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POLYHERBAL–ANTIBIOTIC SYNERGY: A REVIEW ON MECHANISTIC INSIGHTS INTO POLYPHENOLS, FLAVONOIDS, ALKALOIDS, AND TERPENOIDS FOR ENHANCING ANTIMICROBIAL EFFICACY

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ABSTRACT
Background: Antimicrobial resistance (AMR) is one of the most important threats to global public health, accelerating as conventional antibiotics lose efficacy. Pathogens such as Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, and Klebsiella pneumoniae use a variety of resistance mechanisms, including enzymatic drug degradation, efflux pump activation, and biofilm formation. The declining pipeline of newly approved antibiotics highlights the need for alternative and adjunctive therapeutic strategies. **Methodology:** This review critically summarizes studies that analyze polyherbal–antibiotic combinations and their synergistic antimicrobial effects. A systematic review of recent literature on the role of phytochemicals, including alkaloids, flavonoids, terpenoids, tannins, and polyphenolic compounds, in potentiating antibiotic efficacy and reducing antibiotic resistance was conducted. **Results and Discussion:** Integrative synergetic interactions were strongly evidenced between antibiotics and plant-derived phytochemicals. Epigallocatechin gallate (EGCG) synergizes with β-lactam for common resistant strains, and berberine inhibits efflux pumps to enhance antibiotic activity. A wide range of flavonoids and polyphenolic extracts have been reported to exhibit antimicrobial activity, with mechanisms involving membrane disruption, biofilm inhibition, and interference with quorum-sensing pathways, thereby promoting multifaceted action. **Conclusion:** Synergy between polyherbal treatment and antibiotics is an innovative approach to combat AMR and should be prioritized. This approach highlights various leads for future antimicrobial therapeutics by combining traditional ethnopharmacological knowledge with innovative pharmaceutical paradigms.

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INTRODUCTION

Microbial Resistance to Antibiotics

Microbial resistance to antibiotic classes has emerged as one of the fastest-growing issues worldwide. According to the WHO, AMR can be lethal and affect treatment for infections caused by bacteria, viruses, fungi, and parasites. Unethical usage of antibiotics in the health system, agriculture, and animal husbandry led to the creation of enormous selective pressure on microorganisms so that resistant strains could survive and, thus, over the years, malignant strains of pathogens such as *S. aureus, P. aeruginosa, E. coli*, and *K. pneumoniae* have evolved to become a greater threat with the passage of time and resistance to most conventional treatments. Thus, this increasing resistance translates into more cases of infection & death, followed by increased healthcare costs, erasing decades of progress in infection control [1].

While pharmaceutical development focused on antibiotic discovery has made amazing strides, the pace of antibiotic discovery has arguably fallen short of the pace of microbial resistance development. Conventional antibiotics that were once called "wonder drugs" lose their efficacy over time as bacteria evolve mechanisms to evade them, such as antibiotic degradation by enzymes, alteration of drug-target sites, activation of efflux pumps, or biofilm penetration. The trepidation about such selected defenses incites practitioners, in most cases, to prescribe higher doses, sometimes in combination with broad-spectrum antibiotic agents. Unfortunately, such clinical functioning has notable complications, making the patient susceptible to newer infections. Globally, a more investigative approach is needed to address this issue more effectively. This may result in developing a better version of existing antibiotics or simply replacing them with new treatment alternatives [2]. Ayurveda has explored the combined use of herbs for their effectiveness and synergy, made possible by the metabolic pathways of the numerous phytoconstituents present, and it also overcomes AMR due to its diversity [3].

Therefore, a herbal formulation containing an antibiotic can be a very effective way to treat AMR. Along with that, the phytochemicals present will also act synergistically with the antibiotic by targeting the bacterial membrane and the enzyme responsible for resistance. These kinds of combinations can help achieve the lowest among many substitutes; herbal products remain strong in the scientific domain due to the presence of various phytoconstituents responsible for their therapeutic activities. The medicinal system requires an antibiotic dose, reduces undesirable side effects, and delays the emergence of resistance. Furthermore, the combinations may be effective against resistant strains and other biofilm-forming pathogens that are difficult to treat with standard therapies alone [4, 5]. Thus, the integration of herbal pharmacology with modern-day antimicrobial therapy appears to be a sustainable and innovative approach to addressing the challenge of AMR. Given suitable scientific validation, standardization, and optimization of the formulation, the polyherbal-antibiotic combinations hold promise to become the next generation of antimicrobial medicines, expected to be efficacious yet environmentally friendly, thus saving our antibiotics for generations to come.

POLYHERBAL FORMULATIONS

Concept and Therapeutic Rationale

Polyherbal formulations have been a constant and important aspect of the traditional medical systems of Ayurveda, Siddha, Unani, and traditional Chinese medicine. Various medicinal plants are combined to enhance therapeutic effect; hence, polyherbal formulations represent an enhancement beyond that of a single herb. From a modern perspective, these formulations will act on different targets in the body, with complementary or even synergistic effects of their various bioactive compounds (Figure 1). Classical texts of Ayurveda suggest that such combinations could balance efficacy, on the one hand, with possible toxicity or side effects on the other. From a modern scientific perspective, polyherbal formulations are defined as therapeutic preparations with more than one plant-derived ingredient carefully blended to improve potency, bioavailability, and targeting of multiple pathways related to the disease [6,7]. Selected medicinal plants with diverse phytochemical composition and antibacterial activity according to ethnomedicinal and pharmacological literature are graphically depicted in **Figure 1.** The selected plants represent various classes of bioactive compounds, such as polyphenols, flavonoids, alkaloids, and terpenoids, that exert different mechanisms to enhance antibiotic efficacy, such as disruption of cell membrane permeability, inhibition of efflux pumps, interference with quorum sensing, and so on. The schematic depicts the reflection of plants, including *Allium sativum*, *Mentha piperita*, *Syzygium cumini*, *Coriandrum sativum*, *Rubus spp.*, *Curcuma longa*, *Piper nigrum*, *Trigonella foenum-graecum*, *Murraya koenigii*, and *Coprinopsis atramentaria*. All three species have been extensively characterized as medicinal plants rich in bioactive phytochemicals, including flavonoids,

polyphenols, alkaloids & terpenoids, that can contribute to resistance to microbes & modulate antibiotic efficacy [8, 9]. Several mechanisms in which these phytochemicals potentiate antibiotic activity have been reported from previous studies, including:

- Efflux pump inhibitors (usually related to alkaloids and phenolic compounds)
- Changes in microbial cell membranes (often referred to as essential oils and terpenoids)
- Biofilm Inhibition (Decreased microbial resistance and persistence)

Antimicrobial therapy quality, which may also induce oxidative stress, can be reduced overall through its free-radical-scavenging activity. These plants are also known for being commonly used herbs in traditional ethnomedicinal formulations, particularly in South Asia and other parts of the world that practice ethnopharmacology, and for their particularity in combining multiple herbs to achieve greater therapeutic synergy.

