PLANT-DERIVED THERAPEUTICS AS A NOVEL STRATEGY TO COMBAT ANTIMICROBIAL RESISTANCE: CURRENT ADVANCES AND FUTURE PERSPECTIVE

Deeksha Rathor, Pushpendra Kumar, Km. Neha, Km Mohinee, Prachi Kushwaha

Department of Pharmacology, Faculty Of Pharmacy, Uttar Pradesh University of Medical Sciences, Saifai , Etawah 206130, Uttar Pradesh, India

Abstract

Antimicrobial resistance (AMR) has emerged as one of the most critical global public health challenges of the 21st century, significantly compromising the effectiveness of conventional antibiotics and increasing morbidity, mortality, and healthcare costs worldwide. In this context, plant-derived therapeutics have gained considerable scientific attention owing to their diverse bioactive phytoconstituents and broad-spectrum antimicrobial potential. Medicinal plants contain a wide range of secondary metabolites, including alkaloids, flavonoids, terpenoids, phenolic compounds, tannins, saponins, and essential oils, which exhibit antimicrobial activity through multiple mechanisms, such as disruption of microbial cell membranes, inhibition of biofilm formation, suppression of quorum sensing, modulation of efflux pumps, and interference with nucleic acid and protein synthesis. Additionally, synergistic combinations of phytochemicals with conventional antibiotics have demonstrated promising potential for enhancing antibiotic activity and overcoming specific resistance mechanisms. This review comprehensively discusses recent advances in plant-derived antimicrobial agents, their mechanisms of action, activity against MDR pathogens, antibiotic-adjuvant potential, and emerging technological approaches for improving their therapeutic efficacy. Overall, plant-derived therapeutics represent a promising and sustainable avenue for the discovery and development of complementary antimicrobial strategies to address the growing global burden of AMR.

Keywords: *Antimicrobial resistance; Plant-derived therapeutics; Phytochemicals; Multidrug-resistant bacteria; Antibiotic synergy; Drug discovery*

Corresponding Author

Dr. Pushpendra Kumar

Received: 06/08/2026
Revised: 11/08/2026
Accepted: 30/08/2026
DOI: http://doi.org/10.66204/GJPSR-1337-2026-2-9-1

How to Cite

Kumar P, Rathor D, Neha K, Mohinee K, Kushwaha P. Plant-Derived Therapeutics as a Novel Strategy to Combat Antimicrobial Resistance: Current Advances and Future Perspective. Global Journal of Pharmaceutical and Scientific Research. 2026;2(9):1337-1365. ISSN: 3108-0103. http://doi.org/10.66204/GJPSR-1337-2026-2-9-1.

1. Introduction

Antimicrobial resistance (AMR) has become a major global public health concern, threatening the effective prevention and treatment of infectious diseases. When germs develop the capacity to endure or multiply in the presence of antimicrobial drugs that were previously effective against them, antimicrobial resistance (AMR) results. Inappropriate and excessive use of antibiotics, poor infection prevention and control, poor sanitation, and the spread of resistant microorganisms through healthcare, community, agricultural, and environmental settings have all contributed to the rapid progression of antimicrobial resistance, despite the fact that it is a natural evolutionary phenomenon (Prestinaci et al., 2015; World Health Organization, 2023).

1.1 Global Mortality and Burden

AMR has significant economical and health repercussions. According to a global systematic review, bacterial AMR was linked to almost 4.95 million fatalities globally in 2019 and directly caused around 1.27 million deaths (Murray et al., 2022). Treatment failure, extended hospital stays, higher medical expenses, and increased morbidity and death are all consequences of resistant infections. Additionally, the safety of medical treatments that depend on efficient antimicrobial treatment, such major surgery, organ transplantation, and cancer chemotherapy, is threatened by the increasing incidence of resistant microorganisms (World Health Organization, 2023). The scarcity of recently discovered antibiotics against a number of clinically significant resistant bacteria exacerbates the issue and emphasises the critical need for complementary and alternative antimicrobial approaches (World Health Organization, 2024).

By identifying resistant bacterial diseases that require immediate research and development attention, the WHO Bacterial Priority diseases List 2024 highlights the gravity of this problem. Carbapenem-resistant Acinetobacter baumannii, resistant Enterobacterales, rifampicin-resistant Mycobacterium TB, and resistant strains of Pseudomonas aeruginosa and Staphylococcus aureus are some of the most worrisome species (World Health Organization, 2024). The quest for new sources of anti-infective medicines has become more intense due to the longevity of these diseases and the restricted antibacterial pipeline.

One of the most promising sources for the development of antibacterial drugs is natural ingredients. A wide range of structurally varied secondary metabolites, such as alkaloids, flavonoids, phenolic compounds, tannins, terpenoids, saponins, and quinones, are found in medicinal plants, which have historically been utilised to treat infectious disorders (Atanasov

et al., 2021). Through a variety of mechanisms, such as disruption of microbial membranes, inhibition of vital enzymes, interference with nucleic acid synthesis, modulation of quorum sensing, and inhibition of biofilm formation, these phytoconstituents may have antimicrobial effects (Cushnie and Lamb, 2011; Silva et al., 2016). In the setting of AMR, where distinct resistance pathways may jeopardise traditional treatments, the capacity of chemicals originating from plants to act on diverse microbial targets is very pertinent.

Plant-derived chemicals have garnered significant attention as possible antibiotic adjuvants due to their direct antibacterial action. By increasing bacterial membrane permeability, blocking efflux pumps, rupturing biofilms, interfering with resistance-associated enzymes, or altering bacterial virulence mechanisms, some phytochemicals can increase the activity of conventional antibiotics (Silva et al., 2016; Cheesman et al., 2017). These synergistic strategies may offer a chance to increase the therapeutic value of already available antibiotics while lowering dependency on the ongoing creation of completely new antimicrobial classes.

The clinical translation of plant-derived medicines is still difficult, despite these encouraging results. Antimicrobial efficacy and repeatability can be significantly impacted by variations in plant species, geographic origin, growth circumstances, extraction techniques, phytochemical makeup, and formulation. Furthermore, before promising phytochemicals or plant extracts can be turned into dependable medicinal solutions, concerns pertaining to bioavailability, pharmacokinetics, toxicity, standardisation, and clinical effectiveness require comprehensive exploration (Atanasov et al., 2021). Therefore, the discovery of plant-derived antimicrobial agents and antibiotic-adjuvant therapy may be facilitated by combining traditional knowledge with contemporary pharmacological, phytochemical, molecular, and formulation methodologies.

In this regard, plant-derived medicines are a promising and crucial tactic in the worldwide fight against AMR. The main bioactive components and mechanisms of action of plant-derived antimicrobial agents, their potential against resistant pathogens, their synergistic interactions with conventional antibiotics, recent formulation and delivery methods, current obstacles, and future prospects for their development as clinically relevant interventions against antimicrobial resistance are all summarised in this review.

1.2 Factors Contributing to the Rise of Antimicrobial Resistance

A complex interplay of biological, clinical, environmental, agricultural, and socioeconomic variables is responsible for the genesis and quick spread of antimicrobial resistance. Although genetic diversity and selection cause bacteria to naturally acquire resistance, human activity

has significantly sped this process. Developing successful methods to stop the spread of resistant infections requires an understanding of these key elements (Prestinaci et al., 2015; World Health Organization, 2023).

