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Enhancing Antibiotic Efficacy: Synergy Between Medicinal Plant Extracts and Conventional Antibiotics in Combating MDR Infections

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Abstract

Multidrug-resistant (MDR) pathogens are becoming a major global concern, threatening human health, food security, and the effectiveness of modern medical treatments. As traditional antibiotics lose their potency, there is an urgent demand for alternative approaches to treat these resistant strains. This study explored the combined effects of plant-based and standard antibiotics on MDR pathogens. Four medicinal plants known for their antimicrobial properties were chosen*: Allium sativum* (garlic), *Curcuma longa* (turmeric), *Ocimum sanctum* (holy basil or tulsi), and *Azadirachta indica* (neem). Ethanolic extracts of these plants were prepared and tested against clinical isolates of *Staphylococcus aureus* (MRSA*), Escherichia coli* (MDR), *Klebsiella pneumoniae*, and *Candida albicans*, both individually and in combination with ciprofloxacin, amoxicillin, and amphotericin B. Antimicrobial susceptibility was evaluated by disk diffusion and checkerboard assays. All four plant extracts showed inhibitory effects against the MDR strains tested, with garlic and neem exhibiting the strongest standalone activity. When combined with antibiotics, the plant extracts displayed varying levels of interaction, with several combinations showing synergistic effects, as indicated by the Fractional Inhibitory Concentration Index (FICI) values. In these synergistic combinations, the minimum inhibitory concentrations (MICs) of antibiotics were significantly reduced by four- to 8-fold. These results suggest that plant-derived antimicrobials can enhance the effectiveness of conventional antibiotics, thereby providing a promising strategy for addressing MDR pathogens. Further studies are necessary to standardize the extraction methods, determine the optimal dosing regimens, and evaluate the efficacy and safety of these combinations in clinical settings.

Keywords: Plant-derived antimicrobials, Multidrug-resistant pathogens, Synergistic effects, Combination therapy, Antibiotics, Medicinal plants, Phytochemicals, Resistance mechanisms, Antimicrobial activity, Fractional Inhibitory ,Concentration Index (FICI)

1. Introduction

The rise of multidrug-resistant (MDR) pathogens is a significant global threat to human and animal health, food security, and the effectiveness of modern medicine. These pathogens have developed the ability to resist multiple classes of antibiotics, rendering several standard treatments ineffective. The overuse and misuse of antibiotics in healthcare, veterinary, and agricultural practices has accelerated this crisis, resulting in a growing number of untreatable infections worldwide. As the efficacy of conventional antibiotics diminishes, there is an urgent need for alternative strategies to combat MDR

pathogens. Plant-derived antimicrobials have emerged as promising candidates due to their diverse chemical structures and mechanisms of action. (Mallik et al. 2024) The combination of plant-derived compounds with existing antibiotics offers a potential solution to enhance antimicrobial activity and overcome resistance mechanisms. Phytochemicals, the bioactive compounds found in plants, have demonstrated potent antimicrobial properties against a wide range of pathogens, including MDR strains. These natural compounds often exhibit multiple modes of action, making it more challenging for bacteria to develop resistance. (Onyancha et al. 2021) Furthermore, the synergistic effects observed between plant-derived antimicrobials and conventional antibiotics can potentially restore the efficacy of previously ineffective drugs and provide new therapeutic options for treating resistant infections. The utilization of antibiotic adjuvants offer several advantages. Firstly, they can restore the effectiveness of existing antibiotics against resistant strains. Adjuvants can inhibit the mechanism that confer resistance making the pathogens susceptible to the action of antibiotics (Kumar et al. 2023)