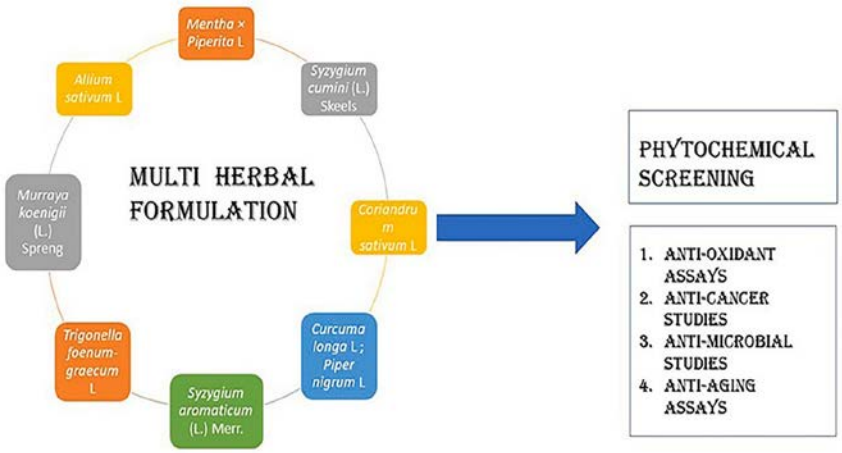

Figure 1: Schematic representation of the multi-herbal formulation comprising *Mentha piperita L., Syzygium cumini (L.) Skeels, Coriandrum sativum L., Curcuma longa L., Piper nigrum L., Syzygium aromaticum (L.) Merr., Trigonella foenum-graecum L., Murraya koenigii (L.) Spreng*, and *Allium sativum L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

With polyherbal formulations, one of the main advantages is the synergy of their phytochemicals. Different plant constituents can act on multiple biochemical pathways, providing a combined effect in biological activity far greater than any single ingredient would achieve on its own, through enhancement or broadening of the therapeutic effect. In fact, among individual plant extracts, the presence of several secondary metabolites, including alkaloids, flavonoids, terpenoids, tannins & phenolics, can be expected to contribute to different pharmacological actions. The intended pharmacological effects are therefore likely to result from synergistic or additive interactions between these agents, thereby enhancing antimicrobial, antioxidant, anti-inflammatory, or immunomodulatory activity. For instance, phenolics can rupture microbial membranes, whereas flavonoids inhibit nucleic acid synthesis, and alkaloids interfere with protein translation, all of which together would render significant antimicrobial activity. Furthermore, certain phytochemicals counteract microbial resistance mechanisms, such as efflux pumps and drug-degrading enzymes, thereby restoring pathogens' sensitivity to antibiotics [10, 11]. Polyherbal formulations are supported by strong pharmacological data demonstrating that combinations of phytochemicals possess synergistic therapeutic effects. Plant-derived bioactive compounds can simultaneously modulate microbial membranes, enzymes, metabolic pathways, and genetic regulatory systems, thereby synergistically potentiating their antimicrobial activity. Apart from the pharmacodynamic interactions mentioned, a few phytochemicals can also increase the bioavailability of other bioactive compounds by enhancing their solubility, stability, or intestinal absorption. Piperine from *Piper nigrum*, for example, is one of the most studied and recognized inhibitors that enhance the bioavailability of various drugs and phytochemicals by inhibiting metabolic enzymes in the liver and gut [12].

Some of the multiple such mechanisms at play are complementary and synergistic, and together they lead to a holistic and balanced therapeutic effect, compared to a single plant-derived extract or synthetic drug. However, the number of phytochemicals that have been successfully translated into clinical practice and/or approved by regulatory agencies is often limited by inherently unfavorable pharmacokinetic

characteristics, resulting in insufficient oral bioavailability. Many classes of phytoconstituents (e.g., polyphenols, flavonoids, alkaloids, and terpenoids) demonstrate poor aqueous solubility, rapid metabolic degradation, inadequate membrane permeability, and low systemic stability. These constraints lower the concentration of active compounds at the desired tissues and thus their pharmacological efficacy [13]. Solubility in water is an important challenge for many phytochemicals. Bioactive polyphenols such as curcumin, quercetin, and resveratrol have long hydrophobic structures that do not diffuse well in physiological fluids and, as a result, exhibit poor gastrointestinal absorption and low oral bioavailability. In addition to the above, polyphenols are characterized by multiple hydroxyl groups, making them prone to oxidation and chemical degradation, which adversely affects their stability during storage and in biological systems.