- **Inappropriate and Excessive Use of Antimicrobials:** The inappropriate prescription and excessive use of antibiotics are among the major drivers of AMR. Unnecessary antibiotic therapy, inappropriate drug selection, incorrect dosage, and prolonged treatment can exert selective pressure on microbial populations, allowing resistant organisms to survive and proliferate (Laxminarayan et al., 2013; World Health Organization, 2023). Self-medication and the use of antibiotics without professional guidance further contribute to inappropriate antimicrobial exposure.
- **Poor Antimicrobial Stewardship:** Inadequate antimicrobial stewardship in healthcare settings can promote the unnecessary use of broad-spectrum antibiotics. Failure to follow evidence-based prescribing practices, insufficient diagnostic support, and inappropriate empirical therapy may increase antimicrobial selection pressure and facilitate the emergence of resistant strains (World Health Organization, 2023).
- **Healthcare-Associated Transmission:** Hospitals and other healthcare facilities provide favorable conditions for the transmission of resistant microorganisms because of high antimicrobial use, frequent invasive procedures, prolonged hospitalization, and the presence of vulnerable patients. Inadequate hand hygiene, insufficient infection-control practices, and poor environmental sanitation can facilitate the transmission of MDR pathogens between patients and healthcare workers (Allegranzi et al., 2017).
- **Agricultural and Veterinary Use:** The extensive use of antimicrobials in livestock, poultry, and aquaculture for therapeutic, prophylactic, and, in some settings, growth-promoting purposes can contribute to the selection of resistant microorganisms. Resistant bacteria and resistance genes may subsequently spread between animals, humans, food products, and the environment, making antimicrobial resistance a significant One Health concern (McEwen and Collignon, 2018; World Health Organization, 2023).
- **Environmental Contamination:** Antimicrobial residues and resistant microorganisms can enter soil and water systems through pharmaceutical and hospital waste, wastewater, agricultural runoff, and inadequately treated sewage. These environments can act as reservoirs and potential transmission routes for antimicrobial

resistance genes, facilitating their persistence and dissemination among microbial populations (Berendonk et al., 2015).

- **Inadequate Infection Prevention and Sanitation:** Poor sanitation, inadequate access to clean water, overcrowding, and insufficient infection-prevention measures increase the transmission of infectious diseases and consequently the demand for antimicrobial treatment. Weak infection-control systems therefore indirectly contribute to the selection and spread of resistant microorganisms (World Health Organization, 2023).
- **Limited Diagnostic Capacity:** In many healthcare settings, particularly where diagnostic facilities are limited, antimicrobial treatment is initiated empirically without identification of the causative pathogen or its susceptibility profile. Such practices may result in unnecessary or inappropriate antimicrobial exposure and increase the selective pressure favoring resistant organisms (World Health Organization, 2023).
- **Limited Development of New Antimicrobial Agents:** The emergence of resistance has progressed faster than the development and introduction of new antimicrobial therapies. Scientific challenges, high costs of research and development, regulatory barriers, and limited commercial incentives have contributed to a relatively restricted antimicrobial pipeline, creating a widening gap between the emergence of resistant pathogens and the availability of effective treatment options (World Health Organization, 2024).

Collectively, these factors create strong selective pressures that favor the survival, persistence, and transmission of resistant microorganisms. Consequently, controlling AMR requires a coordinated approach involving antimicrobial stewardship, improved infection prevention, responsible antimicrobial use in agriculture, environmental management, rapid diagnostics, surveillance, and the development of novel therapeutic strategies, including plant-derived antimicrobial agents (McEwen and Collignon, 2018; World Health Organization, 2023).

1.3 Antimicrobial Resistance: Current Scenario

Antimicrobial resistance (AMR) has emerged and spread quickly, posing a serious threat to contemporary healthcare. Infections that are more challenging to cure are increasingly linked to resistant germs, which can lead to longer illnesses, treatment failure, greater healthcare expenses, and higher death. Because multidrug-resistant pathogens reduce the efficacy of routinely used antimicrobial medicines and limit accessible therapy choices, the worldwide

burden of bacterial infections is especially alarming (Murray et al., 2022). There is a significant gap between the appearance of resistant diseases and the availability of effective therapies due to the ongoing spread of resistance and the sluggish development of new antimicrobial medicines (World Health Organization, 2024).

1.3.1 Recognition and Urgency by WHO

The World Health Organization (WHO), which views antimicrobial resistance (AMR) as one of the key global public health problems needing concerted action, has officially acknowledged the gravity of AMR. Antimicrobial resistance can jeopardise the management of infections related to surgery, cancer therapy, transplantation, and other cutting-edge medical operations, according to the World Health Organization (WHO, 2023). By identifying resistant bacterial pathogens for which research and development of novel antimicrobial therapies are especially crucial, the WHO Bacterial Priority Pathogens List 2024 further emphasises the seriousness of the issue (World Health Organization, 2024).

. The increasing variety and complexity of resistant bacterial diseases cannot be adequately addressed by the present pipeline for antibiotic development. There is an urgent need for new treatment methods since a number of clinically significant diseases have developed resistance to several antimicrobial classes, increasing reliance on older or last-resort medications (World Health Organization, 2024). As a result, alternative antimicrobial strategies such as antimicrobial peptides, bacteriophages, nanoparticles, immunotherapeutics, and bioactive chemicals produced from medicinal plants are receiving more attention in research (Atanasov et al., 2021; Silva et al., 2016).

1.3.2 Projected Impact and Future Threat

If successful treatments are not put in place, it is anticipated that AMR will continue to have a significant impact in the future. According to global modelling studies, AMR may be responsible for millions of deaths per year by 2050, with the burden coming from both direct resistance-related mortality and fatalities linked to resistant diseases (O'Neill, 2016). Additionally, more recent worldwide evaluations have shown that AMR currently accounts for a significant death burden, highlighting the fact that the issue is an existing global health catastrophe rather than just a potential future concern (Murray et al., 2022).

The need for creative and long-lasting treatment approaches is underscored by the rising incidence of resistant diseases, the paucity of antibiotic discoveries, and the ongoing transmission in healthcare, community, agricultural, and environmental contexts. Because of their chemical diversity, variety of biological targets, and capacity to function as either direct

antimicrobial agents or as adjuvants to traditional antibiotics, plant-derived bioactive chemicals constitute an important field of study in this regard. Therefore, investigating these substances may aid in the creation of additional strategies for controlling and preventing diseases brought on by microbes resistant to antibiotics.

1.4 Medicinal Plants as a Source of Antimicrobial Agents: Historical Perspective

Long before contemporary antimicrobial medications were discovered, medicinal plants were a significant source of therapeutic compounds in ancient civilisations. Plant elements including leaves, roots, bark, seeds, flowers, and resins have been used by traditional medicinal systems, such as Ayurveda, Traditional Chinese Medicine, and other indigenous healing techniques, to treat infections and other illnesses. Plants were first used medicinally based on empirical observations and collected traditional knowledge, which later served as a crucial basis for contemporary natural-product research (Petrovska, 2012).

As microbiology and pharmacognosy advanced in the late 19th and early 20th centuries, the antibacterial potential of therapeutic plants attracted scientific interest. Researchers looked into the chemical components and mechanisms of action of plant extracts after discovering that a number of species have inhibitory efficacy against pathogenic bacteria. Following the discovery of bioactive natural products, it was shown that plants may produce structurally varied compounds with important pharmacological characteristics (Cowan, 1999; Atanasov et al., 2021).

The discovery of naturally occurring antimicrobial chemicals, such as quinine from Cinchona species and later a number of additional plant-derived molecules with therapeutically significant biological activity, was a significant turning point in the history of antimicrobial medicine. Even if synthetic and microbiological sources eventually took over the antibiotic era, medicinal plants remained important sources for drug development. The discovery of several pharmacologically active natural products proved that contemporary chemical and pharmacological techniques may be integrated with traditional medical expertise to find substances with therapeutic potential (Newman and Cragg, 2020).

Recent decades have seen a resurgence of scientific interest in medicinal plants due to rising antimicrobial resistance and the slow discovery of new antibiotic families. Plant-derived antimicrobial substances may now be investigated more methodically thanks to developments in phytochemistry, molecular biology, metabolomics, genomics, and analytical tools. Through a variety of methods, phytochemicals such alkaloids, flavonoids, phenolic compounds, tannins, terpenoids, saponins, and quinones have shown antibacterial efficacy

against a wide range of pathogenic microbes (Cushnie and Lamb, 2011; Atanasov et al., 2021).

