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Plant-Derived Antimicrobial Agents: A Promising Solution to Combat Multidrug Resistance

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ABSTRACT

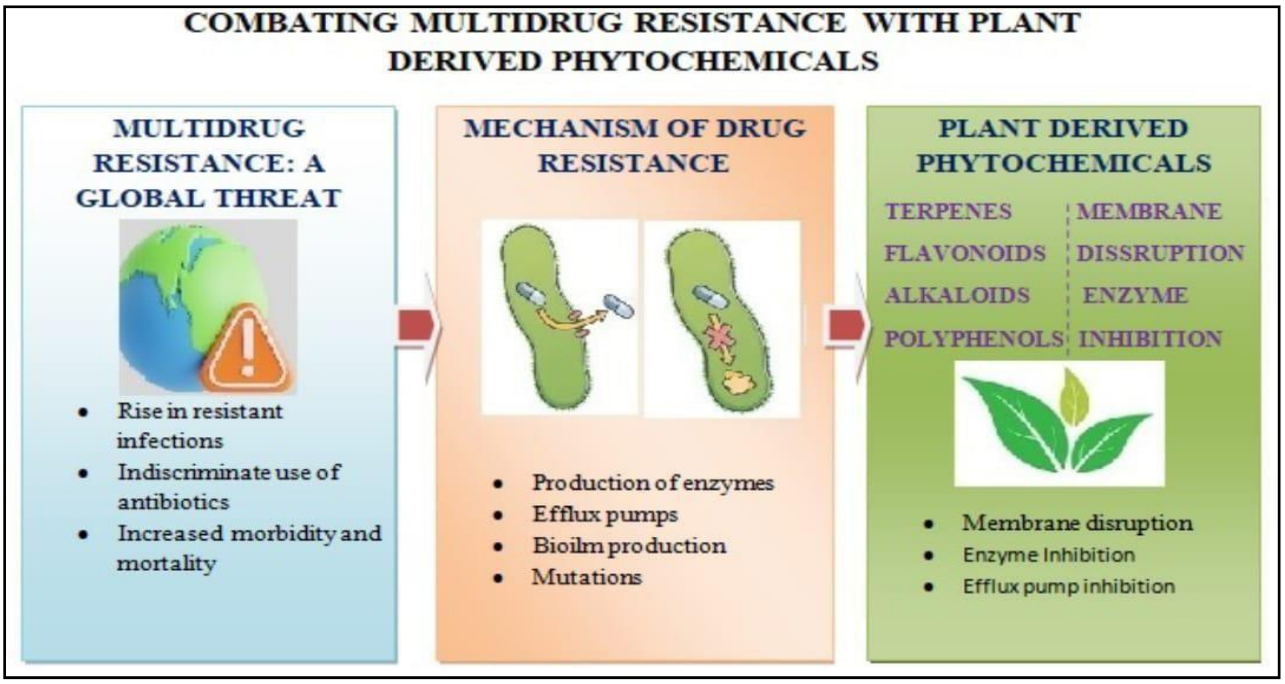
Multidrug resistance (MDR) has emerged as a major global health threat, compromising the effectiveness of conventional treatment therapies and leading to increased morbidity, and mortality. The indiscriminate utilization of antibiotics in human healthcare, agriculture, and veterinary practices has enhanced the development and transmission of antibiotic resistant strains. In response to this alarming condition, there has been a renewed interest in alternative antimicrobial agents, particularly from compounds derived from plants. Medicinal plants are utilized in traditional medicine for many years and offer a promising source of bioactive molecules capable of combating resistant pathogens. Phytochemicals, such as terpenes, alkaloids, flavonoids, and polyphenols have demonstrated significant antimicrobial activity, acting through mechanisms such as membrane disruption, efflux pump inhibition, and enzyme inhibition. This review explores the growing challenge of MDR infections, detailing the mechanisms through which microbes evade antimicrobial agents and role of plant based compounds in fighting drug resistance. Moreover, it discusses the challenges associated with combating multi drug infections and development of novel antimicrobial agents from plants. Despite these challenges, plant-derived antimicrobials offer a promising pathway for developing innovative strategies to combat multidrug resistant (MDR) infections and tackle the escalating threat of antibiotic resistance.

