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Fungal Antimicrobial Activity: Potential Use and Applications in the Food Industry

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ABSTRACT:

Food spoilage caused by microorganisms remains a major challenge for global food systems, leading to economic losses and increasing the risk of foodborne illnesses. Although synthetic preservatives and antibacterial agents are widely used, their role in promoting antimicrobial resistance is limited and context-dependent; however, concerns persist regarding consumer acceptance, regulatory restrictions, and potential stress responses they induce in microorganisms. These limitations have intensified interest in natural alternatives that align with clean-label and sustainable food production trends. Fungal species produce a broad range of secondary metabolites—including organic acids, peptides, enzymes, volatile compounds, and pigments—with documented antimicrobial activity against food-spoiling bacteria and fungi. These metabolites are synthesized during fungal growth or in response to environmental stress, and several have been evaluated for their ability to inhibit microbial contamination or extend product shelf life. Despite this promise, only a limited number of fungal-derived compounds have received regulatory authorization for food use, due to concerns related to toxicity, co-production of mycotoxins, sensory impacts, and regulatory constraints. This review critically examines the antimicrobial potential of fungal metabolites, outlining their chemical diversity, mechanisms of action, and demonstrated applications in food systems. It also discusses essential safety, toxicological, and regulatory authorization requirements necessary for their adoption as bio-preservatives in the food industry. Through this comprehensive evaluation, the review highlights both the opportunities and the challenges associated with integrating fungal-derived antimicrobials into modern food preservation strategies.

KEYWORDS:

Food security; bio-preservatives; biocontrol; Sustainable development; Industrial applications.

1. Introduction

Microbial contamination and spoilage remain major challenges for the global food industry, causing substantial economic losses and posing significant public health risks through foodborne illnesses. To control these hazards, the food sector relies on a combination of good manufacturing practices (GMP), good hygienic practices (GHP), and effective preservation technologies. Traditional preservation methods—including refrigeration, freezing, thermal processing, pH reduction, and water activity control—form the backbone of food safety systems. Chemical preservatives such as sorbates, benzoates, and propionates also play an important but complementary role in inhibiting microbial growth in specific food matrices [1].

Growing consumer demand for minimally processed, "clean-label" foods, coupled with the expansion of ready-to-eat and fresh products with inherently short shelf lives, has increased interest in natural alternatives to synthetic additives [2]. In response, modern preservation approaches—such as bio-preservation, irradiation, and multi-hurdle technologies—have gained prominence. Bio-preservation, in particular, employs beneficial microbes or their metabolites to suppress spoilage and pathogenic microorganisms, offering potential advantages in maintaining product quality and meeting consumer expectations for natural solutions [3,4]. However, bio-preservation strategies must be evaluated carefully to ensure they do not negatively affect sensory properties or stability in complex food systems.

Although synthetic preservatives are generally recognized as safe at regulated levels, consumer preference for natural alternatives has driven exploration of antimicrobial compounds derived from plants, bacteria, and fungi. Food preservatives contribute minimally to global antimicrobial resistance (AMR), yet certain antimicrobials and processing stresses may trigger adaptive responses in microorganisms. More critically, AMR concerns along the food chain arise from contamination with antibiotic-resistant bacteria originating from agricultural or environmental sources. This challenge underscores the importance of integrated “One Health” strategies that link food safety, environmental stewardship, and human health (**Fig. 1**) [5,6].

Fungal-derived metabolites have emerged as promising candidates for natural bio-preservation. Filamentous fungi and macrofungi synthesize a diverse array of secondary metabolites—including organic acids, enzymes, peptides, volatile compounds, and pigments—that exhibit antimicrobial activity against major foodborne pathogens and spoilage organisms such as *Listeria monocytogenes*, *Staphylococcus aureus*, *Escherichia coli* O157:H7, *Campylobacter jejuni*, *Bacillus cereus*, and *Clostridium botulinum* [7,8]. These compounds are produced during normal growth or under environmental stress, providing ecological advantages by suppressing competing microorganisms.

Fungi are already well established in industrial biotechnology, particularly in enzyme production, fermentation processes, and microbial biomass generation [3]. Interest in fungal pigments and bioactive colorants has also expanded due to their natural origin and multifunctional properties.

However, the practical use of fungal metabolites in foods requires rigorous assessment of safety, toxicity, potential co-production of mycotoxins, and compliance with regulatory standards. Notably, natamycin—a widely used antifungal preservative—is produced by *Streptomyces natalensis*, not by fungi, and is included here only as a benchmark for comparison [4].

This review critically evaluates fungal-derived antimicrobial metabolites as natural alternatives to synthetic preservatives. It examines their chemical diversity, mechanisms of action, demonstrated applications in food systems, and the safety and regulatory considerations necessary for their successful adoption. Through this analysis, we aim to clarify both the opportunities and the limitations associated with integrating fungal antimicrobials into modern food preservation strategies.

