

Mini-Review

Plant Phytochemicals in Food Preservation: Antifungal Bioactivity: A Review

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ABSTRACT

Synthetic food additives generate a negative perception in consumers. This fact generates an important pressure on food manufacturers, searching for safer natural alternatives. Phytochemicals (such as polyphenols and thiols) and plant essential oils (terpenoids) possess antimicrobial activities that are able to prevent food spoilage due to fungi (e.g., *Aspergillus*, *Penicillium*) and intoxications (due to mycotoxins), both of which are important economic and health problems worldwide. This review summarizes industrially interesting antifungal bioactivities from the three main types of plant nutraceuticals: terpenoids (as thymol), polyphenols (as resveratrol) and thiols (as allicin) as well as some of the mechanisms of action. These phytochemicals are widely distributed in fruits and vegetables and are very useful in food preservation as they inhibit growth of important spoilage and pathogenic fungi, affecting especially mycelial growth and germination. Terpenoids and essential oils are the most abundant group of secondary metabolites found in plant extracts, especially in common aromatic plants, but polyphenols are a more remarkable group of bioactive compounds as they show a broad array of bioactivities.

HIGHLIGHTS

- Phytochemicals show antifungal activity, and they act in a synergistic manner.
- Polyphenols are effective against important crop pathogenic fungi.
- Most relevant antifungal thiols are allicin and its derivatives.

Key words: Antifungal; Food additive; Nutraceutical; Phytochemicals

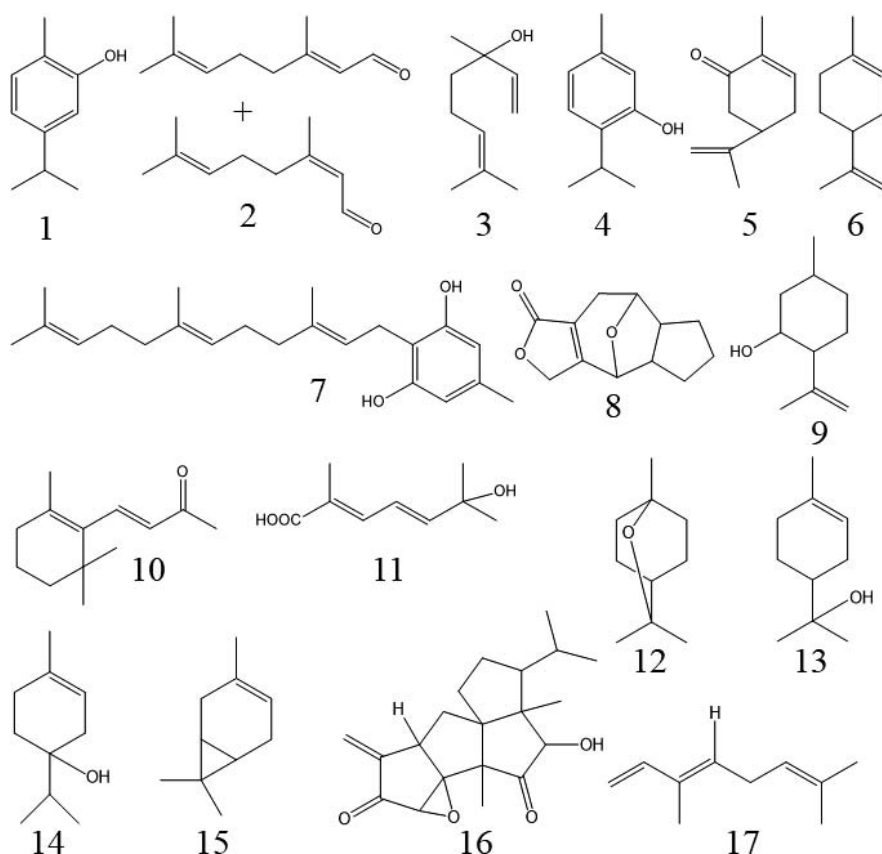
Humans, as well as crops and livestock, are susceptible to be infected by pathogenic fungi (5, 36, 67). Fungi are also one of the main problems associated with food spoilage, because fungal growth on raw and processed foods produces the deterioration of their sensorial properties, rotting, off-flavor, and odor emission (70). They also have the advantage of dispersing easily by spores, and in this stage they are more resistant to food processing and other treatments, such as those implying heat application, especially when the spores have originated by a sexual process (17). Moreover, some species are able to produce mycotoxins, which contaminate approximately 25% of the crops globally and affect human health. Long-term ingestion of these mycotoxins, such as those produced by *Aspergillus*, *Fusarium*, and *Penicillium*, has been associated with liver and kidney tumors, autoimmune illnesses, free radical production, and other teratogenic, carcinogenic, and mutagenic effects (37, 93). For example, some crops are especially vulnerable to being invaded by microorganisms

because of their nutritional characteristics, such as pepper (*Capsicum* sp.), where these mycotoxins are commonly found (9). It is also important to take into account that these contaminations can occur during all food manipulation steps: transport, processing, and storage.

The use of food preservatives can extend food shelf life by inhibiting bacterial and fungal growth, and we have been using them for several centuries, when salt, vinegar, or sugar were the most common preservatives. However, today the demand of ready-to-eat food is increasing and consequently so, too, that of food additives. They have to meet several criteria to ensure food safety, maintaining the nutritional value and sensorial properties while improving quality (color, taste, texture, and freshness). In addition, it is crucial to consider the specificity of the antimicrobial compounds used as additives to prevent our own microbiome being altered (69). But synthetic additives also present negative aspects and have a poor perception among consumers, so the food industry tries to reduce their use, replacing them with natural alternatives (8, 75). The main problem is that some of them show adverse health effects, including carcinogenic effects. For example, after several

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FIGURE 1. Chemical structures of anti-fungal terpenoids. 1, carvacrol; 2, citral; 3, linalool; 4, thymol; 5, carvone; 6, limonene; 7, grifolin; 8, rufuslactone; 9, isopulegol; 10, β -ionone; 11, litseacubebic acid; 12, 1,8-cineole; 13, α -terpineol; 14, terpene-4-ol; 15, 3-carene; 16, crinipellin A; 17, β -ocimene.



reactions, sodium nitrite, used in processed meat, can produce *N*-nitrosamines, recognized as carcinogens (65). The search for new natural molecules with antifungal activity to improve food preservation is therefore very interesting.

Natural compounds with antifungal activity are present in some plants and mushrooms because they need them as protection to survive in their natural environments (81), and many of them also act as nutraceuticals, natural components of food with bioactive functions that provide extra beneficial properties to human health in addition to their nutritional value (32, 76). Some examples of specific molecules with antifungal properties are described herein.

TERPENOIDS AND ESSENTIAL OILS

Terpenes are the widest group of chemical compounds found in plant extracts, showing important antimicrobial activity that can be enhanced by the presence of other phytochemicals (from the plant extract) in a synergistic way. Depending on the plant species and the plant tissue that is extracted, the chemical profile of these essential oils will differ (85).

Grifolin (Fig. 1), a sesquiterpene compound isolated from fruiting bodies of the fungus *Albatrellus dispansus*, inhibits the mycelial growth of plant pathogenic fungi such as *Sclerotinia sclerotiorum* and also produces an almost total inhibition of spore germination on *Fusarium graminearum*, *Gloeosporium fructigenum*, and *Pyricularia oryzae*. Other sesquiterpenes such as rufuslactone (Fig. 1), extracted from the fruiting bodies of the basidiomycete

Lactarius rufus, show also antifungal activity against phytopathogenic fungi (51).

Another fungus, *Crinipellis rhizomaticola*, a species discovered in 2009, synthesizes the compound crinipellin A (Fig. 1), a diterpenoid that shows a strong activity in vivo and in vitro against *Magnaporthe oryzae*, *Collectotrichum coccodes*, *Botrytis cinerea* (gray mold), and *Phytophthora infestans*, some of the most important crop pathogenic fungi (33).