A further major drawback is rapid bio-transformation and elimination. After absorption, most phytochemicals undergo extensive phase I and phase II metabolism in the human liver and intestinal epithelium, including glucuronidation, sulfation, and methylation. They are transformed into water-soluble metabolites through these processes, are quickly excreted, and thus have short plasma half-lives along with limited therapeutic exposure [14]. Nanotechnology-based drug delivery systems offer one solution to overcome these challenges, with great potential to improve the bioavailability and therapeutic efficacy of phytochemicals. Polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanoemulsions, phytosomes, and nanoniosomes are examples of nanocarriers that can create protective microenvironments that enhance solubility and stability and provide controlled drug release [15]. Nanoscale size means greater surface area, allowing better dissolution and cellular impact. In addition, nanocarriers shield phytochemicals from various metabolic degradations and serve as ideal media for cellular uptake and targeted delivery. Coating nanoparticles with polyethylene glycol (PEG) or attaching a ligand to their surface enables localization at sites of infection or inflammation, further increasing therapeutic efficacy without systemic toxicity. In the context of polyherbal–antibiotic therapies, nano-carriers also assist in the co-delivery of phytochemicals and antibiotics, improving penetration into microbial biofilms and increasing intracellular drug concentrations within resistant pathogens. Therefore, novel nanotechnology-mediated delivery systems can overcome pharmacokinetic hurdles and enhance the therapeutic efficacy of polyherbal formulations for the treatment of multidrug-resistant infections [16]. There are many instances of polyherbal formulations of tested antimicrobial efficacy. Ayurveda medications like Triphala (a combination of three fruits – *T. chebula*, *T. bellirica*, and *E. officinalis*) and trikatu (*P. nigrum* (black pepper), *P. longum, Z. officinale*) have been used to cure infections and gastrointestinal diseases for several centuries. Another popular prescription in classic Ayurveda systems-"Dasamoola" comprising ten medicinal roots, is renowned for its overall anti-inflammatory and immunomodulatory potential that supports the moderation of the body's immune response. Formulations of traditional Chinese medicine, such as Huang Lian Jie Du Tang, which includes *Coptis chinensis, Scutellaria baicalensis*, *Phellodendron amurense,* and *Gardenia jasminoides*, exhibit strong antibacterial and anti-inflammatory activity and have also been investigated for their effects against resistant bacterial strains. The realm of contemporary pharmacological studies is in the process of validating such concepts of traditional combinations in present-day antimicrobial therapy [17].

Table 1: Polyherbal formulation along with reported antimicrobial activities

Polyherbal Formulation	Plant Composition	Reported Antimicrobial Activity
Triphala	*Terminalia chebula*, *Terminalia bellirica*, *Emblica officinalis*	Broad-spectrum antibacterial and antifungal activity; effective against *E. coli, S. aureus, C. albicans* [17,18].
Trikatu	*Piper nigrum*, *Piper longum*, *Zingiber officinale*	Antibacterial, antifungal, and antiviral activity; enhances bioavailability of co-administered drugs [19, 20].
Dasamoola	10 roots, including *Bilva*, *Agnimantha*, *Shyonaka*, *Gokshura*	Anti-inflammatory, immunomodulatory, and antibacterial activity; supports host defense [21, 22].
Huang Lian Jie Du Tang	*Coptis chinensis*, *S. baicalensis*, *P. amurense*, *G. jasminoides*	Strong antibacterial and anti-inflammatory activity; effective against resistant bacterial strains [23, 24, 25]
Nishamalaki	*Emblica officinalis*, *Curcuma longa*	Antibacterial and antioxidant activity; effective against Gram-positive and Gram-negative bacteria [26, 27].
Chyawanprash (Ayurvedic)	40+ herbs including *E. officinalis*, *P. longum*, *A. racemosus*	Immunomodulatory; antibacterial, antiviral, and antifungal effects; enhances host immunity [28, 29, 30]

Polyherbal formulations embody the concept of synergy in therapy, wherein multiple phytochemicals act together to enhance efficacy, be far safer, and avoid the risk of resistance. Antimicrobial resistance remains a serious challenge; scientifically validated polyherbal combinations should be considered as a pathway to future therapeutics that integrate both traditional medicine and modern concepts.

MECHANISMS OF ANTIBIOTIC RESISTANCE

Genetic & Biochemical Mechanisms of Antibiotic Resistance

Antibiotic resistance is a complex biological phenomenon in which microorganisms have evolved mechanisms to resist the inhibitory action of antimicrobial agents that would normally prevent growth and kill cells. This adaptability has also compromised all previously effective antibiotics and increased the severity of the worldwide healthcare crisis, as infectious diseases can now be treated with an ever-decreasing efficacy rate. Hence, the genetic and biochemical mechanisms of resistance must be understood to develop novel therapeutic strategies, including the combinatorial use of conventional antibiotics with polyherbal formulations to restore antimicrobial potency [30, 31].

Resistance can be hereditary, resulting from spontaneous mutations in chromosomal genes, or acquired, for example, through horizontal transfer of mobile genetic elements, such as plasmids, transposons, and integrons that harbor antibiotic resistance determinants. Genetic mutations may occur, for instance, in the gyrA and parC genes coding for DNA gyrase and topoisomerase IV, resulting in fluoroquinolone resistance. Mutations in these genes reduce the binding affinity between the antibiotic and its target. Horizontal gene transfer mechanisms such as conjugation, transformation, and transduction are known to facilitate the uptake and dissemination of resistance genes among bacteria. These mechanisms allow for rapid exchange of resistance characteristics within and between microbial communities, especially in clinical and hospital settings with high levels of selection [32]. Bacteria employ various biochemical and cellular strategies to evade the effects of antibiotics. One of their main strategies is to induce efflux pumps, membrane transport proteins that actively extrude antibiotics from the bacterial cytoplasm, thereby decreasing intracellular drug concentrations. On the other hand, enzymatic hydrolysis by β-lactamases inactivates penicillins and cephalosporins. At the same time, aminoglycoside-modifying enzymes can then prevent their binding to ribosomes, thereby inhibiting protein synthesis via acetylation, adenylation, or phosphorylation of the antibiotic [33]. The architecture of biofilms enhances bacterial resilience. Biofilms are structured microbial consortia embedded within a self-produced extracellular polymeric matrix that attach to biotic and abiotic surfaces, such as tissues, catheters, and implants. Cells within biofilms exhibit reduced metabolic activity and restricted antibiotic penetration, rendering them up to a thousand times more resistant than planktonic cells [34]. In addition, methylation of ribosomal RNA, alteration of penicillin-binding proteins, target-site modification, and bypassing metabolic pathways by producing alternative enzymes to avoid inhibited pathways [35]. Antibiotic resistance results from a close interplay between genetic evolution and biochemical adaptation. The combined effects of ceaseless efflux-mediated expulsion, enzyme-mediated inactivation, biofilm-mediated protection, and genetic exchange lead to bacterial survival under antimicrobial pressure. Understanding all those processes will serve as a basis for innovative therapeutic interventions, particularly when synthetic antibiotics are combined with polyherbal formulations to counteract multidrug resistance.

