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Metabolites of medicine food homology-derived endophytic fungi and their activities

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ABSTRACT

Medicine food homology (MFH) substances not only provide essential nutrients as food but also have corresponding factors that can prevent and help treat nutritional imbalances, chronic disease, and other related issues. Endophytic fungi associated with plants have potential for use in drug discovery and food therapy. However, the endophytic fungal metabolites from MFH plants and their effects have been overlooked. Therefore, this review focuses on the various biological activities of 108 new metabolites isolated from 53 MFH-derived endophytic fungi. The paper explores the potential nutritional and medicinal value of metabolites of MFH-derived endophytic fungi for food and medical applications. This research is important for the future development of effective, safe, and nontoxic therapeutic nutraceuticals for the prevention and treatment of human diseases.

1. Introduction

In the face of a global epidemic of diet-related chronic disease, there is increased experimentation with the concept of "food as medicine" interventions to prevent, manage, and treat illness (Downer et al., 2020). Several studies have identified the potential for nutritional interventions in the prevention, management, treatment, and even in some cases reversal of disease (Feng et al., 2015; Lean et al., 2019). Medicine food homology (MFH) is traditionally defined as substances that have both nutritional and medicinal qualities. Since ancient times, Chinese medicine has been based on the theory that medicine and food are of the same origin, and its origin can be traced back to periods in which both disease and hunger were persistent threats (Liu, C., 2018). MFH substances not only provide essential nutrients but also have corresponding functional factors that can aid in the prevention and treatment of nutritional imbalances, chronic diseases, and other issues. Many crude traditional Chinese medicines (TCM) adhere to the principle of MFH (Chau and Wu, 2006). Because MFH plants occur naturally, show positive effects, and may be associated with fewer adverse reactions, they have become the main components of functional foods and are drawing increasing attention (Zhang, T. T. et al., 2013; Zhao, J. et al., 2011, 2016). MFH plants have become a hotspot for modern food and drug development, and their efficacy may be closely related to endophytic fungi that develop symbiotic relationships with plants.

Endophytes are naturally occurring microbes that inhabit plants but do not cause apparent symptoms in them (Chen et al., 2022). The distribution and community structure of endophytic fungi are influenced by factors such as genetic background, age, and host environmental conditions (Higgins et al., 2014; Oono et al., 2014; Pirttilä et al., 2005). Endophytic fungi also have profound effects on their host plants by promoting their growth, increasing their adaptability, and enhancing their tolerance to abiotic and biotic stresses (Kusari et al., 2012; Mendes et al., 2013; Rho et al., 2018; Sampangi-Ramaiah et al., 2020; Shweta et al., 2010; Waller et al., 2005). Some endophytic fungi have evolved special symbiotic relationships with their host plants and can significantly influence metabolite formation in plants, which in turn affects the quality and quantity of active pharmaceutical ingredients (APIs). They are advantageous sources of novel metabolites, agriculturally important promoters, and stress-resisters. Since 1993, when Stierle first isolated an endophytic fungus from the phloem of *Taxus brevifolia* capable of producing the novel anticancer substance paclitaxel (Stierle and Strobel G, 1993), *Taxomyces andreanae*, a growing number of studies have explored endophytic fungi from host plants, uncovering a rich body of metabolites with a variety of biological activities (antioxidant, antimicrobial, anti-inflammatory, and anticancer) (Caicedo et al., 2019; Fu et al., 2019; Nuankeaw et al., 2020; Pan et al., 2019; Xu et al., 2020; Yehia et al., 2020). Endophytic fungal metabolites and their activities have become exciting research topics. Most of the research in this field has focused on

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medicinal plants (Dalzell, 2020; Gómez et al., 2018; Kamel et al., 2019; Selim et al., 2018; Teimoori-boghsani et al., 2020).

However, the endophytic fungal metabolites from most MFH plants and their effects are neglected. The reported MFH plants have various functions, playing purported roles in anti-aging (Feng et al., 2019; Xing, Y. et al., 2022), antifatigue (Lu et al., 2021; Zhu et al., 2021), enhanced immunity (Diling et al., 2017; Gong et al., 2019), antitumor (Mu et al., 2021; Tang et al., 2021), enhanced memory (Li, T. et al., 2020; Wang, Y. et al., 2022), and reduction of blood fat levels (Gonga et al., 2020; Song, D. xing and Jiang, 2017). If the active effects of such metabolites can be tapped, they could be used for the development of novel therapeutic health products. Therefore, this review summarizes metabolites with important biological activities produced by endophytic fungi isolated from MFH plants to explore their potential nutritional and medicinal value.

2. Endophytic fungi of MFH plants and their metabolites

At the time of writing, there was a total of 111 MFH substances described by the Chinese National Health Commission (Ling et al., 2017). Only 53 of them (47.75%), which are sourced from 35 plant species, have been studied for endophytic fungi (Table 1 and Fig. 1). The 35 plant species belong to 23 families, including Zingiberaceae, Orchidaceae, Araliaceae, Moraceae, Poaceae, Saururaceae, Lamiaceae, Piperaceae, Eucommiaceae, Asteraceae, Fabaceae, Iridaceae, Asparagaceae, Solanaceae, Rosaceae, Rhamnaceae, Nelumbonaceae, Myrtaceae, Ginkgoaceae, Dioscoreaceae, Cucurbitaceae, Cornaceae, and Apiaceae (Fig. 1 and S1). Among these families, the number of species associated with Zingiberaceae and Orchidaceae are higher than those of other families and both accounted for 28.30% of all species (Fig. 1 and S1). The Zingiberaceae family includes about 52 genera and more than 1300 species that are dispersed throughout tropical Africa, Asia, and the Americas. This family includes a diversity of aromatic perennial herbs with creeping horizontal or tuberous rhizomes, and many species are economically important as ornamental plants, spices, or for use as a folk medicine. It also includes vital groups of medicinal plants with volatile essential oils and oleoresins of export quality (Chakraborty et al., 2019). The secondary metabolites extracted from different genera of Zingiberaceae, such as *Curcuma*, *Kaempferia*, *Hedychium*, *Amomum*, *Zingiber*, *Alpinia*, and *Elettaria*, have antimicrobial, antiarthritic, antioxidant, anticancer, anti-inflammatory, and antidiabetic properties (Chakraborty et al., 2019). Endophytic fungi belonging to five fungal orders, including Eurotiales, Hypocreales, Pleosporales, Xylariales, and Glomerellales, have been isolated from three genera (*Zingiber*, *Alpinia*, and *Curcuma*) of the Zingiberaceae (Fig. 1 and S1). Various types of metabolites are produced by these endophytes including alkaloids, terpenoids, esters, phenols, and fungal extracts, and they have antimicrobial, antioxidant, and anticancer properties (Figs. S2 and S3). This indicates that Zingiberaceae species have great potential to possess abundant endophytic fungi with diverse bioactivities. Therefore, Zingiberaceae-associated endophytic fungi and their propertied should be explored further in the future.

