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The Future Potential of Medicinal Plants from the Middle East in Combating Antibiotic Resistance

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Abstract

Antibiotic resistance has escalated into a global health crisis, creating an urgent need for new antimicrobial strategies as the pipeline of conventional antibiotics dries up. In this context, medicinal plants—especially those from the Middle East with its rich biodiversity and deep ethnomedical traditions—represent an untapped reservoir of novel antibacterial agents and resistance-modifying compounds. This review provides a comprehensive analysis of how Middle Eastern medicinal plants could help combat antibiotic-resistant bacteria. We first outline the major mechanisms of bacterial resistance, including enzymatic drug inactivation, target modification, efflux pump activity, and biofilm formation, which jointly render many pathogens impervious to current antibiotics. We then highlight the extraordinary diversity of medicinal flora in the Middle East and its history of use against infections, underlining that hundreds of regional plant species (e.g. Allium sativum, Nigella sativa, Thymus vulgaris) exhibit significant antimicrobial properties in traditional practice. Selected case studies of these three emblematic plants are presented, summarizing their bioactive constituents (such as allicin, thymoquinone, thymol) and demonstrated activities against drug-resistant pathogens. We further discuss evidence of synergistic effects between plant-derived compounds and conventional antibiotics – for example, plant phenolics acting as efflux pump inhibitors or biofilm disruptors can restore antibiotic efficacy. Despite the promise, important limitations and scientific gaps remain, including variability in phytochemical content, insufficient clinical trials, and challenges in standardization and safety regulation. Addressing these gaps through robust research and supportive policies is critical. Finally, we recommend a coordinated strategy for future research and policy, advocating for interdisciplinary collaborations to isolate novel phytochemicals, evaluate their pharmacodynamics and pharmacokinetics, and integrate proven plant-based remedies into mainstream antibiotic stewardship. Harnessing Middle Eastern medicinal plants could provide affordable, effective complementary therapies and lead compounds for drug development, thus offering a much-needed boost in the fight against antibiotic-resistant infections.

Keywords: antibiotic resistance, medicinal plants, Middle East, herbal antimicrobials, synergy, Allium sativum, Nigella sativa, Thymus vulgaris, efflux pump inhibitors, phytochemicals

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1. Introduction

Antibiotics have been the cornerstone of modern medicine since the mid-20th century, yet their efficacy is now gravely threatened by the rapid rise of antibiotic-resistant bacteria. Overuse and misuse of antibiotics in human medicine and agriculture have accelerated the emergence of multidrug-resistant (MDR) pathogens, leading to treatment failures for common infections (Davies & Davies, 2010 ; Alav et al., 2018). The World Health Organization has identified antimicrobial resistance as one of the most urgent global health challenges of our time. In 2017, WHO released a list of priority MDR bacterial pathogens (including Acinetobacter baumannii, Pseudomonas aeruginosa, and certain Enterobacteriaceae) for which new treatments are desperately needed (WHO, 2017). Alarmingly, the development pipeline for new antibiotics has dwindled; no truly novel antibiotic classes have been discovered since the late 1980s (Silver, 2011). Pharmaceutical companies have largely retreated from antibiotic research due to economic and regulatory hurdles, creating a "discovery void" in which few new drugs reach the market (Ventola, 2015; O'Neill, (2016). This confluence of rising resistance and stagnant innovation threatens a return to a pre-antibiotic era where minor infections can become life-threatening.

In response, there is growing interest in alternative and complementary approaches to combat resistant microbes.

Natural products have historically been a prolific source of antimicrobial agents – indeed, it is estimated that approximately 70% of new drugs introduced since the 1980s are of natural origin or directly derived from natural compounds (Güzel et al., 2015). Medicinal plants in particular offer a vast chemical arsenal evolved to fend off microbial pathogens, and many traditional herbal remedies have proven antimicrobial activity when investigated scientifically (Cheesman et al., 2017). The Middle East (encompassing the Eastern Mediterranean and surrounding regions) is exceptionally rich in medicinal flora and traditional healing practices. Often referred to as the cradle of herbal medicine, this region's cultural apothecary includes remedies from ancient Mesopotamian, Persian, Arabian, and Greco-Roman medical systems. Today, countries of the Middle East and neighboring Anatolia collectively harbor thousands of medicinal plant species; Turkey alone has over 11,700 plant taxa (30% endemic) and a deep repository of folkloric medicine (Akgul, et al., 2018). A large portion of the population in this region and worldwide still relies on herbal preparations for primary healthcare needs, partly due to cost and accessibility (Khatib et al., 2021; Karageçili, & Gülçin, 2025). This continuity of use suggests that many bioactive plants with antimicrobial potential remain to be scientifically explored.

Given the escalating antibiotic resistance crisis, Middle Eastern medicinal plants represent an under-investigated but potentially invaluable source of new antimicrobial compounds and treatment strategies. Traditional medical texts and ethnobotanical surveys from Middle Eastern communities frequently cite local herbs used for treating infections, ranging from skin and wound ailments to gastrointestinal and respiratory illnesses. Modern research is beginning to validate some of these uses, for example, extracts of Nigella sativa (black cumin) have shown activity against multiple drug-resistant bacteria and fungi in vitro (Gholamnezhad et al., 2016; Alberts et al., 2024). Similarly, Allium sativum (garlic) contains organosulfur compounds like allicin that exhibit broad-spectrum bactericidal and antibiofilm effects even on resistant strains (Bhatwalkar et al., 2021). Notably, the mechanisms of action of many plant-derived antimicrobials differ from those of conventional antibiotics, which means they can bypass existing resistance mechanisms or synergize with antibiotics to enhance efficacy (Cheesman et al., 2017; Taheri-Araghi 2024). For instance, some phytochemicals block bacterial efflux pumps or quorum-sensing systems, thereby resensitizing bacteria to antibiotics (Marchese et al., 2016).

In this review, we examine the future potential of Middle Eastern medicinal plants in the fight against antibiotic resistance. We begin by reviewing the fundamental mechanisms by which bacteria acquire resistance to current antibiotics, as this informs the targets and strategies for any new therapeutics. We then showcase the wealth of medicinal plants in the Middle East and present three case studies (Allium sativum, Nigella sativa, and Thymus vulgaris) to illustrate the anti-infective properties of regional herbs that are well-known in traditional medicine. Following that, we explore how plant-derived compounds can be used in synergy with conventional antibiotics, either as adjuvants that restore antibiotic potency or as combination therapies that achieve better outcomes than single agents. We discuss evidence from recent studies on synergistic interactions, including plant phenols acting as efflux pump inhibitors and essential oils enhancing antibiotic uptake (Cheesman et al., 2017; Bhatwalkaret al., 2021).

This review aims to provide a comprehensive examination of the potential of Middle Eastern medicinal plants in combating antibiotic resistance. It begins with an overview of the molecular mechanisms by which bacteria develop resistance, followed by a discussion of selected traditional plants with proven antimicrobial activity. Case studies of Allium sativum, Nigella sativa, and Thymus vulgaris illustrate specific therapeutic possibilities. Furthermore, the review explores current evidence on synergistic effects with conventional antibiotics and outlines existing limitations and scientific gaps. Finally, future research directions and policy frameworks are proposed to facilitate the responsible integration of these natural compounds into global AMR strategies.