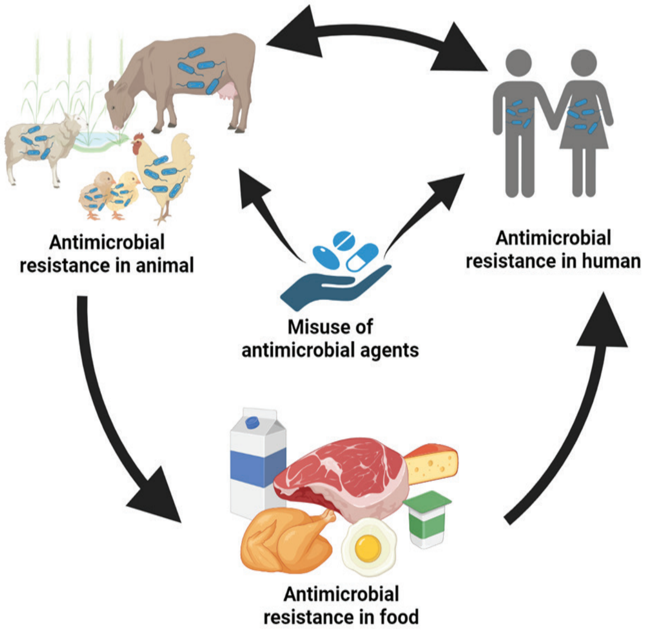

Figure 1: Conceptual illustration of antimicrobial resistance (AMR) transmission within the One Health framework, highlighting interconnected pathways between humans, animals, and the food system, and the selective pressure created by the use and misuse of antimicrobial agents.

2. Traditional Preservation Methods Used in the Food Industry

Traditional preservation methods remain fundamental in sustaining food safety and extending shelf life across the global food industry. These approaches generally fall into three main categories—chemical, biological, and physical—each contributing in different ways to the control of microbial growth and product stability (**Fig. 2**).

2.1: Chemical Methods

Chemical preservatives are widely employed to inhibit microbial proliferation, delay enzymatic spoilage, and prevent oxidative deterioration. Commonly used compounds include sorbic acid and its salts, benzoic acid and benzoates, propionic acid and propionates, and parabens (methyl, ethyl-, and propyl-p-hydroxybenzoates). Their effectiveness depends on food composition and pH, and they are often incorporated into bakery goods, beverages, dairy products, and acidic foods.

Other preservation-related treatments rely on modifying water activity or acidity. Salt curing, for example, reduces water availability and restricts microbial growth; however, salt alone is insufficient to prevent *Clostridium botulinum* in cured meats, making nitrites essential in such products. Sugar creates similar preservative conditions in jams and syrups by lowering water activity. Acidic solutions such as vinegar also contribute to microbial inhibition in pickled foods. Lye (sodium hydroxide) is used in specific traditional products—such as olives and pretzels—to induce characteristic textural or sensory properties, though it is not considered a primary antimicrobial preservation strategy [9,10].

2.2: Biological Methods

Biological preservation relies on microorganisms or their natural metabolites to control spoilage and pathogenic organisms. Lactic acid bacteria (LAB) remain the most widely applied biological preservative agents due to their ability to produce organic acids, antimicrobial peptides such as bacteriocins, hydrogen peroxide, and other inhibitory compounds. LAB fermentation has been used for centuries to preserve dairy products, vegetables, and meats, offering natural inhibition of a wide range of microorganisms. Despite these benefits, fermentation can alter sensory characteristics, and its effectiveness depends heavily on the food matrix and the strains employed [9,10].

2.3: Physical Methods

Physical preservation encompasses both thermal and non-thermal technologies. Thermal treatments such as pasteurization, sterilization, blanching, and boiling inactivate spoilage organisms and pathogens by heat, whereas dehydration removes moisture to reduce water activity and limit microbial survival while also decreasing product weight.

Low-temperature storage methods also play an important role. Refrigeration slows microbial growth, while freezing halts microbial proliferation entirely. However, freezing does not eliminate most microorganisms; they may recover once the product is thawed, necessitating careful handling during storage and distribution.

A range of non-thermal physical methods has been developed to enhance food preservation without significant heat exposure. Irradiation using gamma rays, electron beams, or X-rays effectively reduces microbial load while maintaining product quality. High-pressure processing (HPP) achieves microbial inactivation by exposing foods to very high hydrostatic pressures, making it suitable for heat-sensitive products. Modified-atmosphere and vacuum packaging reduce oxygen availability, although these approaches require proper controls to prevent risks associated with anaerobic pathogens such as *Clostridium botulinum*. Smoking imparts antimicrobial and antioxidant compounds to food surfaces, whereas pickling combines acidic or salty conditions to inhibit microbial growth. These traditional preservation methods continue to form the foundation of food safety and shelf-life extension, supporting modern food systems and complementing emerging natural preservation strategies [9,10].

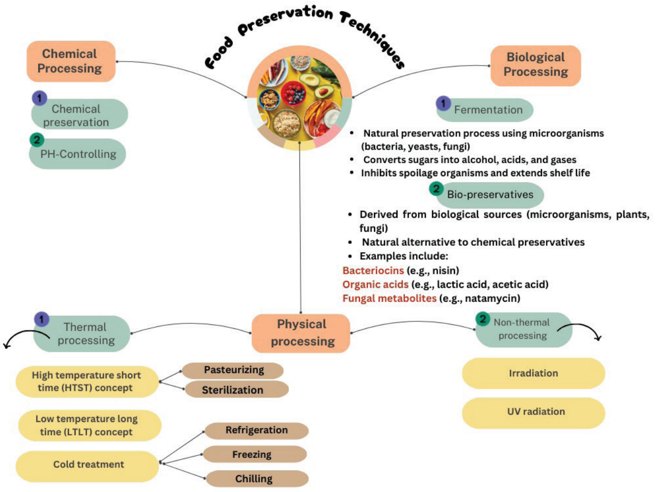

Figure 2: Flow chart presenting the traditional preservatives used in food industries, including chemical, biological, and physical.