Known as the Chinese Orchidaceae medicinal families (COMFs), Orchidaceae is one of the largest and most important medicinal families of plants, with more than 28,000 identified species in about 763 genera (Christenhusz and Byng, 2016; Zhang, S. et al., 2018). The chief genera in the Orchidaceae family are *Pleurothallis* (more than 1000 species), *Dendrobium* (more than 1400 species), *Epidendrum* (more than 1500 species), and *Bulbophyllum* (more than 2000 species) (Sarsaiya et al., 2019). Due to the large number and variety of orchids, they have long been investigated in regard to their biology and associations with diverse fungal endophytes. Recently, endophytic fungi belonging to Eurotiales, Hypocreales, and Xylariales have been isolated from only two genera (*Dendrobium* and *Gastrodia*) of Orchidaceae (Fig. 1 and S1). Orchidaceae fungal endophytes (OFEs) can enhance plant growth, increase resistance to disease-triggering pathogens, reduce weed incidence, and improve tolerance capacity to biotic and abiotic stresses (Sturz et al., 2000). Furthermore, they yield vast secondary metabolites (industrially important bioactive natural compounds) with pharmaceutical potential (Demain, 2014). Many endophytic fungi resist an extensive range of pathogens. OFEs also yield an antimicrobial compound that prevents pathogen development and competes with most pathogen species for nutrition and space (Alurappa et al., 2018). At present, more attention is paid to the effect of fungi on plant growth and development. Research on the metabolites and activity of endophytic fungi in Orchidaceae is still extremely limited, having focused mainly on the genus *Dendrobium* (Jin, Z. et al., 2017; Mei et al., 2010; Sarsaiya et al., 2020; Xing, Y. M. et al., 2011), which is rich in active metabolites.

Endophytic fungal species that have been reported in MFH plants belong to nine orders, including Hypocreales, Eurotiales, Pleosporales, Sordariomycetes, Xylariales, Glomerellales, Botryosphaeriales, Diaporthales, and Magnaporthales (Fig. 1 and S2). Hypocreales mainly includes *Fusarium*, *Drechmeria*, and *Trichoderma*, which may produce alkaloids, terpenoids, polyketides, quinones, polysaccharides, polypeptides, and steroids. Eurotiales mainly includes *Aspergillus* and *Penicillium*, which may produce terpenoids, polyketides, polysaccharides, esters, phenols, and organic acids. Endophytes of *Aspergillus* (El-hawary et al., 2020; Hagag et al., 2022), *Penicillium* (Marie et al., 2020), *Fusarium* (Manoj and Anil, 2016; Marie and Toghueo, 2019), *Drechmeria* (Liang et al., 2018; Yu et al., 2018; Zhao, J. et al., 2018b), and *Trichoderma* (Patel, J. et al., 2019) possess significant antibacterial, antifungal, antioxidant, anti-inflammatory, and anticancer activities.

3. Correlation between MFH plants and their endophytic fungal metabolites

Recent investigations have reported the capacity of multiple endophytic fungi to produce bioactive compounds which are the same or structurally related to those synthesized by their host plants (Bielecka et al., 2022; Sharma et al., 2021; Venieraki et al., 2017; Zhao, J. et al., 2010). Metabolites of the 35 MFH plant species for which endophytes have been reported mainly includes flavonoids, phenols, terpenoids, polysaccharides, glycosides, alkaloids, amino acids, anthocyanins, steroids, vitamins, diarylheptanoids, saponins, organic acids and other compounds (Table S1). Among them, polysaccharides, alkaloids, terpenoids, flavonoids, and phenols were found to be shared by MFH plant and their endophytic fungi (Table S1). However, only a few metabolites of four types (polysaccharides, alkaloids, lignans and terpenoids) produced by the MFH plant-derived endophytic fungi have been reported to have the same or structurally related to those synthesized by their host plants in the recent five years. *Crocus sativus* petals are rich in polysaccharides (Yang et al., 2018). Two homogeneous polysaccharides were isolated and purified from petals of *C. sativus* have been documented for their effects of antioxidant activity, which are potentially important for human health (He et al., 2021). Interestingly, the exopolysaccharide isolated from endophytic fungi *Penicillium citreonigrum* CSL-27 of *C. sativus* exhibited higher antioxidant activity (Mag et al., 2018). Polysaccharides as the dominatingly active component in *Dendrobium officinale* have been found due to their nutritional and pharmacological properties (Xing, X. et al., 2013). Recently, an endophytic fungus *Fusarium solani* DO7 produced polysaccharide showing the similar structure with the host *D. officinale* polysaccharide (DOP) (Zeng, Y. J., Yang, Ou, et al., 2019a,b). Polysaccharides of *Angelica sinensis* also have been confirmed to have functions of enriching blood, regulating immunity and promoting tumor vaccine's antitumor function (Gu et al., 2019; Jin, M. et al., 2012; Liu, W. et al., 2019; Wang, K. et al., 2016). However, the exopolysaccharide of *Alternaria tenuissima* F1 isolated from *A. sinensis* exhibited strong scavenging activity and may be a new source of natural antioxidant (Wang, Y. et al., 2019). Anti-inflammatory and anticancer alkaloid piperine is found in the fruits of *Piper longum* and *P. nigrum* and responsible for their pungent taste (Stojanović-Radić et al., 2019). Endophytic fungi (*Mycosphaerella* sp. PF13, *Colletotrichum*

Table 1
Summary of studies on the metabolites of MFH plants-derived endophytic fungi and their activities.

