinant).
PLGA	Poly(lactic-co-glycolic acid) – biodegradable nanoparticle polymer.
PMF	Proton Motive Force.
ROS	Reactive Oxygen Species.
SLN	Solid Lipid Nanoparticle.
WHO	World Health Organization.
XDR	Extensively Drug Resistant.
XDR-TB	Extensively Drug-Resistant Mycobacterium tuberculosis.

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