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MINI-REVIEW

The potential role of plant secondary metabolites on antifungal and immunomodulatory effect

Xue Zhou[1] · Meng Zeng[1] · Fujiao Huang[1] · Gang Qin[2] · Zhangyong Song[1,3] · Fangyan Liu[1]

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Abstract

With the widespread use of antibiotic drugs worldwide and the global increase in the number of immunodeficient patients, fungal infections have become a serious threat to global public health security. Moreover, the evolution of fungal resistance to existing antifungal drugs is on the rise. To address these issues, the development of new antifungal drugs or fungal inhibitors needs to be targeted urgently. Plant secondary metabolites are characterized by a wide variety of chemical structures, low price, high availability, high antimicrobial activity, and few side effects. Therefore, plant secondary metabolites may be important resources for the identification and development of novel antifungal drugs. However, there are few studies to summarize those contents. In this review, the antifungal modes of action of plant secondary metabolites toward different types of fungi and fungal infections are covered, as well as highlighting immunomodulatory effects on the human body. This review of the literature should lay the foundation for research into new antifungal drugs and the discovery of new targets.

Key points

- *Immunocompromised patients who are infected the drug-resistant fungi are increasing.*
- *Plant secondary metabolites toward various fungal targets are covered.*
- *Plant secondary metabolites with immunomodulatory effect are verified in vivo.*

Keywords Plant secondary metabolites · Fungal infection · Immunoregulation effect · Antifungal mechanism

✉ Zhangyong Song
szy83529@163.com

✉ Fangyan Liu
liufangyan1989@163.com

Xue Zhou
zxlovebb0720@163.com

Meng Zeng
zengmeng19881026@163.com

Fujiao Huang
huang111209@163.com

Gang Qin
qin-lzm@163.com

1 School of Basic Medical Sciences, Southwest Medical University, Luzhou 646000, People's Republic of China

2 Department of Otolaryngology Head and Neck Surgery, The Affiliated Hospital of Southwest Medical University, Luzhou 646000, China

3 Molecular Biotechnology Platform, Public Center of Experimental Technology, Southwest Medical University, Luzhou 646000, People's Republic of China

Introduction

Fungal infections are characterized by high morbidity and mortality. Every year, at least 1.5 million people are killed, and the lives of more than one billion people are affected by fungal infections (Bongomin et al. 2017). In recent years, the frequency of fungal infections has been increasing rapidly. Fungal infections can be divided into superficial and deep infections. Deep fungal infections can cause invasive mycosis, which is an infectious disease caused by fungal invasion of subcutaneous tissues, mucous membranes, and internal organs. About 6 in 100,000 people are infected with invasive fungi each year, although only one-half of fatal cases are diagnosed prior to death (Dignani 2014). Therefore, the lack of timely diagnosis, and treatment, is one of the causes of the high mortality of invasive fungal infections (von Lilienfeld-Toal et al. 2019). At present, invasive fungal infections are mainly caused by species of *Aspergillus*, *Candida*, and *Cryptococcus* (Pathakumari et al. 2020), and echinomycin, flucytosine, polyenes, and triazoles are the drugs used most commonly for their treatment. Superficial fungal infections can lead to cutaneous mycosis and superficial mycosis, which are caused by pathogenic fungi parasitizing keratin tissues, such as hair, nails, and skin. Cutaneous mycosis is one of the most common superficial fungal infections, with an incidence of up to 25% (Havlickova et al. 2008). Cutaneous mycosis is also known as "ringworm." Ringworm infections are caused mainly by species of *Epidermophyton*, *Microsporum*, and *Trichophyton*, with the common skin ringworm infection in human being caused by *Trichophyton rubrum*. At present, topical drugs used to treat superficial fungal infections include allylamines, azoles, and griseofulvin (Ademe 2020; Khurana et al. 2019).

Because of the increased incidence of fungal infections, the limited range of antifungal drugs available in clinics, and the emergence of drug-resistant or multi-drug-resistant fungal strains, the successful treatment of patients with a fungal infection is a challenging issue. For example, multi-drug-resistant *Candida auris* has become one of the major threats to global public health security (Du et al. 2020). At the same time, with the emergence of azole-resistant *Aspergillus* strains, *Aspergillus* infections have gradually become one of the global public health concerns (Zhang et al. 2021b). During the coronavirus disease 2019 (COVID-19) pandemic, it was found that the number of patients with COVID-19 complicated by *Aspergillus* infection was as high as 23.3% (Lai and Yu 2021). In addition, drug-resistant fungal strains are not limited to deep fungal infections, but are also rapidly increasing in association with superficial fungal infections (Saunte et al. 2019). It had found that the incidence of terbinafine-resistant superficial fungal strains ranged from 16 to 77% in India (Singh et al. 2020). Therefore, in order to solve these problems, efforts should be made to develop new antifungal drugs or fungal inhibitors.

In Chinese literature, from Shen Nung, who tested hundreds of grasses, to Li Shizhen's "Compendium of Materia Medica," plants and their derivatives have been successfully used in practice in medicine. For instance, the development of the antimalarial drugs quinine and artemisinin from plants are well-established examples (Achan et al. 2011; Ma et al. 2020). Prescriptions of traditional herbal remedies are still used today, using various active compounds in preparations extracted from plants to treat a range of diseases. Plant secondary metabolites represent an enormous range of small molecular organic compounds developed during the long-term evolution of plants, which are generally not directly involved in plant survival, but which fulfill secondary roles, such as defense chemicals, attractant pigments and fragrances, and plant hormones or growth regulators (Erb and Kliebenstein 2020). At present, research on plant metabolites (primary and secondary) is increasing, although research on the antifungal properties of plant metabolites is still mainly focused on plant secondary metabolites (Mickymaray 2019). More than 200,000 different plant secondary metabolites have been isolated and identified. According to the biosynthetic pathways involved, plant secondary metabolites include nitrogenous organic substances (such as alkaloids, cyanogenic glucosides, and non-protein amino acids), phenolics and terpenoids, as well as other secondary metabolites such as essential oils (Loi et al. 2020). The successful development of drugs derived from plant secondary metabolites has resulted in better treatment of cardiovascular diseases, malignant tumors, and neurodegenerative diseases (Table 1).

Invasive pathogens often occur in people with compromised immunity (Xie et al. 2022). Therefore, antifungal agents could act by either having a direct antifungal (fungicidal or fungistatic) effect on pathogenic fungi or playing a role in upregulating a patient's immunity (Arastehfar et al. 2020; Lei et al. 2023, 2022). There is an urgent need to develop new antifungal drugs, drugs that help to increase the activity of existing antifungal drugs, or drugs with immunomodulatory effects on the host. Additionally, many plant secondary metabolites had been confirmed to show antifungal activity or greatly increase the antifungal action of existing antifungal drugs by synergistic action (Ganesan and Xu 2017; Loi et al. 2020). However, compared with investigations on bacterial infectious diseases of humans, there has been a few review about the role of plant extracts or their components in the treatment of fungal infections. Therefore, more attention needs to be paid to the treatment of fungal infections with plant preparations or individual plant secondary metabolites.