The European Commission has accepted many essential oil components (mainly volatile terpenoids) and other phytochemicals (such as polyphenols) for their use as flavorings in food products. These molecules, such as the terpenoids carvacrol, carvone, citral, limonene, linalool, and thymol (Fig. 1), and the polyphenols cinnamaldehyde, eugenol, and vanillin (Fig. 2), are considered to present no risk to consumer's health. The U.S. Food and Drug Administration classifies crude essential oils of some plants such as clove, oregano, thyme, nutmeg, basil, mustard, and cinnamon as generally recognized as safe compounds (39, 89). Essential oils, or their purified components, are good candidates for use as preservatives, especially in highly perishable foods such as meat or fish (66).

Extracts from *Origanum vulgare* (oregano), *Satureja montana* (winter savory), *Mentha piperita* (peppermint), *Cinnamomum verum* (cinnamon tree), and *Cymbopogon flexuosus* (East Indian lemongrass) exert a potent antifungal activity against the yeast *Candida albicans* (80, 87) and also against *Saccharomyces cerevisiae* in the case of *Origanum* sp. (21). *Origanum* essential oil is rich in terpenoids with antifungal properties, such as carvacrol and thymol (79)

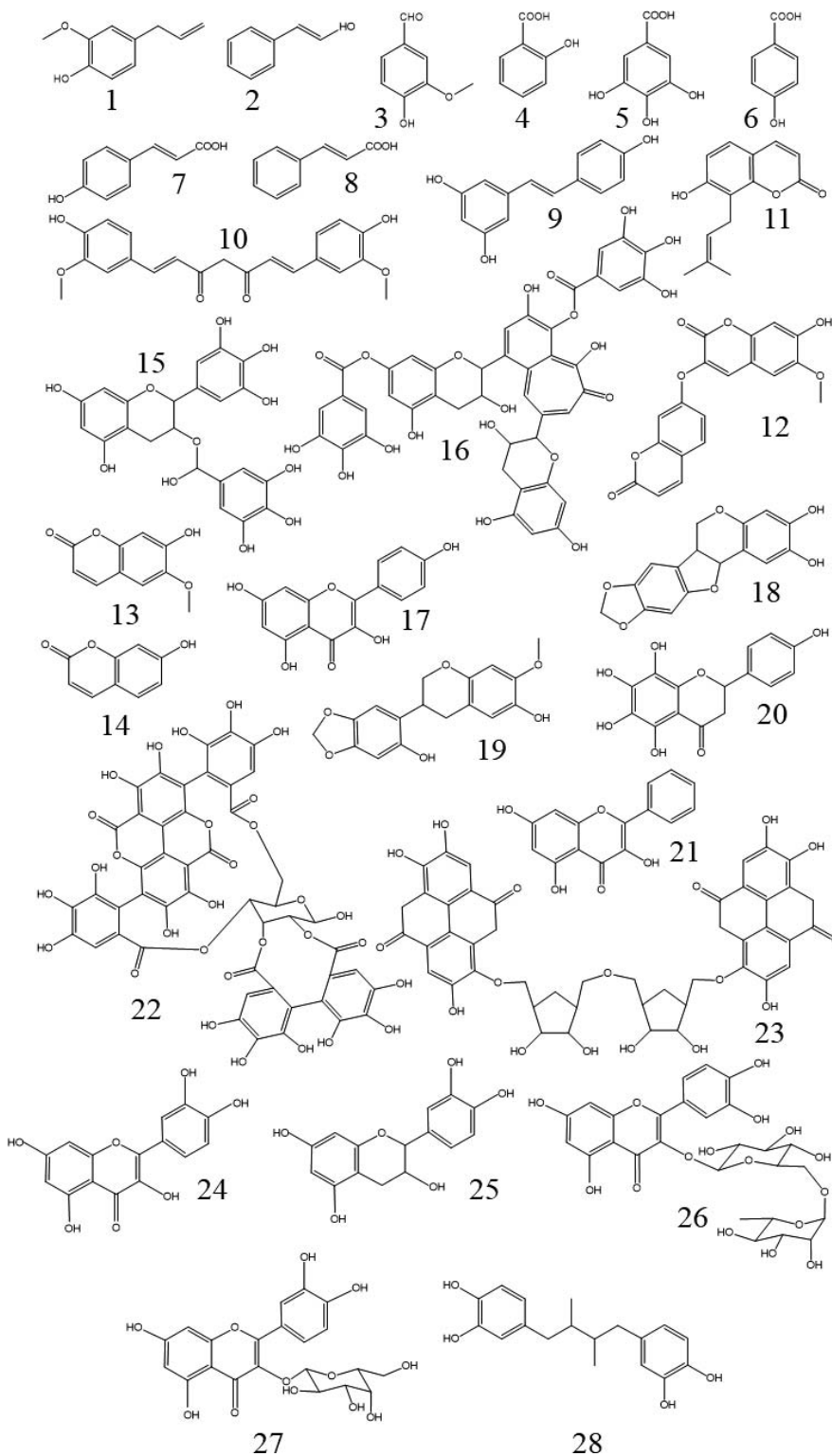


FIGURE 2. Chemical structures of anti-fungal polyphenols. 1, eugenol; 2, cinnamaldehyde; 3, vanillin; 4, salicylic acid; 5, gallic acid; 6, p-hydroxybenzoic acid; 7, p-coumaric acid; 8, cinnamic acid; 9, resveratrol; 10, curcumin; 11, osthenol; 12, daphnoretin; 13, scopoletin; 14, umbelliferone; 15, epigallocatechin gallate; 16, theaflavin digallate; 17, kaempferol; 18, hildegardiol; 19, 2-hydroxy-maackiain; 20, farrerol; 21, galangin; 22, punicalagin; 23, candelitannin; 24, quercetin; 25, catechin; 26, rutin; 27, hyperoside; 28, nordihydroguaiaretic acid.

(Fig. 1). Recently, oregano and clove (*Eugenia* spp.) essential oils have been tested on nanoemulsions in vitro and in salad dressings, and both show activity against *Zygosaccharomyces cerevisiae* (74). Other studies have shown that subinhibitory concentrations of these terpenoids are able to sensitize *Candida albicans* biofilms, making them more sensitive to fluconazole treatment (18). Interestingly, different terpenes show specific activity against biofilms, depending on their developmental state. For example, isopulegol, thymol, carvone, and β -ionone (Fig.

1) are potent inhibitors of biofilm initiation, whereas carvacrol and eugenol were the most efficient against mature biofilms (73). The terpenes linalool and citral (Fig. 1) exhibit great activity against *Candida albicans*, and both compounds have an excellent synergistic effect in combination with fluconazole against a fluconazole-resistant *Candida albicans* strain (98). The bioactivity of citral was tested against another fluconazole-resistant species, *Candida tropicalis*, showing synergistic effects, too, apart from the antifungal activity of isolated citral (84). This compound

also affects the mitochondrial function of *Penicillium digitatum*, the cause of green mold of citrus, by producing a deformation and loss of matrix and consequently the inhibition of its growth (97). By contrast, linalool, the main component of the *Achillea ligustica* (Ligurian yarrow) essential oils, shows antifungal activity against several phytopathogenic fungi, such as *Alternaria solani* or *Fusarium graminearum*, either alone or in combination with terpinen-4-ol and 1,8-cineole (30) (Fig. 1). In addition, as it occurs with citral, linalool is active against a fluconazole-resistant fungus strain, *Trichophyton rubrum* (14).

The essential oils from other aromatic plants such as *Salvia officinalis* (common sage), *Lavandula dentata* (French lavender), and *Laurus nobilis* (laurel) contain the monoterpene 1,8-cineole as their major constituent, which has a high activity against the fungus *Aspergillus carbonarius* (12).

