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Antimicrobial Potential of *Satureja* Species: A Review of Bioactive Compounds and Molecular Mechanisms

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ABSTRACT

Objective: The genus *Satureja* [Lamiaceae], commonly referred to as savory, has been traditionally valued for its medicinal properties, particularly its antimicrobial activity.

Methodology: Methodology: In this review study, the key words satureja, antimicrobial resistance, antibiotics, carvacrol, thymol, multidrug-resistant were used to search for articles. Databases such as Google Scholar, SID, Magiran, PubMed, Scopus were used for searching.

Results: Various species of *Satureja* are rich in bioactive compounds such as thymol, carvacrol, and terpenoids, which exhibit strong antibacterial, antifungal, and antiviral properties. These essential oils primarily act by disrupting bacterial cell membranes, inhibiting biofilm formation, and interfering with bacterial metabolism and DNA replication. This review critically examines the antimicrobial properties of nine Satureja species, focusing on their bioactive compounds, molecular mechanisms, and potential applications.

Conclusion: Given the growing challenge of antimicrobial resistance (AMR), the therapeutic potential of Satureja is discussed in the context of alternative antimicrobial strategies and industrial applications.

Key words: *Satureja*, Antimicrobial resistance, Antibiotics, Carvacrol, Thymol, Multidrug-resistant

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Introduction

Antimicrobial resistance (AMR) is increasingly recognized as a critical public health concern that poses a significant global threat. The rise of AMR results in reduced efficacy of antibiotics, making it challenging to treat common infections and leading to increased morbidity and mortality [1]. AMR is believed to have been responsible for more than 4.95

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million fatalities globally in 2019, along with an estimated economic impact of US$1 trillion in increased healthcare expenses by 2050[1]. Given the combination of environmental factors and human and veterinary practices, the spread of AMR is regarded as a One-Health issue. AMR has emerged and spread at the human level as a result of improper prescription practices in medicine, overuse, and misuse of antibiotics[2]. As a result, there is an urgent need to discover new therapeutic options, such as the use of various medicinal plants, to combat infections caused by antibiotic-resistant microorganisms.

Marjoram [*Satureja*] is a member of the Lamiaceae family and is known as a medicinal and aromatic plant and has been used to treat various ailments such as muscle cramps, muscle pain, nausea, indigestion, diarrhea, and infectious diseases. It has shown antispasmodic, antidiarrheal, antioxidant, sedative, and antimicrobial properties[3]. This plant is also effective against a wide range of microorganisms due to its extensive therapeutic properties and bioactive compounds such as thymol, carvacrol, terpenoids, and flavonoids[4-7]. Therefore, in this study, our focus is on the antimicrobial properties of this plant.

History of Marjoram

The use of marjoram as a medicinal plant dates to ancient times. The ancient Egyptians and Greeks employed marjoram as both a medicinal herb and a spice in cooking. In ancient Rome, marjoram was widely used as a natural remedy for treating infections and enhancing overall health. The renowned Greek physician Hippocrates mentioned the use of marjoram as a herbal medicine for various ailments in his writings [8].

In traditional Iranian and Islamic medicine, marjoram has also held a special place due to its anti-inflammatory and antiseptic properties. In traditional medical texts such as "The Canon of Medicine" by Avicenna, marjoram is recommended as an effective remedy for treating digestive disorders, skin infections, and even respiratory problems. Moreover, in Europe, particularly during the Middle Ages, marjoram was utilized as a protective herb against contagious diseases such as the plague and other infectious illnesses [9].

Growth Areas and Distribution

Marjoram is a plant that grows in temperate and semi-arid regions of the world. This herb is widely found in Mediterranean areas, Southern Europe, the Middle East, and some regions of Central Asia. Depending on the species, marjoram can thrive at mountainous elevations, semi-arid plains, and even in certain coastal areas [10].

