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POTENT ANTIMICROBIAL BIOACTIVE COMPOUNDS FOR THE TREATMENT OF MICROBIAL RESISTANCE AND TOPICAL DISEASES

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Abstract:

The global escalation of antimicrobial resistance (AMR) has emerged as a serious public health threat, limiting the effectiveness of current antibiotics and complicating the treatment of infectious diseases. Multidrug-resistant (MDR) organisms—such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*—have developed sophisticated defense mechanisms, including enzymatic inactivation of drugs, efflux pump overexpression, target site mutations, and robust biofilm formation. As the conventional antibiotic pipeline declines, phytochemicals—bioactive compounds derived from medicinal plants—have re-emerged as promising candidates due to their broad-spectrum antimicrobial properties and low propensity to induce resistance. Phytochemicals such as curcumin, berberine, quercetin, allicin, and eugenol act through diverse molecular mechanisms, including membrane disruption, inhibition of protein and nucleic acid synthesis, ROS generation, and quorum sensing suppression. Many of these compounds can dismantle biofilms and restore the activity of conventional antibiotics via synergistic interactions, offering a dual advantage in the treatment of resistant infections. The recent integration of these agents into advanced delivery systems, such as hydrogels, nano emulsions, liposomes, microneedles, and stimuli-

responsive nanocarriers, has significantly improved their stability, solubility, site-specific delivery, and controlled release, particularly for topical application against chronic wounds, skin infections, and device-associated biofilms. Despite these advances, the path to clinical translation is hindered by issues such as batch-to-batch variability, lack of standardized toxicity profiles, and regulatory ambiguity concerning natural compounds. Overcoming these barriers will require a multidisciplinary approach, incorporating modern pharmacological tools, in silico modeling, robust in vivo studies, and harmonized regulatory frameworks. This review aims to present a comprehensive overview of the antimicrobial potential of phytochemicals, their mechanisms of action, modern formulation approaches for topical delivery, and the key challenges limiting their therapeutic use against AMR-associated diseases.

Keywords: Phytochemicals; Antimicrobial resistance; Multidrug-resistant bacteria; Bioactive natural compounds; Topical drug delivery.

1. Introduction

The global escalation of antimicrobial resistance (AMR) has emerged as one of the foremost public health threats of the 21st century, with multidrug-resistant (MDR) pathogens significantly limiting the efficacy of current antibiotic regimens. The World Health Organization (WHO) has warned that by 2050, deaths attributable to resistant infections could surpass 10 million annually if effective interventions are not implemented (WHO, 2020). Contributing factors include the overuse of antibiotics, poor patient compliance, misuse in agriculture, and the natural adaptability of microbes through mechanisms such as efflux pump activation, enzymatic inactivation, biofilm formation, and genetic mutations (Munita & Arias, 2016).

In response to this growing crisis, there is renewed scientific interest in phytochemicals—plant-derived secondary metabolites known for their structural diversity and multifaceted bioactivity. These include alkaloids, flavonoids, terpenoids, phenolics, and organosulfur compounds, many of which demonstrate significant antimicrobial effects. Unlike conventional antibiotics, which typically target a single bacterial process, phytochemicals act on multiple molecular targets, such as bacterial membranes, virulence factors, quorum sensing pathways, and stress response systems. This polypharmacological behavior reduces the likelihood of resistance development and offers synergistic potential when used in combination with existing antibiotics (Hemaiswarya et al., 2008; Borges et al., 2013).

In addition to their antimicrobial efficacy, phytochemicals are generally associated with low cytotoxicity, broad-spectrum activity, and compatibility with human physiology, making them ideal candidates for both systemic and localized treatments. Notably, their role in topical therapy has gained traction, particularly for managing skin infections, chronic wounds, and biofilm-associated complications, which are notoriously difficult to treat using conventional drugs alone. The integration of phytochemicals into advanced delivery systems—including liposomes, nanoemulsions, hydrogels, microneedles, and biofilm-penetrating nanocarriers—has further enhanced their clinical viability by improving stability, bioavailability, and controlled release at the site of infection (Tang et al., 2020; Sahariah & Másson, 2017).

Despite these advantages, challenges remain in translating phytochemicals from bench to bedside. Issues related to toxicity profiling, quality control, standardization, and regulatory approval must be systematically addressed to ensure safety and efficacy. Moreover,

interdisciplinary approaches integrating in silico modeling, bioassays, and mechanism-based studies are crucial for rational drug discovery and optimization of phytochemical-based antimicrobials.

2. Phytochemicals

Phytochemicals are naturally occurring bioactive compounds found in plants that contribute significantly to their antimicrobial, antioxidant, and anti-inflammatory properties. These compounds, including flavonoids, alkaloids, phenolics, terpenoids, and saponins, have demonstrated the ability to combat a wide range of microbial pathogens by disrupting microbial cell membranes, inhibiting enzymes, or interfering with nucleic acid synthesis (Cowan, 1999). Flavonoids, for instance, exhibit strong antibacterial activity through mechanisms such as inhibition of DNA gyrase and disruption of microbial energy metabolism (Xie et al., 2015). Alkaloids like berberine have shown efficacy against multidrug-resistant strains by targeting bacterial efflux pumps and membrane integrity (Stermitz et al., 2000). Additionally, terpenoids, such as thymol and carvacrol, destabilize microbial membranes, leading to cell lysis (Burt, 2004). These phytochemicals represent a promising avenue for developing novel therapeutics, especially in light of rising antimicrobial resistance and the urgent need for alternative treatment strategies.