Endophyte	Host Plant	Pathogen/Cancer Cell (Inhibition rate or IC_{50} value)	Metabolites	Taxonomy of metabolites	Activity	References
Chaetomium globosum	*Dioscorea Opposita*	HL-60, A-549, SMMC7721, MCF7, SW480 (51–96%)	Yamchaetoglobosin A (**1**)	Alkaloids	Anti-cancer	Ruan et al. (2017)
Trichoderma harzianum	*Zingiber officinale*	*Mycobacterium tuberculosis* (25 mg/mL)	Pretrichodermamide A (**2**)	Alkaloids	Anti-microbial	Harwoko et al. (2021)
Epicoccum nigrum	*Zingiber officinale*	L5178Y, Ramos, Jurkat J16 (1.3–28 mM)	Epicorazine A (**3**)	Alkaloids	Anti-cancer	
Phomopsis sp.	*Polygonatum sibiricum*	A2780	Epoxycytochalasin H (**4**)	Alkaloids	Anti-cancer	Xu (2020)
Phoma sp. JS0228	*Morus alba*	MCF-7 (0.29 mM), LNCaP (0.36 mM)	Macrooxazoles C (**5**)	Alkaloids	Anti-cancer	Ku et al. (2021)
Colletotrichum gloeosporioides	*Piper nigrum*	–	Piperine (**6**)	Alkaloids	Anti-inflammatory	Krishna et al. (2020)
Chaetomium sp. SYP-F7950	*Panax notoginseng*	MDA-MB-231 (26.49 μmol L^{-1})	Chetoseminudin F (**7**)	Alkaloids	Anti-cancer	Peng et al. (2019)
		A549, MDA-MB-231 (2.75–8.68 μmol L^{-1})	Chaetocochin C (**8**), chetomin A (**9**), chetomin C (**10**), chetomin (**11**)	Alkaloids	Anti-cancer	
		Staphylococcus aureus, *Bacillus subtilis*, *Enterococcus faecium*, *Candida albicans* (0.12–9.6 μg mL^{-1})	Chaetocochin C (**8**), chetomin A (**9**), chetomin C (**10**), chetomin (**11**)	Alkaloids	Anti-microbial	
Chaetomium globosum 7951	*Panax notoginseng*	MCF-7, MDA-MB231, H460, HCT-8 (4.5–65.0 mM)	Demethylchaetocochin C (**12**), chaetoperazine A (**13**), 4-formyl-N-(30-hydroxypyridin-20-yl) benzamide (**14**), chetomin (**15**)	Alkaloids	Anti-cancer	Wang, F. et al. (2019)
Penicillium sp. T2-8	*Gastrodia elata*	*Candida albicans* (128 μg/mL)	Preaustinoid D (**16**), dihydroxyneogrifolic acid (**17**)	Terpenoids	Anti-microbial	Duan et al. (2016)
		Bacillus subtilis (8 μg/mL), *Staphylococcus aureus* (32 μg/mL)	Dihydroxyneogrifolic acid (**17**)	Terpenoids	Anti-microbial	
		Bacillus subtilis (4 μg/mL)	Preaustinoid A1 (**18**)	Terpenoids	Anti-microbial	
		Staphylococcus aureus (4 μg/mL)	Austin (**20**), (S)-18,19-dihydroxyneogrifolin (**21**),	Terpenoids	Anti-microbial	
		Escherichia coli (8 μg/mL)	(S)-18,19-dihydroxyneogrifolin (**21**)	Terpenoids	Anti-microbial	
		–	Dehydroaustinol (**19**), neogrifolin (**22**)	Terpenoids	–	
Bipolaris sp. L1-2	*Lycium barbarum*	NCI–H226, MDA-MB-231 (5.5–9.5 μM)	Bipolahydroquinones A-C (**23–25**), cochlioquinones I–N (**26–30 and 33**), isocochlioquinones F and G (**31 and 32**)	Terpenoids	Anti-cancer	Long et al. (2019)
Pestalotiopsis sp. DO14	*Dendrobium officinale*	*Candida albicans, Cryptococcus neoformans*, *Trichophyton rubrum*, *Aspergillus fumigatus* (more than 50 μg/mL)	(4S,6S)-6-[(1S,2R)-1, 2-dihydroxybutyl]4-hydroxy-4-methoxytetrahydro-2H-pyran-2-one (**34**), (6S,2E)-6-hydroxy-3-methoxy-5-oxodec-2-enoic acid (**35**), LL-P880γ (**36**), LL-P880α (**37**)	Terpenoids	Anti-microbial	Wu et al. (2016)
		Candida albicans, Cryptococcus neoformans, *Trichophyton rubrum*, *Aspergillus fumigatus* (higher than 200 μg/mL)	ergosta-5,7,22-trien-3b-ol (**38**)	Terpenoids	Anti-microbial	
		MKN45, LOVO, A549, HL-60 (lower than 200 μM)	(4S,6S)-6-[(1S,2R)-1, 2-dihydroxybutyl]4-hydroxy-4-methoxytetrahydro-2H-pyran-2-one (**34**), (6S,2E)-6-hydroxy-3-methoxy-5-oxodec-2-enoic acid (**35**), LL-P880γ (**36**), LL-P880α (**37**), ergosta-5,7,22-trien-3b-ol (**38**)	Terpenoids	Anti-cancer	
Emericella sp. XL 029	*Panax notoginseng*	*Bacillus subtilis*, *Bacillus cereus*, *Escherichia coli* (25–50 μg/mL)	Emericellins A (**39**) and B (**40**)	Terpenoids	Anti-microbial	Pang et al. (2018)
Penicillium sp.	*Zingiber officinale*	L5278Y, A2780	Shearilicine (**41**)	Terpenoids	Anti-cancer	Ariantari et al. (2019)
Drechmeria sp.	*Panax notoginseng*	*Candida albicans* (12.5 μg/mL)	Drechmerins B (**42**)	Terpenoids	Anti-microbial	Zhao, J. C. et al. (2018)
Hypomontagnella monticulosa Zg15SU	*Zingiber griffithii*	PANC-1 (0.05 ppm), NBT-T2 (0.75 ppm), HCT116 (0.05 ppm)	Terpenoid-alkaloid (**43**)	Terpenoids	Anti-cancer	Lut et al. (2021)
		PANC-1 (0.71 ppm), NBT-T2 (0.30 ppm), HCT116 (0.67 ppm)	Sesterterpenoid (**44**)	Terpenoids	Anti-cancer	
Colletotrichum sp. JS-0361	*Morus alba*	MCF-7 (35.06 and 25.20 μM)	Colletotrichalactones A-Ca (**45–47a**)	Polyketides	Anti-cancer	Bang et al. (2020)
Pleosporales sp. Sigrf05	*Siraitia grosvenorii*	HCT-116, HepG2, BGC-823, NCI–H1650, Daoy (1.26–47.5 μM)	Pleospyrones A-E (**48–52**), congener (**53**)	Polyketides	Anti-cancer	Lai et al. (2020)
Chaetomium globosum	*Polygonatum sibiricum*	HepG-2 (38.6 μM)	Chaephilone C (**54**)	Polyketides	Anti-cancer	Song, C. et al. (2020)

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Table 1 (*continued*)

