Int J Ayurvedic Med,Vol 17 (3), 2026; 598-607

Ayurveda Sahiti Prabha's

International Journal of Ayurvedic Medicine

ISSN No: 0976-5921

Review Article

Synergistic Polyherbal–Antibiotic Combinations: Emerging Trends, Mechanisms, and Therapeutic Implications in Antimicrobial Research

Neelakshi Sharma[1], Bipul Nath[1*], Payal Dasgupta[1], Chayanika Talukdar[1], Manas Jyoti Kapil[2], Amaryllis Langbang[3]

1. Department of Pharmacy, Royal School of Pharmacy, The Assam Royal Global University, Betkuchi, Guwahati-781035, Kamrup, Assam, India.
2. Institute of Pharmacy, Assam Don Bosco University, Tapesia Gardens, Sonapur-782402, Kamrup, Assam, India.
3. Department of Biosciences, School of Life Science, Assam Don Bosco University, Tapesia Gardens, Sonapur-782402, Kamrup, Assam, India.

Received: 07-11-2025 Accepted: 19-06-2026 Published: 30-09-2026

Abstract

Antimicrobial resistance (AMR) has become a pressing global health concern, threatening the efficacy of existing antibiotic therapies and complicating infection management. The indiscriminate and prolonged use of antimicrobial agents has accelerated the emergence of multidrug-resistant (MDR) pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae*. These organisms employ complex resistance mechanisms including enzymatic degradation, efflux pump activation, target modification, and biofilm formation that render conventional antibiotics increasingly ineffective. With a stagnating pipeline for novel antibiotic discovery, alternative strategies are urgently required to restore antimicrobial potency and ensure therapeutic sustainability. Polyherbal formulations, integral to traditional medical systems like Ayurveda, Siddha, and Traditional Chinese Medicine, have recently gained scientific prominence as complementary interventions in antimicrobial therapy. Enriched with structurally diverse phytoconstituents such as alkaloids, flavonoids, terpenoids, and phenolics, these formulations exhibit multi-targeted actions including membrane disruption, inhibition of virulence determinants, modulation of quorum sensing, and enhancement of antibiotic penetration. When combined with conventional antibiotics, polyherbal formulations often demonstrate synergistic effects that amplify antibacterial efficacy, reduce effective antibiotic dosages, and mitigate the emergence of resistance. Accumulating in vitro and in vivo evidence supports the potential of these combinations in addressing therapeutic failures linked to MDR infections. Nevertheless, critical challenges persist concerning phytochemical standardization, mechanistic elucidation, toxicological profiling, and regulatory harmonization. Future research integrating nanotechnology, green synthesis approaches, and targeted delivery systems could further enhance the bioavailability, stability, and site-specific activity of polyherbal–antibiotic combinations. In summary, the synergistic integration of polyherbal formulations with antibiotics represents a promising and sustainable paradigm in antimicrobial research bridging traditional phytotherapy with contemporary pharmacological innovation to counter the escalating threat of AMR.

Keywords: Polyherbal formulations, Antibiotic synergy, Antimicrobial resistance, Phytochemicals, Herb–drug interactions, Nanotechnology in therapeutics

Access this article online

Website: https://ijam.co.in

DOI: https://doi.org/10.47552/ijam.v17i3.6703

Introduction

Antimicrobial resistance (AMR) has emerged as one of the most significant global public health challenges of the twenty-first century, substantially compromising the effectiveness of antimicrobial therapies and threatening the successful management of infectious diseases worldwide. According to the World Health Organization (WHO), AMR occurs when microorganisms such as bacteria, fungi, viruses, and parasites develop the ability to survive exposure to antimicrobial agents that were previously effective against them. The widespread and often inappropriate use of antibiotics in human medicine, veterinary practice, and agriculture has accelerated the emergence and dissemination of resistant microbial strains, resulting in increased morbidity, mortality, prolonged hospitalization, and escalating healthcare costs. Consequently, multidrug-resistant (MDR) pathogens have become a major threat to public health, necessitating the urgent development of innovative therapeutic approaches (1).

*** Corresponding Author:**
Bipul Nath
Department of Pharmacy, Royal School of Pharmacy,
The Assam Royal Global University, Guwahati,
Assam- 781035, India.
Email Id: bipulnath@gmail.com

Among the most clinically relevant MDR pathogens are *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae*, which have developed sophisticated mechanisms to evade the action of antimicrobial agents. These mechanisms include enzymatic degradation of antibiotics, modification of drug targets, activation of efflux pumps, reduced membrane permeability, and biofilm formation. Biofilms represent a particularly challenging mode of microbial survival, as they protect microorganisms from host immune responses and significantly reduce antibiotic penetration, thereby contributing to persistent and recurrent infections. The increasing prevalence of such resistant pathogens has rendered many conventional antibiotics less effective and has highlighted the limitations of current antimicrobial therapies (2).

Despite remarkable advances in pharmaceutical sciences, the discovery and development of novel antibiotics have not kept pace with the rapid evolution of microbial resistance. The antibiotic development pipeline remains limited due to high research and development costs, lengthy regulatory approval processes, and diminishing commercial incentives. As a result, there is growing interest in identifying alternative or adjunctive therapeutic strategies capable of enhancing the efficacy of existing antibiotics while minimizing the emergence and spread of resistance.

Natural products have historically served as a rich source of therapeutic agents and continue to offer immense potential for antimicrobial drug discovery. Medicinal plants contain a diverse range of bioactive secondary metabolites, including alkaloids, flavonoids, tannins, terpenoids, phenolic compounds, and saponins, many of which exhibit antimicrobial, antioxidant, anti-inflammatory, and immunomodulatory activities. Traditional medicinal systems such as Ayurveda, Siddha, Unani, and Traditional Chinese Medicine have long employed polyherbal formulations, wherein multiple medicinal plants are combined to achieve enhanced therapeutic outcomes through complementary and synergistic pharmacological effects. Such formulations often provide broader therapeutic coverage, improved efficacy, reduced toxicity, and a lower propensity for resistance development compared with single-agent therapies (3).

In recent years, the integration of polyherbal formulations with conventional antibiotics has gained considerable attention as a promising strategy for combating antimicrobial resistance. Numerous studies have demonstrated that phytochemicals can potentiate antibiotic activity through diverse mechanisms, including disruption of microbial cell membranes, inhibition of resistance enzymes, suppression of efflux pumps, interference with quorum sensing pathways, and prevention of biofilm formation. These synergistic interactions can reduce the minimum inhibitory concentrations (MICs) of antibiotics, restore susceptibility in resistant microorganisms, enhance antimicrobial efficacy, and potentially reduce the dosage requirements and adverse effects associated with conventional antimicrobial therapy. Furthermore, polyherbal–antibiotic combinations have shown promising activity against MDR and biofilm-forming pathogens, suggesting their potential as effective alternatives or adjuncts to existing treatment regimens (4).