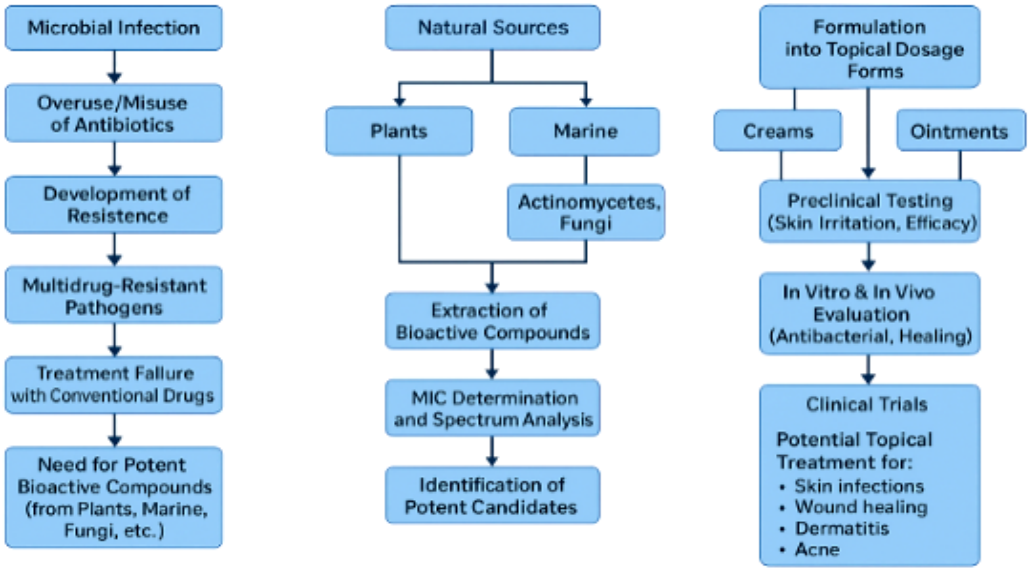

Fig 1: Bioactive Compounds for the Treatment of Microbial Resistance and Topical Diseases

3. Mechanisms of Microbial Resistance

Microbial resistance to antibiotics has become a major global health concern, driven by the ability of bacteria to adapt and evade antimicrobial actions through various biochemical and genetic strategies. These resistance mechanisms not only reduce the effectiveness of treatment but also facilitate the survival and spread of multidrug-resistant (MDR) strains. Understanding the fundamental mechanisms behind microbial resistance—such as enzymatic degradation of antibiotics, alterations in target sites, reduced drug permeability, efflux pump activation, and biofilm formation—is crucial for the development of new antimicrobial agents and therapeutic strategies, including phytochemical-based interventions.

- **Enzymatic degradation (e.g., β-lactamases)**

One of the most prevalent mechanisms of microbial resistance is enzymatic degradation, where bacteria produce enzymes that chemically inactivate antibiotics. Among these, β-lactamases are the most well-known, particularly in Gram-negative bacteria. These enzymes hydrolyze the β-lactam ring, a critical structure in penicillins, cephalosporins, and carbapenems, rendering the antibiotic ineffective. There are several classes of β-lactamases, including extended-spectrum β-lactamases (ESBLs) and carbapenemases, which confer resistance to a wide range of β-lactam antibiotics. These enzymes can be chromosomally encoded or carried on plasmids, facilitating rapid dissemination through horizontal gene transfer (Bush & Bradford, 2016). As a result, infections caused by β-lactamase-producing organisms are often difficult to treat and are associated with higher morbidity and mortality.

- **Efflux pumps**

Efflux pumps are membrane protein transporters that actively expel antibiotics and toxic substances out of microbial cells, thereby reducing intracellular drug concentration below therapeutic levels. These pumps are a significant contributor to multidrug resistance, especially in Gram-negative bacteria. They can be either intrinsic or acquired through genetic mutations or horizontal gene transfer. Efflux systems are classified into major families, such as the resistance-nodulation-division (RND) family in *Pseudomonas aeruginosa* and *Escherichia coli*, and the major facilitator superfamily (MFS) found in *Staphylococcus aureus*. These pumps confer resistance to a wide range of antibiotics, including tetracyclines, fluoroquinolones, macrolides, and β-lactams (Li et al., 2015). The overexpression of efflux

pumps not only reduces drug efficacy but also contributes to biofilm formation and persistence, making infections more difficult to eradicate.

- **Biofilm formation**

Biofilm formation is a key survival strategy that significantly enhances microbial resistance to antibiotics and host immune defenses. In this process, bacterial cells aggregate and embed themselves within a self-produced extracellular polymeric substance (EPS), forming a protective matrix that adheres to surfaces such as tissues, catheters, or wounds. Within biofilms, bacteria exhibit altered metabolic states and reduced growth rates, rendering antibiotics less effective, particularly those targeting active cellular processes. Moreover, the dense EPS barrier limits drug penetration and facilitates horizontal gene transfer, promoting the spread of resistance determinants (Mah & O'Toole, 2001). Biofilm-associated infections, such as chronic wounds, implant-related infections, and cystic fibrosis lung colonization, are notoriously persistent and difficult to treat with conventional antimicrobials alone.

- **Mutation and target modification**

Mutation and target modification are crucial mechanisms by which microbes develop resistance to antibiotics. Spontaneous genetic mutations can alter the structure of key bacterial targets, diminishing antibiotic binding and efficacy. For example, point mutations in the *rpoB* gene confer resistance to rifampicin by altering the RNA polymerase binding site, while changes in DNA gyrase or topoisomerase IV genes result in fluoroquinolone resistance (Blair et al., 2015). Additionally, post-translational modifications such as methylation of ribosomal RNA (e.g., by *erm* genes) can prevent binding of macrolides, lincosamides, and streptogramins. These modifications do not inhibit normal bacterial function but specifically hinder drug-target interaction, enabling bacterial survival in the presence of antibiotics. Once established, these mutations can be vertically transmitted, making them stable and persistent within bacterial populations. Such modifications are particularly concerning because they can be stably inherited and disseminated through vertical gene transmission, ensuring persistence within bacterial populations. Moreover, many resistance mutations impose little or no fitness cost, allowing resistant strains to thrive in both clinical and community settings. This makes target modification one of the most robust and difficult-to-counter resistance mechanisms, highlighting the urgent need for alternative therapies such as phytochemicals that act on multiple, less-specific bacterial pathways.