Crucially, the hunt for plant chemicals that either directly kill or inhibit bacteria is no longer the only focus of current study. When combined with conventional antibiotics, some phytochemicals may increase their effectiveness, while others may interfere with microbial virulence factors, quorum sensing, biofilm formation, membrane integrity, and antimicrobial resistance mechanisms (Silva et al., 2016; Cheesman et al., 2017). Interest in plant-derived chemicals as possible antibacterial agents and antibiotic adjuvants in the treatment of resistant illnesses has grown as a result of this complex action.

Thus, the historical use of medicinal plants provides a valuable foundation for contemporary antimicrobial research. The integration of traditional knowledge with modern phytochemical, pharmacological, molecular, and formulation technologies offers an opportunity to identify and develop plant-derived therapeutics with potential applications against antimicrobial-resistant pathogens.

1.5 Applications of Antimicrobial Peptides (AMPs)

Because of their broad-spectrum action and capacity to operate through a variety of pathways, antimicrobial peptides (AMPs) are becoming more widely acknowledged as prospective substitutes or supplements to traditional antimicrobial drugs. They are used in biotechnology, agriculture, food preservation, pharmaceutical development, and healthcare.

- **Treatment of Drug-Resistant Infections:** AMPs have demonstrated activity against a broad range of Gram-positive and Gram-negative bacteria, including several multidrug-resistant pathogens. Their ability to disrupt microbial membranes and target multiple cellular processes makes them attractive candidates for managing infections that are poorly responsive to conventional antibiotics (Mahlapuu et al., 2016; Magana et al., 2020).
- **Wound Healing and Topical Therapy:** AMPs have considerable potential in wound management because several peptides exhibit both antimicrobial and immunomodulatory properties. They can reduce microbial colonization while supporting tissue repair and modulation of inflammatory responses, making them promising components of topical formulations, wound dressings, hydrogels, and tissue-engineering materials (Mangoni et al., 2016; Hancock et al., 2016).
- **Biofilm Control:** Biofilm-associated infections are particularly difficult to eradicate because microorganisms within biofilms exhibit increased tolerance to antimicrobial

agents. Several AMPs can inhibit bacterial adhesion, interfere with biofilm development, disrupt mature biofilms, and modulate quorum-sensing pathways, providing potential approaches for controlling persistent infections associated with medical devices and chronic wounds (de la Fuente-Núñez et al., 2016).

- **Pharmaceutical and Drug-Delivery Applications:** AMPs can be incorporated into advanced drug-delivery systems, including nanoparticles, liposomes, hydrogels, and other nanocarriers, to improve their stability, localization, and therapeutic performance. Such approaches may also facilitate controlled or targeted delivery while reducing potential toxicity associated with systemic exposure (Mahlapuu et al., 2016).
- **Food Preservation and Food Safety:** The antimicrobial activity of naturally occurring and engineered peptides has attracted interest in food preservation. AMPs can inhibit foodborne pathogens and spoilage microorganisms and may therefore serve as natural or biologically derived alternatives to certain conventional chemical preservatives (Cotter et al., 2013).
- **Veterinary and Animal Health:** AMPs are being investigated for applications in veterinary medicine and livestock production, particularly as alternatives to conventional antibiotics. Their potential to control bacterial infections may contribute to reducing antibiotic consumption in animals and, consequently, help limit the development and dissemination of antimicrobial resistance (Hancock et al., 2016).
- **Agricultural Applications:** Plant-derived and synthetic AMPs have potential applications in crop protection because they can inhibit phytopathogenic bacteria and fungi. Their incorporation into plant-protection strategies may provide an alternative or complementary approach to conventional chemical pesticides and may contribute to sustainable disease management (Montesinos, 2007).

All things considered, AMPs' versatile qualities make them attractive options for a variety of uses, including food preservation, veterinary care, agriculture, and the treatment of biofilm-related illnesses and resistant infections. However, before their wider clinical and commercial application can be realised, issues with stability, proteolytic degradation, toxicity, production cost, pharmacokinetics, and large-scale manufacturing must be resolved (Magana et al., 2020).

1.6 Mechanisms of Action of Plant-Derived Antimicrobials

Because of the structural complexity and chemical diversity of their bioactive components, plant-derived antimicrobials display a variety of modes of action. Many phytochemicals can interact with several physiological components and metabolic processes at once, in contrast to conventional antibiotics that frequently operate on a single pathogen target. Through effects on microbial membranes, cell walls, nucleic acids, proteins, enzymes, and intracellular metabolic processes, major classes of plant-derived compounds, such as flavonoids, phenolics, tannins, alkaloids, terpenoids, saponins, and essential oil constituents, have shown antimicrobial activity (Cowan, 1999; Górniak et al., 2019). Because simultaneous disruption of many cellular processes may lessen the capacity of bacteria to survive through a single resistance mechanism, this multitarget action is especially important in the context of antimicrobial resistance.

Microbial cell membrane and cell-wall integrity breakdown is one of the main processes. Many substances originating from plants, including phenolics, terpenoids, and components of essential oils, can interact with membrane lipids and proteins to change the fluidity and permeability of the membrane. These alterations may lead to intracellular ion and macromolecule leakage, membrane potential dissipation, nutrient transport disruption, and eventually cell death (Cushnie et al., 2014; Swamy et al., 2016). Additionally, certain phytochemicals can disrupt the production and structural integrity of the bacterial cell wall, making the cells more vulnerable to antimicrobial agents and environmental stress. Furthermore, after passing through the microbial barrier, substances generated from plants may interact with intracellular targets. For instance, it has been documented that flavonoids and alkaloids disrupt DNA replication and transcription by interacting with nucleic acids and inhibiting enzymes like DNA gyrase and topoisomerases. Other phytochemicals can hinder the development and survival of microorganisms by interfering with ribosome activity and protein synthesis or by inhibiting vital metabolic enzymes (Cushnie et al., 2014; Górniak et al., 2019).

Antimicrobials generated from plants can also affect the physiological processes of microorganisms that support their pathogenicity and persistence. One way that certain phytochemicals can cause oxidative stress and harm microbial DNA, proteins, lipids, and other cellular components is by producing an excessive amount of reactive oxygen species (ROS) (Cushnie et al., 2014). Biofilm production is another crucial target. Because bacteria incorporated in biofilms show greater resistance to antimicrobial drugs, biofilm formation poses a significant challenge to the treatment of chronic and device-associated infections. A

number of substances produced from plants might hinder the growth or persistence of microbial biofilms by interfering with bacterial adhesion, extracellular polymeric substance formation, biofilm maturation, and stability (Borges et al., 2016; Silva et al., 2016). Additionally, phytochemicals may disrupt quorum sensing, a cell-to-cell communication process that controls motility, biofilm formation, toxin generation, and other traits linked to virulence. Plant chemicals may lessen bacterial pathogenicity without necessarily depending just on direct microbial death by interfering with quorum-sensing mechanisms (Borges et al., 2016).

Modulation of bacterial virulence and resistance pathways is another significant factor related to AMR. Because efflux pumps aggressively eliminate antibiotic chemicals from bacterial cells, lowering their intracellular concentration and efficacy, they play a significant role in antimicrobial resistance. According to Gibbons (2008) and Silva et al. (2016), several phytochemicals have been shown to be able to impede or interfere with efflux-pump function, which may increase the intracellular accumulation of antibiotics and boost their antimicrobial properties. Additionally, bacterial virulence factors such as adhesion, motility, toxin generation, secretion systems, and other pathogenicity-associated activities may be disrupted by chemicals derived from plants. While applying less direct selection pressure than traditional bactericidal methods, such antivirulence effects may reduce bacterial fitness and enhance vulnerability to host immunological responses (Silva et al., 2016).

