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Potential of Plant-Derived Phytochemicals in Combating Antimicrobial Resistance: A Comprehensive Review

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ABSTRACT

Background: Antimicrobial resistance (AMR) represents a critical threat to global health, with drug-resistant infections projected to cause more deaths than cancer by 2050. Conventional antibiotics are increasingly failing due to misuse, overprescription, and the rapid evolution of resistance mechanisms. At the same time, innovation in antibiotic discovery has stagnated, creating an urgent need for alternative therapeutic strategies. Plant-derived phytochemicals have gained attention for their structural diversity, multi-target modes of action, and potential to reverse resistance mechanisms. Objective: This review aims to comprehensively evaluate the potential of plant-derived phytochemicals as novel antimicrobial agents and resistance-modifying adjuvants, highlighting their mechanisms of action, synergistic potential with conventional antibiotics, clinical applications, and translational challenges. Methods: A narrative review methodology was employed, sourcing relevant studies from PubMed, Scopus, Web of Science, and Google Scholar (2000–2025). Inclusion criteria focused on studies investigating the antimicrobial activity, molecular targets, synergistic interactions, and clinical relevance of plant-derived compounds. Results: Phytochemicals demonstrated activity across a wide microbial spectrum by inhibiting efflux pumps, disrupting membranes, interfering with DNA and protein synthesis, and enhancing antibiotic efficacy. Several compounds have progressed to clinical evaluation, showing efficacy in infections such as UTIs, respiratory diseases, and gastrointestinal infections. Conclusion: Plant-derived phytochemicals offer a promising adjunct or alternative to conventional antibiotics. Further mechanistic studies, optimized formulations, and rigorous clinical trials are essential for clinical translation.

Keywords
Antimicrobial resistance, phytochemicals, efflux pump inhibitors, synergistic therapy, plant-derived antimicrobials, alternative therapeutics.

Graphical Abstract Figure 2

INTRODUCTION

Antimicrobial resistance (AMR) is now widely recognized as one of the gravest threats to global public health, with implications that extend far beyond clinical medicine into agriculture, economics, food security, and sustainable development (1). According to the landmark Global Research on Antimicrobial Resistance (GRAM) report, an estimated 4.95 million deaths were associated with bacterial AMR in 2019, including 1.27 million directly attributable deaths—figures that already exceed global deaths caused by HIV/AIDS or malaria (2). Low- and middle-income countries (LMICs) bear a disproportionate share of this burden due to weaker health infrastructure, poor regulatory oversight, and limited access to diagnostics and stewardship programs (3). Without urgent intervention, the World Bank projects that by 2050, annual global mortality from drug-resistant infections could reach 10 million, and cumulative economic losses could exceed USD 100 trillion, reducing global gross domestic product (GDP) by up to 3.8% and pushing an additional 24 million people into extreme poverty (4).

The drivers of this escalating crisis are multifaceted. Excessive and inappropriate antibiotic use in human medicine, often through overprescription or patient non-compliance, continues to accelerate the selection of resistant strains (5). In parallel, the indiscriminate use of antibiotics in livestock production, aquaculture, and agriculture contributes to cross-resistance and horizontal gene transfer in zoonotic and environmental reservoirs (6). Poor infection prevention and control measures, lack of access to quality-assured medicines, and global mobility further amplify the spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) organisms. The emergence of "superbugs" such as methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Enterobacterales*, and multidrug-resistant *Acinetobacter baumannii* has rendered many standard treatments ineffective, challenging even routine surgical procedures and immunosuppressive therapies (7).

A critical challenge compounding the AMR crisis is the so-called "innovation gap" in antibiotic development. Despite the rise of resistance, the pipeline for new antibacterial drugs has stagnated, with fewer than 50 new antibiotics currently in clinical development, many of which are modifications of existing classes rather than novel mechanisms of action (8). The discovery of entirely new antibiotic scaffolds peaked in the mid-20th century, and since the 1980s, there has been a sharp decline in approvals of new antibiotic classes (9). Economic disincentives—including

low profitability, long development timelines, and high regulatory hurdles—have led most major pharmaceutical companies to scale back or abandon antibacterial R&D programs (10). As a result, humanity is locked in an evolutionary arms race with pathogens, often relying on drugs that were developed decades ago and are now increasingly ineffective.

This growing crisis has spurred interest in alternative therapeutic strategies, including bacteriophage therapy, monoclonal antibodies, antimicrobial peptides, and immunomodulatory approaches (11). Among these, plant-derived phytochemicals have emerged as particularly promising candidates due to their remarkable chemical diversity, multi-target mechanisms, and historical safety in human use. Plants have been an integral source of therapeutic agents for millennia, and more than 25% of modern pharmaceuticals are either derived from or inspired by natural products (12). Phytochemicals—including alkaloids, polyphenols, terpenes, coumarins, sulfur-containing compounds, and lectins—display a broad spectrum of antimicrobial activities through mechanisms such as disruption of cell walls and membranes, inhibition of efflux pumps, interference with quorum sensing, suppression of biofilm formation, and modulation of virulence factor expression (13).

Unlike single-target synthetic antibiotics, phytochemicals often exert their antimicrobial effects through simultaneous multi-target interactions, which can reduce the likelihood of resistance development (14). Furthermore, many plant-derived compounds exhibit synergistic interactions with conventional antibiotics, enhancing their efficacy against resistant strains and lowering the minimum inhibitory concentrations required for therapeutic action (15). This multi-pronged activity profile makes phytochemicals attractive as both stand-alone treatments and resistance-modifying adjuvants. Additionally, advances in extraction, purification, and formulation technologies are improving the pharmacokinetic profiles and bioavailability of these natural compounds, bringing them closer to clinical applicability (16).

The rationale for exploring plant-derived antimicrobials extends beyond their pharmacological potential. Many phytochemicals are biodegradable, renewable, and relatively low-cost, offering scalable solutions particularly suited to LMIC contexts where AMR burden is greatest (17). Moreover, plant-based approaches align with a broader shift toward “One Health” strategies, which integrate human, animal, and environmental health considerations into a unified framework for combating resistance. In this context, harnessing botanical diversity represents not only a scientific opportunity but also a socioeconomic imperative.

