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Review Article

Bioactive Compounds From Culinary Spices as Potential Adjunctive Antifungal Agents Against Multidrug-Resistant *Candida auris*

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Candida auris is an emerging multidrug-resistant fungal pathogen that poses a significant threat in healthcare settings. Its resistance to major antifungal classes and ability to persist on surfaces and form biofilms make treatment and infection control particularly challenging. This growing resistance crisis underscores the need for alternative therapeutic strategies. This review analyzes existing literature on *C. auris*, focusing on its clinical impact, resistance mechanisms, and global spread. It further explores the antifungal potential of culinary spices by examining their bioactive components and mechanisms of action. Studies evaluating the in vitro antifungal activity of common spices were assessed, including their synergistic effects with conventional antifungals. Several culinary spices—such as turmeric, cumin, cardamom, cinnamon, and ginger—exhibited antifungal activity against *C. auris*. Active compounds like curcumin, cinnamaldehyde, and thymol disrupted fungal membranes, inhibited biofilm formation, and enhanced the effects of standard antifungal drugs. These spices have demonstrated significant antifungal activity against *C. auris*, with reported minimum inhibitory concentrations ranging from 0.125 to 1 mg/mL and growth inhibition rates of 60% to 80%. These natural products demonstrated low risk of resistance, broad antimicrobial activity, and potential safety advantages. Culinary spices rich in bioactive compounds offer promising antifungal properties against *C. auris* and may serve as affordable adjunct or alternative therapies. While pre-clinical data are encouraging, clinical validation is essential. Integrating these natural agents with conventional treatment may help combat the rising threat of antifungal resistance.

Key words: *Candida auris,* antifungal resistance, culinary spices, treatment, bioactive compounds

INTRODUCTION

Fungal Infections

Fungal infections, or mycoses, represent a significant global health challenge, ranging from superficial skin conditions to severe, life-threatening systemic diseases. They are caused by

a variety of fungi, including yeasts, molds, and dermatophytes. With the increasing number of immunocompromised patients due to conditions like HIV/AIDS, cancer treatments, and organ transplants, the incidence of invasive fungal infections has escalated. [1] This review provides an overview of fungal infections, focusing on their types, pathogenesis, diagnosis, treatment, and prevention strategies.

Types of Fungal Infections

Fungal infections are broadly classified into three categories based on their depth of involvement and the part of the body affected: superficial, subcutaneous, and systemic (**Figure 1**).

Superficial Fungal Infections

Superficial mycoses primarily affect the skin, nails, and hair. Dermatophytes such as *Trichophyton*, *Microsporum*, and *Epidermophyton* are the leading causes of these infections, which include conditions such as athlete's foot, ringworm, and onychomycosis. These infections are generally limited to the outermost layers of the skin and can be treated with topical antifungal medications. [2]

Subcutaneous Fungal Infections

Subcutaneous mycoses involve the deeper layers of the skin and subcutaneous tissues. These infections occur following trauma, leading to the implantation of fungal spores. *Sporothrix schenckii* is a typical causative agent, leading to sporotrichosis, characterized by chronic, ulcerated skin lesions. [3] Other subcutaneous infections include chromoblastomycosis, caused by various dematiaceous fungi.

Systemic (Deep) Fungal Infections

Systemic fungal infections are the most severe and involve internal organs, often in immunocompromised individuals. These infections may be caused by yeasts like *Candida*, *Cryptococcus*, and *Histoplasma*, as well as molds like *Aspergillus*. Systemic mycoses can manifest as pulmonary, neurological, or disseminated infections, with life-threatening consequences if untreated. [4]

Pathogenesis of Fungal Infections

The pathogenicity of fungi is influenced by various factors, including the virulence of the organism, the immune status of the host, and environmental conditions. Fungi are typically opportunistic pathogens, exploiting weaknesses in the host's defense mechanisms, such as immunosuppression, diabetes, or antibiotic use. [1]

Candida spp.

Candida species, particularly *Candida albicans*, are part of the normal microbiota of the gastrointestinal and urogenital tracts. Under certain conditions, such as prolonged antibiotic use, immune deficiency, or diabetes, *Candida* can overgrow, causing mucosal infections (e.g., thrush) or more severe systemic infections, including candidemia. [5]

Aspergillus spp.

Aspergillus species, notably *Aspergillus fumigatus*, are environmental molds that can cause respiratory infections when spores are inhaled. They often affect immunocompromised individuals, particularly those with neutropenia, undergoing chemotherapy, or with chronic obstructive pulmonary disease. Aspergillosis can lead to conditions like allergic bronchopulmonary aspergillosis, aspergilloma, and invasive aspergillosis. [6]

Cryptococcus neoformans

Cryptococcosis is caused by *Cryptococcus neoformans*, a yeast that primarily affects the central nervous system, particularly in individuals with HIV/AIDS. The organism is inhaled from environmental sources, including bird droppings, and can cause meningitis or disseminated infections. The capsule of *Cryptococcus* plays a critical role in its virulence, allowing immune evasion. [7]

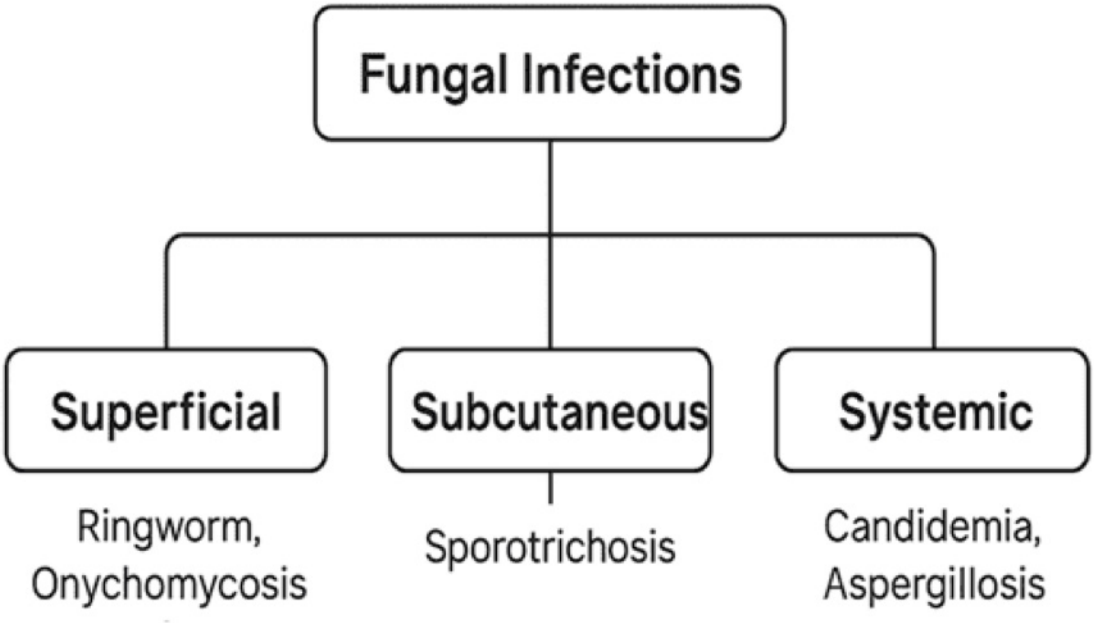

Figure 1: Types of fungal infections.