In response to this alarming situation, there is a renewed interest in exploring alternative and complementary antimicrobial strategies. Among these, plant-derived antimicrobials have attracted considerable attention. For centuries, medicinal plants have been used in traditional systems of medicine worldwide, particularly in regions such as India, where knowledge of herbal treatments is well established. Plants produce a wide array of bioactive compounds—such as alkaloids, flavonoids, tannins, and essential oils—that exhibit antimicrobial properties (Twebaza H 2025). Additionally the review emphasizes current and future research directions for these phytochemicals, including synergism with conventional antibiotic and advanced drug delivery system for treating and eradicating biofilm associated infections (Nwafor et al. 2024) These phytochemicals have mechanisms of action distinct from conventional antibiotics, which may include disrupting microbial cell membranes, inhibiting metabolic enzymes, or interfering with DNA replication. Antimicrobial approaches include dual antibiotic therapy, antimicrobial peptides, monoclonal antibodies, and probiotics (Berger and Loewy 2024).The diverse mechanisms of action exhibited by plant-derived antimicrobials make them promising candidates for combination therapy with conventional antibiotics. Such combinations could potentially enhance the overall efficacy of treatments and reduce the likelihood of the development of resistance. Moreover, the use of plant-based compounds may offer additional benefits such as reduced side effects and improved patient compliance, further contributing to the fight against antimicrobial resistance.

Several plants, such as *Allium sativum* (garlic), *Azadirachta indica* (neem), *Curcuma longa* (turmeric), and *Ocimum sanctum* (tulsi), have shown promising antimicrobial activity against bacteria and fungi. (Jadheerahsan et al. 2022) Although these plant extracts may not always be as potent as modern antibiotics when used alone, their combined use with synthetic drugs has been shown in many studies to produce a synergistic effect. In such combinations, the plant compounds may enhance the activity of antibiotics, reduce the required dosage, or even restore the effectiveness of antibiotics to which pathogens have become resistant. This synergistic approach not only increases the overall efficacy of treatments but also potentially reduces the risk of adverse side effects associated with higher antibiotic doses. Furthermore, the complex nature of plant-derived compounds makes it challenging for microorganisms to develop resistance, potentially extending the useful life of existing antibiotics. As research in this field progresses, it is crucial to conduct rigorous clinical trials to establish the safety and efficacy of these plant-antibiotic combinations for various infections and patient populations. The development of standardized extraction methods and quality control measures for plant-based compounds is essential to ensure consistency in their antimicrobial properties (Chilate et al. 2024) .

Additionally, investigating the molecular mechanisms underlying the synergistic effects between plant extracts and antibiotics could lead to the design of more effective combination therapies. Future research should also explore the potential of these plant-antibiotic combinations in addressing biofilm-associated infections, which are notoriously difficult to treat with conventional antibiotics alone. The integration of plant-derived compounds with antibiotics represents a promising avenue for combating antibiotic resistance and improving treatment outcomes. the synergy observed with conventional antibiotics, coupled with their ability to target specific microbial resistance mechanism underscores the potential of monoterpens in combating antibiotic resistant infection (Kong et al. 2025) This approach could potentially revolutionize the field of infectious disease management by offering more sustainable and effective therapeutic options. As this area of research advances, it will be essential to consider the potential ecological impacts of increased plant compound usage and develop sustainable sourcing strategies to ensure the long-term viability of these novel treatments.

The concept of synergy between plant-derived antimicrobials and conventional antibiotics represents a hopeful approach in the fight against MDR infections. Synergistic combinations can not only improve therapeutic efficacy but also reduce the likelihood of further resistance development by targeting pathogens through multiple pathways. Moreover, the use of plant-based agents—especially those that are locally available and inexpensive—offers an eco-friendly and sustainable solution, particularly for rural and under-resourced areas. The integration of plant-derived compounds with antibiotics presents a promising strategy for addressing the global challenge of antimicrobial resistance. By harnessing the power of nature's diverse arsenal of bioactive molecules, researchers can potentially develop more effective and sustainable treatment options for a wide range of infectious diseases. This approach not only aligns with the principles of traditional medicine but also leverages modern scientific techniques to unlock new possibilities in the field of antimicrobial therapy (Monika et al. 2020) .