Combining plant-derived antimicrobials with traditional antibiotics is becoming a more significant usage. By enhancing bacterial membrane permeability, blocking efflux pumps, rupturing biofilms, interfering with enzymes linked to resistance, or focusing on complimentary biological processes, phytochemicals may function as antibiotic adjuvants. Antibiotic efficacy against some resistant microbes may be restored by these interactions, which can also result in additional or synergistic antimicrobial effects (Cheesman et al., 2017; Ayaz et al., 2019). Consequently, there is a compelling case for the study of plant-derived chemicals as both direct antibacterial agents and adjunctive therapy due to their capacity to concurrently target microbial survival, pathogenicity, biofilm formation, and resistance mechanisms. However, the precise molecular mechanisms vary considerably among plant species and individual phytochemicals, emphasizing the need for standardized extracts, molecular characterization, mechanistic studies, and rigorous pharmacological evaluation before their translation into clinically applicable therapies.

1.7 Factors Influencing the Mechanism of Action of Plant-Derived Antimicrobials

The chemical makeup of the plant material, the concentration of active ingredients, the physicochemical characteristics of the compounds, the traits of the target microorganism, and environmental factors all have an impact on the antimicrobial activity and underlying mechanism of plant-derived compounds. Plant extracts, in contrast to pure synthetic antibacterial drugs, typically include complex combinations of chemicals that may operate singly or in concert. Therefore, rather than coming from a single active component, the observed antimicrobial activity might be the consequence of interactions between many phytochemicals (Cowan, 1999; Atanasov et al., 2021).

One of the most crucial elements influencing antimicrobial action is the concentration and chemical makeup of bioactive components. The amount and makeup of alkaloids, flavonoids, phenolic compounds, terpenoids, tannins, saponins, and other secondary metabolites can vary significantly depending on the plant species, plant sections, development phases, geographic regions, and cultivation circumstances. The target and degree of microbial suppression can also be influenced by the concentration of a particular phytochemical. Higher doses may result in membrane breakdown or direct cellular destruction, whereas lower quantities may mainly interfere with quorum sensing, adhesion, or pathogenicity (Cushnie et al., 2014; Górniak et al., 2019).

The antibacterial profile of plant extracts can be greatly influenced by the extraction technique and solvent system. various types of phytochemicals are preferentially extracted by various polarity solvents, and the stability and yield of bioactive ingredients can be influenced by extraction temperature, time, pH, and processing conditions. As a result, the antibacterial activity and mechanisms of action of extracts made from the same plant using various extraction techniques may differ significantly (Sasidharan et al., 2011; Azwanida, 2015). Therefore, standardising extraction processes is crucial to achieving repeatable antimicrobial activity and determining the components in charge of certain biological effects.

Individual phytochemicals' interactions with microbial cells are also influenced by their physicochemical characteristics. The ability of a molecule to reach and interact with particular microbial targets can be determined by its molecular size, polarity, lipophilicity, charge, structural configuration, and hydrogen bonding capacity. For instance, more polar compounds may affect intracellular enzymes, nucleic acids, or other cellular targets after entering the microorganism, while lipophilic compounds may easily bind to microbial membranes and change their permeability (Swamy et al., 2016; Górniak et al., 2019).

Another important factor influencing antibacterial action is the characteristics of the target bacterium. The cell-envelope architectures of Gram-positive and Gram-negative bacteria differ significantly, which may affect the penetration and efficacy of substances originating from plants. While the thick peptidoglycan layer of Gram-positive bacteria has distinct permeability properties, Gram-negative bacteria have an extra outer membrane that may prevent the entry of some hydrophobic substances (Cushnie et al., 2014). Plant-derived antimicrobial susceptibility can be further altered by microbial species, strain, growth phase, metabolic state, biofilm formation, and pre-existing resistance mechanisms.

The efficacy of phytochemicals can be significantly changed by the existence of biofilms and microbial resistance mechanisms. Because they are shielded by extracellular polymeric materials, microorganisms in biofilms often exhibit decreased sensitivity to antimicrobial treatments. Therefore, distinct effects against planktonic and biofilm-associated cells may be shown by plant-derived chemicals that may penetrate biofilms or interfere with quorum sensing and extracellular matrix production (Borges et al., 2016; Silva et al., 2016). Similarly, intracellular concentrations and target accessibility of chemicals originating from plants can be affected by efflux pumps, enzymatic inactivation, membrane changes, and other resistance mechanisms.

1.8 Plant-Derived Phytochemical Classes and Their Mechanisms

Numerous bioactive secondary metabolites found in medicinal plants contribute to their antibacterial qualities. These phytochemicals may act against microbes through a variety of cellular targets and differ significantly in their chemical structure and biological action. Phenolic compounds, flavonoids, tannins, alkaloids, terpenoids, essential oils, saponins, and quinones are the main phytochemical classes that have been studied for antimicrobial action. They are especially pertinent to the search for novel strategies against antimicrobial-resistant pathogens because of their capacity to disrupt microbial membranes, enzymes, nucleic acids, energy metabolism, biofilm formation, quorum sensing, and resistance-associated mechanisms (Cowan, 1999; Atanasov et al., 2021).

Phenolic compounds, which include phenolic acids, simple phenols, and related chemicals, are a significant class of antimicrobials obtained from plants. Their contact with microbial cell membranes, disruption of membrane permeability, denaturation of proteins, inhibition of enzymes, and interference with cellular energy metabolism are the main ways in which they have antimicrobial effects. Additionally, phenolic chemicals may cause oxidative stress in microbial cells, which can harm proteins, lipids, and nucleic acids (Daglia, 2012; Górniak et

al., 2019). Phenolics are attractive candidates for research against resistant microbes because of their structural variety, which enables them to interact with several microbial targets.

Flavonoids, which comprise flavones, flavonols, flavanones, isoflavones, anthocyanidins, and related subclasses, are polyphenolic chemicals that are extensively found in the kingdom of plants. According to Cushnie and Lamb (2011) and Górniak et al. (2019), their antimicrobial action may include disruption of microbial membranes, suppression of nucleic acid synthesis, interference with bacterial DNA gyrase and topoisomerases, modification of membrane permeability, and inhibition of energy metabolism. Additionally, certain flavonoids have shown antivirulence and anti-biofilm characteristics, and they may disrupt quorum-sensing pathways. These actions imply that flavonoids may have therapeutic benefits in addition to direct microbial suppression.

Proteins and other macromolecules can interact with tannins, which are high-molecular-weight polyphenolic substances. Microbial protein precipitation, extracellular enzyme inhibition, cell-envelope structural modification, and interference with microbial adhesion have all been linked to their antibacterial action. By creating compounds with proteins and metal ions, tannins may also decrease the availability of nutrients and hinder the development of microorganisms (Cowan, 1999; Scalbert, 1991). Their action against pathogenic bacteria and fungus may be attributed to their capacity to disrupt several microbial activities.

Alkaloids are a family of nitrogen-containing chemicals having a wide range of pharmacological effects that are structurally varied. Through breakdown of microbial cell membranes, suppression of protein and nucleic acid production, interference with vital enzymes, and modification of cell division, a number of alkaloids demonstrate antimicrobial activities. Additionally, certain alkaloids have been shown to disrupt virulence-associated pathways and bacterial efflux systems, which makes this class pertinent to antibiotic resistance techniques (Cushnie et al., 2014). Alkaloids' varied molecular structures offer chances to interact with a variety of microbiological targets.

Another significant class of antibacterial compounds produced from plants are terpenoids and essential oils. Terpenoids can alter the fluidity and permeability of microbial membranes, cause internal contents to seep out, and interfere with cellular respiration since they are often lipophilic (Swamy et al., 2016). By disrupting membranes and interfering with intracellular metabolic processes, essential oils—which often include monoterpenes, sesquiterpenes, and phenylpropanoids—may have broad-spectrum antibacterial action. Their potential application against biofilm-associated illnesses and resistant bacteria has drawn a lot of attention due to their capacity to impact many cellular targets concurrently (Nazzaro et al., 2013).