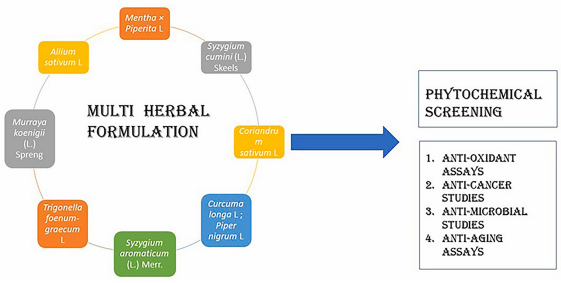
Given the escalating burden of AMR and the urgent need for sustainable antimicrobial strategies, the exploration of synergistic interactions between polyherbal formulations and conventional antibiotics has become an important area of research. Therefore, the present review aims to systematically review and critically evaluate the available evidence on the synergistic antimicrobial activity of polyherbal formulations in combination with conventional antibiotics against multidrug-resistant microorganisms. Specifically, this review seeks to examine the existing literature on herb–antibiotic synergism, evaluate the effectiveness of these combinations against MDR and biofilm-forming pathogens, investigate the underlying mechanisms responsible for synergistic interactions and modulation of microbial resistance pathways, and assess the potential of polyherbal–antibiotic combinations as a viable strategy for combating antimicrobial resistance and improving therapeutic outcomes.

Polyherbal Formulations as Multi-Target Therapeutics: Concept and Rationale

Polyherbal formulations constitute a fundamental component of traditional medicinal systems, including Ayurveda, Siddha, Unani, and Traditional Chinese Medicine (TCM), where therapeutic efficacy is achieved through the strategic combination of multiple medicinal plants. The underlying principle of polyherbalism is that diverse phytoconstituents interact synergistically or additively to produce broader and more potent pharmacological effects than those obtained from individual herbs. Such formulations are increasingly recognized as multi-target therapeutic systems capable of modulating complex biological pathways involved in disease progression and antimicrobial resistance (5).

The medicinal plants incorporated in the present polyherbal formulation *Mentha* × *piperita* L., *Syzygium cumini* (L.) Skeels, *Coriandrum sativum* L., *Curcuma longa* L., *Piper nigrum* L., *Syzygium aromaticum* (L.) Merr., *Trigonella foenum-graecum* L., *Murraya koenigii* (L.) Spreng., and *Allium sativum* L. were selected based on ethnopharmacological relevance and scientific evidence supporting their antimicrobial potential (Figure 1). Each plant contributes distinct classes of bioactive compounds with complementary mechanisms of action. *Curcuma longa* provides curcuminoids with anti-inflammatory and antimicrobial activities; *Allium sativum* contains sulfur-containing compounds such as allicin that exhibit broad-spectrum antimicrobial effects; *Syzygium aromaticum* is rich in eugenol, a potent antimicrobial phenolic compound; while *Piper nigrum* supplies piperine, a well-established bioavailability enhancer. Similarly, *Mentha* × *piperita*, *Coriandrum sativum*, *Murraya koenigii*, *Syzygium cumini*, and *Trigonella foenum-graecum* possess flavonoids, terpenoids, phenolics, and alkaloids known to inhibit microbial growth, attenuate oxidative stress, and modulate host immune responses. The selection of these herbs was therefore guided by their documented antimicrobial efficacy, complementary phytochemical profiles, traditional therapeutic usage, and potential to generate synergistic interactions against multidrug-resistant microorganisms (6).

Figure 1: Schematic representation of the multi-herbal formulation comprising *Mentha* × *piperita L.*, *Syzygium cumini (L.) Skeels*, *Coriandrum sativum L.*, *Curcuma longa L.*, *Piper nigrum L.*, *Syzygium aromaticum (L.) Merr.*, *Trigonella foenum-graecum L.*, *Murraya koenigii (L.) Spreng*, and *Allium sativum L (6).*



From a classical Ayurvedic perspective, polyherbal formulations are designed to optimize therapeutic efficacy while minimizing adverse effects. The principle of *Samyoga* (combination therapy) proposes that carefully selected herbs can influence both pharmacodynamic and pharmacokinetic properties, thereby enhancing overall therapeutic outcomes. In modern pharmacological terms, polyherbal formulations may be defined as therapeutic preparations containing multiple plant-derived ingredients that are systematically combined to improve efficacy, bioavailability, safety, and multi-target activity. This concept closely aligns with contemporary systems pharmacology approaches, which emphasize modulation of interconnected biological networks rather than single molecular targets (7).

One of the principal advantages of polyherbal formulations lies in their capacity to harness phytochemical synergy. Individual medicinal plants contain diverse secondary metabolites such as alkaloids, flavonoids, terpenoids, tannins, phenolic compounds, and saponins, each possessing unique biological activities. When combined, these constituents may interact synergistically to enhance antimicrobial, antioxidant, anti-inflammatory, and immunomodulatory effects. For example, phenolic compounds can disrupt microbial cell membranes, flavonoids may inhibit nucleic acid synthesis, and alkaloids can interfere with protein synthesis. Simultaneously targeting multiple microbial pathways can significantly enhance antimicrobial efficacy while reducing the probability of resistance development (8).

The scientific rationale for polyherbal combinations is further strengthened by evidence demonstrating their ability to overcome microbial resistance mechanisms. Certain phytochemicals inhibit bacterial efflux pumps, suppress quorum sensing pathways, interfere with biofilm formation, or inhibit resistance enzymes responsible for antibiotic degradation. Additionally, specific bioactive compounds improve the pharmacokinetic performance of other constituents. Piperine from *Piper nigrum*, for instance, enhances the absorption and bioavailability of numerous phytochemicals and therapeutic agents by inhibiting intestinal and hepatic metabolic enzymes. Such complementary interactions contribute to the superior therapeutic performance often observed in polyherbal formulations compared with isolated phytochemicals (9).

Several traditional formulations exemplify the effectiveness of polyherbal therapy. Ayurvedic preparations such as Triphala and *Trikatu* have long been used for gastrointestinal, immunomodulatory, and antimicrobial purposes, while *Dasamoola* is recognized for its anti-inflammatory and host-defence-enhancing properties. Likewise, Traditional Chinese Medicine formulations such as Huang Lian Jie Du Tang have demonstrated antibacterial and anti-inflammatory activities against resistant pathogens. Contemporary pharmacological investigations continue to validate these traditional formulations, highlighting the translational potential of polyherbal systems in modern antimicrobial therapy.

Collectively, polyherbal formulations represent a scientifically plausible and therapeutically promising strategy for addressing the growing challenge of antimicrobial resistance. By combining medicinal plants with complementary phytochemical profiles and multiple mechanisms of action, these formulations can enhance antimicrobial efficacy, reduce toxicity, improve bioavailability, and mitigate resistance development. Consequently, the integration of traditional polyherbal wisdom with modern pharmacological approaches may provide a valuable foundation for the development of next-generation antimicrobial therapeutics.

Although numerous other polyherbal formulations have demonstrated antimicrobial potential, the formulations highlighted in Table 1 were selected as representative examples due to the availability of substantial pharmacological evidence and their frequent citation in studies investigating synergistic phytotherapeutic approaches against microbial infections. These formulations collectively demonstrate how combinations of medicinal plants can target multiple microbial pathways, enhance host defence mechanisms, and potentially overcome limitations associated with conventional antimicrobial therapy.

Table 1: Representative polyherbal formulations selected based on documented antimicrobial activity, traditional therapeutic relevance, phytochemical diversity, and potential applicability in combating antimicrobial resistance.