Table 3: Overview of Major Mechanisms of Microbial Resistance

Mechanism	Description	Examples	Clinical Impact
Enzymatic Degradation	Enzymes (e.g., β-lactamases) hydrolyze antibiotics, inactivating them	β-lactamase in *E. coli*, *K. pneumoniae*	Resistance to penicillins, cephalosporins
Efflux Pumps	Transport proteins expel antibiotics out of the cell	RND pumps in *P. aeruginosa*	Multidrug resistance in Gram-negatives
Biofilm Formation	Bacteria embed in a protective matrix, reducing drug penetration	*S. aureus*, *P. aeruginosa*	Chronic wound, device-related infections
Target Site Modification	Mutations alter antibiotic binding sites	*rpoB* mutation in *M. tuberculosis*	Rifampicin and fluoroquinolone resistance
Reduced Permeability	Altered membrane porins limit antibiotic entry	Porin loss in *Enterobacteriaceae*	Carbapenem resistance
Horizontal Gene Transfer	Acquisition of resistance genes via plasmids, transposons, etc.	ESBL, NDM-1 genes	Rapid spread of resistance traits

4. Strategies of Screening of Herbal Derived Bioactive Compounds for Drug Discovery

The screening of herbal-derived bioactive compounds for drug discovery involves a series of integrated strategies aimed at identifying potent candidates with therapeutic potential. Initially, ethnopharmacological knowledge plays a crucial role in selecting plants with historical or traditional medicinal usage, providing a rational basis for investigation (Heinrich et al., 2020). Phytochemical profiling using advanced chromatographic and spectroscopic techniques such as HPLC, LC-MS, and NMR aids in the identification and isolation of active constituents (Zhang et al., 2018). Subsequently, in vitro bioassays, including antimicrobial,

antioxidant, and cytotoxicity assays, are employed to evaluate the biological activity of extracts or purified compounds (Newman & Cragg, 2020). Mechanism-based screening through molecular docking, enzyme inhibition assays, and receptor-binding studies enhances the understanding of compound-target interactions (Sharma et al., 2019). Recent advancements in high-throughput screening (HTS) and in silico approaches, including virtual screening and QSAR modeling, allow rapid identification of lead compounds from large phytochemical libraries (Chen et al., 2021). Integration of these strategies, supported by bioinformatics and chemoinformatics tools, significantly accelerates the herbal drug discovery pipeline while ensuring scientific validation and reproducibility.

4.1. By the Computing Approach

Computational approaches have revolutionized the screening of herbal-derived bioactive compounds by offering cost-effective, rapid, and accurate strategies for drug discovery. Virtual screening and molecular docking are widely used to predict the binding affinity of phytochemicals with specific biological targets, thereby identifying lead candidates without extensive lab experimentation (Lionta et al., 2014). Pharmacophore modeling helps in identifying essential structural features responsible for biological activity, which is particularly useful in refining compound libraries from herbal sources (Yang et al., 2019). Additionally, quantitative structure-activity relationship (QSAR) models allow the prediction of compound efficacy based on molecular descriptors, enhancing the prioritization of active candidates (Cherkasov et al., 2014). Molecular dynamics simulations further assess the stability and interaction dynamics of bioactive compounds within target binding sites (Hollingsworth & Dror, 2018). Integrating these tools with ADMET prediction platforms enables early evaluation of pharmacokinetics and toxicity profiles, thus improving the success rate of natural products in the drug development pipeline. These computational strategies not only streamline the screening process but also bridge traditional medicine with modern pharmacological innovation.

4.2. Bioassays for Phytochemical Testing

Bioassays are essential tools in evaluating the biological activity of phytochemicals and play a pivotal role in screening herbal compounds for therapeutic potential. These assays help determine various pharmacological properties such as antimicrobial, antioxidant, anti-inflammatory, and cytotoxic activities. For antimicrobial assessment, methods like the disc diffusion assay, broth microdilution, and agar well diffusion are commonly used to measure

the inhibition zone or minimum inhibitory concentration (MIC) of plant extracts against specific pathogens (Balouiri et al., 2016). Antioxidant activity is frequently evaluated using assays such as DPPH radical scavenging, ABTS assay, and ferric reducing antioxidant power (FRAP), which provide insight into the compound's ability to neutralize free radicals (Prior et al., 2005). For anti-inflammatory activity, cyclooxygenase (COX) inhibition assays and nitric oxide suppression in macrophages are employed, while MTT and SRB assays are widely used to assess cytotoxicity against cancer cell lines (Mosmann, 1983; Skehan et al., 1990). These bioassays not only validate the pharmacological efficacy of phytochemicals but also facilitate the prioritization of active compounds for further development in drug discovery.