Antifungal mechanisms and immunomodulatory effects of existing antifungal drugs

Currently, antifungal targets have been identified for drugs that treat superficial or systemic fungal infections. Acrylamide targets the fungal enzyme squalene cyclooxylate and then blocks the synthesis of ergosterol, so that squalene accumulates on the cell membrane, increases the cell membrane brittleness, and leads to the rupture and death of fungal cells (Thapa et al. 2015). Although triazole drugs are the most widely used antifungal drugs, with low hepatorenal toxicity, there is widespread triazole resistance among pathogenic fungi. Triazole drugs mainly bind to 14-α-lanosterol demethylase, a key enzyme in ergosterol biosynthesis in fungal cell membranes, with binding causing inhibition of cell membrane synthesis, cell rupture, and death (Chen et al. 2022a). Polyenes, such as amphotericin B (AmB), were among the earliest antifungal drugs; even today, it is still the "gold standard" for the treatment of systemic fungal infections (Mahor et al. 2022). By acting on sterols of the phospholipid bilayer of fungal cell membranes, polyenes can

Table 1 Plant secondary metabolites in the prevention and treatment of diseases

Classification	Name of active compounds/ secondary metabolites	Prevention and treatment of diseases	Reference
Alkaloid	Berberine	Atherosclerosis, depression, diabetes, gastric cancer, lymphoma	Ma et al. (2022a); Qu et al. (2021); Ren et al. (2021); Zhang et al. (2021a); Zhang et al. (2020)
	Matrine	Acute myeloid leukemia, anti-oxidation, anti-inflammation, atherosclerosis, cervical cancer, diabetes, liver cancer	Guo et al. (2021); Liu et al. (2017); Wang et al. (2021b); Zhang et al. (2022a); Zhou et al. (2022)
	Neferine	Diabetes, hypertension, pulmonary hypertension	Wicha et al. (2020); Xiao et al. (2022); Zhang et al. (2018)
	Trigonelline	Atherosclerosis, diabetes	Anwar et al. (2018); Zhao et al. (2021)
	Vincristine	Breast cancer	Wang et al. (2017)
Phenolics	Curcumin	Anti-inflammation, breast cancer, endometriosis (endometrial cancer), rectal cancer	Jahanbakhshi et al. (2021); Moradi-Marjaneh et al. (2018); Wang et al. (2019b); Zhang et al. (2019)
	Ellagic acid	Anti-inflammation, esophageal squamous cell carcinoma, immunoregulation, pancreatic cancer	Cheng et al. (2017); Gu et al. (2014); Xu et al. (2020)
	Quercetin	Anti-inflammation, antioxidant, anti-aging, depression, liver cancer	Cui et al. (2022); Han et al. (2021); Lu et al. (2018); Tang et al. 2019; Wu et al. (2019)
	Rosmarinic acid	Antioxidant, anti-inflammatory, depression, liver cancer, ovarian cancer	Cao et al. (2016); Cui et al. (2022); Lim et al. (2020); Verma et al. (2022)
	Shogaol	Anti-inflammation, cervical cancer, leukemia, oral cancer	Annamalai and Suresh (2018); Han et al. (2017); Liu et al. (2013); Pei et al. (2021)
	Tea polyphenols	Antioxidant, atherosclerosis, cholangiocarcinoma, skin cancer	Kumar et al. (2012); Quezada-Fernandez et al. (2019); Wang et al. 2018; Zhu et al. (2021)
Terpenes	Andrographolide	Anti-inflammation, breast cancer, diabetes, rectal cancer	Burgos et al. (2020); Li et al. (2020a); Paul et al. (2021); Peng et al. (2018)
	Ganoderma triterpenes	Anti-inflammation, anti-tumor, antioxidant	Liu et al. (2015); Sliva et al. (2012); Wang et al. (2019a)
	Geraniol	Antioxidant, anti-inflammation, anti-tumor, cardiovascular disease	Jayachandran et al. (2015); Polo and de Bravo (2006); Wang et al. (2016)
	Paeoniflorin	Alzheimer's disease, anti-inflammation, antioxidant, immunoregulation	Kong et al. (2020); Wen et al. (2019); Zhang and Wei (2020)
	Radix Bupleuri	Anti-inflammation, atherosclerosis, liver cancer	Du et al. (2018); Jiang et al. (2020); Luo et al. (2020)
	Taxol	Breast cancer, lung cancer, ovarian cancer, peripheral arterial disease	Krawisz et al. (2021); Scribano et al. (2021); Weaver (2014); Wu et al. (2018)
Other secondary metabolites	*Citrus bergamia* essential oil	Degenerative diseases	Scuteri et al. (2019)
	Mastic oil	Anti-inflammation, antioxidant, colon cancer, lung adenocarcinoma	Ostovan et al. (2020); Serifi et al. (2019); Spyridopoulou et al. (2017)
	Rosemary essential oil	Degenerative neurological diseases, hypertension	Fernandez et al. (2014); Sasaki et al. (2021)

change the permeability of the cell membrane and generate water-soluble pores, thus leading to the loss of intracellular contents and resulting in fungal cell death. However, due to their potential liver and kidney toxicity, polyenes are used in clinical circumstances with caution (Carolus et al. 2020). Although the price of echinocandin drugs is high, the use of echinocandin drugs in clinical treatment is increasing due to their broad spectrum, low toxicity, and high efficiency. The echinocandin drugs (large lipoprotein molecules) target and non-competitively inhibit activity of the catalytic subunit of β-1,3-D-glucan synthase, encoded by *fks* genes, causing interference with the fungal cell β-1,3-D-glucan synthesis, and resulting in fungal cell wall permeability changes, leading to cell lysis and death (Campoy and Adrio 2017). The drug 5-fluorocytosine exhibits antifungal activity by disrupting fungal DNA and protein synthesis. As mammalian cells lack cytosine deaminase in the antimicrobial pathway, this drug does not have a direct toxic effect on mammals (Delma et al. 2021). Unfortunately, because of the widespread drug-resistant in pathogenic fungi, the use of 5-flucytosine has been greatly reduced. It is only recommended for the treatment of lower urinary tract infections caused by *Candida* (Pappas et al. 2016). However, it has become one of the most reliable treatments for cryptococcal meningitis and complex *Candida* infections in combination with AmB (Perfect et al. 2010).

Following fungal infection, the efficacy of a drug treatment in vivo is influenced by the interaction between the body's autoimmune response and antifungal activity of the drug. In addition to their direct antifungal effects, some antifungal agents also have immunomodulatory effects and thus play a therapeutic role in both pathogen killing and host immune system regulation. Azoles are the most cost-effective drugs for antifungal prophylaxis for immunocompromised patients. For example, itraconazole exerted an anti-inflammatory effect by inhibiting *p*-glycoprotein activity in an acute fungal sinusitis with immune dysregulation in Th2-related epithelial cells. The *p*-glycoprotein activity is positively related to inflammation in primary human sinus epithelial cells. Therefore, itraconazole treatment has a good anti-inflammatory effect and contributes to reducing the incidence of reoperation in patients with acute fungal sinusitis (Lam et al. 2015). Furthermore, in the mouse model of keratoplasty, the infiltration of inflammatory cells in the corneal tissue of the itraconazole treatment group was significantly improved, compared with the phosphate-buffered saline negative control group, and the expression levels of the tumor necrosis factor-alpha (*TNF-α*) and interleukin-6 (*IL-6*) genes were also significantly decreased (Cho et al. 2017). In addition, posaconazole is effective at preventing invasive fungal infection in patients with severe graft-versus-host disease reaction (Furuno et al. 2018). Furthermore, fluconazole (FLC) can activate macrophages through the Toll-like receptor 2 (TLR2)/nuclear factor kappaB (NF-κB) pathway. It could promote the release of TNF-α, interferon-gamma (IFN-γ), and IL-1β and facilitate the achievement of antifungal effects. The production of TNF-α in THP-1 cells, stimulated by *Aspergillus fumigatus* conidia, decreased after voriconazole treatment (Choi et al. 2010). In the situation with polyene treatment, it had been found that AmB treatment increased the expression of the genes encoding IL-1β and IL-20 and decreased the expression of IL-10, IL-2, and IL-3 in human monocytes during response to *A. fumigatus* (Simitsopoulou et al. 2011). In addition, AmB rapidly activates platelets to against *Aspergillus* or *Mucor* infection (Carolus et al. 2020). Further investigation found that AmB treatment induced the secretion of IL-1β and IL-18 and the expression of inflammasome pathway genes (André et al. 2020). It has also been confirmed that AmB could activate immune cells through action on the TLR1/TLR2 and CD14 proteins and, at the same time, form an inflammatory signaling cascade through myeloid differentiation factor 88 (Myd88) and the NF-κB signaling pathway. This activity could promote the release of a number of pro-inflammatory cytokines (Razonable et al. 2005). In addition, intravenous administration of AmB could enhance the phagocytic activity of macrophages and antifungal ability to *A. fumigatus* infection (Nivoix et al. 2020). Among echinocandin drugs, micafungin has also been reported as a fungal prophylactic for bone marrow transplantation, HIV/AIDS, autologous hematopoietic stem cell transplantation, and neutropenia patients (Kim et al. 2022). For example, caspofungin significantly inhibited the release of pro-inflammatory cytokines, such as TNF-α in THP-1 cells (Itoh et al. 2021). At the same time, micafungin may condition THP-1 cells toward an inflammatory response by TLR2/TLR4 recruitment (Simitsopoulou et al. 2018); what is more, micafungin exerts an anti-inflammatory effect by reducing TNF-α concentrations and increasing IL-10 levels in aspergillosis (Moretti et al. 2014). Further investigation confirmed that inhibiting spleen tyrosine kinase (Syk) and its downstream signaling molecules, NF-κB and p38 protein kinase (p38), lead to the decreased secretion of pro-inflammatory factors and chemokines in THP-1 cells (Itoh et al. 2021). Whether antifungal drugs promote or suppress inflammation is still controversial, but there is no doubt that good antifungal drugs are often not limited to suppressing or killing fungi, but also play a role in regulating host immune system function.