Endophyte	Host Plant	Pathogen/Cancer Cell (Inhibition rate or IC_{50} value)	Metabolites	Taxonomy of metabolites	Activity	References
Penicillium citrinum	*Dendrobium officinale*	MG63 (3.49 μmol L^{-1})	Peptide-polyketide hybrid GKK1032B (**55**)	Polyketides	Anti-cancer	Na et al. (2022)
Alternaria sp.	*Ziziphus jujuba*	L5178Y (1.7 μM)	Alternariol (**56**)	Polyketides	Anti-cancer	Orfali et al. (2017)
		L5178Y (7.8 μM)	Alternariol-5-O-methyl ether (**57**)	Polyketides	Anti-cancer	
		L5178Y (6.8 μM)	Altenusin (**58**)	Polyketides	Anti-cancer	
		L5178Y (6.2 μM)	Altertoxin II (**59**)	Polyketides	Anti-cancer	
Trichoderma koningiopsis YIM PH3000	*Panax notoginseng*	*Bacillus subtilis*, *Salmonella typhimurium*, *Escherichia coli* (128 μg/mL)	Koninginin W (**60**), koninginin D (**61**), 7-O-methylkoninginin D (**62**), koninginin T (**63**) and koninginin A (**64**)	Polyketides	Anti-microbial	Wang, Y. L. et al. (2021)
Emericella sp. XL 029	*Panax notoginseng*	*Micrococcus lysodeikticus*, *Salmonella typhimurium* (25–50 μg/mL)	Emericelactones A-D (**65**–**68**)	Polyketides	Anti-microbial	Pang et al. (2018)
Colletotrichum sp. JS-0367	*Morus alba*	–	1,3-dihydroxy-2,8dimethoxy-6-methylanthraquinone (**69**)	Quinones	Anti-inflammatory	Fibroblasts et al. (2021)
Fusarium solani JS-0169	*Morus alba*	HT22	Fusarubin (**70**)	Quinones	Anti-cancer	Choi et al. (2020)
Fusarium solani	*Cassia alata*	–	Ergosterol (**71**)	Quinones	–	Khan et al. (2018)
		–	Anhydrofusarubin (**72**), 4-hydroxybenzaldehyde (**73**), bostrycoidin (**74**), fusarubin (**75**)	Quinones	Anti-oxidant	
		Bacillus megaterium, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*	Anhydrofusarubin (**72**), bostrycoidin (**74**), fusarubin (**75**), 3-deoxyfusarubin (**76**)	Quinones	Anti-microbial	
		Vero (25%)	4-hydroxybenzaldehyde (**73**), bostrycoidin (**74**)	Quinones	Anti-cancer	
		Vero (35%)	Anhydrofusarubin (**72**), 3,5,9-trihydroxyergosta-7,22-diene-6-one (**77**)	Quinones	Anti-cancer	
Alternaria tenuissima F1	*Angelica sinensis*	–	EPS (**78**)	Polysaccharides	Anti-oxidant	Wang, Y. et al. (2019)
Fusarium solani DO7	*Dendrobium officinale*	–	DGS1 (**79**) and DGS2 (**80**)	Polysaccharides	Anti-oxidant	Zeng, Y. J., Yang, Wu, et al. (2019a,b)
Penicillium citreonigrum CSL-27	*Crocus sativus*	–	EPS (**81**)	Polysaccharides	Anti-oxidant	Mag et al. (2018)
		K562 (46.16%), A549 (44.97%), HL-60 (44.95%), HeLa (33.10%)	EPS (**81**)	Polysaccharides	Anti-cancer	
Aspergillus terreus-RTN3	*Alpinia chinensis*	–	MM_2 (**82**)	Esters	Anti-oxidant	Suhartati (2020)
		MCF-7 (42.26 μg/mL), Hela (39.21 μg/mL), HepG2 (48.30 μg/mL), NCI–H460 (50.26 μg/mL)	MM_2 (**82**)	Esters	Anti-cancer	
Penicillium sp.	*Panax notoginseng*	HepG2 (0.024 μM)	Brefeldin A (**83**) and brefeldin A 7-O-acetate (**84**)	Esters	Anti-cancer	Xie et al. (2017)
Aspergillus austroafricanus CGJ-B3	*Zingiber officinale*	–	EAE (**85**)	Phenols	Anti-oxidant	Danagoudar et al. (2017)
Aspergillus flavipes DZ-3	*Eucommia ulmoides*	–	3,4-dihydroxybenzeneacetic acid (**86**), 3,4-dihydroxyphenylacetic acid methyl ester (**87**)	Phenols	Anti-oxidant	Liu, W. et al. (2021)
Phomopsis sp. XP-8	*Eucommia ulmoides*	HepG2	Pinoresinol (Pin) (**88**), Pinoresinol monoglucoside (PMG) (**89**)	Phenols	Anti-cancer	Li, Q. et al. (2016)
Fusarium tricinctum	*Hordeum sativum*	Gram-positive and Gram-negative bacteria	Enniatins (ENs) (**90**)	Polypeptides	Anti-microbial	Zaher et al. (2015)
Fusarium sp. TP-G1	*Dendrobium officinale*	*Staphylococcus aureus* (2 μg/mL), MRSA (2 μg/mL), *Acinetobacter baumannii* (>128 μg/mL)	Trichosetin (**91**), beauvericin A (**93**)	Polypeptides	Anti-microbial	Zaher et al. (2015)
		Staphylococcus aureus (4 μg/mL), MRSA (4 μg/mL), *Acinetobacter baumannii* (>128 μg/mL)	Beauvericin (**92**)	Polypeptides	Anti-microbial	
		Staphylococcus aureus (128 μg/mL), MRSA (128 μg/mL), *Acinetobacter baumannii* (>128 μg/mL)	Enniatin B (**94**),	Polypeptides	Anti-microbial	
		Staphylococcus aureus (32 μg/mL), MRSA (32 μg/mL), *Acinetobacter baumannii* (>128 μg/mL)	Enniatin H (**95**)	Polypeptides	Anti-microbial	
		Staphylococcus aureus (8 μg/mL), MRSA (16 μg/mL), *Acinetobacter baumannii* (>128 μg/mL)	Enniatin I (**96**)	Polypeptides	Anti-microbial	
			Enniatin MK1688 (**97**)	Polypeptides		

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Table 1 (*continued*)

Endophyte	Host Plant	Pathogen/Cancer Cell (Inhibition rate or IC_{50} value)	Metabolites	Taxonomy of metabolites	Activity	References
		Staphylococcus aureus (4 μg/mL), MRSA (8 μg/mL), *Acinetobacter baumannii* (>128 μg/mL)			Anti-microbial	
		Staphylococcus aureus (>128 μg/mL), MRSA (>128 μg/mL), *Acinetobacter baumannii* (64 μg/mL)	Fusaric acid (**98**)	Polypeptides	Anti-microbial	
		Staphylococcus aureus (>128 μg/mL), MRSA (>128 μg/mL), *Acinetobacter baumannii* (128 μg/mL)	Dehydrofusaric acid (**99**)	Polypeptides	Anti-microbial	
		MCF-7 (12.4 μg/mL)	Beauvericin (**92**)	Polypeptides	Anti-cancer	
		MCF-7 (12.22 μg/mL)	Enniatin B (**94**)	Polypeptides	Anti-cancer	
		MCF-7 (11.46 μg/mL)	Enniatin H (**95**)	Polypeptides	Anti-cancer	
		MCF-7 (10.27 μg/mL)	Enniatin I (**96**)	Polypeptides	Anti-cancer	
		BL16F10 (15.2 μg/mL)	Beauvericin (**92**)	Polypeptides	Anti-cancer	
		BL16F10 (10.64 μg/mL)	Enniatin B (**94**)	Polypeptides	Anti-cancer	
		BL16F10 (8.39 μg/mL)	Enniatin H (**95**)	Polypeptides	Anti-cancer	
		BL16F10 (9.46 μg/mL)	Enniatin I (**96**)	Polypeptides	Anti-cancer	
Fusarium sp.	*Mentha longifolia*	*Candida albicans* (8.3 μg/disc)	Fusaristerol A (**100**)	Steroids	Anti-microbial	Chester et al. (2017)
		HCT-116 (0.21 μM)	Fusaristerol A (**100**)	Steroids	Anti-cancer	
Lasiodiplodia venezuelensis BJA-1	*Syzygium samarangense*	–	5,7-dihydroxy-6,8-dimethyl flavanone (**101**)	Flavonoids	Anti-oxidant	Budiono et al. (2019)
Aspergillus aculeatus MBT 102	*Rosa damascena*	MDA-MB-231 (16.6 μM)	Secalonic acid derivative F-7 (**102**)	Organic acids	Anti-cancer	Farooq et al. (2020)
Curvularia papendorfii	*Vernonia amygdalina*	HCoV 229 E, FCV F9 (128 μg/mL)	The EtOAc extract of *Curvularia papendorfii* (**103**)	Fungal Extractives	Anti-microbial	Khiralla et al. (2020)
		MCF-7 (21.5 ± 5.9 μg/mL)	The EtOAc extract of *Curvularia papendorfii* (**103**)	Fungal Extractives	Anti-cancer	
Fusarium sp. CK F05-5	*Dendrobium lindleyi*	–	The CK F05-5-EtOAc extract (**104**)	Fungal Extractives	Anti-oxidant	Bungtongdee et al. (2019)
Fusarium oxysporum TY5	*Dendrobium officinale*	HepG2 (320 μg/mL)	The TY5-EtOAc extract (**105**)	Fungal Extractives	Anti-cancer	Ty et al. (2018)
Phomopsis heveicola	*Piper longum*	*Pseudomonas aeruginosa* (20%), *Shigella sonnei* (25%), *Streptococcus pyogenes* (17%), *Salmonella typhimurium* (23%)	Valproic acid-treated Fungal Extractives of *Phomopsis heveicola* (**106**)	Fungal Extractives	Anti-microbial	Ameen et al. (2021)
Aspergillus cejpii ST9.1	*Nelumbo nucifera*	MRSA (2.5 mg/mL)	The ST9.1-EtOAc extract (**107**)	Fungal Extractives	Anti-microbial	Techaoei et al. (2020)
Fusarium spp.	*Ginkgo biloba*	Hela	The EtOAc extract of *Fusarium* spp. (**108**)	Fungal Extractives	Anti-cancer	Engel (2019)
Colletotrichum sp.	*Curcuma longa*	MCF-7 (500 ppm)	The EtOAc extract of *Colletotrichum* sp. (**109**)	Fungal Extractives	Anti-cancer	Line et al. (2016)
Nigrospora sphaerica	*Cornus florida*	U251, A549 (10 μg/mL)	The EtOAc extract of *Nigrospora sphaerica* (**110**)	Fungal Extractives	Anti-cancer	Maheshwari et al. (2018)
Gaeumannomyces sp. JS0464	*Phragmites communis*	–	The JS0464-EtOAc extract (**111**)	Fungal Extractives	Anti-inflammatory	Lee et al. (2017)
Aspergillus sp. AP5	*Phragmites australis*	*Staphylococcus aureus* (53.04%), *Escherichia coli* (61.23%), *Klebsiella* sp. (51.16%), *Proteus vulgaris* (15.44%), *Pseudomonas aeruginosa* (30.25%)	The AP5-EtOAc extract (**112**)	Fungal Extractives	Anti-microbial	Abdelgawad et al. (2022)
		Candida albicans (40.14%)	The AP5-EtOAc extract (**112**)	Fungal Extractives	Anti-microbial	
Colletotrichum coccodes	*Houttuynia cordata*	*Candida albicans* (125 μg/mL), *Staphylococcus aureus* (125 μg/mL), *Escherichia coli* (125 μg/mL), *Pseudomonas aeruginosa* (250 μg/mL)	The EtOAc extract of *Colletotrichum coccodes* (**113**)	Fungal Extractives	Anti-microbial	(Talukdar et al., 2021; Talukdar et al., 2021)
		Staphylococcus aureus (19 mm), *Escherichia coli* (19 mm), *Pseudomonas aeruginosa* (18 mm), *Candida albicans* (21 mm)	The EtOAc extract of *Colletotrichum coccodes* (**114**)	Fungal Extractives	Anti-microbial	
Phyllosticta capitalensis	*Houttuynia cordata*	*Staphylococcus aureus* (23 mm), *Escherichia coli* (14 mm), *Pseudomonas aeruginosa* (14 mm), *Candida albicans* (22 mm)	The EtOAc extract of *Phyllosticta capitalensis* (**115**)	Fungal Extractives	Anti-microbial	Talukdar et al. (2021)
Penicillium sp. SNF123	*Panax ginseng*	B16F10, MNT-1 (2.5–50 μg/mL)	Acremonidin E (**116**)	Fungal Extractives	Anti-cancer	Kim et al. (2019)