4.3 Mechanistic Perspectives on Botanical Research

Understanding the mechanisms of action of herbal-derived bioactive compounds is crucial for validating their therapeutic potential and integrating them into modern drug development. Mechanistic studies focus on elucidating how phytochemicals interact with biological targets at the molecular, cellular, and systemic levels. Many plant-derived compounds exert antimicrobial effects by disrupting bacterial membranes, inhibiting key enzymes, or interfering with nucleic acid synthesis (Gibbons, 2005). For instance, phenolic compounds often damage microbial membranes and cause leakage of cellular contents, while alkaloids may bind to DNA or inhibit topoisomerase enzymes (Borges et al., 2013). On a cellular level, bioactive compounds such as flavonoids modulate signaling pathways like NF-κB, MAPK, and PI3K/Akt, leading to anti-inflammatory and antioxidant effects (Zhang et al., 2019). At the systemic level, certain phytochemicals enhance host immunity or modulate the microbiome to support therapeutic outcomes. Modern omics platforms—including transcriptomics, proteomics, metabolomics, and metagenomics—have revolutionized mechanistic studies by offering a comprehensive view of biological responses to phytochemicals. These technologies help identify differentially expressed genes, protein targets, and metabolic pathways affected by botanical treatments (Choi et al., 2020). For example, RNA-seq analyses have shown that berberine modulates genes associated with biofilm inhibition and oxidative stress in *Pseudomonas aeruginosa*, while metabolomic profiling reveals alterations in fatty acid metabolism and membrane composition after exposure to phenolic acids. These mechanistic perspectives are essential to translate traditional knowledge into evidence-based therapeutics.

Table1: Names of bioactive molecules and their mechanism of action

Bioactive Molecule	Source Plant	Target Organism(s)	Mechanism of Action
Berberine	*Berberis vulgaris*	*E. coli*, MRSA	Efflux pump inhibition, DNA intercalation
Curcumin	*Curcuma longa*	*S. aureus*, *P. aeruginosa*	Biofilm inhibition, anti-inflammatory activity
Eugenol	*Syzygium aromaticum*	*Candida albicans*, *S. aureus*	Membrane disruption, protein denaturation
Quercetin	Apples, Onions	*P. aeruginosa*, *E. coli*	ROS generation, efflux pump suppression
Allicin	*Allium sativum*	*K. pneumoniae*, MRSA	Inhibition of thiol enzymes, quorum sensing
Epigallocatechin gallate	*Camellia sinensis* (Green Tea)	*S. aureus*, *E. coli*	β-lactamase inhibition, membrane destabilization
Thymol	*Thymus vulgaris*	*S. aureus*, *E. coli*	Membrane permeabilization, ATP depletion
Resveratrol	Grapes, Berries	*Acinetobacter baumannii*	Inhibition of cell division proteins, anti-biofilm activity
Kaempferol	Tea, Broccoli	*E. coli*, *H. pylori*	DNA gyrase inhibition, membrane destabilization
Cinnamaldehyde	*Cinnamomum verum*	*S. aureus*, *Listeria monocytogenes*	Cell membrane disruption, inhibition of ATPase activity

Baicalein	*Scutellaria baicalensis*	MRSA, *P. aeruginosa*	Inhibition of quorum sensing and efflux pumps