Antifungal mechanism and immunomodulatory effects of terpenoids

Terpenoids, also known as isoprenoid compounds, are synthesized via the mevalonate pathway in the cytoplasm and the deoxyxylulose-5-phosphate pathway in plastids. More than 80,000 terpenoids are known to exist across various plant species (Rudolf et al. 2021). Terpenoids include compounds with the 5-C isoprene unit as the basic structural unit and their derivatives. The molecular formula is $(C_5H_8)_n$, with *n* being the number of connected isoprene units. Based on the number of carbon atoms on the skeleton, terpenoids can be divided into monoterpenoids, sesquiterpenoids, diterpenoids, triterpenoids, tetraterpenoids, and polyterpenoids (Yazaki et al. 2017). A wide range of biological functions, such as antibacterial, antifungal, anticancer, anti-inflammatory, analgesic, and food preservative, have been reported (Balahbib et al. 2021; Pandey et al. 2016).

With respect to antifungal activity, investigations have found that carvacrol, from plants of the *Lamiaceae* family, has an antifungal action similar to FLC, which inhibits fungal ergosterol synthesis, destroys the fungal cell membrane integrity, and then promotes the dissolution and death of fungal cells (Ahmad et al. 2011). Kaurene, isolated from members of the *Asteraceae* family, has good anti-cluster induction activity against *C. albicans* (Dal Piaz et al. 2018). The upregulated expression of the terpene synthase gene *OsTPS19* in rice can promote the production of limonene and enhance its defense against *Aspergillus oryzae* infection (Chen et al. 2018). Meanwhile, limonene can induce *C. albicans* apoptosis via induction of fungal cell wall/membrane destruction, oxidative and nucleolar stress, DNA damage, and the metacaspase-dependent pathway (Thakre et al. 2018). In addition, limonene showed significant antifungal activity against *A. fumigatus*, *Cryptococcus neoformans*, *T. rubrum*, and *T. mentagrophytes* (Pinto et al. 2017). Citronellal can inhibit the growth of *C. albicans* by destroying the cell membrane integrity, inhibiting biofilm formation, and blocking the fungal cell cycle (Trindade et al. 2022; Zore et al. 2011). What is more, citronellal can downregulate expression of the *erg3* gene to inhibit the transformation of lanosterol into ergosterol, inhibiting the growth of *Penicillium* (OuYang et al. 2021). Moreover, the combination of carvone and AmB greatly increased the inhibition of the growth rate of *C. albicans* (O'Brien et al. 2019). In addition, geraniol, widely distributed in geranium, rose, bee-sweet mint, and other plant species, could inhibit *C. albicans* from forming pseudomycelia and chlamydia spores and increased fungal cell membrane permeability, leading to intracellular potassium outflow (Leite et al. 2015). At the same time, it was also found that geraniol has a marked antifungal effect on *A. niger* (Kamatou et al. 2013). Thymol, a monoterpenoid phenolic derivative isolated from *Syringa*, among other species, had a significant antifungal effect on *C. albicans* and *C. tropicalis*; moreover, the minimum inhibitory concentration (MIC) value of nystatin was decreased by 87.4% after combination with thymol (de Castro et al. 2015). Moreover, it was also found in in vivo models, where carveol has been successfully used in the treatment of vulvovaginal *Candida* infection in mice; the antifungal target of carveol results in inhibition of the production of yeast plasma membrane H^+-ATPase (Cacciatore et al. 2015; Menon et al. 2021). In the mouse vaginal *Candida* model, limonene treatment significantly reduced the fungal load (Munoz et al. 2020).

In recent years, further investigations have found that terpenoids regulate the immune function of the human body and improve various symptoms caused by inflammation. Soybean saponins played an anti-inflammatory role by inhibiting the degradation of an inhibitor of NF-κBα (IκBα) and activating NF-κB to downregulate the production of cyclooxygenase-2 (COX-2), nitric oxide synthase (iNOS), human macrophage chemoattractant protein-1 (MCP-1), and TNF-α in lipopolysaccharide (LPS)-stimulated RAW264.7 cells (Kang et al. 2005). Meanwhile, quinoa saponins, with a dose-dependent action, could downregulate the secretion of TNF-α, nitric oxide (NO), and IL-6 in LPS-activated RAW264.7 cells (Yao et al. 2014), and geniposide, the main bioactive component of *Gardenia jasminoides* fruits, could inhibit the activation of NF-κB in a concentration-dependent manner, downregulating gene expression of *IFN-γ* and *iNOS* in LPS-activated RAW264.7 cells (Koo et al. 2004). In addition, laurene can inhibit the activation of NF-κB, c-Jun N-terminal kinase (JNK), and p38 in human chondrocytes induced by IL-1β. Furthermore, compared with IL-1β-induced inflammatory cells, laurene has an anti-inflammatory effect by reducing the activity of extracellular regulated protein kinases (ERK1/2) (Rufino et al. 2015). β-patchoulene significantly altered sepsis-induced neuroinflammation and microglia activation and improved the peripheral immune function (Tian et al. 2023). In a mouse model of acute inflammation, β-patchoulene alleviated edema and inflammatory cell infiltration. β-patchoulene, in a dose-dependent manner, inhibited the secretion of IL-6, TNF-α, and IL-1β in a mouse model of inflammation and could significantly downregulate the expression of genes *iNOS* and *COX-2* (Zhang et al. 2016b). Furthermore, ganoderic acid, a triterpenoid compound extracted from the Chinese medicinal mushroom *Ganoderma lucidum*, was found to significantly inhibit phorbol ester-induced inflammation in mice (Akihisa et al. 2007). Therefore, terpenoids have an effect on the growth, inhibition, and killing of common human-pathogenic fungi and phytopathogenic fungi. At the same time, some terpenoids can also help the host to regulate and balance the inflammatory state of the body in the face of fungal infection by regulating the secretion of related cytokine.

Antifungal targets and immunomodulatory effects of phenolic compounds

Phenolic compounds are one of the most common classes of plant secondary metabolites; more than 8000 phenolic compounds with known structures are found in plants. Most phenolic compounds in plants are synthesized by the shikimic acid (the major pathway) and malonic acid pathways. These compounds are formed by an aromatic ring or rings combined with one or multiple hydroxyl groups. Phenolics are mainly composed of polymeric or monomeric structures, which can exist in the form of glycosides, aglycones, substrates, or free-binding compounds (Alara et al. 2021). Phenolic compounds include flavonoids, phenolic acids, and polyphenols and tannins and can be found in fruits, vegetables, legumes, and tea. In addition, biological functions of phenolic compounds include antioxidant, antibacterial, anti-inflammatory, analgesic, antipyretic, and anti-tumor, among others (Alara et al. 2021), as well as in the prevention of Alzheimer's disease, cardiovascular disease, obesity, and other diseases (de Araújo et al. 2021). In recent years, more and more natural plant phenolic compounds have been recognized, and they have become an important research target for the development of novel antifungal agents (Chtioui et al. 2022).

