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Article

Synergistic antibacterial activity of *Azadirachta indica* and *Hyptis suaveolens* against multi-antibiotic-resistant Bacteria

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SUMMARY

Antimicrobial resistance (AMR) remains one of the foremost threats to global public health, with multi-antibiotic-resistant (MAR) bacteria rendering numerous conventional therapeutic options ineffective. Natural plant products represent a promising alternative, and combinatorial strategies using plant extracts have increasingly been highlighted for their enhanced antibacterial efficacy. This study reviews the synergistic antibacterial activity of *Azadirachta indica* (Neem) and *Hyptis suaveolens* leaves against clinical MAR bacteria. Clinical bacterial isolates can be morphologically and biochemically characterized or confirmed by 16S rRNA molecular sequencing. The multidrug resistance can be assessed via the disc diffusion antibiogram. Plant leaf extracts were individually and synergistically discussed, while their potential antibacterial activities were reviewed from other literature. This study contributes to the growing evidence base for plant-derived combinatorial strategies as viable alternatives to conventional antibiotics.

Keywords: Antimicrobial resistance; *Azadirachta indica; Hyptis suaveolens;* synergistic antibacterial activity

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INTRODUCTION

Medical communities have been dealing with new and re-emerging bacterial infectious diseases since the 1950s, and these emerging pathogens are now regarded as a significant threat to public health [1]. For over 70 years, antibiotics have been used to treat bacterial infections, saving a significant number of lives [2]. However, the escalating issue of antibiotic resistance resulting from the misuse and overuse of conventional antimicrobial drugs has posed significant burdens on patients. The emergence and spread of multi-

antibiotic resistant (MAR) bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa,* and *Staphylococcus aureus* remain severe threats to public health [3]. These drug-resistant bacterial species have developed various mechanisms that ultimately alter the potential of multiple antibiotics, causing the emergence of infectious diseases with no cure [4,5]. There is an urgent need for alternative therapeutic strategies. Recent studies have highlighted that 20% of reported death cases globally result from infectious diseases, representing the devastating consequences of the inefficacies of antimicrobial agents in this "post-antibiotic era" [6,7].

Natural products, the backbone of traditional medicine, have shown significant potential for modern medicine [8]. Plants have been used in various ethnomedicinal applications for decades to treat infections. Between 1981 and 2014, botanical pharmaceuticals, unmodified natural products, or their derivatives accounted for 26% of all newly authorized medications and 33% of all newly approved small-molecule medications [7]. This highlights the enormous phytomedicinal potential yet to be explored; the bioactive components of plants are now at the forefront of research as novel antibacterial agents [3].

Azadirachta indica, commonly known as Neem, is well known for its therapeutic applications, possessing antimicrobial, anti-inflammatory, anti-allergic, larvicidal, insecticidal, antimalarial, anti-ulcer, and antioxidant properties found across its leaf, bark, flower, fruit, seed, and oil.[9,3] Similarly, *Hyptis suaveolens*, commonly known as "pignut," is used in traditional medicine for skin, respiratory, and gastrointestinal diseases.[4] Recent studies have highlighted the improved antimicrobial activities of synergistic use of plant extracts, which targets pathogens more effectively by suppressing the growth and survival of drug-resistant strains.[10]

Over 700,000 people globally die annually from complications resulting from antimicrobial resistance (AMR) [11]. Infectious diseases caused by drug-resistant pathogenic bacteria account for a significant proportion of recorded deaths worldwide [12]. Drug-resistant bacterial strains decrease treatment efficacy and contribute to morbidity and mortality while increasing healthcare costs [2]. Despite continuous introduction of novel antibiotics, bacterial resistance has outpaced therapeutic options. According to the World Health Organization (WHO), up to 10 million people could die by 2050 if better antimicrobial therapeutic options are not provided [11].

The global surge in MAR bacterial species has rendered various conventional antibiotics less effective in combating infectious diseases [3]. Several bacterial pathogens have been recorded to be resistant to multiple drug classes, including glycopeptides, fluoroquinolones, β-lactams, aminoglycosides, tetracyclines, rifamycins, sulphonamides, trimethoprim, and polymyxins [2]. Natural products from plants remain highlighted in recent research as potential antimicrobial agents against drug-resistant bacterial strains [7,3].