2. Mechanisms of Bacterial Resistance

Bacteria have evolved a variety of mechanisms to withstand the effects of antibiotics. An understanding of these resistance mechanisms is crucial in order to devise new therapies, whether from synthetic sources or plant-derived compounds, to circumvent or neutralize bacterial defenses. The major mechanisms by which bacteria achieve antibiotic resistance include: (1) enzymatic drug inactivation, (2) alteration of antibiotic targets, (3) reduced intracellular accumulation of the drug (through decreased permeability or active efflux), and (4) formation of protective biofilms. Often, a single bacterial strain (especially an MDR strain) employs multiple resistance strategies in concert (Alav et al., 2018; Hajiagha & Kafil, 2023). Below, we briefly describe each mechanism:

2.1. Enzymatic Degradation or Modification of the Antibiotic

Many bacteria produce enzymes that chemically destroy or modify antibiotics before they can reach their targets. A classic example is the production of β-lactamase enzymes by Staphylococcus, Enterobacteriaceae, and other organisms, which hydrolyze the β-lactam ring of penicillins, cephalosporins, and related drugs, rendering them ineffective (Wright, 2011; Blair et al., 2015). Extended-spectrum β-lactamases (ESBLs) and carbapenemases are evolved variants that confer resistance to a broad range of β-lactams, including last-resort drugs like carbapenems. Other examples include aminoglycoside-modifying enzymes (acetyltransferases, phosphotransferases, etc.) that chemically alter aminoglycoside antibiotics, and chloramphenicol acetyltransferase, which inactivates chloramphenicol. These enzymatic defenses are often encoded by genes on plasmids or transposons, facilitating their horizontal transfer between bacteria (Dzidic & Bedeković, 2003). The net effect is that the antibiotic is neutralized and fails to bind its intended target.

2.2. Alteration of Target Sites

Bacteria can become resistant by mutating or modifying the molecular targets that antibiotics bind to, so that the drug no longer fits. For example is rifampicin resistance via mutations in the rpoB gene coding for the RNA polymerase β-subunit (the rifampicin binding site), and fluoroquinolone resistance through mutations in DNA gyrase or topoisomerase IV (the drug targets) so that the drug binds less efficiently. Bacteria may also protect targets by other means: Enterococci and some Streptococcus pneumoniae become vancomycin-resistant by altering the peptidoglycan precursors (terminating in D-Ala-D-Lac instead of D-Ala-D-Ala), preventing vancomycin binding. Additionally, post-transcriptional modifications of ribosomal RNA can confer resistance to macrolides, lincosamides, and streptogramin antibiotics (the MLS-B resistance), e.g. erm genes encode rRNA methyltransferases that modify the 23S rRNA target of erythromycin and related drugs (Blair et al., 2015). Target alterations are a common and often durable form of resistance, since they involve stable changes to essential bacterial proteins or RNA.

2.3. Reduced Drug Accumulation: Efflux Pumps and Permeability Barriers

Even if an antibiotic is not destroyed and the target is susceptible, bacteria may evade killing by keeping intracellular drug levels low. Gram-negative bacteria in particular have an outer membrane that can act as a permeability barrier, blocking or slowing the entry of many drugs. Mutations that down-regulate or alter porin channels (as in some β-lactam-resistant Pseudomonas or Klebsiella) reduce antibiotic uptake into the cell (Blair et al., 2015; Alav et al., 2018). The other major strategy is active expulsion of the antibiotic via efflux pumps, transport proteins in the bacterial cell membrane that pump out toxic substances. Bacteria possess both narrow-spectrum efflux pumps (specific for certain drugs) and multidrug efflux pumps that can eject a broad range of structurally unrelated antibiotics, biocides, and other compounds (Blair et al., 2015). For example, Escherichia coli and Salmonella have the AcrAB-TolC efflux system which can export quinolones, chloramphenicol, tetracyclines, and more; P. aeruginosa has MexAB-OprM and other pumps; and S. aureus uses pumps like NorA for fluoroquinolones. Overexpression of efflux pumps is a key factor in multidrug resistance, often giving bacteria low-level resistance to multiple classes simultaneously. Beyond conferring resistance, efflux pumps can also influence pathogenic traits; notably, studies have found that certain efflux pumps contribute to biofilm formation by exporting quorum-sensing signals or other molecules involved in biofilm development (Vert et al., 2012; Hajiagha & Kafil, 2023).

2.4. Biofilm Formation and Persister Cells

Many bacteria can grow in communities attached to surfaces and encased in a self-produced matrix, known as biofilms. Biofilm growth is a major contributor to antibiotic resistance in clinical settings, especially in chronic and device-related infections. In a biofilm, bacterial cells are embedded in a protective extracellular polymeric substance (EPS) matrix composed of polysaccharides, proteins, DNA, and lipids. This matrix acts as a diffusion barrier that slows the penetration of antibiotics and can sequester or neutralize drugs (Rodis et al., 2020). Conditions within biofilms (such as nutrient gradients and high cell density) also induce physiological changes, bacteria in biofilms often have lower metabolic and growth rates and can enter a quasi-dormant state. Such persister cells are not genetically resistant (if removed from the biofilm they are antibiotic-susceptible) but they tolerate antibiotics by virtue of their slow or non-growing state and activation of stress responses (Hajiagha & Kafil, 2023). The net effect is that biofilm-associated bacteria are dramatically harder to kill: the minimum

inhibitory concentration (MIC) of antibiotics needed to eradicate biofilm cells can be 10 to 1000 times higher than that for planktonic (free-living) bacteria of the same strain (Wu et al., 2015). Biofilms also facilitate the exchange of resistance genes by keeping cells in close proximity; for example, plasmid transfer is enhanced in biofilm communities. Clinically, biofilms underlie persistent infections such as those in cystic fibrosis lungs, chronic wounds, and on indwelling medical devices (catheters, prosthetics), where they resist not only antibiotics but also immune clearance (Rodis et al., 2020).

2.5. Other Mechanisms

Bacteria can deploy various additional tactics, such as overproduction of the antibiotic target (to titrate out the drug), bypassing metabolic pathways inhibited by the antibiotic, or regulating entry into dormant spore-like states. Horizontal gene transfer (via plasmids, transposons, bacteriophages) is not a resistance mechanism per se but is a crucial process that spreads resistance determinants (genes encoding the above mechanisms) across bacterial populations and species (Dzidic & Bedeković, 2003). For instance, the mcr-1 gene conferring colistin resistance and NDM-1 carbapenemase gene have disseminated globally through plasmids.

3. Medicinal Plants from the Middle East: An Untapped Resource

The Middle East and surrounding areas (including North Africa and West Asia) are home to a vast diversity of plant life, much of it adapted to the region's varied climates from Mediterranean coasts to arid deserts and high mountains. This region is one of the cradles of civilization where use of medicinal plants is interwoven with cultural history – from the herb gardens of ancient Egypt and Mesopotamia to the Greco-Arab Unani medicine and Persian traditional medicine. Many remedies mentioned in medieval texts by scholars like Ibn Sina (Avicenna) and Al-Razi rely on native Middle Eastern herbs for treating infections and wounds. Today, ethnobotanical knowledge in Middle Eastern communities remains vibrant, and folk medicine practitioners (e.g. Attars or herbalists in the Levant and Arabia) continue to prescribe local plants for ailments including infectious diseases. This continuity suggests that these plants, honed by both evolution and empirical use, may harbor compounds effective against pathogens, some of which modern science has yet to fully characterize. Ethnopharmacological surveys across the Middle East have consistently reported the use of various medicinal plants in the treatment of infectious diseases. Table 1 presents a comparative overview of three widely used species (Nigella sativa, Allium sativum, and Thymus vulgaris) along with their respective regions of traditional use, targeted infectious conditions, and the most common microbial pathogens they are traditionally believed to combat. This table illustrates the deep-rooted cultural knowledge surrounding plant-based treatments and provides a valuable foundation for identifying candidate species for antimicrobial drug development.

Table 1. Traditional Use of Medicinal Plants.