This review will focus on nine species within the *Satureja* genus that have demonstrated notable antimicrobial activity. Each species is characterized by its unique bioactive compounds, such as essential oils, flavonoids, and phenolic acids, which have been shown to inhibit the growth of various pathogens, including multidrug-resistant strains [11]. The underlying molecular mechanisms through which these compounds exert their antimicrobial effects will be carefully examined, accounting for their potential to disrupt bacterial cell membranes, inhibit biofilm formation, or target specific bacterial metabolic pathways.

The primary objective of this review is to evaluate the potential of *Satureja* species as alternatives to synthetic antibiotics, particularly in addressing the challenge posed by multidrug-resistant [MDR] pathogens. By identifying and understanding the active components and their mechanisms of action, this work aims to contribute to the development of new therapeutic strategies that can effectively combat AMR. The exploration of these natural compounds not only supports the search for safer and more effective antimicrobial agents but also encourages the integration of traditional knowledge with modern scientific approaches, paving the way for innovative solutions in the fight against infectious diseases caused by resistant microorganisms.

Methodology

To conduct this review, a comprehensive search of scientific databases [PubMed, Scopus, and Google Scholar] was performed, focusing on studies published between 2000 and 2024. Keywords such as "*Satureja*," "antimicrobial activity," "essential oils," and "molecular mechanisms" were used. Only peer-reviewed articles that investigated the antimicrobial activity and molecular mechanisms of *Satureja* species were included. Studies focusing on in vitro, in vivo, and clinical applications were prioritized to provide a thorough understanding of the species' medicinal potential.

Antimicrobial Activity of *Satureja* Species

Satureja species exhibit significant antimicrobial effects due to their rich content of essential oils, particularly thymol,

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carvacrol, and various terpenoids. The following sections provide a detailed examination of the antimicrobial activities of nine prominent *Satureja* species [12].

Satureja hortensis (Garden Savory)

Satureja hortensis L. belongs to the Lamiaceae Lindl family of annual herbaceous plants. relatives. L. hortensis Sdot. is indigenous to Southern and Southeastern Europe, the Middle East, Central Asia, and North Africa. It is related to thyme and rosemary. Carvacrol, γ-terpinene, thymol, p-cymene, β-arylene, linalool, and other terpenoids are among the numerous phenolic and unstable components found in Satureja species in varying concentrations [15].

Garden savory is well-known for its high concentrations of carvacrol and thymol, two compounds that are primarily responsible for its antimicrobial properties. It demonstrates broad-spectrum activity:

Garden savory is effective against Gram-positive bacteria, including *Staphylococcus aureus* and *Streptococcus pneumoniae*, as well as Gram-negative bacteria like *Escherichia coli* and *Salmonella* spp and inhibits *Candida albicans* and *Aspergillus niger,* which cause skin and systemic infections [13, 14]. The compound has also been assessed for its ability to inhibit the replication of SARS-CoV and HSV-1 in laboratory settings by visually evaluating the cytopathic effects induced by the virus after infection. Both the essential oil of S. thymbra (1%) and its hydrosol fraction (100%) have been noted to exhibit significant bactericidal properties against bacterial biofilms that develop on stainless steel from various beneficial, technological, and pathogenic bacteria [17].

Satureja montana (Winter Savory)

The pharmacological activity of *S. montana* is highly valued and has several uses. In addition to its culinary uses, it is also used as an active ingredient in medicinal preparations and as a component of perfumery. In traditional medicine, *S. montana* is widely used to treat a number of ailments, such as inflammation of the respiratory system, antiseptic requirements, carminative qualities, digestive aid, expectorant stimulation, gastrointestinal support, and antidiarrheic effects [18].

Winter savory is characterized by its resilience and robust essential oil profile. It is particularly noted for its activity against antibiotic-resistant bacteria.it might be effective against Methicillin-resistant *Staphylococcus aureus* [MRSA], *Stereptococcus agalactiae, Acinetobacter baumanii* and *Pseudomonas aeruginosa.* It also shows strong inhibition of pathogenic fungi, including *Candida* species and dermatophytes [15]. *S. montana* essential oil and ethanol extracts have antimicrobial properties that make them potential ingredients for use in foodborne disease treatments, oral liquids, and sprays for wound care, oral infections, and other infectious diseases. Additional investigation has revealed that *S. montana* is rich in essential oils, especially phenolic monoterpenes that contain oxygen, such as thymol and carvacrol [18].