3. Fungal Metabolites and Their Antimicrobial Properties

Fungal metabolites have gained increasing attention as potential natural preservatives due to their chemical diversity and their ability to inhibit a broad range of microorganisms. Many filamentous fungi—particularly those belonging to the *Ascomycota*—produce secondary metabolites with antibacterial and antifungal activity, reflecting their ecological role in competing within complex microbial environments [11,12]. Figure 3 summarizes major classes of fungal metabolites with representative examples relevant to food preservation.

Among these bioactive compounds, fungal pigments have been of particular interest. Although traditionally valued as natural colorants, several fungal pigments also possess noteworthy antimicrobial properties. Species such as *Monascus purpureus*, long used in Asian fermented foods, produce yellow, orange, and red pigments that exhibit inhibitory effects against a variety of fungi, including Aspergillus, Trichoderma, Mucor, Penicillium, and Fusarium, as well as against bacterial genera such as Bacillus, Pseudomonas, Escherichia, and Streptomyces [13]. Pigments from other fungi—such as *Monodictys castaneae*, *Sporobolomyces* spp., *Fusarium* spp., *Aspergillus* spp., and *Penicillium* spp.—have also demonstrated broad-spectrum activity [14], underscoring the potential of fungal colorants as multifunctional bio-preservatives.

The antimicrobial efficacy of fungal pigments can vary depending on their chemical composition and mode of extraction. Studies have shown that modifying culture conditions, such as supplementing growth media with specific amino acids, can enhance pigment bioactivity, particularly against Gram-positive bacteria. Minimum inhibitory concentration (MIC) values have been reported for several pigment derivatives, demonstrating their capacity to suppress microbial growth in food contexts [13]. Applications have been explored in meat products—including sausages and beef burgers—where *Monascus* pigments have contributed both color and antimicrobial effects [15]. Nevertheless, careful control of pigment concentration and purity is necessary to ensure both safety and effectiveness.

Despite their promise, fungal pigments face several obstacles on the path to commercial adoption. Safety concerns—most notably the risk of co-producing the mycotoxin citrinin—have restricted the use of *Monascus* pigments in Europe and the United States. As a result, research has focused on developing production strategies that suppress mycotoxin biosynthesis while maintaining pigment yield and bioactivity [16]. These efforts remain essential for ensuring regulatory compliance and consumer safety.

Beyond pigment-producing fungi, species inhabiting environmentally stressed or polluted habitats have also emerged as valuable sources of bioactive metabolites. Such environments exert selective pressure that may promote the production of potent antimicrobial compounds. Recent studies have isolated filamentous fungi from heavily polluted streams in the Amazon region and demonstrated that their metabolites can inhibit extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli*, highlighting their potential as sources of novel antimicrobial agents [11,17]. Although these findings expand the range of fungi with promising antimicrobial properties, isolates from polluted environments require rigorous toxicological evaluation before any consideration for food-related applications.

Overall, fungal metabolites represent a rich reservoir of compounds with antimicrobial activity relevant to food preservation. However, their practical deployment requires careful attention to safety, purity, regulatory approval, and reliable production methods.

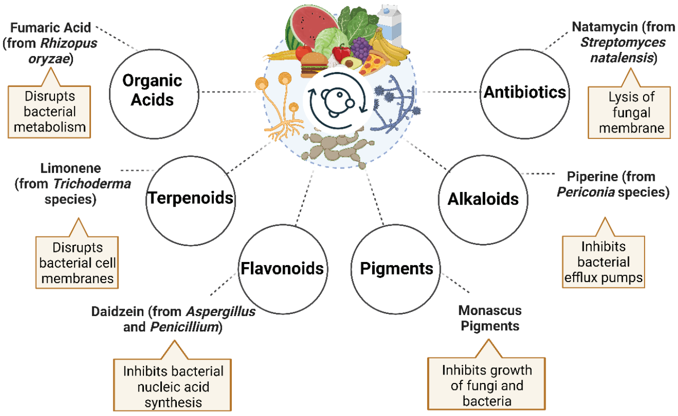

Figure 3: Types of fungal metabolites used in food industries with their mechanism of action as antimicrobials.

3.1: Antimicrobial Activity of Fungal Isolates

Segundo et. al. (2023) studied the antimicrobial activity of 67 fungal isolates that were subjected to a 14-day submerged bioprocessing. Hexane- and ethyl acetate (EtOAc)-based extraction methods were employed to isolate the metabolites, and their antibacterial effect was examined by agar diffusion against *E. coli* (ESBL-positive) and *E. coli* [17]. These findings demonstrated that both hexane- and EtOAc-based extracts exhibited antibacterial activity, with inhibition zones ranging from 1 to 35.9 mm. Notably, *A. stygium* and *C. rosea* exhibited the largest inhibition zones against *E. coli* and ESBL-positive *E. coli* [17]. The MICs of the EtOAc extracts from *A. stygium*, *C. rosea*, and *C. rosea* were determined using a microdilution assay. The MIC for both *E. coli* and the ESBL-positive *E. coli* strain was found to be 400 μg/mL [17]. Natamycin is a prominent example of a microbial-derived antifungal preservative, which, although not of fungal origin, is included here as a reference compound due to its extensive application in food preservation.