Plant Name	Region	Traditional Use	Targeted Pathogens
Nigella sativa	Middle East	Respiratory infections	S. aureus, E. coli
Allium sativum	Syria/Iran	Wound healing, GI infections	H. pylori, MRSA
Thymus vulgaris	Turkey/Lebanon	Cough, sore throat	S. pneumoniae, Klebsiella

3.1. Biodiversity and Ethnobotany of the Region

The Middle East's flora encompasses parts of several biodiversity hotspots (such as the Mediterranean basin and the Irano-Anatolian region). Countries like Turkey, Iran, and Yemen have exceptionally high plant endemism. Turkey, for example, boasts over 11,000 plant species with hundreds recognized as medicinal (Akgul, et al., 2018). A recent ethnobotanical survey in Hatay Province (Southern Turkey) documented 202 medicinal plant taxa used by local people, 39 of which were either newly recorded in ethnomedicine or used for novel therapeutic purposes not previously reported (Güzel et al., 2015). Likewise, an extensive study in the western region of Syria (Latakia and Tartus) catalogued 258 medicinal plant species used in traditional Arabic medicine, including many for treating infectious and inflammatory conditions. These numbers illustrate the sheer scale of botanical resources available. Notably, a significant fraction of the plants in such surveys have folk uses aligned with antimicrobial activity, for instance, in the Syrian study, of the 258 species, 185 were used for digestive

disorders (many likely microbial in origin such as diarrhea or dysentery), 118 for respiratory ailments (which often involve infections), and 91 for skin diseases including infected wounds and eczema (Khatib et al., 2021).

The traditional pharmacopoeia of the Middle East includes well-known herbs such as thyme, garlic, myrrh, cumin, frankincense, and aloes, but also countless less-familiar endemic plants. For instance, Pistacia atlantica (wild pistachio tree), native to the Eastern Mediterranean, has been used for stomach and respiratory infections; research confirms its extracts have antimicrobial and antifungal properties (Ahmed et al., 2021).. Sideritis species (ironwort) known as "mountain tea" in Anatolia are traditionally drunk for colds and throat infections, and have yielded antibacterial and anti-inflammatory compounds (Tilkat et al., 2024). In Yemen and the Arabian Peninsula, Commiphora (myrrh) and Boswellia (frankincense) resins are applied to wounds and oral infections, and indeed show antiseptic and biofilm-inhibiting activities in studies. The Middle East is also the center of origin for Nigella sativa (black seed), Trigonella foenum-graecum (fenugreek), Zataria multiflora (Iranian thyme), Lawsonia inermis (henna), and many others with reported antimicrobial constituents. Yet, for many of these plants, modern research is still in early stages. Ethnopharmacological relevance is high: one analysis in Antakya (Turkey) found that for 43 medicinal plants, the traditional uses were corroborated by at least one biomedical study demonstrating relevant biological activity (Güzel et al., 2015). This underscores that folk usage can guide discovery of effective agents.

Despite this promise, the potential of Middle Eastern medicinal plants remains underexploited in the context of antibiotic resistance. Pharmaceutical research has historically focused more on microorganisms (e.g. soil actinomycetes for antibiotics) and plants from other regions (like Chinese or Indian Ayurvedic medicine) for drug leads. Middle Eastern remedies have received comparatively less global attention, though that is beginning to change. A number of review papers and screenings have emerged in recent years cataloguing Middle Eastern herbs with antiviral or antibacterial potential. For example, a 2023 review in Turkey gathered antiviral properties of 24 Anatolian medicinal plant taxa, reinforcing the rich bioactivity of the region's flora. Another study virtually screened nearly 13,000 natural compounds from 200 Middle-Eastern medicinal plants for activity against a viral enzyme, demonstrating that computational approaches can rapidly mine the chemical space of regional botanicals (Hashim et al., 2024; Tilkat et al., 2024). By extension, similar large-scale in silico and in vitro screens against bacterial targets (like efflux pumps or quorum sensing regulators) could yield novel inhibitors from Middle Eastern plants.

3.2. Unique Phytochemicals and Modes of Action

Middle Eastern plants produce a wealth of phytochemicals – including phenolic acids, flavonoids, terpenoids, alkaloids, and sulfur compounds – some of which have distinct modes of antimicrobial action. For instance, thymol and carvacrol, abundant in thyme (Thymus vulgaris) and oregano (Origanum syriacum, wild za'atar), disrupt bacterial cell membranes and have been shown to inhibit bacterial efflux pumps and stimulate reactive oxygen species production in pathogens (Marchese et al., 2016). Allicin, the famous garlic compound, reacts with thiol groups in bacterial enzymes and also compromises membrane integrity, leading to a multi-targeted kill mechanism that bacteria find difficult to circumvent (Bhatwalkar et al., 2021). Thymoquinone, the chief constituent of Nigella sativa, has exhibited antibacterial effects against MRSA and Pseudomonas spp., potentially by interfering with bacterial cell wall synthesis and inducing oxidative stress in cells (Gholamnezhad et al., 2016; Alberts et al., 2024). Moreover, many Middle Eastern plants are rich in antioxidants (flavonoids like quercetin, luteolin, etc.) which can mitigate the tissue-damaging inflammation associated with infections (Alberts et al., 2024; Karageçili, & Gülçin, 2025). This dual action (antimicrobial and anti-inflammatory) is valuable in managing infections without causing excessive host tissue damage.

Another advantage is that some plant compounds target bacterial communication or virulence rather than viability, imposing less selective pressure for resistance. For example, extracts from Middle Eastern sage and mint species have been found to inhibit quorum sensing in bacteria (the chemical signaling that coordinates virulence and biofilm formation) (Cheesman et al., 2017; Karageçili, & Gülçin, 2025). By disarming pathogens rather than directly killing them, such agents might reduce the likelihood of resistance development.

3.3. Conservation and Sustainability

As we look to medicinal plants for solutions, it is important to consider sustainability. Overharvesting of wild medicinal plants can threaten local biodiversity and the very resource we aim to use. Many Middle Eastern medicinal plants (e.g., certain Origanum and Salvia species) are already subject to heavy wild collection.

Ethnobotanical research emphasizes conservation, documenting traditional knowledge also helps in devising strategies to cultivate and sustainably use these plants (Akgul, et al., 2018). Any large-scale development of plant-derived antimicrobials should include plans for cultivation (domestication or farming) of the source plants or laboratory synthesis of the active compounds to avoid depleting wild populations.

In summary, the Middle East offers a treasure trove of medicinal plants with compounds that could be harnessed against antibiotic-resistant microbes. While many have been used for centuries to treat infections, modern science is only beginning to validate and understand these remedies. The following sections will delve into specific examples (garlic, black cumin, and thyme) to illustrate the antimicrobial power of Middle Eastern botanicals and later discuss how they might synergize with conventional antibiotics to enhance treatment outcomes.

4. Selected Case Studies

To concretely illustrate the potential of Middle Eastern medicinal plants in combating antibiotic resistance, we present three case studies of well-known regional plants with demonstrated antimicrobial properties: Allium sativum (garlic), Nigella sativa (black cumin seed), and Thymus vulgaris (thyme). These examples were chosen for their rich history in traditional medicine, the extensive research available on their bioactive constituents, and their relevance to managing bacterial infections. Each subsection will review the plant's ethnomedicinal uses, key antimicrobial compounds and mechanisms of action, and evidence for activity against resistant pathogens or in combination with antibiotics. As summarized in Table 2, studies have reported that Nigella sativa, Allium sativum, and Thymus vulgaris exhibit strong antimicrobial activity against clinically relevant pathogens such as Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa. The presence of potent compounds like thymoquinone and allicin underpins these effects, which have been observed in both in vitro and in vivo contexts, suggesting potential for further therapeutic exploration.

Table 2. Antibacterial Activity of Selected Medicinal Plants.

Plant Name	Bioactive Compound	Target Bacteria	Study Type
Nigella sativa	Thymoquinone	S. aureus, E. coli, P. aeruginosa	In vitro
Allium sativum	Allicin	H. pylori, MRSA	In vitro & In vivo
Thymus vulgaris	Thymol, Carvacrol	S. pneumoniae, Klebsiella spp.	In vitro

4.1. Allium sativum (Garlic)

Ethnomedical background: Garlic has been used as both food and medicine for millennia across the Middle East, the Mediterranean, and beyond. In many cultures, it was reputed to fight "infections" long before microbes were known, for example, garlic cloves were applied to wounds as an antiseptic and consumed to treat coughs, throat infections, and intestinal illnesses. Ancient Egyptian medical papyri, Greek writings, and Islamic Unani texts all cite garlic for its curative powers. This cross-cultural longevity suggests garlic possesses genuine antimicrobial efficacy, which modern science now attributes mainly to its sulfur-rich compounds.

