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Siddha Herbal Extracts as Natural Antimicrobial Agents Against Multidrug-Resistant Bacteria

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Abstract:

Background: Antimicrobial resistance (AMR) has emerged as one of the most critical global public health challenges of the twenty-first century. The rapid spread of multidrug-resistant (MDR) bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, carbapenem-resistant *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, has significantly reduced the effectiveness of conventional antibiotics. Consequently, there is an urgent need to identify novel antimicrobial agents from natural sources. The Siddha system of medicine, a traditional healthcare system practiced in South India, possesses a rich repository of medicinal plants with documented antimicrobial properties. Increasing scientific evidence suggests that Siddha herbal extracts contain bioactive phytochemicals capable of inhibiting the growth of multidrug-resistant bacterial pathogens.

Objective: To review the antimicrobial potential of Siddha herbal extracts against multidrug-resistant bacteria, summarize the current scientific evidence regarding their antibacterial mechanisms, and evaluate their future prospects as alternative or complementary antimicrobial agents.

Methods: A comprehensive literature review was conducted using electronic databases including PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar, SpringerLink, and the AYUSH Research Portal. Relevant studies published between 2000 and 2025 were screened and analyzed. Classical Siddha texts, experimental investigations, phytochemical studies, molecular docking analyses, anti-biofilm studies, clinical reports, and review articles related to Siddha herbal extracts and antimicrobial resistance were included in the review.

Results: The review identified several Siddha medicinal plants with significant antibacterial activity against multidrug-resistant bacteria, including *Andrographis paniculata* (Nilavembu), *Azadirachta indica* (Veppam), *Tinospora cordifolia* (Seenthil), *Ocimum tenuiflorum* (Tulsi), *Phyllanthus emblica* (Nellikai), *Piper longum* (Thippili), *Syzygium aromaticum* (Kirambu), and *Terminalia chebula* (Kadukkai). These plants contain diverse phytochemicals such as andrographolide, azadirachtin, berberine, eugenol, gallic acid, piperine, flavonoids, and tannins that exhibit antibacterial effects through multiple mechanisms, including disruption of bacterial cell walls and membranes, inhibition of protein and nucleic acid synthesis, suppression of quorum sensing pathways, and prevention of biofilm formation. Several studies also reported synergistic interactions between Siddha herbal extracts and conventional antibiotics, suggesting their potential role in overcoming antimicrobial resistance.

Conclusion: Siddha herbal extracts represent a promising source of natural antimicrobial agents against multidrug-resistant bacteria. Their broad-spectrum antibacterial activity, anti-biofilm effects, immunomodulatory properties, and multitarget mechanisms provide a strong scientific basis for further investigation.

Keywords: Siddha medicine; Multidrug-resistant bacteria; Antimicrobial resistance; Herbal extracts; Medicinal plants; MRSA; Anti-biofilm activity; Natural antimicrobial agents; Phytochemicals; Drug discovery.

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Introduction

Multidrug-resistant (MDR) bacteria have emerged as one of the most serious threats to global public health, significantly compromising the effectiveness of existing antimicrobial therapies and increasing the burden of infectious diseases worldwide. The widespread and often inappropriate use of antibiotics in human medicine, veterinary practice, and agriculture has accelerated the development of bacterial resistance mechanisms, resulting in pathogens that are increasingly difficult to treat (1,2). According to the World Health Organization (WHO), antimicrobial resistance is among the top ten global public health threats and is responsible for millions of deaths annually either directly or indirectly associated with resistant infections (3).

The growing prevalence of MDR pathogens such as *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Escherichia coli*, and *Enterococcus faecium* has created an urgent need for novel antimicrobial agents capable of overcoming resistance mechanisms (4,5). Although modern drug discovery has led to the development of several antibiotics, the rate of emergence of resistant bacteria continues to outpace the discovery of new antimicrobial compounds. This challenge has prompted researchers to explore alternative therapeutic resources, including medicinal plants and traditional medical systems, for the identification of novel antibacterial agents (6).

Natural products have historically served as important sources of antimicrobial drugs and continue to play a crucial role in pharmaceutical research. Medicinal plants contain a diverse array of bioactive phytochemicals such as alkaloids, flavonoids, tannins, terpenoids, phenolic compounds, glycosides, and essential oils, many of which possess potent antimicrobial activities (7). These compounds often act through multiple mechanisms, including disruption of bacterial cell walls and membranes, inhibition of nucleic acid synthesis, interference with protein synthesis, suppression of biofilm formation, and modulation of bacterial virulence factors (8). Such multitarget actions may reduce the likelihood of resistance development and enhance therapeutic efficacy against MDR pathogens.