Natamycin (E235) is a natural polyene macrolide antifungal produced by the bacterium *Streptomyces natalensis* (actinobacteria). It is currently the only antimicrobial metabolite derived from microorganisms that is widely and commercially used as a food preservative. Natamycin is approved in many countries for surface treatment of dairy products, particularly cheese [16], where it effectively inhibits the growth of molds and yeasts without adversely affecting the sensory properties of food, making it a benchmark antifungal preservative in the dairy industry [18].

Further analysis identified two active metabolites: daidzein and nodulisporone. Nodulisporone, a tetralone derived from the *Nodulisporium* genus (Ascomycota), displayed antimicrobial activity, with inhibition zones of 13 mm against *Trichoderma harzianum* and 10 mm against *Candida albicans* [17]. Tetralones are known to inhibit DNA replication by blocking cellular DNA topoisomerase, thereby affecting gene expression and recombination in microorganisms [17]. Daidzein, a well-known flavonoid commonly found in plants, was also detected in the genera *Aspergillus*, *Penicillium*, and *Trichoderma*. Flavonoids are recognized for their ability to inhibit the formation of bacterial nucleic acids, metabolism, and interfere with cell membrane permeability [19].

Various classes of antimicrobial metabolites, including alkaloids, terpenoids, flavonoids, phenols, steroids, and volatile oils, have been extracted from endophytic fungi [20,21]. One noteworthy bioactive substance, 7-amino-4-methylcoumarin, produced by the endophytic fungus *Xylaria* sp., found in association with *Ginkgo biloba* L., has demonstrated wide inhibitory effects against a variety of bacterial and fungal infections responsible for foodborne illnesses and spoilage. As a result, it has been suggested as a potential natural food preservative [22]. Additionally, *Fusarium* sp. displayed antagonistic properties against infection caused by bacteria and fungi. Similarly, *Phoma* sp., derived from *Dendrobium devonianum* and *D. thyrsiflorum*, showed a potent inhibitory effect against multiple human-infecting agents, including *E. coli*, *Bacillus subtilis*, *S. aureus*, *Candida albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus* [23].

3.2: Application of Filamentous Fungi in the Meat Industry

Non-toxigenic species like *P. chrysogenum* and *P. nalgiovense*, which are frequently utilized in the preparation of meat, have the potential to be exploited as biocontrol agents, according to additional research on filamentous fungi. Strains of *P. chrysogenum* purified from dry-cured ham have been shown to inhibit the growth and formation of ochratoxin A (OTA) by *P. verrucosum* in vitro. Similarly, *P. nalgiovense* strains from the commercial culture TEXEL PN1 have been found to limit the growth of common spoilage fungi, such as *A. flavus* and *P. restrictum* [17].

3.3: Marine-Derived Fungi and Their Antimicrobial Compounds

Fungi derived from marine sources serve as valuable sources of bioactive compounds with notable antimicrobial activities, especially from the genera *Neosartorya* and *Aspergillus*. Different compounds were isolated from the soil fungus *Neosartorya siamensis*, marine *N. takakii*, coral-associated *N. laciniosa*, and marine-derived *Aspergillus elegans*, which was obtained from the marine sponge *Monanchora unguiculata*. These compounds were assessed for their antimicrobial activity, particularly focusing on their MICs to evaluate their role as bacterial efflux pump inhibitors. Several of the compounds demonstrated inhibitory effects on the growth of *S. aureus*, although none were effective against *Salmonella enterica* serovar Typhimurium [24]. Yeasts exhibiting antifungal characteristics were sourced from marine ecosystems, indicating significant potential as bioprotective materials for postharvest treatment of fruits and vegetables. According to a study conducted in the South China Sea, 56% of the isolates from deep-sea fungi had antibiotic activity against at least one pathogenic bacterium. Such as *Arthrinium*, *Aspergillus*, and *Penicillium* demonstrated both antibacterial and antifungal properties, whereas *Acremonium*, *Cladosporium*, *Geomyces*, and *Phaeosphaeriopsis* exhibited only antifungal effect [25]. Additionally, the marine yeast *Rhodosporidium paludigenum*, sourced from the East China Sea, demonstrated effective inhibition of *Penicillium expansum* on pears and *Alternaria alternata* on jujube fruits [26].

4. Applications in the Food Industry

In the realm of food preservation, fungal metabolites have demonstrated considerable potential due to their capacity to inhibit spoilage organisms and pathogenic microbes, thereby extending shelf life and enhancing food safety. While bacteria are traditionally recognized in the synthesis of various antimicrobial agents, there has been increasing interest in the antifungal properties of yeasts. Yeasts, present in various environments including cereals, vegetables, fruits, meat, dairy, and processed foods, have long played a role in preserving food by the fermentation of products such as wine, beer, dough, and certain cheeses, contributing to both preservation and flavor enhancement [27]. Yeasts exert antimicrobial activity by competing for nutrients, acidifying their environment, resisting stressors like ethanol, and producing antimicrobial molecules, known as mycocins or killer proteins, that inhibit fungal growth. Furthermore, yeasts can colonize fruits, seeds, berries, and leaves, competing effectively with other microorganisms for space and nutrients, rendering them useful biocontrol agents in reducing postharvest decay [28,29].