Satureja spicigera

Numerous studies have documented the antibacterial and antifungal properties of the essential oils derived from various *Satureja* species [19]. This species Targets Gram-negative bacteria like *Proteus vulgaris* and *Escherichia coli*. It also inhibits *Candida albicans*, preventing infections in the skin and mucosal tissues [16].

Satureja thymbra

Known for its robust flavor and antimicrobial potency, *Satureja thymbra* is rich in phenolic compounds such as thymol. Antibacterial properties of this species might be effective against both Gram-positive and Gram-negative bacteria, including *Salmonella* spp and *Escherichia coli.* Additionally, it inhibits fungi responsible for genital and cutaneous infections, including *Candida albicans* [17].

Satureja cuneifolia [Narrow-leaved Savory]

In 99–89% of the oil from *S. cuneifolia*, thirty components were found. The two main compounds identified were p-cymene (21.61%) and carvacrol (44.99%). Thymol (9.01 %), c-terpinene (4.35 %), borneol (2.51 %), and terpinen4-ol (2.04 %) were additional significant compounds [21].

Although p-Cymene alone is ineffective against bacteria, it has been shown to work in concert with carvacrol to combat Bacillus cereus in rice and in vitro. 1,8-cineole-rich essential oils have been shown to be effective against *Listeria monocytogenes* and other Gram-positive and Gram-negative bacteria. Alkyl alcohols [e.g. linalool] were found to have strong to moderate effects on a number of bacteria. Since the location of the alcohol

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functional group was found to influence the component's molecular characteristics, including its ability to form hydrogen bonds, terpinen-4-ol was effective against *Psedumonas aeruginosa*, whereas a-terpineol was ineffective [18]. Also, *S. cuneifolia* is commonly used as a spice and potentially as a natural preservative to prevent E. coliO157:H7 in the food manufacturing sector [21].

Satureja subspicata

Resilient to harsh environmental conditions, *Satureja subspicata* shares similar medicinal properties with other species. It demonstrates activity against *Helicobacter pylori*, a common cause of gastrointestinal infections. Furthermore, it might be effective against resistant fungi, such as *Candida* spp and *Aspergillus* spp [19].

Satureja kitaibelii

Endemic to the Balkans, *Satureja kitaibelii* contains flavonoids and phenolic compounds that contribute to its antimicrobial activity. *Satureja kitaibelii* is effective against *Staphylococcus aureus* and *Listeria monocytogenes*. It also inhibits *Candida albicans*, which causes mucosal infections [20].

Satureja macrantha

This species, found in mountainous regions, is known for its larger flowers and high essential oil content. It is active against gastrointestinal pathogens like *Salmonella spp* and *Escherichia coli.* This specious also inhibits skin and systemic fungi, particularly *Aspergillus* species [21].

Satureja intermedia

Thriving in semi-arid regions, Satureja intermedia showcases diverse bioactive compounds with potent medicinal applications. It can Inhibit *Clostridium* spp and *Escherichia coli,* both of which cause gastrointestinal and urinary infections. Additionally, it is effective against fungi responsible for oral and skin infections [22].

Molecular Mechanisms of Action

The antimicrobial activity of Satureja species is largely attributed to their essential oils, which exert multifaceted effects on microorganisms. The major bioactive compounds, such as thymol and carvacrol, disrupt bacterial structures and processes at various levels [23].

Membrane Disruption

Thymol and carvacrol destabilize bacterial cell membranes through their integration into the lipid bilayer. This process involves the hydrophobic properties of these compounds allowing them to insert themselves into the membrane structure, which subsequently increases the permeability of the membrane. As the membrane integrity is compromised, this alteration leads to the leakage of intracellular contents, including essential metabolites, ions, and proteins, resulting in a loss of cellular homeostasis [24].