Keywords: *Antibiotic Resistance, Phytochemicals, Drug Development, Multidrug Resistance (MDR), Plant extract..*

1. INTRODUCTION

Antibiotic resistance has become a serious health issue, extending beyond hospital settings to become a widespread issue within communities [1]. The increasing prevalence of drug-resistant infections is compounded by the limited development of novel antimicrobial agents with higher activity. One of the major contributing to this issue is the extensive and unregulated use of antibiotics in healthcare, veterinary practices, and agriculture, which has increased the evolution and spread of multidrug resistant (MDR) strains [2]. Various pathogens including bacteria, viruses, fungi, protozoa, and helminths employ multiple mechanisms to resist antimicrobial treatments. These include point mutations, enzymatic degradation or modification of drugs, and alterations of drug targets. In fungi and protozoa, mechanisms such as reduced drug uptake and active efflux are more prevalent [3]. In response to the growing challenge of antibiotic resistance, there has been a renewed interest in discovering alternative antimicrobial agents especially from natural sources. Medicinal plants are utilized in traditional medicine system for longer time and are gaining renewed scientific attention for their potential to combat resistant pathogens. It has been emphasized that antimicrobial properties of plant derived compounds, laying the groundwork for further exploration [4]. More recent investigations have identified various types of phytochemical compounds such as terpenes, alkaloids, flavonoids, and phenylpropanoids that demonstrate significant activity against MDR microorganisms [5]. These compounds, whether isolated or as constituents of plant extracts and essential oils, have shown promising antimicrobial effects [6]. This

review explores the global burden of antibiotic resistance, outlines the underlying mechanisms driving resistance across different microbial strains, and highlights the usefulness of plant- derived compounds as viable alternative antimicrobial agents.



GRAPHICAL ABSTRACT

2. UNDERSTANDING MULTIDRUG RESISTANT BACTERIA

Globally, MDR infections contribute significantly in increasing mortality and healthcare costs. Antibiotic resistance spreads rapidly due to the ease with which genes are transferred among bacteria in major pathogens like *E. coli*, *Campylobacter*, *Salmonella, Listeria*, and *Staphylococcus aureus* in humans and animals [8]. Importantly, MDR is no longer remaining confined to healthcare facilities. Community associated multidrug- resistant (CA-MDR) strains have become a significant cause of infections unlike hospital isolates. CA-MDR pathogens persist without continuous antibiotic exposure and can colonize healthy individuals. Methicillin-resistant *Staphylococcus aureus* strains (MRSA), remains the most widespread community acquired MDR pathogen. However, there is growing focus on extended spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* in community settings, which may also harbor carbapenemase genes [9]. Initially antibiotic resistance is linked to chromosomal mutations more often develop due to mobile genetic elements like plasmids, transposons, and integrons acquired from the environment. These resistant bacteria can spread globally, leading to treatment failures and serious public health concerns [11].MRSA is a challenging and serious bacterial infection to manage. There are of two main types: one that spreads in hospitals called as healthcare associated MRSA or HA-MRSA, usually affecting people who are already at sick, and another that spreads in the community called community-associated MRSA or CA-MRSA, which can infect even healthy individuals. CA- MRSA is often more dangerous and easier to spread. It may produce potent toxins such as Panton valentine leukocidin (PVL) and includes fast transmissible strains USA300 and ST80. These types are more common in the U.S. than in Europe, but they could spread quickly, which is a significant concern [12]. A concerning development in antimicrobial resistance is the growing prevalence of *Acinetobacter baumannii* strains that are resistant to carbapenems. This resistance is largely due to the bacteria's ability to produce class D β-lactamases enzymes such as OXA-23, OXA-24, and OXA-58 that break down carbapenem antibiotics and render them ineffective. These enzymes, along with other resistance mechanisms such as porin loss and target mutations effects treatment options [14]. *Escherichia coli*, a leading cause of community and nosocomial infections, has shown increased resistance due to the production of ESBLs (CTX-M-15), AmpC

lactamases, and carbapenemases (NDM, KPC, OXA-48). These bacteria are increasingly common in community-acquired urinary tract infections (UTIs) and bloodstream infections, often requiring the use of antibiotics such as carbapenems [15]. The role of agriculture in driving resistance has been well documented. For instance, the glycopeptide antibiotic avoparcin (AVO), which is used in livestock feed in Europe, led to the emergence of vancomycin resistant *enterococci (*VRE) carring VanA gene in both meat products and healthy individuals. Although, after ban on AVO in the EU, VRE levels in meat and human carriers dropped significantly, underscoring the connection between antibiotic use in animals and human resistance [16].