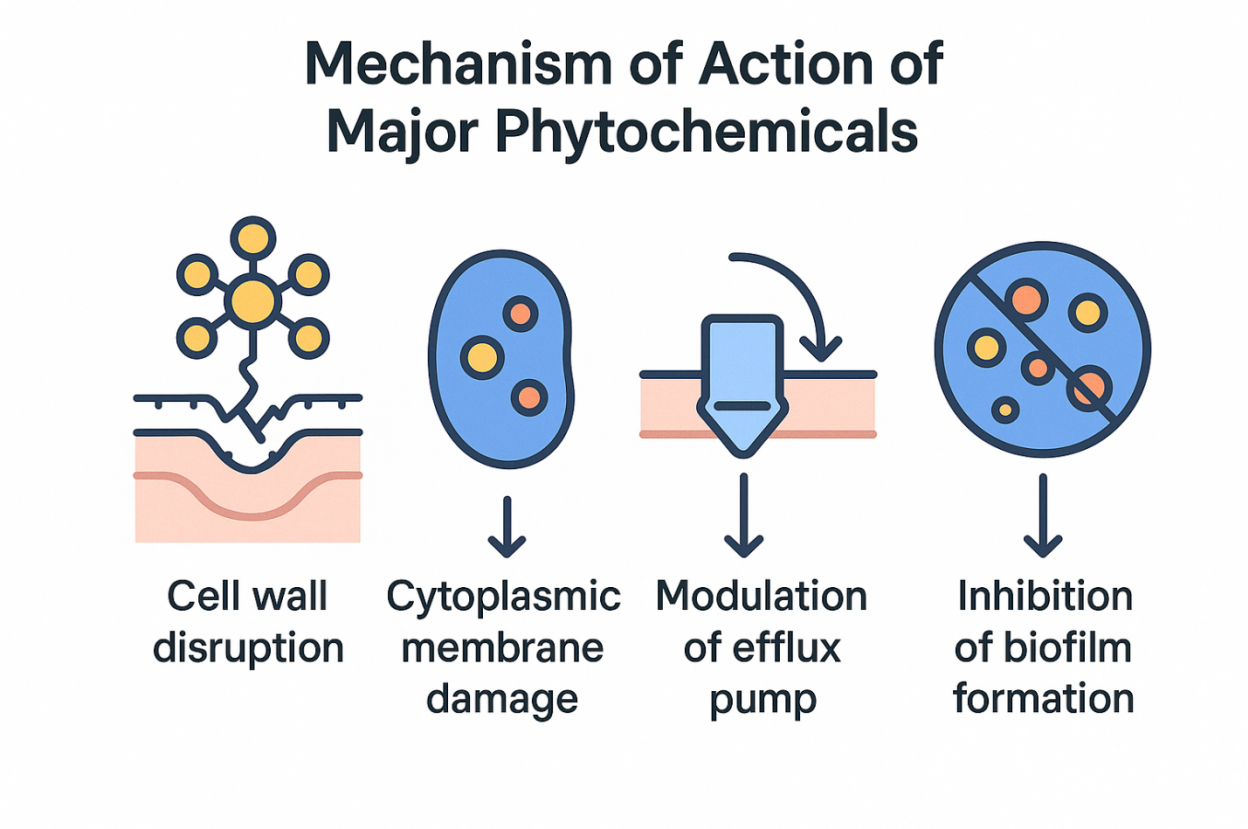

Figure 2: Mechanism of Action of Major Phytochemicals

5. Mechanisms of Action of Bioactive Compounds

Bioactive phytochemicals exert antimicrobial effects through diverse and multifaceted mechanisms that disrupt essential microbial functions. Unlike conventional antibiotics that often target a single cellular process, phytochemicals act on multiple pathways, making them less prone to resistance development. These mechanisms include disruption of cell membranes, inhibition of nucleic acid and protein synthesis, suppression of virulence factors, interference with quorum sensing, and inhibition of biofilm formation. Understanding these molecular actions is crucial for validating the therapeutic potential of plant-derived compounds and for guiding the development of novel antimicrobial formulations.

- **Disruption of cell wall/membrane**

Many phytochemicals exert antimicrobial effects by compromising the integrity of microbial cell walls and membranes, leading to cell lysis and death. This mechanism is particularly effective because the cell membrane is essential for maintaining osmotic balance and cellular structure. Compounds such as eugenol, thymol, and carvacrol insert into the lipid bilayer, increasing membrane permeability and causing leakage of intracellular contents. This disruption also impairs membrane-bound enzyme activity and ion gradients, ultimately resulting in loss of cellular function and viability (Trombetta et al., 2005). The amphipathic nature of these molecules allows them to integrate into both Gram-positive and Gram-negative membranes, making them broad-spectrum in action. This multi-targeted membrane disruption reduces the likelihood of resistance development and enhances their suitability for topical and systemic antimicrobial applications.

- **Inhibition of protein or nucleic acid synthesis**

Several phytochemicals exert antimicrobial effects by interfering with the synthesis of essential macromolecules such as proteins and nucleic acids. Flavonoids, alkaloids, and phenolic compounds are known to disrupt DNA replication, RNA transcription, or ribosomal function, thereby inhibiting microbial growth and viability. For instance, berberine intercalates into bacterial DNA and prevents DNA and RNA synthesis, while quercetin inhibits DNA gyrase, an enzyme vital for DNA supercoiling and replication (Cushnie & Lamb, 2005). Additionally, compounds like epigallocatechin gallate (EGCG) bind to bacterial ribosomes, disturbing protein translation processes. By targeting these fundamental pathways, phytochemicals not only impair microbial proliferation but also reduce the risk of resistance development due to their multi-targeted mode of action.

- **ROS generation and oxidative stress**

Many bioactive phytochemicals exert antimicrobial effects by inducing reactive oxygen species (ROS) generation, leading to oxidative stress within microbial cells. Elevated ROS levels—such as hydrogen peroxide, superoxide anions, and hydroxyl radicals—can damage essential cellular components, including DNA, proteins, and lipids, ultimately resulting in cell death. Compounds like curcumin, quercetin, and epigallocatechin gallate (EGCG) have been shown to trigger intracellular ROS production, overwhelming bacterial antioxidant defenses (Apel & Hirt, 2004). This oxidative assault disrupts redox homeostasis and impairs vital metabolic pathways, particularly in multidrug-resistant strains where conventional antibiotics may fail. Moreover, ROS-mediated damage is often non-specific, reducing the

potential for resistance development and making this mechanism especially valuable for combination therapies.

- **Biofilm disruption**

Phytochemicals play a crucial role in disrupting microbial biofilms, which are structured communities of bacteria encased in a protective extracellular matrix. Biofilms contribute significantly to antibiotic resistance and chronic infections due to their reduced drug permeability and altered metabolic states. Certain plant-derived compounds, such as curcumin, berberine, and eugenol, can inhibit biofilm formation, degrade the biofilm matrix, or disrupt bacterial communication systems like quorum sensing, which regulates biofilm development. For example, curcumin inhibits the expression of genes involved in EPS production and adhesion, while eugenol alters biofilm architecture by increasing membrane permeability and interfering with cell signaling (Khan et al., 2017). These actions not only reduce microbial load but also sensitize biofilm-associated bacteria to conventional antibiotics, making phytochemicals valuable in treating persistent and device-related infections.

6. Safety, Toxicity, and Regulatory Challenges

The exploration of herbal-derived bioactive compounds has gained global attention as a promising strategy for combating microbial resistance and managing topical diseases. These natural agents, sourced from medicinal plants, offer diverse chemical structures and mechanisms of action that differ from conventional antibiotics, making them valuable in addressing drug-resistant infections. However, while their therapeutic potential is significant, ensuring safety, minimizing toxicity, and meeting regulatory standards are essential steps in translating these compounds into clinically approved products. A balanced approach involving scientific validation, standardization, and regulatory compliance is critical to fully harness their benefits in modern medicine.

- **Cytotoxicity concerns**

Cytotoxicity is a major safety consideration in the development of herbal-derived bioactive compounds, as some phytochemicals can harm healthy human cells along with pathogenic microbes. Compounds such as alkaloids, saponins, and certain essential oils may exhibit potent biological activity but also demonstrate dose-dependent cytotoxic effects, including apoptosis or necrosis in non-target cells (Wink, 2012). The variability in plant composition due to geographical, seasonal, and extraction differences further complicates toxicity

assessments. In vitro assays like MTT, LDH release, and neutral red uptake are commonly used to evaluate cytotoxicity, but translating these results into safe dosage guidelines for humans remains challenging (Fotakis & Timbrell, 2006). Moreover, long-term exposure or accumulation of certain plant metabolites can lead to organ toxicity, particularly in the liver and kidneys. Therefore, rigorous toxicological profiling, including both in vitro and in vivo studies, is essential to ensure the safe therapeutic application of herbal compounds.