Role of multidrug-resistant (MDR) pathogens in therapeutic failure

The emergence of MDR pathogens has become a serious impediment to modern medicine and is, therefore, often associated with therapeutic failure during the management of infections. An MDR pathogen is any bacterium that is resistant to at least 1 drug in 3 or more antibiotic classes. The spread of multidrug-resistant (MDR) pathogens in clinical settings limits therapeutic strategies. It is almost always responsible for prolonged illness, higher rates of complications, greater mortality, and high costs for treatment [36]. Treatment failure occurs when standard antibiotics become ineffective against resistant bacteria. Diseases like UTIs, pneumonia, and postoperative wound infections now demand prolonged and high-dose treatments owing to the MDR. As a result, clinicians are left with only the option of last-resort antibiotics that can be more toxic and expensive. In addition, longer courses of therapy may worsen the patient's clinical status [37]. Pathogens that cause these MDR infections use numerous survival strategies to escape the action of antimicrobials, such as genetic resistance mechanisms, biofilm formation, and actively pumping drugs out through efflux pumps. This process is considered one of the most serious forms of resistance. These adaptations also confer cross-

resistance to a wide range of antibiotics and enable bacteria to survive adverse conditions, such as low oxygen levels and nutrient scarcity [38, 39].

Multidrug resistance is a major health concern and most commonly results in secondary infections, which can be lethal, especially in immunocompromised patients such as newborns or older adults, compromising the overall healthcare scenario. From a more general perspective, the emergence of MDR organisms is costly to the health care system, as they exploit resources, increase treatment costs, and weaken implemented infection prevention and control programs [40, 41]. Novel approaches to deal with failed treatments are also not confined to antibiotic therapy alone. One such approach that holds great promise is a combination of traditional antibiotics with polyherbal formulations, which has demonstrated amelioration of antimicrobial activity, reversibility of antibiotic sensitivity, and reduced resistance evolution. Coupled with strong antibiotic stewardship programs, rapid diagnostics, and ongoing resistance surveillance, these strategies will be important in the fight against MDR pathogens [42].

Global impact of antimicrobial resistance on public health

AMR is threatening public health, drugs, and the hard-won control of infectious diseases. According to the WHO, AMR provides a very real possibility for large human populations to sustain ill-health through death by infection or to cause an economic burden. Resistant infections yearly account for about 1.27 million deaths, and perhaps even more, leading to chronic illness or complications due to ineffective treatment. This problem is magnified in low- and middle-income countries, where access to effective antibiotics is limited, healthcare infrastructure is weak, and resistance is inadequately monitored [43, 44]. AMR makes treatment of several common infections, i.e., respiratory infections, urinary tract infections, and bloodstream infections, more complicated; it increases the duration of hospitalization and intensity of care. MDR bacteria, such as Escherichia coli, Klebsiella pneumoniae, and Staphylococcus aureus, can cause severe outcomes, including septicemia and organ failure [45, 46]. Apart from these infections, resistant strains also negatively affect other interventions, such as surgeries, chemotherapies, and organ transplantation, where antibiotics form the backbone of infection prevention. The challenge posed by AMR can further be viewed from the economic perspective. Patients sometimes must be treated with more expensive or more toxic alternatives, or with prolonged hospitalization, or with more sophisticated medical interventions, all of which put more burdens on the healthcare system. Globally, the burden of AMR may rise substantially by 2050, significantly affecting the health system. AMR frightens the medical system globally as resistant microorganisms spread uncontrolled across borders through travel, trade, and environmental pollution. Overcoming this challenge requires joint efforts from experts across multiple fields, with sustained monitoring and careful planning focused on antimicrobial resistance [47, 48].

PHYTOCHEMICALS WITH ANTIMICROBIAL POTENTIAL

Phytochemicals from medicinal plants have proven to be a valuable resource in natural products, owing to their potential therapeutic effects against microbial diseases, leading to increasing interest in them. Alkaloids, flavonoids, tannins, terpenoids, and phenolic compounds are among the diverse classes of phytochemicals that have attracted attention for their significant antimicrobial activities (Table 2). Alkaloids with nitrogen atoms in their molecular structure have anti-microbial properties that interfere with cellular mechanisms, including inhibition of DNA and RNA synthesis, blocking protein synthesis, and affecting the integrity of microbial cell membranes. Some widely used alkaloids (e.g., berberine, sanguinarine) are broad-spectrum antibacterial agents. Flavonoids and glycosides are also found in fruits, vegetables, and medicinal plants; they inhibit the growth of micro-organisms by suppressing nucleic acid synthesis, affecting cell membrane stability, and disrupting cellular energy metabolism [49, 50]. Tannins are high-molecular-weight polyphenolic compounds that can suppress the growth of micro-organisms by protein precipitation, enzyme inactivation, and chelation of metal ions essential for their metabolism. Among these secondary metabolites, Terpenoids (mono- and diterpenes) primarily act by disrupting bacterial membrane structure, altering cytoplasmic membrane permeability, and eventually causing cell lysis and death. Phenolics generate oxidative stress in microbial cells and also inhibit the enzymes required for microbial growth and replication [51, 52]. One of the greatest benefits of phytochemicals is their potential to target multiple microbial endpoints concurrently, greatly reducing the likelihood of resistance. The multiple ways in which phytochemicals can damage cell membranes, inhibit enzymatic pathways, and disrupt nucleic acid synthesis, including quorum sensing and biofilm formation, constitute a multidirectional attack that is

most effective in persistent infections among resistant isolates. Phytochemicals can be synergistic in their activity. This may be illustrated by the actions of flavonoids and alkaloids in jointly blocking nucleic acid synthesis and compromising cell membranes, as tannins increase the permeability of the cell wall, allowing other compounds to more easily penetrate the cell. These combinations increase antimicrobial activity while decreasing the risk of resistance. Overall, phytochemicals represent an extremely diverse and powerful weaponry against microbial infections. Its multi-target activity and ability to work synergistically have made it a promising alternative or complement to the current antibiotics, especially in the ongoing battle against multidrug-resistant pathogens [53, 54].