The disruption of membrane integrity ultimately causes cell lysis, where the cell can no longer maintain its structural integrity and function properly. Various studies indicate that this mechanism of action is particularly effective against Gram-positive bacteria such as *Staphylococcus aureus*, which possess a thick peptidoglycan layer in their cell wall. The presence of this layer renders them more susceptible to agents that disrupt membrane integrity, as the overall stability of the cell wall can be adversely affected by the increased fluidity and permeability instigated by thymol and carvacrol [25].

Moreover, research demonstrates that cell lysis induced by these compounds is not only due to physical disruption but may also involve the generation of reactive oxygen species [ROS] and oxidative stress, further contributing to the antimicrobial efficacy. The capacity of thymol and carvacrol to impair membrane potential and disrupt essential cellular processes underscores their potential as effective antimicrobial agents for combating resistant bacterial strains [26-28].

Inhibition of Biofilm Formation

Biofilm formation poses a considerable challenge in the treatment of bacterial infections, significantly complicating the effectiveness of antibiotic therapies. Biofilms are structured communities of bacteria that adhere to surfaces, embedded within a self-produced matrix of extracellular polymeric substances [EPS] which include polysaccharides, proteins, and extracellular DNA [29]. This matrix provides a protective niche, allowing bacteria to evade both the host's immune system and the actions of antibiotics, rendering conventional treatments often ineffective [30].

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Biofilms enhance bacterial resistance in numerous ways. They create a physical barrier that inhibits the penetration of antimicrobial agents, which may reach the outer layers but struggle to permeate deeper into the biofilm. Research has shown that biofilm-embedded bacteria are typically 10 to 1,000 times more resistant to antibiotics compared to their planktonic [free-floating] counterparts. Consequently, infections associated with biofilm formation are challenging to eradicate and require innovative therapeutic strategies [31].

Satureja essential oils, derived from plants such as those in the genus *Satureja*, have shown promise in combating biofilm formation. These essential oils possess antimicrobial properties that can disrupt bacterial activities, including the ability of pathogens, such as Pseudomonas aeruginosa, to form biofilms. Studies indicate that *Satureja* essential oils can inhibit the growth of periodontal pathogens while maintaining safety on human keratinocytes, suggesting their potential for therapeutic use against biofilm-associated infections [32, 33].

The mechanism through which *Satureja* essential oils exert their effects likely involves several pathways. These essential oils may affect bacterial adhesion to surfaces, which is a critical first step in biofilm development. By interfering with the adhesion process, these oils can significantly reduce the initial colonization of bacterial cells, thus preventing the progression to biofilm formation [34].

Moreover, *Satureja* essential oils may interact with the signaling mechanisms of bacteria, particularly the quorum sensing systems that are pivotal in biofilm development. Quorum sensing is a process of bacterial communication that allows for the regulation of gene expression based on cell density, impacting biofilm maturation and virulence factor production. By disrupting this communication, *Satureja* essential oils could hinder the bacterial capacity to establish and maintain biofilm structures, enhancing the effectiveness of existing antibiotic treatments [35, 36].

In conclusion, the use of *Satureja* essential oils represents a promising approach for the inhibition of biofilm formation, providing a potential adjunctive strategy to improve the treatment outcomes of bacterial infections, especially those caused by antibiotic-resistant strains like Pseudomonas aeruginosa. Their multifaceted action not only diminishes biofilm establishment but also synergizes with traditional antimicrobial therapies to combat difficult-to-treat infections.

Disruption of Metabolic Pathways

Essential oils from the *Satureja* genus exhibit remarkable antimicrobial properties by disrupting metabolic pathways in bacteria. This disruption is primarily achieved through the inhibition of key enzymes involved in energy production and cell wall synthesis, which are vital for bacterial growth and reproduction [37, 38].