(*continued on next page*)

Table 1 (*continued*)

Endophyte	Host Plant	Pathogen/Cancer Cell (Inhibition rate or IC_{50} value)	Metabolites	Taxonomy of metabolites	Activity	References
Aspergillus terreus	*Glycine max*	*Anti*-COVID-19	Aspergillide B1 (**117**), 3a-Hydroxy-3, 5-dihydromonacolin L (**118**)	Fungal Extractives	Anti-microbial	El-Hawary et al. (2021)
Penicillium griseofulvum MPR1	*Mentha pulegium*	*Escherichia coli* (45.5 mm)	The EtOAc extract of *Penicillium griseofulvum* MPR1 (**119**)	Fungal Extractives	Anti-microbial	Amina et al. (2018)
		Escherichia coli (41 mm)	The $CHCl_2$ extract of *Penicillium griseofulvum* MPR1 (**120**)	Fungal Extractives	Anti-microbial	
Arthrinium sp. MFLUCC16-1053	*Zingiber cassumunar*	*Staphylococcus aureus* (31.25 μg/mL), *Escherichia coli* (7.81 μg/mL)	The MFLUCC16-1053-EtOAc extract (**121**)	Fungal Extractives	Anti-microbial	Pansanit and Pripdeevech (2018)

Note: "-" indicates the activity of these compounds are not mentioned in the cited references.