Polyherbal Formulation	Plant Composition	Reported Antimicrobial Activity	References
Triphala	*Terminalia chebula*, *Terminalia bellirica*, *Emblica officinalis*	Broad-spectrum antibacterial and antifungal activity; effective against *E. coli*, *S. aureus*, *C. albicans*	(10), (11)
Trikatu	*Piper nigrum*, *Piper longum*, *Zingiber officinale*	Antibacterial, antifungal, and antiviral activity; enhances bioavailability of co-administered drugs	(12), (13)
Dasamoola	10 roots including *Bilva*, *Agnimantha*, *Shyonaka*, *Gokshura*	Anti-inflammatory, immunomodulatory, and antibacterial activity; supports host defense	(14)
Huang Lian Jie Du Tang	*Coptis chinensis*, *Scutellaria baicalensis*, *Phellodendron amurense*, *Gardenia jasminoides*	Strong antibacterial and anti-inflammatory activity; effective against resistant bacterial strains	(15)
Nishamalaki	*Emblica officinalis*, *Curcuma longa*	Antibacterial and antioxidant activity; effective against Gram-positive and Gram-negative bacteria	(16) (17)
Chyawanprash (Ayurvedic)	40+ herbs including *Emblica officinalis*, *Piper longum*, *Asparagus racemosus*	Immunomodulatory; antibacterial, antiviral, and antifungal effects; enhances host immunity	(18) (19)

Mechanistic Basis of Antibiotic Resistance

Genetic and Biochemical Determinants of Antimicrobial Resistance

Antibiotic resistance is a complex and dynamic biological phenomenon in which microorganisms develop the capacity to survive or proliferate in the presence of antimicrobial agents that would ordinarily inhibit their growth or induce cell death. This adaptive evolution severely undermines the efficacy of conventional antibiotics and represents a growing global public health challenge. Elucidating the genetic and biochemical mechanisms underlying resistance is therefore essential for designing innovative therapeutic interventions, including synergistic combinations of conventional antibiotics with

polyherbal formulations aimed at restoring antimicrobial effectiveness (20)(21).

At the genetic level, antibiotic resistance can emerge through spontaneous chromosomal mutations or via horizontal gene transfer (HGT) involving mobile genetic elements such as plasmids, transposons, and integrons that encode resistance determinants. These genetic events may result in the modification of antibiotic target sites, thereby reducing drug–target binding affinity. For example, mutations in the gyrA and parC genes encoding DNA gyrase and topoisomerase IV confer resistance to fluoroquinolones. Horizontal gene transfer through conjugation, transformation, and transduction facilitates the rapid dissemination of resistance genes, accelerating the emergence of multidrug-resistant (MDR) strains, particularly in clinical and nosocomial environments (22).

At the biochemical and cellular level, bacteria employ multiple defense strategies to neutralize antibiotic activity. One of the most prevalent mechanisms involves the overexpression of efflux pumps, transmembrane proteins that actively export antibiotics from the bacterial cytoplasm, thereby maintaining sub-lethal intracellular concentrations. Another major strategy is enzymatic inactivation or modification of antibiotic molecules. For instance, β-lactamases hydrolyze the β-lactam ring of penicillins and cephalosporins, nullifying their bactericidal effect, while aminoglycoside-modifying enzymes such as acetyltransferases, adenyltransferases, and phosphotransferases chemically alter the antibiotic, preventing its binding to bacterial ribosomes and subsequent inhibition of protein synthesis (23).

Biofilm formation provides an additional layer of protection. Biofilms are structured microbial aggregates encased within a self-produced extracellular polymeric substance (EPS) matrix that adheres to both biotic and abiotic surfaces, including tissues, medical devices, and implants. Within these biofilms, bacteria exhibit reduced metabolic activity, restricted antibiotic diffusion, and enhanced horizontal gene exchange, rendering them up to a thousand times more resistant to antimicrobial agents than their planktonic counterparts (24).

Other mechanisms contributing to resistance include target site modification such as methylation of ribosomal RNA or alterations in penicillin-binding proteins (PBPs) and metabolic pathway bypass, wherein bacteria synthesize alternative enzymes to circumvent the inhibited metabolic routes (25).

In summary, antibiotic resistance arises from a sophisticated interplay between genetic evolution and biochemical adaptation, encompassing efflux-mediated expulsion, enzymatic degradation, biofilm-associated protection, and gene transfer processes. A comprehensive understanding of these molecular mechanisms provides a critical foundation for developing novel combinatorial approaches, particularly those that integrate polyherbal formulations with conventional antibiotics, to effectively combat multidrug resistance and restore the clinical efficacy of antimicrobial therapies.

Clinical Impact of Multidrug-Resistant (MDR) Pathogens on Therapeutic Outcomes

The global proliferation of multidrug-resistant (MDR) pathogens represents a critical obstacle in contemporary clinical practice, frequently resulting in therapeutic failure and complicating the management of infectious diseases. MDR pathogens are typically defined as bacterial strains resistant to at least one agent in three or more distinct antibiotic classes. Their increasing prevalence in healthcare environments drastically restricts available treatment options, leading to prolonged disease courses, elevated morbidity and mortality rates, and escalating healthcare costs (26).

Therapeutic failure arises primarily from the diminished or complete loss of efficacy of conventional antibiotics against these resistant strains. Clinically significant MDR bacteria such as Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa are implicated in severe infections including septicemia, urinary tract infections, pneumonia, and post-surgical wound infections. In such scenarios, clinicians are often compelled to resort to last-line antibiotics, such as polymyxins, carbapenems, or glycopeptides, which may possess limited availability, unfavorable pharmacokinetic profiles, and higher toxicity risks. Delayed or inappropriate therapy, along with the overuse or misuse of these agents, further exacerbates clinical outcomes and accelerates resistance development (27).

At the molecular level, MDR pathogens evade antibiotic action through complex genetic and biochemical mechanisms. Genetically, resistance may emerge through the acquisition of plasmid-borne, integron-associated, or chromosomal resistance determinants, enabling simultaneous defense against multiple antibiotic classes. Biochemically, bacteria employ efflux pump overexpression, drug-inactivating enzyme production, and biofilm formation as major resistance strategies. Biofilms, in particular, form highly organized microbial communities encapsulated within an extracellular polymeric matrix that acts as a physical and metabolic barrier, limiting antibiotic penetration and facilitating bacterial persistence even under high antimicrobial pressure. Moreover, MDR strains exhibit enhanced metabolic adaptability, allowing survival in nutrient-deprived and immune-challenged environments, thereby contributing to recurrent and chronic infections (28).

Clinically, infections caused by MDR organisms prolong hospitalization, increase the risk of secondary and opportunistic infections, and elevate complication rates. Immunocompromised individuals, elderly patients, and neonates represent particularly vulnerable groups with higher susceptibility to MDR-associated complications. On a broader scale, the widespread dissemination of MDR pathogens imposes a substantial economic burden on healthcare systems, challenges infection control measures, and necessitates the urgent development of novel therapeutic paradigms (29)(30).

Addressing MDR-related therapeutic failure requires innovative and integrative approaches that extend beyond conventional antibiotic monotherapy. The combination of antibiotics with polyherbal formulations has shown considerable promise in restoring antibiotic efficacy, enhancing antimicrobial activity through synergistic interactions, and mitigating the emergence of resistance. When integrated with antibiotic stewardship programs, rapid diagnostic tools, and continuous surveillance of resistance trends, such polyherbal–antibiotic strategies offer a sustainable and holistic framework to improve clinical outcomes and counter the escalating global threat of MDR pathogens (31).