Bioactive compounds and mechanisms: The primary antimicrobial agent in garlic is allicin, a thiosulfinate that is produced when garlic cloves are crushed (the enzyme alliinase converts alliin to allicin). Allicin is relatively unstable but highly reactive. Its mode of action is multi-faceted: allicin can penetrate bacterial cell membranes and then react with thiol (-SH) groups in various enzyme targets inside the cell, effectively inactivating critical metabolic enzymes. By binding to sulfur-containing enzymes (like alcohol dehydrogenase, thioredoxin reductase, and others), allicin disrupts essential cellular functions. Additionally, garlic's organosulfur compounds (including allicin and its transformation products such as ajoenes and diallyl sulfides) have been shown to exhibit bactericidal effects and also specific anti-virulence activities: they can inhibit bacterial toxin production, quorum sensing, and biofilm formation (Bhatwalkar et al., 2021). Notably, these compounds do not target one specific site; for example, allicin's broad reactivity means bacteria would need multiple simultaneous mutations to develop resistance – which partly explains why resistance to garlic's effects is rarely observed (Magryś et al., 2021). Another interesting feature is that allicin does not need actively dividing cells to exert lethal effect (unlike β-lactams which need cell growth); it can kill even stationary-phase bacteria by oxidative and metabolic interference.

Garlic's spectrum of activity is remarkably wide: laboratory studies have shown that garlic or pure allicin inhibits many Gram-positive and Gram-negative bacteria, including Staphylococcus aureus (even MRSA), Enterococcus faecium (even vancomycin-resistant strains), Pseudomonas aeruginosa, Escherichia coli, Salmonella, Klebsiella, Proteus, Helicobacter pylori, Mycobacterium tuberculosis, and others. It also has antifungal and antiparasitic activity, though those are beyond our scope. Importantly, some studies have directly tested garlic against clinical multidrug-resistant isolates. For instance, one study found that allicin completely inhibited 88% of 30 MRSA isolates at a concentration of 32 μg/mL, showing potency on par with vancomycin. Another reported that garlic extract was effective against Helicobacter pylori strains and could even suppress H. pylori in the stomach when combined with conventional therapy (Bhatwalkar et al., 2021).

Mechanistically, beyond enzyme inhibition, garlic's compounds compromise the bacterial cell membrane. They can insert into lipid bilayers, increasing permeability and causing leakage of cellular contents. This membrane effect contributes to bactericidal action and can also enhance uptake of other antibiotics. Additionally, garlic has antibiofilm properties: it can prevent the initial attachment of bacteria to surfaces and disrupt mature biofilms. In P. aeruginosa, garlic extract inhibited biofilm formation and enhanced the efficacy of tobramycin in eradicating biofilm cells in a cystic fibrosis model (Bhatwalkar et al., 2021). A component called ajoene has been singled out for strong antibiofilm activity via blocking quorum-sensing signals in P. aeruginosa.

Evidence against resistant strains and in combinations: A compelling aspect of garlic is its ability to synergize with antibiotics and other agents. Garlic doesn't share cross-resistance with conventional drugs, so even bacteria resistant to multiple antibiotics remain susceptible to garlic's action. Moreover, combining garlic or allicin with standard antibiotics often yields synergistic effects. For example, allicin has shown strong synergy with vancomycin against vancomycin-resistant Enterococcus faecium (VRE), one experiment noted that when allicin was combined with sub-inhibitory vancomycin, it could completely inhibit VRE growth, whereas either agent alone could not. Similarly, allicin significantly enhanced the activity of cefoperazone and tobramycin against P. aeruginosa in vitro (Bhatwalkar et al., 2021).

4.2. Nigella sativa (Black Cumin)

Ethnomedical background: Nigella sativa, commonly known as black cumin or black seed, is a flowering plant native to Western Asia and the Middle East. Its seeds have been used as a spice and a medicine for over 2000 years. In Islamic tradition, black seed is famously referred to as "the remedy for all diseases except death." This saying underscores its revered status; indeed, the seeds (and their oil) have been used traditionally for a wide range of conditions: from coughs, nasal congestion, toothache, and intestinal worms to more chronic ailments like bronchial asthma, diabetes, and hypertension (Alberts et al., 2024). For infectious diseases, Nigella sativa seeds were often employed to boost immunity and fight off fevers or microbial infections. The seeds or oil are still commonly used in Middle Eastern and South Asian households as a home remedy for colds and skin infections. This breadth of use suggests an overall tonic or broad-acting medicinal effect, which modern research has been investigating.

Bioactive compounds and mechanisms: The most studied active constituent of black cumin is thymoquinone (TQ), a bioactive quinone found in the seed oil. Black seeds also contain other terpenes (e.g. p-cymene, carvacrol, α-pinene) and alkaloids, but thymoquinone is considered the principal component responsible for many of its pharmacological effects. Thymoquinone has demonstrated a variety of biological activities, including antioxidant, anti-inflammatory, anticancer, antiviral, and antimicrobial effects vitro (Gholamnezhad et al., 2016; Alberts et al., 2024).

Black seed's efficacy has been demonstrated against some clinical isolates of resistant bacteria. For instance, Nigella sativa extracts showed inhibitory activity against MRSA strains and multi-drug resistant P. aeruginosa in some studies (though MICs were relatively higher, in the range of hundreds of μg/mL) (Gholamnezhad et al., 2016). Beyond thymoquinone, other constituents might contribute: p-cymene (a fragrant terpene in black seed) is known for its antimicrobial and even efflux pump inhibitory properties. Black seed's essential oil (rich in these terpenes) has been tested against Listeria monocytogenes and shown not only direct antibacterial action but also the ability to sensitize Listeria to antibiotics (Alberts et al., 2024).

Synergy and therapeutic potential: One of the promising aspects of Nigella sativa in the context of antibiotic resistance is its synergistic effect with conventional drugs. As mentioned earlier, an authoritative 2024 review highlights that Nigella sativa seeds may have a synergistic effect with other drugs such as antibiotics, potentially leading to a reduction in the required therapeutic dose and helping to overcome drug resistance. For example, experiments have demonstrated that adding thymoquinone to certain antibiotics can result in improved bacterial

killing. A study on MRSA found that thymoquinone enhanced the effectiveness of oxacillin against MRSA by downregulating the mecA-mediated resistance mechanism. In another case, Nigella extract combined with streptomycin showed synergy against Brucella infection in mice, achieving better clearance than antibiotic alone. Mechanistically, thymoquinone is thought to increase antibiotic uptake by damaging bacterial membranes and/or inhibit stress responses that bacteria use to tolerate antibiotics. Moreover, Nigella sativa has immunomodulatory benefits – it can stimulate certain immune cells and antioxidant defenses in the host (Alberts et al., 2024). This could mean that in an infection scenario, black seed might help the body's immune system clear pathogens more effectively when used alongside antibiotics.

4.3. Thymus vulgaris (Thyme)

Ethnomedical background: Thymus vulgaris (garden thyme) is an aromatic herb native to the Mediterranean region and widely cultivated in the Middle East. Thyme has a long history of use as a culinary spice and as a medicinal herb, particularly for respiratory and gastrointestinal ailments. Traditional healers have used thyme infusions or oil for treating coughs, bronchitis, and sore throat (owing to its antiseptic and expectorant qualities), as well as for disinfecting wounds and even preserving foods. In Turkey and the Levant, wild thyme (Thymus, Origanum, and related genera often collectively called "za'atar") is both a food and a remedy; people have long observed that it prevents food spoilage and helps fight infections. The use of thyme in traditional medicine aligns well with modern findings of its potent antimicrobial properties.