Even in less populated countries like Australia and New Zealand, community-onset ESBL producing *E. coli* infections are emerging due to international travel and healthcare-associated exposure. A large study revealed several risk factors, including birth in the Indian subcontinent, recent UTIs, travel to high-prevalence regions, prior antibiotic use, and recent contact with healthcare facilities. Most strains carried the bla CTX-M gene, and nearly half were of the pandemic ST-131 lineage, demonstrating how resistance spreads through both international travel and local healthcare systems [17]. The development of drug resistance in microorganisms is often facilitated by the acquisition of resistance genes through horizontal gene transfer, typically via mobile genetic elements such as plasmids. Additionally, the overexpression of multidrug efflux pumps helps bacteria to expel a extensive array of antibiotics, therefore reducing their intracellular concentrations and effectiveness [2]. The common multi drug resistant bacteria and their resistance mechanism have been summarized in Table-1.

Pathogen	**Resistance Mechanisms**	**Infections**	**References**
Staphylococcus aureus (MRSA)	Methicillin resistance (mecA gene), PVL toxin (in CA-MRSA), resistance to β-lactams and others	Skin infections, pneumonia, bloodstream, both hospital & community	DeLeo *et al.,* 2010; Witte, 2009; van Duin and Paterson, 2016; Karaman *et al.,* 2020
Enterococcus spp. (VRE)	Vancomycin resistance (VanA-type), gene transfer from food chain	Hospital infections, gut colonization	Klare *et al.,* 1999; Karaman *et al.,* 2020
Escherichia coli	ESBLs (e.g., CTX-M-15), Amp C β-lactamases (viz; CMY), carbapenemases (e.g., NDM, OXA-48), ST131 lineage	UTIs, bloodstream infections, enteric diseases	Pitout, 2013; Rogers *et al.,* 2014; Urban-Chmiel et al., 2022; van Duin and Paterson, 2016
Klebsiella pneumoniae	ESBL and carbapenemase production (e.g., KPC, NDM)	Hospital-acquired infections	Bharadwaj *et al.,* 2022; Karaman *et al.,* 2020
Acinetobacter baumannii	CHDLs (OXA-23, OXA-24, OXA-58), metallo-β-lactamases (VIM, IMP), porin loss (CarO), PBP modifications	Pneumonia, wound, bloodstream (esp. ICU patients)	Poirel and Nordmann, 2006
Pseudomonas aeruginosa	Efflux pump inhibition, porin changes, β-lactamases (e.g., AmpC)	Respiratory tract infections in immunosuppresed patients	Bharadwaj *et al.,* 2022; Wartu *et al.,* 2019
Salmonella spp.	Efflux pump inhibition, porin changes, β-lactamases (e.g., AmpC)	Foodborne illness, enteritis	Urban-Chmiel *et al.,* 2022

Campylobacter spp.	Macrolide and fluoroquinolone resistance, gene transfer	Gastroenteritis, foodborne illness	Urban-Chmiel *et al.,* 2022
Listeria monocytogenes	Emerging resistance (less studied), horizontal gene transfer	Foodborne disease, meningitis	Urban-Chmiel *et al.,* 2022

Table-1 Common multidrug-resistant (MDR) bacteria, resistance mechanisms, infection sources, and references

3. HERBAL PLANT EXTRACTS WITH ANTIMICROBIAL POTENTIAL

Antibiotic resistance has become an alarming global health concern, leading to an increased attention and interest in developing alternative antimicrobial agents from natural source particularly medicinal plants. In a study by Zouine and co-workers (2024), conducted research between 2014 to 2024, and highlighted plant extracts with minimum inhibitory concentrations (MIC) ≤625 µg/mL. Among 81 plants, the extracts of *Quercus coccifera, Ocimum gratissimum,* and *Curcuma longa* demonstrated notable activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus,* and *Escherichia coli*. The plants of families such as *Myrtaceae*, *Lamiaceae,* and *Apiaceae* were found to be the most potent, with leaves being the most commonly used plant part and methanol and ethanol the preferred solvents. Supporting these findings, Pane (2024), reviewed the effectiveness of traditional herbs such as *Curcuma longa*, *Opuntia ficus-indica,* and *Linum usitatissimum* against multidrug-resistant (MDR) pathogens. While *C. longa* showed the significant antibacterial action, *O. ficus-indica* showed efficacy even in autoclaved forms, and *L. usitatissimum* found beneficial in combination therapies. The synergistic potential of these herbs with conventional antibiotics was particularly noteworthy in reducing necessary dosages.

Gonelimali and co-workers (2018), further confirmed the antimicrobial effects of *Hibiscus sabdariffa*, *Rosmarinus officinalis*, *Syzygium aromaticum,* and *Thymus vulgaris* extracts against various foodborne pathogens. These workers demonstrated both antibacterial and antifungal activity, with mechanisms involving cell membrane disruption in *Staphylococcus aureus* and *E. coli.* They also found that ethanolic extracts, especially from clove and thyme, were effective against yeast *Candida albicans*.