This review aims to provide a comprehensive synthesis of the current evidence on plant-derived phytochemicals as potential tools in the global fight against antimicrobial resistance. Specifically, it (i) examines the global AMR landscape and the underlying causes of resistance; (ii) explores the structural diversity and mechanistic basis of phytochemicals with antimicrobial activity; (iii) evaluates evidence for their synergistic interactions with conventional antibiotics; (iv) discusses clinical applications and progress in human trials; and (v) identifies key challenges—including purification, standardization, formulation, and regulatory considerations—along with future directions for research and development. Through this integrated perspective, the review seeks to inform strategies for leveraging phytochemicals as sustainable, effective, and complementary solutions in the post-antibiotic era.

METHODS

This review was conducted as a comprehensive narrative synthesis aimed at collating, analyzing, and critically evaluating current evidence on the potential of plant-derived phytochemicals to combat antimicrobial resistance (AMR). Given the complexity and interdisciplinary nature of the topic—spanning microbiology, pharmacology, natural product chemistry, and clinical sciences—a narrative approach was selected over a systematic review design to allow greater breadth and contextual depth in integrating diverse lines of evidence (1).

Search Strategy and Information Sources

A structured literature search was performed using major scientific databases including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. The search covered publications from January 2000 to June 2025 to capture both foundational discoveries and the latest developments in phytochemical research. Additional sources, such as reference lists of key articles, relevant book chapters, and reports from the World Health Organization (WHO) and United Nations Environment Programme (UNEP), were manually screened to ensure comprehensive coverage. Keywords and Boolean operators were used in various combinations, including “phytochemicals,” “plant-derived antimicrobials,” “antimicrobial resistance,” “efflux pump inhibitors,” “biofilm inhibition,” “synergy,” “antibiotic adjuvants,” and “clinical trials.”

Eligibility Criteria

The inclusion criteria focused on peer-reviewed publications and authoritative reports that addressed one or more of the following: (i) the antimicrobial activity of plant-derived compounds against clinically relevant pathogens; (ii) mechanistic insights into how these compounds modulate resistance determinants such as efflux pumps, biofilms, quorum sensing, or virulence factors; (iii) preclinical or clinical evaluation of phytochemicals either alone or in combination with conventional antibiotics; (iv) safety, toxicity, or pharmacokinetic considerations; and (v) regulatory and translational perspectives. Articles written in English and reporting original research, reviews, meta-analyses, or clinical data were included. Exclusion criteria were non-peer-reviewed sources (unless they were authoritative reports), conference abstracts without full data, and studies with incomplete methodology or unclear results.

Data Extraction and Synthesis

Relevant data from eligible studies were extracted independently by two reviewers and cross-verified for accuracy. Extracted information included study design, target microorganisms, type and source of phytochemicals, mechanisms of action, experimental models (in vitro, in vivo, or clinical), synergistic interactions with antibiotics, and reported safety outcomes. Special attention was given to studies that explored structure–activity relationships (SAR), pharmacokinetic properties, and formulation challenges, as these aspects are critical for clinical translation.

Given the narrative nature of this review, a formal risk-of-bias assessment was not performed. However, the strength of evidence was qualitatively evaluated based on study design (e.g., randomized controlled trials, in vivo animal studies, or in vitro assays), reproducibility of results, and relevance to clinical contexts. Findings were then thematically organized into sections reflecting major phytochemical classes, mechanisms of antimicrobial action, synergistic effects with antibiotics, clinical applications, safety considerations, and regulatory challenges.

Limitations

This narrative approach, while comprehensive, carries inherent limitations, including potential selection bias and the absence of meta-analytical quantification. The emphasis on English-language sources may have excluded relevant studies published in other languages. Nonetheless, the

broad and integrative methodology provides a robust synthesis of current knowledge and highlights critical research gaps in the development of phytochemicals as next-generation antimicrobial agents (2).

PHYTOCHEMICAL CLASSES AND STRUCTURAL DIVERSITY

Plant-derived phytochemicals represent a vast and chemically diverse group of bioactive compounds that have co-evolved as part of plants' defense mechanisms against pathogens, herbivores, and environmental stressors (1). This evolutionary complexity has resulted in an extraordinary range of molecular structures with antimicrobial, antioxidant, and immunomodulatory properties. Many of these secondary metabolites—classified broadly into alkaloids, phenolics, coumarins, terpenes, sulfur-containing compounds, and lectins—exert their effects through multi-target mechanisms that disrupt critical bacterial processes such as membrane integrity, protein synthesis, DNA replication, and quorum sensing (2). Their structural diversity and biochemical versatility not only provide a natural reservoir for novel antimicrobial agents but also offer valuable scaffolds for synthetic modification and drug development.

Alkaloids

Alkaloids are nitrogen-containing heterocyclic compounds produced by more than 300 plant families and are among the most pharmacologically active natural products (3). Historically, alkaloids such as morphine, quinine, and berberine have served as the basis for numerous therapeutic agents. Their antimicrobial properties arise from diverse mechanisms, including efflux pump inhibition, DNA intercalation, and enzyme inhibition (4).

One of the most studied alkaloids, berberine—isolated from *Berberis vulgaris*—has shown broad-spectrum activity against *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans*. Its mechanism involves inhibition of topoisomerase IV and DNA gyrase, intercalation into nucleic acids, and suppression of RNA polymerase activity (5). Piperine, derived from *Piper nigrum*, is another potent alkaloid known to inhibit efflux pumps, thereby sensitizing resistant bacterial strains to antibiotics such as ciprofloxacin and gentamicin (6). Similarly, quinoline alkaloids such as dictamnine and kokusagine inhibit type II topoisomerases, disrupting bacterial DNA replication (7).

Alkaloids are particularly valuable as resistance-modifying agents. Studies have demonstrated that combining piperine with β-lactams significantly reduces minimum inhibitory concentrations (MICs) against multidrug-resistant *S. aureus*, while tomatidine—an alkaloid from *Solanum* species—enhances aminoglycoside activity against *Enterococcus faecalis* and *Pseudomonas aeruginosa* (8). These synergistic interactions highlight the potential of alkaloids to extend the lifespan of existing antibiotics.

Phenolic Compounds and Polyphenols

Phenolic compounds—characterized by one or more hydroxyl groups attached to aromatic rings—represent one of the largest classes of plant secondary metabolites (9). They include simple phenolic acids, complex flavonoids, tannins, and quinones. Many phenolics display potent antimicrobial effects by altering membrane permeability, disrupting metabolic enzymes, inhibiting efflux pumps, and suppressing quorum sensing (10).