Diáñez et al. (16) tested 12 different essential oils facing eight pathogenic fungi, including pathogens. The most effective oils were those from clove, rose geranium, peppermint and patchouli, having total or partial inhibitory effect against *Fusarium oxysporum*, *Sclerotinia sclerotiorum*, *Phytophthora parasitica*, *Alternaria brassicae*, and *Cladobotryum mycophilum*. These pathogenic fungi infect several important crops such as tomato and cabbage and the mushroom *Agaricus bisporus*.

Venkatesh et al. (90) studied the response of 15 pathogen fungi to *Boswellia serrata* (Indian oli-banum) essential oil extract (mostly composed by the monoterpenes 3-carene and β -ocimene and the tetranotriterpene D-limonene; Fig. 1), with *Alternaria brassicicola*, *Alternaria geophila*, and *Curvularia tetramera* being the most susceptible fungi. This extract also showed a significant antifungal activity in comparison to synthetic fungicides, such as Fungicop-50. Moreover, the aflatoxin B₁ production by *Aspergillus flavus* was totally inhibited. In a similar way, production of the mycotoxin fumonisin B₁ by *Fusarium verticilloides* was almost totally inhibited as well.

Raimundo et al. (71) compared the action of essential oils from *Gallesia integrifolia* (garlic wood), native to Brazil, with the action of the synthetic antifungal ketoconazole. This essential oil was 25 times more effective against *Aspergillus fumigatus*, *Aspergillus versicolor*, *Aspergillus ochraceus*, and *Trichoderma viride* than ketoconazole.

The fruit essential oil of the tree *Litsea cubeba* (aromatic litsea) contains 75% citral and is widely used as a flavor enhancer in foods, as an antimicrobial and insecticidal agent, and as raw material for the synthesis of vitamin A. This essential oil also contains the monoterpeneoid litseacubebic acid (Fig. 1), which shows good fungicidal activity against diverse plant pathogenic fungi such as *Sclerotinia sclerotiorum*, *Rhizoctonia solani*, *Phaeoseptoria musae*, and *Colletotrichum gloeosporioides* (96), even though the most active compound in *Litsea cubeba* is citral (92). The leaf extract of another species of this genus, *Litsea monopetala*, also has a significant antifungal activity against *Aspergillus niger*, *Saccharomyces cerevisiae*, and *Candida albicans* (34).

Growth of *Phytophthora drechsleri*, a phytopathogenic fungi that damages many crops consumed by humans, has

been successfully inhibited by application of *Zataria multiflora* (satar) essential oil (55). Similar results have been reported with essential oils from black and green pepper (*Piper nigrum* and *Capsicum annuum*) or eucalyptus (*Eucalyptus* spp.), which are also rich in sesquiterpenes and monoterpenes, preventing yeast spoilage of fruit juices (62, 88).

The tea tree (*Melaleuca alternifolia*) essential oil contains mainly α -terpineol and terpine-4-ol (Fig. 1), the most effective compounds of this oil against the fungus *Aspergillus niger*, causing metabolic and morphological damage on it. This fungus grows on the grape (*Vitis vinifera*) pericarp and pulp and causes black mold disease after harvesting. Also, it produces mycotoxins, affecting human health. Therefore, tea tree oil could be a potential grape crop preservative (4).

Rice (*Oryza sativa*) seeds are susceptible to be infected by several species of the genera *Alternaria*, *Fusarium*, *Bipolaris*, and *Pyricularia*. Such infections cause losses in product quality and can be dangerous because some *Fusarium* species produce mycotoxins. *Origanum compactum* essential oil causes fungal growth inhibition on rice samples spiked with *Alternaria alternata*, *Bipolaris oryzae*, and *Fusarium* spp., suggesting that this essential oil could be useful as a rice preservative (79).

MICs of carvacrol and thymol can completely block ergosterol biosynthesis, a fungal membrane sterol, and below the MIC they cause a decrease in ergosterol content in a dose-dependent manner, which can explain their antifungal effects against *Candida* species (2). This disruption of ergosterol biosynthesis has also been found for other species, such as *Fusarium graminearum*, with thymol (28), and the mechanism of action of the compound citral, mentioned previously, is also based on the interruption of the biosynthesis pathway of ergosterol, as Sousa et al. (84) evidenced testing it against *Candida tropicalis*.

POLYPHENOLS

Penicillium expansum is an aggressive fungus that can affect apples (*Malus domestica*), one of the most cultivated and consumed fruits worldwide, spreading quickly and producing the mycotoxin patulin, potentially harmful to human health. Salicylic acid (Fig. 2), a phenolic acid involved in plant growth development, has shown antifungal properties against postharvest pathogens, including *Penicillium expansum*, *Botrytis cinerea*, and *Rhizopus stolonifera*, even at low concentrations. Because salicylic acid is considered safe for the environment and human health, and because of its good antifungal properties, it has been proposed as an alternative to the fungicides used against apple postharvest infections (13). *Penicillium expansum* is also vulnerable to one Italian endemic variety of *Allium sativum* (wild garlic), called Rosato, whose phenolic extract is mainly composed of gallic acid, hyperoside (Fig. 2), and allyl isothiocyanate, a thiol derivative (Fig. 3). Another Italian endemic variety, Caposele, has antifungal activity against *Aspergillus versicolor* and *Penicillium citrinum*, due to the same chemical compounds (24). Similarly, several *Fusarium* species can cause plant diseases that produce losses in agricultural crops

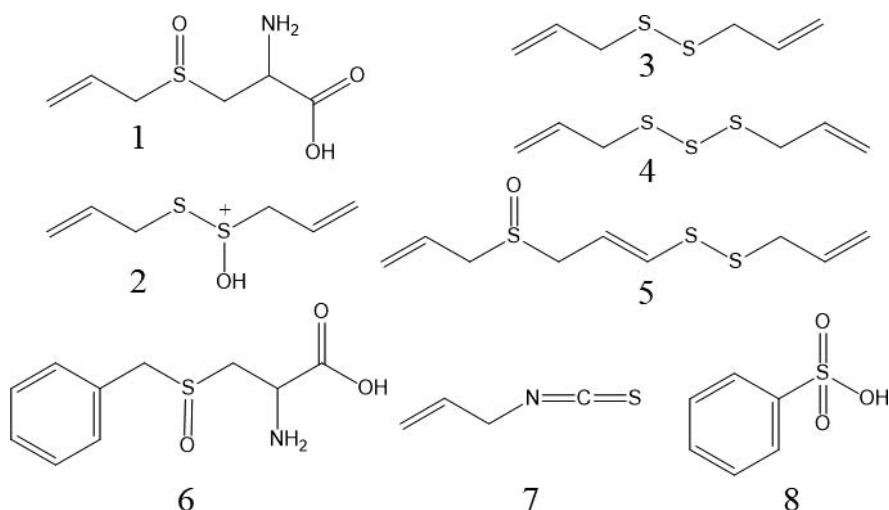


FIGURE 3. Chemical structures of anti-fungal thiols. 1, alliin; 2, allicin; 3, diallyl disulfide; 4, diallyl trisulfide; 5, ajoene; 6, petiveriin; 7, allyl isothiocyanate; 8, benzylsulfonic acid.

and a risk to human health due to their ability to produce mycotoxins. Gallic acid (Fig. 2), the main compound of *Spirulina* LEB-18 cyanobacteria extract, reduces mycelial growth of *Fusarium graminearum* while decreasing the mycotoxin concentration (64). This compound, isolated from *Terminalia nigrovenulosa* bark, was also effective against *Fusarium solani*, decreasing root rot diseases; thus, it is recommended to control these types of infections in some plants such as cucumber (*Cucumis sativus*) (61). *Coprinopsis atramentaria* mushroom extract, containing *p*-hydroxybenzoic, *p*-coumaric, and cinnamic acids (Fig. 2), shows antifungal activity against *Aspergillus* and *Penicillium*, with a remarkable demelanizing activity over *Aspergillus niger*, *Aspergillus fumigatus*, and *Penicillium verrucosum* var. *cyclopium*, an effect that is interesting as melanin is an important factor in fungal virulence (35).