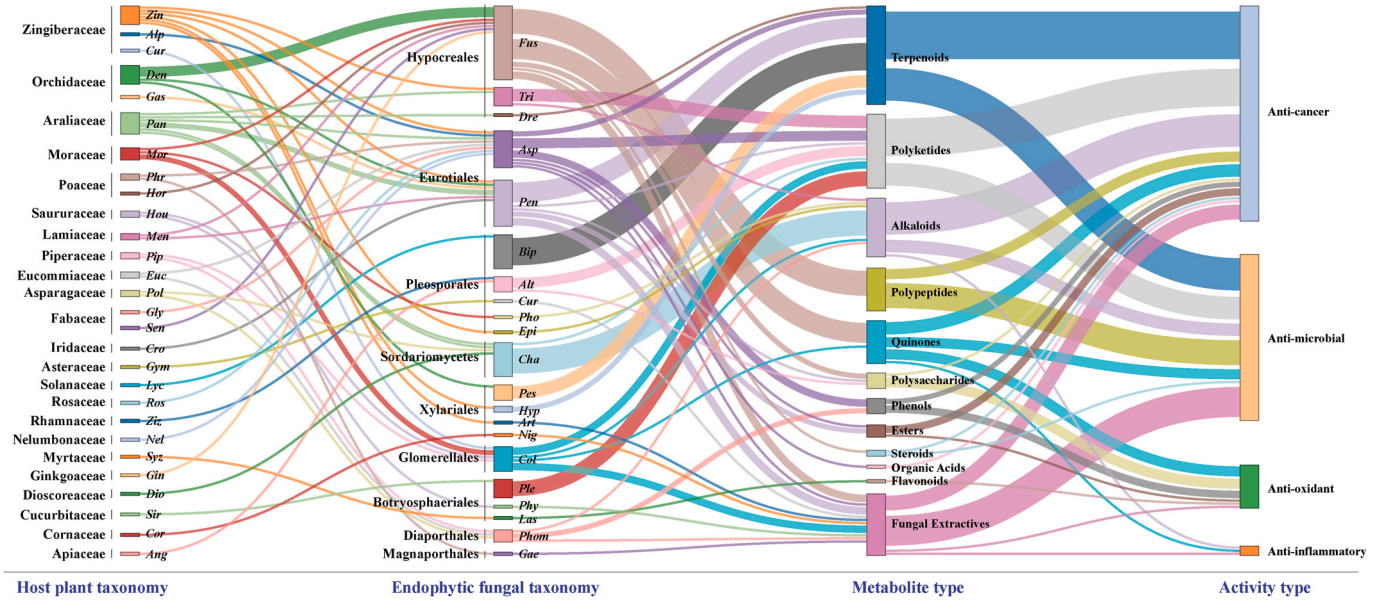

Fig. 1. Metabolites of MFH plant-derived endophytic fungi and their activities. *Zin*, *Zingiber*; *Alp*, *Alpinia*; *Cur*, *Curcuma*; *Den*, *Dendrobium*; *Gas*, *Gastrodia*; *Pan*, *Panax*; *Mor*, *Morus*; *Phr*, *Phragmites*; *Hor*, *Hordeum*; *Hou*, *Houttuynia*; *Men*, *Mentha*; *Pip*, *Piper*; *Euc*, *Eucommia*; *Pol*, *Polygonatum*; *Gly*, *Glycine*; *Sen*, *Senna*; *Cro*, *Crocus*; *Gym*, *Gymnanthemum*; *Lyc*, *Lycium*; *Ros*, *Rosa*; *Ziz*, *Ziziphus*; *Nel*, *Nelumbo*; *Syz*, *Syzygium*; *Gin*, *Ginkgo*; *Dio*, *Dioscorea*; *Sir*, *Siraitia*; *Cor*, *Cornus*; *Ang*, *Angelica*; *Fus*, *Fusarium*; *Tri*, *Trichoderma*; *Dre*, *Drechmeria*; *Asp*, *Aspergillus*; *Pen*, *Penicillium*; *Bip*, *Bipolaris*; *Alt*, *Alternaria*; *Cur*, *Curvularia*; *Pho*, *Phoma*; *Epi*, *Epicoccum*; *Cha*, *Chaetomium*; *Pes*, *Pestalotiopsis*; *Hyp*, *Hypomontagnella*; *Art*, *Arthrinium*; *Nig*, *Nigrospora*; *Col*, *Colletotrichum*; *Ple*, *Pleosporales*; *Phy*, *Phyllosticta*; *Las*, *Lasiodiplodia*; *Phom*, *Phomopsis*; *Gae*, *Gaeumannomyces*. The line thickness represents the number.

gloeosporioides and *Periconia* sp.) isolated from *P. nigrum* or *P. longum* could produce piperine (Chithra et al., 2014a; Chithra et al., 2014b; Verma et al., 2011). Pinoresinol diglucoside (PDG), one of the major lignans with various pharmacological functions, is an important anti-hypertensive compound in *Eucommia ulmoides* (Shi, J. et al., 2012). Endophytic fungus *Phomopsis* sp. XP-8 isolated from the bark of *E. ulmoides* could produce Pin (the precursor of PDG) (Li, Q. et al., 2016). Ginkgolides, one of the main terpenoids found in the leaves and bark of *Ginkgo biloba*, has potent antagonist effects on platelet activating factors, involved in the development of a number of cardiovascular, renal, respiratory and central nervous system disorders (Liu, X. G. et al., 2021). Ginkgolide B produced endophytic fungus (*Fusarium oxysporum*) isolated from *G. biloba*, which is the main phytochemicals of *G. biloba* (Cui et al., 2012).

Whether other endophytic fungal metabolites of these shared types correlate with their host plants requires further confirmation. To date, the ability of endophytes to produce the same or similar bioactive compounds as their hosts raises several intriguing questions that have yet to be answered, including whether the compound is first synthesized by the plant or by the fungus and whether there is a transfer of genetic information between the two (Caruso et al., 2020). As these questions are addressed, it may be possible in the future to extract more functionalities from endophytic fungi of MFH plants that are similar to the edible and medicinal characteristics of their hosts.

4. Classification of MFH plant-derived endophytic fungal metabolites

We searched the literature published between 2017 and 2022, and 121 metabolites belonging to 12 chemical classes were reported: terpenoids, polyketides, alkaloids, polypeptides, quinones, phenols, polysaccharides, esters, steroids, flavonoids, organic acids, and fungal extracts (Fig. 1 and S3). With respect to biochemistry, terpenoids and polyketides are the most purified antimicrobial secondary metabolites from endophytes (Mousa and Raizada, 2013). Terpenoids are one of the most commonly isolated metabolites of plant endophytic fungi. *Trichoderma*, *Aspergillus*, *Penicillium*, *Xylaria*, *Diaporthe*, *Pestalotiopsis*, and *Paraconiothyrium* are the principal producers of terpenoids. Cytotoxic, antimicrobial, and anti-inflammatory properties are the most commonly identified biological activities of these terpenoids (Amirzakariya and Shakeri, 2022). Endophytes are a rich source of structurally novel bioactive natural products (Gunatilaka, 2016), predominantly polyketides and non-ribosomal peptides (Fischbach and Walsh, 2006). They represent a structure class that often gives rise to clinically relevant pharmaceuticals (Butler et al., 2014; Clardy et al., 2006; Newman and Cragg, 2012).

4.1. Alkaloids

Many alkaloids have been discovered from the endophytic fungi of MFH plants. For example, a new cytochalasin has been isolated from *Chaetomium globosum* fermented in Chinese yam (*Dioscorea opposita*) and named yamchaetoglobosin A (**1**) (Ruan et al., 2017). A new epidithiodiketopiperazine (ETP), pretrichodermamide A (**2**), and epicorazine A (**3**) have been isolated from cultures of *Trichoderma harzianum* and *Epicoccum nigrum*, endophytic fungi associated with *Zingiber officinale* and *Salix* sp., respectively (Harwoko et al., 2021). A fungal metabolite from *Phomopsis*, identified as epoxycytochalasin H (**4**), has been isolated from the flowering plant *Polygonatum sibiricum* (Xu, 2020). An oxazole-type compound named macrooxazoles C (**5**) has been isolated from ethyl acetate (EtOAc) extract of *Phoma* sp. JS0228 cultures, an endophytic fungus of *Morus alba* (Ku et al., 2021). *Colletotrichum gloeosporioides* has been isolated from black pepper (*Piper nigrum*), with alkaloid piperine (**6**) in its extract (Krishna et al., 2020).

Chaetomium sp. SYP-F7950 isolated from *Panax notoginseng* produces a large number of alkaloids (**7**–**11**) (Peng et al., 2019). In addition, demethylchaetocochin C (**12**) and chaetoperazine A (**13**) (two new ETP alkaloids), the novel pyridine benzamide 4-formyl-N-(30-hydroxypyridin-20-yl) benzamide (**14**), and the ETP derivative chetomin (**15**) have been isolated from acetate extracts of *Chaetomium globosum* 7951 solid cultures (Wang, F. et al., 2019).

4.2. Terpenoids

Some endophytic fungi from MFH plants produce fungus-specific components of meroterpenoids. For example, a new meroterpenoid preaustinoid D (**16**) and a new neogrifolin derivative dihydroxyneogrifolic acid (**17**), along with other five previously reported meroterpenoids (**18**–**22**), have been isolated from the endophytic fungus *Penicillium* sp. T2–8 associated with *Gastrodia elata* (Duan et al., 2016). Eleven new meroterpenoids, bipolahydroquinones A–C (**23**–**25**), cochlioquinones I–N (**26**–**30** and **33**), and isocochlioquinones F and G (**31** and **32**), along with six known ones, have been obtained from endophytic fungus *Bipolaris* sp. L1–2 from *Lycium barbarum* (Long et al., 2019).

Moreover, there are several other endophytic fungi from MFH plants that produce monoterpenoids, sesquiterpenes, indole diterpenes, and heptaterpenes with antibacterial and anticancer activities. For example, two novel cytotoxic and antifungal monoterpenoid constituents (**34** and **35**), and three known compounds (**36**–**38**) have been isolated from the metabolites of endophytic fungi *Pestalotiopsis* sp. DO14 from *Dendrobium officinale* (Wu et al., 2016). Two novel sesquiterpenoids, namely, emericellins A (**39**) and B (**40**), have been isolated from liquid cultures of endophytic fungus *Emericella* sp. XL 029 associated with the leaves of *Panax notoginseng* (Pang et al., 2018a). Shearilicine (**41**) has been isolated from the endophyte *Penicillium* sp. (strain ZO-R1-1) isolated from the roots of *Zingiber officinale* (Ariantari et al., 2019). Drechmerin B (**42**) has been isolated from fermentation broth of *Drechmeria* sp. isolated from the root of *Panax notoginseng* (Zhao, J. C. et al., 2018a). Terpenoid-alkaloid (**43**) and sesterterpenoid (**44**) have been isolated from the endophytic fungi *Hypomontagnella monticulosa* residing within the rhizome of *Z. griffithii* from northern Sumatra (Lut et al., 2021).