Terminalia bellirica and *Terminalia chebula* are main plants in harbal medicine, are known for their antibacterial, anti-inflammatory, and antioxidant properties, particularly in treating gastrointestinal infections. Tiwana and co-workers (2024), evaluated their fruit extracts against various bacteria like *Bacillus cereus, Shigella sonnei*, *Shigella flexneri*, and *Salmonella typhimurium*. The extracts showed strong antibacterial effects and worked synergistically with various antibiotics. LC-MS analysis confirmed the presence of tannins such as gallic and ellagic acid. Toxicity tests confirmed that the extracts are safe, and has great potential for developing new antibiotics [20]. *Terminalia bellirica* Roxb. (Bahera), is widely found in Southeast Asia and is very useful in traditional medicine. Its key phytochemicals include tannins, gallic acid, ellagic acid, and chebulanic acid, which contribute to a broad range of medicinal effects. Various parts of this plant show antisecretory, antimicrobial, antidiabetic, antioxidant, anti-inflammatory, anticancer, and hepatoprotective effects [21]. *Terminalia chebula* which is also known as the king of medicinal plants in Ayurveda, is widely used for its therapeutic benefits. This plant is rich in phytochemicals such as chebulagic acid, chebulinic acid, and rutin, which contribute to its antioxidant, antimicrobial, anti-inflammatory, and digestive effects. Results from *in vivo* studies supports its role in managing cardiovascular, immune, cancer, and neurological conditions [22].

The underlying mechanisms of resistance and role of phytochemicals in overcoming them were examined by Jubair and co-workers (2021). They discussed how plants carrying a variety of secondary metabolites like alkaloids, tannins, quinones, and flavonoids offer antimicrobial properties through diverse mechanisms. These mechanisms include efflux pump inhibition and disruption of bacterial structures. These phytochemicals can function both independently and in synergy with antibiotics to combat MDR strains. Ahmed and co-workers (2023), elaborated this perspective by discussing how plant derived secondary metabolites not only provide direct antibacterial effects but also modulate immune responses and interfere with resistance mechanisms. They highlighted the significance of understanding protein interactions and pharmacokinetics in order to fully harness the therapeutic potential of medicinal herbs. Cowan (1999), laid foundational insights into the contribution of plant products as antimicrobial agents, noting the historical use of plant products in traditional medicine. Despite 25–50% of pharmaceutical drugs originating from plants, only few are formally recognized as antimicrobials. Nonetheless, tannins, terpenoids, alkaloids, and flavonoids have demonstrated *in vitro* efficacy, justifying further research into their clinical applications.

Vaou and co-workers (2021), highlighted the present limitations in standardizing extraction techniques and antimicrobial testing protocols, which hinder reproducibility and clinical translation. They called for improved understanding of pharmacological profiles and optimized methodologies to ensure effective development of plant-based antimicrobials. Building upon these findings, Álvarez-Martínez and co-workers (2021), identified 101 relevant studies conducted between 2016 and 2021, cataloging 41 phytochemicals and 39 plant extracts or essential oils. Polyphenols and terpenes stood out as most active agents, with plasma membrane disruption being the primary antimicrobial mechanism. Structural features such as hydroxyl groups and sugar conjugation played crucial roles in activity. Notably, beta-lactam combinations with phytochemicals were effective due to synergistic efflux pump inhibition. Porras and co-workers (2021), performed a systematic review of 459 plant-derived compounds reported between 2012 and 2019. Phenolic derivatives constituted 50.8% of the compounds, followed by terpenoids (26.6%), alkaloids (5.7%), and other metabolites. Among these, 183 compounds were examined in details for their mechanisms of action, biosynthetic pathways, and structure activity relationships. These studies emphasize the rich antimicrobial potential of plant-derived compounds and the necessity for advanced methodologies to fully integrate them into modern therapeutic strategies. The phytochemicals and their antimicrobial potential have been illustrated in Fig-1 and Table-2.