Histoplasma capsulatum

Histoplasmosis is caused by *Histoplasma capsulatum*, a dimorphic fungus found in soil enriched with bat or bird droppings. Inhalation of conidia leads to pulmonary infection, and in immunocompromised individuals, it can disseminate to other organs, including the liver, spleen, and bone marrow. Histoplasmosis is endemic in regions such as the Americas and parts of Africa. [4]

Clinical Manifestations

Superficial Infections

These often present as pruritic, erythematous lesions. For instance, tinea corporis (ringworm) presents as round, scaly patches on the skin, while onychomycosis causes thickening, discoloration, and brittleness of nails. [8.9]

Subcutaneous Infections

Subcutaneous fungal infections like sporotrichosis manifest as nodules and ulcers, typically on the arms or legs, often with a history of trauma. These lesions may eventually spread to lymph nodes. [10]

Systemic Infections

Systemic fungal infections, such as candidemia, present with fever, chills, and organ dysfunction. [11] *Aspergillus* infection may cause respiratory symptoms, including cough, hemoptysis, and pleuritic chest pain. [12] Cryptococcosis typically presents with headache, fever, and neck stiffness, indicating meningitis. [13–15]

Diagnosis of Fungal Infections

Timely and accurate diagnosis is crucial for the management of fungal infections. Diagnostic techniques include:

Microscopy and Culture

Direct microscopy, such as potassium hydroxide (KOH) preparations, is used to examine skin scrapings, nails, or sputum for fungal elements. [16–18] Culture remains the gold standard for identifying fungal pathogens, allowing for species identification and susceptibility testing. [16–18]

Serology

Serological tests can detect fungal antigens or antibodies. For example, Candida antigens can be detected in blood and urine in cases of invasive candidiasis. [11] Cryptococcus antigen testing is particularly useful in diagnosing cryptococcosis. [13–15]

Polymerase Chain Reaction (PCR)

PCR-based methods offer high sensitivity and specificity for detecting fungal DNA. This is particularly useful for diagnosing infections with fungi that are difficult to culture, such as *Histoplasma* or *Aspergillus*. [19]

Treatment of Fungal Infections

Treatment depends on the type of infection, its severity, and the patient's immune status.

Topical Antifungals

Topical antifungal agents like clotrimazole, terbinafine, and ketoconazole are effective for superficial fungal infections. These medications inhibit fungal cell wall synthesis or ergosterol production, leading to cell death. [16–18]

Surgical Intervention

In cases of aspergillomas or fungal infections of bones and joints, surgery may be necessary to remove infected tissues or drain abscesses. [12]

Systemic Antifungals

Systemic antifungals, such as fluconazole, itraconazole, voriconazole, and amphotericin B, are used for more severe or invasive infections. Amphotericin B remains the treatment of choice for life-threatening systemic fungal infections, although its toxicity limits its use. [20]

Antifungal Resistance

Antifungal resistance has emerged as a significant concern in the treatment of fungal infections. Resistance is particularly concerning for common pathogens such as *Candida* species and *Aspergillus*.

Candida Resistance

Resistance to azoles (e.g., fluconazole) in *C. albicans* and *Candida glabrata* has been increasingly reported, especially in immunocompromised patients. Resistance mechanisms include mutations in the drug targets (e.g., lanosterol demethylase), overexpression of efflux pumps, and biofilm formation. [13–15]

Aspergillus Resistance

Resistance in *A. fumigatus* to azoles, especially voriconazole, is growing and linked to mutations in the Cyp51A gene, which is involved in ergosterol biosynthesis. [13–15]

Impact of Resistance

Resistance complicates the treatment of fungal infections, leading to longer hospital stays, higher treatment costs, and worse outcomes. It underscores the need for improved antifungal stewardship and the development of new antifungal agents. [13–15]

Prevention and Control

Preventive measures include minimizing fungal exposure in high-risk environments, such as hospitals or areas contaminated with bird droppings. For immunocompromised patients, antifungal prophylaxis may be indicated, particularly for those undergoing chemotherapy or organ transplantation. [13–15] Healthcare settings should adopt rigorous infection control measures to prevent nosocomial fungal infections, including the use of antifungal stewardship programs to guide appropriate treatment.

CULINARY SPICES

Culinary spices are plant-derived substances used primarily to flavor food. While these spices are used in the culinary world

for their ability to enhance taste, they also contain compounds that have long been recognized for their potential medicinal properties. Spices contain a variety of bioactive compounds such as alkaloids, terpenes, phenolic compounds, and essential oils, many of which have demonstrated antimicrobial and antifungal activity. The antimicrobial properties of these spices have become increasingly important as the world faces growing concerns regarding antimicrobial resistance (**Figures 2 and 3**).

Different Types of Culinary Spices With Antimicrobial and Antifungal Properties

Turmeric (Curcuma longa)

Turmeric is renowned for its anti-inflammatory and antimicrobial properties, particularly due to the compound curcumin. Studies have shown that curcumin exhibits antimicrobial activity against a variety of bacterial pathogens, including *Escherichia*

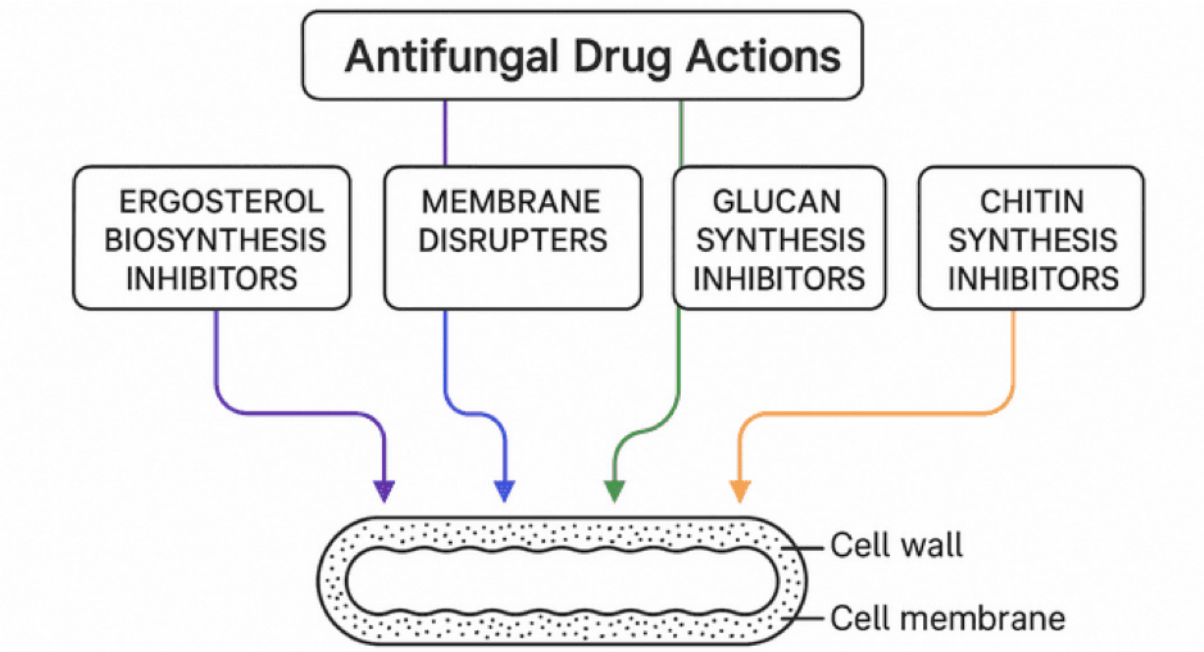

Figure 2: Antifungal drug action.