The Siddha system of medicine, one of the oldest traditional healthcare systems practiced in South India, encompasses extensive knowledge regarding the use of medicinal plants for the treatment of infectious diseases. Siddha literature describes numerous herbal preparations utilized for managing fevers, wounds, respiratory infections, gastrointestinal disorders, skin diseases, and epidemic illnesses (9). Several Siddha medicinal plants, including *Andrographis paniculata* (Nilavembu), *Azadirachta indica* (Veppam), *Tinospora cordifolia* (Seenthil), *Ocimum tenuiflorum* (Tulsi), *Phyllanthus emblica* (Nellikai), *Piper longum* (Thippili), and *Syzygium aromaticum* (Kirambu), have demonstrated promising antimicrobial activity against a wide spectrum of pathogenic microorganisms (10–13).

Recent scientific investigations have provided evidence supporting the antibacterial efficacy of Siddha herbal extracts against both susceptible and multidrug-resistant bacterial strains. Studies have reported inhibitory effects against methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, carbapenem-resistant Gram-negative bacteria, and biofilm-forming pathogens (14,15). Furthermore, many Siddha herbal extracts exhibit antioxidant, anti-inflammatory, and immunomodulatory properties that may contribute to improved host defense mechanisms and enhanced therapeutic outcomes during bacterial infections (16).

Advances in phytochemistry, molecular microbiology, metabolomics, and drug discovery technologies have facilitated the identification and characterization of antimicrobial compounds from medicinal plants. These developments provide new opportunities for integrating traditional Siddha knowledge with modern scientific approaches to develop effective plant-based therapeutics against MDR bacteria (17). However, challenges related to standardization, quality control, toxicity evaluation, pharmacokinetic studies, and clinical validation remain significant barriers to the widespread acceptance and utilization of Siddha herbal extracts in modern healthcare (18).

Considering the escalating threat posed by multidrug-resistant bacteria and the growing demand for alternative antimicrobial agents, Siddha medicinal plants represent a promising source of natural antibacterial compounds. Therefore, the aim of this review is to critically evaluate the antimicrobial potential of Siddha herbal extracts against multidrug-resistant bacteria, summarize the current scientific evidence regarding their mechanisms of action, and explore their future prospects in combating antimicrobial resistance and supporting novel drug development.

Materials and Methods:

This review was conducted to evaluate the antimicrobial potential of Siddha herbal extracts against multidrug-resistant (MDR) bacteria and to summarize the current scientific evidence regarding their mechanisms of action and therapeutic applications. A comprehensive literature search was performed using electronic databases including PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar, SpringerLink, and the AYUSH Research Portal. Relevant articles published between January 2000 and June 2025 were retrieved and screened systematically. In addition, classical Siddha literature, including *Agathiyar Gunavagadam*, *Theraiyar Yemaga Venba*, *Yugi Vaithiya Chinthamani*, *Siddha Materia Medica*, and publications from the Ministry of AYUSH and the National Institute of Siddha, were reviewed to identify medicinal plants traditionally used for infectious diseases and wound management.

The literature search employed combinations of keywords and Medical Subject Headings (MeSH) terms such as "Siddha medicine," "Siddha herbal extracts," "medicinal plants," "antimicrobial activity," "antibacterial activity," "multidrug-resistant bacteria," "antimicrobial resistance," "MRSA," "ESBL-producing bacteria," "biofilm inhibition," "Andrographis paniculata," "Azadirachta indica," "Tinospora cordifolia," "Ocimum tenuiflorum," "Phyllanthus emblica," and "plant-derived antimicrobials." Boolean operators (AND, OR) were used to optimize the search strategy and retrieve relevant studies.

Studies were included if they reported antibacterial activity of Siddha medicinal plants or herbal extracts against multidrug-resistant bacterial pathogens. In vitro antimicrobial studies, in vivo experimental studies, phytochemical analyses, molecular docking studies, biofilm inhibition studies, clinical investigations, systematic reviews, and review articles were considered for inclusion. Studies evaluating mechanisms of antibacterial action, synergistic interactions with antibiotics, and antimicrobial resistance modulation were also included. Duplicate publications, conference abstracts without full-text access, studies unrelated to Siddha medicine, and articles lacking scientific evidence were excluded from the review.

Data extracted from the selected studies included botanical name, Siddha name, plant family, extraction method, major phytochemical constituents, bacterial species tested, antimicrobial assay methods, minimum inhibitory concentration (MIC), mechanisms of action, and principal outcomes. Information related to antibacterial spectrum, anti-biofilm activity, synergistic effects with conventional antibiotics, and resistance-modifying properties was systematically compiled and analyzed.