Global Consequences of Antimicrobial Resistance: A Public Health Perspective

Antimicrobial resistance (AMR) stands as one of the most pressing global health emergencies, threatening the efficacy of essential medicines and reversing decades of progress in infectious disease control. The World Health Organization (WHO) has identified AMR as a top-tier public health priority because of its capacity to cause widespread morbidity, mortality, and economic disruption. Resistant infections are estimated to directly

cause 1.27 million deaths annually, with millions more suffering prolonged illnesses due to ineffective treatments. The crisis is especially acute in low- and middle-income nations, where limited access to potent antibiotics, fragile healthcare infrastructure, and inadequate surveillance systems intensify the consequences of resistance (32).

AMR complicates the management of routine infections such as respiratory tract infections, urinary tract infections, and sepsis, often necessitating extended hospital stays and aggressive interventions. Multidrug-resistant (MDR) organisms including *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* pose severe threats, leading to critical conditions like bloodstream infections and organ failure. Moreover, resistance jeopardizes modern medical practices such as surgeries, organ transplants, and chemotherapy, all of which rely on antibiotics for infection prevention. The economic implications are equally severe: patients often require high-cost or toxic alternatives, prolonged hospitalizations, and complex therapeutic regimens, placing immense strain on healthcare budgets. If unaddressed, the global economic toll of AMR is projected to reach trillions of dollars by 2050, significantly affecting productivity and healthcare sustainability (33)(34).

Beyond clinical and economic challenges, AMR poses a major threat to global health security, as resistant pathogens can disseminate rapidly across borders via travel, trade, and environmental transmission. Addressing this escalating crisis necessitates a globally coordinated response encompassing antibiotic stewardship, public awareness initiatives, research investment in novel antimicrobials, and robust surveillance networks to track and mitigate resistance. In essence, AMR represents a multifaceted and evolving threat with profound clinical, societal, and economic repercussions. Effective containment demands a unified approach that integrates responsible antibiotic use, innovation in therapeutic development, and sustained international collaboration to safeguard global health (35)(36).

Bioactive Phytochemicals: Nature's Arsenal Against Microbial Infections

Plants synthesize a diverse range of secondary metabolites, collectively known as phytochemicals, which have gained significant attention for their potent antimicrobial activities. These naturally occurring compounds constitute the plant's intrinsic defense mechanism against invading microorganisms such as bacteria, fungi, viruses, and parasites. Among the principal classes of phytochemicals, alkaloids, flavonoids, tannins, terpenoids, and phenolic compounds have demonstrated remarkable antimicrobial efficacy **(Table 2).**

Alkaloids, characterized by their nitrogen-containing structures, exhibit antimicrobial action by interfering with DNA and RNA synthesis, inhibiting protein biosynthesis, or compromising cell membrane integrity. Compounds like berberine and sanguinarine exemplify broad-spectrum antibacterial activity. Flavonoids, widely distributed in fruits, vegetables, and medicinal herbs, inhibit nucleic acid synthesis, disrupt microbial membranes, and impede energy metabolism, effectively curbing microbial proliferation. Tannins, which are high-molecular-weight polyphenols, exert their effects by binding to microbial proteins, deactivating essential enzymes, and chelating metal ions vital for microbial metabolism. Terpenoids, encompassing monoterpenes and diterpenes, disrupt microbial membrane integrity and permeability, often leading to cell lysis. Phenolic compounds, on the other hand, induce oxidative stress within microbial cells and inhibit key enzymes necessary for growth and replication.

A notable advantage of phytochemicals is their multi-targeted mechanism of action, which significantly reduces the likelihood of resistance development. These compounds can simultaneously disrupt membranes, inhibit enzymatic functions, and interfere with genetic material synthesis. Furthermore, many phytochemicals modulate quorum sensing and biofilm formation, making them particularly effective against persistent infections. Their synergistic interactions amplify antimicrobial potency such as the combined effects of flavonoids and alkaloids in blocking nucleic acid synthesis while compromising membrane integrity, or tannins enhancing permeability to facilitate the entry of other active molecules.

In essence, phytochemicals represent a diverse and powerful reservoir of antimicrobial agents. Their ability to target multiple cellular pathways, coupled with their synergistic potential, positions them as promising alternatives or adjuncts to conventional antibiotics especially in the ongoing fight against multidrug-resistant (MDR) pathogens.

Table 2: Phytochemicals with Antimicrobial Potential

Phytochemical Class	Representative Compounds	Antimicrobial Mechanism	Reported Synergistic Effects	References (examples)
Alkaloids	Berberine, Piperine, Quinine	DNA intercalation, enzyme inhibition, disruption of cell wall and membrane	Enhanced antibacterial activity when combined with flavonoids or terpenoids	(37)(38)
Flavonoids	Quercetin, Catechin, Kaempferol	Inhibit nucleic acid synthesis, alter membrane permeability, inhibit energy metabolism	Synergistic effects with alkaloids and phenolics against MDR bacteria	(39)(40)
Tannins	Gallotannins, Ellagitannins, Catechins	Protein precipitation, enzyme inhibition, metal ion chelation	Increased antifungal and antibacterial potency in combination with flavonoids	(41)(42)
Terpenoids	Limonene, Carvacrol, Thymol	Disruption of microbial membranes, leakage of cell contents, interference with quorum sensing	Synergy with flavonoids and alkaloids enhances bactericidal effect	(43)(44)
Phenolics	Gallic acid, Caffeic acid, Resveratrol	Oxidative stress induction, membrane disruption, enzyme inhibition	Improved activity with tannins or terpenoids against resistant strains	(45)(46)(47)

Synergistic Interplay Between Polyherbal Formulations and Antibiotics: Mechanistic Perspectives

The integration of polyherbal formulations with conventional antibiotics presents a promising strategy to combat the escalating challenge of antimicrobial resistance (AMR). Medicinal plants are abundant sources of bioactive phytochemicals capable of enhancing antibiotic efficacy through multifaceted and complementary mechanisms. These synergistic effects operate at both the pharmacodynamic level by amplifying antibacterial action through diverse molecular targets—and the pharmacokinetic level by influencing drug absorption, distribution, metabolism, and excretion. Together, these interactions can significantly improve antibiotic bioavailability and therapeutic effectiveness (48)(49).

One of the primary mechanisms underlying this synergy is the disruption of bacterial cell walls and membranes. Phytochemicals such as alkaloids, terpenoids, and phenolic compounds can compromise bacterial membrane integrity, increasing permeability and facilitating antibiotic entry. Additionally, several plant-derived molecules function as efflux pump inhibitors, obstructing bacterial mechanisms responsible for expelling antibiotics, thereby reinstating their intracellular concentration and potency. Polyherbal extracts also inhibit biofilm formation a major barrier to antibiotic penetration by interfering with bacterial adhesion, aggregation, and growth processes (50).

Another vital mechanism involves the modulation of quorum sensing, the bacterial communication system regulating virulence, biofilm development, and resistance gene expression. Certain phytoconstituents disrupt quorum-sensing pathways, thereby attenuating bacterial pathogenicity and sensitizing microbes to antibiotic treatment. Collectively, these interactions not only potentiate the antimicrobial effects of antibiotics but also enable dose reduction, minimizing adverse effects and delaying the emergence of resistance (51).