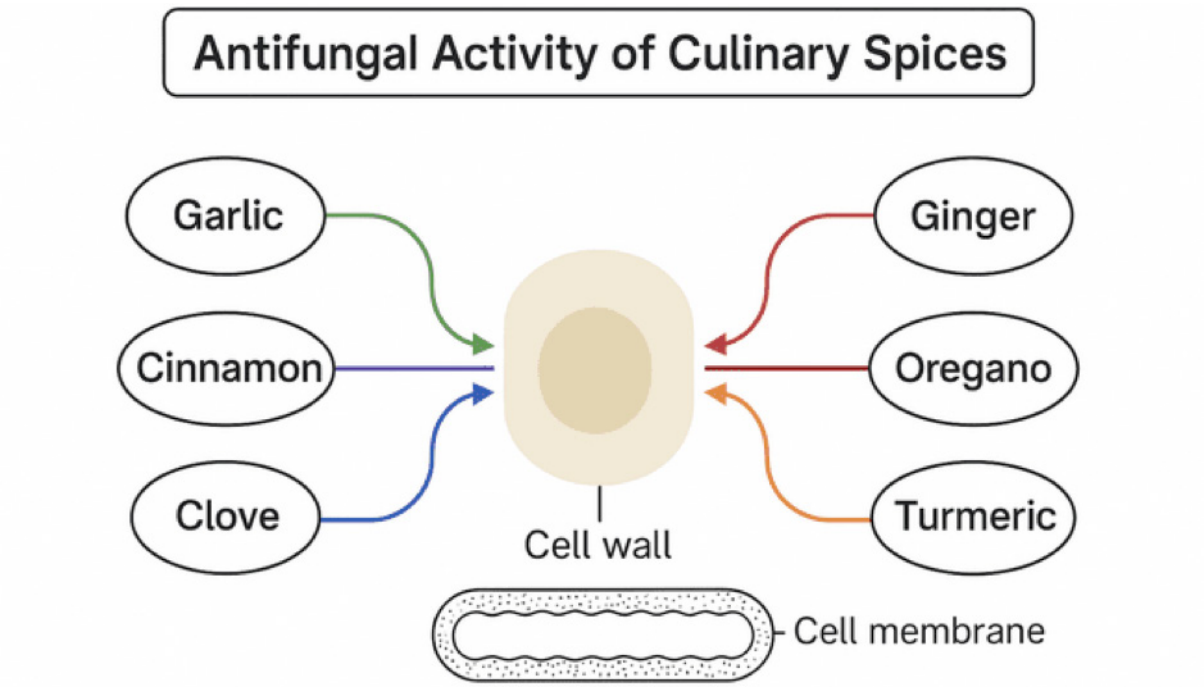

Figure 3: Common antifungal activity of culinary spices.

coli and *Staphylococcus aureus*. Additionally, turmeric has antifungal properties against *C. albicans*. [21]

Cumin (Cuminum cyminum)

Cumin is used in many cuisines around the world. Research indicates that cumin contains compounds that demonstrate antimicrobial properties, particularly against *Salmonella* and *E. coli*. Cumin also exhibits antifungal activity, especially against *Aspergillus flavus*. [22]

Coriander (Coriandrum sativum)

Coriander is used globally for both culinary and medicinal purposes. Its essential oil has shown significant antimicrobial effects against *Salmonella* and *S. aureus*. Coriander oil also demonstrates antifungal activity against *C. albicans*. [23]

Cardamom (Elettaria cardamomum)

Cardamom contains essential oils such as 1,8-cineole and limonene, which are known for their antimicrobial properties. Studies have shown its ability to inhibit *E. coli* and *S. aureus*. Cardamom also displays antifungal effects, particularly against *C. albicans*. [24]

Cinnamon (Cinnamomum verum)

Cinnamon is well-known for its antimicrobial effects, largely due to cinnamaldehyde, its primary bioactive compound. Studies have confirmed its effectiveness against pathogens such as *E. coli* and *Salmonella*. Cinnamon also exhibits antifungal properties against *C. albicans*. [25]

Ginger (Zingiber officinale)

Ginger is another spice with known antimicrobial properties, thanks to compounds like gingerol. It has been shown to inhibit bacterial growth, including *E. coli* and *S. aureus*. Ginger also has antifungal properties, particularly against *Candida* species. [26]

Black pepper (Piper nigrum)

Black pepper is rich in piperine, a compound known for its antimicrobial activity. Studies have demonstrated that piperine can inhibit the growth of bacteria such as *E. coli* and *S. aureus*. It also shows antifungal effects, particularly against *A. flavus*. [27]

Cloves (Syzygium aromaticum)

Cloves are rich in eugenol, which has demonstrated significant antimicrobial properties. Cloves inhibit the growth of bacteria like *E. coli* and *Salmonella*. Furthermore, clove oil is effective against fungal pathogens such as *C. albicans*. [28]

Mustard seeds (Brassica spp.)

Mustard seeds contain compounds like allyl isothiocyanate, which have been shown to exhibit antimicrobial properties against *E. coli* and *Salmonella*. Mustard seeds also show antifungal activity against *C. albicans*. [29]

Saffron (Crocus sativus)

Saffron is not only prized for its flavor but also for its antimicrobial properties. Studies have shown that saffron extracts can inhibit *E. coli* and *Salmonella*. Saffron also demonstrates antifungal effects against *Aspergillus niger* and *C. albicans*. [30]

Fenugreek (Trigonella foenum-graecum)

Fenugreek is used both as a culinary spice and in traditional medicine. It has been found to have antimicrobial activity against *E. coli*, *Salmonella*, and *S. aureus*. Additionally, fenugreek has antifungal effects, particularly against *C. albicans*. [31]

Paprika (Capsicum annuum)

Paprika contains capsaicin, which is well known for its antimicrobial properties. Studies suggest that paprika is effective against *E. coli* and *Salmonella*. Capsaicin also has antifungal properties, inhibiting *C. albicans*. [32]

Bay leaves (Laurus nobilis)

Bay leaves, often used to flavor stews and soups, have shown antimicrobial activity. Studies indicate that bay leaf extracts can inhibit the growth of bacteria such as *E. coli* and *S. aureus*. They also demonstrate antifungal activity, especially against *A. niger* and *C. albicans*. [33]

Thyme (Thymus vulgaris)

Thyme is rich in thymol, which has strong antimicrobial properties. Research has shown that thyme oil can effectively combat bacterial pathogens, including *E. coli* and *S. aureus*. Thyme also exhibits antifungal activity, particularly against *C. albicans*. [34]

Oregano (Origanum vulgare)

Oregano contains carvacrol and thymol, both of which have potent antimicrobial properties. Studies have shown that oregano oil is effective against *E. coli*, *Salmonella*, and *S. aureus*. Additionally, oregano oil is effective against fungal pathogens like *C. albicans*. [35]

Chili powder (Capsicum spp.)

Chili powder contains capsaicin, a compound that exhibits antimicrobial activity against *E. coli* and *Salmonella*. Capsaicin also inhibits the growth of fungal pathogens such as *A. niger* and *C. albicans*. [36]

Allspice (Pimenta dioica)

Allspice, with its clove-like flavor, contains eugenol, which has significant antimicrobial properties. Studies show that allspice is effective against *E. coli* and *S. aureus*. It also has antifungal effects, inhibiting *C. albicans*. [37]

Tarragon (Artemisia dracunculus)

Tarragon contains essential oils that have demonstrated antimicrobial and antifungal properties. Studies have shown that tarragon inhibits the growth of *E. coli* and *S. aureus*. It also has antifungal effects against *C. albicans*. [38]

Rosemary (Rosmarinus officinalis)

Rosemary, known for its distinct aroma, has been shown to possess antimicrobial properties. Rosemary oil is effective

against *E. coli* and *S. aureus*. It also demonstrates antifungal activity against *C. albicans*. [39]

Mint (Mentha spp.)