Another aggressive fungus that affect crops (e.g., pineapple [*Ananas comosus*], avocado [*Persea americana*]) is *Phytophthora cinnamomi*. Polyphenolic extracts from *Larrea tridentata* (greasewood) and *Flourensia cernua* (tarbush) are effective against it, with very low MICs (6.96 and 8.6 mg/L), showing mycelium growth inhibition (9).

Resveratrol (Fig. 2) is a stilbene phytoalexin produced by some plants in response to UV radiation and the growth of fungal pathogens, such as *Botrytis cinerea*, reducing germination of the conidia and mycelial growth (20, 74). Resveratrol, found in red wine, red grapes, peanuts (*Arachis hypogaea*), cranberries, and blueberries (*Vaccinium* spp.) (91), also induces apoptosis in the human pathogen *Candida albicans* through the caspase-dependent mitochondrial pathway (46). It also inhibits other dermatophytes such as *Trichophyton mentagrophytes*, *Trichophyton tonsurans*, *Trichophyton rubrum*, *Epidermophyton floccosum*, and *Microsporum gypseum* (91). In addition, resveratrol analogs are being analyzed for antifungal activity with favorable results, probably related to their imine group (54).

Curcumin (Fig. 2) is a polyphenol produced in the rhizome of the plant *Curcuma longa* (turmeric), and in addition to its antioxidant, antimutagenic, and antitumoral properties, it also has a potent antifungal property, with stronger activity than fluconazole in the inhibition of *Paracoccidioides brasiliensis* and *Candida* spp. growth

(53). Curcumin is also active against *Sporothrix schenckii*, the cause of sporotrichosis, redistributing chitin in its cell wall (38). The activity of this compound can be modified in combination with other molecules, such as dodecanol or ascorbic acid (42, 95). This antifungal activity could reside in the induction of alterations of membrane-associated ATPases, ergosterol biosynthesis inhibition, and reduction in the levels of proteinase secretion, an important virulence factor (60, 95). However, curcumin is insoluble in water, so it must be microencapsulated to be used as a preservative in food, thereby increasing the solubility and antifungal effect of curcumin (14, 31).

Different coumarins (Fig. 2) were tested against *Candida albicans*, *Aspergillus fumigatus*, and *Fusarium solani*. Osthenol, a prenylated coumarin with an alkyl group at C-8 position (Fig. 2) found in the seeds of *Apium graveolens* (celery) and *Angelica pubescens* (shishiudo) (6), among others, showed the best results, with a MIC of 125 $\mu\text{g}/\text{mL}$ for *Fusarium solani* and 250 $\mu\text{g}/\text{mL}$ for *Candida albicans* and *Aspergillus fumigatus* (57). Daphnoretin (Fig. 2) is a biscoumarin from the medicinal plant *Loeselia mexicana* (Mexican false calico), which is used in Mexican traditional medicine to treat skin diseases caused by dermatophytes. This compound, along with its two monomeric precursors scopoletin and umbelliferone (Fig. 2), exhibit good antifungal activity against *Candida albicans*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum* (59). Other natural derivatives of coumarin (simple coumarins, furanocoumarins, and pyranocoumarins) have shown a remarkable antifungal activity against fungi such as *Sclerotinia sclerotium*, *Botrytis cinerea*, *Fusarium graminearum*, *Fusarium oxysporum*, and *Fusarium solani* (48, 83).

Flavonoids inhibit fungal spore germination and have been proposed to control fungal pathogens (11, 68). Flavonoids from leaves of *Camelia sinensis* (tea tree), such as epi-gallocatechin-3-gallate (Fig. 2) and theaflavin digalate (Fig. 2), exhibit a concentration-dependent fungicidal activity against several pathogenic fungi (26). Moreover, with flavonoid diglycosides, extracted from *Mentha piperita* (peppermint), inhibition against *Phoma sorghina* and *Fusarium moniliforme* was observed, reducing their mycelium growth. This is an important result because both species

cause several diseases in cereal crops (40). Maize (*Zea mays*), one of the most important crops for human and animal nutrition, can be contaminated with *Fusarium* spp., resulting in mycotoxin contamination (86). The plant extract from *Equisetum arvense* (common horsetail), rich in flavonoids such as kaempferol (Fig. 2), has significant inhibition on *Fusarium* growth and could be used to control maize optimal cultivation and growth (29). Extracts from the trees *Eysenhardtia texana* (Texas kidneywood), *Terminalia bellirica* (bahera), and *Hildegardia barteri* contain the flavonoids hildegardiol, 2-hydroxymaackiain, and farrerol (Fig. 2), all of which are active against *Candida albicans* growth (55). Another plant species, *Praxelis clematidea* (praxelis), contains flavonoids with antifungal activity against different *Candida albicans* strains, too, perhaps interfering with ergosterol and its function in the cell wall (22). Also, some flavonoids have been isolated from mango (*Mangifera indica*) leaves, and they inhibit the growth of *Alternaria alternata*, *Aspergillus fumigatus*, *Aspergillus niger*, *Macrophomina phaseolina*, and *Penicillium citrii* (41). Furthermore, the antibacterial and antifungal activity of bee propolis has been attributed, at least partially, to its phenolic content (flavonoids, phenolic acids, and their esters), such as the flavonoid galangin (25, 63) (Fig. 2), although the composition of the propolis varies depending on the plant and bee species of each location (72).

Calendula (marigold) is a plant with a high nutritional value that is usually added to several beverages, salads, and soups. Its extract contains mainly saponins, flavonoids (quercetin derivatives), and caffeic acid, all of which show activity against several fungi. For example, *Calendula suffruticosa* subsp. *algarbensis* is particularly active against *Aspergillus* sp., against yeasts such as *Cryptococcus neoformans*, and also against some dermatophytes species such as *Microsporum canis*, *Microsporum gypseum*, and *Trichophyton mentagrophytes* (19).

Other plant compounds with interesting antifungal activities are tannins. The major active component of pomegranate (*Punica granatum*) fruit peel extract, the ellagitannin punicalagin (Fig. 2), selectively inhibits the growth of the dermatophyte fungi *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Microsporum canis*, and *Microsporum gypseum* (23). This compound could be used to combat tomato wilt because it has antifungal activity against *Fusarium oxysporum* (78). Punicalagin also displays good antifungal activity against *Candida parapsilosis* (MIC of 6.25 $\mu\text{g/mL}$), *Candida krusei* (MIC of 6.25 $\mu\text{g/mL}$), *Candida albicans* (MIC of 12.5 $\mu\text{g/mL}$) (50), and *Cryptococcus neoformans* (MIC of 0.5 to 4 $\mu\text{g/mL}$) (82). Currently, this pomegranate peel extract, which contains catechin and rutin (flavonoids) in addition to the major compound punicalagin, has been used to inhibit *Colletotrichum gloeosporioides*, a fungus that infects *Persea americana* (avocado tree). This antifungal activity was enhanced by adding an alginate and chitosan coating (58). This antifungal edible coating could be developed on other perishable fruits.

Candelitannin (Fig. 2) and the ellagitannins of *Euphorbia antisyphilitica* (candelilla) have also shown growth inhibition of plant pathogens such as *Alternaria*

alternata, *Fusarium oxysporum*, *Colletotrichum gloeosporioides*, and *Rhizoctonia solani* (49). Ellagitannins from the Brazilian medicinal plant *Ocotea odorifera* (American cinnamon) show potent inhibitory activity against *Candida parapsilosis* (MIC of 1.6 μM) (94), and these compounds were also extracted from *Rubus idaeus* (raspberry) by Klewicka et al. (45), who verified their antifungal activity against the fungus *Geotrichum candidum* to use them as food biopreservatives.