Glycosidic substances known as saponins are distinguished by their capacity to interact with membrane sterols. They can attach to microbial membranes and enhance membrane permeability due to their amphiphilic nature, which may lead to intracellular component leaking and cellular lysis. Therefore, saponins have shown action against a variety of bacterial and fungal species and may contribute to the antimicrobial activity of crude plant extracts (Morrissey and Osbourn, 1999). Additionally, their ability to target membranes may make it easier for them to interact with other phytochemicals and traditional antibacterial drugs.

Reactive chemical structures found in quinones and similar substances allow them to interact with nucleophilic biological components and take part in redox processes. They may cause oxidative stress, interfere with electron transport, block vital enzymes, and alter microbial proteins as part of their antibacterial activities. For instance, anthraquinones and naphthoquinones have shown antibacterial qualities against a variety of pathogenic microbes and may function via a number of cellular pathways (Cowan, 1999; Gibbons, 2008). Their promise for additional antibacterial research stems from their capacity to influence microbial metabolism and redox balance.

1.9 Plant-Derived Antimicrobials Against Multidrug-Resistant Pathogens

The hunt for antimicrobial drugs that may overcome traditional resistance mechanisms has been more intense due to the growing frequency of multidrug-resistant (MDR) bacteria. Due to their structural diversity and capacity to interact with a variety of microbiological targets, chemicals produced from plants have garnered significant attention. Phytochemicals can concurrently impact microbial membranes, metabolic enzymes, nucleic acids, virulence pathways, biofilm formation, and resistance mechanisms, in contrast to conventional antibiotics, which often target a small number of cellular processes. Investigating medicinal plants as possible sources of therapeutic drugs against MDR microbes is strongly justified by this multitarget activity (Jubair et al., 2021; Atanasov et al., 2021).

1.9.1 Activity Against Methicillin-Resistant *Staphylococcus aureus*

Resistant to methicillin Staphylococcus aureus (MRSA) has become resistant to a number of widely used antimicrobial drugs and is a significant source of infections linked to healthcare and the population. Through mechanisms including membrane disruption, inhibition of bacterial enzymes, interference with nucleic acid synthesis, and suppression of virulence-associated processes, plant-derived compounds like flavonoids, phenolic acids, tannins, terpenoids, and essential oil constituents have shown inhibitory activity against MRSA

(Cushnie et al., 2014; Górniak et al., 2019). According to Cheesman et al. (2017), several chemicals produced from plants have the potential to be antibiotic adjuvants since they can increase the efficacy of β-lactam and other antibiotics against resistant S. aureus.

1.9.2 Activity Against Vancomycin-Resistant *Enterococcus*

Due to its resistance to several antibiotic classes, vancomycin-resistant enterococci (VRE), especially vancomycin-resistant Enterococcus faecium, provide a significant treatment problem. Through their effects on membrane function, cell-envelope integrity, and vital metabolic activities, a number of plant secondary metabolites have shown action against enterococci. Because they can target membranes through different pathways than traditional antibiotics, phenolic chemicals and essential oil components may be especially significant (Swamy et al., 2016). The research of plant-derived chemicals as supplemental antibacterial methods is further supported by their potential to increase the susceptibility of resistant enterococci to conventional antibiotics.

1.9.3 Activity Against Extended-Spectrum β-Lactamase-Producing and Carbapenem-Resistant *Enterobacterales*

Difficult-to-treat urinary, bloodstream, respiratory, and healthcare-associated infections are mostly caused by Enterobacterales that produce extended-spectrum β-lactamase (ESBL) and are resistant to carbapenem. Efflux-pump activity, changes in membrane permeability, β-lactamase synthesis, and other resistance mechanisms are often linked to their resistance. By rupturing bacterial membranes, blocking efflux mechanisms, interfering with β-lactamase-associated resistance, and decreasing biofilm formation, plant-derived phytochemicals may be effective against these species (Gibbons, 2008; Silva et al., 2016). Because blocking resistance routes may raise the intracellular concentration and efficacy of traditional antibiotics, these processes are very important.

1.9.4 Activity Against Multidrug-Resistant *Pseudomonas aeruginosa*

Due to its innate resistance, acquired resistance mechanisms, effective efflux systems, limited membrane permeability, and potent biofilm-forming abilities, MDR Pseudomonas aeruginosa is linked to serious illnesses connected to healthcare. Conventional treatment options are significantly restricted by these features. By impairing membrane integrity, decreasing biofilm formation, interfering with quorum sensing, and modifying virulence-associated pathways, a number of substances derived from plants and essential oils have shown efficacy against P. aeruginosa (Borges et al., 2016; Nazzaro et al., 2013). Because quorum sensing and

biofilm formation play a major role in P. aeruginosa infection persistence and antibiotic resistance, targeting these pathways is especially intriguing.

1.9.5 Activity Against Carbapenem-Resistant *Acinetobacter baumannii*

Due to its capacity to develop many resistance mechanisms and endure in medical settings, carbapenem-resistant Acinetobacter baumannii has become one of the most challenging bacterial infections to treat. By focusing on bacterial membranes, oxidative balance, biofilm formation, and virulence-associated activities, phytochemicals produced from plants may provide alternative strategies. Flavonoids, terpenoids, phenolic compounds, and other secondary metabolites have shown antibacterial activity against resistant Gram-negative bacteria, indicating potential for additional research against carbapenem-resistant A. baumannii (Álvarez-Martínez et al., 2021; Jubair et al., 2021). However, comprehensive research using well-characterized phytochemicals and therapeutically relevant resistance isolates is still required.

1.9.6 Activity Against Drug-Resistant *Mycobacterium tuberculosis*

One of the biggest threats to world health is drug-resistant TB, especially multidrug-resistant and rifampicin-resistant Mycobacterium tuberculosis. The intricate lipid-rich mycobacterial cell membrane and the length of time needed for therapy make it challenging to create successful treatments. By interfering with cell-wall-associated processes, energy metabolism, oxidative balance, and other crucial cellular pathways, a number of substances originating from plants, such as phenolics, flavonoids, terpenoids, and alkaloids, have shown antimycobacterial action (Copp and Pearce, 2007). Plant-derived compounds offer a useful chemical reservoir for the discovery of novel antimycobacterial candidates and possible adjunctive treatments, even if the majority of the data currently available is preclinical.

1.9.7 Activity Against Multidrug-Resistant Fungal Pathogens

Clinically significant fungi can also become resistant to existing antifungal treatments, therefore antimicrobial resistance is not limited to bacteria. Due to their capacity to last in healthcare settings and exhibit resistance to several antifungal classes, resistant Candida species—especially Candida auris—have sparked serious concerns. Through mechanisms like disruption of fungal membranes, modification of membrane sterols, oxidative stress, inhibition of morphogenesis, and interference with biofilm formation, plant-derived compounds such as essential oils, phenolics, terpenoids, and flavonoids have shown antifungal activity (Silva et al., 2018). These results suggest that chemicals originating from

plants may have wider uses in the fight against antimicrobial resistance in bacterial and fungal diseases.

All things considered, the information that is now available suggests that antimicrobials derived from plants have significant promise against a wide variety of MDR infections. Direct microbial suppression, destruction of biofilms and virulence mechanisms, interference with processes linked to resistance, or synergistic interactions with traditional antimicrobial medications are all possible causes of their efficacy. However, the majority of the information now comes from experimental and in vitro research, and there are still significant gaps in knowledge regarding pharmacokinetics, safety, standardisation, bioavailability, and clinical effectiveness. In order to ascertain the therapeutic value of plant-derived antimicrobials against MDR infections, future research should give priority to well-characterized phytochemicals, clinically relevant resistant isolates, mechanism-based combination studies, sophisticated delivery systems, and suitably planned clinical investigations.