Mint is commonly used in both savory and sweet dishes, and its essential oil has been shown to have antimicrobial properties. Mint oil inhibits the growth of *E. coli* and *S. aureus*. It also demonstrates antifungal effects, particularly against *C. albicans*. [40]

OTHER NATURAL PRODUCTS WITH EFFECTIVE ANTIFUNGAL ACTIVITIES

Neem (*Azadirachta indica*)

The neem tree (*A. indica*) is a broad-spectrum medicinal plant rich in bioactive phytochemicals such as limonoids, tannins, and terpenoids. Extracts from neem leaves, seeds, and bark exhibit notable antifungal activity against a range of pathogenic fungi, including *Candida* species and food-spoilage fungi like *Aspergillus* and *Fusarium*. [41]

Coconut (*Cocos nucifera*)

Coconut oil comes in two varieties: virgin and refined. Coconut oil should be used in the treatment of fungal infections, given the emergence of drug-resistant Candida species. In recent years, virgin coconut oil has been a potential antifungal agent. [42]

Aloe vera (*Aloe vera barbadensis* Miller)

Aloe vera shows significant antifungal activity against *C. albicans*, mainly due to bioactive compounds such as phenols, flavonoids, and anthraquinones. The antifungal effect varies with plant part, with whole leaf extracts generally more potent than the gel, as they contain higher concentrations of active compounds. Aloe vera gel also demonstrates dose-dependent inhibition of fungal growth, becoming more effective at higher concentrations. Overall, Aloe vera is a promising natural antifungal agent and may serve as an alternative or complementary therapy in managing fungal infections, especially with increasing drug resistance. [43,44]

Essential Oils

Essential oils, obtained from different plant parts, contain bioactive compounds such as phenols, aldehydes, and terpenes (e.g., thymol, carvacrol, eugenol) that exhibit strong antifungal activity. These compounds act by disrupting fungal cell membranes, altering permeability, inhibiting enzymes, and preventing biofilm formation. Oils like tea tree, lavender, and lemongrass show dose-dependent inhibitory and fungicidal effects, even at relatively low concentrations. Their multi-component composition also lowers the risk of resistance development and may support restoration of normal microbial balance. Overall, essential oils are effective, eco-friendly, and promising alternatives or adjuncts to conventional antifungal treatments. [45]

CLINICAL DATA ON THE USE OF CULINARY SPICES IN TREATING FUNGAL INFECTIONS

Some articles collectively indicate that culinary spices show promising antifungal activity against *C. albicans*, including drug-resistant strains, based on clinical and experimental evidence. Laboratory and device-based studies demonstrate that these spices can inhibit fungal growth, reduce biofilm formation (especially in catheter-associated infections), and exhibit measurable potency through low minimum inhibitory concentrations—particularly for ginger and garlic. Additionally, a systematic review of clinical trials involving botanical antifungals in oral candidiasis found that these plant-based treatments (including spice-derived compounds) often show comparable or sometimes superior clinical outcomes to conventional antifungal drugs in terms of lesion improvement (**Table 1**).

However, a critical evaluation reveals that the clinical evidence remains limited and heterogeneous. Many findings are based on small-scale trials (10–30 participants), in vitro experiments, or device models rather than large, well-controlled human studies. While some trials report similar efficacy to standard drugs like nystatin or miconazole, others show inconsistent results, and issues such as high risk of bias, lack of standardized dosages, and variability in extraction methods reduce reliability. Therefore, although culinary spices have strong potential as alternative or adjunct antifungal therapies, especially for resistant infections, their routine clinical application is not yet fully established and requires further robust clinical validation. [46–48]

Candida auris

C. auris belongs to the *Candida* genus, which includes other pathogenic yeasts such as *C. albicans*. However, unlike *C. albicans*, *C. auris* has demonstrated high resistance to common antifungal classes, including azoles, echinocandins,

Table 1: Conventional treatment versus culinary spices against *Candida auris*.

Aspect	Conventional antifungal treatment	Culinary spices treatment
Agents used	Echinocandins, azoles, Amphotericin B	Garlic, turmeric, ginger, clove, cinnamon, etc.
Mechanism of action	Inhibit ergosterol synthesis or cell wall synthesis	Disrupt cell wall, inhibit enzymes, and alter membrane integrity
Effectiveness	Variable due to resistance in *C. auris*	Promising in vitro, requires more in vivo validation
Resistance	High and increasing globally	Low risk of resistance reported so far
Side effects	Kidney toxicity, liver dysfunction, drug interactions	Generally safe, some may cause allergies or irritation
Availability	Requires prescription and hospital access	Widely available and affordable
Regulatory status	FDA-approved	Not formally approved for antifungal treatment
Research stage	Well-studied with clinical guidelines	Emerging evidence, mostly pre-clinical and in vitro

and even amphotericin B. [49] This multidrug resistance makes *C. auris* particularly challenging to treat, especially in patients who are immunocompromised or have prolonged hospital stays. [50] In addition to its antifungal resistance, *C. auris* is notorious for its ability to form biofilms on medical devices and hospital surfaces, which increases the difficulty of eradicating it from healthcare environments. Biofilms are resilient clusters of microorganisms encased in a protective matrix, and they contribute to the persistence of the pathogen in clinical settings, enabling it to survive on surfaces for extended periods. [51]

Clinical Impact of *C. auris*

The clinical impact of *C. auris* is particularly severe in healthcare settings, where it predominantly affects vulnerable populations, such as patients undergoing chemotherapy, organ transplants, or those in intensive care units (ICUs). [52] Invasive infections caused by *C. auris*, such as bloodstream infections, are associated with high morbidity and mortality rates, ranging from 30% to 60%. [52] Given its ability to evade early detection, delayed treatment often results in poor outcomes, particularly in critically ill patients. Moreover, *C. auris* is known for its rapid transmission in hospital settings, particularly within ICUs and long-term care facilities. The pathogen's ability to persist on surfaces and resist disinfection methods contributes to its spread, often leading to significant outbreaks. [13–15] These outbreaks can be difficult to contain, especially in settings with limited resources for infection control.

Epidemiology and Global Spread

C. auris has been reported in over 40 countries worldwide, with significant outbreaks occurring in the United States, Europe, Asia, and parts of Africa. [13–15] The pathogen's global spread has been facilitated by factors such as international travel, movement of patients between healthcare facilities, and its capacity to persist in hospital environments. [53] In some countries, including India and parts of Latin America, *C. auris* has emerged as a leading cause of healthcare-associated infections. [53] The pathogen's ability to survive on environmental surfaces and its resistance to common disinfectants make infection control in healthcare settings a significant challenge. In some instances, entire hospital wards have been closed to contain outbreaks, and hospitals have implemented enhanced infection control measures, such as rigorous surface cleaning protocols and patient isolation. [54] However, these measures are not always sufficient, particularly in resource-limited settings where disinfection and isolation practices may not be consistently followed (**Figure 4**).