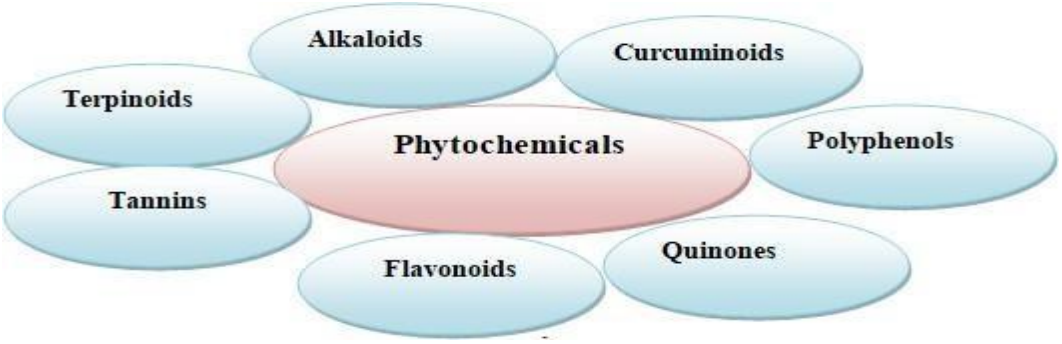


Fig-1 Plant-derived phytochemicals

Plant extract	Class	Target Microorganisms	Mechanism of Action	References
Quercus coccifera extract	Polyphenols, Tannins	*Pseudomonas aeruginosa*	Disruption of bacterial cell wall	Zouine *et al.* (2024)
Ocimum gratissimum extract	Essentialoils (e.g., Eugenol)	*Staphylococcus aureus*	Membrane disruption	Zouine *et al.* (2024)
Curcuma longa (Turmeric)	Curcuminoids	*Escherichia coli, MDR strains*	Synergistic effect with antibiotics; disrupts cell processes	Zouine *et al.* (2024), Pane (2024)
Opuntia ficus-indica	Polyphenols, Flavonoids	MDR pathogens	Antibacterial even after autoclaving	Pane (2024)
Linum usitatissimum (Flaxseed)	Lignans, Omega-3 fatty acids	MDR bacteria	Synergistic action in combination therapies	Pane (2024)
Hibiscus sabdariffa	Anthocyanins, Organic acids	Foodborne pathogens	Membrane disruption	Gonelimali *et al.* (2018)

Rosmarinus officinalis	Terpenoids, Carnosic acid	*E. coli, S. aureus, fungi*	Antibacterial and antifungal activity	Gonelimali *et al.* (2018)
Syzygium aromaticum (Clove)	Eugenol (Phenylpropanoid)	*Candida albicans, S. aureus, E. coli*	Disrupts membrane integrity	Gonelimali *et al.* (2018)
Thymus vulgaris (Thyme)	Thymol, Carvacrol (Terpenoids)	*Candida albicans,* bacteria	Membrane disruption	Gonelimali *et al.* (2018)
General phytochemicals	Alkaloids, Tannins, Flavonoids, Quinones	MDR strains	Efflux pump inhibition, enzyme inhibition, membrane disruption	Jubair *et al.* (2021), Cowan (1999)
Various plant metabolites	Polyphenols, Terpenoids	Multiple bacteria and fungi	Plasma membrane disruption, efflux pump inhibition	Álvarez-Martínez *et al.* (2021)
Broad spectrum phytochemicals	Phenolic derivatives (50.8%), Terpenoids (26.6%), Alkaloids (5.7%)	Various resistant strains	Diverse mechanisms including structural interference and biosynthetic inhibition	Porras *et al.* (2021)

Exploring plant derived antimicrobial agents

Recently, the exploration of plant based antimicrobial agents has gained significant attention as researchers from diverse fields such as ethnopharmacology, botany, microbiology, and chemistry of natural product delve into the potential of herbal compounds in fighting infectious diseases. A significant part of modern medicines, ranging from 25% to 50%, are derived from plants, though only a few have been adopted as antimicrobial agents. Historically, traditional medicine practitioners believe on herbal remedies for infection treatment and prevention, Western world is now trying to replicate these successes. Plants generate a diverse range of secondary metabolites, including tannins, terpenoids, alkaloids, and flavonoids, all of which have shown antimicrobial properties [4,26].

Plant derived antimicrobial agents are increasingly seen as viable alternatives to traditional antibiotics and chemical preservatives [25]. It was evident that combination of multiple natural compounds has demonstrated synergistic effects with enhanced antimicrobial activity. However, obtaining pure compounds remains a complex and time-consuming process, despite advances such as microwave assisted and supercritical fluid extraction. Additionally, large volumes of plant waste are produced during extraction, necessitating effective waste management strategies to ensure sustainability. Toxicological studies are mandatory to ensure the safety of these substances before their widespread use in clinical or commercial settings [28]. Recent advancements increased antimicrobial potential of plant derived compounds, especially terpenes, flavonoids, alkaloids, and phenylpropanoids. These bioactive substances, whether isolated or within complex extracts and essential oils, have shown strong activity against multidrug-resistant strains. Disruption of bacterial membranes is one of the most commonly observed mechanisms of effect, with hydroxyl groups and molecular conjugation being important factors in their effectiveness. Combining plant derived compounds with conventional antibiotics such as beta-lactams can offer promising strategies to combat drug resistance, including the inhibition of efflux pumps. Despite these promising results, further exploration using tools like omics technologies and network pharmacology is needed to fully unlock their therapeutic potential and optimize antimicrobial formulations for clinical use [6, 7].