Extensive research has explored the use of yeasts that produce mycocin to prevent fungal spoilage, with applications in foods and beverages, including wine, olives, soy sauce, and salted vegetables [30]. However, careful consideration must be given to the selection of yeast strains, as they may negatively impact product quality. Yeasts such as *Meyerozyma guilliermondii*, *Candida fructus*, *Issatchenkia orientalis*, and *C. quercitrusa* have been identified on fruits and plant surfaces, displaying antagonistic effects against fungal pathogens [31]. *Wickerhamomyces anomalus*, isolated from avocados, has been shown to inhibit *Colletotrichum gloeosporioides* and *C. acutatum*, the causative agents of avocado anthracnose. Similarly, *Pichia membranifaciens*, either alone or combined with chitosan, has been demonstrated to suppress *C. gloeosporioides* in citrus anthracnose by reducing mycelial growth and spore germination [32]. Additionally, *Hanseniaspora uvarum*, extracted from grapes, has been documented as an effective bio-preservative, controlling gray mold (*Botrytis cinerea*) in postharvest grapes [33] and inhibiting green mold (*Penicillium digitatum*) that affects citrus fruits [34]. Recently, yeast antifungal applications expanded into dry-cured ham [35] and sausages [36], where they are used to control toxigenic *Penicillium* species responsible for spoilage and OTA production. Strains of *Debaryomyces hansenii* have demonstrated antifungal effect against *Penicillium verrucosum* and *P. nordicum*, reducing OTA levels. Although *D. hansenii* can cause spoilage of fresh cheese and cream, it is also widely used as a starter culture to produce surface-ripened cheese and naturally occurs in meat and fruit products [16].

Certain filamentous fungi, like *Penicillium nalgiovense* and *P. chrysogenum*, play a positive role in enhancing the taste and visual quality of fermented foods, such as surface-ripened cheeses [37] and dry-cured ham [38]. These fungi are also employed as antifungal agents, particularly in low-water-activity environments where LAB is unable to thrive. Commercial strains of *P. nalgiovense* and *P. chrysogenum* are widely used in the meat industry [39]. Recent research has demonstrated that *P. chrysogenum*, sourced from dry-cured ham, inhibits spoilage fungi such as *Aspergillus flavus* and *P. restrictum* through the production of antifungal proteins [40]. Similarly, *P. nalgiovense* from the TEXEL PN1 culture has been shown to limit the multiplication and OTA secretion of *P. verrucosum* [41]. Furthermore, combining *P. chrysogenum* with reduced water activity (aw) during the ripening process has been proposed as a strategy to prevent black spot formation in dry-cured ham [38]. Overall, both yeasts and filamentous fungi produce antimicrobial peptides (AMPs), which offer a valuable approach for limiting fungal spoilage and mycotoxin production.

The use of fungal metabolites in food production is critical to reducing food contamination during the agricultural process and in industry. These biocontrol agents diminish the reliance on chemical preservatives, thereby supporting more sustainable agricultural practices and food processing. Furthermore, their use aligns with the United Nations' Sustainable Development

Goals (SDGs), which target food security and agricultural sustainability by 2030. Organic acids like fumaric acid, produced by fungi such as *Rhizopus oryzae*, are also employed in food preservation. Fumaric acid disrupts bacterial metabolism and inhibits the growth of foodborne pathogens like *Salmonella* and *E. coli*. This organic acid is commonly applied in products such as baked goods, beverages, and processed meats, contributing to extended shelf life and improved food safety [42].

Furthermore, endophytes serve as highly effective biocontrol agents by protecting host plants from phytopathogens through mechanisms such as antibiosis, parasitism, and competition. These organisms offer a sustainable substitute to chemical fungicides, which contribute to the emergence of resistant strains and environmental degradation. In addition to disease control, endophytes produce a wide array of bioactive compounds with antimicrobial, insecticidal, and other pharmacological properties, underscoring their importance in promoting sustainable agriculture and plant health management [43]. Among the most studied endophytic fungi are those from the *Trichoderma* genus, widely recognized for their diverse biocontrol traits. These include parasitism, antibiosis, secondary metabolite production, and the induction of plant defense systems. *Trichoderma* species, in particular, produce compounds such as terpenoids that demonstrate potent antifungal activity against plant pathogens, making them valuable tools for disease control in agricultural systems [44].

5. Mechanisms of Fungal Metabolites Antimicrobial Action

In dry-fermented foods, specific yeasts and molds act as effective antifungal agents by inhibiting the growth of spoilage fungi. Their efficacy stems from their ability to compete for space and nutrients and the production of antifungal agents, including antifungal proteins and volatile organic compounds [45]. *Debaryomyces hansenii* isolates produce 2-methyl-1-butanol and other volatile compounds, including unidentified diffusible molecules, that inhibit *Penicillium verrucosum* in dry-cured ham [35]. Similarly, *Meyerozyma guilliermondii*, when combined with *Lactobacillus plantarum* and *Wickerhamomyces anomalus*, generates ethyl acetate and β-1,3-glucanase during dough fermentation, successfully protecting bread from fungal contamination while preserving its taste and texture [16].