Flavonoids such as quercetin, catechin, and apigenin have shown inhibitory effects against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Mycobacterium tuberculosis* by disrupting membrane integrity and interfering with bacterial adhesion (11). Tannins, high-molecular-weight polyphenols, exert antimicrobial activity by precipitating microbial proteins, chelating metal ions essential for enzymatic activity, and intercalating into bacterial DNA (12). Quinones, another subgroup, can form stable complexes with microbial proteins, impairing their function and leading to cell death (13). Coumarins—a class of phenolic lactones—are particularly notable for their dual role as antimicrobials and resistance modulators. Compounds such as bergapten and esculetin inhibit efflux pumps and suppress biofilm formation, while others act as DNA gyrase inhibitors effective against *Helicobacter pylori* and methicillin-resistant *S. aureus* (MRSA) (14). Additionally, many phenolics enhance antibiotic efficacy. For example, epigallocatechin gallate from green tea restores β-lactam activity against MRSA by inhibiting β-lactamases and reducing cell wall integrity (15).

Sulfur-Containing Phytochemicals

Sulfur-containing compounds, including allicin, ajoene, and isothiocyanates, are widely distributed in the *Allium* and *Brassicaceae* families and exhibit potent antimicrobial activity against Gram-positive and Gram-negative pathogens (16). Allicin, produced enzymatically from alliin in crushed garlic (*Allium sativum*), inhibits bacterial thiol-containing enzymes, impairs protein and DNA synthesis, and disrupts membrane permeability (17). Ajoene enhances the activity of antibiotics against *Pseudomonas aeruginosa* and *Streptococcus agalactiae* by interfering with quorum sensing and inhibiting biofilm formation (18). Isothiocyanates, derived from glucosinolate hydrolysis in plants like *Raphanus sativus* and *Brassica* species, inhibit ATPases and increase membrane permeability, resulting in metabolic disruption and bacterial death (19). These sulfur compounds are especially effective against foodborne pathogens and have shown promise in reducing bacterial virulence in biofilm-associated infections.

Terpenes and Essential Oils

Terpenes, built from isoprene units, are among the most structurally diverse phytochemicals, encompassing monoterpenes, sesquiterpenes, diterpenes, and triterpenes (20). They are the major constituents of essential oils and are known for their broad-spectrum antimicrobial activity, often exerted through disruption of cell membranes, leakage of intracellular contents, and interference with ATP synthesis (21). Thymol and carvacrol, found in *Thymus vulgaris* and *Origanum vulgare*, respectively, increase membrane permeability and inhibit ATPase activity, leading to bacterial cell lysis (22). Cinnamaldehyde, a phenylpropanoid component of cinnamon oil, inhibits bacterial metabolism by interfering with ATP synthesis and glucose uptake (23). Terpenes also exhibit strong antibiofilm activity; for example, geraniol enhances antibiotic efficacy against *Acinetobacter baumannii* and disrupts biofilm formation by *Listeria monocytogenes* and *Klebsiella pneumoniae* (24). The complex mixtures in essential oils often provide synergistic effects superior to those of isolated components. Tea tree oil, composed of terpinen-4-ol, 1,8-cineol, and α-terpineol, has demonstrated potent activity against *S. aureus*, *E. coli*, and *Candida albicans*, even in multidrug-resistant strains (25).

Lectins and Polypeptides

Although less extensively studied, plant-derived lectins and antimicrobial peptides (AMPs) contribute significantly to innate plant defense and have shown potential against a range of pathogens (26). Lectins bind to bacterial cell wall carbohydrates, interfering with adhesion and invasion

processes, while AMPs disrupt membrane integrity through pore formation. Their broad-spectrum activity and low propensity for resistance development make them attractive candidates for therapeutic development (27).

MECHANISTIC INSIGHTS OF PLANT-DERIVED PHYTOCHEMICALS

Understanding the mechanisms by which plant-derived phytochemicals exert their antimicrobial effects is fundamental to harnessing their therapeutic potential against resistant pathogens. Unlike conventional antibiotics, which typically target a single molecular pathway, phytochemicals often act through **multi-target mechanisms**—disrupting essential cellular processes, weakening bacterial defenses, and potentiating the effects of existing drugs (1). This multi-faceted action not only enhances their antimicrobial spectrum but also reduces the likelihood of resistance development. The following sections summarize the principal mechanistic strategies through which phytochemicals counteract microbial survival and resistance.

Disruption of Cell Wall Biosynthesis

The bacterial cell wall is a primary target for many phytochemicals due to its vital role in structural integrity and protection against osmotic stress. Several phenolics, alkaloids, and quinones interfere with **peptidoglycan synthesis** by inhibiting key enzymes involved in the polymerization of *N*-acetylglucosamine and *N*-acetylmuramic acid, the building blocks of the bacterial cell wall (2). Flavonoids, such as apigenin and quercetin, have demonstrated the ability to bind membrane-associated proteins and enzymes, causing increased permeability and structural instability (3).

Electron microscopy studies show that the combination of flavonoids with β-lactams produces synergistic damage to the bacterial cell wall, leading to detachment of the outer membrane and collapse of the cytoplasmic structure (4). Quinones like anthraquinone from *Cassia italica* further enhance bactericidal activity by targeting cell wall integrity in species such as *Burkholderia pseudomallei* and *Corynebacterium pseudodiphtheriticum* (5). These interactions can sensitize bacteria to conventional antibiotics, overcoming resistance mechanisms based on altered cell wall permeability.

2. Membrane Permeabilization and ATPase Inhibition

The bacterial cell membrane is another critical target for phytochemicals, particularly terpenes, essential oils, and sulfur-containing compounds. Many of these compounds act as **membrane disruptors**, altering lipid bilayer fluidity and increasing permeability, which leads to leakage of cytoplasmic contents and metabolic collapse (6). Thymol and carvacrol, for instance, integrate into the lipid bilayer and create transient pores, resulting in loss of ions and metabolites (7).