Flavonoids are hydroxylated phenolic molecules with a C_6-C_3-C_6 carbon skeleton structure, connecting two aromatic rings with a heterocyclic ring containing three carbon atoms. Since the first discovery of flavonoids in orange peel in 1930, more than 4000 flavonoids have been identified in plants. Therefore, flavonoids represent one of the most important classes of the phenolic family and account for one-half of the total number of phenolic compounds. For the human body, flavonoids in fruits and vegetables are directly related to the health status of the human diet, contributing to anticancer activity and prevention of cardiovascular diseases (Middleton 1998; Tungmunnithum et al. 2018). In addition, investigations have found that natural flavonoids have the ability to act directly as antifungal molecules and to interact synergistically with other antifungals (Jin 2019). It has also been reported that some flavonoids can significantly reduce the spore germination of plant-pathogenic fungi, such as *Botryosphaeria* (Ma et al. 2022b). Therefore, flavonoids are expected to become one of the important research targets from which to develop antifungal drugs. It has been confirmed that certain flavonoid compounds have antifungal activities against human pathogens such as *Aspergillus* (Wang et al. 2021a), *Candida* (da Fonseca et al. 2022), *Cryptococcus* (Fowler et al. 2011), and *Malassezia* spp. (Alves et al. 2017). For example, the flavonoids 4′,5-dihydroxy-7-methoxy-6-(3-methyl-[2-butenyl])-(2S)-flavanone, isolated from the shrub *Eysenhardtia texana* (Wächter et al. 1999), and 7-hydroxy-3′,4′-(methylenedioxy)-flavan, isolated from the tree *Terminalia bellirica*, have antifungal activity toward *C. albicans* (Valsaraj et al. 1997). The reason why the propolis has an inhibitory effect on *Aspergillus niger* and *C. albicans* is that it contains a high concentration of flavonoids (Vică et al. 2022). In addition, curcumin from *Curcuma longa* L. has a fungistatic effect on *A. flavus* (Temba et al. 2019). Additionally, the flavonoid baicalin, the main bioactive component of the traditional Chinese medicinal plant *Scutellaria baicalensis*, exerts a concentration-dependent antifungal effect by inhibition of *C. albicans* biofilm formation and increasing the apoptosis rate of this human pathogen (Cao et al. 2008). Meanwhile, further studies have found that the biofilm inhibition mechanism of baicalin is caused by the upregulated expression of many redox-related genes (such as *CAP1*, *SOD2*, and *TRR1*), increasing the Ca^{2+} concentration in the cytosol, damaging the cell ultrastructure, and increasing the *C. albicans* apoptosis rate (Cao et al. 2008; Yang et al. 2014). In addition to *C. albicans*, baicalin also has antifungal effects on *A. fumigatus*, *T. rubens*, and *T. trichophyton* (Da et al. 2019). Moreover, quercetin, extracted from *Morus alba* L., showed antifungal activity against *A. fumigatus*, with the fungal load in the corneal tissue of mice treated with quercetin being significantly lower than in control mice (Yin et al. 2021).

In addition to flavonoids, the polyphenol chlorogenic acid, widely found in apple, coffee, potato, and tomato, has a synergistic antifungal effect (in combination with FLC) on *C. albicans* and *Malassezia* spp. (Rhimi et al. 2020). In addition, chlorogenic acid was found to have antifungal effects against phytopathogenic fungi such as *Fusarium* spp. and *Verticillium dahliae* through a reactive oxygen species (ROS)-dependent mode of action and alteration of fungal cell membrane permeability (Kai et al. 2021). In addition, gallic acid, another class (phenolic acid) of phenolic compound, also had antifungal effects on *C. albicans* (Teodoro et al. 2018). In addition to effects on *A. fumigatus* and *A. niger*, resveratrol (another polyphenol) not only inhibits biofilm formation of *C. albicans*, but also has an inhibitory effect on the growth of superficial skin fungi, especially *Epidermophyton floccosum*, *Microsporum gypseum*, *T. mentagrophytes*, *T. tonsurans*, and *T. rubrum* (Jediyi et al. 2020; Okamoto-Shibayama et al. 2021). Pterostilbene (a demethylated derivative of resveratrol), extracted from grape leaves, is one of the more active antifungal compounds against *C. albicans*, with the antifungal mechanism acting on the Ras/cAMP pathway of *C. albicans*, downregulating the expression of genes involved in ergosterol biosynthesis (Li et al. 2014). In addition, in the biofilm model of rat central venous catheter, defects in *C. albicans* biofilm formation were observed in the lumen at a treatment concentration of 16 μg/mL pterostilbene, whereas no biofilm formation was observed and no fungal cells were even detected in the lumen of central venous catheter in the treatment groups at concentrations of 32 μg/mL and 64 μg/mL (Kolouchova et al. 2018; Li et al. 2014). Interestingly, the antifungal effect of pterostilbene against *C. albicans* exceeded that of resveratrol. Recent investigations found that the licochalcone A in the ethanol extract from the licorice roots of *Glycyrrhiza* species significantly inhibited the formation of the *C. albicans* biofilm, and the fungal load in tongues of mice treated with these isoprene acylated ketones was significantly lower in the oral *Candida* mouse model than that in the control mice (Seleem et al. 2016).

Many phenolic compounds have anti-inflammatory and antioxidant effects (Dominguez-Avila et al. 2021). For example, gingerol extracted from ginger rhizomes has high antioxidant activity. The potential antioxidant mechanism of gingerol in human intestinal epithelial cells prevents the degradation of Keap1-Nrf2 protease, promotes the translocation of Nrf2 into the nucleus, increases the expression of *Nrf2* target genes, and increases the level of the antioxidant reduced glutathione, decreasing the concentration of ROS. Moreover, gingerol also reduces the production of NO and prostaglandin E2 (PGE2) in RAW264.7 cells (Mao et al. 2019; Zhang et al. 2013). Quercetin acts on immune cells and then targets intracellular signaling kinases, phosphatases, and membrane proteins to regulate cell-specific functions. Therefore, there is a hypothesis that quercetin is an immunomodulatory molecule. In LPS-activated RAW264.7 cells, quercetin inhibits phosphatidylinositol kinase (PI3K) phosphorylation and subsequent TLR4/MyD88/PI3K complex formation via nonreceptor tyrosine kinase c (Src) and Syk (Domínguez-Avila et al. 2022). Kaempferol, a flavonol, which is a type of flavonoid, also exerts anti-inflammatory effects by inhibiting the activity of hyaluronidase and reducing the level of ROS produced during cell stimulation (Yang et al. 2020). Chlorogenic acid, gallic acid, and kaempferol showed anti-inflammatory activities by inhibiting the expression of *iNOS*, secretion of pro-inflammatory factors, and production of ROS in LPS-induced RAW264.7 cells (Yang et al. 2020). Ferulic acid, a phenolic acid compound, has been shown to play an anti-inflammatory role in bovine endometrial epithelial cells by inhibiting IκB degradation, the phosphorylation of NF-κB (p65) and mitogen-activated protein kinase, and reducing the production of the pro-inflammatory cytokines IL-1β, IL-6, IL-8, and TNF-α (Yin et al. 2019). Quercetin and resveratrol exert anti-inflammatory effects by downregulating expression at the mRNA and protein levels of NO, iNOS, TNF-α, IL-1β, IL-6, and the granulocyte–macrophage colony-stimulating factor (GM-CSF) (Endale et al. 2013). Moreover, quercetin reduced IL-8 production in LPS-activated lung A549 cells (Geraets et al. 2007). It was also reported that quercetin and resveratrol could significantly reduce TNF-α production in LPS-activated microglia, and resveratrol also could inhibit IL-1 production (Bureau et al. 2008), whereas quercetin was also found to have immunomodulatory effects in mast cells, T lymphocytes, and peripheral blood mononuclear cells (Li et al. 2016; Yang et al. 2015). After feeding quercetin to healthy broiler chickens for 6 weeks, the concentration of serum immunoglobulin, IL-4, as well as the spleen index, thymus index, and bursa of Fabricius index, were all increased. These data indicated that quercetin can enhance the immune ability of animals by stimulating the development of immune organs and the subsequent amplification of humoral immunity (Yang et al. 2020). A small number of phenolic compounds such as quercetin and resveratrol with antifungal effects also have immunomodulatory effects on the body, which is one of the promising new drug research and development targets.