As reviewed by Delgado et al, the antifungal peptides produced from molds, such as cysteine-rich antifungal proteins (AFPs), have molecular weights between 5.5 and 10 kDa. These AFPs are highly stable under acidic conditions, heat, and proteolysis, making them suitable for use in fermented foods like cheese and meat [45,46]. Once bound to fungal cell walls or internalized, AFPs disrupt chitin synthesis or increase intracellular reactive oxygen species (ROS) levels, resulting in membrane permeabilization and cell death [45]. The mechanisms of action of antifungal yeasts and *Bacillus* species used to control postharvest diseases are multifaceted. They involve competition for essential nutrients like carbon and iron [47,48], the release of antifungal peptides and lipopeptides to inhibit pathogens [49], and mycoparasitism, where lytic enzymes such as glucanases, chitinases, and proteases break down other fungi, and induction of host resistance [27]. Cyclic lipopeptides like surfactins, fengycins, and iturins, produced by *Bacillus subtilis* and related species, aid in surface colonization and have strong antifungal effects, with fengycins and iturins being particularly harmful to fungi [50].

Antifungal volatile compounds produced by these microorganisms offer another promising mode of action, with potential applications in bio-fumigation for food spoilage control, provided safety can be ensured [51]. Compounds such as 2-phenylethanol, 2-methyl-1-butanol, and 3-methyl-1-butanol were identified for their antifungal properties. Notably, 2-phenylethanol produced by *Penicillium expansum* R82 inhibits various postharvest fungal pathogens, and its mechanism against *Penicillium digitatum* and *Penicillium italicum* has been well-documented [52].

Yeasts used to control grape pathogens employ various strategies, such as producing laminarians, antifungal volatiles, growth-inhibiting compounds, and competing for carbon and iron [53]. Many yeast strains show multiple antifungal actions. For example, *Pichia anomala* strain WRL-076, which is used to reduce aflatoxin in tree nuts, produces 2-phenylethanol, a compound that prevents spore germination, fungal growth, and aflatoxin production in *Aspergillus flavus* [54]. Fungal secondary metabolites, naturally occurring compounds not essential for fungal growth or reproduction,

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demonstrate significant antimicrobial activity due to their structural diversity [55]. These metabolites can be categorized by their biosynthetic pathways, including terpenoids, alkaloids, and flavonoids. Investigating these compounds can help discover new mechanisms to combat AMR, improve healthcare, and control foodborne and waterborne pathogens [56].

The increasing threat of foodborne and waterborne diseases, exacerbated by rising antimicrobial resistance, poses a considerable challenge. However, fungal secondary metabolites offer effective solutions through their diverse mechanisms of action. For example, monoterpenes such as limonene ($C_{10}H_{16}$), due to their small molecular size, exhibit enhanced membrane penetration. The hydrophobic nature of their methyl groups allows them to interact with the phospholipid bilayer, disrupting membrane fluidity, leading to the loss of intracellular contents, and causing a breakdown of membrane potential. This results in potent bactericidal activity [57].

Limonene, derived from *Trichoderma* species, shows strong inhibitory effects against gastroenteritis-causing bacteria, such as *E. coli*, rendering it a promising candidate for food preservation. Fumaric acid is also a fungal secondary metabolite used as a preservative that exhibits activity against various bacterial species, including *E. coli* and *Salmonella* spp., through multiple mechanisms. One such mechanism involves the disruption of bacterial energy metabolism. Fumaric acid acts as an intermediate in the Krebs cycle, positioned between succinate and malate. Its molecular structure, containing two carboxyl groups, enables it to serve as an electron acceptor during anaerobic respiration, allowing its reduction to succinate. Additionally, the trans double bond in fumaric acid enables effective binding to enzyme active sites [58]. When present in excess, fumaric acid overwhelms the fumarate reductase enzyme, inhibiting anaerobic respiration, reducing ATP production, and ultimately suppressing bacterial growth [28].

The above study concludes the critical role of fungal secondary metabolites in healthcare due to their natural origin and lower toxicity compared to conventional antimicrobial agents. These compounds inhibit bacterial mycotoxins and contribute to the global effort to combat AMR, a major public health concern today, as presented in Table 1.