Another study analyzes research data from the last two decades on the antibacterial properties of active compounds found in widely used East Asian herbs. These compounds viz; alkaloids, flavonoids, essential oils, terpenes, organic acids, coumarins, and lignans, exhibit notable antimicrobial activity. Moreover, multi herb formulations often shown greater antibacterial efficacy than individual herbs. Their mechanisms of action include perturbation of bacterial cell membranes, interference

with protein and nucleic acid synthesis, and altering osmotic balance within microbial cells. These findings suggest that these herbal compounds and formulations may serve as promising candidates for next-generation antibacterial therapies [29]. The World Health Organization identifies antibiotic resistance as an escalating global health threat. In light of this, several approaches, such as developing antibiotics with novel mechanisms, inhibiting multidrug resistance (MDR) efflux pumps, and disrupting bacterial biofilm formation, has been explored. Among natural compounds, flavonoids have received considerable attention for their antibacterial potential. More than 150 studies since 2005 have revealed their effectiveness against various bacterial pathogens. The chalcones subclass of flavonoids possessed antibacterial activity up to six times greater than conventional antibiotics. Synthetic flavonoid derivatives have shown even greater potency, exhibiting 20 to 80-fold greater efficacy against multidrug resistant bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. The mechanisms of effect of flavonoids include disrupting bacterial membranes, inhibiting nucleic acid and protein synthesis, interfering with enzyme function, and suppressing efflux pump activity. These findings underscore the usefulness of flavonoids as a foundation for novel antimicrobial agents [30]. Specific research on some flavonoids has uncovered their different antibacterial mechanisms. For instance, quercetin's antibacterial action is believed to be due to its inhibition of DNA gyrase, while sophoraflavone G and (−)-epigallocatechin gallate are believed to disrupt the cytoplasmic membrane. Several other flavonoids, such as licochalcones A and C, may interfere with energy metabolism. Continued investigation into their antimicrobial mechanisms could pave the way for the development of effective and clinically viable antimicrobial agents [31].

Diallyl thiosulfinate, or allicin, the bioactive compound present in garlic, is well known for its antibacterial and antifungal properties. This compound when tested against *Salmonella typhimurium*, was found to delay inhibition at bacteriostatic concentrations, followed by a period of suppressed growth and eventual return to growth at a slower rate. Allicin targets RNA synthesis leading to complete inhibition, while DNA and protein synthesis are partially affected. These findings provide important insights into the mechanisms underlying allicin's antibacterial action [32]. Coumarin which is a plant-derived QS inhibitor was known to decrease biofilm development and virulence in *P. aeruginosa*. This compound inhibited QS in a biosensor strain, suppressed protease and pyocyanin production, along with significantly affected key genes involved in the QS systems, type III secretion, and c-di-GMP metabolism. The outcomes of this study highlights coumarin's potential as an anti-biofilm and anti-virulence agent for treating *P. aeruginosa* infections [33]. Terpenes produced by various plants and animals, have a broad range of biological activities, including antimicrobial effects. Terpenoids' effects on pathogens and skin permeability highlight their potential in modern medicine, justifying broader use in healthcare [34]. Mechanisms of action of the plant derived antimicrobial compounds have been illustrated in Fig-2 and Table-3.

Compound	**Mechanism of Action**	**References**
Tannins, Terpenoids, Alkaloids, Flavonoids	Disrupt bacterial membranes, interfere with protein and nucleic acid synthesis, and alter osmotic balance in microbial cells.	Cowan, 1999
Flavonoids (e.g., Chalcones)	Disrupt bacterial membranes, inhibit nucleic acid and protein synthesis, interfere with enzyme function, and suppress efflux pump activity.	Farhadi *et al.,* 2018
Quercetin (flavonoid)	Inhibit DNA gyrase.	Cushnie *et al.,* 2006
Sophoraflavone G (flavonoid)	Disrupt cytoplasmic membrane.	Cushnie *et al.,* 2006
(−)-Epigallocatechin gallate (flavonoid)	Disrupt cytoplasmic membrane.	Cushnie *et al.,* 2006
Licochalcones A and C (flavonoids)	Interfere with energy metabolism.	Cushnie *et al.,* 2006