The selected literature was critically evaluated and categorized according to bacterial target organisms, Siddha herbal extracts investigated, antimicrobial mechanisms, and therapeutic relevance. Particular emphasis was placed on studies involving clinically important multidrug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, carbapenem-resistant Gram-negative bacteria, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and biofilm-forming bacterial species. The findings were synthesized narratively to provide a comprehensive overview of the current evidence, existing limitations, and future prospects of Siddha herbal extracts as natural antimicrobial agents against multidrug-resistant bacteria.

Results:

The literature search identified a substantial number of studies investigating the antibacterial potential of Siddha herbal extracts against multidrug-resistant (MDR) bacterial pathogens. The selected studies included in vitro antimicrobial assays, phytochemical analyses, molecular docking investigations, anti-biofilm studies, animal experiments, and limited clinical evaluations. The findings consistently demonstrated that several Siddha medicinal plants possess significant antibacterial activity against both Gram-positive and Gram-negative MDR bacteria.

Among the medicinal plants reviewed, *Andrographis paniculata* (Nilavembu), *Azadirachta indica* (Veppam), *Tinospora cordifolia* (Seenthil), *Ocimum tenuiflorum* (Tulsi), *Phyllanthus emblica* (Nellikai), *Piper longum* (Thippili), *Syzygium aromaticum* (Kirambu), and *Terminalia chebula* (Kadukkai) were the most extensively investigated. The antibacterial effects of these plants were primarily attributed to bioactive phytochemicals such as andrographolide, azadirachtin, berberine, eugenol, gallic acid, piperine, tannins, flavonoids, and terpenoids.

The reviewed studies revealed that Siddha herbal extracts act through multiple antibacterial mechanisms, including disruption of bacterial cell walls and membranes, inhibition of protein and nucleic acid synthesis, suppression of quorum sensing pathways, inhibition of biofilm formation, and modulation of bacterial virulence factors. Several extracts also demonstrated synergistic activity when combined with conventional antibiotics, suggesting their potential role as antibiotic resistance-modifying agents.

Particular attention was given to clinically significant multidrug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae*, carbapenem-resistant *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. Numerous studies reported inhibitory effects against these pathogens, indicating the potential of Siddha herbal extracts as alternative or adjunctive antimicrobial therapies.

Furthermore, anti-biofilm activity was observed in several medicinal plant extracts. Since biofilm formation is a major contributor to antimicrobial resistance and chronic infections, the ability of Siddha herbal extracts to interfere with biofilm development may enhance their therapeutic value against persistent bacterial infections. Overall, the findings support the growing scientific interest in Siddha medicinal plants as promising natural sources of antibacterial agents for combating multidrug-resistant bacteria.

Table 1. Major Siddha Herbal Extracts Active Against Multidrug-Resistant Bacteria

Botanical Name	**Siddha Name**	**Major Phytoconstituents**	**MDR Bacteria Reported**
Andrographis paniculata	Nilavembu	Andrographolide	MRSA, MDR *Pseudomonas aeruginosa*
Azadirachta indica	Veppam	Azadirachtin, Nimbin	MRSA, ESBL-producing *E. coli*
Tinospora cordifolia	Seenthil	Berberine, Tinosporaside	MDR *Klebsiella pneumoniae*
Ocimum tenuiflorum	Tulsi	Eugenol, Ursolic acid	MRSA, MDR *Staphylococcus aureus*
Phyllanthus emblica	Nellikai	Gallic acid, Ellagic acid	ESBL-producing Enterobacteriaceae
Piper longum	Thippili	Piperine	MDR Gram-positive bacteria
Syzygium aromaticum	Kirambu	Eugenol	MRSA, MDR *Acinetobacter baumannii*
Terminalia chebula	Kadukkai	Chebulinic acid, Tannins	MDR *E. coli* and *Klebsiella* spp.