Table 2: Phytochemicals with Antimicrobial Potential

Phyto-chemical Class	Representative Compounds	Antimicrobial Mechanism with molecular target	Reported Synergistic Effects
Alkaloids	Berberine, Piperine, Quinine	DNA Intercalation–mediated inhibition of DNA gyrase and topoisomerase IV, enzyme inhibition such as β-lactamase inhibition, dihydrofolate reductase inhibition, and peptidoglycan synthesis-related enzymes, disruption of cell wall and membrane	Enhanced antibacterial activity when combined with flavonoids or terpenoids [55, 56].
Flavonoids	Quercetin, Catechin, Kaempferol	Inhibit nucleic acid synthesis (Dihydrofolate reductase, DNA gyrase), alter membrane permeability, and inhibit energy metabolism.	Synergistic effects with alkaloids and phenolics against MDR bacteria [57, 58].
Tannins	Gallotannins, Ellagitannins, Catechins	Protein precipitation, enzyme inhibition, metal ion chelation	Increased antifungal and antibacterial potency in combination with flavonoids [59, 60].
Terpenoids	Limonene, Carvacrol, Thymol	Disruption of microbial membranes, leakage of cell contents, and interference with quorum sensing	Synergy with flavonoids and alkaloids enhances bactericidal effect [61, 62].
Phenolics	Gallic acid, Caffeic acid, Resveratrol	Oxidative stress induction, membrane disruption, enzyme inhibition	Improved activity with tannins or terpenoids against resistant strains [63, 64].

POLYHERBAL–ANTIBIOTIC SYNERGY: MECHANISTIC INSIGHTS

Many studies have been conducted to combat the deadly AMR, leveraging the synergistic effects of phytochemicals present in medicinal plants to escalate actions through various parallel mechanisms. This interlinkage can occur pharmacodynamically by enhancing antibacterial action across multiple cellular targets, or at the pharmacokinetic level through improved drug absorption, distribution, metabolism, and elimination. Together, these techniques increase the overall bioavailability and effectiveness of antibiotics [65, 66]. The main technique for such synergy involves disrupting bacterial cell walls and membranes. Some alkaloids, terpenoids, and phenols among phytochemicals weaken bacterial membranes, making them more permeable to antibiotics. The application of other plant compounds acts as an efflux pump inhibitor, inhibiting bacterial mechanisms that expel antibiotics, thereby restoring potency. Further, it disrupts protective biofilms that normally form a barrier around bacteria, rendering them immune to drugs, by interfering with growth and adhesion processes [67]. Regulation of quorum sensing is another very important mechanism. Quorum sensing is generally known as the communication system of bacteria, or as a plethora of events that lead to virulence and resistance. Some plant-derived bioactive compounds can disrupt signaling pathways, thereby reducing pathogenicity and increasing the effectiveness of antibiotics. Thus, these combined effects enhance antibiotic activity and would likely lead to lower doses with fewer side effects [68]. Understanding how combinations of polyherbal and antibiotic therapies actually work together can contribute to developing safer and more effective treatment alternatives for multidrug-resistant infections.

EXPERIMENTAL EVIDENCE OF SYNERGISTIC ANTIMICROBIAL ACTIVITY: INSIGHTS FROM IN VITRO AND IN VIVO STUDIES

The synergistic antimicrobial activity of natural products, especially plant-derived bioactive compounds and polyherbal extracts, with traditional antibiotics has been supported by experimental studies (in vitro and in vivo); however, rigorous

scientific data are limited. Such synergistic combinations are said to improve antimicrobial effectiveness, decrease the effective antibiotic dose, and postpone the emergence of resistance. Characterization of drug interactions is done through in vitro methods such as checkerboard assays, time-kill kinetic studies, and biofilm inhibition assays. Results from these investigations often show increased bactericidal and antimicrobial activity when phytochemicals are combined with antibiotics. Similar observations are supported in vivo by animal models, with complementary data showing reduced bacterial burden, diminished tissue damage, and improved therapeutic impact. Together, these studies imply that a combination of natural bioactive compounds and antibiotics could be a promising strategy to amplify the efficacy of antimicrobial agents and prolong the clinical longevity of currently available antibiotics against multidrug-resistant pathogens [69, 70]. *Pseudomonas aeruginosa* has been used as a model organism in numerous experimental studies due to its intrinsic resistance mechanisms and its robust ability to form biofilms. One such study explored the synergistic anti-Pseudomonas effect of ciprofloxacin and berberine against clinical and reference strains of P. aeruginosa, thereby diminishing their virulence by inhibiting biofilm formation.

The combination showed a strong synergistic effect, significantly increasing bacterial killing and inhibiting biofilm formation at concentrations below the sub-MIC of each agent alone. The synergism between ciprofloxacin and berberine also indicates that, as a combination therapy, they may represent an adjunctive treatment option for the management of resistant *P. aeruginosa* infections [71]. In addition, a potent synergistic effect has been reported between daptomycin and fosfomycin against methicillin-resistant *Staphylococcus aureus* (MRSA). This combination treatment markedly improved inhibition of microbial ergosterol synthesis and decreased the mutation-prevention concentration (MPC), thereby narrowing the resistance-selection window. Genomic analyses showed that bacterial strains exposed to the combination therapy lacked resistance-associated mutations. Moreover, the combination exhibited significantly greater biofilm inhibition and eradication than monotherapy, providing a rationale for its potential role in preventing resistance development and improving therapeutic efficacy against MRSA infections [72]. One well-known example is the synergistic effect of glabridin and colistin against both sensitive and resistant strains of *Escherichia coli*. Mechanistic studies showed that glabridin inhibits the FabI enzyme responsible for fatty acid biosynthesis, which augments colistin's antibacterial activity. This combination also reduced biofilm formation and prevented the emergence of resistance. Significantly, glabridin exhibited bactericidal activity and considerable protective effects in in vitro studies and in experimental models of urinary tract infections in mice, making it a potential antibiotic adjuvant against Gram-negative pathogens [72]. Numerous studies have shown that polyphenolic compounds, abundant in many medicinal plants, exhibit a wide range of pharmacological activity, including antioxidant, anti-inflammatory, anticancer, antimicrobial, and cardioprotective effects. Recent studies have investigated their potential to synergize with standard antibiotics to enhance drug bioavailability and therapeutic efficacy, while exhibiting a good safety profile. This expanding research area highlights the potential of employing polyphenol-based cocktails as a multicomponent approach to control several infectious diseases and address the worldwide issue of antimicrobial resistance [73].