This research aims to investigate the synergistic interactions between selected medicinal plant extracts and commonly used antibiotics against MDR pathogens. The study involves isolating resistant bacterial and fungal strains from clinical or environmental sources and evaluating the antimicrobial potential of various plant extracts alone and in combination with antibiotics using standard microbiological methods. The objective is to determine whether these natural and synthetic agents can work more effectively together than separately, and to assess their potential application in medical and agricultural contexts. The findings from this research could pave the way for novel treatment strategies that combine the best of traditional and modern medicine. By harnessing the power of plant-derived compounds alongside conventional antibiotics, we may be able to overcome existing resistance mechanisms and extend the lifespan of our current antibiotic arsenal. Additionally, this approach could lead to the development of new therapeutic options that are more accessible and affordable for communities worldwide, potentially bridging the gap in healthcare disparities. The integration of traditional medicinal knowledge with modern scientific methodologies presents a promising avenue for addressing the global challenge of antimicrobial resistance. This research not only aims to discover new therapeutic combinations but also seeks to validate and potentially modernize age-old healing practices. By exploring the synergistic potential of plant extracts and antibiotics, this study could contribute to a more holistic and sustainable approach to combating infectious diseases.

In conclusion, the synergistic approach represents a bridge between traditional knowledge and modern medicine. It offers a promising pathway toward developing effective, affordable, and sustainable therapies to combat antibiotic-resistant infections—one of the most urgent health challenges of our time.

This research not only addresses the immediate need for new antimicrobial strategies but also highlights the importance of preserving and studying traditional medicinal practices. The integration of natural compounds with conventional antibiotics could potentially reduce the side effects associated with high-dose antibiotic treatments, improving patient outcomes and compliance. Furthermore, this approach may inspire a paradigm shift in drug discovery, encouraging pharmaceutical companies to explore combination therapies and natural product research more extensively. The implications of this research extend beyond the realm of infectious diseases, potentially influencing the treatment of other medical conditions where combination therapies could be beneficial. By demonstrating the value of traditional knowledge in modern scientific research, this study may encourage greater respect for and preservation of indigenous healing practices worldwide. Additionally, the success of this approach could pave the way for more interdisciplinary collaborations between ethnobotanists, pharmacologists, and medical practitioners, fostering a more integrated and holistic approach to healthcare.

Review of Literature

The escalating issue of multidrug-resistant (MDR) pathogens has greatly influenced both global health and agricultural productivity. With conventional antibiotics proving inadequate against these resistant strains, researchers are increasingly investigating alternative and complementary therapies, particularly focusing on the promising potential of plant-derived antimicrobials.

Plants generate a diverse range of bioactive substances, including alkaloids, phenolics, terpenoids, and flavonoids. These secondary metabolites exhibit broad-spectrum antimicrobial properties and are crucial for the plant's defence mechanism against microbial invasions. When extracted and applied in vitro or in vivo, these compounds have shown significant antimicrobial effects against various bacterial and fungal pathogens. They not only prevent microbial proliferation but also interfere with critical processes such as cell wall formation, protein activity, and DNA replication.

The notion of combining plant-derived compounds with synthetic antibiotics has increasingly gained attention over time. This synergy can boost the effectiveness of antibiotics, even against strains that have developed resistance. Such interactions typically lead to a decreased minimum inhibitory concentration for both agents, allowing them to exert stronger antimicrobial effects while minimizing side effects and toxicity. This strategy is particularly useful when confronting pathogens that have evolved resistance mechanisms, such as efflux pumps or enzyme-mediated antibiotic degradation.

Certain compounds found in plants are known to hinder the formation of biofilms, which play a crucial role in antibiotic resistance. Biofilms serve as a protective shield for bacteria, enhancing their resistance to treatment. By disrupting or preventing the development of biofilms, plant-based antimicrobials make pathogens more susceptible to the effects of antibiotics. This approach is vital for managing persistent infections and agricultural diseases where biofilms are commonly present.

Additionally, the adaptability of medicinal plants renders them beneficial in both medical and agricultural contexts. In areas that are rural or have limited resources, they provide a sustainable and easily accessible option. Incorporating them into local healthcare strategies not only helps preserve traditional knowledge but also promotes environmentally friendly methods of disease management.

While these findings are promising, challenges persist in achieving standardized concentrations of plant extracts, ensuring reproducibility, and conducting large-scale studies. Nonetheless, integrating plant-based antimicrobials with conventional antibiotics presents a promising strategy for addressing the intricate problem of drug resistance.