5. Polyketides

Polyketide compounds are also produced by endophytic fungi from MFH plants. For example, three unusual polyketides with a 5/6/10-fused ring system, named colletotrichalactone A-Ca (**45**–**47a**), have been isolated from cultures of the endophytic fungus *Colletotrichum* sp. JS-0361 isolated from a leaf of *Morus alba* (Bang et al., 2020). Five new chlamydosporol derivatives, named pleospyrone A–E (**48**–**52**), along with one known congener (**53**), have been isolated from a culture of the endophytic fungus *Pleosporales* sp. Sigrf05 obtained from *Siraitia grosvenorii* (Lai et al., 2020). A new azaphilone, chaephilone C (**54**), has been isolated from *Chaetomium globosum*, an endophytic fungus of *Polygonatum sibiricum* (Song, C. et al., 2020). Chemical investigation of the culture extract of an endophytic *Penicillium citrinum* from *Dendrobium officinale* afforded nine citrinin derivatives and one peptide-polyketide hybrid GKK1032B (**55**) (Na et al., 2022). In one study, *Alternaria* sp. was isolated from *Ziziphus jujuba*, and its liquid extract yielded four natural products (**56**–**59**) (Orfali et al., 2017).

Endophytic fungi isolated from *Panax notoginseng* produce polyketide compounds. For example, a new compound named koninginin W (**60**) and four known polyketides (**61**–**64**), have been isolated from the endophytic fungus *Trichoderma koningiopsis* YIM PH30002 (Wang, Y. L. et al., 2021). *Emericella* sp. XL 029 has yielded four novel polyketides, emericelactone A–D (**65**–**68**) (Pang et al., 2018b).

5.1. Quinones

Endophytic fungi isolated from *Morus alba* produce quinones. *Colletotrichum* sp. JS-0367 produces the quinone 1,3-dihydroxy-2,8dimethoxy-6-methylanthraquinone (**69**) (Fibroblasts et al., 2021). Chemical investigation of cultures of the fungus *F. solani* JS-0169 resulted in the isolation of six compounds, including one new γ-pyrone, one known γ-pyrone, fusarester D, and four known naphthoquinones (karuquinone B, javanicin, solaniol, and fusarubin [**70**]) (Choi et al., 2020). In addition, *F. solani* has been isolated from *Cassia alata* and naphthoquinones and aza-anthraquinones (**71–77**) are present in its metabolites (Khan et al., 2018).

5.2. Polysaccharides

In recent years, the development and use of microbial polysaccharides has received increasing attention due to its potential industrial applications (Donot et al., 2012; Nwodo et al., 2012). Extracellular polysaccharides (EPSs) are a group of microbial polysaccharides biosynthesized mainly by bacteria and fungi through intracellular or extracellular pathways (Freitas et al., 2011; Kumar et al., 2007). Endophytic fungi are important sources of bioactive EPSs, and these structurally novel polysaccharides not only play an important role in plant–endophyte interactions but also have a variety of beneficial biological functions in humans, such as antioxidant, anti-inflammatory, and anticancer properties, with potential application in the health food and pharmaceutical industries (Cultures, 2016; Li, P. et al., 2011; Liu, J. et al., 2016; Zeng, Y. et al., 2019).

However, EPS-producing endophytic fungi from MFH plants have been poorly explored. An EPS (**78**)-producing endophytic fungus has been isolated from *Angelica sinensis* and identified as *Alternaria tenuissima* F1 (Wang, Y. et al., 2019). Two polysaccharides, DGS1 (**79**) and DGS2 (**80**), have been obtained via solid-state fermentation (SSF) of *Fusarium solani* DO7, an endophytic fungus isolated from the orchid *Dendrobium officinale* (Zeng, Y. J., Yang, Wu, et al., 2019a,b). The endophytic fungus *Penicillium citreonigrum* CSL-27 has been isolated from *Crocus sativus* and its EPS (**81**) includes mannose, glucose, galactose xylose, and arabinose at a molar ratio of 25.6:16.5:1.0:3.8:5.4 (Mag et al., 2018).

5.3. Esters

Endophytic fungi of MFH plants produce metabolites that can be employed as antibiotics, some of which are esters. *Aspergillus terreus*-RTN3, isolated from young stems of *Alpinia chinensis*, yields the compound MM_2 (**82**) (methyl 2-((4-amino-2-bromo-3-methyl-5-thioxocyclopenta-1,3-dien-1-yl) oxygen)-4-hydroxy-6-methoxybenzoate) (Suhartati, 2020). *Penicillium* sp. has been isolated from the healthy roots of *Panax notoginseng* and five macrolide antibiotics have been synthesized, including brefeldin A (**83**) and brefeldin A 7-O-acetate (**84**) (Xie et al., 2017).

5.4. Phenols

Studies have shown that phenolic compounds including phenol and phenolic acids are frequently isolated from endophytic fungi of MFH plants, and have strong antioxidant activity.

For example, the ethyl acetate extract of *Aspergillus austroafricanus* CGJ-B3 (EAE) (**85**) isolated from *Z. officinale* is a promising pharmaceutical agent and can be used as an alternative source of polyphenols such as *p*-coumaric acid, ferulic acid, and cinnamic acid (Danagoudar et al., 2017). Endophytic fungal extracts from the well-known MFH plant *Eucommia ulmoides* contain phenolic compounds. Furthermore, 3, 4-dihydroxybenzeneacetic acid (**86**) and 3,4-dihydroxyphenylacetic acid methyl ester (**87**) have been obtained from EtOAc extracts of *Aspergillus flavipes* DZ-3 (Liu, W. et al., 2021). *Phomopsis* sp. XP-8 produces the lignan molecules pinoresinol (Pin) (**88**) and pinoresinol monoglucoside (PMG) (**89**) (Li, Q. et al., 2016).

5.5. Polypeptides

Some endophytic fungi from MFH plants, particularly *Fusarium* sp., also produce polypeptides. Enniatins (ENs) (**90**), a group of antibiotics commonly produced by various strains of *Fusarium*, are six-membered cyclic depsipeptides formed by the union of three molecules of D-α-hydroxyisovaleric acid and three N-methyl-L-amino acids. The endophyte *Fusarium tricinctum* has been isolated from the fruits of *Hordeum sativum* (Zaher et al., 2015). Trichosetin (**91**), beauvericins (**92–93**), enniatins (**94–97**), fusaric acid (**98**), and dehydrofusaric acid (**99**) are produced by the endophytic fungus *Fusarium* sp. TP-G1 derived from the root of *D. officinale* (Zaher et al., 2015).

5.6. Steroids, flavonoids, and organic acids

Steroids, flavonoids, and organic acids can also be produced by endophytic fungi of MFH plants. For example, *Fusarium* sp. isolated from the roots of *Mentha longifolia*, produce fusaristerol A (**100**) (Chester et al., 2017). *Lasiodiplodia venezuelensis* BJA-1 has been isolated from healthy leaves of *Syzygium samarangense*, and its ethyl acetate extract contains 5,7-dihydroxy-6,8-dimethyl flavanone (**101**) (Budiono et al., 2019). A new secalonic acid derivative F-7 (**102**) has been isolated from the endophytic *Aspergillus aculeatus* MBT 102, associated with *Rosa damascena* (Farooq et al., 2020).