- **Standardization and quality control**

Standardization and quality control are critical challenges in the development of herbal-derived bioactive compounds, as the therapeutic efficacy and safety of plant-based products depend heavily on their chemical consistency. Unlike synthetic drugs, herbal extracts are complex mixtures of numerous constituents whose concentrations can vary due to differences in plant species, geographic origin, harvesting time, and extraction methods (Mukherjee et al., 2011). Standardization involves the identification and quantification of key bioactive markers using validated analytical techniques such as HPLC, GC-MS, and FTIR, ensuring batch-to-batch uniformity (Kunle et al., 2012). Quality control also includes checks for contaminants like heavy metals, pesticides, and microbial loads, which are critical for product safety. Moreover, Good Manufacturing Practices (GMP) and adherence to pharmacopeial standards are essential for regulatory approval. Without these measures, variability in herbal formulations can lead to inconsistent clinical outcomes, reduced efficacy, and potential toxicity, undermining their credibility in therapeutic applications.

- **Regulatory hurdles in natural compound approval**

The approval of natural compounds, especially those derived from herbal sources, faces several regulatory hurdles due to their complex composition and variability. Unlike synthetic drugs, which consist of single active molecules, herbal products often contain multiple constituents, making it difficult to define their pharmacological activity and standardize formulations (Ekor, 2014). Regulatory agencies such as the FDA and EMA require comprehensive data on efficacy, safety, quality control, pharmacokinetics, and toxicological profiles, which can be challenging to obtain for multi-component herbal extracts (Sahoo et al., 2010). Additionally, many traditional herbal products enter the market as dietary supplements or cosmetics, often bypassing stringent clinical requirements, leading to limited post-marketing surveillance and inconsistent safety standards. Moreover, the lack of globally

harmonized regulatory frameworks creates disparities in the approval process, impeding international commercialization. To overcome these challenges, there is a need for clear guidelines, validated analytical methods, and robust clinical trials specifically tailored to botanical drugs.

7. Formulation Approaches for Topical Delivery

Topical delivery of herbal-derived bioactive compounds is an effective strategy for treating localized infections and skin-related disorders. This route offers direct access to the affected area, reduces systemic side effects, and enhances patient compliance. However, many phytochemicals face challenges such as poor solubility, instability, and limited skin penetration. To address these issues, innovative formulation approaches—ranging from traditional gels and creams to advanced carriers like liposomes, nanoemulsions, and microneedles—have been developed to improve therapeutic efficacy and bioavailability in topical applications.

7.1 Hydrogels, nanoemulsions, liposomes, microneedles

- **Hydrogels** offer a versatile platform for delivering herbal actives due to their high water content, soft consistency, and ability to provide sustained release. They can encapsulate a variety of phytochemicals—especially flavonoids, tannins, and alkaloids—and have been used in wound healing, acne, and dermatitis treatments. The incorporation of herbal extracts like *Aloe vera*, *Centella asiatica*, and *Curcuma longa* into hydrogels has shown enhanced wound closure and anti-inflammatory effects in preclinical studies (Boateng et al., 2008). Additionally, hydrogels can be modified with polymers like chitosan or hyaluronic acid to improve skin adherence and bioactivity.
- **Nanoemulsions**, with droplet sizes typically below 200 nm, offer improved solubility for lipophilic herbal compounds like essential oils, terpenoids, and polyphenols. Their small droplet size facilitates deep skin penetration and increased surface contact with the epidermis, enhancing antimicrobial and anti-inflammatory efficacy. Nanoemulsion-based formulations of *Neem*, *Tea Tree Oil*, and *Eucalyptus* have demonstrated strong activity against skin pathogens such as *Staphylococcus aureus* and *Candida albicans* (Baspinar et al., 2010).
- **Liposomes** improve the bioavailability and therapeutic index of herbal drugs by protecting them from enzymatic degradation and enhancing penetration through the

stratum corneum. Phytoconstituents such as curcumin, quercetin, and resveratrol have been successfully encapsulated in liposomes for enhanced dermal delivery. Liposomal formulations are particularly useful in treating psoriasis, fungal infections, and UV-induced damage due to their high biocompatibility and ability to merge with skin lipids (Pardeike et al., 2009).

- **Microneedles** represent a next-generation delivery system capable of delivering large and poorly permeable herbal compounds directly into the viable epidermis. They are fabricated using biodegradable polymers or metals and are ideal for drugs like hydrophilic alkaloids or plant-based peptides. Recent studies have shown successful delivery of herbal actives such as *baicalein* and *ginsenosides* using microneedles, with improved absorption and therapeutic effects against chronic skin inflammation and infections (Nguyen et al., 2019). This minimally invasive method bypasses the skin barrier and can be combined with patches for controlled release.