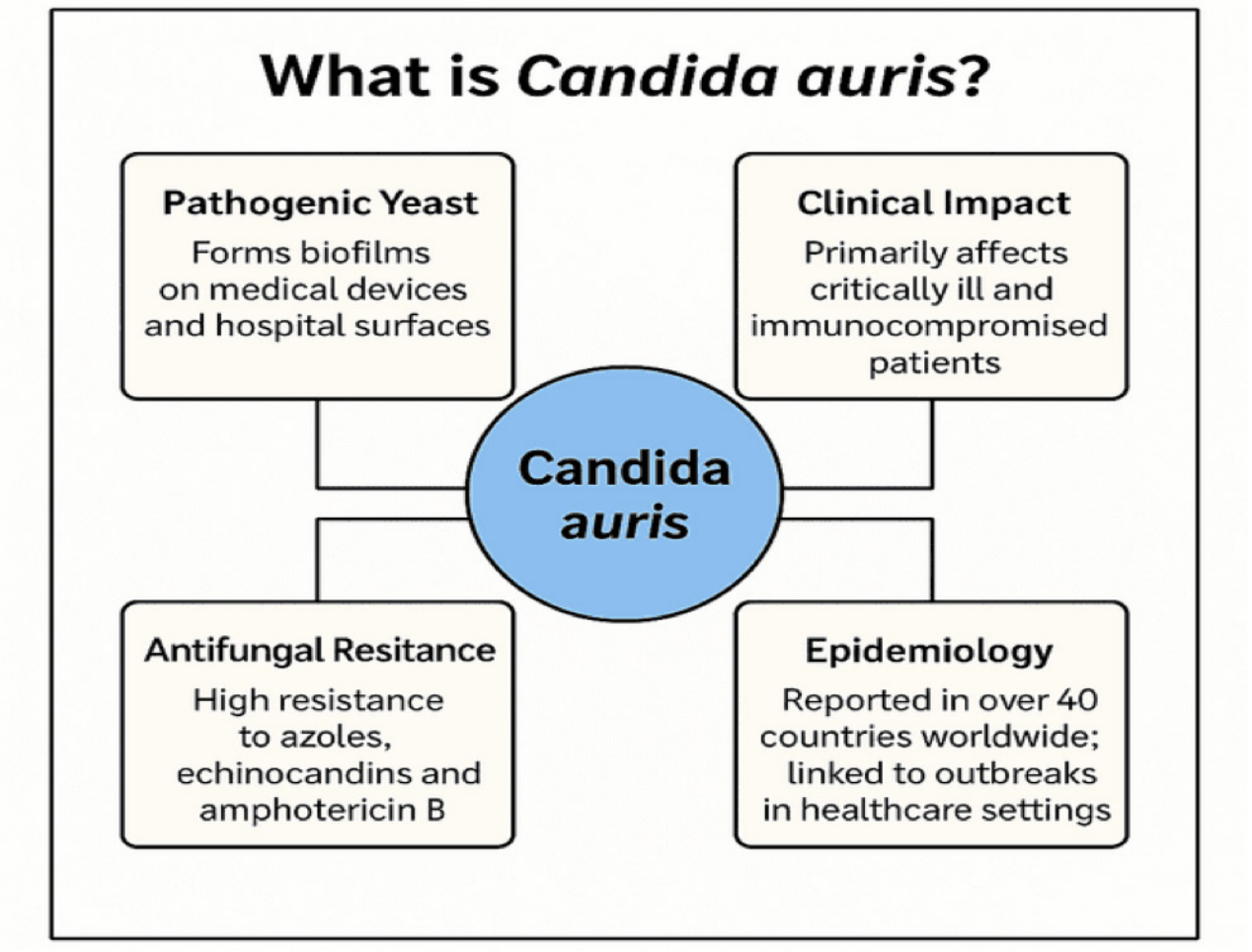

Figure 4: Diagrammatic representation of *Candida auris*.

Challenges in Diagnosis and Treatment

The diagnosis of *C. auris* infections is complicated by the pathogen's similarity to other *Candida* species. Traditional diagnostic methods, such as microbial cultures, often misidentify *C. auris* as other *Candida* species, leading to delays in appropriate treatment. [55] Newer diagnostic methods, such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) and PCR, have proven more accurate, but they are not universally available. [56] The treatment of *C. auris* infections is challenging due to its multidrug resistance. Many strains of *C. auris* are resistant to fluconazole, which is the most commonly used antifungal for *Candida* infections, and to echinocandins, which are the first-line therapy for invasive candidiasis. [57] In some instances, even amphotericin B, a broad-spectrum antifungal agent, has shown limited efficacy. [57] The emergence of resistant strains highlights the need for new antifungal agents and alternative treatment strategies to manage *C. auris* infections effectively.

Infection Control and Prevention

Effective infection control measures are essential in preventing the spread of *C. auris* in healthcare settings. Healthcare facilities must adopt stringent infection control protocols, including early identification of infected patients, isolation precautions, and the use of personal protective equipment. [13–15] Enhanced cleaning and disinfection are critical due to the pathogen's ability to persist on surfaces, but the limited efficacy of many standard hospital disinfectants against *C. auris* requires the use of more potent cleaning agents. [58] Hospitals must also implement active surveillance programs to monitor for *C. auris* infections and prevent outbreaks. Surveillance and rapid reporting can help identify potential clusters of infection and trigger timely intervention. Moreover, healthcare providers must be vigilant in identifying at-risk patients and ensuring that infection control practices are followed consistently. [59]

More on *C. auris*

Multidrug Resistance

C. auris 's resistance to multiple classes of antifungal drugs is a major concern, as it limits treatment options and complicates management. Resistance to commonly used drugs, such as fluconazole and echinocandins, has been reported in a significant proportion of isolates worldwide. [60] This highlights the need for the development of novel antifungal agents and alternative therapeutic approaches to combat infections caused by *C. auris* (**Figure 5**). [61]

ANTIFUNGAL RESISTANCE IN OTHER *CANDIDA* SPECIES OTHER THAN *C. AURIS*

The other reviews critically show that antifungal resistance in *Candida* species beyond *C. auris* is an evolving but comparatively underemphasized problem, driven by both intrinsic traits and acquired mechanisms under antifungal pressure. While *C. auris* is highlighted as a model for multidrug