Azadirachta indica and *Hyptis suaveolens* are both known for their ethnomedicinal importance, containing crucial bioactive compounds including alkaloids, tannins, phenols, and flavonoids [5,13]. Current research focuses on the potential of each plant's extracts

to combat bacterial pathogens [4,3]. Hence, this study sought to explore the synergistic antibacterial efficiency of these plant extracts as a potential strategy against antibiotic resistance. This study aims to review the synergistic antibacterial efficacy of *Azadirachta Indica* and *Hyptis suaveolens* against clinical multidrug-resistant bacteria.

Antimicrobial Resistance

Antimicrobial resistance (AMR) occurs when microorganisms develop the ability to resist the effects of antimicrobials, making infections more difficult to treat effectively. AMR has emerged as one of the greatest threats to global public health in the 21st century, owing to the rapid increase in AMR infections and the lack of innovation in developing new antimicrobial compounds [14]. The main cause of this drug resistance is mostly attributed to the inappropriate use of antibiotics in healthcare and farming sectors; AMR is often referred to as the "silent pandemic" [15].

Since the discovery of antibiotics in the early 20th century, life expectancy worldwide has risen by 23 years. Antibiotic resistance was observed soon after the discovery of penicillin, as microorganisms acquired the ability to produce enzymes such as penicillinase, which destroys antibiotics [16]. More than 150 antibiotics have since been discovered; however, their excessive use has led to the emergence of multidrug-resistant (MDR) pathogens known as superbugs [17]. Bacterial AMR contributes to prolonged hospital stays, higher healthcare costs, poorer treatment outcomes, and greater mortality [18].

Global Burden of Antimicrobial Resistance

In 2019, AMR resulted in more than one million deaths globally, with projections suggesting this may reach 10 million per year by 2050 if no action is taken [14]. AMR may be significantly amplified by antibiotic use in agriculture and food systems, and zoonosis — the spread of antibiotic-resistant bacteria between humans and animals — poses a significant risk of transmission [19]. Currently, the highest estimated deaths are recorded in Asia and Africa, attributed mostly to large populations and less stringent regulations on antibiotic use [14].

Prevalence of Antibiotic Resistance in Nigeria

AMR has been recognized as a serious problem in low- and middle-income countries, including Nigeria. The widespread abuse and overuse of antibiotics in both human health and agriculture, facilitated by their availability without prescription, encourages self-medication, improper dosage, and unfinished treatment regimens [20]. High levels of resistance have been found in common bacterial infections such as *Escherichia coli, Staphylococcus aureus,* and *Klebsiella pneumoniae* in Nigerian hospitals. A systematic review unveiled an AMR-related mortality rate of more than 75/100,000 in West Africa [21].

Nosocomial Multidrug-Resistant Bacteria

Nosocomial infections, also called hospital-acquired infections (HAIs), are infections caused by pathogens during a patient's hospitalization for another condition. MDR bacteria responsible for nosocomial infections include Staphylococcus aureus (including

MRSA), *Pseudomonas aeruginosa, Acinetobacter baumannii*, and *Enterobacteriaceae* such as *E. coli and K. pneumoniae*. These bacteria cause surgical site infections, bloodstream infections, urinary tract infections, and respiratory infections, particularly in intensive care units [22,23].

Public Health Implications of Nosocomial MDR Bacteria

Nosocomial MDR infections cause prolonged illness, higher mortality, extended hospital stays, and increased healthcare costs. MDR bacteria imposes a strain on health services through requirements for costly or dangerous antibiotics and further diagnostic testing [22,23]. Furthermore, the emergence of MDR bacteria threatens modern medical practices such as organ transplantation that depend on antibiotic effectiveness [24,25].

Medicinal Plants as Alternative Therapeutics Against MAR Bacteria

Humans have long recognised the therapeutic properties of certain plants. Since herbal remedies were widely used to treat a range of illnesses before the development of antibiotics, plant-based medications represent natural, profitable substitutes [26]. Many secondary metabolites that plants produce for defence have antibacterial properties and are widely used in traditional medicine [27].