Furthermore, *Alternaria alternata*, *Fusarium oxysporum*, *Colletotrichum gloeosporioides*, and also *Botrytis cinerea* polyphenol vulnerability was studied by Aguirre-Joya et al. (1). Polyphenols from *Larrea tridentata* leaves were extracted, and the most abundant polyphenol was nordihydroguaiaretic acid and the flavonoids kaempferol and quercetin (Fig. 2). All these species were affected by the polyphenol extract, especially *Fusarium oxysporum*. Moreover, it was possible to make films adding glycerol, pectin, and wax to the polyphenols extract, aiming to coat natural fruits with them. The results showed that some of the polyphenol films protected the fruits without changing organoleptic properties, respiration rate, or maturity processes.

THIOLS AND DERIVATIVES

Cysteine, an important amino acid implicated in plant sulfur assimilation, is crucial in resistance against pathogens, among other vital pathways. Roblin et al. (77) verified the cysteine capacity of inhibiting completely or partially the growth of some fungal pathogens (*Phaeoconiella chlamydospora* and *Phaeoacremonium minimum*), affecting both spore germination and mycelium development. This could be tested and applied to control wood-degrading diseases. Cysteine sulfoxides such as alliin (Fig. 3), from *Allium* species such as garlic (*Allium sativum*) and ransom (*Allium ursinum*), are transformed to allicin by the enzyme alliinase when plant tissues are damaged, and allicin, in the presence of oxygen, gives rise to diallyl sulfides (3, 52) (Fig. 3). Allicin is able to inactivate essential enzymes from diverse pathogens, by reacting with their thiol groups (47). *Allium ursinum* extracts, for example, have shown antifungal activity against *Candida albicans*, *Candida famata*, *Candida glabrata*, and *Candida krusei* at concentrations of 1 mg/mL. The molecular basis for this may be interference with proton translocation across membranes, causing ATP depletion (7). Also, allicin and diallyl trisulfide (Fig. 3) from garlic extract are able to inhibit conidia germination of the saprophytic fungus *Botrytis cinerea* on harvested table grapes, in a similar way to the food additive sodium metabisulfite (27).

The extract from *Petiveria alliacea* (guinea henweed) contains other cysteine sulfoxides derivatives that have been tested against the fungi *Aspergillus flavus*, *Candida albicans*, *Candida tropicalis*, *Mucor racemosus*, *Pseudallescheria boydii*, and *Issatchenkia orientalis*. In these experiments, the most active compounds were the *S*-benzylcysteine sulfoxide petiveriin (Fig. 3) and especially benzyldisulfonic acid (Fig. 3), the most active compound (44).

Ajoene (Fig. 3), a dimerization derivative of allicin and the most stable constituent of garlic (42), possesses also a strong antifungal activity, associated to phosphatidylcholine biosynthesis inhibition (leading to shortage in membrane

precursors), alterations in the fungal cell membrane structure, glutathione oxidase inhibition (causing oxygen radicals increase), and binding to sulfhydryl groups of fungal proteins (at L-cysteine residues) (34).

CONCLUSIONS

Food additives are used to diminish microbial contamination, which may be associated with spoilage (due to fungi and other microorganisms), intoxications (due to mycotoxins production in the stored food matrix) or foodborne diseases (due to pathogenic fungi). However, chemical additives or physical control techniques (such as thermal treatments) may alter the nutritional or organoleptic properties of a given food, or be perceived as nonhealthy processing treatments by consumers. Therefore, at industrial level, plant metabolites such as terpenoids, polyphenols, and thiols are gaining increasing importance as food additives. The antifungal activities for some of these plant nutraceuticals have been tested *in vitro* in the stored food matrix, shedding natural light in the complex field of food additives and preservatives. Known antifungal mechanisms of action for these phytochemicals include inhibition of cellular membrane biosynthesis or spore germination, alteration of cellular membrane permeability, or reactivity with protein thiol-moieties, all of which cause reduction in fungal fitness, cell death, or both. Hence, these phytochemicals are promising and should be further studied for possible applications in the food industry.

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REFERENCES

- Aguirre-Joya, J. A., L. Pastrana-Castro, D. Nieto-Oropeza, J. Ventura-Sobrevilla, R. Rojas-Molina, and C. N. Aguilar. 2018. The physicochemical, antifungal and antioxidant properties of a mixed polyphenol based bioactive film. *Heliyon* 4:e00942.
- Ahmad, A., A. Khan, F. Akhtar, S. Yousuf, I. Xess, L. A. Khan, and N. Manzoor. 2011. Fungicidal activity of thymol and carvacrol by disrupting ergosterol biosynthesis and membrane integrity against *Candida*. *Eur. J. Clin. Microbiol. Infect. Dis.* 30:41–50.
- Amagase, H., B. L. Petesch, H. Matsuura, S. Kasuga, and Y. Itakura. 2001. Intake of garlic and its bioactive components. *J. Nutr.* 131:955S–962S.