Essential oils derived from *Satureja* species, such as *Satureja* hortensis and *Satureja macrantha*, have been shown to effectively inhibit enzymes that play a critical role in the tricarboxylic acid [TCA] cycle, a vital part of bacterial cellular respiration [39].

The primary enzymes disrupted include: Isocitrate Dehydrogenase [ICDH] which is crucial for the oxidative decarboxylation of isocitrate to alpha-ketoglutarate within the TCA cycle. Inhibition of ICDH can lead to reduced energy production through ATP synthesis [40]. Citrate Synthase [CS] catalyzes the first step of the TCA cycle, linking the glycolytic pathway to the citric acid cycle. Inhibition affects the influx of carbon into the cycle, limiting energy production [41]. Alpha-Ketoglutarate Dehydrogenase [α-KGDH] facilitates the conversion of alpha-ketoglutarate to succinyl-CoA, another critical step in energy production. When inhibited, the energy yield from metabolic substrates is significantly diminished [42].

By targeting these enzymes, essential oils from *Satureja* can effectively decrease the metabolic activity of bacteria, impairing their ability to generate ATP [adenosine triphosphate], which is the energy currency essential for various cellular functions [43].

In addition to inhibiting energy production, Satureja essential oils also interfere with the synthesis of bacterial cell walls. Essential oils contain phenolic compounds [e.g., carvacrol and thymol] that can disrupt the integrity of the bacterial cell membrane. This disruption can compromise the cell wall's structural integrity, leading to cell lysis and death [44].

The antibacterial action is not limited to a single species; studies show that *Satureja* essential oils effectively inhibit a wide range of foodborne pathogens, including *Escherichia coli* and *Salmonella* spp. This broad-spectrum activity is indicative of their potential applications in food preservation and in combating bacterial infections[45].

The cumulative effect of enzyme inhibition and disrupted cell wall synthesis leads to significant physiological changes in bacterial populations. Bacteria subjected to *Satureja* essential oils exhibit slower growth rates as a direct

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consequence of impaired metabolism. Studies indicate that the metabolic viability of treated bacterial cells significantly decreases compared to untreated controls, showcasing the efficacy of these essential oils as antimicrobial agents. Essential oils can also impede bacterial reproduction through the disruption of essential metabolic pathways. By inhibiting the processes that supply the energy and building blocks necessary for cell division, these oils effectively reduce the overall population of viable bacteria in the environment[46].

The essential oils from *Satureja* species are potent disruptors of metabolic pathways in bacteria, characterized by their ability to inhibit key enzymes involved in energy production and compromise cell wall integrity. This dual action results in impaired growth and reproduction of bacterial populations, highlighting the essential oils' potential role as natural antibacterial agents in various applications, from food preservation to therapeutic uses. Their effectiveness further emphasizes the importance of exploring natural products for combating antibiotic resistance and ensuring food safety[47].

Interaction with Bacterial DNA

Certain compounds present in the *Satureja* genus, particularly flavonoids, have been shown to have a significant impact on bacterial DNA. These compounds can effectively bind to bacterial DNA, which interferes with critical processes such as replication and transcription. When flavonoids bind to the DNA, they stabilize the DNA-gyrase complex, thereby inducing DNA cleavage and preventing the normal functioning of the DNA replication machinery [48-51]. This interaction disrupts the cell cycle, a series of events that cells go through as they grow and divide, ultimately leading to inhibition of bacterial proliferation. As a result, the growth and reproduction of bacteria are significantly curtailed, making flavonoids a valuable component in the development of antibacterial agents [52-54].

Additionally, flavonoids are known to interact with various microbial proteins, enhancing their antibacterial efficacy. This ability to disrupt bacterial DNA function, combined with their direct actions on cellular structures, underpins the potential of these compounds in combating bacterial infections. The implications of such interactions highlight the important role of flavonoids in medicinal chemistry, particularly in the context of developing new antimicrobial strategies against resistant bacteria [55, 56].