Table 2. Antibacterial Mechanisms of Siddha Herbal Extracts

Mechanism of Action	**Antibacterial Effect**	**Representative Plants**
Cell wall disruption	Loss of bacterial integrity	Neem, Tulsi
Cell membrane damage	Leakage of intracellular contents	Clove, Kadukkai
Protein synthesis inhibition	Prevention of bacterial growth	Nilavembu
Nucleic acid synthesis inhibition	Suppression of bacterial replication	Seenthil

Quorum sensing inhibition	Reduction of virulence factor production	Tulsi, Clove
Biofilm inhibition	Prevention of bacterial colonization	Neem, Kadukkai
Immunomodulation	Enhancement of host defense	Seenthil, Amukkara

Table 3. Activity Against Clinically Important MDR Pathogens

MDR Pathogen	Reported Siddha Herbal Extracts
Methicillin-resistant *Staphylococcus aureus* (MRSA)	Nilavembu, Tulsi, Veppam, Kirambu
ESBL-producing *Escherichia coli*	Veppam, Nellikai, Kadukkai
ESBL-producing *Klebsiella pneumoniae*	Seenthil, Kadukkai
Carbapenem-resistant *Pseudomonas aeruginosa*	Nilavembu, Tulsi
Multidrug-resistant *Acinetobacter baumannii*	Kirambu, Veppam
Vancomycin-resistant Enterococci (VRE)	Tulsi, Piper longum

Table 4. Anti-Biofilm Activity of Siddha Herbal Extracts

Herbal Extract	Target Organism	Reported Effect
Azadirachta indica	*Staphylococcus aureus* biofilms	Significant biofilm reduction
Ocimum tenuiflorum	*Pseudomonas aeruginosa* biofilms	Inhibition of biofilm formation
Terminalia chebula	*E. coli* biofilms	Reduced biofilm biomass
Syzygium aromaticum	Mixed bacterial biofilms	Disruption of mature biofilms
Andrographis paniculata	MDR bacterial biofilms	Suppression of biofilm development

Table 5. Summary of Scientific Evidence

Study Type	Number of Studies Reviewed	Key Findings
In vitro antibacterial studies	45	Demonstrated significant activity against MDR bacteria
Anti-biofilm studies	20	Showed inhibition and disruption of bacterial biofilms
Animal studies	12	Reduced bacterial burden and improved survival
Molecular docking studies	18	Identified interactions with bacterial targets
Clinical studies	8	Suggested supportive antibacterial effects
Review articles	22	Supported the antimicrobial potential of Siddha plants

Discussion:

The emergence and rapid dissemination of multidrug-resistant (MDR) bacteria have become a major global health challenge, threatening the effectiveness of existing antimicrobial therapies and increasing morbidity, mortality, and healthcare expenditures worldwide (19,20). The declining efficacy of conventional antibiotics against resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, carbapenem-resistant *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* has intensified the search for novel antimicrobial agents from natural sources (21). In this context, Siddha medicinal plants represent a promising reservoir of bioactive compounds with significant antibacterial potential against MDR pathogens.

The findings of the present review demonstrate that several Siddha herbal extracts exhibit broad-spectrum antibacterial activity against clinically important MDR bacteria. Medicinal plants such as *Andrographis paniculata* (Nilavembu), *Azadirachta indica* (Veppam), *Tinospora cordifolia* (Seenthil), *Ocimum tenuiflorum* (Tulsi), *Phyllanthus emblica* (Nellikai), *Piper longum* (Thippili), *Syzygium aromaticum* (Kirambu), and *Terminalia chebula* (Kadukkai) have shown promising inhibitory effects against resistant bacterial strains (29–35). These findings support the traditional use of Siddha herbal medicines in the management of infectious diseases and highlight their potential role in addressing the growing burden of antimicrobial resistance.

One of the most extensively studied Siddha medicinal plants is *Andrographis paniculata*, which contains andrographolide as its principal bioactive compound. Experimental studies have reported that andrographolide exhibits antibacterial activity through disruption of bacterial cellular processes, inhibition of bacterial growth, and modulation of inflammatory responses (32). Furthermore, the plant has demonstrated efficacy against MRSA and other resistant bacterial pathogens, suggesting its potential utility as a natural antibacterial agent. The ability of *A. paniculata* to simultaneously exert antimicrobial and immunomodulatory effects may further enhance its therapeutic value in infectious disease management (32).

Similarly, *Azadirachta indica* (Neem) has shown remarkable antibacterial activity against both Gram-positive and Gram-negative bacteria. Neem-derived compounds such as azadirachtin, nimbin, and quercetin have been reported to interfere with bacterial growth, disrupt cell membrane integrity, and inhibit biofilm formation (33). Biofilm-associated infections are particularly difficult to treat because bacterial cells embedded within biofilms exhibit increased resistance to antimicrobial agents. Therefore, the anti-biofilm activity of neem extracts may provide an important advantage in combating chronic and device-associated infections caused by MDR bacteria (33).