Diallyl thiosulfinate (Allicin)	Primarily targets RNA synthesis, with secondary inhibition of DNA and protein synthesis.	Feldberg *et al.,* 1988
Coumarin	Inhibit quorum sensing (QS), reduce biofilm formation, down regulate key genes in QS systems, type III secretion, and c-di- GMP metabolism.	Zhang *et al.,* 2018
Terpenes	Disrupt cell membranes; affect skin permeability, antimicrobial effects, cancer chemoprevention, anti-inflammatory effects.	Paduch *et al.,* 2007

Table- 3 Functional mechanisms of plant based antimicrobial compounds

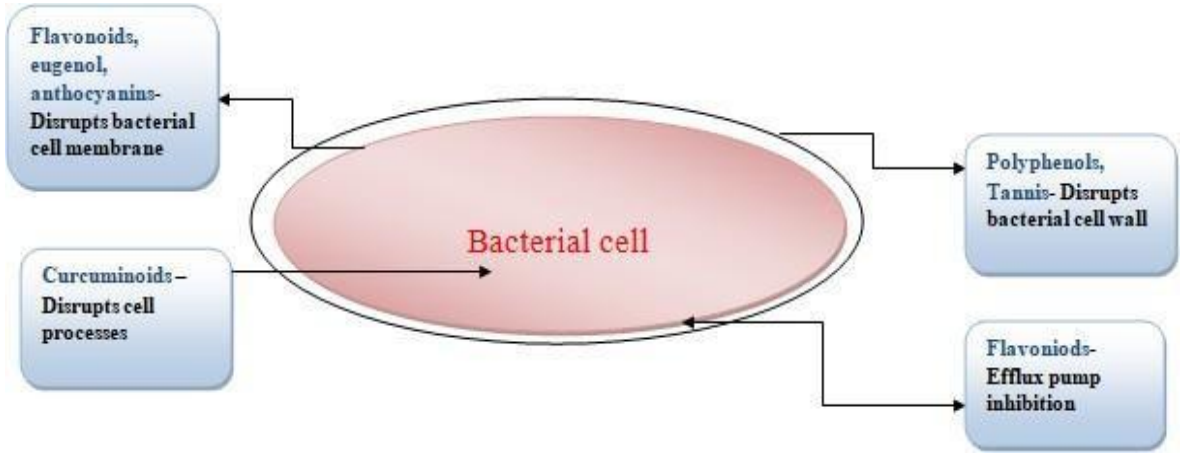


Fig-2 Functional mechanisms of plant based antimicrobial compounds

Interactions between phytochemicals and antibiotic agents

Despite of various advancements in antimicrobial drug development, multidrug resistance remains a serious public health challenge, contributing to increasing mortality rates. Recent research has explored alternative treatment strategies to fight with resistant pathogens. Among them combination therapies are emerging as a promising solution. By targeting different pathways, drug combinations such as plant extracts, essential oils, and nanomaterials may produce synergistic effects, increased efficacy and selectivity as compared to single agents. It was observed that these combinations when used in optimal ratios can boost therapeutic outcomes at lower doses [35]. While conventional antimicrobials remain useful in combating multi drug resistance, plant-based compounds offer promising alternatives. Phytochemicals are now being explored in combination with existing drugs to overcome resistance. These natural compounds can inhibit resistance mechanisms, like drug degrading enzymes and efflux pumps, thereby enhancing drug effectiveness. Numerous herbal extracts, essential oils, and pure compounds have shown synergisms with antibiotics and antifungals, leading to reduced minimum inhibitory concentrations and improved susceptibility [36]. In a study the synergistic effects of plant extracts with cefixime was assessed against drug resistant clinical isolates. Using disc diffusion, microbroth dilution, checkerboard, and time-kill assays, several extracts rich in gallic acid, quercetin, and cinnamic acid demonstrated significant antibacterial activity when combined with cefixime. Synergism was found to be both time and concentration dependent with combinations significantly reducing bacterial growth and protein content. These results support the potential use of certain plant extracts as antibiotic adjuvants to combat resistant infections [37]. Another study highlights the effectiveness of plant flavonoids to enhance antibiotic effectiveness, with notable synergistic effect against *Staphylococcus aureus* and *Escherichia coli.* These results advocates the strategic use of flavonoid antibiotic combinations to combat antimicrobial resistance and reinforce the importance of a holistic “One Earth-One Health” approach in addressing AMR through ecosystem-based solutions [38]. Plant derived compounds can act as synergistic enhancers, which boost the effectiveness of standard antibiotics even if they show little or no antimicrobial activity on their own. Combining plant extracts with antibiotics has shown promising results

against resistant pathogens, offering novel options for treating infections. This synergy also helps to reduce toxicity and dosage by allowing lower concentrations of both agents. Therefore, ongoing research into plant based modulators of multidrug resistance is necessary [39]. In a study conducted by Nascimento and co-workers (2000), the antimicrobial properties of various plant extracts and bioactive compounds of plants was assessed against both antibiotic sensitive and resistant