1.10 Plant-Derived Compounds as Antibiotic Adjuvants

There is a pressing need for methods that can maintain and improve the therapeutic efficiency of currently available antibiotics due to the rising incidence of antimicrobial resistance. In this regard, chemicals originating from plants are being studied as both direct antibacterial agents and antibiotic adjuvants, which are molecules that, when used in conjunction with traditional antibiotics, increase their action. Membrane permeability, efflux-pump activity, biofilm formation, quorum sensing, and antibiotic-inactivating enzymes are just a few of the bacterial processes that phytochemicals may target due to their varied chemical structures and biological activities (Gibbons, 2008; Cheesman et al., 2017).

Modulation of bacterial membrane permeability is a key way that phytochemicals can increase antibiotic action. Bacterial membranes can interact with certain phenolic chemicals, flavonoids, terpenoids, and components of essential oils to change their structural integrity. Conventional antibiotics may be able to enter bacterial cells more easily and have a higher intracellular concentration if membrane permeability is increased (Swamy et al., 2016; Álvarez-Martínez et al., 2021). The outer membrane of Gram-negative bacteria can serve as a significant barrier to drug entrance, making this process especially pertinent against them. Plant-derived substances may make intracellular antibiotic targets more accessible by breaching this barrier.

Another significant method via which phytochemicals may reinstate antibiotic action is the inhibition of bacterial efflux pumps. Efflux pumps help bacteria develop resistance to certain antibiotic classes by aggressively removing antimicrobial drugs from their cells. It has been shown that a number of substances originating from plants can block efflux-pump systems, which may increase the intracellular accumulation of antibiotics and improve their antibacterial effects (Gibbons, 2008). Because a single adjuvant may possibly affect sensitivity to many antimicrobial drugs, efflux-pump inhibition is especially appealing for the development of combination therapy against multidrug-resistant bacteria.

By disrupting biofilms and inhibiting quorum sensing, chemicals originating from plants can also increase the effectiveness of antibiotics. Extracellular polymeric matrices shield biofilm-associated bacteria, and they often show greater resistance to antimicrobial therapy. Bacterial adhesion, extracellular matrix synthesis, biofilm maturation, and quorum-sensing mechanisms that control microbial communication and pathogenicity can all be disrupted by phytochemicals (Borges et al., 2016; Silva et al., 2016). When these defence systems are compromised, germs may become more vulnerable to traditional antibiotics and chronic infections may be more effectively eliminated.

Antibiotic-resistant enzyme inhibition is another intriguing approach. Enzymes like β-lactamases, which hydrolyse and render β-lactam antibiotics inactive, are produced by some resistant bacteria. Antibiotics may be shielded from enzymatic breakdown by some plant-derived chemicals that interact with these resistance-associated enzymes and decrease their activity (Gibbons, 2008; Cheesman et al., 2017). These interactions might be especially useful against bacterial infections that produce ESBL and other β-lactam-resistant bacteria. However, each phytochemical's inhibitory action differs greatly, necessitating confirmation using resistant clinical isolates, pure enzymes, and suitable mechanistic studies.

The potential of plant-derived compounds as antibiotic adjuvants is therefore significant in the context of AMR. Rather than replacing conventional antibiotics entirely, phytochemicals may help restore the activity of existing antimicrobial agents against resistant pathogens and extend the useful lifespan of established therapies. Nevertheless, promising *in vitro* synergistic effects cannot automatically be translated into clinical efficacy. Differences in absorption, metabolism, bioavailability, toxicity, pharmacokinetic interactions, and achievable concentrations at the site of infection must be carefully evaluated. Future investigations should therefore focus on identifying well-characterized phytochemical-antibiotic combinations, elucidating their molecular mechanisms, establishing safety profiles,

and validating their efficacy through appropriate *in vivo* and clinical studies (Ayaz et al., 2019; Atanasov et al., 2021).

1.11 Plant-Derived Antimicrobials Against Biofilm-Associated Infections

A crucial survival tactic used by microbes, biofilm development poses a significant obstacle to the treatment of recurring and chronic illnesses. Biofilms, which offer defence against antimicrobial drugs and host immunological responses, are organised microbial colonies embedded in an extracellular polymeric material matrix. Treatment failure and infection persistence may result from microorganisms in biofilms having a significantly higher susceptibility to antimicrobial treatment than their planktonic counterparts (Donlan and Costerton, 2002; Hall and Mah, 2017). Because biofilm-associated diseases involving multidrug-resistant microbes are becoming more common, there is a growing interest in alternate strategies that can either disrupt or prevent the production of biofilms.

Because they may disrupt several phases of biofilm formation, chemicals derived from plants have shown significant promise for regulating biofilms. Flavonoids, phenolic compounds, terpenoids, tannins, alkaloids, and components of essential oils are examples of phytochemicals that may prevent early microbial adhesion, disrupt the formation of extracellular matrix, change cellular communication, and encourage the disruption of mature biofilms (Borges et al., 2016; Silva et al., 2016). Antibiofilm phytochemicals can influence microbial behaviours and structural traits that are crucial for biofilm formation and persistence, in contrast to traditional antimicrobial treatment, which may mainly target actively expanding planktonic cells.

Inhibition of initial adhesion and biofilm development is a key mechanism. An important initial step in the formation of biofilms is the adhesion of bacteria to biotic or abiotic surfaces. In order to stop the formation of mature biofilms, several substances produced from plants can change the characteristics of cell surfaces, interfere with adhesins, and decrease microbial adhesion to surfaces (Borges et al., 2016). This characteristic could be especially helpful in stopping the colonisation of wound surfaces, medical equipment, and other areas where biofilm-associated infections often arise.

Quorum sensing, a bacterial communication system that synchronises population-dependent behaviours such biofilm formation, locomotion, virulence-factor synthesis, and extracellular matrix creation, may also be disrupted by substances derived from plants. According to Silva et al. (2016), a number of phytochemicals can disrupt quorum-sensing signals or their regulatory mechanisms, which can hinder biofilm growth and bacterial communication.

Because it may lessen microbial pathogenicity and biofilm formation without only relying on direct bactericidal action, targeting quorum sensing is especially appealing.

The combination of plant-derived compounds with conventional antibiotics represents a particularly promising approach for biofilm-associated infections. Phytochemicals may increase antibiotic penetration, disrupt biofilm architecture, inhibit efflux pumps, or interfere with resistance and virulence mechanisms, thereby enhancing the susceptibility of biofilm-associated microorganisms to conventional treatment (Cheesman et al., 2017). Synergistic combinations may therefore allow lower concentrations of antibiotics to achieve greater antibiofilm activity and could potentially reduce the selective pressure associated with prolonged antibiotic exposure.