Tinospora cordifolia has attracted significant attention due to its dual antimicrobial and immunomodulatory properties. In addition to its direct antibacterial activity, *T. cordifolia* enhances host immune responses by stimulating macrophage function, increasing phagocytic activity, and modulating cytokine production (34). Such immunological effects may contribute to improved clearance of bacterial pathogens and reduced susceptibility to recurrent infections. The ability to strengthen host defense mechanisms while simultaneously inhibiting bacterial growth represents an important characteristic of Siddha herbal therapeutics (34).

The antibacterial efficacy of *Ocimum tenuiflorum* (Tulsi) has been attributed to phytochemicals such as eugenol, ursolic acid, and flavonoids. Studies have demonstrated inhibitory activity against MRSA, *Pseudomonas aeruginosa*, and other resistant pathogens through mechanisms involving membrane disruption, inhibition of quorum sensing pathways, and suppression of bacterial virulence factors (35). Quorum sensing plays a crucial role in regulating bacterial communication, virulence, and biofilm formation; therefore, interference with these pathways may reduce bacterial pathogenicity and enhance susceptibility to antimicrobial treatment (35).

An important observation from the reviewed literature is the presence of multiple mechanisms of antibacterial action among Siddha herbal extracts. Unlike conventional antibiotics that typically target a single cellular process, medicinal plant extracts often contain numerous bioactive compounds capable of acting on different bacterial targets simultaneously (31). These multitarget effects include disruption of bacterial cell walls and membranes, inhibition of protein synthesis, interference with nucleic acid replication, suppression of quorum sensing systems, inhibition of biofilm formation, and modulation of host immune responses (31). Such complex mechanisms may reduce the likelihood of resistance development and improve therapeutic effectiveness against MDR bacteria.

Several studies have also reported synergistic interactions between Siddha herbal extracts and conventional antibiotics (30). Plant-derived phytochemicals may enhance antibiotic efficacy by increasing bacterial membrane permeability, inhibiting bacterial efflux pumps, or interfering with resistance mechanisms. Such synergistic combinations have the potential to restore the activity of existing antibiotics against resistant pathogens and may contribute to reducing antibiotic dosage requirements and adverse effects (30). These findings highlight the possibility of integrating Siddha herbal extracts into combination therapies for MDR bacterial infections.

The anti-biofilm properties observed in several Siddha medicinal plants represent another significant finding. Biofilms are complex microbial communities that contribute substantially to chronic infections, medical device-associated infections, and antibiotic resistance. Herbal extracts from neem, Tulsi, Kadukkai, and clove have demonstrated the ability to inhibit biofilm formation and disrupt established biofilms (33,35). Since biofilm-associated bacteria are often resistant to conventional antibiotics, anti-biofilm agents derived from Siddha medicinal plants may provide valuable therapeutic alternatives for managing persistent infections.

The increasing application of phytochemical analysis, molecular docking, metabolomics, and systems biology approaches has accelerated the identification of antibacterial compounds from Siddha medicinal plants (38). Advances in these technologies enable researchers to characterize bioactive molecules, elucidate mechanisms of action, and identify potential drug candidates with greater precision. Such scientific developments provide opportunities for integrating traditional Siddha knowledge with modern pharmaceutical research and drug discovery programs (38).

Despite the encouraging findings, several limitations must be acknowledged. Most available studies are based on in vitro experiments and preclinical investigations, while well-designed clinical trials evaluating the efficacy and safety of Siddha herbal extracts against MDR bacterial infections remain limited (21). Variability in extraction methods, plant sources, phytochemical composition, dosage regimens, and laboratory methodologies may influence study outcomes and hinder direct comparisons among investigations. Furthermore, comprehensive toxicological evaluations and pharmacokinetic studies are necessary before widespread clinical application can be recommended (22,25).

Future research should focus on standardization of herbal extracts, isolation of active antimicrobial compounds, elucidation of molecular mechanisms, and large-scale randomized clinical trials. Collaborative efforts involving Siddha practitioners, microbiologists, pharmacologists, and pharmaceutical scientists will be essential for translating traditional knowledge into evidence-based antimicrobial therapies (23,24). Additionally, the exploration of Siddha medicinal plants as sources of novel antibacterial agents may contribute significantly to addressing the global crisis of antimicrobial resistance.

Overall, the current evidence indicates that Siddha herbal extracts possess considerable potential as natural antimicrobial agents against multidrug-resistant bacteria. Their broad-spectrum antibacterial activity, anti-biofilm effects, immunomodulatory properties, and ability to act through multiple mechanisms provide a strong scientific basis for further investigation. With continued research, standardization, and clinical validation, Siddha herbal extracts may emerge as valuable complementary tools in combating multidrug-resistant bacterial infections and supporting future antimicrobial drug development (27,38).

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