Antifungal mechanism and immunomodulatory effects of nitrogenous secondary compounds

Nitrogenous secondary compounds are another type of secondary metabolites in plants, most of which are synthesized from amino acids. Their metabolism is complicated and can be affected by plant hormones and environmental stress (Cho et al. 2008). Nitrogen-containing secondary metabolites include alkaloids, cyanogenic glycosides (CNGs), and non-protein amino acids. CNGs, glycosides with α-hydroxynitrile, are composed of an aglycone with a sugar group attached (Bolarinwa et al. 2015). CNGs are potentially highly toxic substance, releasing hydrogen cyanide when hydrolyzed, although the compounds themselves are not toxic, and may lead to acute cyanide poisoning (Cressey et al. 2013). Another class of plant nitrogenous compounds is non-protein amino acids, which are important stores of nitrogen in plants. In addition to their antibacterial, antifungal, and anticancer effects, non-protein amino acids primarily help plants to resist harmful insects (Huang et al. 2011). Alkaloids are found in over 20% of plant species and are generally found in high concentrations in plant families such as the *Fabaceae*, *Apocynaceae*, *Polygonaceae*, *Papaveraceae*, *Ranunculaceae*, *Rutaceae*, and *Solanaceae*. They are compounds that contain at least one nitrogen atom in a naturally occurring heterocyclic ring. According to the chemical structure classification, alkaloids can be divided into pyridine, isoquinoline, indole, scopolamine, and organic amine alkaloids, among others. Alkaloids have a range of biological activities and are used in treatment of bacterial infections, cancer, dementia, and pain and are an important source of many drugs (Adamski et al. 2020). Here, the antifungal effects of alkaloids will be discussed. Alkaloids extracted from sea buckthorn (*Hippophae rhamnoides*), including acridone, fluoroquinolone, and 4-quinolone, play an inhibitory role against fungi by downregulating the expression of the *ICL1* gene in *C. albicans* (Kamal et al. 2021). Magnoflorine, present in *Acorus calamus*, *Tinospora cordifolia*, and *Celastrus paniculatus*, exerts antifungal effects by inhibiting α-glucosidase activity and reducing biofilm formation in *C. albicans* (Kim et al. 2018). Meanwhile, magnoflorine can also damage the *T. rubrum* cell membrane, increasing the leakage of nucleic acids from fungal cells, reducing the activities of squalene epoxidase and 14-α-lanosterol demethylase, and reducing the concentration of ergosterol in mycelia (Luo et al. 2021). In addition, graveoline, from rue (*Ruta graveolens*), showed significant antifungal activity against *C. albicans*, *Fusarium oxysporum*, and *T. rubrum* (Cantrell et al. 2005; Duraipandiyan and Ignacimuthu 2009). Pteleine, one of the furanoquinoline alkaloids, exhibits antifungal activity against *C. albicans* (Shang et al. 2018). Recent investigations also found that 8-acetylnorchylerythrine and 8-methoxydictamnine, from *Zanthoxylum* (*Toddalia*) *asiatica*, exhibit antifungal activity against *C. albicans*, *Candida glabrata*, and *Candida tropicalis* (Hu et al. 2014). The half-maximal inhibitory concentration (IC_{50}) values of 2,3-dihydro-1H-indolizinium chloride, an indoleazine alkaloid extracted from the fern *Dryopteris enneaphylla*, against *A. fumigatus* and *C. neoformans* were 0.3 μg/mL and 4.0 μg/mL, respectively (Samoylenko et al. 2009; Thawabteh et al. 2019). Berberine, isolated from *Coptis chinensis* and *Phellodendron* *chinense*, exerted an antifungal effect on *C. albicans* by upregulating the expression of core genes (*sln1*, *ssk2*, *hog1*, and *pbs2*) and inducing ROS accumulation and inhibiting the expression of the chitin synthase gene (*chs3*) and the β-(1,3)-glucan synthase gene (*gsc1*) to damage the integrity of the cytoplasm, inhibit the formation of germ tubes and hyphae, and destroy the integrity of cell wall (Huang et al. 2021). Berberine also exerted synergistic antifungal spread ability in vivo when combined with AmB or FLC; when berberine was combined with AmB, the survival time of mice with disseminated infection of pathogenic *C. albicans* was increased from 14 to 36 d (Huang et al. 2022; Quan et al. 2006).

To regulate the immune response, steroidal alkaloids, from the bulbs of *Fritillaria* spp. of the *Liliaceae*, blocked LPS-induced phosphorylation and degradation of both IκBα and JNK and significantly inhibited the production of NO, IL-6, and TNF-α in RAW264.7 cells (Wang et al. 2021d). In addition, oral administration of sinomenine could reduce the activities of iNOS and COX-2 in rats (Zhu et al. 2019). Furthermore, aconitine can improve LPS-induced acute lung injury in rats by inhibiting the activation of NF-κB and reducing the concentrations of TNF-α, IL-6, and IL-1β (Wang et al. 2019c). Moreover, berberine and matrine (from *Sophora* sp.) are more effective against inflammation, with berberine reducing the concentration of COX-2 and inhibiting the synthesis of PGE2 to achieve the anti-swelling effect in the formalin-induced foot swelling mice model (Yao et al. 2019). Berberine also had an inhibitory effect on the secretion of inflammatory factors, including TNF-α, IL-8, IL-6, and MCP-1, in dinitrofluorobenzene-induced delayed-type hypersensitivity rat model. Meanwhile, to alleviate chronic colitis, berberine could regulate the production of INF-γ and IL-17A in $CD4^+$ T cells through activation of adenosine 5′-monophosphate-activated protein kinase (AMPK) (Takahara et al. 2019; Yu et al. 2019). Recent studies also found that matrine, isolated from the roots of *Sophora flavescens*, has a strong negative regulatory effect on the secretion of TNF-α, IL-8, and IL-1α in THP-1 cells (Zhou et al. 2019). It also exerted anti-inflammatory effects by downregulating the expression of the genes encoding lipopolysaccharide recognition receptor, lipopolysaccharide-binding protein, CD14 and TLR4, and the transcription of the nuclear factors *c-Jun* and *c-fos* in the mouse model of foot swelling (Li et al. 2020b). In addition, matrine inhibited the NF-κB signaling pathway in mouse airway epithelial cells, reduced the expression of suppressors of cytokine signaling 3, and reduced the production of ROS and inflammatory factors in alveolar macrophages to inhibit airway inflammation in a mouse model of asthma (Li et al. 2019). Therefore, alkaloids mainly improve inflammation by inhibiting related inflammatory factors and signaling pathways and then play a role in immune regulation in the body.