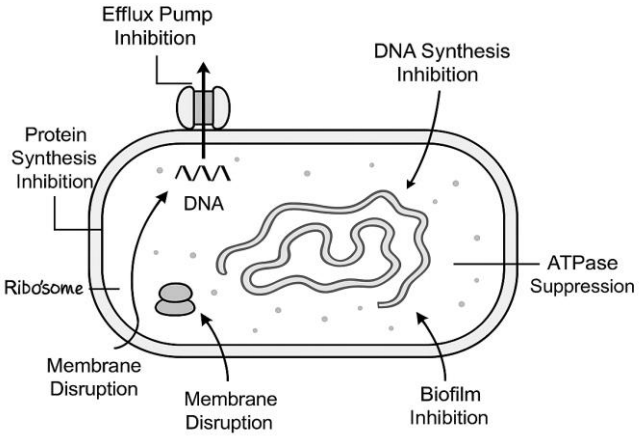

Figure 1 Mechanisms of Plant Derived Agents Targeting Bacterial Resistance

Beyond physical disruption, phytochemicals can also inhibit membrane-bound enzymes such as **ATPases**, which are essential for maintaining membrane potential and energy production. Cinnamaldehyde and catechins reduce intracellular ATP levels by blocking ATPase-dependent metabolic pathways and impairing glucose uptake (8). This dual mechanism—structural destabilization and metabolic inhibition—creates a hostile intracellular environment that can rapidly kill bacteria or enhance antibiotic susceptibility.

Essential oils from *Melaleuca alternifolia* (tea tree oil), composed of sesquiterpenes and monoterpenes, exemplify this effect by disrupting membrane integrity in *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans* (9). These effects are particularly valuable against multidrug-resistant (MDR) strains, where membrane impermeability is a common resistance mechanism.

Efflux Pump Inhibition and Modulation of Intracellular Targets

Efflux pumps are membrane transport proteins that actively expel antibiotics from bacterial cells, thereby reducing intracellular drug concentrations and contributing to multidrug resistance. Many alkaloids and polyphenols act as **efflux pump inhibitors (EPIs)**, reversing this resistance mechanism and restoring antibiotic efficacy (10). Piperine from *Piper nigrum* significantly decreases the minimum inhibitory concentrations (MICs) of fluoroquinolones against *Staphylococcus aureus* by inhibiting NorA efflux pump activity (11). Similarly, synthetic piperine analogues have demonstrated potent inhibition of NorA overexpressing strains, further confirming the role of alkaloids as resistance modulators (12).

Berberine also modulates efflux activity while simultaneously targeting multiple intracellular processes, including topoisomerase IV inhibition, DNA intercalation, and RNA polymerase suppression (13). These effects disrupt DNA replication, transcription, and protein synthesis—core processes essential for bacterial survival. Quinoline alkaloids such as kokusagine have shown similar effects by suppressing type II topoisomerase enzymes, leading to cell cycle arrest and death (14).

Quorum Sensing Interference and Virulence Suppression

Bacterial communication via quorum sensing (QS) is central to coordinating virulence, biofilm formation, and resistance development. Phytochemicals, particularly phenolics, terpenoids, and sulfur compounds, can disrupt this communication system by **inhibiting signal synthesis, blocking receptor binding, or degrading signaling molecules** (15). For example, ajoene from garlic inhibits quorum sensing-controlled gene expression in *Pseudomonas aeruginosa*, thereby reducing toxin production and pathogenicity (16). Coumarins and flavonoids can also modulate QS systems, leading to reduced biofilm formation and decreased expression of virulence factors such as capsular polysaccharides in *Staphylococcus aureus* and *Klebsiella pneumoniae* (17). These compounds weaken bacterial defense mechanisms without exerting direct selective pressure, potentially minimizing the emergence of resistant mutants.

Biofilm Inhibition and Disruption

Biofilms—structured microbial communities embedded in an extracellular polymeric matrix—are a major contributor to chronic infections and antibiotic tolerance. Many phytochemicals disrupt biofilm formation at **sub-inhibitory concentrations**, often by downregulating genes associated with adhesion, motility, and exopolysaccharide production (18). Trans-cinnamaldehyde, for example, reduces biofilm formation in *Vibrio spp.* by interfering with autoinducer-2-mediated quorum sensing (19). Geraniol, thymol, and essential oils from *Thymus vulgaris* and *Origanum vulgare* have demonstrated potent antibiofilm activity against *Klebsiella pneumoniae*, *Listeria monocytogenes*, *Escherichia coli*, and *Pseudomonas aeruginosa* (20). Importantly, these effects often occur without affecting planktonic growth, suggesting a targeted disruption of biofilm-specific pathways (21). This characteristic is highly desirable for managing device-associated infections and biofilm-related resistance.

Table 1. Plant-derived phytochemicals, their mechanisms of action, and clinical applications

Plant source (scientific name; common name)	Phytochemical class	Molecule name	Mechanism of action	Clinical / Antimicrobial applications	Ref.
Rauwolfia serpentina **(Indian snakeroot)**	Alkaloid	Reserpine	Efflux pump inhibitor (EPI)	Active against *Micrococcus* spp., *Streptococcus* spp., *Staphylococcus* spp.	(24)
Piper nigrum **(Black pepper)**	Alkaloid	Piperine	Efflux pump inhibition	Potentiates activity against *Staphylococcus aureus*	(25)
Berberis vulgaris **(Barberry)**	Alkaloid	Berberine	DNA synthesis and protein synthesis inhibition	Active against *Escherichia coli*, *Candida albicans*	(26)
Solanum lycopersicum **(Tomato) /** ***Berberis*** **spp.**	Steroidal alkaloid	Tomatidine	ATPase inhibition	Active against *Bacillus* spp., *Listeria* spp., *Staphylococcus* spp.	(27)
Camellia sinensis **(Tea plant)**	Phenolic compound	Chebulinic acid	DNA gyrase inhibition	Active against *Mycobacterium tuberculosis*	(28)
Camellia sinensis **(Tea plant)**	Flavonoid	Rhamentin	Efflux pump inhibition	Active against *Staphylococcus aureus*	(29)
Cedrus deodara **(Himalayan cedar)**	Flavonoid	Apigenin	D-alanine ligase inhibition	Active against *Escherichia coli*, *Helicobacter pylori*	(30)
Rubus ulmifolius **(Thornless blackberry)**	Sulfur-containing compound	Sulforaphane	Membrane permeability enhancement	Active against *Escherichia coli*	(31)
Allium sativum **(Garlic)**	Organosulfur compound	Allicin	DNA and protein synthesis inhibition	Active against *Staphylococcus epidermidis*, *Streptococcus agalactiae*, *Pseudomonas aeruginosa*	(32)
Raphanus sativus **(Radish)**	Isothiocyanate	Isothiocyanate	ATPase inhibition	Active against *Staphylococcus aureus*, *S. epidermidis*, *Bacillus subtilis*, *Enterococcus faecalis*, *Enterobacter aerogenes*, *Salmonella typhimurium*, *E. cloacae*, *E. coli*	(33)
Azadirachta indica **(Neem tree)**	Flavonoid	β-sitosterol	Cell wall/membrane modulation (proposed)	Used for urinary tract infections caused by MDR bacteria	(34)
Ferulago campestris **(Besser)**	Coumarin	Agasyllin	DNA gyrase inhibition	Active against *Staphylococcus aureus*, *Salmonella Typhi*, *Enterobacter aerogenes*, *Helicobacter pylori*, *Enterobacter cloacae*	(35)
Mesua ferrea **(Ceylon ironwood)**	Furanocoumarin	Bergamottin epoxide	NorA efflux pump inhibition	Active against methicillin-resistant *Staphylococcus aureus* (MRSA)	(36)
Thymus vulgaris **(Garden thyme)**	Monoterpene	Thymol	Efflux pump inhibition, ATPase inhibition, membrane disruption	Active against *Candida albicans*	