Table1. Antibacterial activity of Satureja essential oil and extracts against pathogenic bacteria

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Plant	**Bacterial Target**	**Mecanism of Action**	**Using Part**	**Extraction**	**Inhibition Zone [IZ] (mm)**	**Minimum Inhibitory Concentrations (MIC) (mg/ml)**	**Reference**
Satureja bachtiarica	*Staphylococcus aureus PTCC 1337*	Negative effect on bacterial growth	different types	Ethanolic aqueous	80[14.4±0/28] 80[11.7±0/28]	8 32	[57]
Satureja bachtiarica	*Escherichia coli PTCC 1330*	inhibition upon the growth of the bacteria	different types	Ethanolic aqueous	80[11.7 ±0/28] 80[8.6 ±0/28]	16 64	[57]
summer savory (Satureja hortensis L)	*Streptococcus mutans*	inhibition upon the growth of the bacteria	aerial	essential oil	13.3±2.08	3.125	[58]
summer savory (Satureja hortensis **L)**	*Streptococcus salivarius*	inhibition upon the growth of the bacteria	aerial	essential oil	11.3±1.15	1.5625	[58]
Satureja hortensis	*Clostridium sporogenes*	inhibition upon the growth of the bacteria	different types	essential oil: Thymol Carvacrol	 23.5 17.5		[59]
Satureja hortensis	Klebsiella pneumoniae	inhibition upon the growth of the bacteria	different types	essential oil: Thymol Eugenol	 17 20		[59]
Satureja montana (Winter savory)	Salmonella enterica sv Anatum SF2	inhibition upon the growth of the bacteria	Leaves and stem	essential oils[carvacrol]		250	[60]
Satureja montana	Staphylococcus aureus ATCC	inhibition upon the	Leaves and stem	essential oils[carvacrol]		150	[60]

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Clinical and Industrial Applications

The antimicrobial properties of Satureja species have broad implications for both human health and industry. In clinical settings, Satureja may serve as a natural alternative to synthetic antibiotics, particularly in treating infections caused by MDR bacteria. Moreover, Satureja essential oils are increasingly being explored for their use as natural preservatives in the food industry, where they can inhibit microbial spoilage and enhance food safety [44, 63].

Limitations and Future Directions

The essential oils of all Satureja species are also found to have strong antimicrobial properties, albeit to varying degrees, against organisms that are important for food poisoning and/or spoiling [*Salmonella*, *Listeria*, *Penicillium,* and *Aspergillus*] as well as those that are of interest to the medical field (*Staphyloccocus*, *Apergillus fumigatus*, and *Candida*). Most essential oils are categorized as Generally Recognized As Safe (GRAS). While effective antimicrobial doses may surpass organoleptically acceptable levels, flavor considerations may limit their use as preservatives in foods. Legislative changes are also supporting the strong consumer trends toward natural antimicrobial agents rather than chemical ones. Due to the need to balance antimicrobial efficacy and sensory acceptability in food matrix, preparation, and potential toxicology, there is a growing need for precise knowledge of essential oil MIC.

Conclusion

The genus Satureja represents a valuable source of antimicrobial agents, particularly considering the growing threat posed by AMR. The essential oils derived from different *Satureja* species, rich in compounds such as thymol and carvacrol, exhibit potent antimicrobial activities through mechanisms including membrane disruption, biofilm inhibition, and metabolic interference. Additional research is needed to assess the effectiveness of plant extracts as natural antibacterial agents in packaged foods, the implications of herbal essential oils in complementary medicine, or their potential as substitutes for synthetic antibiotics. Achieving the right balance between essential oils and conventional drug doses may pose challenges in living organisms.

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Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

Not applicable.

Author contributions:

AA, AA, SN, ZM: design of the study. AA, ZM, MG, HH: acquisition of data. AA, SN, ZM, SFAR: evaluation of data, preparation of the manuscript. AA, AA, ZM, MY, EM: assessment of data. All authors read and approved the final manuscript.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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