Table 1. Modern Approaches in Plant-Based AMR Research

Modern approach	**Principle / application**	**Role in AMR research**	**Key advantages**	**Reference**
Metabolomics	Comprehensive profiling of plant metabolites using LC-MS, GC-MS, and NMR	Identifies metabolites associated with antimicrobial activity and potential bioactive markers	Enables chemical profiling and correlation of metabolites with biological activity	Wolfender et al. (2019)
HPLC and LC-MS/MS	Separation, identification, and quantification of phytochemicals	Characterizes antimicrobial constituents in complex plant extracts	High sensitivity, selectivity, and reproducibility	Wolfender et al. (2019)
GC-MS	Analysis of volatile and semi-volatile phytochemicals	Particularly useful for essential oils and volatile antimicrobial compounds	Provides detailed chemical fingerprints	Nazzaro et al. (2013)
Bioassay-guided fractionation	Sequential separation of extracts according to antimicrobial	Identifies fractions and compounds responsible for antimicrobial effects	Links biological activity with specific constituents	Atanasov et al. (2021)

	activity			
High-throughput screening	Rapid screening of multiple extracts or compounds against microorganisms	Facilitates identification of candidates active against resistant pathogens	Accelerates early-stage antimicrobial discovery	Atanasov et al. (2021)
Molecular docking	Computational prediction of interactions between phytochemicals and microbial targets	Predicts potential interactions with resistance-associated enzymes, efflux pumps, and virulence proteins	Reduces time and cost during preliminary drug discovery	Pinzi and Rastelli (2019)
Artificial intelligence and machine learning	Computational analysis and prediction of antimicrobial activity and molecular properties	Prioritizes promising phytochemicals and predicts structure-activity relationships	Accelerates candidate selection and reduces experimental workload	Vamathevan et al. (2019)
Genomics and transcriptomics	Analysis of microbial genomes and gene-expression responses following phytochemical exposure	Identifies resistance pathways, molecular targets, and cellular responses	Provides mechanistic insight into antimicrobial action	Khameneh et al. (2019)
Proteomics	Analysis of changes in microbial protein expression after treatment	Identifies affected proteins and metabolic pathways	Supports molecular-mechanism validation	Atanasov et al. (2021)

Synergy studies	Evaluation of phytochemical-antibiotic combinations	Identifies combinations capable of enhancing or restoring antibiotic activity	May improve efficacy and reduce antibiotic requirements	Cheesman et al. (2017)
Biofilm models	Evaluation of phytochemicals against planktonic and biofilm-associated microorganisms	Determines activity against persistent and antimicrobial-tolerant populations	Relevant to chronic and device-associated infections	Borges et al. (2016)
Nanotechnology-based delivery	Incorporation of phytochemicals into nanoparticles, nanoemulsions, liposomes, phytosomes, or nanogels	Improves delivery of poorly soluble or unstable antimicrobial compounds	Can improve stability, bioavailability, and therapeutic performance	McClements (2013)
In vivo validation	Assessment of antimicrobial efficacy and safety in appropriate animal models	Determines whether promising in vitro activity translates into biological efficacy	Provides efficacy and preliminary safety evidence	Atanasov et al. (2021)
Multi-omics integration	Integration of metabolomic, genomic, transcriptomic, and proteomic datasets	Provides comprehensive information on plant-derived compounds and microbial responses	Facilitates mechanism-driven antimicrobial discovery	Wolfender et al. (2019)

Table note: LC-MS: liquid chromatography-mass spectrometry; GC-MS: gas chromatography-mass spectrometry; HPLC: high-performance liquid chromatography; NMR: nuclear magnetic resonance; AMR: antimicrobial resistance; MDR: multidrug resistance.

1.12 Challenges and Limitations in the Development of Plant-Derived Antimicrobial Therapeutics

Despite their promising antimicrobial potential, the development of plant-derived therapeutics against AMR is associated with several limitations. Variability in phytochemical composition is a major concern because plant species, geographical origin, cultivation conditions, harvesting time, storage, and extraction methods can significantly influence the biological activity of plant extracts (Atanasov et al., 2021). Therefore, appropriate standardization, authentication, quality control, and reproducible extraction procedures are essential for ensuring consistent therapeutic activity (Sasidharan et al., 2011).

Another important challenge is the identification of active constituents and their mechanisms of action. Complex plant extracts may contain numerous compounds that interact synergistically, additively, or antagonistically, making it difficult to determine the compounds responsible for antimicrobial activity (Cheesman et al., 2017). Many promising phytochemicals also exhibit poor solubility, instability, limited bioavailability, or rapid metabolism, which can restrict their therapeutic effectiveness. Advanced delivery systems such as nanoparticles, nanoemulsions, and liposomes may help overcome some of these limitations (Atanasov et al., 2021).

Safety, toxicity, and clinical validation remain major barriers to translation. The natural origin of a compound does not necessarily indicate complete safety, and potential toxicity, drug interactions, and adverse effects must be systematically evaluated (Ekor, 2014). Moreover, much of the available evidence is based on *in vitro* studies, while well-designed animal studies and clinical trials remain comparatively limited. Differences in experimental methods, extract composition, dosage, and study design further complicate comparison between investigations.

Finally, regulatory, manufacturing, and commercial challenges can hinder the development of plant-derived antimicrobial products. Consistent quality, scalable production, sustainable sourcing, and clearly defined regulatory standards are necessary for successful clinical translation.

1.13 Future Perspectives

The future of Monoterpenes and monoterpenoids as antimicrobial agents against multidrug-resistant (MDR) pathogens lies in addressing current challenges through innovative research approaches and interdisciplinary collaboration.The future of combating antimicrobial

resistance (AMR) lies in developing and integrating natural antibacterial agents into clinical practice through a multifaceted approach.

1.14 Conclusion

Antimicrobial resistance has emerged as a major global health challenge, creating an urgent need for novel and sustainable therapeutic strategies. Plant-derived therapeutics represent a promising source of antimicrobial agents because of their rich phytochemical diversity and ability to act through multiple mechanisms, including membrane disruption, enzyme inhibition, biofilm inhibition, quorum-sensing interference, and modulation of resistance mechanisms. Several phytochemical classes, including flavonoids, phenolics, alkaloids, terpenoids, tannins, saponins, and quinones, have demonstrated potential against pathogenic and multidrug-resistant microorganisms. Their ability to enhance the activity of conventional antibiotics further supports their potential as antibiotic-adjuvant therapies. However, limitations related to standardization, bioavailability, toxicity, reproducibility, and limited clinical evidence continue to restrict their translation into clinical practice. Integration of modern approaches such as metabolomics, molecular modelling, multi-omics, synergistic screening, and nanotechnology may accelerate the discovery and development of effective plant-derived antimicrobial therapies. Future research should focus on rigorous mechanistic studies, standardized formulations, safety evaluation, and well-designed clinical trials to establish their therapeutic efficacy. Overall, plant-derived therapeutics offer a valuable and complementary strategy for addressing the growing threat of antimicrobial resistance and may contribute significantly to the development of next-generation antimicrobial interventions.

1.15 Acknowledgements

The authors would like to express their sincere gratitude to all the researchers and institutions whose work has contributed to the development of this review.

1.16 Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this review.

1.17 References

- Atanasov AG, Zotchev SB, Dirsch VM, Supuran CT. Natural products in drug discovery: advances and opportunities. Nature Reviews Drug Discovery. 2021;20:200-216.

- Akiyama H, Fujii K, Yamasaki O, Oono T, Iwatsuki K. Antibacterial action of several tannins against Staphylococcus aureus. Journal of Antimicrobial Chemotherapy. 2001;48(4):487-491.
- Álvarez-Martínez FJ, Barrajón-Catalán E, Herranz-López M, Micol V. Antibacterial plant compounds, extracts and essential oils: an updated review on their effects and putative mechanisms of action. Phytomedicine. 2021;90:153626.
- Atanasov AG, Zotchev SB, Dirsch VM, Supuran CT. Natural products in drug discovery: advances and opportunities. Nature Reviews Drug Discovery. 2021;20:200-216.
- Ayaz M, Ullah F, Sadiq A, Ullah F, Ovais M, Ahmed J, Devkota HP. Synergistic interactions of phytochemicals with antimicrobial agents: a promising strategy for combating antimicrobial resistance. Phytotherapy Research. 2019;33(10):2735-2748.
- Azwanida NN. A review on the extraction methods use in medicinal plants, principle, strength and limitation. Medicinal & Aromatic Plants. 2015;4(3):196.
- Borges A, Abreu AC, Dias C, et al. New perspectives on the use of phytochemicals as an emergent strategy to control bacterial infections including biofilms. Molecules. 2016;21(7):877.
- Borges A, Saavedra MJ, Simões M. The activity of several essential oils on pathogenic bacteria and their biofilms. J Appl Microbiol. 2012;113(3):599-608.
- Cheesman MJ, Ilanko A, Blonk B, Cock IE. Developing new antimicrobial therapies: are synergistic combinations of plant extracts/compounds with conventional antibiotics the solution? Pharmacognosy Reviews. 2017;11(22):57-72.
- Copp BR, Pearce AN. Natural product growth inhibitors of mycobacterium tuberculosis. Natural Product Reports. 2007;24(2):278-297.
- Cotter PD, Ross RP, Hill C. Bacteriocins—a viable alternative to antibiotics? Nature Reviews Microbiology. 2013;11:95-105.
- Cowan MM. Plant products as antimicrobial agents. Clinical Microbiology Reviews. 1999;12(4):564-582.
- Cushnie TPT, Lamb AJ. Recent advances in understanding the antibacterial properties of flavonoids. Int J Antimicrob Agents. 2011;38(2):99-107.
- Daglia M. Polyphenols as antimicrobial agents. Current Opinion in Biotechnology. 2012;23(2):174-181.