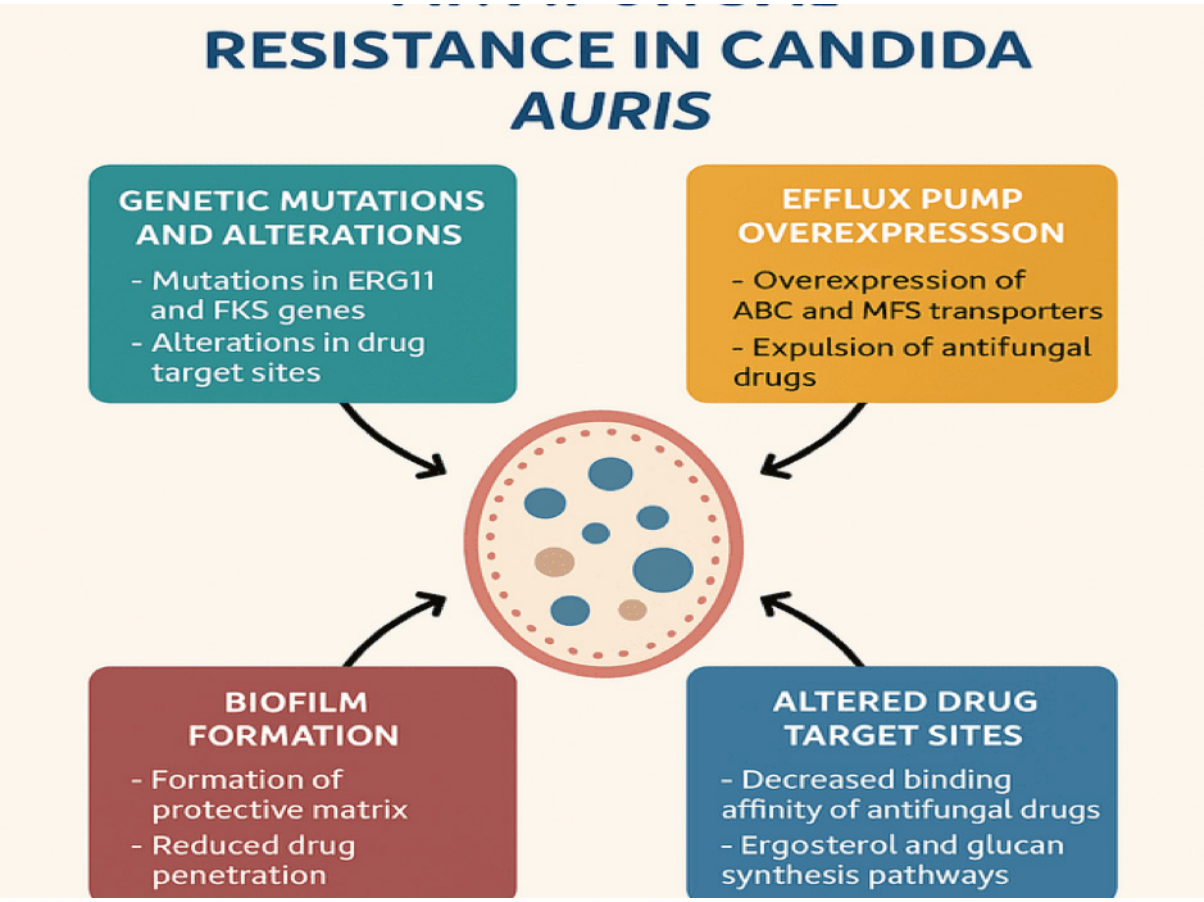

Figure 5: Diagrammatic representation of *Candida auris* drug resistance.

resistance, the paper implies that other *Candida* species (e.g., *C. albicans* complex and emerging species like *Candida africana*) are also demonstrating shifts in susceptibility, though currently at lower prevalence. Resistance mechanisms across these species largely involve mutations in key target genes, such as ERG11 (azole resistance), alterations in FKS1 (echinocandin resistance), and overexpression of efflux pumps, as well as biofilm-mediated tolerance that reduces drug penetration. The review critically links these adaptations to selective pressures from widespread clinical and environmental antifungal use, including agricultural azoles, and highlights that incomplete treatment and subtherapeutic exposure further accelerate resistance development. However, compared to *C. auris*, there remains limited genomic and epidemiological data on other *Candida* species, representing a major knowledge gap. Overall, the paper argues that antifungal resistance in non-*auris Candida* species is likely underestimated and may expand into a significant public health concern without improved surveillance, stewardship, and research into resistance mechanisms and clinical impact. Other systematic reviews and meta-analyses highlight a clear epidemiological shift from *C. albicans* to non-albicans *Candida* (NAC) species, which are increasingly associated with antifungal resistance—particularly to fluconazole. Resistance varies markedly by species, with very high intrinsic resistance in *C. krusei* (~78%), and moderate but clinically significant resistance in *C. glabrata* (~15.9%), *C. tropicalis* (~13%), and *C. dubliniensis* (~11.1%). Importantly, resistance trends are rising over time (especially post-2014) for several NAC species, reflecting selective pressure from widespread azole use, expanding immunocompromised populations, and healthcare-associated exposures. Mechanistically, antifungal resistance in these species is multifactorial and parallels—but is not identical to—*C. albicans*. Key mechanisms include ERG11 mutations (altering the azole target), overexpression of efflux pumps (e.g., CDR1, MDR1), biofilm formation (notably in *C. tropicalis* and *C. parapsilosis*), and genomic plasticity (especially in *C. glabrata*), all of which reduce drug susceptibility and contribute to therapeutic failure. Resistance is further complicated by significant geographic variability and methodological differences in susceptibility testing, which can alter reported resistance rates. Overall, the study underscores that antifungal resistance in NAC species is dynamic, species-specific, and globally increasing—necessitating standardized testing, regional surveillance, and tailored antifungal stewardship strategies. [62,63]

Vulnerable Populations

C. auris disproportionately affects immunocompromised patients, including those with cancer, diabetes, and those undergoing organ transplants. These patients are particularly vulnerable to invasive infections, and the emergence of multidrug-resistant (MDR) pathogens like *C. auris* further threatens their health. [49] Preventing and treating *C. auris* infections in these high-risk populations is crucial to reducing mortality and morbidity.

Healthcare-Associated Infections

C. auris is a leading cause of healthcare-associated infections, particularly in ICUs and long-term care settings. Its ability to persist on surfaces and resist disinfection makes infection control in healthcare facilities particularly challenging. [58] If left unchecked, the spread of *C. auris* could lead to widespread outbreaks that strain already overburdened healthcare systems. [59]

Global Health Threat

The global spread of *C. auris* underscores the need for a coordinated international response to address this growing threat. The pathogen's ability to cross borders highlights the importance of global surveillance, research, and collaborative efforts to enhance diagnostic capabilities, improve infection control measures, and develop new antifungal treatments. [64] Without global cooperation, the spread of *C. auris* will likely continue to pose a major threat to public health worldwide.

***C. auris* Resistance to Antifungal Drugs**

C. auris is an emerging MDR pathogen that has caused significant concern in healthcare settings. First identified in 2009, *C. auris* has since been responsible for outbreaks of invasive infections, particularly in immunocompromised patients. Its ability to resist conventional antifungal treatments substantially challenges public health. This review explores the underlying mechanisms behind the antifungal resistance of *C. auris*, examining genetic factors, the role of biofilm formation, and the overuse or misuse of antifungal agents. Recent studies (2022–2024) have contributed valuable insights into the resistance patterns and potential therapeutic strategies. [65] Recent studies from 2026 confirm that *C. auris* has evolved into a globally significant MDR fungal pathogen, with resistance patterns that are both highly prevalent and increasingly dynamic. Large-scale surveillance data from 2022 to 2023 show that fluconazole resistance is nearly universal (~95%–96%)**,** while amphotericin B resistance is rising (≈15%–19%), and echinocandin resistance—though still low (~1%)—is emerging and clinically concerning. Notably, the detection of pan-resistant strains (<1%) highlights the beginning of a potential era of limited or no effective antifungal options. Temporal trends indicate that resistance is not static; instead, it is increasing over time, particularly for azoles and amphotericin B, suggesting ongoing evolutionary adaptation under antifungal pressure. The narrative review further strengthens this concern by demonstrating that resistance in *C. auris* is heterogeneous and clade-dependent, with some lineages (e.g., South Asian and African clades) showing >90% resistance to azoles and higher rates of multidrug resistance. Importantly, echinocandin resistance—once rare—is now emerging, often driven by treatment exposure, and cases have increased in recent years. The persistence of the organism in healthcare environments, prolonged patient colonization, and intense antimicrobial use—especially during the COVID-19 era—have created ideal conditions for selection, amplification, and transmission of resistant strains. Collectively, these studies indicate that *C. auris* resistance is not only widespread but progressively intensifying**,** posing a serious challenge to current treatment strategies and reinforcing the need for continuous surveillance, antifungal stewardship, and development of new therapies. [66,67]

MECHANISMS OF ANTIFUNGAL RESISTANCE IN *C. AURIS*

Genetic Mutations and Alterations

Genetic mutations are a primary factor in the resistance of *C. auris* to antifungal drugs. The fungus exhibits mutations in genes

that encode the targets of antifungal agents, including those involved in the ergosterol biosynthesis pathway, which is the primary target of azoles. For example, mutations in the *ERG11* gene, which encodes lanosterol demethylase, a critical enzyme in ergosterol synthesis, are commonly observed in *C. auris* isolates resistant to azoles. Furthermore, alterations in the *FKS* genes, which encode β-glucan synthase, are linked to resistance to echinocandins, another class of antifungal drugs. [68]

Efflux Pump Overexpression

Efflux pumps play a significant role in the development of antifungal resistance by actively expelling antifungal drugs from the fungal cell before they can reach effective concentrations. *C. auris* has been shown to overexpress several ATP-binding cassette (ABC) transporters and major facilitator superfamily transporters that are involved in the efflux of azoles, echinocandins, and polyenes. [64] The overexpression of these efflux pumps reduces the intracellular accumulation of antifungal agents, contributing to resistance.