Synergistic Modulation of Antibiotic Activity

One of the most clinically significant features of phytochemicals is their ability to **enhance the efficacy of conventional antibiotics** through synergistic interactions. These synergistic effects occur through multiple mechanisms, including efflux pump inhibition, increased membrane permeability, enzyme inhibition, and suppression of resistance gene expression (22). For instance, geraniol potentiates β-lactam activity against MDR *Acinetobacter baumannii* by increasing cell wall permeability (23). Epigallocatechin gallate (EGCG) from green tea restores the activity of penicillin and ampicillin against MRSA by inhibiting β-lactamases and disrupting peptidoglycan synthesis (24). Similarly, tomatidine enhances the activity of aminoglycosides and fluoroquinolones against resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* (25). Such interactions reduce the required antibiotic dosage, lower toxicity risks, and extend the lifespan of existing therapies.

Modulation of Bacterial Stress Responses and Metabolism

Emerging evidence suggests that some phytochemicals exert their antimicrobial effects by modulating bacterial stress response pathways and metabolic processes. Certain polyphenols induce **oxidative stress** by increasing reactive oxygen species (ROS) production within bacterial cells, leading to macromolecular damage and apoptosis-like death (26). Others interfere with metabolic enzymes or nutrient acquisition systems, depriving bacteria of essential metabolites required for growth and virulence (27). These mechanisms represent an additional layer of antimicrobial activity that complements more direct bactericidal effects.

ANTIMICROBIAL SPECTRUM OF PHYTOCHEMICALS

The breadth of antimicrobial activity exhibited by plant-derived phytochemicals is remarkable, spanning Gram-positive and Gram-negative bacteria, fungi, parasites, and even viruses. This wide-ranging efficacy is primarily attributed to their structural diversity and multi-target mechanisms, which allow them to act against pathogens with varying cell wall architectures, metabolic profiles, and resistance determinants (1).

One of the most studied phytochemicals, **curcumin**—a polyphenolic compound derived from *Curcuma longa*—demonstrates potent antibacterial activity against both Gram-positive and Gram-negative species, including *Staphylococcus aureus*, *Escherichia coli*, and *Helicobacter pylori* (2). Curcumin not only inhibits bacterial growth but also suppresses quorum sensing and biofilm formation, enhancing its relevance in treating chronic and device-associated infections (3). Moreover, its efficacy extends to *Mycobacterium tuberculosis* and intracellular pathogens, where it disrupts signaling pathways crucial for virulence (4). Curcumin's antifungal and antiviral properties further highlight its potential as a broad-spectrum antimicrobial, effective against *Candida* species and various viral infections (5).

Essential oils represent another category with extensive antimicrobial activity. Components such as thymol, carvacrol, and eugenol have demonstrated effectiveness against a wide range of pathogens, including *Salmonella enterica*, *Vibrio parahaemolyticus*, *Listeria monocytogenes*, and *Enterococcus faecalis* (6). Essential oils often exhibit greater activity as complex mixtures than as individual components, suggesting synergistic interactions that enhance their antimicrobial potency (7). Notably, tea tree oil has been shown to inhibit *Candida albicans*, *S. aureus*, and *E. coli*, including strains resistant to conventional antibiotics (8).

Sulfur-containing compounds such as **allicin** and **isothiocyanates** further expand the antimicrobial spectrum. Allicin, produced by *Allium sativum*, inhibits a variety of Gram-positive and Gram-negative bacteria by targeting thiol-dependent enzymes and interfering with essential metabolic pathways (9). Isothiocyanates, generated from glucosinolate hydrolysis in cruciferous vegetables, have shown strong activity against foodborne pathogens like *Staphylococcus aureus*, *Enterobacter cloacae*, and *Salmonella typhimurium* (10).

A particularly notable example of phytochemical diversity in action is **Azadirachta indica** (neem), which exhibits antibacterial, antifungal, antiviral, and antiparasitic properties. Neem extracts target both planktonic and biofilm-associated bacteria, including multidrug-resistant *S. aureus* and *Pseudomonas aeruginosa*, and inhibit fungal pathogens such as *Aspergillus fumigatus* (11). Its broad antimicrobial spectrum has also been linked to anti-virulence activities, including suppression of toxin production and modulation of host immune responses (12).

The diversity of antimicrobial targets—ranging from cell wall synthesis and efflux pump inhibition to virulence regulation—underscores the versatility of phytochemicals as both primary therapeutics and adjunctive agents. Their activity against resistant, biofilm-forming, and intracellular pathogens suggests a wide range of potential clinical applications, from wound infections and respiratory diseases to urinary tract infections and gastrointestinal illnesses. Furthermore, their activity across kingdoms (bacteria, fungi, viruses, and parasites) positions them as promising candidates for integrated anti-infective strategies.