A deeper understanding of these synergistic mechanisms provides a robust scientific foundation for the development of integrated therapeutic strategies that combine herbal bioactives with antibiotics offering a safer, more effective approach to managing multidrug-resistant infections.

Experimental Validation of Polyherbal–Antibiotic Synergy: Insights from In Vitro and In Vivo Investigations

Extensive experimental research has established strong evidence for the synergistic antimicrobial potential of polyherbal and plant-derived bioactives when combined with conventional antibiotics. Such combinations not only enhance antimicrobial potency but also reduce the required drug dosage, limit resistance emergence, and improve therapeutic efficacy. In vitro assays including checkerboard microdilution, time–kill kinetics, and biofilm inhibition studies have repeatedly demonstrated marked potentiation of antibiotic activity. Complementary in vivo evaluations using animal infection models further substantiate these outcomes, revealing decreased bacterial burden, mitigated tissue injury, and superior therapeutic recovery. Collectively, these findings reinforce that integrating natural bioactives with antibiotics represents a rational and sustainable strategy for strengthening antimicrobial therapy and counteracting multidrug resistance (MDR) (52).

A notable instance involves Pseudomonas aeruginosa, a pathogen notorious for its intrinsic resistance and biofilm-forming ability. In a study assessing ciprofloxacin and berberine hydrochloride, the combined treatment exhibited pronounced synergistic antibacterial and antibiofilm activity at sub-minimum inhibitory concentrations (sub-MIC). This combination achieved potent bactericidal effects, indicating its promise as an adjunct therapeutic regimen against P. aeruginosa infections (52). Similarly, the co-administration of daptomycin and fosfomycin produced strong synergy against methicillin-resistant Staphylococcus aureus (MRSA), significantly reducing the mutant prevention concentration (MPC) and resistance selection window. Genomic analyses confirmed the absence of resistance-associated mutations in treated strains, while enhanced biofilm inhibition further validated its clinical potential in MRSA management (53).

In another study, glabridin (GLA) a flavonoid from Glycyrrhiza glabra showed potent synergy with colistin (COL) against resistant Escherichia coli. Mechanistic evaluation revealed that GLA targets the FabI enzyme, thereby augmenting COL efficacy, inhibiting biofilm formation, and delaying resistance onset. Both in vitro and murine urinary tract infection models demonstrated remarkable bacterial clearance and tissue protection under the combination therapy (54).

Furthermore, polyphenolic compounds renowned for their antioxidant, anti-inflammatory, and antimicrobial attributes have been reported to improve antibiotic bioavailability and therapeutic indices while maintaining safety. Reviews emphasize their synergistic potential in overcoming resistance and enhancing treatment outcomes (55). Supporting this, combinations of plant extracts with cefixime against resistant clinical isolates revealed significant bacterial growth suppression and protein reduction, attributed to key bioactives such as gallic acid, quercetin, and cinnamic acid identified via RP-HPLC profiling (56).

Overall, both in vitro and in vivo findings affirm that the integration of antibiotics with phytoconstituents like berberine, glabridin, and polyphenols significantly amplifies antimicrobial efficacy, reduces resistance development, and enhances therapeutic success establishing a robust scientific foundation for polyherbal–antibiotic synergistic interventions as next-generation antimicrobial therapeutics.

Design, Optimization, and Evaluation of Polyherbal Formulations: An Integrated Approach

The development of polyherbal formulations is an interdisciplinary and evidence-based process that bridges ethnopharmacological wisdom with modern pharmaceutical science. It involves a sequence of well-defined steps encompassing plant selection, extraction, standardization, formulation, and evaluation. Medicinal plants are initially chosen based on traditional therapeutic use, ethnobotanical relevance, and preclinical or clinical evidence supporting their pharmacological efficacy. Extraction methods such as maceration, Soxhlet extraction, ultrasonic-assisted extraction, or supercritical fluid extraction are employed to isolate the bioactive phytoconstituents responsible for therapeutic effects. The standardization of extracts ensures reproducibility and batch-to-batch consistency by maintaining constant levels of key biomarkers. Compatibility and preformulation studies are then performed to assess the physicochemical and pharmacodynamic interactions among the plant extracts and excipients, ensuring formulation stability, safety, and synergistic potential. Depending on therapeutic intent and route of administration, formulations are developed into dosage forms such as gels, ointments, suspensions, capsules, emulsions, or advanced nanocarriers including liposomes, phytosomes, and nanoparticles (57).

Comprehensive evaluation parameters are employed to assess quality and functionality. Physicochemical tests such as pH, viscosity, homogeneity, spreadability, particle size, and zeta potential determine formulation uniformity and performance. Microbiological assays evaluate sterility and antimicrobial efficacy, while accelerated stability studies under variable environmental conditions establish shelf-life and ensure long-term reliability. Such a systematic approach guarantees that polyherbal formulations are safe, standardized, and therapeutically consistent (57).

One study formulated a polyherbal phytosomal gel incorporating extracts of *Acalypha indica, Pergularia daemia,* and *Coleus amboinicus* for pharyngitis management. The optimized formulation (F3) showed 72.5% yield, 86.94% entrapment efficiency, particle size of 158 nm, and zeta potential of –8 mV, with strong in vitro antibacterial and anti-inflammatory activities, validating its potential for topical therapeutic use (57). Another investigation developed gels containing essential oil (EO) of *Grindelia tarapacana* targeting oral pathogens (Streptococcus mutans, S. sanguinis, S. salivarius). GC–MS analysis identified bornyl acetate and E-nerolidol as principal actives, and the 2% EO gel demonstrated antibacterial activity comparable to chlorhexidine, alongside excellent physicochemical stability (58).

Similarly, a polyherbal anti-acne gel formulated with R*ubia cordifolia, Aloe barbadensis* and *Allium cepa* exhibited potent antibacterial activity against Cutibacterium acnes, with the optimized formulation (FCEG-4) matching the efficacy of clindamycin. In vivo evaluations confirmed its safety, stability, and effectiveness, positioning it as a sustainable herbal alternative for mild acne management (59).

Overall, these findings illustrate the scientific rigor and therapeutic promise of polyherbal formulations, reinforcing their potential as standardized, eco-friendly, and patient-compliant alternatives that merge traditional ethnomedicine with modern formulation science.

Safety, Toxicological, and Pharmacological Perspectives in Polyherbal–Antibiotic Therapeutics

The integration of polyherbal formulations with conventional antibiotics necessitates meticulous evaluation of both therapeutic synergy and toxicological safety. Systematic toxicity assessments encompassing acute, sub-chronic, and chronic studies are crucial to identify dose-dependent and organ-specific effects, as well as hematological and biochemical alterations. Such investigations ensure that synergistic interactions among multiple phytochemicals do not culminate in additive or cumulative toxicity, thereby maintaining systemic safety and pharmacological compatibility (60)(61).

A critical pharmacological consideration involves herb–drug interactions, as phytoconstituents can modulate cytochrome P450 enzymes, efflux transporters, and plasma protein binding. These alterations can significantly impact antibiotic absorption, metabolism, or elimination, resulting in variable therapeutic outcomes. Hence, rational formulation design demands careful plant selection, bioassay-guided standardization, and precise dose optimization. Analytical techniques such as chromatographic fingerprinting are indispensable for ensuring phytochemical consistency, efficacy, and minimal adverse interactions. Defining safe and effective therapeutic ranges remains a pivotal step in translating polyherbal–antibiotic combinations into clinically viable interventions (61).

