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Overview of the control of plant fungal pathogens by natural products derived from medicinal plants

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Abstract: Chemical fungicides can cause drug resistance of plant pathogenic fungi, environmental pollution, and potential threats to humans and animals. Therefore, developing low-toxicity, high-efficient and environment-friendly biological control products is critical for green prevention, controlling plant fungal diseases, and maintaining ecological balance. Biocontrol research mainly includes the following aspects: antagonistic microorganisms, fungicidal proteins, RNA interference techniques and botanical fungicides. Significantly, natural products extracted from medicinal plants are valuable repertoire for inhibiting plant fungal diseases. This review systematically reviewed the research advances of using natural products from medicinal plants to inhibit plant pathogenic fungi, including the types of natural products, extraction methods, and antifungal mechanisms. The further prospects for the study and application, which provide the reference for botanical fungicide development and practical application in preventing and controlling plant fungal disease, were also discussed.

Keywords: medicinal plants; natural products; fungal disease; biological control; botanical fungicide

Plant fungal disease is one of the most detrimental factors causing agricultural disasters, threatening crop production in commercial and smallholder farming (Knogge 1996). The control strategies mainly include the optimisation of plant cultivation and management pattern, resistance breeding, chemical fungicide control, biocontrol and comprehensive control. Chemical fungicide is one of the most effective strategies to control plant fungal disease. However, long-term overuse of chemical fungicides

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can lead to increased resistance to pathogenic fungi (Sabarwal et al. 2018; Ons et al. 2020; Rani et al. 2021). For example, Miyamoto et al. (2020) showed that flutianil and pyriofenone had lost their ability to control cucumber powdery mildew. Graf (2017) found that the resistance of *Blumeria graminis* f. sp. *tritici* to metrafenone increased significantly. Poloni et al. (2020) showed that *Magnaporthe oryzae* had significant and extensive resistance to both tebuconazole and epoxiconazole. In addition, chemical fungicides can also reduce the safety of agricultural products, destroy the ecological balance and endanger human health (Sabarwal et al. 2018; Ons et al. 2020; Rani et al. 2021). Therefore, developing biocontrol products with low toxicity, high efficiency, and eco-friendliness will significantly promote the green prevention and control of plant fungal disease, the protection of human and animal health, and the maintenance of ecological balance.

Plant-based natural products, known as plant secondary metabolites, are mainly small organic compounds with significant biological activities, which are generated in the long-term evolution of plants to resist the infection of pathogenic microorganisms. Plant-based natural products usually cover alkaloids, flavonoids, polyphenols, terpenoids, etc., which have anti-microbial and anti-inflammatory functions and are widely used in health, food, clinical treatment of human and animal disease and control of plant diseases (Zaynab et al. 2018; Isah 2019). In recent years, medicinal plant-based natural products have become a research hotspot in the biocontrol of plant fungal disease due to their excellent antifungal activity (Ons et al. 2020).

In this review, we emphasise the types, extraction methods and antifungal mechanisms of medicinal plant-based natural products, which will provide references for botanical fungicides development and practical application in preventing and controlling plant fungal diseases.