Biofilm Formation

Biofilm formation is another critical factor that contributes to the persistence and resistance of *C. auris*. Biofilms are dense clusters of cells encased in a protective extracellular matrix, shielding microorganisms from the host immune system and antifungal treatments. *C. auris* is known for its ability to form robust biofilm on medical devices and tissues, significantly complicating treatment options. [69] The presence of biofilms not only hinders drug penetration but also facilitates a high rate of genetic exchange, leading to increased resistance.

Altered Drug Target Sites

C. auris has demonstrated alterations in its drug target sites that decrease the binding affinity of antifungal agents. For example, mutations in the *ERG11* gene, encoding the enzyme involved in the final step of ergosterol synthesis, can alter the shape of the enzyme's active site, thus rendering azole drugs ineffective. [70] Additionally, *C. auris* exhibits reduced sensitivity to echinocandins due to mutations in the *FKS1* and *FKS2* genes involved in glucan synthesis and the integrity of the fungal cell wall. [71]

FACTORS CONTRIBUTING TO RESISTANCE

Overuse and Misuse of Antifungal Drugs

The overuse and misuse of antifungal drugs, particularly azoles, have accelerated the development of resistance in *C. auris*. Azoles are commonly used in both medical and agricultural settings, leading to environmental reservoirs of resistant strains. The excessive use of azoles in agriculture has contributed to the selection of resistant *C. auris* strains that can spread into clinical environments. [72] In hospitals, the widespread use of antifungals for the treatment of immunocompromised patients has further exacerbated resistance issues, as it creates selective pressure that favors resistant strains.

Cross-Resistance Between Drug Classes

C. auris is known for its ability to exhibit cross-resistance between different classes of antifungal agents. For instance, strains resistant to azoles may also show resistance to echinocandins and polyenes, complicating treatment options. This cross-resistance is likely facilitated by genetic factors, such as mutations in key genes that affect the structure or function of drug targets. [65] The simultaneous resistance to multiple antifungal drug classes has led to the characterization of *C. auris* as a pan-resistant pathogen in some instances. [64]

Environmental Persistence and Transmission

C. auris has demonstrated remarkable environmental persistence, which is an essential factor in its resistance to antifungal drugs. It can survive on surfaces and medical equipment for extended periods, making it challenging to eradicate from healthcare environments. Studies have found that *C. auris* can persist on inanimate surfaces, such as bed rails and catheters, even after routine cleaning and disinfection protocols. [69] This environmental resilience increases the likelihood of transmission and further promotes the spread of resistant strains.

IMPLICATIONS FOR TREATMENT

The resistance of *C. auris* to antifungal drugs has significant implications for treatment. Due to the lack of effective antifungal options, clinicians are often forced to rely on combination therapy or experimental drugs, which may not always yield successful outcomes. Additionally, the rapid emergence of resistance highlights the need for more accurate diagnostic methods to identify *C. auris* infections and monitor resistance patterns. Efforts are ongoing to develop novel antifungal agents targeting alternative pathways or repurposing existing drugs in combination therapies. [65]

THE EFFECTIVENESS OF CULINARY SPICES AGAINST ANTIFUNGAL RESISTANT *C. AURIS*

C. auris has emerged as an MDR fungal pathogen causing hospital-associated infections with high morbidity and mortality. Its resistance to multiple classes of antifungal drugs, including azoles, echinocandins, and polyenes, has made it a significant public health threat. Recent studies have suggested that natural products, including culinary spices, may offer an alternative or adjunctive approach to combatting antifungal-resistant pathogens like *C. auris*. [49] This review explores the antifungal properties of commonly used culinary spices and their potential to inhibit *C. auris* growth, focusing on their bioactive compounds and mechanisms of action.

CULINARY SPICES WITH ANTI *C. AURIS* PROPERTIES (FIGURE 6)

Turmeric *(Curcuma longa)*

Turmeric, containing the bioactive compound curcumin, has shown promising antifungal activity. Studies have demonstrated that curcumin inhibits the growth of various *Candida* species, including *C. auris*. Curcumin works by interfering with cell membrane integrity and reducing biofilm formation, which is a key factor in *C. auris* resistance to antifungal treatments. It has also been shown to enhance the antifungal efficacy of conventional drugs, suggesting its potential as an adjunctive therapy. [73]

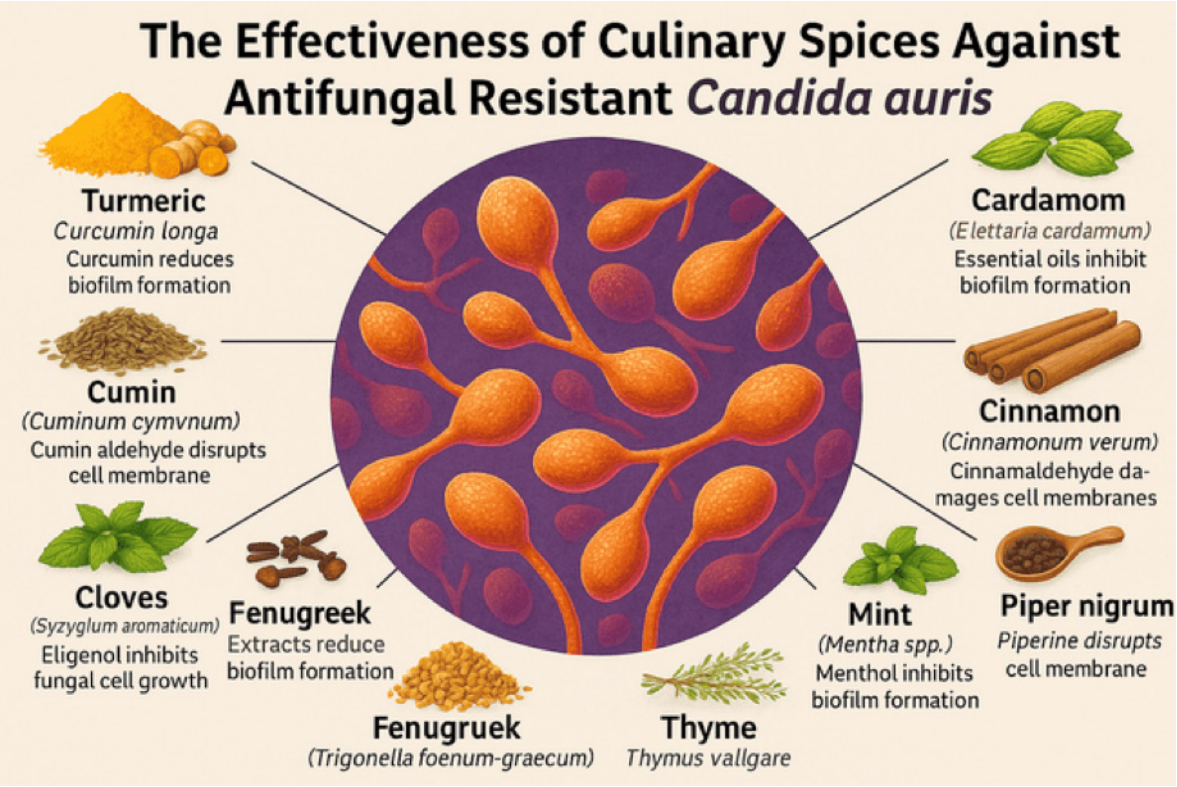

Figure 6: Culinary spices and their effect on drug-resistant *Candida auris*.