The antibacterial activity of plant extracts in combination with cefixime against resistant clinical bacterial isolates was analyzed in another study. RP-HPLC profiling indicated that gallic acid, quercetin, and cinnamic acid were the main bioactive components in the extract. Synergistic antibacterial activity was observed in the combined treatments, leading to pronounced time- and dose-dependent reductions in both bacterial growth and cellular protein levels. Such findings set the stage for using plant-derived bioactive compounds as natural antibiotic adjuvants to enhance therapeutic efficacy and to help overcome antimicrobial resistance [74]. There is increasing evidence from both in vitro and in vivo studies that the concurrent application of antibiotics with phytochemicals such as berberine, glabridin, and polyphenolic compounds can significantly enhance antimicrobial activity, delay the development of resistance, and improve therapeutic efficacy. Thus, there is increasing interest in the development of polyherbal–antibiotic synergistic formulations as novel antimicrobial approaches [75].

Recent literature shows that plant-derived phytochemicals can synergistically enhance the bioactivity of antibiotics and lower the minimum inhibitory concentration (MIC) by as much as several-fold. The degree of MIC reduction depends on the phytochemical class, bacterial species, and mechanism of synergy. One of the most extensively studied combinations to

date, the berberine–ciprofloxacin combination, showed high potentiation against multidrug-resistant Gram-negative pathogens. In mechanistic studies, it was evident that berberine could potentiate antibiotic activity by inhibiting multidrug efflux pumps, such as MexAB-OprM, thereby increasing intracellular ciprofloxacin levels and restoring bacterial susceptibility to fluoroquinolone antibiotics [76]. Interstudy comparative analyses show variable but notable reductions in MIC values. In one study with multidrug-resistant *Escherichia coli* and *Klebsiella pneumoniae*, the MIC of ciprofloxacin decreases by almost 50% when combined with berberine [77].

In *E. coli*, efflux pump inhibition was reported to dramatically increase the intracellular concentration of antibiotics and improve antibacterial activity. Of note, flavonoids and phenolic compounds similarly exhibit dramatic reductions in MIC when administered in conjunction with antibiotics. Various phenolic derivatives have been shown to inhibit MRSA efflux transporters, resulting in reductions in ciprofloxacin MICs of up to 4-fold. It is widely known in the scientific community that these phenomena are caused by membrane permeabilization, disruption of the biofilm matrix, and inhibition of resistance-related enzymes, thereby promoting more effective antibiotic penetration into bacterial cells [78].

On the contrary, many studies have shown a moderate-to-strong reduction in the minimum inhibitory concentration (MIC) of flavonoid-rich plant extracts when combined with β-lactam or fluoroquinolone antibiotics, depending on the extract's complexity and specific bacterial resistance mechanisms. Although isolated compounds like berberine are predominantly associated with efflux pump inhibition, their therapeutic effects can be multifactorial (e.g., polyphenol-rich extracts can include membrane destabilization [79], quorum-sensing disruption, inhibition of cell wall synthesis-related enzymes, and many other mechanisms).

In general, a critical analysis of available experimental evidence suggests that combinations focused on efflux pump inhibition tend to produce the most consistent MIC reductions, ranging from two-fold to several-fold. Conversely, approaches that primarily target membrane disruption or biofilm inhibition may yield a more variable synergistic response. This underscores the need for mechanism-based selection of phytochemical adjuvants to develop antibiotic-potentiating strategies against multidrug-resistant pathogens rationally.

HERBAL FORMULATION DEVELOPMENT AND ITS EVALUATION

Herbal formulation development is multidisciplinary, integrating ethnopharmacology, pharmaceutical formulation science, phytochemistry, and modern analytical evaluation methodologies. Medicinal plants are initially selected based on established therapeutic knowledge and scientific evidence of their pharmacological potential in humans. Ethnomedicinal data are often the first step toward identifying botanicals with high therapeutic relevance [80]. Once the plants are selected, extraction techniques are used to isolate the therapeutic activity of the bioactive phytoconstituents. Commonly used extraction techniques include maceration, Soxhlet extraction, ultrasonic-assisted extraction, and supercritical fluid extraction. It enables the recovery of a variety of phytochemicals, including polyphenols, flavonoids, alkaloids, and terpenoids, thereby enhancing the therapeutic potential of herbal medicines [81]. This makes standardization an important step in the development of herbal formulations, as it promotes consistency and reproducibility between production batches. While synthetic drugs usually feature a single active pharmaceutical ingredient, herbal formulations can be heterogeneous mixtures comprising numerous bioactive ingredients. Hence, the key phytochemical markers should remain constant to ensure therapeutic outcomes. Next, both preformulation and compatibility studies are conducted to assess potential interactions between herbal extracts and formulation excipients. These studies help ensure formulation stability, safety, and optimal therapeutic activity. Herbal extracts can be included in a multitude of dosage forms depending on the first indicated target and route of administration. Traditional dosage forms: Gels, ointments, suspensions, capsules, and emulsions; Novel drug delivery systems: Nanoparticles, liposomes, and phytosomes are also being investigated [82].

All herbal formulations have undergone extensive physicochemical and microbiological studies. Physicochemical characterization is performed with respect to pH, viscosity, particle size, and homogeneity and spreadability to assess safety and effectiveness, and microbiological testing, including sterility assessment and antimicrobial activity studies, is performed to support these assessments. Stability studies performed under controlled environmental conditions also provide information on the shelf life and long-term performance of the formulations. These standardized herbal therapeutic products, with proven safety and efficacy, are the result of

systematic procedures described above. Phytochemical composition is naturally variable and is one of the biggest challenges in herbal medicine. The chemical composition of therapeutic plants can vary depending on factors such as geographical origin, climatic conditions, harvest season, cultivation practices, and extraction procedures. Such changes can have profound effects on the pharmacological activity and therapeutic reliability of herbal formulations. Thus, stringent analytical techniques are needed to guarantee both batch-to-batch consistency & quality control. Chromatographic fingerprinting is one of the most promising methods for standardization and quality control of herbal medicines. It creates a specific chemical chromatogram of plant extracts, enabling the identification of phytochemical markers and the comparison of chemical composition across batches. The chromatographic fingerprinting, which provides comprehensive information on the chemical constituents of a formulation, is essential for ensuring authenticity, consistency, and reproducibility [83]. Among various chromatographic techniques, High-Performance Thin Layer Chromatography (HPTLC) is one of the most commonly used methods for qualitative and semi-qualitative analysis of phytochemicals. HPTLC fingerprinting generates a unique chromatographic stripe that reflects the global phytochemical profile of any plant-derived extract. This technique allows simultaneous detection of various classes of phytoconstituents such as flavonoids, phenolic acids, alkaloids, and terpenoids. The occurrence and relative abundance of these compounds can be used as indicators of the quality and uniformity of herbal preparations. Among various techniques, HPTLC offers the advantages of simplicity and low cost, speed, and the ability to analyze several samples simultaneously; thus, it is widely used in routine quality control in both herbal pharmaceutical research and industry [84]. Neutral HPTLC provides only a complete chemical profile, whereas LC–MS offers significantly improved sensitivity, selectivity, and molecular specificity. LC–MS enables precise identification and quantification of individual phytochemicals, even at very low concentrations. The method relies on mass spectral data and fragmentation to elucidate the molecular structure of bioactive compounds responsible for pharmacological activity. In particular, LC–MS is invaluable for detecting low-abundance constituents that may contribute to therapeutic effects, including compounds involved in mechanisms such as antimicrobial potentiation, efflux pump inhibition, and membrane disruption [85].