Bioactive compounds and mechanisms: The primary active constituents of Thymus vulgaris are found in its essential oil, which is rich in phenolic compounds such as thymol and carvacrol, along with other terpenoids like p-cymene and linalool. Thymol, in particular, is a monoterpene phenol that constitutes a significant fraction of thyme oil (often 20–50% depending on chemotype) (Nagoor Meeran et al., 2017). Thymol and carvacrol are well-established for their strong antimicrobial activity. Their mode of action largely involves disruption of bacterial cell membranes: these lipophilic molecules insert into the lipid bilayer, destabilizing membrane integrity and causing leakage of vital cell contents (Vassiliou et al., 2023). This results in a rapid bactericidal effect. Thymol has been shown to be effective against a range of bacteria, including Staphylococcus aureus, E. coli, Pseudomonas aeruginosa, and various others, as well as against fungi like Candida species.

One interesting mechanism identified for thymol (and some related plant phenols) is inhibition of bacterial efflux pumps. Research indicates that thymol can interfere with the function of major efflux transporters, thereby increasing the intracellular concentration of antibiotics or other antimicrobial agents (Marchese et al., 2016). For example, thymol was observed to inhibit the AcrAB-TolC efflux system in E. coli and NorA pump in S. aureus in certain studies, which enhances the susceptibility of these bacteria to antibiotics that are normally pumped out. Additionally, thymol may induce oxidative stress in bacteria by promoting the formation of reactive oxygen species.

Another key property of thyme is its antibiofilm activity. Thymol and carvacrol can prevent biofilm formation and even disrupt pre-formed biofilms by S. aureus, E. coli, and Candida albicans. They penetrate the biofilm matrix and kill cells or weaken the EPS structure. A study on Helicobacter pylori (which forms biofilm-like colonies in the stomach) found that thyme extracts had strong anti-H. pylori activity and could be a helpful adjunct to conventional therapy (Almanea et al., 2019). Indeed, thyme has been traditionally consumed as a tea for stomach ailments, which may have helped manage H. pylori infections long before they were known scientifically.

Evidence against resistant bacteria and synergy: Thyme essential oil has demonstrated efficacy against some antibiotic-resistant strains. For instance, thyme oil (and its component carvacrol) was effective in inhibiting MRSA and showed an additive effect when used with oxacillin, effectively lowering the oxacillin MIC against MRSA in one laboratory experiment. Carvacrol was also reported to resensitize vancomycin-intermediate S. aureus (VISA) to vancomycin, possibly by disrupting cell membranes and making it easier for vancomycin to reach its cell-wall targets. Another study reported that carvacrol had potent activity against Streptococcus pneumoniae and Haemophilus influenzae strains, including those resistant to multiple drugs, suggesting it could be useful for respiratory infections.

Synergistic interactions between thyme's components and antibiotics have been noted. Carvacrol (from thyme and oregano) was found to work synergistically with ciprofloxacin against Salmonella, by possibly increasing antibiotic uptake and simultaneously attacking the cell membrane (Vassiliou et al., 2023). Thymol showed synergy with fluroquinolones in E. coli by inhibiting efflux (so the antibiotic stays inside the bacterium longer) (Marchese et al., 2016).

Thyme's broad antimicrobial action also makes it valuable as a natural preservative. Even the vapor of thyme oil has been tested and shown to inhibit bacterial growth on food products (its fumes can kill bacteria in the air or on surfaces at sufficient concentrations) (Antih et al., 2021). This highlights a possible use of thyme compounds to sanitize hospital environments or equipment, potentially reducing transmission of resistant bacteria on surfaces.

5. Synergistic Effects with Conventional Antibiotics

One of the most promising approaches to overcoming antibiotic resistance is combination therapy, using two or more agents together to achieve a stronger antimicrobial effect than either could alone. In this context, medicinal plant derivatives can play a crucial role as antibiotic adjuvants, working in synergy with conventional antibiotics. By enhancing the efficacy of existing antibiotics or resensitizing resistant bacteria, plant-based compounds could extend the useful life of our antibiotic arsenal and reduce the doses needed (thereby minimizing side effects). The concept of synergistic combinations is not new in pharmacology, a classic example is the beta-lactam antibiotic amoxicillin combined with clavulanic acid, a β-lactamase inhibitor derived from a microbe, which protects the antibiotic from enzymatic destruction. Researchers are now seeking similar helpers from plant sources, sometimes dubbed "herbal boosters" for antibiotics (Cheesman et al., 2017).

5.1. Efflux Pump Inhibitors (EPIs)

As described earlier, efflux pumps are a major mechanism by which bacteria expel antibiotics and achieve multidrug resistance. Certain plant compounds have been identified that can block these pumps. By co-administering an efflux pump inhibitor, the intracellular concentration of an antibiotic can be increased to effective levels. Many plant alkaloids and phenolics have shown this property. A striking example is reserpine, an alkaloid from the plant Rauvolfia serpentina (though not a Middle Eastern plant, it set the paradigm): reserpine inhibits the NorA efflux pump in Staphylococcus aureus, thereby restoring the activity of fluoroquinolone antibiotics against resistant strains (Cheesman et al., 2017). From the Middle Eastern flora, compounds like piperine (from Piper nigrum, black pepper, commonly used in Middle Eastern spice mixtures) and capsaicin (from chili peppers) have shown EPI activity in S. aureus. Piperine has been reported to inhibit the MsrA pump, for example, and indeed piperine synergizes with the antibiotic rifampicin against MRSA, significantly lowering the rifampicin MIC needed (Mgbeahuruike et al., 2019). In one study, piperine combined with rifampicin achieved a synergistic kill of S. aureus that neither agent could accomplish alone. Similarly, plant phenolics like catechin (from green tea) and curcumin (from turmeric) have been shown to inhibit efflux pumps in E. coli and Helicobacter, respectively, enhancing the effect of antibiotics. In the context of thyme (as noted), thymol can inhibit efflux systems in Gram-negatives (Marchese et al., 2016), which might underlie synergy seen between thymol-rich oils and antibiotics.

5.2. Biofilm Disruptors

Many plant extracts can prevent or disrupt bacterial biofilms, as detailed with garlic, thyme, and others. Using such agents alongside antibiotics can expose the previously protected bacteria to the antibiotic's action. For instance, garlic extract (allicin) was found to synergize with tobramycin in eradicating P. aeruginosa biofilms in a lung infection model; garlic helped to break down the biofilm matrix and stationary-phase cells, making the bacteria more vulnerable to tobramycin (Mondal et al., 2021).

5.3. Targeting Bacterial Metabolism or Stress Responses

Some phytochemicals hit bacteria in ways that complement antibiotic action. For example, certain antibiotics are less effective in stationary-phase or non-growing bacterial cells. Honey and some plant sugars can stimulate bacteria to resume metabolic activity, thereby making them more susceptible to antibiotics that require active targets. A combination of manuka honey (derived from Leptospermum plants) with linezolid was found to clear persistent MRSA much more effectively than linezolid alone, potentially because the honey components disrupted the MRSA cells' stress tolerance and triggered susceptibility (Gholamnezhad et al., 2016). While honey is not a single plant product, it is rich in plant-derived compounds and has been a traditional Middle Eastern remedy. This principle could apply to other plant metabolites that modulate bacterial metabolism or global regulators, rendering them defenseless against antibiotics.

5.4. Immunomodulatory Synergy

Sometimes the synergy is indirect, by reducing inflammation or enhancing immune clearance, plant compounds can help antibiotics perform better. For example, curcumin (from Curcuma longa, not Middle Eastern but used in Unani medicine) has anti-inflammatory properties that, when combined with antibiotics, improved outcomes in a mouse model of sepsis by dampening harmful inflammation without impeding the antibiotic's bactericidal action. In a tuberculosis model, adding curcumin to standard TB therapy accelerated bacterial clearance and protected lungs from damage. Similarly, Nigella sativa (black seed) oil given with antibiotics in mice not only directly inhibited bacteria but also boosted macrophage antibacterial functions (Gholamnezhad et al., 2016; Alberts et al., 2024). This kind of synergy, working on the host side, is harder to quantify in vitro but can be important in vivo.