Regulatory compliance and quality assurance are equally vital. Challenges such as inconsistent phytochemical profiles, inadequate toxicological validation, and lack of manufacturing standardization hinder clinical acceptance. Adherence to Good Manufacturing Practice (GMP), harmonized safety protocols, and stringent regulatory oversight can enhance product reproducibility, quality, and patient safety (61).

Empirical evidence supports the safety of polyherbal formulations. For instance, the formulation 18KHT01 comprising *Quercus acutissima*, *Camellia sinensis*, *Geranium thunbergii*, and *Citrus limon* demonstrated an excellent safety margin in ICR mice, with a no-observed-adverse-effect level (NOAEL) of 2 g/kg and confirmed safety below 500 mg/kg/day. UPLC-DAD analysis further validated its analytical reliability (60)(63). Conversely, systematic reviews identifying 33 medicinal plants with potential toxicities emphasize the importance of toxicokinetic profiling and safety standardization (61). Overall, establishing a comprehensive safety and pharmacological framework integrating toxicological validation, pharmacokinetic assessment, and regulatory compliance is essential for advancing polyherbal–antibiotic therapeutics as safe, effective, and clinically translatable antimicrobial interventions.

Challenges and Future Outlook in Polyherbal–Antibiotic Synergy

Despite encouraging evidence supporting polyherbal–antibiotic combinations, multiple scientific, technological, and translational challenges continue to impede their advancement. A major scientific hurdle arises from the complex phytochemical nature of herbal extracts, which complicates the identification of active constituents, elucidation of mechanisms, and understanding of herb–drug interactions. The absence of standardized analytical protocols and reproducible experimental methods often results in inconsistent findings across studies, limiting comparability and validation. Variations in plant species, regional origins, extraction techniques, and formulation processes further affect product quality and pharmacological activity, underscoring the need for robust quality control parameters and validated analytical methods to ensure batch-to-batch consistency.

Regulatory and clinical translation barriers remain significant. The scarcity of comprehensive clinical trials, limited toxicological datasets, and lack of harmonized global guidelines for evaluating herbal–synthetic drug combinations delay regulatory acceptance and therapeutic adoption. Moreover, the rigorous pharmacokinetic and pharmacodynamic assessments required by authorities demand extensive time, cost, and technical expertise.

Looking forward, emerging nanotechnological interventions including liposomes, niosomes, and polymeric nanoparticles offer innovative solutions to enhance solubility, stability, and targeted delivery of phytoconstituents with antibiotics. The green synthesis of nanomaterials using medicinal plant extracts promotes sustainable and biocompatible approaches, while targeted delivery systems promise improved site-specific action, reduced systemic toxicity, and mitigation of antimicrobial resistance.

Conclusion

The escalating global challenge of antimicrobial resistance (AMR) demands innovative therapeutic paradigms that extend beyond conventional antibiotic therapy. The integration of polyherbal formulations with standard antibiotics offers a scientifically grounded and sustainable strategy to restore antibiotic efficacy, attenuate resistance development, and minimize dose-dependent

toxicity. This synergistic interaction operates through diverse mechanisms such as cell wall disruption, efflux pump inhibition, quorum sensing modulation, and biofilm interference collectively enhancing bacterial susceptibility and therapeutic outcomes. The multicomponent phytochemical matrix inherent in medicinal plants provides complementary pharmacological actions that potentiate antibiotic activity while reducing adverse effects. Nevertheless, despite promising experimental and preclinical outcomes, standardization, reproducibility, and regulatory validation remain critical challenges restricting clinical translation. Future research must prioritize mechanistic elucidation, molecular docking, metabolomic profiling, and clinical validation to define optimal formulations and dosing regimens. Advanced analytical and biotechnological tools, coupled with nanotechnology-driven targeted delivery systems and green synthesis approaches, hold immense potential to improve bioavailability, safety, and site-specific efficacy. In conclusion, polyherbal–antibiotic synergy represents a frontier in antimicrobial therapy that harmonizes traditional phytomedicine with modern pharmacological innovation offering a holistic, eco-compatible, and efficacious strategy to counter the global AMR crisis and promote the development of next-generation antimicrobial therapeutics.