The integrated utilization of HPTLC and LC–MS offers a multidimensional analytical approach for the standardization of herbal formulations. HPTLC generates a global phytochemical fingerprint for batch comparison, and LC–MS yields specific molecular characterization & precise quantification of bioactive components. Collectively, these complementary approaches help preserve the chemical purity of polyherbal formulations and aid in the characterization of therapeutically relevant marker compounds [86]. Consistency from batch to batch is a prime requirement for preparations, especially for polyherbal formulations that serve synergistic therapeutic purposes. Changes in phytochemical composition may affect biological activity, especially for preparations used to boost antibiotic potency or counter antimicrobial resistance. Chromatographic fingerprinting thus becomes an indispensable quality control method to assure the chemical homogeneity of each batch and reproduce biological activity. Numerous studies indicated the development of standardized polyherbal formulations utilizing modern pharmaceutical technologies. Examples of such preparations include phytosomal gelatin containing *A. indica, P. daemia* & *C. amboinicus* for the treatment of pharyngitis [87]. The optimized formulation exhibited beneficial physicochemical properties and antibacterial and anti-inflammatory effects. Likewise, the physicochemical properties of gels obtained from the essential oil of *G. tarapacana* were not altered compared to those without antibacterial action against oral pathogens such as *S. mutans* [88]. In another investigation, an anti-acne gel formulated with *Rubia cordifolia*, *Aloe barbadensis*, and *Allium cepa* extracts exhibited promising topical antimicrobial activity against Cutibacterium acnes and favorable formulation characteristics [89]. So, the use of chromatographic fingerprinting techniques such as HPTLC and LC–MS provides an important tool for assessing the chemical profile of herbal formulations, aiding in their quality control and standardization. Such analytical approaches support the scientific corroboration of herbal medicines and their advancement toward a consistent, clinically useful therapeutic product by offering direct phytochemical discrimination, thereby allowing identification of bioactive constituents.

SAFETY, TOXICITY, AND PHARMACOLOGICAL CONSIDERATIONS

While a growing body of in vitro and animal studies has shown major synergistic effects between phytochemicals and antibiotics, available clinical evidence on such combinations remains scarce. Several phytochemicals, such as berberine,

Curcumin, and *Epigallocatechin gallate*, have demonstrated antibiotic-potentiating activity in experimental models. These compounds increase antimicrobial activity by inhibiting efflux pumps, disrupting bacterial membranes, and suppressing microbial biofilms, demonstrating their considerable potential as antibiotic adjuvants against multidrug-resistant (MDR) pathogens. The escalating global burden of infections caused by MDR bacteria has led to an urgent need for novel treatment approaches that can synergistically enhance the efficacy of readily available antibiotics while mitigating the risk associated with high-dose antibiotic regimens. Phytochemicals, in combination with antibiotics, have shown remarkably enhanced antimicrobial potency and the potential to reduce the dose of antibiotics used, according to preclinical and early translational studies. Although these findings are promising, their translation into human clinical practice remains limited, underscoring the need for well-designed randomized clinical trials (RCTs) to validate the combination strategies in terms of safety and therapeutic value [62, 90].

Systematic evaluation of safety, pharmacokinetics, and therapeutic efficacy is necessary in future clinical trials to compare standard antibiotic therapy with phytochemical–antibiotic combinations. Microbiological clearance reductions of bacterial load will be the key outcome measures, in addition to clinical recovery, modulation of inflammatory biomarkers, and assessment for herb–drug interactions. These studies are necessary to confirm the clinical significance of phytochemical–antibiotic synergism in the treatment of MDR infections. So, while developing polyherbal formulations intended for use as antibiotic adjuvants, it is paramount to balance antimicrobial synergistic effects with toxicological safety. They should undergo thorough toxicological assessments of acute, sub-chronic, and chronic toxicity with appropriate experimental models. This assessment is useful for establishing dose–response relationships, assessing organ-specific toxicity, or identifying potential biochemical or hematological changes following prolonged exposure. Notably, multiple-table phytochemicals, vigilantly marked by synergistic interactions, may increase therapeutic activity without additive or cumulative toxic effects, thereby retaining pharmacological safety. Another major issue in the treatment of infections with polyherbal–antibiotic therapy is the potential herb–drug interactions, which may significantly affect the pharmacokinetics and pharmacodynamics of antibiotics. Phytochemicals may also interact with drug-metabolizing enzymes, efflux transporters, and plasma protein binding sites, leading to changes in the absorption, metabolism, distribution, or elimination of antibiotics. Some interactions can enhance the bioavailability and clinical effectiveness of antibiotics, while others can diminish their activity or cause toxic effects. Rational formulation design thus requires careful selection of plants to include, optimized dosing strategies, and bioassay-guided phytochemical standardization. Analytical approaches, including chromatographic fingerprinting, are crucial for achieving batch-to-batch consistency and reducing unwanted interactions [91]. Beyond the pharmacological aspect, polyherbal–antibiotic formulations must be accompanied by robust regulatory and quality-control frameworks to ensure clinical translation and commercial availability. A few significant issues are variability in phytochemical composition, lack of standardized manufacturing processes, and limited toxicological data. Standardized safety assessment tests, Good Manufacturing Practice (GMP), and robust regulatory validation can markedly improve product reproducibility, quality, and patient safety. A structured framework for the safety evaluation of polyherbal–antibiotic combinations is essential to achieve translational reliability. Phytochemical characterization and standardization of herbal extracts are then followed by in vitro cytotoxicity studies and herb–drug interaction.