Antifungal mechanism and immunomodulatory effects of other secondary metabolites

In addition to terpenoids, phenolics, and nitrogen-containing secondary compounds, plant-derived essential oils, also known as volatile oils, have attracted much attention for their antifungal activities. Essential oils are a mixture of secondary metabolites. Most are volatile aromatic oil-like liquids, containing aliphatic compounds, aromatic compounds, sulfur and nitrogen compounds, and terpenes and their oxygen derivatives. Since 1987, more than 500 articles have reported on the antifungal properties of essential oils (Kalemba and Kunicka 2003). Essential oils have been listed as the most widely used special plant metabolites due to their anti-infective properties (Plant et al. 2019). Investigations have shown that essential oils have significant antifungal effects, not only on deep fungal infections caused by *Aspergillus* and *Candida*, but also on superficial fungal infections caused by *Microsporum canis*, *M. gypseum*, *T. rubrum*, and *T. mentagrophytes*, and even on phytopathogenic fungi in crops (Bakkali et al. 2008; Danielli et al. 2018). The antifungal targets of essential oils mainly involve inhibition of fungal cell growth and mycotoxin synthesis, for example, by disruption of cell membrane permeability and intracellular electron transport chains, resulting in intracellular metabolic disorders (Mirza Alizadeh et al. 2022). Investigations have found that rosemary (*Rosmarinus officinalis*) essential oil not only targets mycelial ergosterol synthesis to inhibit toxin biosynthesis in *A. flavus*, but also inhibits mycelium growth to play an antifungal effect on the phytopathogen *F. oxysporum* (da Silva Bomfim et al. 2020; Hussein et al. 2020). Furthermore, *Rhododendron tomentosum* essential oils not only have an inhibitory effect on *Candida parapsilosis*, but also play an antifungal role in affecting the permeability of cell membranes in the yeast, *Saccharomyces cerevisiae* (Judzentiene et al. 2020). The concentrations of thyme essential oil and ginger essential oil were 11.25 μg/mL and 364 μg/mL, respectively, which exerted a marked antifungal effect on *Fusarium* and an inhibitory effect on the synthesis of *Fusarium* mycotoxins such as deoxypyrimethamine and zearalenone (Romoli et al. 2022). In addition to extensive antibacterial activity, *Bupleurum rigidum* essential oil can also play an antifungal role by changing the ultrastructure of *C. albicans*, *C. neoformans*, and *T. rubrum* (Zuzarte et al. 2021). *Melaleuca alternifolia* essential oil, which is mainly pinene-4-alcohol, showed antifungal activity in vitro against *A. niger* and both azole-sensitive and azole-resistant *C. albicans* (Hammer et al. 2002; Kumar 2020); in the rat vaginal *C. albicans* infection model, this essential oil also had a great impact on eliminating *C. albicans* infection and enhancing the anti-infection ability (Mondello et al. 2006). Oregano oil at a concentration of 0.25 mg/mL completely inhibited the growth of *C. albicans* in vitro. In addition, it also inhibited spore germination and mycelium growth in a concentration-dependent manner (Manohar et al. 2001). In vivo, the survival rate of the mice was as high as 80% after continuous treatment with oregano oil for 30 days in a mouse systemic candidiasis model, whereas the fungal load in mouse kidney tissue was close to zero (Manohar et al. 2001). Sodium houttuyfonate (SH), a volatile oil from *Houttuynia cordata*, exerted an antifungal effect on *C. albicans* by affecting gene expression in the Ras1-cAMP-Efg1 pathway and decreasing biofilm formation and the production of cAMP. Compared with the infected group, the survival rate of the SH-treated group was significantly higher in the experimental model of *Galleria mellonella* caterpillars (Wu et al. 2020). In addition, our previous investigation also found that sodium new houttuyfonate (SNH), which were modified compounds of SH, had a

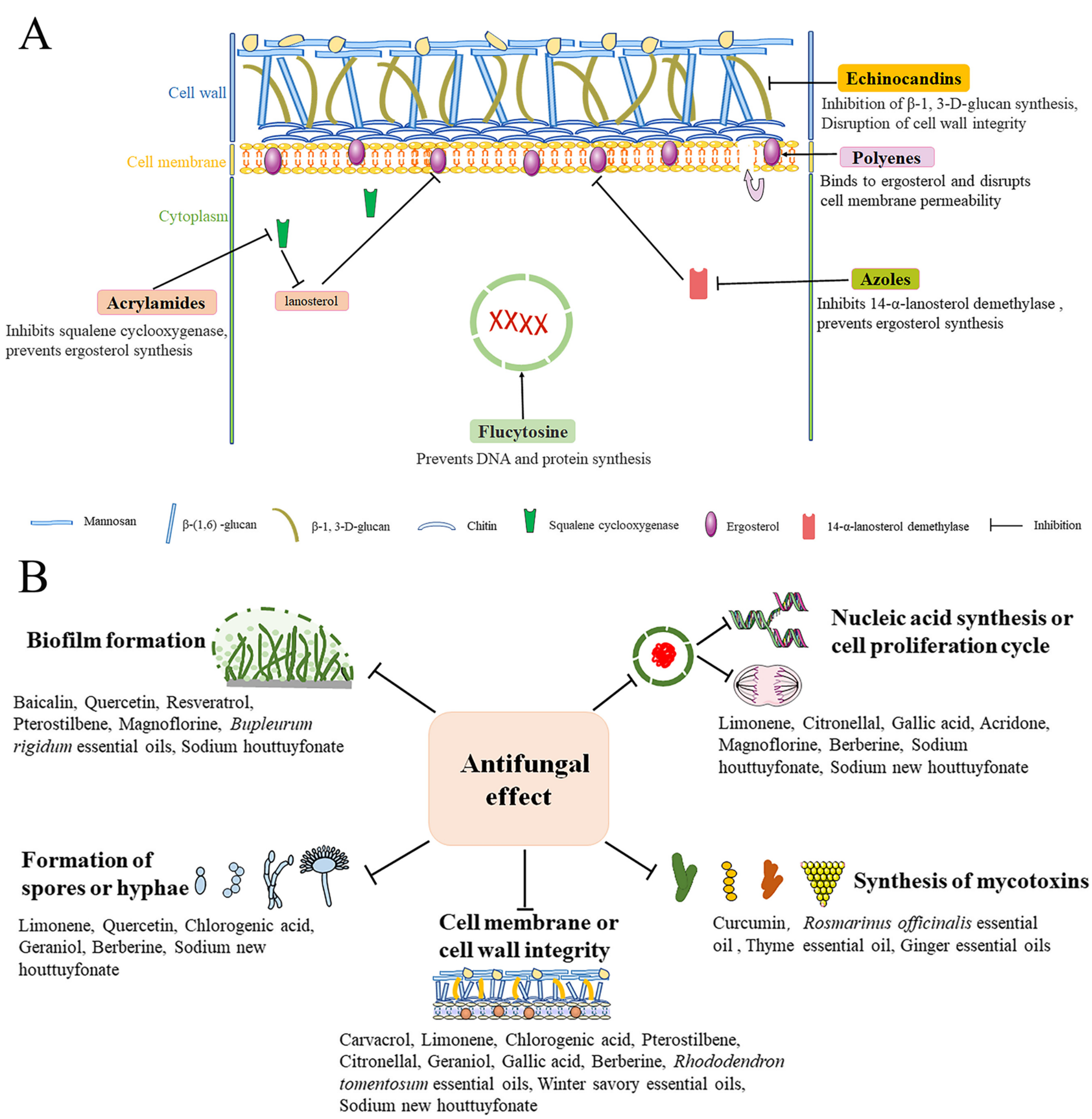

Fig. 1 Mechanism of antifungal action of existing antifungal drugs and plant secondary metabolites. **A** Antifungal targets had been confirmed in the existing antifungal drug. Existing antifungal agents include allylamines, azoles, polyalenes, echinocins, and flucytosine. **B** Antifungal targets had been confirmed in the plant secondary metabolites. The antifungal pathway of plant secondary metabolites include (1) prevention of fungal biofilm formation and destruction of the established fungal biofilm; (2) alteration of cellular DNA replication and disruption of the cell cycle; (3) inhibition of fungal mycotoxin synthesis; (4) prevention of ergosterol synthesis, disruption of cell membrane permeability, and promotion of cell wall destruction and lysis; and (5) decrease in the number of spores and the growth of hyphae

Table 2 Regulatory immune mechanisms of plant secondary metabolites in vitro and in vivo