SYNERGISTIC EFFECTS WITH CONVENTIONAL ANTIBIOTICS)

One of the most promising aspects of plant-derived phytochemicals is their ability to act synergistically with conventional antibiotics, enhancing efficacy against resistant pathogens while potentially reducing required dosages and associated toxicity (13). This synergism arises from complementary mechanisms—such as efflux pump inhibition, increased membrane permeability, β-lactamase suppression, and interference with resistance gene expression—that together overcome bacterial defense systems.

Several studies have documented dramatic reductions in the minimum inhibitory concentrations (MICs) of antibiotics when combined with phytochemicals. For instance, the combination of β-lactams with α-mangostin, a xanthone from *Garcinia mangostana*, significantly restores β-lactam activity against resistant *S. aureus* by inhibiting β-lactamase enzymes (14). Similarly, **epigallocatechin gallate (EGCG)** from green tea has been shown to resensitize MRSA strains to β-lactam antibiotics by disrupting cell wall integrity and inhibiting penicillin-binding protein activity (15).

Alkaloids also play a crucial role in synergy. Tomatidine enhances the bactericidal activity of aminoglycosides such as gentamicin and amikacin against *Enterococcus faecalis* and *Pseudomonas aeruginosa* (16). Piperine enhances fluoroquinolone activity against *S. aureus* by inhibiting NorA efflux pumps, resulting in significantly lower MICs (17). Moreover, conessine restores the activity of rifampicin and novobiocin against resistant *Acinetobacter baumannii* strains (18). Phenolic compounds also exhibit synergy with antibiotics. Nalidixic acid combined with extracts of *Camellia sinensis* significantly lowers the MIC against *Salmonella typhi*, while isoflavones from *Lupinus argentens* inhibit efflux mechanisms and enhance the intracellular accumulation of berberine and norfloxacin (19). Similarly, plant-derived pyridine compounds potentiate the activity of fluoroquinolones against *S. aureus* by inhibiting NorA efflux (20). These synergistic effects are not limited to antibacterial therapies. Combinations of phytochemicals and antifungals have also shown enhanced activity. Essential oils from *Agastache rugosa* and *Pelargonium graveolens* significantly increase the antifungal effects of ketoconazole and amphotericin B against *Aspergillus* species (21).

The clinical implications of these findings are substantial. Synergistic phytochemical–antibiotic therapies may allow lower antibiotic dosages, thereby reducing side effects and slowing the emergence of resistance. They may also broaden the spectrum of antibiotic activity, enabling older drugs to remain clinically relevant. However, the translation of in vitro synergy into clinical efficacy requires careful evaluation of pharmacokinetics, pharmacodynamics, and potential drug–drug interactions. Factors such as absorption, distribution, metabolism, and elimination must be considered, as phytochemicals can modulate the activity of cytochrome P450 enzymes or drug transporters, potentially altering antibiotic bioavailability (22).

CLINICAL APPLICATIONS AND HUMAN TRIALS

Despite their promising preclinical efficacy, only a small fraction of phytochemicals have progressed to clinical evaluation. Nevertheless, several plant-derived compounds have demonstrated safety and therapeutic potential in human studies, particularly in treating urinary tract infections (UTIs), gastrointestinal infections, respiratory diseases, and wound infections (23).

Urinary Tract Infections (UTIs):

Arctostaphylos uva-ursi (bearberry) is widely used in Europe for UTI management. Its active compound, arbutin, is hydrolyzed in vivo to hydroquinone, which exerts antimicrobial activity in the urinary tract (24). Clinical trials (e.g., NCT03151603) have demonstrated its efficacy in reducing UTI recurrence, although long-term use is limited by potential hydroquinone toxicity. Similarly, *Juniperus communis* extracts, rich in terpenoids, exhibit both diuretic and antibacterial effects, offering symptomatic relief and microbial clearance (25). Cranberry (*Vaccinium*

macrocarpon) and blueberry (*Vaccinium myrtillus*), both rich in proanthocyanidins and tannins, prevent bacterial adhesion to uroepithelial cells, thereby reducing infection recurrence (26).

Gastrointestinal Infections:

Berberis vulgaris (barberry) alkaloids, particularly berberine, have been extensively studied for gastrointestinal infections, including *Vibrio cholerae*-associated diarrhea and *Helicobacter pylori* infection (27). Clinical trials have shown berberine to be as effective as, or superior to, standard antibiotics in treating acute diarrhea, often with fewer side effects (28). Combination therapies incorporating berberine with streptomycin or chloramphenicol have demonstrated improved cure rates for bacillary dysentery and gastroenteritis (29).

Respiratory and ENT Infections:

Eucalyptus viminalis (white gum) yields eucalimin, a triterpenoid with activity against Gram-positive bacteria implicated in pharyngitis, laryngitis, and sinusitis (30). Clinical studies report significant symptom reduction and microbial clearance in patients treated with eucalimin-based formulations, particularly against *Streptococcus pneumoniae* and *Staphylococcus aureus* (31).

Wound and Skin Infections:

Sanguiritrin, an alkaloid mixture from *Macleaya cordata* and *M. microcarpa*, has shown efficacy against Gram-positive and Gram-negative bacteria, including MDR strains, in the treatment of wound infections and acute intestinal infections (32). Its mechanism—disruption of bacterial cell walls and nucleic acids—renders it effective even where conventional antibiotics fail (33). While these examples demonstrate significant clinical promise, several challenges remain. Standardization of plant extracts, variability in bioactive compound concentrations, and inconsistent dosing regimens have limited reproducibility and regulatory approval (34). Furthermore, many clinical studies are small, lack randomized controlled designs, or fail to report pharmacokinetic and toxicity data comprehensively. Addressing these limitations through rigorously designed clinical trials is essential to translating phytochemical research into therapeutic reality.

SAFETY, TOXICOLOGY, AND PHARMACOKINETICS

The therapeutic promise of phytochemicals is closely tied to their safety profile, which is generally favorable compared to many synthetic antimicrobials. Nevertheless, ensuring safety, understanding toxicological boundaries, and optimizing pharmacokinetic properties are essential prerequisites for their successful clinical translation. Although many plant-derived compounds have centuries of traditional use supporting their biocompatibility, rigorous scientific evaluation remains crucial to address variability, dose dependence, and potential interactions with conventional drugs (1).