Table 1: Major classes of fungal secondary metabolites with antimicrobial activity and their potential applications in food systems

Category	Metabolite	Producing fungus	Target microorganisms	Mechanism of action	Potential application /limitations	References
Terpenoids (VOCs)	Monoterpenes (e.g., α-pinene, limonene)	*Trichoderma* spp.	*Escherichia coli*, spoilage fungi	Disruption of cell membrane integrity	Indirect application via active or modified-atmosphere packaging; limited direct use due to volatility and rapid dissipation	[59,60]
Alkaloids	Periconicin-type alkaloids	*Periconia* sp.	*Staphylococcus aureus*	Inhibition of efflux pumps and cellular stress pathways	Experimental antimicrobial agents; safety and regulatory approval not established	[61,62]
Polyketides (phenolic compounds)	Flavonoid-like polyketides	*Colletotrichum gloeosporioides*	*E. coli*	Interference with ATP synthesis and metabolic enzymes	Laboratory-scale studies only; sensory and toxicological evaluation required	[63]
Organic acids	Fumaric acid	*Rhizopus oryzae*	*Salmonella* spp.	Acidification and disruption of bacterial metabolism	Approved acidulant; already used in food systems within regulated limits	[28,58]
Quinones (polyketides)	Ustic acid	*Aspergillus ustus*	*E. coli*	Redox cycling and disruption of cell wall integrity	Experimental antimicrobial compound; co-production of toxic metabolites limits food application	[61,64]

6. Global food preservatives market

Rapid technological advancement and globalization are increasing consumer demand for safe, healthy food, as the presence of harmful chemicals, such as artificial additives, continues to rise. The key drivers of the market include the growing global population, changing consumer lifestyles, and heightened awareness of food safety. Consumers' demands drive companies to start reducing synthetic preservatives and using natural and organic food preservatives like essential oils, plants extract, and organic acids. The global food preservatives market is projected to experience a significant increase from 2018 to 2030, with both natural and synthetic preservatives playing key roles. Natural preservatives, including edible oils, rosemary extracts, natamycin, vinegar, and chitosan, are gaining popularity due to their perceived health benefits and the rising demand for clean-label products. Synthetic preservatives such as propionates, sorbates, and benzoates remain widely used in food production because of their cost-effectiveness and strong antimicrobial effect. The market outlook for food preservatives is also categorized by function, with antimicrobial and antioxidant properties being the primary drivers of their use. Antimicrobial preservatives are essential for preventing microbial spoilage, while antioxidants protect food products from oxidative damage, thereby extending shelf life. In terms of application, preservatives are extensively used across various sectors, including meat and poultry, bakery products, dairy, beverages, and snacks. These sectors rely on preservatives to ensure product safety, maintain quality, and extend shelf life, with the meat and poultry industry representing a significant share of the market. The market is expected to continue expanding across these segments due to growing global demand for processed and convenient foods [65,66].

The demand for extended shelf-life food products is driven by increasing urbanization and a growing working population, particularly in cities. By 2050, the global population is expected to reach 9.7 billion, with 70% residing in urban areas, prompting a rise in the consumption of convenience foods. To meet this demand, food manufacturers are incorporating natural preservatives, such as vinegar and rosemary extract, to extend product shelf life while maintaining quality, especially with the increasing preference for clean-label products. In the Asia Pacific, the food processing industry is expanding rapidly, particularly in India and China, due to rising populations and evolving consumption trends. Government support has fueled the sector's growth, with India's food processing industry contributing significantly to both domestic and export markets. In 2020, it accounted for 32% of the country's total food market. However, the demand for preservative-free foods is also increasing as consumers become more health-conscious, particularly in the U.S., Europe, and China. While synthetic preservatives are considered generally safe, some consumers express concerns about their potential health risks, including links to attention deficit hyperactivity disorder (ADHD), cardiovascular diseases, and obesity, especially in children. Despite these concerns, there remains a strong preference for high-quality, flavorful food products [66].

7. Safety, Sensory Impact, Toxicology, and Dose–Response Validation of Antifungal Metabolites

Despite the growing interest in fungal- and microbial-derived antifungal metabolites as natural alternatives to synthetic food preservatives, comprehensive safety evaluations remain limited for many candidate compounds. While numerous studies report strong antifungal efficacy *in vitro*, systematic assessments of toxicological safety, sensory impact, and dose–response relationships under realistic food conditions are largely absent, representing a major barrier to regulatory approval and industrial adoption.

7.1: Safety and Toxicological Considerations

Many antifungal metabolites produced by filamentous fungi belong to chemically diverse classes such as polyketides, non-ribosomal peptides, terpenoids, and alkaloids, some of which are structurally related to known mycotoxins. This structural similarity raises justified safety concerns, as several fungal secondary metabolites exhibit cytotoxic, genotoxic, or immunosuppressive effects at higher concentrations [64,67]. For example, compounds such as chaetoglobosins and epipolythiodioxopiperazines (ETPs), while demonstrating antifungal or antibacterial activity, have been reported to interfere with mammalian cellular redox balance and immune responses, limiting their direct application in foods [68–70].

Toxicological evaluations, including acute and chronic toxicity, mutagenicity, teratogenicity, and carcinogenicity studies, are rarely conducted for emerging antifungal metabolites. Regulatory agencies such as the European Food Safety Authority (EFSA) and the U.S. Food and Drug Administration (FDA) require such data before approval; however, for most fungal-derived antifungal compounds, no acceptable daily intake (ADI) values or no-observed-adverse-effect levels (NOAELs) have been established [71–73].

7.2: Dose–Response Validation and Sensory Impact

A critical limitation in the development of antifungal metabolites as food preservatives is the lack of robust dose–response validation in real food matrices. Antifungal activity is frequently reported at concentrations determined under in vitro conditions, while corresponding safety margins and sensory thresholds are rarely assessed in parallel. Moreover, MICs obtained in laboratory media often fail to translate directly to complex food systems, where interactions with lipids, proteins, and carbohydrates can significantly reduce antimicrobial efficacy or alter compound bioavailability [74]. In the absence of validated dose–response relationships, it remains unclear whether effective antifungal concentrations can be achieved within acceptable toxicological and sensory limits.