5.5. Notable Study Examples

A 2017 review by Cheesman et al. surveyed numerous plant-antibiotic combinations and found encouraging results across the board. Some highlights include: Berberine (an alkaloid from Berberis species) which on its own is only moderately antibacterial, but in presence of 5'-methoxyhydnocarpin (a plant flavonolignan) shows synergistic killing of S. aureus by blocking its efflux pump – interestingly, plants themselves often contain both compounds as a self-defense strategy (Cheesman et al., 2017). Epigallocatechin gallate (EGCG) from green tea synergizes with β-lactam antibiotics against MRSA by interfering with cell wall synthesis and perhaps β-lactamase activity. Cinnamon oil was shown to synergize with amphotericin B against resistant Candida, a concept that might extend to bacterial contexts too. Research from Archives of Microbiology (2025) notes that combining certain plant polyphenols (like sericin from silk – albeit animal-derived, used traditionally in the region) with antibiotics had additive to synergistic effects against H. pylori, reducing antibiotic MICs significantly (Ding et al., 2025). Another recent mini-review (Taheri-Araghi, 2024) on antimicrobial peptides (AMPs) and antibiotics underscores that synergy often arises from complementary mechanisms, akin to how plant compounds (which can act like membrane disruptors, efflux inhibitors, etc.) complement classical antibiotic mechanisms.

5.6. Implications for Therapy

Harnessing such synergies could take several forms in practice. One approach is developing fixed herbal-antibiotic combination drugs or adjunct supplements. For example, encapsulating a purified plant EPI with an antibiotic in the same pill. Another approach is dietary or nutraceutical: encouraging patients to consume certain herbs (like garlic, black seed, thyme) alongside their antibiotic treatment – something that is already done in folk medicine. However, this should be approached scientifically to ensure effective concentrations and avoid any potential pharmacokinetic interactions (some herbs can affect drug metabolism).

The ultimate vision suggested by experts is a **"resistance-resistant" therapy:** using a cocktail where the antibiotic kills susceptible bacteria, and the plant-derived adjuvant knocks out the resistance mechanisms of the rest (Cheesman et al., 2017). For instance, one could combine a β-lactam antibiotic with a plant efflux inhibitor and a quorum-sensing blocker – such a multi-pronged assault might prevent the emergence of further resistance. In a sense, we would be mimicking the natural strategy of plants, which rarely rely on a single toxin but rather on a blend of compounds to deter pathogens.

6. Limitations and Scientific Gaps

While the prospects of using Middle Eastern medicinal plants to combat antibiotic resistance are exciting, there are significant limitations, knowledge gaps, and practical challenges that must be acknowledged and addressed. Moving herbal remedies from traditional practice into evidence-based modern therapy is a complex process. Here we discuss the key limitations and what is needed to overcome them. As shown in Table 3, major barriers to the clinical translation of plant-based antimicrobial agents include the absence of large-scale clinical trials, variability in bioactive compound levels due to environmental and genetic factors, and unclear regulatory frameworks. Addressing these challenges through chemoprofiling, standardization, and targeted policy reforms is essential for future drug development efforts.

Table 3. Challenges in Medicinal Plant-Based Antimicrobial Research

Challenge Area	Description	Suggested Solution
Lack of Clinical Trials	Few high-quality human studies to validate efficacy.	Promote randomized controlled trials (RCTs).
Variability in Bioactive Compound Levels	Concentrations vary by species, geography, and harvesting.	Develop regional monographs and chemoprofiling tools.
Regulatory Hurdles	Complex approval process for plant-based formulations.	Streamline herbal regulation under WHO guidelines.
Limited Pharmacokinetic Data	Insufficient data on absorption, distribution, metabolism.	Encourage ADME/Tox studies of key phytochemicals.
Standardization of Extracts	Lack of unified guidelines for preparation and dosing.	Adopt global pharmacopoeia standards for herbal extracts.

6.1. Variability in Phytochemical Content and Potency

Medicinal plants are not uniform products – their chemical composition can vary widely based on species, growing conditions, harvest time, storage, and preparation methods. This variability leads to inconsistent efficacy. For example, the concentration of thymoquinone in Nigella sativa seeds can differ by an order of magnitude between different strains or origins (Alberts et al., 2024). Thymol content in thyme oil likewise varies by chemotype. Such differences make it hard to standardize dosing. Traditional usage often relies on approximate measures (a handful of seeds, a few sprigs of herb), which may work in a folkloric context but are not acceptable in clinical practice. To develop reliable plant-based therapies, **standardization** is crucial: defining the active constituents and ensuring each batch of product contains a consistent amount. This requires robust quality control and perhaps cultivating plants under controlled conditions or producing the compounds semi-synthetically. The need for standardization is frequently highlighted; for instance, a review on Nigella sativa noted that few clinical trials reported phytochemical analyses of the exact supplement used (Gholamnezhad et al., 2016). This gap must be filled to lend scientific credibility and reproducibility to herbal treatments.

6.2. Limited Clinical Evidence

For most medicinal plants (with a few exceptions like cranberry for UTIs or psyllium for fiber), there is a lack of large-scale, high-quality clinical trials evaluating their efficacy and safety against infections. Many supportive data come from in vitro studies or small animal experiments. Clinical trials that do exist are often small sample, not rigorously controlled, or have methodological issues (Gholamnezhad et al., 2016). For example, while numerous lab studies show garlic's antibacterial effects, clinical trials using garlic for infections are scarce; partly due to difficulties in blinding (garlic's odor) and determining appropriate dosing. Similarly, black seed has shown promise in pilot studies (like the H. pylori trial and some viral studies), but larger trials are needed to confirm benefits. Ethical and practical considerations come in: one cannot test a herbal remedy alone in serious infections due to risk of failure, so trials often evaluate adjunct use with antibiotics. Designing such trials to clearly attribute effects is challenging. Additionally, regulatory pathways for approval of botanicals as drugs (rather than as foods or supplements) are arduous and expensive, which discourages clinical research by companies since plant products are hard to patent for exclusive profits. This creates a gap where traditional use is widespread but formal evidence is thin. Bridging this gap requires academic and perhaps government-supported research initiatives to systematically test promising plant compounds in clinical scenarios.

6.3. Safety and Toxicity Concerns

The adage "natural is safe" is a misconception. Many plant compounds can have side effects or toxicities, especially at high doses or with prolonged use. For instance, thymol, while effective as an antiseptic, can cause irritation of mucous membranes and even systemic toxicity if ingested in large quantities (leading to symptoms like dizziness, nausea). Some herbs may contain components that are hepatotoxic, nephrotoxic, or carcinogenic if not used properly. Aristolochia species (not discussed here, but historically in some Middle Eastern remedies) caused severe kidney damage and urothelial cancers in patients; a cautionary tale of herbal risk. Even generally safe herbs like garlic can cause bleeding tendency in high amounts (due to antiplatelet activity). Therefore,

thorough toxicological evaluation is needed for any plant-derived product intended for medical use, to establish its safety profile, maximum tolerated dose, and potential interactions with other drugs. The lack of such data is a hurdle. Many user-friendly herbal products are sold as dietary supplements without rigorous safety testing (under the presumption of traditional use equals safety). When combining with antibiotics, there's also potential for pharmacokinetic interactions – for example, certain plant extracts can induce or inhibit liver enzymes (CYP450s) that metabolize drugs, thus affecting antibiotic levels in the body. St. John's Wort is a well-known example (causing reduced efficacy of various drugs via enzyme induction). For Middle Eastern herbs, these interactions remain understudied. Ensuring safety will require specific studies on drug-herb interactions and careful consideration of which patient populations (pregnant women, children, those with organ impairment) can be given these therapies.