Cumin *(Cuminum cyminum)*

Cumin is a spice rich in essential oils, particularly cumin aldehyde, which has demonstrated antifungal effects against several *Candida* species. In vitro studies have shown that cumin essential oil can inhibit the growth of *C. auris* by disrupting the fungal cell membrane. Additionally, cumin has been found to synergistically enhance the antifungal effects of azoles when used in combination. [74]

Cardamom *(Elettaria cardamomum)*

Cardamom, particularly its essential oils, contains compounds like 1,8-cineole and alpha-terpinyl acetate, which have demonstrated antifungal activity against a range of fungi, including *C. auris*. These compounds work by inhibiting fungal growth and biofilm formation. Cardamom has been studied for its potential to reduce the virulence factors of *C. auris*, making it a valuable addition to antifungal treatments. [74]

Cinnamon *(Cinnamomum verum)*

Cinnamon, with its active ingredient cinnamaldehyde, has shown potent antifungal activity against *Candida* species. Cinnamaldehyde works by interacting with fungal cell membranes, causing structural damage and increasing membrane permeability. [75] This compound has demonstrated a strong inhibitory effect against *C. auris*, both as a single treatment and in combination with conventional antifungals. [74]

Ginger *(Zingiber officinale)*

Ginger contains bioactive compounds like gingerol, which have exhibited antifungal effects against a variety of pathogens, including *C. auris*. Gingerol has been shown to inhibit fungal growth by interfering with cell wall biosynthesis and the formation of hyphae. [74] Moreover, ginger can enhance the penetration of antifungal drugs into the fungal cell, making it a useful adjunct in treating resistant *C. auris* infections. [76]

Black Pepper *(Piper nigrum)*

The active compound in black pepper, piperine, has demonstrated antifungal properties. Piperine has been found to inhibit the growth of *C. auris* by disrupting its cell membrane and enhancing the activity of antifungal agents like fluconazole. This synergistic effect could be useful in overcoming *C. auris* resistance to conventional antifungal therapies. [77,78]

Cloves *(Syzygium aromaticum)*

Clove essential oil, containing eugenol as its active compound, has been shown to possess potent antifungal activity. Eugenol disrupts the fungal cell membrane and inhibits biofilm formation, both of which are key factors in the pathogenesis of *C. auris*. Cloves may offer a natural adjunct to antifungal therapy by reducing *C. auris* viability and resistance mechanisms. [74,79]

Fenugreek *(Trigonella foenum-graecum)*

Fenugreek seeds are rich in alkaloids and saponins, which have shown antifungal activity against a variety of pathogens, including *C. auris*. Fenugreek extracts have been found to inhibit *C. auris* growth by targeting its cell wall integrity and reducing biofilm formation. [80,81]

Thyme *(Thymus vulgaris)*

Thyme, rich in thymol and carvacrol, has shown potent antifungal effects against *C. auris* by inhibiting fungal cell growth and biofilm formation. These compounds work by disrupting the cell wall and membrane, leading to increased permeability and leakage of intracellular contents. [82]

Oregano *(Origanum vulgare)*

Oregano oil, containing carvacrol and thymol, is known for its strong antifungal properties. It has been shown to inhibit *C. auris* by disrupting the fungal membrane and interfering with ergosterol biosynthesis. Oregano oil also enhances the activity of traditional antifungal drugs, providing a potential synergistic effect. [83]

Mint *(Mentha spp.)*

Mint contains menthol and other compounds that have shown antifungal effects. Studies suggest that mint oil can inhibit the growth of *C. auris* by disrupting its cell membrane and inhibiting biofilm formation. Mint offers potential as a natural antifungal agent against drug-resistant *C. auris*. [84]

SAFETY AND REGULATORY STATUS OF USING CULINARY SPICES FOR MEDICINAL PURPOSES

The use of culinary spices for medicinal purposes raises important safety and regulatory considerations, particularly as their application extends beyond traditional dietary use. While spices are generally recognized as safe when consumed in typical food quantities, their therapeutic use involves higher doses, concentrated extracts, or prolonged exposure, which may introduce potential health risks. These risks include contamination with microorganisms, mycotoxins, heavy metals, or pesticide residues, as well as possible interactions with conventional drugs and variability in active constituents. Moreover, adverse effects associated with herbal and spice-based products are often underreported, especially in low- and middle-income countries, due to weak pharmacovigilance systems and limited awareness among both consumers and healthcare professionals. Therefore, the assumption that "natural" equates to "safe" remains scientifically unfounded and necessitates cautious use supported by evidence-based evaluation. From a regulatory perspective, spices and their extracts are primarily governed under food safety frameworks rather than as medicinal products, leading to significant variability in standards across countries and regions. International bodies such as the Codex Alimentarius and organizations like the Joint FAO/WHO Expert Committee on Food Additives (JECFA) guide safe use levels and quality standards, but these are largely focused on their role as food additives rather than therapeutic agents. Consequently, national regulations differ in terms of permissible contaminants, processing methods (e.g., irradiation, fumigation), and solvent residues in spice extracts. While some regions have begun integrating herbal products into formal regulatory and pharmacovigilance systems, gaps remain in standardization, quality control, and clinical validation. Strengthening regulatory frameworks, ensuring good manufacturing practices, and expanding pharmacovigilance to include spice-derived medicinal products are essential steps to ensure their safe and effective use. [85–87]

C. auris represents a formidable challenge due to its high resistance to existing antifungal agents, rapid transmission in healthcare environments, and significant mortality among vulnerable populations. Current diagnostic limitations and the inefficacy of standard antifungal therapies underscore the urgent need for innovative approaches. The review establishes that culinary spices rich in bioactive compounds possess notable antifungal activity, with several demonstrating efficacy against *C. auris* through mechanisms such as membrane disruption, inhibition of biofilm formation, and synergism with existing drugs. These findings suggest that natural products can play a significant role in developing adjunctive or alternative antifungal therapies.

Enhanced surveillance and diagnostics: Healthcare facilities should invest in advanced molecular diagnostics like PCR and MALDI-TOF to improve early and accurate identification of *C. auris*.

Infection control measures: Hospitals must implement stringent disinfection protocols, patient isolation, and staff education to prevent nosocomial transmission.

Antifungal stewardship programs: Rational use of antifungal agents is crucial to limit the development of resistance.

Integrative therapy research: Clinical trials should be initiated to evaluate the safety and efficacy of combining culinary spice extracts with conventional antifungals.

Global collaboration: International cooperation is essential to monitor outbreaks, share data, and coordinate research on resistant fungal pathogens like *C. auris*.

CONCLUSIONS

Culinary spices represent a promising, low-cost, and widely accessible strategy in the fight against MDR *C. auris*, as their bioactive compounds demonstrate significant antifungal activity—particularly through membrane disruption, inhibition of biofilm formation, and enhancement of conventional drug efficacy. However, despite strong in vitro and preliminary clinical indications, the current evidence base remains limited, heterogeneous, and largely derived from small-scale or pre-clinical studies, underscoring the urgent need for well-designed, large-scale clinical trials to establish their safety, efficacy, and standardized use in clinical settings. Importantly, the most realistic and impactful application lies not in replacing standard antifungal therapies but in integrating these natural agents as adjuncts, where synergistic effects could enhance treatment outcomes, reduce drug resistance, and offer a sustainable approach to managing the growing global threat of antifungal-resistant infections.

AUTHORS' CONTRIBUTION

All authors have significantly contributed to the work, whether by conducting literature searches, drafting, revising, or critically reviewing the article. They have given their final approval of the version to be published, have agreed with the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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None.

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