Plant Phytochemicals and Their Role in Antibacterial Activities

Many structurally and functionally diverse phytochemicals produced by plants are effective against pathogenic bacteria and could be investigated for the development of new antimicrobials. These naturally occurring, low-molecular-weight secondary metabolites may act independently to kill bacteria, inhibit molecular targets within the cell essential for growth and division, or work in concert with current antibiotics by blocking resistance determinants [27].

Alkaloids

Alkaloids are nitrogenous substances found in plants, animals, bacteria, and fungi. More than 300 plant species contain alkaloids, and their biological activity stems from the presence of nitrogen, which enables inhibition of efflux pumps [28]. For example, sanguinarine increases the efficacy of antibiotics against gram-positive and gram-negative bacteria by disrupting bacterial DNA, inhibiting the FtsZ protein, and destabilising the cell membrane [29].

Polyphenols

Over 8,000 polyphenolic substances have been characterised, comprising flavonoids, lignans, stilbenes, and phenolic acids. The antibacterial action of polyphenols involves interference with efflux pumps, enzymatic reactions, and the destruction of bacterial membranes [30]. Flavonoids such as kaempferol and quercetin have shown synergistic interactions with antibiotics against MDR pathogens [31,32].

Saponins

Saponins are phytochemicals of an amphiphilic nature, exhibiting a broad range of biological activities including anti-inflammatory, antioxidant, anticancer, and antimicrobial properties [33]. Saponins from *Melanthera elliptica* have been shown to have antibacterial effects against MDR *E. coli* and *Shigella flexneri* and demonstrated promise in working synergistically with antibiotics [34].

Terpenes

Terpenoids form the largest category of plant secondary metabolites, comprising an estimated 55,000 chemicals. Carvacrol and thymol have potent antibacterial effects against both Gram-positive and Gram-negative bacteria through mechanisms of membrane disruption and electrolyte efflux [35].

Coumarins

Coumarins are benzopyrones abundant in medicinal plants, possessing anti-inflammatory, antihypertensive, anticoagulant, anticancer, antifungal, antiviral, and antibacterial properties [36]. Their mechanism of action involves passive transport into bacteria due to their planar nature and lipophilicity, ultimately inhibiting enzymes such as tyrosyl-tRNA synthase and DNA gyrase [37].

Azadirachta indica

Azadirachta indica (A.I), commonly referred to as the neem tree, has been used as a traditional remedy for years, treating a multitude of human ailments. Due to the presence of potent secondary metabolites, primarily limonoids and tetranortriterpenoids such as azadirachtin, its bark, leaves, seeds, fruits, and flowers are frequently used in medicinal therapy [38].

Botanical Description

The neem tree is an evergreen tree known for its rapid growth, typically reaching 15–20 metres, though it can attain 35–40 metres under favourable conditions. It features a large flat canopy, alternate pinnate leaves 20–40 cm long with 20–30 leaflets, small fragrant white flowers in axillary panicles, and olive-shaped drupe fruits. The plant belongs to the family *Meliaceae* (Table 1) [39,40].

Table 1: Scientific Classification of *Table 1: Scientific Classification of Azadirachta indica (Devi and Sharma, 2023) [19].*

Scientific Classification	
Kingdom	*Plantae*
Order	*Spindales*
Family	*Meliaceae*
Sub-Family	*Melioideae*
Genus	*Azadirachta*
Species	*Indica*

Geographical Distribution

Neem originated in India but is now widely grown worldwide, especially in drier tropical and subtropical regions of Asia, Africa, the Americas, Australia, and the South Pacific. In Africa, neem trees are abundant across the Sahel and Savannah regions, including Nigeria, Niger, Burkina Faso, Mali, Senegal, and Sudan [40]. Using the Maxent model, Musawa et al. predicted that Neem could colonise 75% of Nigeria in the North and 25% in the East, thriving particularly in semi-arid and savanna regions [41].

Phytochemical Composition

The primary active phytochemical components found in neem are mainly oxidised tetranortriterpenoids, including a variety of limonoids such as *azadirachtin A, azadirachtin B, azadirachtin D, azadirachtin H, azadirachtin I, azadirachtanin, azadiradione, nimbolide, salannin*, and others. Over 135 phytochemicals have been discovered within various parts of neem trees [38,39].