microorganisms including their potential synergistic effects with antibiotics. These workers evaluated extracts from plants such as clove (*Caryophyllus aromaticus*), jambolan (*Syzygyum joabolanum*), guava, pomegranate, and thyme, along with benzoic acid, cinnamic acid, eugenol, and farnesol. Clove and jambolan showed the strongest antimicrobial activity, by inhibiting 64.2% and 57.1% of tested strains, with maximum effectiveness (83.3%) against antibiotic-resistant bacteria. However, no antimicrobial effects were observed for sage and yarrow exhibited. Notably, combinations of plant extracts and antibiotics displayed synergistic effects, particularly against *Pseudomonas aeruginosa,* even when used at low concentrations with antibiotics that were otherwise ineffective [40]. In another study the synergistic antibacterial effects of *Jatropha curcas* seed extracts, seed oil, and antibiotics has been demonstrated against clinical, MDR, and ATCC bacterial strains. Methanolic extracts showed strong activity, especially against *Staphylococcus aureus*. Combinations of the methanolic extract with rifampicin exhibited highest synergism, particularly against *MRSA, E. coli, A. baumannii,* and *P. aeruginosa*. Overall it was found that methanolic extracts showed 44.71% synergism in combinations, indicating enhanced antibiotic efficacy and potential in combating drug resistant infections [41].

Challenges associated with development of novel antimicrobial agents from plants

Despite of extensive research in exploiting antibacterial potential of plant derived compounds, some challenges hinder their clinical application. The major challenges include restricted availability of sources, frequent rediscovery of known agents, suboptimal pharmacokinetic properties, and a limited understanding of molecular targets and mechanisms of action. Critical examination of these issues, the advancement of plant derived agents as viable solutions can be adopted to fight global antimicrobial resistance crisis [42]. The most deeply studied novel bacterial targets for drug development include quorum sensor biosynthesis, bacterial virulence factors, bacterial cell division machinery, bacterial cell wall synthesis, PDF inhibitors, biofilm synthesis, and fatty acid biosynthesis. Nonetheless, these innovative discovery approaches have resulted in the identification of agents now undergoing preclinical evaluation [43]. Plant derived compounds, with their structural diversity and unique mechanisms of action, offer significant usefulness in fighting against various infections. This approach not only enhance therapeutic arsenal but also supports ecological and cultural preservation. Continued research in this field may pave the way for effective, eco-friendly, and globally relevant solutions to today's infectious disease challenges [44]. Furthermore, through the integration of extensive research, nanotechnology, and computational approaches such as in silico modeling and fragment-based drug design (FBDD), there will be improvements in antimicrobial actions and selectivity at target sites [45]. Plantextracts have the ability to bind with protein domains and modify their interactions with other proteins, thus influencing key biological functions. This feature enables herbal compounds to play a role in modulating host immune responses [46].

As limited numbers of antibacterial drugs are under development, survey has been conducted to identify obstacle and effective way to develop these agents for clinical application. The primary challenges identified were financial and regulatory in nature. Addressing multidrug- resistant strains requires rapid diagnostics, updated regulatory policies, and adapted trial endpoints and designs. Both regulatory authorities and collaborative public-private efforts are actively working to overcome these hurdles [47]. Recent research on antimicrobial compounds from plants has rapidly expanded current knowledge on these agents, exploring their origins, mechanisms of action, and effectiveness in fighting infections [48,49].

4. CONCLUSION AND FUTURE PERSPECTIVE

The growing threat of antibiotic resistance, driven by indiscriminate use of antibiotics, poses a serious global health challenge. Multidrug resistant pathogens are no longer confined to hospitals, and their increasing prevalence in communities demands urgent attention to handle this problem. In this context, plant derived antimicrobial agents offer a promising and sustainable alternative. Phytochemicals like flavonoids, alkaloids, terpenes, and polyphenols have demonstrated promising antimicrobial activities and mechanisms that complement or enhance existing antibiotics. Looking ahead, the integration of plant based compounds into mainstream antimicrobial strategies holds great potential. Future research should focus on standardizing extraction methods, understanding pharmacodynamics and pharmacokinetics, and conducting rigorous clinical trials. Pharmacological and bioinformatics studies can further help to develop novel plant derived candidates and optimization of synergistic effects with conventional antibiotics. With a multidisciplinary approach and continued scientific investment, plant derived antimicrobials may play a critical role in the fight against antibiotic resistance.

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Conflict of interest

Authors has no conflict of interest to declare.

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