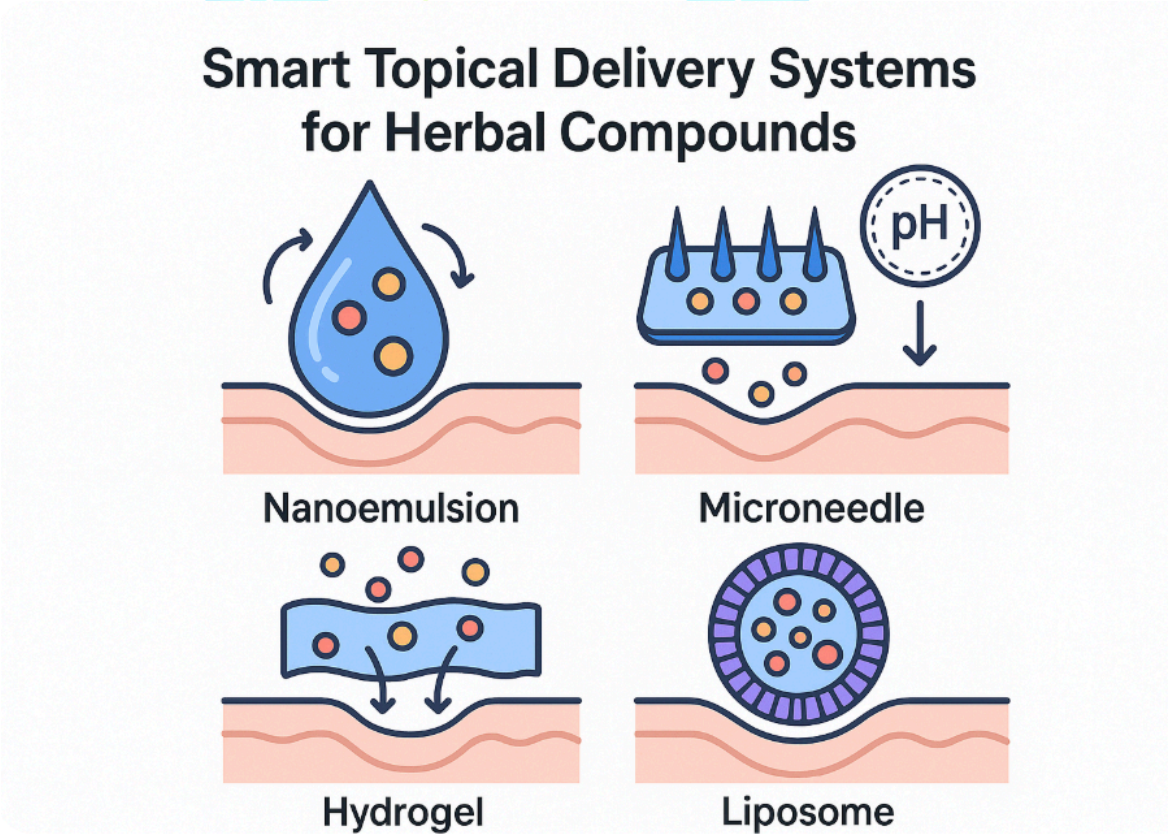

Figure 3: Smart Topical Delivery Systems for Herbal Compounds

7.2 Biofilm-penetrating carriers

Biofilm-penetrating carriers represent a promising advancement in the topical delivery of herbal bioactive compounds, particularly for treating chronic wounds and resistant skin infections where microbial biofilms pose a significant barrier. Biofilms—structured microbial communities embedded in an extracellular polymeric matrix—are inherently resistant to antibiotics and conventional topical therapies. To overcome this, nanocarriers such as liposomes, polymeric nanoparticles, dendrimers, and nanogels have been engineered to enhance penetration into and disruption of biofilms (Koo et al., 2017).

Herbal compounds like curcumin, allicin, eugenol, and berberine, known for their anti-biofilm and quorum-sensing inhibition properties, show enhanced efficacy when delivered via such advanced carriers. For instance, curcumin-loaded polymeric nanoparticles have demonstrated effective dispersion of *Staphylococcus aureus* biofilms and improved skin healing in infected wounds (Shen et al., 2019). Chitosan-based nanogels not only facilitate penetration through the biofilm matrix but also exhibit intrinsic antimicrobial and bioadhesive properties, making them ideal for mucosal or dermal applications (Sahariah & Másson, 2017).

These biofilm-targeting systems often incorporate surface modifications, such as cationic or enzyme-sensitive coatings, which enhance targeting of bacterial aggregates and controlled release of actives in response to the biofilm environment. Their ability to bypass the biofilm barrier and deliver herbal compounds directly to embedded pathogens significantly increases treatment efficacy and reduces recurrence of infection.

7.3 Smart release systems (e.g., pH-responsive)

Smart release systems, particularly pH-responsive carriers, offer an innovative strategy for the targeted and controlled delivery of herbal bioactive compounds in topical applications. These systems exploit the pathophysiological changes in infected or inflamed skin, such as lowered pH levels, to trigger drug release precisely at the site of infection or injury (Zhang et al., 2016). pH-responsive carriers are often designed using polymers like chitosan, Eudragit, or polyacrylic acid, which undergo swelling, degradation, or conformational changes under acidic conditions, enabling a rapid and localized release of encapsulated phytochemicals.

Herbal compounds such as curcumin, quercetin, and baicalin have been successfully incorporated into pH-sensitive nanocarriers, demonstrating enhanced antimicrobial activity against resistant skin pathogens and accelerated wound healing (Tang et al., 2020). These

systems not only improve the bioavailability and stability of poorly soluble phytochemicals but also minimize systemic absorption, thereby reducing potential side effects. Additionally, smart carriers can be co-engineered with enzymatic or redox-sensitive triggers for multi-stimuli responsiveness, further refining the precision of herbal drug delivery in chronic wounds and skin infections.

8. Antibiotics multiple resistance conditions causes and treatment strategy for treating drug resistant bacteria are

The emergence of multiple antibiotic resistance among bacterial pathogens is a pressing global health concern, primarily driven by the excessive and inappropriate use of antibiotics in human medicine, veterinary practices, and agriculture. Factors such as overprescription, incomplete treatment regimens, and reliance on broad-spectrum antibiotics have accelerated the selection of resistant strains. Bacteria further amplify resistance through mechanisms like enzymatic degradation of antibiotics (e.g., β-lactamases), efflux pumps, target site modification, and the formation of protective biofilms. Additionally, horizontal gene transfer via plasmids and transposons facilitates the rapid spread of resistance genes among different bacterial species, worsening the problem (Munita & Arias, 2016; Ventola, 2015).