6.4. Challenges in Formulation and Delivery

Many phytochemicals have suboptimal pharmacokinetic properties – they may be poorly soluble, unstable, or rapidly metabolized in the human body. Allicin, for instance, is potent but highly unstable, decomposing quickly into other sulfur compounds. Thymoquinone is hydrophobic and not very water-soluble, which might limit its bioavailability when taken orally. Essential oils like thymol can evaporate or degrade. Therefore, creating effective formulations (such as encapsulations, nano-delivery systems, or chemical modifications) is a necessary step to turn these compounds into viable medicines. If an herbal extract is to reach a systemic infection, one must ensure its active constituents can be absorbed into the bloodstream and reach the infection site at therapeutic concentrations. This often hasn't been demonstrated – in vivo efficacy sometimes fails even when in vitro results were good, simply because the compound never reaches the bug in the body in sufficient amount. Innovative drug delivery approaches, including liposomal packaging of oils or conjugating phytochemicals with carriers, are being explored to overcome this. Without solving formulation issues, promising plant compounds might be dismissed prematurely due to lack of apparent efficacy in animal/human studies.

6.5. Scientific Gaps in Mechanistic Understanding

Many plant extracts are mixtures of dozens or hundreds of compounds. It is often unclear which specific component or combination of components is responsible for the antimicrobial effect and by what mechanism. Traditional usage doesn't pinpoint mechanisms – it's empirical. Modern science requires mechanism-of-action elucidation to facilitate drug development (e.g. to ensure a compound isn't hitting a human target causing toxicity, or to predict resistance development). For some herbal agents, like allicin or thymol, we have a decent idea (enzyme sulfhydryl reaction, membrane disruption). But for others like complex polyherbal mixtures or crude extracts, the mechanisms might involve multiple targets or synergistic interactions between components. Dissecting this synergy scientifically is challenging: isolating individual compounds can sometimes reduce activity seen in whole extract, suggesting multi-compound cooperation which our reductionist lab models aren't always set up to analyze. Moreover, bacteria can respond to plant stressors in ways we don't fully map – for example, sub-lethal herbal extract might induce some defense genes in bacteria; understanding these responses could guide how to best use the herb (e.g. avoid chronic low doses that let bacteria adapt). There's also a lack of data on whether bacteria can develop resistance to certain phytochemicals if exposed repeatedly (some evidence suggests it's harder for them to resist multi-target agents like essential oils, but this isn't guaranteed). Addressing these scientific questions will require more molecular biology and microbiology research focused on plant-derived substances.

6.6. Regulatory and Policy Hurdles

Bringing a new antimicrobial to market, especially from natural sources, faces regulatory scrutiny. If a plant compound is to be sold as a drug, it must go through rigorous clinical trials for approval, which is expensive and time-consuming. On the other hand, if marketed as a supplement or herbal remedy, the standards for proof are lower, but then claims must be limited (cannot claim to cure disease explicitly) and quality control might be inconsistent. There's a somewhat gray zone where many promising plant products languish – proven somewhat effective but not developed into pharmaceuticals due to lack of investment. Policy changes or incentives may be required to stimulate development in this area (similar to how orphan drug status or antibiotic incentives are given). Moreover, integrating herbal options into mainstream medicine requires education of healthcare providers, official guidelines, and perhaps changes in attitude – many physicians remain skeptical of herbal

medicine, sometimes rightly due to lack of evidence or standardization. Overcoming this will rely on building a solid evidence base and ensuring quality (so that one can prescribe, say, a standardized Nigella sativa capsule knowing it reliably contains X mg thymoquinone, much like a drug).

6.7. Supply and Sustainability Issues

If a particular plant-based treatment becomes widely adopted, there could be supply challenges. Large-scale cultivation or harvesting would be needed, and this must be done sustainably to avoid environmental damage or loss of biodiversity. As mentioned in the ethnobotany section, about 30,000 plant species globally are known to be used in traditional medicine (Karageçili, & Gülçin, 2025), but many are wild-collected. Developing them into modern remedies might require creating agricultural programs or synthetic biology approaches to produce the compounds. This is both a gap and a limitation: it requires agronomy research, considerations of land use, and time to establish a reliable supply chain. An example is Taxus trees for the anticancer drug paclitaxel; initially, supply was a big problem until semisynthesis from cultivated yews was achieved. We could face similar issues if, say, a certain endemic Middle Eastern plant proves to be "the next big antibiotic" – ensuring we don't overharvest it to extinction is critical.

6.8. Public Perception and Usage

There is also the practical aspect of how these remedies might be used by patients. Herbal medicines are often available over-the-counter and people may self-medicate with them. This can lead to misuse (e.g., using a herbal remedy alone for a serious infection and delaying proper care) or interactions with prescription drugs that patients don't inform their doctors about. Public perception swings between seeing herbs as panaceas or as quackery; a balanced understanding must be promoted. Clear guidelines will be needed for integration (for example, if black cumin seed is recommended as an adjunct in treating H. pylori or MRSA carriage, patients need to know it's complementary to, not a replacement for, antibiotics in those cases).

7. Future Research and Policy Recommendations

Medicinal plants from the Middle East offer a promising yet largely untapped reservoir of solutions to antibiotic resistance. Realizing this potential will require concerted efforts across scientific research, clinical practice, and public health policy. In this section, we outline recommendations for future research directions and policy initiatives to facilitate the safe and effective integration of plant-based therapies into combating antibiotic-resistant infections.

7.1. Interdisciplinary and Collaborative Research Programs

To unlock the potential of medicinal plants, interdisciplinary collaboration is essential. Botanists, ethnopharmacologists, microbiologists, chemists, and clinicians should work together in identifying and developing new antimicrobial agents from plants. We recommend establishing research consortia or centers of excellence focused on natural antimicrobials and resistance, possibly under the auspices of international bodies or regional governments. These centers could systematically catalog medicinal plants (leveraging ethnobotanical knowledge), screen extracts/compounds for antimicrobial and resistance-modifying activity, and advance the most promising candidates through preclinical development. Collaborative efforts can also involve researchers in both the Middle East and global institutions, ensuring knowledge exchange. Such teamwork is in line with suggestions that integrating traditional wisdom with modern scientific research will lead to discovery of new compounds, and that collaborative efforts between botanists, pharmacologists, and clinicians are needed to translate findings into clinically validated solutions (Tilkat et al., 2024).

7.2. Rigorous Clinical Trials and Evidence Building

As emphasized earlier, there is a pressing need for well-designed clinical trials to evaluate herbal interventions either as stand-alone or adjunct therapies. Funding agencies and health ministries should earmark resources for clinical studies on plant-based treatments for infections, particularly those addressing resistant pathogens. These could start as pilot studies (for safety and preliminary efficacy) and progress to larger randomized controlled trials. Regulatory bodies could provide fast-track or orphan-like status to trials of plant-derived adjuvants for

serious resistant infections, recognizing the urgency of AMR. Additionally, academic journals and conferences should encourage publication and discussion of negative results too (if an herb doesn't work, that is also important to know). Over time, accumulating evidence can feed into clinical guidelines. For instance, if multiple trials confirm that a certain herbal extract significantly improves outcomes in MRSA skin infections, guidelines could incorporate that as an adjunct recommendation. It is worth noting that acceptance of herbal therapies by the medical community will rely on having robust evidence analogous to that required for pharmaceuticals.

7.3. Standardization, Quality Control, and Good Manufacturing Practices (GMP)

Any plant-based product intended for medicinal use must be produced under strict quality control to ensure consistent composition and absence of contaminants (such as pesticides, heavy metals, or adulterants). We recommend developing standardized extracts for the key medicinal plants identified (e.g., a standardized Nigella sativa oil with defined thymoquinone content, or a garlic preparation with a guaranteed allicin yield). Pharmacopeial standards should be created for these herbal extracts, possibly via national or regional pharmacopeias. Moreover, licensing of these products as registered herbal medicines could enforce GMP production. Policymakers should strengthen regulations around herbal supplements such that products making antimicrobial claims are required to meet quality and efficacy benchmarks. This might involve creating a new category of "antimicrobial phytomedicines" under drug regulatory laws, streamlining their approval if evidence is presented, but also ensuring quality and consistency. The experience of countries like Germany (with Commission E monographs) can be instructive in how to regulate and integrate herbal medicine.