2. Materials and Methods

2.1 Selection of Plant Materials

This study focused on four medicinal plants known for their antimicrobial properties:

- *Allium sativum* (Garlic),
- *Curcuma longa* (Turmeric),
- *Ocimum sanctum* (Holy Basil or Tulsi), and
- *Azadirachta indica* (Neem).

All plant materials were sourced from certified herbal suppliers and authenticated by a qualified botanist linked to a recognized institution.

2.2 Preparation of Plant Extracts

Fresh parts of plants, such as garlic bulbs, turmeric rhizomes, and leaves from tulsi and neem, were cleaned, allowed to air-dry in the shade, and then finely ground into powder. Each powdered sample, weighing 100 grams, underwent ethanol extraction using a Soxhlet apparatus for a duration of 6 to 8 hours. The resulting crude extracts were concentrated under reduced pressure with a rotary evaporator and subsequently stored at 4°C in amber-colored vials until needed.

2.3 Microorganisms and Antibiotics

Pathogens exhibiting resistance to multiple drugs were collected from a tertiary care hospital:

- *Staphylococcus aureus* (MRSA)
- *Escherichia coli* (MDR)
- *Klebsiella pneumoniae*
- *Candida albicans* (fungal pathogen)

The antibiotics used for comparison and combination included:

- Ciprofloxacin (broad-spectrum fluoroquinolone)
- Amoxicillin (β-lactam antibiotic)
- Amphotericin B (antifungal agent)

2.4 Antimicrobial Susceptibility Testing

Disk Diffusion Assay:

To prepare sterile Mueller-Hinton Agar plates, microbial suspensions standardized to 0.5 McFarland were used, while Sabouraud Dextrose Agar was selected for Candida. Discs containing plant extracts (30 µg/disc), antibiotics, and their combinations were placed on the agar. The plates were then incubated at 37°C for 24 hours, after which the inhibition zones were measured in millimeters.

Checkerboard Assay:

To ascertain the Minimum Inhibitory Concentrations (MICs), the broth micro dilution method was utilized. Synergistic effects were analysed through the application of the Fractional Inhibitory Concentration Index (FICI):

- FICI ≤ 0.5: Synergistic
- 0.5 < FICI ≤ 1.0: Additive
- < FICI ≤ 4.0: Indifferent
- FICI > 4.0: Antagonistic

3. Results

3.1 Antimicrobial Activity of Individual Plant Extracts

The study found that all four plant extracts were effective in inhibiting the growth of multidrug-resistant (MDR) bacterial and fungal strains. Among these, Allium sativum (Garlic) and Azadirachta indica (Neem) were particularly potent, showing the strongest individual effects against Staphylococcus aureus (MRSA) and Escherichia coli, respectively.

Pathogen	**Zone of Inhibition (mm) by Extract Alone**
***S. aureus* (MRSA)**	Garlic (18 mm) and Neem (16 mm)
E. coli (MDR)	Neem (20 mm) and Turmeric (15 mm)
K. pneumoniae	Tulsi (14 mm) and Garlic (13 mm)
Candida albicans	Garlic (17 mm) and Tulsi (12 mm)

3.2 Synergistic Effects with Conventional Antibiotics

Combining plant extracts with antibiotics resulted in varying interactions, with some combinations showing synergistic effects as evidenced by the FICI values.

Pathogen	**Plant Extract**	**Antibiotic**	**FICI**	**Interaction**
***S.aureus* (MRSA)**	Garlic (*A. sativum*)	Ciprofloxacin	0.29	Synergistic
***E. coli* (MDR)**	Neem *(A. indica)*	Amoxicillin	0.44	Synergistic
K. pneumoniae	Tulsi (*O. sanctum*)	Ciprofloxacin	0.72	Additive
C. albicans	Garlic (*A. sativum)*	Amphotericin B	0.32	Synergistic
***E. coli* (MDR)**	Turmeric (*C. longa)*	Amoxicillin	0.51	Additive

3.3 Reduction in Minimum Inhibitory Concentrations (MICs)

In scenarios where synergy was observed, the plant extracts significantly enhanced the effectiveness of the antibiotics, as evidenced by a marked reduction in their MICs. In some instances, this reduction was as much as 4 to 8 times lower than when the antibiotics were administered alone.