To address these challenges, multiple treatment strategies have been developed. Combination therapy, using antibiotics alongside β-lactamase inhibitors or other synergistic agents, can enhance efficacy and overcome resistance. Natural bioactive compounds such as berberine, curcumin, and allicin have shown the ability to inhibit resistance mechanisms and potentiate antibiotic action, offering promising adjunctive therapy (Stermitz et al., 2000). Phage therapy, which employs viruses that specifically target bacterial pathogens, has re-emerged as a viable approach for multidrug-resistant infections, especially when antibiotics fail (Dedrick et al., 2019). Antimicrobial peptides (AMPs) like defensins and cathelicidins offer broad-spectrum activity by disrupting bacterial membranes and exhibit a low risk of resistance development (Mahlapuu et al., 2016). Additionally, nanotechnology-based delivery systems and metallic nanoparticles have shown efficacy in penetrating biofilms and enhancing drug uptake (Hajipour et al., 2012). Cutting-edge gene-editing approaches such as CRISPR-Cas systems are also being explored to selectively target and deactivate resistance genes, offering a precision-based treatment solution (Lemire et al., 2018). These multidisciplinary strategies are critical in combating the growing threat of antibiotic resistance and ensuring effective treatment for drug-resistant bacterial infections.

9. Popularity of phytochemicals for the removewal of antibiotics multiple resistances by following reasons such as

Phytochemicals have gained significant popularity as alternatives or adjuncts to conventional antibiotics in combating multiple antibiotic resistance due to their unique and multifaceted therapeutic properties. One of the key advantages of phytochemicals is their ability to act through multiple mechanisms, such as disrupting bacterial membranes, inhibiting virulence factors, interfering with quorum sensing, and degrading biofilms. This multi-targeted action makes it more difficult for bacteria to develop resistance compared to single-target antibiotics (Hemaiswarya et al., 2008). Furthermore, many phytochemicals demonstrate synergistic effects when used alongside antibiotics. Compounds like berberine, eugenol, and quercetin have been shown to inhibit bacterial efflux pumps or β-lactamase enzymes, thereby restoring the effectiveness of otherwise ineffective antibiotics (Stermitz et al., 2000).

Another compelling reason for their growing use is their low potential to induce resistance, owing to their complex chemical structures and diverse biological actions. Additionally, several phytochemicals such as curcumin, cinnamaldehyde, and allicin possess anti-biofilm and anti-quorum sensing properties, helping to disrupt bacterial communities and prevent colonization—key strategies in managing persistent infections (Kalia, 2013). Their natural origin and general biocompatibility further enhance their appeal, especially in topical and adjunctive applications, where safety is a major concern. Many phytochemicals also exhibit broad-spectrum activity against both Gram-positive and Gram-negative bacteria, including multidrug-resistant strains like *MRSA*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* (Borges et al., 2013). Finally, the traditional use of herbal remedies in systems like Ayurveda and Traditional Chinese Medicine provides a strong empirical foundation for their antimicrobial potential, supporting further scientific exploration and integration into modern therapeutic strategies.

10. Conclusion

The relentless rise of antimicrobial resistance has rendered many frontline antibiotics ineffective, necessitating the urgent exploration of alternative therapeutic strategies. In this context, phytochemicals—bioactive compounds derived from medicinal plants—have demonstrated tremendous promise due to their broad-spectrum antimicrobial activity and low tendency to induce resistance. Unlike conventional antibiotics that often act on a single microbial target, phytochemicals exert multi-pronged effects, including disruption of

microbial membranes, inhibition of virulence factors, interference with quorum sensing, suppression of biofilm formation, and modulation of host immune responses. These characteristics make them powerful candidates not only for direct antimicrobial action but also as adjuvants that enhance the efficacy of existing antibiotics through synergistic interactions.

Recent advancements in formulation science have further propelled the clinical relevance of phytochemicals, especially for topical infections. Technologies such as nanoemulsions, liposomes, microneedles, hydrogels, and smart-responsive carriers have significantly improved the bioavailability, site-specific delivery, and sustained release of these compounds, while overcoming barriers like poor solubility and skin permeability. Moreover, the ability of certain delivery systems to penetrate biofilms or respond to infection-site-specific triggers (e.g., pH or enzymes) has opened new possibilities for the targeted treatment of chronic wounds, dermatological infections, and resistant skin pathogens.

Nevertheless, despite these promising advances, there are significant scientific and regulatory hurdles to overcome. Challenges include variability in phytochemical composition due to environmental and genetic factors, lack of standardized extraction and purification methods, inadequate in vivo toxicological data, and the absence of clear regulatory frameworks for plant-based therapeutics. These gaps hinder the progression of phytochemicals from bench to bedside. Addressing these issues will require multidisciplinary collaboration, involving pharmacologists, formulation scientists, microbiologists, and regulatory authorities.

In conclusion, the integration of traditional plant wisdom with modern pharmacological and nanotechnological tools offers a powerful approach to combating antibiotic resistance. As we move toward a post-antibiotic era, the strategic use of phytochemicals—supported by robust scientific validation and smart delivery platforms—may pave the way for a new class of sustainable, effective, and accessible antimicrobial therapies. Further preclinical and clinical research, along with policy-level support for natural product drug development, will be key to unlocking their full therapeutic potential.

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12. Conflict of interest

All authors declare that they have no conflicts of interest .

13. References

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