- An, P., X. Yang, J. Yu, J. Qi, X. Ren, and Q. Kong. 2019. α -Terpineol and terpene-4-ol, the critical components of tea tree oil, exert antifungal activities *in vitro* and *in vivo* against *Aspergillus niger* in grapes by inducing morphous damage and metabolic changes of fungus. *Food Control* 98:42–53.
- Arroyo-Esquivel, J., F. Sanchez, and L. A. Barboza. 2019. Infection model for analyzing biological control of coffee rust using bacterial anti-fungal compounds. *Math. Biosci.* 307:13–24.
- Baek, S. C., M. G. Kang, J. E. Park, J. P. Lee, H. Lee, H. W. Ryu, C. M. Park, D. Park, M. L. Cho, S. R. Oh, and H. Kim. 2019. Osthenol, a prenylated coumarin, as a monoamine oxidase A inhibitor with high selectivity. *Bioorganic Med. Chem. Lett.* 29:839–843.
- Bagiu, R. V., B. Vlaicu, and M. Butnariu. 2012. Chemical composition and *in vitro* antifungal activity screening of the *Allium ursinum* L. (Liliaceae). *Int. J. Mol. Sci.* 13:1426–1436.
- Beyki, M., S. Zhavah, S. T. Khalili, T. Rahmani-Cherati, A. Abollahi, M. Bayat, M. Tabatabaei, and A. Mohsenifar. 2014. Encapsulation of *Mentha piperita* essential oils in chitosan–cinnamic acid nanogel with enhanced antimicrobial activity against *Aspergillus flavus*. *Ind. Crops Prod.* 54:310–319.
- Castillo-Reyes, F., F. D. Hernández-Castillo, J. A. Clemente-Constantino, G. Gallegos-Morales, R. Rodríguez-Herrera, and C. N. Aguilar. 2015. *In vitro* antifungal activity of polyphenols-rich plant extracts against *Phytophthora cinnamomi* Rands. *Afr. J. Agric. Res.* 10:4554–4560.
- Costa, J., R. Rodríguez, E. Garcia-Cela, A. Medina, N. Magan, N. Lima, P. Battilani, and C. Santos. 2019. Overview of fungi and mycotoxin contamination in *Capsicum* pepper and in its derivatives. *Toxins* 11:27.
- Cushnie, T. P. T., and A. J. Lamb. 2005. Antimicrobial activity of flavonoids. *Int. J. Antimicrob. Agents* 26:343–356.
- Dammak, I., Z. Hamdi, S. Kammoun El Euch, H. Zemni, A. Mliki, M. Hassouna, and S. Lasram. 2019. Evaluation of antifungal and anti-ochratoxigenic activities of *Salvia officinalis*, *Lavandula dentata* and *Laurus nobilis* essential oils and a major monoterpene constituent 1,8-cineole against *Aspergillus carbonarius*. *Ind. Crops Prod.* 128:85–93.
- da Rocha Neto, A. C., M. Maraschin, and R. M. Di Piero. 2015. Antifungal activity of salicylic acid against *Penicillium expansum* and its possible mechanisms of action. *Int. J. Food Microbiol.* 215:64–70.
- de Silva, A. C., P. D. de Freitas Santos, J. T. do Prado Silva, F. V. Leimann, L. Bracht, and O. H. Gonçalves. 2018. Impact of curcumin nanoformulation on its antimicrobial activity. *Trends Food Sci. Technol.* 72:74–82.
- de Oliveira Lima, M. I., A. C. Araújo de Medeiros, K. V. Souza Silva, G. N. Cardoso, E. de Oliveira Lima, and F. de Oliveira Pereira. 2017. Investigation of the antifungal potential of linalool against clinical isolates of fluconazole resistant *Trichophyton rubrum*. *J. Mycol. Med.* 27:195–202.
- Diénez, F., M. Santos, C. Parra, M. J. Navarro, R. Blanco, and F. J. Gea. 2018. Screening of antifungal activity of 12 essential oils against eight pathogenic fungi of vegetables and mushroom. *Lett. Appl. Microbiol.* 67:400–410.
- Dijksterhuis, J. 2019. Fungal spores: highly variable and stress-resistant vehicles for distribution and spoilage. *Food Microbiol.* 81:2–11.
- Doke, S. K., J. S. Raut, S. Dhawale, and S. M. Karuppaiyil. 2014. Sensitization of *Candida albicans* biofilms to fluconazole by terpenoids of plant origin. *J. Gen. Appl. Microbiol.* 60:163–168.
- Faustino, M. V., D. C. G. A. Pinto, M. J. Gonçalves, L. Salgueiro, P. Silveira, and A. M. S. Silva. 2018. *Calendula* L. species polyphenolic profile and *in vitro* antifungal activity. *J. Funct. Foods* 45:254–267.
- Favaron, F., M. Lucchetta, S. Odorizzi, A. T. Pais da Cunha, and L. Sella. 2009. The role of grape polyphenols on trans-resveratrol activity against *Botrytis cinerea* and of fungal laccase on the solubility of putative grape PR proteins. *J. Plant Pathol.* 91:579–588.
- Fikry, S., N. Khalil, and O. Salama. 2019. Chemical profiling, biostatic and biocidal dynamics of *Origanum vulgare* L. essential oil. *AMB Express* 9:41.
- Filho, A. A. O., H. B. D. Oliveira, J. P. de Sousa, D. R. P. Meireles, G. L. de Azevedo Maia, J. M. B. Filho, J. P. de Siqueira Júnior, and E. de Oliveira Lima. 2016. *In vitro* anti-*Candida* activity and mechanism of action of the flavonoid isolated from *Praxelis clematidea* against *Candida albicans* species. *J. Appl. Pharm. Sci.* 6:066–069.
- Foss, S. R., C. V. Nakamura, T. Ueda-Nakamura, D. A. G. Cortez, E. H. Endo, and B. P. Dias Filho. 2014. Antifungal activity of pomegranate peel extract and isolated compound punicalagin against dermatophytes. *Ann. Clin. Microbiol. Antimicrob.* 13:32.
- Fratianni, F., R. Riccardi, P. Spigno, M. N. Ombra, A. Cozzolino, P. Tremonte, R. Coppola, and F. Nazzaro. 2016. Biochemical characterization and antimicrobial and antifungal activity of two endemic varieties of garlic (*Allium sativum* L.) of the Campania region, southern Italy. *J. Med. Food* 19:686–691.