References

1. Mussarat S, Adnan M, Begum S, Rehman SU, Hashem A, Abd Allah EF. Antimicrobial screening of polyherbal formulations traditionally used against gastrointestinal diseases. Saudi J Biol Sci. 2021;28(12):6829-6843. doi:10.1016/j.sjbs.2021.07.053.
2. Karole S, Shrivastava S, Thomas S, Soni B, Khan S, Dubey J, et al. Polyherbal formulation concept for synergic action: a review. J Drug Deliv Ther. 2019;9(1 Suppl):453-466. doi:10.22270/jddt.v9i1-s.2339.
3. Atta S, Waseem D, Fatima H, Naz I, Rasheed F, Kanwal N. Antibacterial potential and synergistic interaction between natural polyphenolic extracts and synthetic antibiotic on clinical isolates. Saudi J Biol Sci. 2023;30(3):103576. doi:10.1016/j.sjbs.2023.103576.
4. Mandrika I, Kumar S, Zandersone B, Eranezhath SS, Petrovska R, Liduma I, et al. Antibacterial and anti-inflammatory potential of polyherbal formulation used in chronic wound healing. Evid Based Complement Alternat Med. 2021;2021:9991454.
5. Pandeya PR, Lamichhane R, Lamichhane G, Lee KH, Lee HK, Rhee SJ, et al. 18KHT01, a potent anti-obesity polyherbal formulation. Front Pharmacol. 2021;12:807081. doi:10.3389/fphar.2021.807081.
6. Samdavid Thanapaul RJR, Nambur CK, Giriraj K. Development of multi-herbal formulation with enhanced antimicrobial, antioxidant, cytotoxic, and anti-aging properties. J Indian Chem Soc. 2024;101(11):101402. doi:10.1016/j.jics.2024.101402.
7. Patel VR, Saini S, Dwivedi J, Gupta AK, Shrivastava AK, Misra A. Exploring the concept and scope of polyherbal formulations: a comprehensive review. Int J Herbal Med. 2025;13(2):9-16. doi:10.22271/flora.2025.v13.i2a.973.
8. Aladejana EB. Biological properties of polyherbal formulations: a review of their antimicrobial, anti-inflammatory, antioxidant, and toxicological activities. Pharmacogn J. 2023;15(5):933-963. doi:10.5530/pj.2023.15.178.
9. Dev SK, Choudhury PK, Srivastava R, Sharma M. Antimicrobial, anti-inflammatory and wound healing activity of polyherbal formulation. Biomed Pharmacother. 2019;111:555-567. doi:10.1016/j.biopha.2018.12.075.
10. Vijaya PS, Bethur SS, Somanna P, Sampath R. Comparative evaluation of antimicrobial effect, calcium ion release, and pH change using herbal combinations of nanoparticle calcium hydroxide: an in vitro study. Int J Clin Pediatr Dent. 2025;18(9):1103-1109. doi:10.5005/jp-journals-10005-3275.
11. Razi MA, Sharma R, Koppula SK, Bhargava N, Hassan MK. Comparative evaluation of antimicrobial efficacy of aqueous and alcoholic formulations of Triphala and Curcumin mouthrinses against periodontal pathogens. J Pharm Bioallied Sci. 2025;17(Suppl 2). doi:10.4103/jpbs.jpbs_188_25.
12. Sharma R, Jadhav M, Choudhary N, Kumar A, Rauf A, Gundamaraju R, et al. Deciphering the impact and mechanism of Trikatu, a spices-based formulation on alcoholic liver disease employing network pharmacology analysis and in vivo validation. Front Nutr. 2022;9:1063118. doi:10.3389/fnut.2022.1063118.
13. Kaushik R, Jain J, Khan AD, Rai P. Trikatu – a combination of three bioavailability enhancers. Int J Green Pharm. 2018;12(3 Suppl).
14. Ranjana Urs KL, Sweta KM. Conceptual understanding of the anti-inflammatory effects of Dashamoola with relevant modern perspective: a critical study. J Ayu Int Med Sci. 2022;7(11):155-160.
15. Qi Z, Xu D, Wang Q, Liu L, Liu W, Wang J. Huang-Lian-Jie-Du decoction ameliorates sepsis through dynamic regulation of immune response and gut microbiota–metabolite axis. Microb Pathog. 2025;199:107246. doi:10.1016/j.micpath.2024.107246.
16. Ghosh B, Bose A, Parmanik A, Ch S, Paul M, Biswas S, et al. Facile fabrication of Nishamalaki churna mediated silver nanoparticles with antibacterial application. Heliyon. 2023;9(8). doi:10.1016/j.heliyon.2023.e18788.
17. Panda V, Vaswani L, S S, et al. Evaluation of the wound healing effect of Nishamalaki, an Ayurvedic formulation comprising Curcuma longa and Phyllanthus emblica in aging rats. Clin Phytosci. 2024;10:3. doi:10.1186/s40816-024-00367-w.
18. Sharma R, Martins N, Kuca K, Chaudhary A, Kabra A, Rao MM, et al. Chyawanprash: a traditional Indian bioactive health supplement. Biomolecules. 2019;9(5):161. doi:10.3390/biom9050161.
19. Balkrishna A, Tomer M, Manik M, Srivastava J, Dev R, Haldar S, et al. Chyawanprash, an ancient Indian Ayurvedic medicinal food, regulates immune response in zebrafish model of inflammation by moderating inflammatory biomarkers. Front Pharmacol. 2021;12:751576. doi:10.3389/fphar.2021.751576.
20. Nazir A, Nazir A, Zuhair V, Aman S, Sadiq SUR, Hasan AH, et al. The global challenge of antimicrobial resistance: mechanisms, case studies, and mitigation approaches. Health Sci Rep. 2025;8(7). doi:10.1002/hsr2.71077.
21. Devi NS, Mythili R, Cherian T, Dineshkumar R, Sivaraman GK, Jayakumar R, et al. Overview of antimicrobial resistance and mechanisms: The relative status of the past and current. Microbe. 2024;3:100083. doi:10.1016/j.microb.2024.100083.
22. Halawa EM, Fadel M, Al-Rabia MW, Behairy A, Nouh NA, Abdo M, et al. Antibiotic action and resistance: Updated review of mechanisms, spread, influencing factors, and alternative approaches for combating resistance. Front Pharmacol. 2024;14:1305294. doi:10.3389/fphar.2023.1305294.