APPLICATION OF MEDICINAL PLANT-BASED NATURAL PRODUCTS

Alkaloids, flavonoids, polyphenols, terpenoids and other plant-based natural products have various biological activities such as bactericidal, anti-inflammatory, antioxidant, anti-ageing, hypoglycemic, antilipemic and anti-tumour effects (Ekiert et al. 2020; Ekiert et al. 2022). Plant-based natural products, therefore, are widely used in food processing and preservation (Kowalska et al. 2017), cosmetics (Xue et al. 2023), pharmaceuticals (Wen et al. 2011), agriculture and other fields (Sparks et al. 2017). For example, limonene, a terpenoid, is the main component of citrus (*Citrus reticulata*) essential oil, and the citrus oil can be used to maintain fruits, vegetables, meat, fish and processed food freshness (Mahato et al. 2019). Carvacrol extracted from *Origanum vulgare* L.) and eugenol extracted from *Syringa oblata* Lindl. could delay the decay time of peaches (Zhou et al. 2018). In addition, plant-based natural products have an inhibitory effect on foodborne pathogens and a good antifungal effect on plant pathogens. As early as in the first half of the 19th century, pyrethrin (isolated from *Tanacetum* L.) and rotenone (isolated from *Derris trifoliata* Lour.) successively entered the empirical use and research application stage and were finally commercialised. Plant-based fungicides with azadirachtin (isolated from *Azadirachta Indica* A. Juss.) and matrine (isolated from *Sophora flavescens*) were considered as main active components and have been marketed (Zhang et al. 2020b). In the cosmetics field, natural product flavonoids and polyphenols, which have excellent antioxidant activity, and anti-ageing effects on the skin, have been developed as cosmetic products with antioxidant activity, sunscreen effect, and physical properties (Cefali et al. 2019; de Lima Cherubim et al. 2020). In addition, medicinal plant-based natural products also play a critical role in treating human diseases, with the main active ingredients in the drugs playing a key role in the efficacy. For instance, ginsenosides (isolated from ginseng) and artemisinin (isolated from *Artemisia carvifolia*) have excellent anti-cancer properties, which saved the lives of millions of malaria patients (Tu 2011; Jung et al. 2022). Plant-based natural products also play a role in agriculture; the following will focus on the research progress of medicinal plant-based natural products to inhibit plant pathogenic fungi.

MEDICINAL PLANT-BASED NATURAL PRODUCTS WITH ANTIFUNGAL ACTIVITY

Alkaloids

Alkaloids were initially defined as alkaline substances extracted from plants with biological activity. This definition has been refined multiple times to include compounds from outside the plant king-

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dom that share a biosynthetic origin with alkaloids but do not have basic nitrogen (Aniszewski 2015; Lichman 2021).

In recent years, the inhibitory function of alkaloids in plant pathogenic fungi has been reported (Table 1). The antifungal activities of 12 isoquinoline alkaloids such as berberine, coptidine, rhizobine and sanguine were studied *in vitro* and found that these compounds had different degrees of inhibition on pathogenic fungi with 100 μg/mL sanguine showing the strongest and broadest antifungal effects. The inhibition rates of sanguine to *Rhizoctonia solani*, *Fusarium* spp., *Sclerotinia sclerotiorum* and *Magnaporthe oryzae* were all above 60%, which was much higher than azoxystrobin (Zhao et al. 2019). Chinese goldthread (*Coptis chinensis* Franch) is a traditional Chinese medicine that could inhibit *Valsa mali* Miyabe et Yamada, the substance with antifungal activity from it was identified as berberine and palmatine, which belong to alkaloids (Chen et al. 2013). Jian et al. (2023) found that quinoline alkaloids from the roots of *Orixa japonica* could inhibit *R. solani*, *M. oryzae*, and *Phomopsis* sp. Dethoup et al. (2018) found that the *Coscinium fenestratum* had a high inhibition rate against *Alternaria brassicicola* both *in vitro* and *in vivo* and identified berberine as the main antifungal component of *C. fenestratum* based on the analysis of the chromatographic techniques and nuclear magnetic resonance spectroscopy; it was revealed that berberine could be a potent lead compound for development as an agrochemical for *Alternaria* black spot management. One active ingredient, antofine (7-demethoxylophorine) isolated from the total alkaloids extracted from *Cynanchum komarovii* was found to have a higher inhibitory rate on *F. oxysporum* than chlorothalonil and carbendazim at a low concentration of antofine (20 μg/mL) (Liu 2017). The antifungal rate is proportional to the concentration of antofine; antofine can be directly used as a natural product or lead compound to control plant fungal disease (Liu 2017).

Flavonoids

Flavonoids are distributed in roots, stems, leaves, flowers and fruits of plants, with the highest content in angiosperms (Tan et al. 2022). Until now, more than 8 000 natural products have been classified as flavonoids (García-Lafuente et al. 2009). By their chemical structure, they can be classified as chalcones, flavanones, flavanonols, flavones, flavonols, isoflavones, etc. (Shamsudin et al. 2022). Flavonoids have good antifungal activity; the recent reports of their inhibiting plant pathogenic fungi are shown in Table 1.