7.4. Integration into Antibiotic Stewardship Programs

Antibiotic stewardship traditionally focuses on optimal use of antibiotics to slow resistance. We propose expanding stewardship to consider complementary therapies that might reduce antibiotic consumption or enhance outcomes. For example, if certain herbal adjuvants allow for shorter antibiotic courses or lower doses, that should be explored. Stewardship committees and infectious disease specialists should stay informed about validated herbal options. Hospitals might consider offering evidence-supported herbal adjuncts as part of treatment protocols for specific cases (with patient consent and proper monitoring). One could envision, in the future, a hospital AMR policy that includes using a thyme oil inhalation therapy in ventilated patients to reduce VAP (ventilator-associated pneumonia) incidence, or using a topical honey/herbal dressing for colonized wounds to reduce systemic antibiotic use. However, these integrations must always be data-driven.

7.5. Conservation and Sustainable Sourcing Initiatives

As demand for certain medicinal plants increases, there must be parallel efforts in conservation. Governments and agricultural bodies in Middle Eastern countries should promote the cultivation of high-value medicinal plants to supply pharmaceutical needs, which will also provide economic opportunities for local communities. Cultivation takes pressure off wild populations. Seed banks and botanical gardens should preserve germplasm of important species. Additionally, techniques like plant tissue culture or microbial fermentation of plant compounds (synthetic biology) can be pursued for sustainable production of key phytochemicals. International cooperation may be needed if a plant is native to only one country but the demand is global; benefit-sharing agreements (per the Nagoya Protocol on genetic resources) should ensure that source countries and indigenous knowledge holders are fairly compensated for their contributions if a product becomes commercial.

7.6. Education and Training

Both healthcare professionals and the public need education regarding the proper use of medicinal plants for infections. In many Middle Eastern countries, traditional medicine is popular but not always communicated to doctors. We advocate for including evidence-based information on herbal antimicrobials in medical and pharmacy curricula, so future clinicians are aware of them – including their benefits and limitations. At the same time, traditional healers and herbalists should be educated about the importance of antibiotic therapy and dangers of severe infections, so they can appropriately refer patients or combine treatments responsibly. This mutual understanding can prevent delays in care (e.g., someone relying only on herbs for a serious infection without improvement). Clear communication to the public through health campaigns could promote "integrative" approaches: for instance, advising that if you have a mild infection, certain home remedies may help, but also

providing red flags for when antibiotics and doctor visits are necessary. Such balanced messaging can reduce misuse of both antibiotics and herbs.

7.7. Supportive Policies and Funding

Policymakers should recognize traditional medicine as a potential resource in addressing AMR. This could translate to funding more research (as mentioned), but also to establishing regulatory frameworks that encourage innovation. For example, creating grant programs or public-private partnerships specifically for developing plant-based antimicrobial adjuvants. Policy could also encourage pharma companies to invest in natural product research by providing incentives like extended market exclusivity for an herb-based drug, or tax breaks. Additionally, global organizations like the WHO can incorporate traditional medicine into their AMR action plans – indeed, WHO's Traditional Medicine Strategy (2014–2023) emphasizes harnessing the contributions of traditional remedies in health systems (Tilkat et al., 2024). Perhaps a WHO guideline or monograph series on "Herbal interventions for common infections" could be developed, compiling evidence and recommendations, which member states can adapt.

7.8. Global Collaboration and Knowledge Sharing

Antibiotic resistance knows no borders, and many medicinal plants have a broad distribution. An international open database of plant-derived compounds with antimicrobial activity could be maintained, where scientists contribute findings (similar to how there are databases for new antibiotic compounds). Also, countries with advanced research infrastructure can help analyze plants from biodiversity-rich Middle Eastern regions; a model of collaboration that ensures capacity building and equitable sharing of any resulting benefits. Given that numerous cultures (Chinese, Indian, African) face similar challenges and have their own pharmacopoeias, cross-cultural exchange of knowledge could identify overlapping leads or unique remedies from each tradition that could be globally useful.

7.9. Monitoring and Pharmacovigilance

Once plant-based therapies begin to be used more widely, systems should be in place to monitor their effectiveness and safety in real-world settings. Just as we track antibiotic resistance patterns, it would be wise to track outcomes from herbal use and any adverse events. Over time, this can inform best practices (for instance, if a certain herbal approach consistently fails for a particular infection, it should no longer be recommended; conversely, strong successes can bolster confidence and guideline inclusion).

8. Conclusion

In the battle against antibiotic-resistant microbes, medicinal plants from the Middle East emerge as a beacon of hope and a source of innovative solutions. This review has highlighted that these plants, long revered in traditional practice, are rich in bioactive compounds capable of inhibiting pathogens and augmenting conventional antibiotic therapy. From the broad-spectrum antibacterial effects of garlic's allicin to the efflux pump-inhibiting action of thyme's thymol and the immune-boosting properties of black cumin's thymoquinone, Middle Eastern flora offers a pharmacopeia of mechanisms to counter microbial resistance. Harnessing these natural agents could transform how we manage infections: rather than relying on antibiotics alone, we can deploy combination strategies that disarm bacterial defenses (biofilms, pumps, enzymes) while directly killing them.

However, enthusiasm must be tempered with scientific diligence. We have underscored that significant research gaps and practical hurdles remain. The journey from a healing herb in a farmer's field to an approved medicine in a hospital is complex. It demands standardizing extracts, proving efficacy in rigorous trials, ensuring safety, and obtaining regulatory endorsement. These challenges, while non-trivial, are surmountable with coordinated effort. The landscape is already beginning to shift: researchers worldwide are paying renewed attention to natural products as evidenced by increasing studies on plant-antibiotic synergies and phytochemicals overcoming resistance. International bodies like the WHO have also recognized the value of traditional medicine and call for integrating it into contemporary health care strategies.

A future scenario illustrates the possibilities: A patient with a chronic MRSA wound infection receives a treatment regimen that includes a low-dose conventional antibiotic, a topical ointment containing standardized

thyme and sage extracts to disrupt the biofilm and locally kill bacteria, and an oral supplement of black seed oil proven to enhance immune response and reduce inflammation. Over a short period, the wound clears, something unattainable with antibiotics alone due to resistance. In another scenario, hospitalised pneumonia patients inhale an aerosolized essential oil blend (formulated from Thymus and Origanum species) that significantly reduces ventilator-associated pneumonia by preventing colonization, cutting down the need for systemic antibiotics. These are not flights of fancy but tangible outcomes that could be achieved if the groundwork described in this paper is laid.

Crucially, adopting medicinal plants in the fight against antibiotic resistance is not about replacing antibiotics, but about complementing and strengthening our therapeutic arsenal. Antibiotics will remain central players, but plant-derived adjuvants and alternatives can relieve some of the pressure on these drugs, slow the march of resistance, and treat infections that have become unresponsive to standard care. Furthermore, exploring plant chemistry could lead to discovery of entirely new classes of antimicrobial compounds (the next penicillin might well be hiding in a desert shrub or mountain herb). As one study aptly noted, nature has already solved many chemical problems through evolution; tapping into that wisdom could inspire novel antibiotics or resistance breakers.

In conclusion, the medicinal plants of the Middle East, with their rich tapestry of history and bioactivity, hold significant promise in addressing one of the 21st century's greatest health challenges. Realizing this promise will require diligent research, open-minded policy, and respect for traditional knowledge. If we succeed, the payoff will be substantial: a more resilient and multifaceted approach to treating infections, improved health outcomes, and a revaluation of the treasure trove that is our planet's botanical diversity. As the world grapples with antibiotic resistance, the age-old remedies of the Middle East might indeed become part of the next wave of solutions, a fusion of ancient practice and modern science that benefits global health for generations to come.

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