Classification	Name of active compounds/ secondary metabolites	Experimental model	Mechanism of action	Reference
Alkaloid	Aconitine	Rat	Inhibit the activation of NF-κB and the production of TNF-α, IL-6, and IL-1β	Wang et al. (2019c)
	Berberine	Mice	Reduce the synthesis of COX-2 and PGE2	Yao et al. (2019)
		Rat	Inhibit the secretion of TNF-α, IL-8, IL-6, and MCP-1	Yu et al. (2019)
		$CD4^+$ T cells	Activate AMPK signal pathway	Takahara et al. (2019)
	Matrine	Mice	downregulate the expression of CD14 and TLR4	Li et al. (2020b)
		Mouse airway epithelial cells	Inhibit the production of SOCS3 and ROS by NF-κB signal pathway	Li et al. (2019)
		THP-1 cells	Negative regulate the secretion of TNF-α, IL-8, and IL-1α	Zhou et al. (2019)
	Sinomenine	Rat	Inhibit the activities of iNOS and COX-2	Zhu et al. (2019)
Phenolics	Gingerol	Human intestinal epithelial cell	Increase the expression of *Nrf2* and the level of the antioxidant reduced glutathione and decrease the concentration of ROS	Mao et al. (2019)
		RAW264.7 cell	Inhibit the production of NO and PGE2	Zhang et al. (2013)
	Quercetin	RAW264.7 cell	Inhibit PI3K phosphorylation and TLR4/MyD88/PI3K complex formation via Src and Syk	Domínguez-Avila et al. (2022)
		Lung A549 cell	Inhibit the production of IL-8	Geraets et al. (2007)
		Microglia	Inhibit the production of TNF-α	Bureau et al. (2008)
		Broiler chickens	Activate the NF-κB signal pathway	Yang et al. (2020b)
	Resveratrol	Microglia	Inhibit the production of TNF-α and IL-1	Bureau et al. (2008)
	Ferulic acid	Bovine uterine epithelial endometrial cell	Inhibit the production of IL-1β, IL-6, IL-8, and TNF-α by IκB/ NF-κB/ MAPK signal pathway	Yin et al. (2019)
Terpenes	Geniposide	RAW264.7 cell	Inhibit the activation of NF-kB and expression of *IFN-γ* and *iNOS*	Koo et al. (2004)
	Laurene	Human chondrocytes	Inhibit the activation of NF-κB, JNK, ERK1/2, and p38	Rufino et al. (2015)
	Quinoa saponin	RAW264.7 cell	Downregulate the expression of *TNF-α*, *IL-6* and *iNOS*	Yao et al. (2014)
	Soybean saponins	RAW264.7 cell	Inhibit the degradation of IκBα and activation of NF-κB, and the production of COX-2, iNOS, MCP-1, and TNF-α	Kang et al. (2005)
	β-patchoulene	Mice	Inhibit the production of IL-6, TNF-α, and IL-1β, and the expression of *iNOS* and *COX-2*	Zhang et al. (2016b)

Table 2 (continued)

Classification	Name of active compounds/ secondary metabolites	Experimental model	Mechanism of action	Reference
Other plant secondary metabolites	Lavender essential oil	Rat	Reduce inflammatory exudates	Silva et al. (2015)
	Rosemary essential oil	Mice	Inhibit the activity of MPO and the level of IL-6	Borges et al. (2019)
	Citrus bergamia essential oil	Syrian hamster	Inhibit the secretion of IL-1α and TNF-α	Sun et al. (2020)
	Lanxangia tsaoko essential oil	THP-1 cells	Inhibit the production of Caspase-1, the activation of JAK/STAT, and the expression of *iNOS* and *COX-2*	Chen et al. (2017); Chen et al. (2021)
	Nutmeg essential oil	Rat	Inhibit the expression of *COX-2* and the release of *P*-substance	Ashokkumar et al. (2022); Zhang et al. (2016a)
	Peppermint essential oil	Mice	Inhibit the production of NO and PGE2	Sun et al. (2014)
		RAW264.7 cell	Inhibit the ERK/NF-κB signaling pathway and the expression of *COX-2*, *iNOS*, *IL-6*, and *IL-1β*	Kim et al. (2021)
	Essential oil from *Citrus* flower	RAW 264.7 cell	Blocked the MAPK signaling pathway and downregulate the expression of *IL-6*, *IL-1β*, and *TNF-α*	Shen et al. (2017)
	Sodium new houttuyfonate	Mice	Inhibit the secretion of IL-6 and IL-17A	Zhang et al. (2022b)

AMPK adenosine 5′-monophosphate (AMP)-activated protein kinase, *Caspase-1* cysteinyl aspartate-specific proteinase, *COX-2* cyclooxygenase-2, *ERK* extracellular regulated protein kinases, *GM-CSF* granulocyte–macrophage colony stimulating factor, *GSH* gonad-stimulating hormone, *iNOS* inducible nitric oxide synthase, *IL-1* interleukin-1, *IL-6* interleukin-6, *IL-8* interleukin-8, *IL-17A* interleukin-17A, *INF-γ* interferon-gamma, *IκB* inhibitor of NF-κB, *JNK* c-Jun N-terminal kinase, *JAK* janus kinase, *MAPK* mitogen-activated protein kinase, *MCP-1* monocyte chemoattractant protein-1, *MPO* myeloperoxidase, *Myd88* myeloid differentiation factor 88, *NF-κB* nuclear factor kappa-B, *NO* nitric oxide, *Nrf2* nuclear factor erythroid 2, *NLRP3* nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3, *PGE2* prostaglandin E2, *PI3K* phosphatidylinositol-3-kinase, *p38* phosphorylated p38 mitogen-activated protein kinase, *ROS* reactive oxygen species, *SOCS3* recombinant suppressors of cytokine signaling 3, *STAT* signal transducer and activator of transcription, *Src* nonreceptor tyrosine kinase c, *Syk* spleen tyrosine kinase, *TNF* tumor necrosis factor; *TLR4* toll-like receptor 4

marked antifungal effect on *A. fumigatus*. SNH achieves antifungal effects by inhibiting the synthesis of ergosterol in the cell membrane of *A. fumigatus*. In addition, in a mouse model of systemic *A. fumigatus* infection, SNH treatment significantly reduced the fungal load in the tissues (Zhang et al. 2022b). Studies have also found that essential oils can synergistically improve the antifungal effect when combined with existing antifungal drugs. For example, the combination of oregano essential oil and winter savory essential oil with the synthetic antifungal drug clotrimazole significantly reduced the metabolic activity of *C. glabrata*. At the same time, low concentrations of winter savory essential oil combined with clotrimazole caused organellar disorder in this fungus, with autophagic vacuoles, whereas high concentrations of winter savory essential oil combined with clotrimazole caused complete destruction of *C. glabrata* organelles (Massa et al. 2018).

Recent investigations have also reported that peppermint essential oil could alleviate the excessive inflammation exhibited by LPS-induced RAW264.7 cells by inhibiting the ERK/NF-κB pathway and the gene expression of *COX-2*, *iNOS*, *IL-6*, and *IL-1β* (Kim et al. 2021). It also found that the essential oil from *Citrus* flower blocked the MAPK signaling pathway by inhibiting the phosphorylation of p38 and JNK and downregulating the gene expression of *IL-6*, *IL-1β*, and *TNF-α* in RAW264.7 cells (Shen et al. 2017). In addition, *Lanxangia tsaoko* (black cardamom, formerly *Amomum tsao-ko*) essential oil could reduce the activation of the NLRP3 inflammasome by inhibiting the production of Caspase-1 and downregulate the expression of inflammatory mediators iNOS and COX-2 by inhibiting the activation of JAK/STAT and the processing of IL-1β and pyroptosis in THP-1 cells (Chen et al. 2017, 2021). Like dexamethasone, 1-h early injection of lavender essential oil had a therapeutic effect in the rat model of kappa-carrageenan-induced pleurisy. Further research found that the volume and total protein concentration of the exudate collected from the rats were both significantly reduced, while the total numbers