Solanum tuberosum leaves can be used as a medicinal plant because they contain anthocyanin compounds, secondary metabolites of flavonoid and polyphenol groups (Saputri et al. 2020). When the concentration of purple sweet potato leaf extract was 40%, the inhibition rate against *Fusarium* was 89.2% (Saputri et al. 2020). Glabridin is the primary, secondary metabolite of the rhizomes of *Glycyrrhiza glabra*, which belongs to flavonoids (Singh et al. 2021a). Li et al. (2021) reported that glabridin exhibited pronounced fungicidal activities against *S. sclerotiorum* with an EC_{50} value of 6.78 μg/mL and was 8-fold more potent than azoxystrobin (EC_{50}, 57.39 μg/mL). The mycelial growth and spore germination of *F. oxysporum* were inhibited absolutely when the concentration of total flavonoids from artichoke reached 10 mg/mL (Liu et al. 2020). 4'-*O*-methylglabridin, hispaglabridin B and glabridin were also very good in the inhibition of *R. solani*, *S. sclerotiorum* and *F. graminearum*, and these compounds have the potential to be developed as bio fungicides (Xu et al. 2020).

Phenols

Phenolics are compounds with one or more aromatic rings and one or more hydroxyl groups; they are widely distributed in the plant kingdom and exist in all organs of the plant body. So far, more than 8 000 phenolic structures are known, ranging from simple molecules such as phenolic acids to highly polymerised substances such as tannins, and they can help plants resist ultraviolet ray damage and pathogen infection (Dai et al. 2010).

Phenols from medicinal plants have preferable antifungal activity (Table 1). Relevant research indicated that *Berberis vulgaris* extracts containing a high concentration of polyphenols could inhibit the mycelial growth of *Penicillium verrucosum*, *Fusarium proliferatum*, *Aspergillus ochraceous*, *A. niger*, and *A. flavus* (El-Zahar et al. 2022). The EC50 values of eugenol from *Syzygium aromaticum* were 42.04 mg/L against *V. mali* and 190.58 mg/L against *F. graminearum*, showing excellent antifungal activity (Yang et al. 2020). In addition, eugenol had certain inhibitory effects on *Botryosphaeria rhodina*, *Alternaria* spp., and *Rhizoctonia* sp. *Penicillium chrysogenum*, *F. avenaceum*, *F. oxysporum* and *Botrytis cinerea* (Faria et al. 2006; Campaniello et al. 2010;

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Table 1. Antifungal activity and extraction methods of medicinal plant-derived natural products