Toxicity Profiles and Dose Dependence

Most phytochemicals exhibit **low acute toxicity** at therapeutic doses. However, toxicity is often dose-dependent, and some compounds can cause adverse effects when consumed in excessive amounts or over prolonged periods. For instance, **berberine**, despite its broad-spectrum antimicrobial activity, has been associated with gastrointestinal disturbances, hypotension, and potential hepatotoxicity at high doses (2). **Allicin**, a potent sulfur compound, may induce hemolysis or liver toxicity in sensitive individuals if consumed in large quantities (3). Similarly, **isothiocyanates**, though effective antimicrobials, can cause irritation of mucosal membranes and gastrointestinal discomfort when concentrated beyond physiological levels (4).

In addition, certain phytochemicals generate **reactive oxygen species (ROS)** as part of their antimicrobial mechanism. While beneficial for pathogen clearance, excessive ROS can cause collateral damage to host tissues. Polyphenols like quercetin and catechins are generally safe but can exert pro-oxidant effects at supraphysiological doses, potentially leading to oxidative stress (5).

Drug–Drug and Herb–Drug Interactions

Herb–drug interactions are a significant safety consideration, particularly for patients receiving polypharmacy. Many phytochemicals modulate cytochrome P450 (CYP) enzymes and drug transporters, thereby altering the pharmacokinetics of co-administered medications (6). For example, **piperine** inhibits CYP3A4 and P-glycoprotein, increasing the bioavailability of various drugs but potentially causing toxicity when combined with narrow-therapeutic-index agents such as anticoagulants or immunosuppressants (7). **St. John's wort**, though not primarily antimicrobial, induces CYP3A4 and reduces the efficacy of antibiotics and antiviral drugs (8). Such interactions necessitate careful clinical evaluation and patient counseling.

Pharmacokinetics and Bioavailability Challenges

Despite their potent bioactivity, many phytochemicals suffer from **poor pharmacokinetic profiles**, including low aqueous solubility, rapid metabolism, poor absorption, and short half-lives. Curcumin, for example, exhibits low oral bioavailability due to extensive first-pass metabolism and rapid systemic elimination (9). Strategies such as **nanoformulations, liposomal encapsulation, self-emulsifying drug delivery systems (SEDDS), and cyclodextrin inclusion complexes** have shown promise in enhancing solubility, stability, and systemic availability (10). Combination approaches also improve pharmacokinetics. Co-administration of piperine with curcumin, for example, increases curcumin bioavailability by up to 2000% by inhibiting glucuronidation (11). Similarly, micelle-based encapsulation of polyphenols significantly improves their intestinal absorption and plasma concentration, enabling more consistent therapeutic effects (12).

Safety Assessments and Preclinical Evaluation

Comprehensive preclinical safety assessments—including acute, sub-chronic, and chronic toxicity studies—are critical before clinical translation. Evaluations typically include hematological, biochemical, and histopathological analyses to assess systemic effects. Genotoxicity, mutagenicity, teratogenicity, and carcinogenicity testing are also recommended, particularly for long-term use scenarios (13). Additionally, in vitro and in vivo pharmacokinetic profiling, including absorption, distribution, metabolism, and excretion (ADME) studies, is essential for establishing safe dosage ranges and optimizing therapeutic regimens.

REGULATORY AND MANUFACTURING CONSIDERATIONS

The successful translation of phytochemicals from laboratory research to clinical therapeutics requires careful navigation of complex regulatory and manufacturing landscapes. Regulatory requirements vary globally, but common challenges include ensuring product quality, standardization, reproducibility, and safety while meeting the rigorous documentation standards required for market approval (14).

Classification and Regulatory Pathways

Phytochemicals may be classified as **dietary supplements, botanical drugs, or pharmaceutical agents** depending on their composition, intended use, and claims. In the United States, the Food and Drug Administration (FDA) regulates botanical drugs under the same framework as synthetic pharmaceuticals if they are intended for therapeutic use (15). The European Medicines Agency (EMA) employs similar guidelines, with the Committee on Herbal Medicinal Products (HMPC) overseeing the evaluation of herbal medicinal products based on quality, safety, and efficacy data (16).

Products marketed as dietary supplements or traditional medicines face less stringent requirements but cannot make therapeutic claims without clinical evidence. However, this regulatory flexibility is a double-edged sword: while it facilitates market entry, it can also lead to inconsistent quality and variable efficacy among commercially available products (17).

Standardization and Quality Control

One of the greatest challenges in phytochemical development is **batch-to-batch variability** due to differences in plant genetics, growing conditions, harvesting times, and extraction methods. Standardization—ensuring consistent concentrations of active compounds—is critical for reproducibility and regulatory approval (18). Techniques such as **high-performance liquid chromatography (HPLC)**, **liquid chromatography–mass spectrometry (LC-MS)**, and **nuclear magnetic resonance (NMR)** are routinely employed for quality control and quantification of marker compounds (19).

Moreover, contaminants such as heavy metals, pesticides, and microbial residues must be monitored and eliminated to meet Good Manufacturing Practice (GMP) standards. The use of authenticated plant materials, traceable supply chains, and validated extraction processes are essential for ensuring safety and efficacy (20).

Intellectual Property and Commercialization

Intellectual property (IP) protection can be complex for phytochemicals, especially those derived from traditional medicine. While naturally occurring compounds cannot be patented in their raw form, novel formulations, extraction methods, and synthetic analogues can be protected (21). Strategic IP management is crucial for attracting investment and encouraging industrial development.

Global Harmonization and Future Trends

The lack of harmonization among regulatory agencies poses challenges for international commercialization. Efforts such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals (ICH) and the WHO's Traditional Medicine Strategy aim to establish global standards, but discrepancies remain (22). As evidence supporting the clinical efficacy of phytochemicals grows, regulatory frameworks are evolving to accommodate botanical therapeutics within mainstream drug development pathways.

CURRENT CHALLENGES AND FUTURE DIRECTIONS

Despite promising evidence, significant challenges must be addressed before phytochemicals can be fully integrated into mainstream antimicrobial therapy. These challenges span scientific, technological, regulatory, and economic domains.

Scientific and Technical Barriers

One major limitation is the **complexity of plant extracts**, which often contain dozens or even hundreds of bioactive components. This complexity makes it difficult to identify the primary active compounds, elucidate their mechanisms, and predict pharmacological outcomes (23). Advanced analytical techniques, such as metabolomics, proteomics, and network pharmacology, are increasingly employed to deconvolute these complex mixtures and identify key therapeutic constituents (24).