25. Freires, I. A., V. C. P. P. Queiroz, V. F. Furlletti, M. Ikegaki, S. M. de Alencar, M. C. T. Duarte, and P. L. Rosalen. 2016. Chemical composition and antifungal potential of Brazilian propolis against *Candida* spp. *J. Mycol. Med.* 26:122–132.
26. Friedman, M. 2007. Overview of antibacterial, antitoxin, antiviral, and antifungal activities of tea flavonoids and teas. *Mol. Nutr. Food Res.* 51:116–134.
27. Gándara-Ledezma, A., C. Corrales-Maldonado, M. Rivera-Domínguez, M. Á. Martínez-Téllez, and I. Vargas-Arispuro. 2015. Post-harvest control of gray mold in table grapes using volatile sulfur compounds from *Allium sativum*. *J. Sci. Food Agric.* 95:497–503.
28. Gao, T., H. Zhou, W. Zhou, L. Hu, J. Chen, and Z. Shi. 2016. The fungicidal activity of thymol against *Fusarium graminearum* via inducing lipid peroxidation and disrupting ergosterol biosynthesis. *Molecules* 21:1–13.
29. Garcia, D., A. J. Ramos, V. Sanchis, and S. Marín. 2013. Equisetum arvense hydro-alcoholic extract: phenolic composition and antifungal and antimycotoxigenic effect against *Aspergillus flavus* and *Fusarium verticillioides* in stored maize. *J. Sci. Food Agric.* 93:2248–2253.
30. Giamperi, L., A. E. A. Bucchini, D. Ricci, F. Papa, and F. Maggi. 2019. Essential oil of *Achillea ligustica* (Asteraceae) as an antifungal agent against phytopathogenic fungi. *Nat. Prod. Commun.* 13:1934578X1801300.
31. Gómez-Estaca, J., M. P. Balaguer, G. López-Carballo, R. Gavara, and P. Hernández-Muñoz. 2017. Improving antioxidant and antimicrobial properties of curcumin by means of encapsulation in gelatin through electrohydrodynamic atomization. *Food Hydrocoll.* 70:313–320.
32. Gurău, F., S. Baldoni, F. Prattichizzo, E. Espinosa, F. Amenta, A. D. Procopio, M. C. Albertini, M. Bonafè, and F. Olivieri. 2018. Antisenescence compounds: a potential nutraceutical approach to healthy aging. *Ageing Res. Rev.* 46:14–31.
33. Han, J. W., M. Oh, Y. J. Lee, J. Choi, G. J. Choi, and H. Kim. 2018. Crinipellins A and I, two diterpenoids from the basidiomycete fungus *Crinipellis rhizomaticola*, as potential natural fungicides. *Molecules* 23:2377.
34. Hasan, M., M. Iqbal, and M. Uddin. 2016. Antibacterial and antifungal activity of *Litsea monopetala* leaves on selected pathogenic strains. *Eur. J. Med. Plants* 12:1–8.
35. Heleno, S. A., I. C. F. R. Ferreira, A. Ćirić, J. Glamočlija, A. Martins, M. J. R. P. Queiroz, and M. Soković. 2014. *Coprinopsis atramentaria* extract, its organic acids, and synthesized glucuronated and methylated derivatives as antibacterial and antifungal agents. *Food Funct.* 5:2521–2528.
36. Hilmioglu-Polat, S., S. Seyedmousavi, M. Ilkit, M. T. Hedayati, R. Inci, E. Tumbay, and D. W. Denning. 2018. Estimated burden of serious human fungal diseases in Turkey. *Mycoses* 62:22–31.
37. Hossain, F., P. Follett, K. Dang Vu, M. Harich, S. Salmieri, and M. Lacroix. 2016. Evidence for synergistic activity of plant-derived essential oils against fungal pathogens of food. *Food Microbiol.* 53:24–30.
38. Huang, L., J. Zhang, T. Song, L. Yuan, J. Zhou, H. Yin, T. He, W. Gao, Y. Sun, X. Hu, and H. Huang. 2016. Antifungal curcumin promotes chitin accumulation associated with decreased virulence of *Sporothrix schenckii*. *Int. Immunopharmacol.* 34:263–270.
39. Hyldgaard, M., T. Mygind, and R. L. Meyer. 2012. Essential oils in food preservation: mode of action, synergies, and interactions with food matrix components. *Front. Microbiol.* 3:1–24.
40. Iboudo, O., S. Bonzi, I. Tapsoba, I. Somda, and Y. L. Bonzi-Coulibaly. 2016. In vitro antifungal activity of flavonoid diglycosides of *Mentha piperita* and their oxime derivatives against two cereals fungi. *Comptes Rendus Chim.* 19:857–862.
41. Kanwal, Q., I. Hussain, H. Latif Siddiqui, and A. Javaid. 2010. Antifungal activity of flavonoids isolated from mango (*Mangifera indica* L.) leaves. *Nat. Prod. Res.* 24:1907–1914.
42. Khalil, O. A. K., O. M. M. De Faria Oliveira, J. C. R. Velloso, A. U. De Quadros, L. M. Dalposso, T. K. Karam, R. M. Mainardes, and N. M. Khalil. 2012. Curcumin antifungal and antioxidant activities are increased in the presence of ascorbic acid. *Food Chem.* 133:1001–1005.
43. Khorshed Alam, M., M. Obydul Hoq, M. Shahab Uddin, and C. Md Khorshed Alam. 2016. Medicinal plant *Allium sativum* = a review. *J. Med. Plants Stud.* 72:72–79.
44. Kim, S., R. Kubec, and R. A. Musah. 2006. Antibacterial and antifungal activity of sulfur-containing compounds from *Petiveria alliacea* L. *J. Ethnopharmacol.* 104:188–192.
45. Klewicka, E., M. Sójka, R. Klewicki, K. Kolodziejczyk, L. Lipińska, and A. Nowak. 2016. Ellagitannins from raspberry (*Rubus idaeus* L.) fruit as natural inhibitors of *Geotrichum candidum*. *Molecules* 21:E908.
46. Lee, J., and D. G. Lee. 2015. Novel antifungal mechanism of resveratrol: apoptosis inducer in *Candida albicans*. *Curr. Microbiol.* 70:383–389.
47. Leontiev, R., N. Hohaus, C. Jacob, M. C. H. Gruhlke, and A. J. Slusarenko. 2018. A comparison of the antibacterial and antifungal activities of thiosulfinate analogues of allicin. *Sci. Rep.* 8:1–19.
48. Li, K. M., X. Dong, Y. N. Ma, Z. H. Wu, Y. M. Yan, and Y. X. Cheng. 2019. Antifungal coumarins and lignans from *Artemisia annua*. *Fitoterapia* 134:323–328.
49. Lipińska, L., E. Klewicka, and M. Sójka. 2014. The structure, occurrence and biological activity of ellagitannins: a general review. *Acta Sci. Pol. Technol. Aliment.* 13:289–299.
50. Liu, M., D. R. Katerere, A. I. Gray, and V. Seidel. 2009. Phytochemical and antifungal studies on *Terminalia mollis* and *Terminalia brachystemma*. *Fitoterapia* 80:369–373.
51. Luo, D.-Q., F. Wang, X.-Y. Bian, and J.-K. Liu. 2005. Rufuslactone, a new antifungal sesquiterpene from the fruiting bodies of the basidiomycete *Lactarius rufus*. *J. Antibiot.* 58:456–459.
52. Marchese, A., R. Barbieri, A. Sanches-Silva, M. Daglia, S. F. Nabavi, N. J. Jafari, M. Izadi, M. Ajami, and S. M. Nabavi. 2016. Antifungal and antibacterial activities of allicin: a review. *Trends Food Sci. Technol.* 52:49–56.
53. Martins, C. V. B., D. L. da Silva, A. T. M. Neres, T. F. F. Magalhães, G. A. Watanabe, L. V. Modolo, A. A. Sabino, A. de Fátima, and M. A. de Resende. 2009. Curcumin as a promising antifungal of clinical interest. *J. Antimicrob. Chemother.* 63:337–339.
54. Martins, F. J., M. Senra, C. A. Caneschi, J. A. dos Santos, A. D. da Silva, and N. R. B. Raposo. 2019. New group of azastilbene analogs of resveratrol: synthesis, anticandidal activity and toxicity evaluation. *J. King Saud Univ. Sci.* 31:158–163.
55. Meragelman, T. L., K. D. Tucker, T. G. McCloud, J. H. Cardellina, and R. H. Shoemaker. 2005. Antifungal flavonoids from *Hildegardia barteri*. *J. Nat. Prod.* 68:1790–1792.
56. Mohammadi, A., M. Hashemi, and S. M. Hosseini. 2015. Comparison of antifungal activities of various essential oils on the *Phytophthora drechsleri*, the causal agent of fruit decay. *Iran. J. Microbiol.* 7:31–37.
57. Montagner, C., S. M. de Souza, C. Groposoa, F. Delle Monache, E. F. A. Smânia, and A. Smânia. 2004. Antifungal activity of coumarins. *Z. Naturforsch. B J. Chem. Sci.* 63:21–28.
58. Nair, M. S., A. Saxena, and C. Kaur. 2018. Characterization and antifungal activity of pomegranate peel extract and its use in polysaccharide-based edible coatings to extend the shelf-life of *Capsicum* (*Capsicum annum* L.). *Food Bioprocess Technol.* 11:1317–1327.
59. Navarro-García, V. M., G. Rojas, M. Avilés, M. Fuentes, and G. Zepeda. 2011. In vitro antifungal activity of coumarin extracted from *Loeselia mexicana* brand. *Mycoses* 54:e569–e5671.
60. Neelofar, K., S. Shreaz, B. Rimple, S. Muralidhar, M. Nikhat, and L. A. Khan. 2011. Curcumin as a promising anticandidal of clinical interest. *Can. J. Microbiol.* 57:204–210.
61. Nguyen, D. M. C., D. J. Seo, H. B. Lee, I. S. Kim, K. Y. Kim, R. D. Park, and W. J. Jung. 2013. Antifungal activity of gallic acid purified from *Terminalia nigrovenulosa* bark against *Fusarium solani*. *Microb. Pathog.* 56:8–15.
62. Nikolić, M., D. Stojković, J. Glamočlija, A. Ćirić, T. Marković, M. Smiljković, and M. Soković. 2015. Could essential oils of green and black pepper be used as food preservatives? *J. Food Sci. Technol.* 52:6565–673.