Plant-derived natural products	Medicinal plants	Phytopathogenic fungi	Extraction method	Reference
Alkaloids	*Chimonanthus praecox*	*Alternaria brassicicola, Botrytis cinerea, Cladosporium fulvum*	Reflux extraction	Zhang et al. 2016
	Cortex phellodendri	*Monilinia fructicola*	Enzyme extraction; Maceration extraction	Pei et al. 2019; Fu et al. 2017
	Coscinium fenestratum, Zingiber cassumunar, Piper betle, Syzygium aromaticus	*A. brassicicola*	Maceration extraction	Dethoup et al. 2018
	Picrasma quassioides	*Alternaria solani, A. alternata, Fusarium oxysporum, Fusarium graminearum, Curvularia lunata, Glomerella cingulate, Valsa mali*	Ultrasound-assisted extraction	Wang 2020
	Peganum harmala	*F. oxysporum*	Maceration extraction	Zhu et al. 2022
Flavonoids	*Artemisia argyi*	*Valsa mali, F. oxysporum*	Ultrasound-assisted extraction	Wang et al. 2019b
	Cirsium japonicum	*F. oxysporum*	Ultrasound-assisted extraction	Liu et al. 2020
	Glycyrrhiza uralensis	*Rhizoctonia solani, Sclerotinia sclerotiorum, B. cinerea, Magnaporthe oryzae, F. graminearum, F. oxysporum, Colletotrichum gloeosporioides, Xanthomonas oryzae* (bacteria)	Reflux extraction	Xu et al. 2020
	Plectranthus hadiensis, Pimenta dioica, Pentastelma auritum	*Colletotrichum gloeosporioides, C. acutatum*	Ultrasound-assisted extraction	Silva et al. 2021
Phenols	*Brassica carinata, Brunfelsia calyicina, Salvia guaraniticaand, Punica granatum*	*F. oxysporum*	Maceration extraction; Ultrasound assisted extraction	Rongai et al. 2015
	Syzygium aromaticum	*F. oxysporum, R. solani, A. solani*	Maceration extraction	Hamad et al. 2019
	Ballota nigra, Magnolia officinalis	*A. alternata*	Hydrodistillation	Sebaa et al. 2019; Chen et al. 2019
	Syzygium aromaticum	*V. mali, F. graminearum*	Soxhlet extraction	Yang et al. 2020
	Magnolia officinalis	*R. solani*	Ultrasound assisted extraction	Yan 2021
	Artemisia argyi	*B. cinerea, Rhizoctonia cerealis, F. oxysporum, Colletotrichum orbiculare, A. alternata, Alternaria mali, Phytophthora nicotianae*	Microwave assisted extraction; Maceration extraction; Ultrasound assisted extraction	Wang et al. 2023
Terpenoids	*Ageratum conyzoides*	*Puccinia arachidis*	Maceration extraction	Yusnawan et al. 2018
	Magnolia grandiflora	*X. oryzae* (bacteria)	Maceration extraction	Cao. 2019
	Chrysanthemum morifolium	*F. oxysporum, M. oryzae, Verticillium dahliae*	Maceration extraction	Xue et al. 2019; Zhang et al. 2020a
Volatile oil	*Armeniaca sibirica*	*F. oxysporum, A. solani*	Hydrodistillation	Geng et al. 2016
	Eupatorium adenophorum	*Phytophthora capsici, Alternaria tenuissima, Fusarinm solani, Bipolaris sorokiniana, P. myriotylum*	Ultrasound assisted extraction	Liu et al. 2017a; Liu et al. 2017b
	Syzygium aromaticum, Artemisia sieberi, Coriandrum sativum	*B. cinerea*	Hydrodistillation	Sernaite et al. 2020; Ghasemi et al. 2020; Dėnė et al. 2023
	Thymus vulgaris	*F. oxysporum*	Hydrodistillation	Omar et al. 2021
	Vitex agnus-castus	*Penicillium digitatum, P. italicum*	Hydrodistillation	Rahmati-Joneidabad et al. 2021

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Olea et al. 2019; Yang et al. 2020). The combination of different medicinal plant natural products can enhance antifungal activity. For example, the mixture of honokiol with thyme, geranium essential oil with perilla alcohol, incense, perilla aldehyde or geraniol terpene compounds synergises plant pathogenic fungi (Yan 2021). Oufensou et al. (2020) found that the combination of thymol and pachylignan had an additive inhibitory effect on *F. graminearum*, possibly due to the different ways in which the two compounds act or the ability of one compound in the mixture to cross the fungal membrane, thereby improving the delivery of the other compound.

Moreover, the combination of medicinal plant natural products and chemical fungicides improves the efficacy in controlling plant fungal disease and reduces the use of chemical fungicides. The inhibition rate of thymol and honokiol against *B. cinerea* was significantly increased when the mixture of thymol and honokiol with chlorothalonil was in a reasonable proportion (Li et al. 2021b). Combining carvacrol with fungicide thifluzamide in a ratio of 4 : 1 significantly enhanced the inhibitory effect against *R. solani* (Wang et al. 2020). This synergy of medicinal plants' phenolic substances and chemical agents broadens the methodologies for controlling plant fungal disease.

Terpenoids

Terpenoids, also known as isoprenoids, are the largest and most diverse class of organic compounds in nature (Hoshino et al. 2023). Terpenoids have good antifungal activity, and the recent reports of their inhibiting plant pathogenic fungi are shown in Table 1.

Methyl thujate is a monoterpenoid substance; Ma et al. (2020) found that it could effectively against *Penicillium expansum*. Pterocaryalactone, a derivative of 1-hydroxyplatyphyllide, belongs to a class of terpenes. Ngo et al. (2020) found that *Pterocarya tonkinensis* extract containing pterocaryalactone has a potential disease control efficacy against rice blast and tomato late blight caused by *M. oryzae* and *Phytophthora infestans*, respectively. Research has shown that some cultivars of *Chrysanthemum morifolium* Ramat have an inhibitory effect on *F. oxysporum, M. oryzae* and *Verticillium dahliae*, and terpenoids play a major role in antifungal activity (Xue et al. 2019).