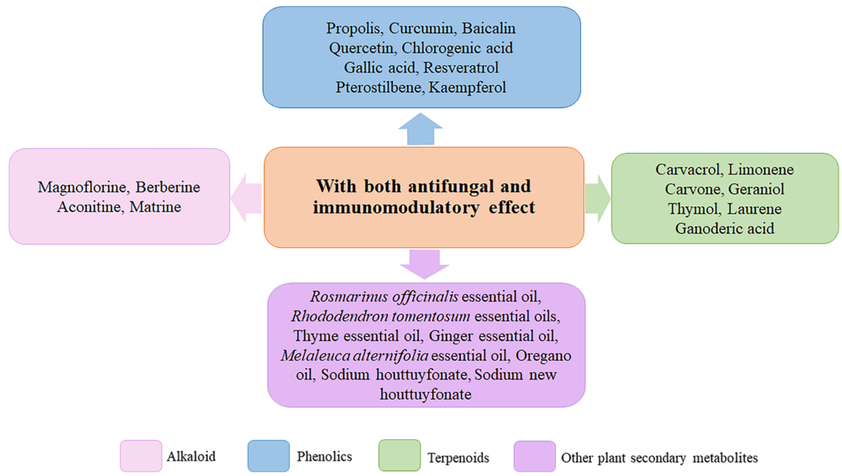

Fig. 2 Summary of plant secondary metabolites with both antifungal and immunomodulatory effect. These compounds are derived from alkaloids, phenols, terpenoids, and other plant secondary metabolites, respectively

of leukocytes and polymorphocytic leukocytes migrating into the pleural cavity were also reduced (Silva et al. 2015). This phenomenon also occurred in an animal model of carrageenan-induced pleurisy treated with rosemary essential oil. Investigations found that rosemary essential oil could induce leukocyte migration in vivo as well as induce chemotaxis in vitro. Recent studies found that dietary supplementation of rosemary essential oil significantly reduced MPO activity and IL-6 level in a 2,3,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis mouse model (Borges et al. 2019). The effect of *Citrus bergamia* (bergamot orange) essential oil on acne vulgaris was explored in the *Mesocricetus auratus* (golden hamster) model. It was found that the serum levels of IL-1α and TNF-α decreased in response to the oil in a dose-dependent manner after treatment (Sun et al. 2020). Recently, nutmeg (*Myristica fragrans*) essential oil extract was found to have anti-inflammatory activity in rodents, associated with reduced release of COX-2 and P-substances in the blood, as well as reduction of joint swelling induced by Freund's adjuvant injection in rats (Ashokkumar et al. 2022; Zhang et al. 2016a). Moreover, intragastric administration of SNH could significantly reduce fungal load in tissues and exerted anti-inflammatory effects through downregulating the production of inflammatory cytokines IL-6 and IL-17A in a mouse model of systemic *A. fumigatus* infection (Zhang et al. 2022b). Peppermint essential oil has marked anti-inflammatory effect, not only inhibiting NO and PGE2 production in LPS-activated RAW264.7 cells, but also inhibiting the production of NO and PGE2 on croton oil-induced ear edema in mice (Sun et al. 2014). Because of the antifungal potential of some essential oils when used alone or in combination, and of the efficacy of some essential oils in regulating inflammation, plant-derived essential oils also have great development potential in antifungal applications.

Conclusion

This review first briefly summarizes the current situation of clinical antifungal treatments of common superficial and deep fungal infections, the antifungal mechanisms of existing antifungal drugs (Fig. 1A), and their immunomodulatory effects on the host. At present, although there are few types of antifungal drugs and their targets, antifungal drugs can better help treat fungal infections by regulating the secretion of pro-inflammatory or anti-inflammatory factors to regulate the immune function of the host. So, can plant secondary metabolites cause similar effects? The mode of action of different antifungal plant secondary metabolites against various pathogenic fungi and the immunomodulatory effects of plant metabolites on the host were further reviewed. The antifungal mechanisms of plant secondary metabolites primarily include (1) inhibition of fungal mycotoxin synthesis; (2) prevention of fungal biofilm formation and destruction of the established fungal biofilm; (3) decrease in the number of spores and the growth of hyphae; (4) prevention of ergosterol synthesis, disruption of cell membrane permeability, and promotion of cell wall destruction and lysis; and (5) alteration of cellular DNA replication and disruption of the cell cycle (Fig. 1B). At the same time, it was found that many plant secondary metabolites also reduced tissue inflammation and played an immunoregulatory function by reducing the release of pro-inflammatory factors (Table 2). In summary, many plant secondary metabolites have both antifungal and immunomodulatory effect (Fig. 2). And most of them have been used in clinical therapy independently or combined with existing antifungal drugs to better exert antifungal effects (Table 3). Therefore, plant secondary metabolites have broad prospects for the development of novel antifungal drugs.

Table 3 Summary of plant secondary metabolites that have been used clinically or have synergistic effects with existing antifungal drugs

Classification	Name of active compounds/secondary metabolites	Clinical application research	Fungus	In combination	Synergistic effects	In vivo	Reference
Alkaloids	Magnoflorine	–	*C. albicans*, *T. rubrum*	MCZ	+	–	Kim et al. (2018)
	Berberine	Improve insulin resistance	*C. albicans*	AmB, FLC, VRC, CAS	+	Mice	Han and Lee (2005); Imenshahidi and Hosseinzadeh (2019)
Phenolics	Propolis	Anti-viral treatment	*A. niger*, *C. albicans*	–	–	Rat	Ali and Kunugi (2021); Freires et al. (2016)
	Curcumin	Treatment and prevention of type 2 diabetes	*A. flavus*	AmB, ITR	+	–	Pivari et al. (2019); Rocha et al. (2021)
	Baicalin	Treatment of pancreatic injury	*C. albicans*, *A. fumigatus*, *T. rubens*, *T. trichophyton*	FLC	+	–	Wang et al. (2015); Wen et al. (2020)
	Quercetin	Treatment of metabolic diseases	*A. fumigatus*	AmB, FLC	+	Mice	Yi et al. (2021); Yin et al. (2021)
Terpenes	Limonene	Dissolve cholesterol in gallstones and prevent cancer	*C. albicans*, *A. fumigatus*, *C. neoformans*, *T. rubrum*, *T. mentagrophytes*	FLC, AmB	+	Mice	Nidhi et al. (2020); Sun (2007)
	Citronellal	–	*C. albicans*, *Penicillium*	AmB, FLC	+	Rat	Liu et al. (2021)
	Geraniol	Treatment for irritable bowel syndrome	*C. albicans*, *A. niger*, *A. flavus*	AmB, FLC, KET	+	–	Ricci et al. (2022); Shin (2003)
	Thymol	Adjuvant treatment of periodontitis	*C. albicans*, *C. tropicalis*	AmB, FLC	+	Mice	Anand et al. (2012); Jafri and Ahmad (2020)
Other secondary metabolites	Rosemary essential oil	Treatment of Raynaud' s phenomena associated with systemic sclerosis	*A. flavus*, *F. oxysporum*	–	–	–	Vagedes et al. (2022)
	Thyme essential oil	Treatment of helicobacter pylori infection	*Fusarium*, *C. albicans*	–	–	–	Nikolić et al. (2023)
	Melaleuca alternifolia essential oil	Improve photoaged skin	*A. niger*, *C. albicans*	–	–	Mice	Hugo Infante et al. (2023); Mondello et al. (2006)
	Sodium houttuyfonate	–	*C. albicans*	FLC	+	Mice	Chen et al. (2022b)
	Sodium new houttuyfonate	–	*A. fumigatus, C. albicans*	FLC, CAS, ITR	+	Mice, *Galleria mellonella*	Wu et al. (2020); Zhang et al. (2022b)

AmB amphotericin B, *CAS* caspofungin, *FLC* fluconazole, *ITR* itraconazole, *KET* ketoconazole, *MCZ* miconazole, *VRC* voriconazole, "–", no study were mentioned in the corresponding references; "+", synergistic or additive action

There are an estimated 420,000 plant species in nature, and some of them have been used as traditional herbal medicines to treat diseases since ancient times (Wang et al. 2021c). Generally, plant extracts are complex mixtures, and their active ingredients vary according to plant species, chemical types, and extraction methods. Each ingredient may have multiple targets in the body. Therefore, it is still necessary to explore the specific mechanisms of individual antifungal plant metabolites against fungi or for immunoregulation in vivo. Additionally, the development of antifungal and immunomodulatory drugs from plant secondary metabolites is still at the preliminary stage. The available clinical references are extremely scarce, and such drugs are still a long way from being used in the clinic. Therefore, what techniques should be used to extract plant secondary metabolites, which secondary metabolites have antifungal or broad-spectrum antifungal effects, how do they affect the immune status of the host body, and can they be used as antifungal or immunomodulatory drugs in clinical? All these issues need to be addressed urgently. It is up to more funding institutions and researchers to invest more human and material resources into exploring the vast "plant kingdom."

Author contribution ZYS had the idea for the article; MZ, FJH, and GQ performed the literature search and data analysis; and XZ and FYL drafted and/or critically revised the work. All authors read and approved the manuscript.

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Declarations

Conflict of interest The authors declare no competing interests.

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