- de la Fuente-Núñez C, Cardoso MH, de Souza Cândido E, Franco OL, Hancock REW. Synthetic antibiofilm peptides. Biochimica et Biophysica Acta (BBA) - Biomembranes. 2016;1858(5):1061-1069.
- Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant microorganisms. Clinical Microbiology Reviews. 2002;15(2):167-193.
- Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Frontiers in Pharmacology. 2014;4:177.
- Francis G, Kerem Z, Makkar HPS, Becker K. The biological action of saponins in animal systems: a review. British Journal of Nutrition. 2002;88(6):587-605.
- Gibbons S. Phytochemicals for bacterial resistance—strengths, weaknesses and opportunities. Planta Medica. 2008;74(6):594-602.
- Gorniak I, Bartoszewski R, Króliczewski J. Comprehensive review of antimicrobial activities of plant flavonoids. Phytochemistry Reviews. 2019;18:241-272.
- Hall CW, Mah TF. Molecular mechanisms of biofilm-based antibiotic resistance and tolerance in pathogenic bacteria. FEMS Microbiology Reviews. 2017;41(3):276-301.
- Hancock REW, Haney EF, Gill EE. The immunology of host defence peptides: beyond antimicrobial activity. Nature Reviews Immunology. 2016;16:321-334.
- Hussain H, Green IR, Ahmed I, et al. Lapachol and its derivatives: a comprehensive review. Phytochemistry Reviews. 2018;17:1163-1183.
- Jubair N, Rajagopal M, Chinnappan S, et al. Review on the antibacterial mechanism of plant-derived compounds against multidrug-resistant bacteria (MDR). Evidence-Based Complementary and Alternative Medicine. 2021;2021:3663315.
- Khameneh B, Iranshahy M, Soheili V, Bazzaz BSF. Review on plant antimicrobials: a mechanistic viewpoint. Antimicrobial Resistance & Infection Control. 2019;8:118.
- Magana M, Pushpanathan M, Santos AL, et al. The value of antimicrobial peptides in the age of resistance. The Lancet Infectious Diseases. 2020;20(9):e216-e230.
- Mahlapuu M, Håkansson J, Ringstad L, Björn C. Antimicrobial peptides: an emerging category of therapeutic agents. Frontiers in Cellular and Infection Microbiology. 2016;6:194.
- Mangoni ML, McDermott AM, Zasloff M. Antimicrobial peptides and wound healing. Expert Review of Anti-infective Therapy. 2016;14(8):737-749.
- McClements DJ. Edible lipid nanoparticles: digestion, absorption, and potential toxicity. Progress in Lipid Research. 2013;52(4):409-423.

- Montesinos E. Antimicrobial peptides and plant disease control. FEMS Microbiology Letters. 2007;270(1):1-11.
- Murray CJL, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet. 2022;399(10325):629-655.
- Nahar PD, Vatsh A, Arora B, Dhakar A, Samant RS. Ethnopharmacological significance, phytochemical and pharmacological activities of Helicteres isora: a comprehensive review. Global Journal of Pharmaceutical and Scientific Research. 2026;2(5):770-787. doi:10.66204/GJPSR-770-2026-2-5-5.
- Nazzaro F, Fratianni F, De Martino L, Coppola R, De Feo V. Effect of essential oils on pathogenic bacteria. Pharmaceuticals. 2013;6(12):1451-1474.
- Newman DJ, Cragg GM. Natural products as sources of new drugs over nearly four decades from 01/1981 to 09/2019. Journal of Natural Products. 2020;83(3):770-803.
- O'Neill J. Tackling drug-resistant infections globally: final report and recommendations. Review on Antimicrobial Resistance; 2016.
- Petrovska BB. Historical review of medicinal plants' usage. Pharmacognosy Reviews. 2012;6(11):1-5.
- Pinzi L, Rastelli G. Molecular docking: shifting paradigms in drug discovery. International Journal of Molecular Sciences. 2019;20(18):4331.
- Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. Pathog Glob Health. 2015;109(7):309-318.
- Sasidharan S, Chen Y, Saravanan D, Sundram KM, Latha LY. Extraction, isolation and characterization of bioactive compounds from plants' extracts. African Journal of Traditional, Complementary and Alternative Medicines. 2011;8(1):1-10.
- Scalbert A. Antimicrobial properties of tannins. Phytochemistry. 1991;30(12):3875-3883.
- Sieniawska E, Sawicki R. Antimicrobial activity of plant extracts and essential oils. Current Medicinal Chemistry. 2015;22(30):3533-3552.
- Silva S, Negri M, Henriques M, Oliveira R, Williams DW, Azeredo J. Candida glabrata, Candida parapsilosis and Candida tropicalis: biology, epidemiology, pathogenicity and antifungal resistance. FEMS Microbiology Reviews. 2012;36(2):288-305
- Singh A, Yadav VK, Agrahari H. Recent advances in phytosomal drug delivery systems for topical applications. Global Journal of Pharmaceutical and Scientific Research. 2026;2(8):1170-1186. doi:10.66204/GJPSR-1170-2026-2-8-1.

- Swamy MK, Akhtar MS, Sinniah UR. Antimicrobial properties of plant essential oils against human pathogens and their mode of action: an updated review. Evidence-Based Complementary and Alternative Medicine. 2016;2016:3012462.
- Tiwari S, Wasiullah M, Yadav P, Yadav V. Phytomedicine: The role of AI in phytomedicine. Global Journal of Pharmaceutical and Scientific Research. 2026;2(4):536-552. doi:10.66204/GJPSR-536-2026-2-4-2.
- Vamathevan J, Clark D, Czodrowski P, et al. Applications of machine learning in drug discovery and development. Nature Reviews Drug Discovery. 2019;18:463-477.
- Wasiullah M, Yadav P, Musharraf M, Yadav MK. Systematic review on nanotechnology for phyto medicine research and drug development. Global Journal of Pharmaceutical and Scientific Research. 2025;1(5).
- Wolfender JL, Litaudon M, Touboul D, Queiroz EF. Innovative omics-based approaches for prioritisation and dereplication in natural product research. Natural Product Reports. 2019;36(6):855-868.
- World Health Organization. 2023 antibacterial agents in clinical and preclinical development: an overview and analysis. Geneva: WHO; 2024.
- World Health Organization. Antibacterial products in clinical development for priority pathogens. Geneva: World Health Organization; 2025.
- World Health Organization. Antimicrobial resistance. Geneva: World Health Organization; 2023.
- World Health Organization. Antimicrobial resistance. Geneva: World Health Organization; 2023.
- World Health Organization. WHO bacterial priority pathogens list, 2024. Geneva: World Health Organization; 2024.
- World Health Organization. WHO bacterial priority pathogens list, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. Geneva: WHO; 2024.
- Yadav V. Comprehensive study of turmeric and its main compound curcumin. Global Journal of Pharmaceutical and Scientific Research. 2026;2(8):1317-1326. doi:10.66204/GJPSR-1317-2026-2-8-8.