Volatile oils

Volatile oils, also known as essential oils, are usually stored in medicinal plants' epidermis as oil droplets or coexist with resin in the resin duct, which is widely distributed in medicinal plants (Cascaes et al. 2021). Volatile oils of medicinal plants are mixtures of many compounds; these substances can be classified as alcohols, aldehydes, ketones, ethers, esters, acids and oxides according to their functional groups (Dudai et al. 2001; Kim et al. 2018). Volatile oils have good antifungal activity, their antifungal function is also the result of the synergistic action of many compounds (Wang et al. 2019), and the recent reports of its inhibiting plant pathogenic fungi are shown in Table 1.

Experimental evidence indicated that some of the volatile oil mixtures extracted from plants such as *Eupatorium adenophorum* (Liu et al. 2017a, Liu et al. 2017b), *Armeniaca sibirica* (Geng et al. 2016), *Vitex agnus-castus* (Rahmati et al. 2021) and are involved in the prevention and control of fungal diseases. *E. adenophorum* volatile oils had a good inhibition effect on *Pythium myriotylum*, and GC/MS identified twelve compounds of the volatile oils; the main components were 10Hβ-9-oxo-agerophorone (37.03%), 10Hα-9-oxo-agerophorone (37.73%) and 9-oxo-10, 11-dehydro-agerophorone (23.41%) (Liu et al. 2017b). Twenty-one different components of *A. sibirica* volatile oils were identified, the highest components were benzaldehyde (62.52%), benzoic acid (14.80%) and hexadecane (3.97%), and the volatile oils showed a good inhibitory against *F. oxysporum* and *Alternaria solani* (Geng et al. 2016). *Penicillium digitatum* and *P. italicum* can be effectively inhibited by *Vitex agnus-castus* volatile oils, and the volatile oils contain rich phenols (91.74 mg GAE/g) and flavonoids (52.32 mg QE/g) (Rahmati-Joneidabad et al. 2021).

COMMON EXTRACTION METHODS OF NATURAL PRODUCTS FROM MEDICINAL PLANTS

The most suitable extraction method should be selected according to the properties of the target natural products. Different extraction methods must sometimes be combined to achieve better quality and purity (Peng & Cao 2021).

Traditional extraction methods

Maceration extraction. Maceration extraction is a simple and operable method; however, its short-

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comings are also apparent, e.g., the long extraction time, the relatively low extraction efficiency and the larger reagent consumption (Buldini et al. 2002). Sometimes the material can be mechanically shaken to improve extraction efficiency (Xue et al. 2019; Zhang et al. 2020a). Furthermore, using different extraction solvents also affects the extraction rate of the target products. We must choose the solvent according to the types and polarities of the target products to be extracted. Water was usually used as an extraction solvent for the more polar compounds, intermediate polar compounds can be extracted with aqueous alcohol systems, and less polar compounds can be extracted with acetone (Chuo et al. 2020). In addition, synergistic extraction with different solvents can increase the yield of the target products (Saini et al. 2021).

Reflux extraction. Reflux extraction is a method of extracting medicinal ingredients by volatile organic solvent. The detailed procedure follows: the plants and volatile organic solvent mixture was heated, distilled and condensed back into the extractor until the active ingredients were extracted entirely (Manzoor et al. 2019). The extraction efficiency is relatively high, and the extraction solvent can be recycled (Manzoor et al. 2019; Yang et al. 2021a). However, this method is cumbersome with higher energy consumption, lower product purity, and long solvent heating time, which will decompose thermosensitive substances easily (Manzoor et al. 2019).

Soxhlet extraction. Soxhlet extraction is a method of extracting compounds from solid substances by solvent reflux and siphoning. This method has excellent simplicity and operability with low cost and high extraction efficiency. Still, it uses large amounts of samples, large amounts of solvent usage, long extraction times, and excessive loss of heat energy (Sridhar et al. 2021).