23. Elshobary ME, Badawy NK, Ashraf Y, Zatioun AA, Masriya HH, Ammar MM, et al. Combating antibiotic resistance: Mechanisms, multidrug-resistant pathogens, and novel therapeutic approaches: An updated review. Pharmaceuticals (Basel). 2025;18(3):402. doi:10.3390/ph18030402.
24. Kerek Á, Román I, Szabó Á, Kovács D, Kardos G, Kovács L, et al. Antibiotic resistance genes in *Escherichia coli*: Literature review. Crit Rev Microbiol. 2025;51(1):1-35. doi:10.1080/1040841X.2025.2492156.
25. Muteeb G, Kazi RNA, Aatif M, Azhar A, El Oirdi M, Farhan M. Antimicrobial resistance: Linking molecular mechanisms to public health impact. SLAS Discov. 2025;33:100232. doi:10.1016/j.slasd.2025.100232.
26. Teng J, Imani S, Zhou A, Zhao Y, Du L, Deng S, et al. Combatting resistance: Understanding multidrug-resistant pathogens in intensive care units. Biomed Pharmacother. 2023;167:115564. doi:10.1016/j.biopha.2023.115564.
27. Noguerol Andrade JCB, Santos BS, Del Fiol FS. Impact of an antimicrobial stewardship program on antibiotic consumption, bacterial susceptibility, and costs in a high-complexity public hospital. Antibiotics (Basel). 2026;15(3):264. doi:10.3390/antibiotics15030264.
28. Marino A, Maniaci A, Lentini M, Ronsivalle S, Nunnari G, Cocuzza S, et al. The global burden of multidrug-resistant bacteria. Epidemiologia (Basel). 2025;6(2):21. doi:10.3390/epidemiologia6020021.
29. Bharadwaj A, Rastogi A, Pandey S, Gupta S, Sohal JS. Multidrug-resistant bacteria: Their mechanism of action and prophylaxis. J Immunol Res. 2022;2022:5419874. doi:10.1155/2022/5419874.
30. Mallik S, Dash S, Mishra S, Mohanty RB, Sahoo S, Patra A, et al. Threat of multidrug-resistant bacteria: The role of genomic solutions and a call to action. Gene Rep. 2025;41:102298. doi:10.1016/j.genrep.2025.102298.
31. Almutairy B. Extensively and multidrug-resistant bacterial strains: Case studies of antibiotic resistance. Front Microbiol. 2024;15:1381511. doi:10.3389/fmicb.2024.1381511.
32. World Health Organization. Antimicrobial resistance [Internet]. Geneva: World Health Organization; 2023 Nov 21 [cited 2025 Nov 7]. Available from: World Health Organization Antimicrobial Resistance Fact Sheet
33. Salam MA, Al-Amin MY, Salam MT, Pawar JS, Akhter N, Rabaan AA, et al. Antimicrobial resistance: A growing serious threat for global public health. Healthcare (Basel). 2023;11(13):1946. doi:10.3390/healthcare11131946.
34. Ahmed SK, Hussein S, Qurbani K, Ibrahim RH, Fareeq A, Mahmood KA, et al. Antimicrobial resistance: Impacts, challenges, and future prospects. J Med Surg Public Health. 2024;2:100081. doi:10.1016/j.glmedi.2024.100081.
35. Minarini LADR, Andrade LN, De Gregorio E, Grosso F, Naas T, Zarrilli R, et al. Antimicrobial resistance as a global public health problem: How can we address it? Front Public Health. 2020;8:612844. doi:10.3389/fpubh.2020.612844.
36. Deori C, Sonowal T, Das M. Antimicrobial resistance: A looming threat to public health and global well-being. Indian J Community Fam Med. 2024;10(1):18-25. doi:10.4103/ijcfm.ijcfm_1_24.
37. Alipour Noghabi S, Ghamari Kargar P, Bagherzade G, Beyzaei H. Comparative study of antioxidant and antimicrobial activity of berberine-derived Schiff bases, nitro-berberine and amino-berberine. Heliyon. 2023;9(12):e22783. doi:10.1016/j.heliyon.2023.e22783.
38. Barati M, Modarresi Chahardehi A. Alkaloids: The potential of their antimicrobial activities of medicinal plants. In: de Oliveira MS, de Aguiar Andrade EH, Kumar R, Mali SN, editors. Medicinal plants: Chemical, biochemical, and pharmacological approaches. London: IntechOpen; 2023. doi:10.5772/intechopen.112364.
39. Jan R, Khan M, Asaf S, Lubna, Asif S, Kim KM. Bioactivity and therapeutic potential of kaempferol and quercetin: New insights for plant and human health. Plants (Basel). 2022;11(19):2623. doi:10.3390/plants11192623.
40. Hasnat H, Shompa SA, Islam MM, Alam S, Richi FT, Emon NU, et al. Flavonoids: A treasure house of prospective pharmacological potentials. Heliyon. 2024;10(6):e27533. doi:10.1016/j.heliyon.2024.e27533.
41. Ozogul Y, Ucar Y, Tadesse EE, Rathod N, Kulawik P, Trif M, et al. Tannins for food preservation and human health: A review of current knowledge. Appl Food Res. 2025;5(1):100738. doi:10.1016/j.afres.2025.100738.
42. Sójka M, Hejduk A, Piekarska-Radzik L, Ścieszka S, Grzelak-Błaszczyk K, Klewicka E. Antilisterial activity of tannin-rich preparations isolated from raspberry (*Rubus idaeus* L.) and strawberry (*Fragaria* × *ananassa* Duch.) fruit. Sci Rep. 2025;15(1):10196. doi:10.1038/s41598-025-94731-6.
43. Di Matteo A, Lavorgna M, Russo C, Orlo E, Isidori M. Natural plant-derived terpenes: Antioxidant activity and antibacterial properties against foodborne pathogens, food spoilage and lactic acid bacteria. Appl Food Res. 2024;4(2):100528. doi:10.1016/j.afres.2024.100528.
44. Wiles D, Pearson JS, Beddoe T. Harnessing plant-derived terpenoids for novel approaches in combating bacterial and parasite infections in veterinary and agricultural settings. Curr Microbiol. 2025;82(4):134. doi:10.1007/s00284-025-04113-4.
45. Contero R, Cachipuendo C, Felicita O, Gordillo G. Essential oils of dill and nettle as a natural alternative to reduce pathogenic bacteria on dairy production surfaces. Microorganisms. 2026;14(2):412. doi:10.3390/microorganisms14020412.
46. Bhattacharya M, Mandal S. Antibacterial activity of caffeic acid from plant sources: A review based on in silico, in vitro and in vivo approaches. Microbe. 2025;8:100541. doi:10.1016/j.microb.2025.100541.
47. Wang X, Liu M, Yu C, Li J, Zhou X. Biofilm formation: Mechanistic insights and therapeutic targets. Mol Biomed. 2023;4(1):49. doi:10.1186/s43556-023-00164-w.
48. Rezaie P, Pourhajibagher M, Chiniforush N, Hosseini N, Bahador A. The effect of quorum-sensing and efflux pump interactions in *Pseudomonas aeruginosa* against photooxidative stress. J Lasers Med Sci. 2018;9(3):161-167. doi:10.15171/jlms.2018.30.
49. Nithyanand P, Boya BR, Lee JH, Lee J. Polymicrobial biofilms: Interkingdom interactions, resistance and therapeutic strategies. Microb Biotechnol. 2025;18(8):e70218. doi:10.1111/1751-7915.70218.
50. Dawan J, Li Y, Lu F, He X, Ahn J. Role of efflux pump-mediated antibiotic resistance in quorum sensing-regulated biofilm formation by *Salmonella Typhimurium*. Pathogens (Basel). 2022;11(2):147. doi:10.3390/pathogens11020147.
51. Zeraatpisheh A, Moradi M, Arshadi M, et al. The in vitro evaluation of synergistic effects of ciprofloxacin and berberine hydrochloride against *Pseudomonas aeruginosa*. BMC Microbiol. 2025;25:487. doi:10.1186/s12866-025-04223-w.
52. Ai Q, Wang S, Chen Z, Zheng S, Chen Z, Zhang N, et al. Synergistic antibacterial activity and prevention of drug resistance of daptomycin combined with fosfomycin against methicillin-resistant *Staphylococcus aureus*. Antimicrob

Agents Chemother. 2025;69:e01609-24. doi:10.1128/AAC.01609-24.
53. Yang J, Zhang L, He X, Gou X, Zong Z, Luo Y. In vitro and in vivo enhancement effect of glabridin on the antibacterial activity of colistin against multidrug-resistant *Escherichia coli* strains. Phytomedicine. 2024;130:155732. doi:10.1016/j.phymed.2024.155732.
54. Mitra S, Tareq AM, Das R, Emran TB, Nainu F, Chakraborty AJ, et al. Polyphenols: A first evidence in the synergism and bioactivities. Food Rev Int. 2023;39(7):4419-4441. doi:10.1080/87559129.2022.2026376.
55. Atta S, Waseem D, Fatima H, Naz I, Rasheed F, Kanwal N. Antibacterial potential and synergistic interaction between natural polyphenolic extracts and synthetic antibiotic on clinical isolates. Saudi J Biol Sci. 2023;30:103576. doi:10.1016/j.sjbs.2023.103576.
56. Vijayakumar V, Rathinam T, Rajmohan SR, Elumalai K. Formulation and evaluation of phytosomes loaded polyherbal gel for pharyngitis. J Young Pharm. 2025;17(1):176-186. doi:10.5530/jyp.20251325.
57. Sánchez-Tito M, Tay LY, Zea-Gamboa F, Cartagena-Cutipa R, Flores-Gómez A, Spigno-Paco B, et al. Development and evaluation of the antibacterial properties of an experimental herbal gel against cariogenic bacteria. Clin Exp Dent Res. 2025;11(1):e70076. doi:10.1002/cre2.70076.
58. Gaur PK, Mishra R, Kaushik R, Verma KK, Kumar N, Lata K. Polyherbal antiacne gel: In vitro antibacterial activity and efficacy evaluation against *Cutibacterium acnes*. Assay Drug Dev Technol. 2024;22(7):373-386. doi:10.1089/adt.2024.031.
59. Pandeya PR, Lamichhane R, Lamichhane G, Lee KH, Jung HJ. Toxicological evaluation of a polyherbal formulation (18KHT01) and validation of UPLC-DAD method for quality control. Biomed Res Int. 2024;2024:1767618. doi:10.1155/2024/1767618.
60. Mugale MN, Dev K, More BS, Mishra VS, Washimkar KR, Singh K, et al. A comprehensive review on preclinical safety and toxicity of medicinal plants. Clin Complement Med Pharmacol. 2024;4(1):100129. doi:10.1016/j.ccmp.2024.100129.
61. Edo GI, Obasohan P, Makia RS, et al. The use of quality control parameters in the evaluation of herbal drugs: A review. Discov Med. 2024;1:168. doi:10.1007/s44337-024-00177-6.

*****