Antibacterial Activity of *Azadirachta indica*

Secondary metabolites such as glycosides, alkaloids, flavonoids, and

saponins, abundant in A. indica contribute to its antibacterial, antifungal, and antioxidant properties [38]. The neem plant has been shown to inhibit *Staphylococcus aureus* and *E. coli,* with neem oil demonstrating significant inhibitory effects against *Streptococcus mutans* (27 mm zone of inhibition) and notable zones against *Enterococcus faecalis* (18 mm) and *Lactobacillus acidophilus* (24 mm) [39].

Hyptis suaveolens

Hyptis suaveolens (L.) Poit. is one of the most valuable medicinal plants used in traditional medicine. Its secondary metabolites have been described to have antimicrobial, antispasmodic, anti-rheumatic, anti-colic, anti-fertility, sedative, diuretic, anti-pyretic, anti-soporific, anti-inflammatory, and anti-cancer qualities [42].

Botanical Description

Hyptis suaveolens is an annual or perennial plant exhibiting unique genotypic polymorphism and morphological and physiological plasticity. Its sturdy stem is quadrangular and velvety; leaves are simple, opposite, decussate, and petiolate with uneven serrated borders. The inflorescence consists of panicles or short umbels with two to five blue-purplish zygomorphic flowers. The plant belongs to the family *Lamiaceae, sub*-family *Nepetoideae (Table 2) [42].*

Table 2: Scientific Classification of *Hyptis suaveolens (Mishra et al., 2021) [24].*

Scientific Classification	
Kingdom	*Plantae*
Phylum/Division	*Tracheophyta*
Class	*Magnoliopsida*
Order	*Lamiales*
Family	*Lamiaceae*
Sub-Family	*Nepetiodeae*
Genus	*Hyptis*
Species	*Suaveolens*

Geographical Distribution

H. suaveolens has been found growing in over 50 countries, including parts of South America, Latin America, Africa (including Nigeria, Ghana, Tanzania, Kenya, and South Africa), North America, Asia, Oceania, and Pacific regions [43,44].

Phytochemical Composition

Hyptis suaveolens contain phenolic compounds, flavonoids, terpenoids, alkaloids, tannins, saponins, steroids, and essential oils. Phenolic compounds are the major secondary metabolites, including vanillic acid, caffeic acid, rosmarinic acid, ferulic acid, and p-coumaric acid, attributed to antioxidative, neuroprotective, hepatoprotective, and antimicrobial activities [45,46]. Flavonoid compounds include quercetin, rutin, chlorogenic acid, gallic acid, and flavones. Terpenoids, particularly sesquiterpenes, diterpenes, monoterpenes, and triterpenes including cineole, sabinene, caryophyllene, betulinic acid, and ursolic acid, are also present [42].

Antibacterial Activity of *Hyptis suaveolens*

H. suaveolens has been reported to have strong antibacterial activity against *Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella typhi, Escherichia coli, Vibrio vulnificus*, and *Streptococcus faecalis,* attributed to its significant phenolic and flavonoid contents [45]. Since Gram-positive bacteria lack the complex outer hydrophilic membrane of Gram-negative bacteria, the antibacterial activity exerted by the phenolics and flavonoids in *H. suaveolens* is more pronounced on such organisms compared to Gram-negative bacteria.

CONCLUSION

This study reviewed literature on the synergistic antibacterial potential of *Azadirachta indica* and *Hyptis suaveolens* against clinically significant MAR bacteria such as *Escherichia coli, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae.* With antimicrobial resistance threatening to render conventional antibiotics obsolete, plant-derived combinatorial strategies represent a sustainable and cost-effective avenue for new antimicrobial development. The rich phytochemical profiles of both *A. indica* (including limonoids, alkaloids, flavonoids, and saponins) and *H. suaveolens* (including phenolics, flavonoids, terpenes, and alkaloids) provide the pharmacological rationale for anticipated synergistic activity. Research findings from this study can contribute valuable evidence towards the development of plant-based alternatives in the fight against antimicrobial resistance.

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