Hydrodistillation. Hydrodistillation means that the plant material is totally immersed in water, which is brought to the boiling point to break the plant cytoplasm and liberate the essential oil components (Shen et al. 2009). The method, which does not require complicated equipment, is easy to operate with low cost and large output; however, the extraction procedure takes a long time, requires high temperature and is performed in an open system (Shen et al. 2009; Beoletto et al. 2016). During extraction, thermosensitive substances and oxidisable components are easily destroyed and volatilised (Shen et al. 2009).

Modern extraction method

Ultrasound-assisted extraction. Ultrasound-assisted extraction mainly makes use of ultrasonic "cavitation" and "high-frequency vibration" to accelerate the dissolution of active ingredients from plants and promote the diffusion of chemical components into the solvent (Wen et al. 2018; Macías-Cortés et al. 2022). At the same time, the ultrasonic field has a fixed distribution that can act on the flowing material evenly, maximising the processing capacity of the material (Wen et al. 2018). This method can be completed quickly and has high extraction efficiency (Wen et al. 2018; Macías-Cortés et al. 2022). In addition, this technique can be handled at room temperature, which is friendly to the thermosensitive active ingredients (Wen et al. 2018).

Microwave-assisted extraction. The application of microwaves for heating the solvents and plant tissues in the extraction process, which increases the kinetic of extraction, is called microwave-assisted extraction (Delazar et al. 2012). It has a number of advantages, e.g., shorter extraction time, less solvent, higher extraction rate and lower cost, over traditional methods of extraction of compounds from various matrices, especially natural products (Delazar et al. 2012).

Supercritical fluid extraction. Target substances can be extracted by supercritical fluid extraction at a higher temperature and pressure; after restoring to normal temperature and pressure, the components in the fluid will dissolve in the absorption liquid immediately, resulting in separation from the gaseous fluid (Chuo et al. 2020). This method has the advantages of a simple extraction process, high extraction efficiency, low energy consumption, no residual organic solvent, and environmental friendliness (Uwineza & Waśkiewicz 2020).

Enzyme extraction. Due to the high efficiency of enzymes, a trace amount of them can achieve the high extraction efficiency of natural products. This method has mild extraction conditions, high extraction efficiency, a simple process, short time consumption, and less energy consumption. Replacing chemical reagents with enzymes is more environmentally friendly due to their no toxic residue. However, the purity and yield of the product are low, and the reaction conditions and experimental equipment are strict (Nadar et al. 2018; Das et al. 2021).

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MECHANISM OF MEDICINAL PLANT NATURAL PRODUCTS INHIBITING PATHOGENIC FUNGI

Destruction the cell structure of pathogenic fungi

Medicinal plant-based natural products execute the antifungal function by destroying the cell structure of pathogenic fungi, such as inhibiting spore germination, affecting mycelial morphology and growth, and destroying the cell membrane integrity and permeability.

It is well known that the normal development of mycelia is crucial to the propagation of pathogenic fungi. The fungal cells contain mainly ergosterol; if these sterols are bound by antifungal drugs or their synthesis is inhibited by ergosterol biosynthesis inhibitors, the cell membrane's integrity will disrupt (Lagrouh et al. 2017). When the fungal cell membrane is damaged, the intracellular electrolyte will extravasate, leading to changes in the conductivity of the solution, and the degree of cell membrane damage is proportional to the conductivity (Anthony et al. 2015). Recently, research evidence indicated that medicinal plant-based natural products could inhibit or even destroy fungal mycelia. A series of compounds Aa1-Db1, inspired by the simplification of quinine structure, were extracted and identified from structure 2.8-bis(trifluoromethyl)-4-quinolinol. Among them, Ac12 had significant antifungal activity against *B. cinerea* by inhibiting spore germination and destroying mycelia structure, which resulted in changing cell membrane permeability and content leakage (Chen et al. 2021). Research has shown that *C. chinensis* could inhibit the spore formation and germination of *S. sclerotiorum* and increase cell membrane permeability (Zhang et al. 2015). Chen et al. (2019) identified two compounds, magnolol and honokiol, from *M. officinalis* and found that magnolol and honokiol inhibited the mycelial growth of *A. alternata* in a dose-dependent manner, the antifungal activity can be associated with the hyphal distortion that resulted from the disruption of the cell membrane integrity. As a kind of alkaloid, antofine could increase the electrolyte leakage of *Penicillium italicum* (Peng et al. 2022). Oil extracts of *E. adenophorum* can significantly inhibit the growth of *Phytophthora capsici*, and change the cell membrane permeability.