Another challenge lies in **structure–activity relationship (SAR)** optimization. Many phytochemicals have suboptimal potency or bioavailability, requiring chemical modification to enhance their antimicrobial efficacy. Semi-synthetic derivatives and analogues offer a promising path forward, combining the structural diversity of natural products with the potency of synthetic drugs (25).

Standardization and Reproducibility

Lack of standardization remains a significant obstacle. Variations in plant sourcing, cultivation, extraction, and processing can lead to inconsistent therapeutic effects (26). Establishing validated protocols, reference standards, and international quality benchmarks will be crucial for building confidence among clinicians and regulators.

Clinical Evidence and Translational Gaps

While preclinical studies abound, **robust clinical trials** are relatively scarce. Many existing studies are small, observational, or lack rigorous controls. Large-scale, randomized controlled trials (RCTs) are needed to establish efficacy, safety, dosing, and pharmacokinetics in diverse patient populations (27). Furthermore, understanding how phytochemicals perform in combination with standard antibiotics in real-world clinical scenarios remains a priority.

Economic and Commercial Considerations

Pharmaceutical companies often view phytochemicals as commercially less attractive due to challenges in intellectual property protection, standardization, and profitability (28). Public–private partnerships, government incentives, and global initiatives—such as the WHO's Global AMR Action Plan—could help overcome these barriers by supporting research, funding clinical trials, and creating regulatory incentives.

Future Perspectives

The integration of **artificial intelligence (AI)** and machine learning (ML) into natural product drug discovery offers exciting opportunities for accelerating phytochemical research. AI-based modeling can predict bioactivity, optimize lead compounds, and identify synergistic combinations with existing antibiotics (29). Advances in synthetic biology and metabolic engineering may also enable the scalable production of rare phytochemicals in microbial or plant-based systems, overcoming supply constraints (30). In the near future, phytochemicals are likely to play a dual role: as **stand-alone therapeutics** for specific infections and as **resistance-modifying adjuvants** that extend the lifespan of conventional antibiotics. Their integration into precision medicine approaches—tailored to individual microbiomes, infection types, and resistance profiles—could revolutionize antimicrobial therapy.

CONCLUSION

Antimicrobial resistance represents one of the most pressing global health challenges of the 21st century, threatening to render once-curable infections untreatable and undermine decades of medical progress. Plant-derived phytochemicals offer a compelling and multifaceted solution to this crisis. Their chemical diversity, multi-target mechanisms, synergistic potential with existing antibiotics, and generally favorable safety profiles make them promising candidates for the development of next-generation antimicrobial agents. -From disrupting bacterial membranes and inhibiting efflux pumps to interfering with quorum sensing and biofilm formation, phytochemicals act on multiple fronts, weakening bacterial defenses and restoring drug susceptibility. Moreover, their broad-spectrum activity, demonstrated synergy with conventional antibiotics, and emerging clinical evidence underscore their translational potential. However, realizing this potential will require overcoming significant challenges, including standardization, bioavailability enhancement, regulatory harmonization, and the execution of large-scale clinical trials. As the world enters a post-antibiotic era, phytochemicals stand at the forefront of innovative antimicrobial strategies. By bridging traditional knowledge with modern scientific advances, they offer not only new therapeutic options but also a sustainable, accessible, and globally relevant approach to combating drug-resistant infections. Their integration into mainstream antimicrobial therapy could transform the future of infectious disease management and help avert the looming threat of a global AMR catastrophe.

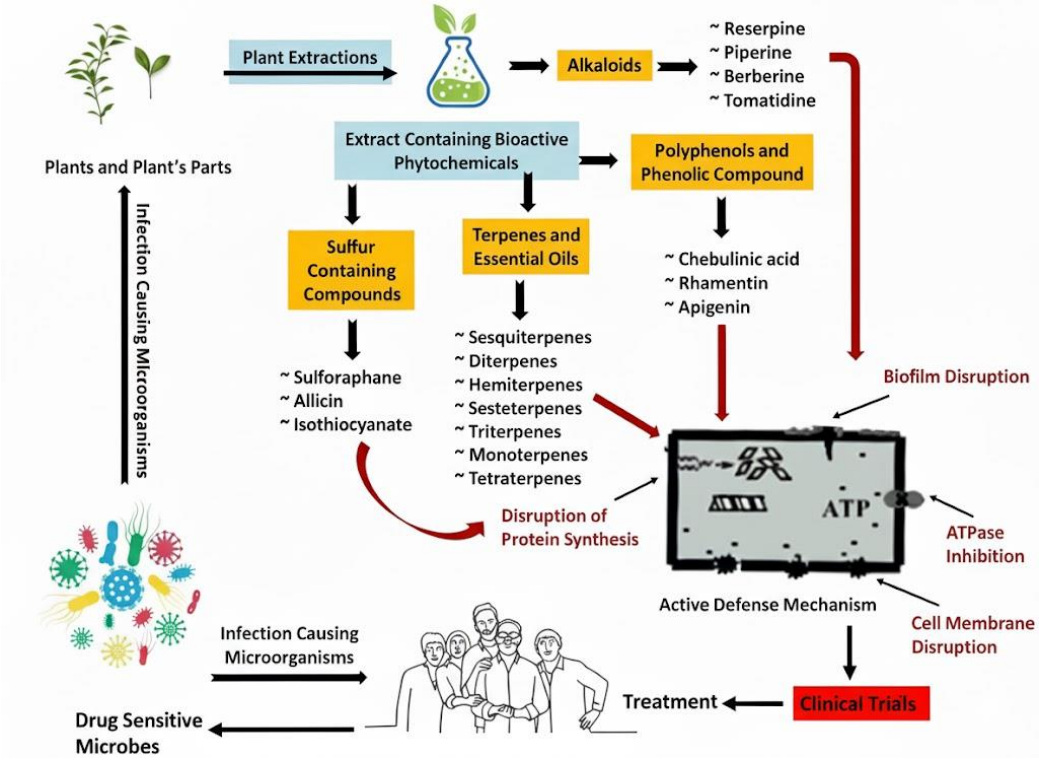

Figure 2 Graphical Abstract; Mapping the multi-target, antimicrobial action of phytochemicals from plants to the clinic.

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