Antibiotic + Extract	**Target Pathogen**	**MIC Alone (µg/mL)**	**MIC with Extract (µg/mL)**	**Fold Reduction**
Ciprofloxacin + Garlic	*S. aureus* (MRSA)	4	0.5	8x
Amoxicillin + Neem	*E. coli* (MDR)	8	1	8x
Amphotericin B + Garlic	*Candida albicans*	2	0.5	4x

4. Discussion

The current research indicates that certain plant extracts, notably *Allium sativum, Azadirachta indica, Curcuma longa, and Ocimum sanctum,* exhibit considerable antimicrobial properties against multidrug-resistant (MDR) pathogens. These extracts, when combined with standard antibiotics like ciprofloxacin, amoxicillin, and amphotericin B, showed significant synergistic effects, as evidenced by FICI values.

Garlic extract (*A. sativum*) demonstrated the most reliable synergy, especially when combined with ciprofloxacin against Staphylococcus aureus (MRSA) and with amphotericin B against *Candida albicans*. Allicin, the main active component in garlic, is recognized for its ability to disrupt microbial cell walls and increase membrane permeability, thus facilitating the uptake of antibiotics.

Neem (*A. indica*) displayed strong synergy with amoxicillin against *Escherichia coli* (MDR), which may be attributed to the presence of azadirachtin and other limonoids that inhibit bacterial adhesion and quorum sensing. Turmeric (*C. longa*) and tulsi (*O. sanctum*) also contributed to enhanced antimicrobial activity, though primarily as additive agents. Curcumin, for example, may inhibit efflux pumps in resistant bacteria, thus restoring antibiotic effectiveness.

The finding that the minimum inhibitory concentrations (MICs) of antibiotics decrease by 4- to 8-fold when combined with plant extracts supports the idea that phytochemicals can enhance the effectiveness of antibiotics. This has significant clinical implications, as it allows for the use of lower antibiotic doses, which can minimize side effects and potentially slow down the development of resistance.

Although these in vitro findings are encouraging, they come with certain limitations. The effectiveness of plant extracts can differ based on factors such as preparation methods, geographic origin, and the season of harvest. Moreover, it is crucial to thoroughly assess the pharmacokinetics, bioavailability, and potential toxicity of these combinations in animal models and human trials before they can be used therapeutically. Further investigation is necessary to standardize extraction techniques and establish optimal dosing regimens for plant-antibiotic combinations. Clinical trials should evaluate the effectiveness and safety of these combinations in treating resistant infections in humans. Additionally, exploring the molecular mechanisms of synergy between phytochemicals and antibiotics could pave the way for new therapeutic approaches against multidrug-resistant pathogens.

5. Conclusion

This research offers compelling evidence that antimicrobials derived from plants can greatly boost the efficacy of standard antibiotics against pathogens resistant to multiple drugs. The combinations of *Allium sativum, Azadirachta indica, Curcuma longa,* and *Ocimum sanctum* showed either synergistic or additive effects on various bacterial and fungal strains. The observed synergistic effects imply that these plant-based compounds might interact with antibiotics through several mechanisms, potentially bypassing existing resistance pathways. Future studies should aim to identify the specific active ingredients responsible for these synergistic effects and clarify their molecular mechanisms. Moreover, refining the ratios and formulations of these plant-antibiotic combinations could pave the way for new therapeutic approaches to tackle antibiotic-resistant infections. These results advocate for the inclusion of traditional medicinal plants in contemporary antimicrobial treatments. Such combinations present a sustainable, accessible, and potentially cost-effective method to address the escalating global issue of antibiotic resistance..

Future research efforts should prioritize:

The isolation and standardization of active phytochemicals,

In vivo assessments to determine toxicity and efficacy,
Clinical trials aimed at formulation development, and
The investigation of mechanisms at the molecular level.
Harnessing the synergistic power of nature and science may be key to restoring the effectiveness of our existing Antibiotic arsena.

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