63. Ota, C., C. Unterkircher, V. Fantinato, and M. T. Shimizu. 2001. Antifungal activity of propolis on different species of *Candida*. *Mycoses* 44:375–378.
64. Pagnussatt, F. A., E. M. Del Ponte, J. Garda-Buffon, and E. Badiale-Furlong. 2014. Inhibition of *Fusarium graminearum* growth and mycotoxin production by phenolic extract from *Spirulina* sp. *Pestic. Biochem. Physiol.* 108:21–26.
65. Park, J. E., J. E. Seo, J. Y. Lee, and H. Kwon. 2015. Distribution of seven N-nitrosamines in food. *Toxicol. Res.* 31:279–288.
66. Patel, S. 2015. Plant essential oils and allied volatile fractions as multifunctional additives in meat and fish-based food products: a review. *Food Addit. Contam. Part A Chem. Anal. Control Expo. Risk Assess.* 32:1049–1064.
67. Pawlowska, A. M., E. Zannini, A. Coffey, and E. K. Arendt. 2012. “Green preservatives”: combating fungi in the food and feed industry by applying antifungal lactic acid bacteria. *Adv. Food Nutr. Res.* 66:217–238.
68. Peralta, M. A., M. A. Da Silva, M. G. Ortega, J. L. Cabrera, and M. G. Paraje. 2015. Antifungal activity of a prenylated flavonoid from *Dalea elegans* against *Candida albicans* biofilms. *Phytomedicine* 22:975–980.
69. Pisoschi, A. M., A. Pop, C. Georgescu, V. Turcuş, N. K. Olah, and E. Mathe. 2018. An overview of natural antimicrobials role in food. *Eur. J. Med. Chem.* 143:922–935.
70. Quéro, L., V. Girard, A. Pawtowski, S. Tréguer, A. Weill, S. Arend, B. Cellière, S. Polsinelli, V. Monnin, A. Van Belkum, V. Vasseur, P. Nodet, and J. Mounier. 2018. Development and application of MALDI-TOF MS for identification of food spoilage fungi. *Food Microbiol.* 81:76–88.
71. Raimundo, K. F., W. de C. Bortolucci, J. Glamočlija, M. Soković, J. E. Gonçalves, G. A. Linde, N. B. Colauto, and Z. C. Gazim. 2018. Antifungal activity of *Gallesia integrifolia* fruit essential oil. *Braz. J. Microbiol.* 49:229–235.
72. Ramón-Sierra, J., E. Peraza-López, R. Rodríguez-Borges, A. Yam-Puc, T. Madera-Santana, and E. Ortiz-Vázquez. 2019. Partial characterization of ethanolic extract of *Melipona beecheii* propolis and in vitro evaluation of its antifungal activity. *Rev. Bras. Farmacogn.* 29:319–324.
73. Raut, J. S., R. B. Shinde, N. M. Chauhan, and S. M. Karuppaiyl. 2013. Terpenoids of plant origin inhibit morphogenesis, adhesion, and biofilm formation by *Candida albicans*. *Biofouling* 29:87–96.
74. Ribes, S., A. Fuentes, and J. M. Barat. 2019. Effect of oregano (*Origanum vulgare* L. ssp. *hirtum*) and clove (*Eugenia* spp.) nanoemulsions on *Zygosaccharomyces bailii* survival in salad dressings. *Food Chem.* 295:630–636.
75. Ribes, S., A. Fuentes, P. Talens, and J. M. Barat. 2018. Prevention of fungal spoilage in food products using natural compounds: a review. *Crit. Rev. Food Sci. Nutr.* 58:2002–2016.
76. Rigacci, S., and M. Stefani. 2016. Nutraceutical properties of olive oil polyphenols. An itinerary from cultured cells through animal models to humans. *Int. J. Mol. Sci.* 17:1–28.
77. Roblin, G., S. Octave, M. Faucher, P. Fleurat-Lessard, and J. M. Berjeaud. 2018. Cysteine: a multifaceted amino acid involved in signaling, plant resistance and antifungal development. *Plant Physiol. Biochem.* 129:77–89.
78. Rongai, D., P. Pulcini, B. Pesce, and F. Milano. 2017. Antifungal activity of pomegranate peel extract against fusarium wilt of tomato. *Eur. J. Plant Pathol.* 147:229–238.
79. Santamarina, M. P., J. Roselló, F. Sempere, S. Giménez, and M. A. Blázquez. 2015. Commercial *Origanum compactum* Benth. and *Cinnamomum zeylanicum* Blume essential oils against natural mycoflora in Valencia rice. *Nat. Prod. Res.* 29:2215–2218.
80. Sarikurku, C., G. Zengin, M. Oskay, S. Uysal, R. Ceylan, and A. Aktumsek. 2015. Composition, antioxidant, antimicrobial and enzyme inhibition activities of two *Origanum vulgare* subspecies (subsp. *vulgare* and subsp. *hirtum*) essential oils. *Ind. Crops Prod.* 70:178–184.
81. Shuping, D. S., and J. Eloff. 2017. The use of plants to protect plants and food against fungal pathogens: a review. *Afr. J. Tradit. Complement. Altern. Med.* 14:120–127.
82. Silva, T. C., A. L. de S. A. Zara, F. A. da S. Sá, M. T. F. Bara, R. I. de Ávila, C. R. Costa, M. C. Valadares, A. S. Dos Santos, V. A. Q. Freitas, and M. D. R. R. Silva. 2018. Antifungal potential of punicalagin against *Cryptococcus neoformans* species complex. *Rev. Inst. Med. Trop. Sao Paulo* 60:1–6.
83. Song, P. P., J. Zhao, Z. L. Liu, Y. B. Duan, Y. P. Hou, C. Q. Zhao, M. Wu, M. Wei, N. H. Wang, Y. Lv, and Z. J. Han. 2017. Evaluation of antifungal activities and structure–activity relationships of coumarin derivatives. *Pest Manag. Sci.* 73:94–101.
84. Sousa, J., A. Costa, M. Leite, F. Guerra, V. Silva, C. Menezes, F. Pereira, and E. Lima. 2015. Antifungal activity of citral by disruption of ergosterol biosynthesis in fluconazole resistant *Candida tropicalis*. *Int. J. Trop. Dis. Heal.* 11:1–11.
85. Stappen, I., N. Tabanca, A. Ali, J. Wanner, B. Lal, V. Jaitak, D. E. Wedge, V. K. Kaul, E. Schmidt, and L. Jirovetz. 2018. Antifungal and repellent activities of the essential oils from three aromatic herbs from western Himalaya. *Open Chem.* 16:306–316.
86. Stepień, Ł., K. Gromadzka, J. Chelkowski, A. Basińska-Barczak, and J. Lalak-Kańczugowska. 2019. Diversity and mycotoxin production by *Fusarium temperatum* and *Fusarium subglutinans* as causal agents of pre-harvest *Fusarium* maize ear rot in Poland. *J. Appl. Genet.* 60:113–121.
87. Tampieri, M. P., R. Galuppi, F. Macchioni, M. S. Carelle, L. Falcioni, P. L. Cioni, and I. Morelli. 2005. The inhibition of *Candida albicans* by selected essential oils and their major components. *Mycopathologia* 159:339–345.
88. Tyagi, A. K., D. Bukvicki, D. Gottardi, G. Tabanelli, C. Montanari, A. Malik, and M. E. Guerzoni. 2014. Eucalyptus essential oil as a natural food preservative: in vivo and in vitro antiyeast potential. *Biomed Res. Int.* 2014:969143.
89. U.S. Food and Drug Administration. 2018. Code of Federal Regulations (CFR). Title 21—Food and drugs, chap. I—Food and Drug Administration, Department of Health and Human Services, subchap. B—Food for human consumption (continued), part 182—Substances generally recognized as safe (GRAS). U.S. Food and Drug Administration, Washington, DC.
90. Venkatesh, H. N., T. N. Sudharshana, R. U. Abhishek, S. Thippeswamy, K. Manjunath, and D. C. Mohana. 2017. Antifungal and antimycotoxigenic properties of chemically characterised essential oil of *Boswellia serrata* Roxb. ex Colebr. *Int. J. Food Prop.* 20:1856–1868.
91. Vestergaard, M., and H. Ingmer. 2019. Antibacterial and antifungal properties of resveratrol. *Int. J. Antimicrob. Agents* 53:716–723.
92. Wang, H., Z. Yang, G. Ying, M. Yang, Y. Nian, F. Wei, and W. Kong. 2018. Antifungal evaluation of plant essential oils and their major components against toxigenic fungi. *Ind. Crops Prod.* 120:180–186.
93. Wang, L., Q. Zhang, Z. Yan, Y. Tan, R. Zhu, D. Yu, H. Yang, and A. Wu. 2018. Occurrence and quantitative risk assessment of twelve mycotoxins in eggs and chicken tissues in China. *Toxins* 10:1–18.
94. Yamaguchi, M. U., F. P. Garcia, D. A. G. Cortez, T. Ueda-Nakamura, B. P. D. Filho, and C. V. Nakamura. 2011. Antifungal effects of ellagitannin isolated from leaves of *Ocotea odorifera* (Lauraceae). *Antonie van Leeuwenhoek Int. J. Gen. Mol. Microbiol.* 99:507–514.
95. Yamawaki, C., M. Oyama, Y. Yamaguchi, A. Ogita, T. Tanaka, and K. I. Fujita. 2019. Curcumin potentiates the fungicidal effect of dodecanol by inhibiting drug efflux in wild-type budding yeast. *Lett. Appl. Microbiol.* 68:17–23.
96. Yang, Y., J. Jiang, L. Qimei, X. Yan, J. Zhao, H. Yuan, Z. Qin, and M. Wang. 2010. The fungicidal terpenoids and essential oil from *Litsea cubeba* in Tibet. *Molecules* 15:7075–7082.
97. Zheng, S., G. Jing, X. Wang, Q. Ouyang, L. Jia, and N. Tao. 2015. Citral exerts its antifungal activity against *Penicillium digitatum* by affecting the mitochondrial morphology and function. *Food Chem.* 178:76–81.
98. Zore, G. B., A. D. Thakre, S. Jadhav, and S. M. Karuppaiyl. 2011. Terpenoids inhibit *Candida albicans* growth by affecting membrane integrity and arrest of cell cycle. *Phytomedicine* 18:1181–1190.