Sensory impact represents an additional, yet underexplored, constraint on the practical application of antifungal metabolites. Many fungal-derived compounds possess intense pigmentation, bitterness, or characteristic odors, which may adversely affect food appearance, flavor, and overall consumer acceptance. For example, pigmented antifungal metabolites such as pulcherrimin and azaphilone derivatives can induce visible color changes in food products, limiting their suitability for applications where visual quality is critical [16,75].

Bitterness is particularly problematic for several classes of antifungal peptides and alkaloids. Defensin-like peptides and non-ribosomal lipopeptides, produced by fungi and bacteria, have been reported to impart bitter or metallic off-flavors. In particular, iturin- and fengycin-type lipopeptides, despite their strong antifungal efficacy, have been associated with perceptible bitterness at concentrations in the low mg/L range in food model systems [76,77]. Similarly, peptaibols, such as alamethicin produced by *Trichoderma* species, are short, highly hydrophobic antifungal peptides rich in α-aminoisobutyric acid; their rigid helical structures and hydrophobic side chains are strongly correlated with bitter taste perception [78,79]. Alkaloids represent another class of antifungal metabolites with pronounced sensory effects. Ergot alkaloids (e.g., ergometrine and ergine), produced by *Claviceps* species, are intensely bitter and have historically been associated with strong aversive sensory properties even at trace concentrations. Although their toxicity precludes their use as food preservatives, they illustrate the potent sensory impact that antifungal alkaloids can exert [80].

Despite these well-documented sensory challenges, formal sensory evaluation studies, including trained panel assessments and consumer acceptability testing, are seldom incorporated into antifungal metabolite research. Most studies continue to focus predominantly on antimicrobial efficacy, highlighting the need for integrated experimental approaches that simultaneously address dose–response behavior, toxicological safety, and sensory impact to support the realistic application of antifungal metabolites in food preservation.

8. Conclusion, challenges, and future perspectives

There has been significant scientific interest in exploring fungal metabolites as potential antimicrobial agents for food preservation, primarily driven by the need to control spoilage microorganisms and extend shelf life under increasingly restrictive regulatory frameworks for synthetic preservatives. Laboratory-scale studies have demonstrated that fungi are capable of producing a diverse array of secondary metabolites—including organic acids, peptides, enzymes, volatile compounds, and pigments—with measurable antimicrobial activity against foodborne bacteria and spoilage fungi. However, the translation of these findings into practical food applications remains limited, and the current contribution of fungal-derived metabolites to commercial food preservation is modest.

A major constraint to the adoption of fungal metabolites as food preservatives is their safety and toxicological profile. Many fungal secondary metabolites are structurally related to, or co-produced with, known mycotoxins, raising significant concerns regarding cytotoxicity, genotoxicity, and chronic exposure risks. Consequently, only a very limited number of microbial-derived antifungal compounds have received regulatory authorization for food use, and the majority of fungal metabolites discussed in the literature lack Generally Recognized as Safe (GRAS) status or approval by regulatory authorities such as the EFSA or the FDA. These regulatory limitations underscore the importance of distinguishing between experimental antimicrobial activity observed in vitro and compounds that are legally and toxicologically acceptable for use in real food systems.

In addition to safety concerns, technological and sensory challenges further restrict industrial feasibility. The stability of fungal secondary metabolites within complex food matrices is often uncertain, as interactions with food components, processing conditions, and storage environments can reduce antimicrobial efficacy or lead to degradation products with unknown safety profiles. Moreover, several fungal metabolites, particularly pigmented compounds and hydrophobic peptides, may negatively affect food color, flavor, or aroma, thereby limiting consumer acceptance. These factors highlight the need for cautious evaluation of fungal metabolites beyond antimicrobial potency alone.

At present, compounds with realistic pathways toward application are largely restricted to well-characterized and tightly regulated examples, such as natamycin—which, although of bacterial origin, serves as an important benchmark for antifungal biopreservation—or carefully purified fungal-derived proteins and enzymes that can be produced under controlled conditions with minimal risk of toxic co-metabolite formation. Broad generalizations regarding the commercial readiness of fungal metabolites as bio-preservatives are therefore not supported by the current regulatory and toxicological landscape.

Future research should focus on addressing these fundamental limitations through integrated, multidisciplinary approaches. Priority areas include comprehensive toxicological evaluation, assessment of mycotoxin co-production, establishment of dose–response relationships in relevant food matrices, and formal sensory analysis. In parallel, standardized extraction and purification protocols, alongside rigorous strain selection and characterization, are essential to ensure reproducibility and safety. Advances in genomics, transcriptomics, and metabolomics offer valuable tools for identifying fungal strains and metabolic pathways capable of producing antimicrobial compounds while minimizing safety risks. Ultimately, aligning antifungal efficacy with regulatory authorization, toxicological safety, and sensory acceptability will be critical to determining whether fungal metabolites can transition from promising laboratory findings to credible and limited roles in modern food preservation systems.

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