A conglomeration of these pathway processes leads to the translational integration. Toxicological evaluations in vivo, such as acute and sub-chronic toxicity studies, provide information on key safety parameters, including the No Observed Adverse Effect Level (NOAE) and therapeutic index. Subsequent pharmacokinetic interaction studies, followed by controlled clinical trials, are conducted in humans before the therapeutic potential can be confirmed. Phytochemical standardization via UPLC-DAD was reliable for the polyherbal preparation 18KHT01, which yielded an NOAEL of 2 g/kg in ICR mice, with safety below 500 mg/kg/day [92]. So, an effective approach to combining polyherbal formulations and conventional antibiotics must take a multidisciplinary perspective, encompassing pharmacological validation, toxicological evaluation, phytochemical standardization, and a stringent regulatory framework. Coordinated approaches of this kind are critical to bridging the gap between promising experimental data and clinically safe, adequate, and reproducible therapeutic strategies against multidrug-resistant infections.

CHALLENGES AND FUTURE PERSPECTIVES

Although offering an interesting therapeutic application, polyherbal formulations, when used in combination with conventional antibiotics, encounter several hurdles on the scientific, technological, and translational fronts. Scientific and technological limitations in the complex phytochemical composition of herbal extracts pose another major challenge to the isolation of active ingredients, elucidating their mechanisms of action, and understanding their interactions with traditional antibiotics. Moreover, given the lack of advanced analytical platforms and standardized protocols for describing experimental procedures, inconsistent and non-reproducible results are often observed across studies. Progress in this area is invariably hampered by the associated problems of variation in the plant species used, their geographical sources, extraction methods, and formulation processes, all of which directly affect the quality and bioactivity of herbal constituents. Therefore, establishing robust quality control measures and validated analytical protocols is indispensable for ensuring the consistency and reproducibility of polyherbal-antibiotic formulations.

On another note, challenges also arise in clinical translation and regulatory approval for this type of synergistic formulation. Restricted clinical data, incomplete toxicological profiling, and the absence of uniform guidelines for the global evaluation of herbal-synthetic combinations are factors delaying their acceptance in antimicrobial therapy. Rigorous pharmacokinetics and pharmacodynamics, as well as safety evaluations outlined for traditional pharmaceuticals, would thus be excruciatingly demanding in terms of resources, time, and scientific validation. However, looking ahead, emerging technologies will help overcome such hurdles. Nanocarriers such as liposomes, niosomes, and polymeric nanoparticles could improve the solubility, stability, and targeted delivery of both phytoconstituents and antibiotics, thereby maximizing synergistic efficacy [93].

Recent progress in green nanotechnology opens new avenues for augmenting phytochemical–antibiotic interactions. However, phytochemicals of plant origin (e.g., polyphenols, flavonoids, terpenoids), which are used as natural reducing and stabilizing agents in green synthesis of metallic nanoparticles, can also augment their antimicrobial activity by promoting drug delivery, increasing microbial membrane interactions, and enhancing intracellular antibiotic accumulation [94].

CONCLUSION

Antimicrobial resistance (AMR) has become one of the most urgent global public health threats in the twenty-first century, with wide-ranging clinical and economic impacts. Recent global estimates found that over 1.27 million deaths each year are directly caused by bacterial AMR, and drug-resistant infections are associated with around 4·7–5 million deaths globally. However, the burden of AMR is unevenly distributed across regions. It is in this context that the WHO South-East Asia Region has remained one of the most impacted, with surveillance data indicating almost a third of bacterial infections are resistant to commonly used antibiotics and are responsible for around 1.39 million deaths annually in just South Asia. Despite comparatively lower resistance rates across the European Region (partly due to strong antimicrobial stewardship programs and surveillance systems), AMR nevertheless accounts for over 130,000 deaths each year in Europe. Indeed, if appropriate strategies are not put in place globally, AMR is projected to cause more than 39 million deaths cumulatively from 2025 to 2050, further highlighting the dire necessity for novel therapeutic propensities.

In contrast, phytochemical–antibiotic synergistic therapy is an emerging therapeutic approach that has attracted considerable attention for enhancing the effectiveness of current antimicrobial agents [43, 95]. Several experimental and preclinical studies provide evidence that plant-derived bioactive compounds, such as polyphenols, flavonoids, alkaloids, and terpenoids, enhance antibiotic activity through multiple mechanisms. These include the disruption of bacterial cell membranes, inhibition of efflux pumps, repression of biofilm formation, alteration of quorum sensing, and manipulation of bacterial metabolic pathways. Phytochemicals can enhance the efficacy of antibiotics, lower the minimum required therapeutic dose, and simultaneously delay resistance by targeting multiple cellular processes. Given the recent advances in polyherbal formulations, nanotechnology-based delivery systems, and green synthesis approaches, there exists a robust translational potential for combinations of phytochemicals and antibiotics. Nanocarrier systems, including nanoparticles, liposomes, and phytosomes, can enhance the solubility, stability, and bioavailability of phytochemicals, thereby enabling controlled and targeted drug delivery and overcoming pharmacokinetic limitations. Despite these encouraging developments, clinical translation is still limited. To make progress from here, the underlying metabolites

will need to undergo thorough toxicological evaluation, and pharmacokinetic and pharmacodynamic assessments of the new formulations will need to be standardized. Rigorous randomized clinical trials will be required before we establish safety and therapeutic efficacy. Moreover, the reproducibility and clinical reliability of herbal medicines require robust regulatory frameworks, quality control measures, and phytochemical standardization. In summary, combining phytochemical-based approaches with traditional antibiotic therapy is a promising multidimensional approach to treating infections resistant to multiple drugs. Further research, translational studies, and transnational cooperation are vital to turning these promising concepts into clinically proven, sustainable therapeutic solutions to tackle the growing global AMR crisis.

FINANCIAL ASSISTANCE
NIL

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTION
Neelakshi Sharma is involved in literature retrieval and the initial drafting of the manuscript. Bipul Nath conceived the review, supervised and edited the work, and drafted the manuscript. Trishna Das helped with data curation and critical review of the manuscript. Manas Jyoti Kapil helped with the editing and compilation of manuscripts. Amaryllis Langbang helped with the literature review and the reference control. All authors have read and confirmed the final manuscript.

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