Furthermore, the oil extracts cause complete disorganisation of intracellular organelles, cytoplasm depletion, and disruption of cytoplasmic membranes and the cell wall (Liu et al. 2017). Camphor is a kind of bicyclic monoterpenoid. Research has shown that camphor could destroy the cell membrane of *Fusarium* (*F. oxysporum* G5, *F. solani* G9, *F. verticillioide*, and *F. graminearum*), enhance the permeability of cytomembrane and release intracellular macromolecules, such as nucleic acids and proteins (Kong et al. 2022). The peroxidation of fungal cell membrane lipids occurs typically when the cells are damaged under external environment stress, resulting in oxidisation and even destroying cell membrane skeleton phospholipid molecules. Malondialdehyde (MDA) is the final degradation product of membrane lipid peroxidation, and its content can reflect the degree of cell damage (Gaweł et al. 2004). Yan et al. (2021) found that isoxanthohumol caused membrane lipid peroxidation, thus accelerating the death of *B. cinerea*. Zhang (2016) found that the enzyme activity indexes, including superoxide dismutase, catalase, cellulase, pectinase and *β*-glucosidase, and soluble protein content of *F. oxysporum* decreased after treatment with crude extraction of *Chrysanthemum coronarium*, while the content of MDA increased. The enzyme activity decreased with the increase of crude extract concentration, and the increased MDA content indicated that the concentration of crude extraction of *Ch. coronarium* was proportional to the damage degree of *F. oxysporum* cells.

Interferes with thallus metabolism

The medicinal plant natural products can affect pathogenic fungi's energy and substance metabolism. BTG 505, a bicyclic 1.4-naphthoquinone dunnione (a natural product obtained inadvertently as a by-product of a synthesis programme), inhibits oxidative phosphorylation of mitochondrial cytochrome, which affects energy metabolism and respiration of pathogenic fungi (Khambay et al. 2003). Zeylenone is an extract of *Uvaria grandiflora*; it can increase the soluble protein content of *Phytophthora capsicum*, reduce the content of reducing sugar and pyruvate, and affect its energy metabolism (He et al. 2021). Yan et al. (2021) found that isoxanthohumol could effectively inhibit *B. cinerea in vitro*, and the antifungal mechanism of it is mainly related to metabolism; it affected the carbohydrate metabolic process, destroyed the tricarboxylic acid (TCA) cycle, and hindered the generation of ATP by inhibiting respiration.

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Improving the resistance of host plants

Superoxide dismutase (SOD), peroxidase (POD), catalase (CAT), polyphenol oxidase (PPO), phenylalanine ammonia-lyase (PAL) and chitinase are curial defence response-related enzymes in plants, and these defence-related enzymes remain relatively stable in the process of plants growing normally. When pathogens infect plants, the balance of the plant defence-related enzyme system is broken, and the activity of defence enzymes in plant cells changes (Lebeda et al. 1999; Gaweł et al. 2004). These changes in plant defence enzyme activities are closely related to plants' physiological, metabolic characteristics and energy distribution, making them ideal indicators of plant defence response (He et al. 2021).

Experimental evidence indicated that reactive oxygen metabolism-related enzymes (SOD, POD, CAT), defence response-related enzymes (PPO, PAL, chitinase) and cell membrane permeability (soluble protein content) of watermelon seedlings increased following treatment of *C. coronarium* crude extraction. In contrast, the MAD content of watermelon seedlings decreased. Together, the data showed that the resistance of watermelon seedlings was improved under the treatment of natural products extracted from *C. coronarium* (He et al. 2021). Research has shown that the enzyme activity of watermelon plants PPO and SOD increased observably after treating the extraction of *S. aromaticum*, *Stellera chamaejasme*, and *Glycyrrhiza uralensis* (Zhang 2019). In addition, induced stress in plants causes changes in antioxidant and photosynthetic systems, Dėnė et al. (2023) found that *Coriandrum sativum* could increase the photosynthetic capacity and antioxidant response of strawberry plants; however, it had a negative effect on the suppression of strawberry grey mould.

Synergy mechanism

Medicinal plant natural products usually target multiple fungal pathways simultaneously. *P. talicum* mycelium treated with caseflone was wrinkled and collapsed on its surface, the cell membrane permeability increased significantly, intracellular substances such as sugar were released to the extracellular, and the contents of H_2O_2 and MDA increased (Luo et al. 2020). The synergistic attacks mentioned above could inhibit the infection of *P. italicum*, and reduce the disease incidence and spot diameter of *P. italicum* (Luo et al. 2020). Glabridin is a main secondary metabolite of glycyrrhiza roots, which strongly inhibits *F. graminearum*. It was speculated that glabridin could act on ergosterol biosynthesis of pathogenic fungi, destroy the integrity of cell membrane structure, lead to abnormal transmembrane transport and affect the activity of intracellular enzymes, which resulted in the disorder of intracellular content and energy metabolism, the deformed mycelium morphologies, the inhibited growth and development and eventually death (Yang et al. 2021a). Vanillin is a kind of organic phenolic aldehyde compound that widely exists in *Vanilla planifolia*, it relieves the symptoms of apple decay caused by *A. alternata* and *P. expansum*, and it could induce an elevation in the activities of defence-related enzymes in apple fruit, such as phenylalanine ammonia-lyase (PAL), chitinase (CHI) and β-1.3-glucanase (β-1.3-GA), and increase the contents of total phenols and flavonoids (Wang et al. 2022). Matrine can effectively inhibit mycelial growth and spore germination and change the cell membrane permeability of *B. dothidea* by affecting the lipid peroxidation process (Pan 2018). At the same time, ATP content and AT-Pase activity in the mycelium of *B. dothidea* are increased, the glycolysis pathway is inhibited, tricarboxylic acid cycle (TCA) is accelerated, mitochondrial oxygen consumption and complex enzyme I activity are increased (Pan 2018). Honokiol could damage mycelial morphology and cell membrane integrity, disrupt mitochondrial functioning, affect respiration and destroy the TCA cycle of *R. solani*, which finally inhibited ATP production (Yan et al. 2020). In addition, research showed that honokiol could induce cell canceration and inhibit cellular respiration of *Phytophthora nicotianae*; when tobacco plants are treated with honokiol, SOD and POD activities increased till reaching a maximum and then declined with further incubation, and MDA content declined significantly after honokiol treatment, which indicated that honokiol could inhibit membrane lipid peroxidation and enhance disease resistance (Wang et al. 2023).

CONCLUSION AND PROSPECTS

Biological fungicides of medicinal plants are safer and more environment-friendly than chemical fungicides. Medicinal plants are rich in nature, laying a foundation for botanical fungicide research and

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development. In recent years, there has been more and more research on the inhibition of pathogenic fungi by plant-based natural products, which has become the research hotspot.

There are few medicinal plant-based fungicides in the market, and the antifungal mechanism research is relatively shallow. The study of antifungal mechanisms and product development of medicinal plant-based natural products is still in the preliminary stage and has lots of space. To develop more competitive bio-fungicides derived from medicinal plants, expanding the research scope of medicinal plant resources and constantly exploring new natural products with higher and broad-spectrum antifungal activity is necessary. We should focus on several aspects as follows. Firstly, we should pay attention to and utilise wild plant resources reasonably, improve the technology of artificial cultivation, ensure sufficient raw materials, and realise sustainable utilisation of wild plant resources. The optimisation for extraction, separation and purification processes of plant-derived natural products is also an aspect that needs our attention, which is essential to save plant resources and improve the extraction quantity and quality of natural products. In addition, the structural identification and modification of plant-based active compounds need to improve their biological activity. This benefits the development of botanical fungicides and makes each active natural compound synergistic. What is more, the antifungal mechanism of plant-based natural products should be further studied, especially in genes (gene clusters) involved in synthesising antifungal compounds, which will guide the design of new botanical fungicides. Lastly, the development, production, processing and application of botanical fungicides should also be emphasised to improve their effectiveness and stability.

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