5.7. Fungal extracts

In addition, mixes of metabolites and unclassified extracts have been reported. In one study, an endophytic fungus isolated from *Vernonia amygdalina*, an MFH plant from Sudan, was taxonomically characterized as *Curvularia papendorfii* (Khiralla et al., 2020). A crude extract of ethyl acetate (**103**) was prepared from it. In another study, *Fusarium* sp. CK F05-5 was isolated from the flower of *Dendrobium lindleyi*, and an ethyl acetate extract (**104**) was obtained from it (Bungtongdee et al., 2019). In yet another study, *Fusarium oxysporum* TY5 was isolated from *D. officinale*, and again an ethyl acetate extract (**105**) was obtained (Ty et al., 2018). In Ameen et al. (2021), seven endophytic fungi were isolated from the tropical MFH plant *Piper longum* L. After preliminary screening, *Phomopsis heveicola* was selected for epigenetic activation treatments. Endophytic fungi were treated with different concentrations of valproic acid to obtain extracts (**106**). In another study, ethyl acetate extract of endophyte *Aspergillus cejpii* ST9.1 (**107**) was isolated from the aquatic plant *Nelumbo nucifera*; the major component of the crude extract was 5-(1H-Indol-3-yl)-4,5-dihydro-[1,2,4]triazin-3-ylamine ($C_{11}H_{11}N_5$) (Techaoei et al., 2020). Three strains of *Fusarium* species (J-1, J-2, and J-3) have been isolated from *Ginkgo biloba*, yielding a crude extract (**108**) (Engel, 2019). *Colletotrichum* sp. has been isolated from *Curcuma longa* L., yielding a filtrate (**109**) (Line et al., 2016). *Nigrospora sphaerica* has been isolated from *Cornus florida*, yielding a crude extract (**110**) (Maheshwari et al., 2018).

A study reported a dark septate endophytic fungal strain (JS0464) identified as *Gaeumannomyces* sp. isolated from the rhizome of the halophyte *Phragmites communis*. This strain was cultured on a large scale and extracted with ethyl acetate (**111**). Chemical investigations of JS0464 extracts have identified two glycosylated dialkylresorcinol derivatives, an anthraquinone derivative, and eight known compounds (Lee et al., 2017). The endophytic fungus *Aspergillus* sp. AP5 has been isolated from the leaves of *Phragmites australis*; AP5-EtOAc extract (**112**) has been prepared with ethyl acetate (Abdelgawad et al., 2022).

Other studies have isolated *Colletotrichum coccodes* from healthy leaf tissues of *Houttuynia cordata* Thunb. (yielding ethyl acetate extracts [**113**] and [**114**]) (Talukdar et al., 2021a; Talukdar et al., 2021b) and *Phyllosticta capitalensis* (yielding ethyl acetate extract [**115**]) (Talukdar et al., 2021a).

Penicillium sp. SNF123 has been isolated from the roots of *Panax ginseng*, and its extract contains Acremonidin E (**116**) (Kim et al., 2019). *Aspergillus terreus* has been isolated from the roots of soybean *Glycine max*; 18 compounds have been identified in its extract (including aspergillide B1 [**117**] and 3a-hydroxy-3, 5dihydromonacolin L [**118**]) (El-Hawary et al., 2021), with the highest content being quinones, polyketides, and isocoumarins.

An endophytic fungus identified as *Penicillium griseofulvum*, which shows considerable antimicrobial activity, has been isolated from *Mentha pulegium* Extracts using ethyl acetate (**119**) and dichloromethane (**120**) show antimicrobial and anticancer activity (Amina et al., 2018). In one study, *Arthrinium* sp. MFLUCC16-1053 was isolated from *Zingiber cassumunar* and identified morphologically; an ethyl acetate extract (**121**) was obtained and it showed antimicrobial and anticancer activity (Pansanit and Pripdeevech, 2018).

6. Activities of metabolites produced by endophytic fungi from MFH plants

As our review shows, endophytic fungi of MFH plants are diverse, and the wide range of metabolites they produce have many bioactive properties, including antioxidant, antimicrobial, anti-inflammatory, and anticancer activities. They are an important source of biologically active metabolites.

6.1. Antioxidants

During the growth of living organisms, free radicals are continuously produced in the body. If these are not scavenged in time and accumulate in the body to excessive levels, they can cause serious harm to human health (Biswas et al., 2017; Jamshidi-kia et al., 2020; Yashin et al., 2017). There are a variety of endophytic fungal metabolites of MFH plants that demonstrate effective free-radical scavenging and antioxidant functions (Xiaoyue et al., 2020).

Bostrycoidin (**74**) exhibits significant antioxidant activity with an IC_{50} value of 1.6 μg/mL, which is comparable to butylated hydroxyanisole (BHA), Trolox, and ascorbic acid. Anhydrofusarubin (**72**), 4-hydroxybenzaldehyde (**73**), and fusarubin (**75**) exhibit good antioxidant activity with IC_{50} values of 12.4, 28.9, and 34.8 μg/mL, respectively (Khan et al., 2018). EPS (**78**) slightly affects the scavenging of the superoxide radical. Hydroxyl radical-scavenging activity is concentration-dependent (Wang, Y. et al., 2019). In one study, when the EPS (**81**) concentration was increased to 0.4 mg/mL, the DPPH radical scavenging activity reached 95.50% (Mag et al., 2018). MM_2 (**82**) has high antioxidant activity, and the ability to scavenge α, α-diphenyl-β-picrylhydrazyl (DPPH) free radicals increases linearly with concentration (Suhartati, 2020). EAE (**85**) shows a varying degree of antioxidant activity, comparable to ascorbic acid (Danagoudar et al., 2017). 3,4-dihydroxybenzeneacetic acid (**86**) and 3,4-dihydroxyphenylacetic acid methyl ester (**87**) show potent antioxidant capacities with IC_{50} values of 14.4 μM and 27.1 μM, respectively (Liu, W. et al., 2021). 5,

7-dihydroxy-6,8-dimethyl flavanone (**101**) also has high antioxidant activity (IC_{50} of 49.96 μg/mL) (Budiono et al., 2019). The ethyl acetate extract of CK F05-5 (**104**) exhibits antioxidant activity with an IC_{50} value of 89.6 μg/mL (Bungtongdee et al., 2019).

6.2. Antimicrobial compounds

The widespread use of antibiotics has enhance the drug resistance of many microbes including large numbers of pathogens (Fadiji and Babalola, 2020). Therefore, it is essential for new antimicrobials to be developed. Endophytic fungi from MFH plants also produce a wide range of antimicrobial substances that deserve further research (Gao et al., 2010; MT et al., 2018; Pavithra et al., 2020; Rajani et al., 2021; Zabalgogeazcoa, 2008).

6.3. Antibacterial and antifungal compounds

When the body's immune function or resistance decreases and the normal flora is dysregulated, bacteria such as *Escherichia coli* and *Candida albicans* can invade cells and cause a variety of local tissue and organ infections such as in the human gastrointestinal tract, resulting in disease (Bischoff et al., 2014; Tlaskalova-Hogenova et al., 2005; Tlaskalová-Hogenová et al., 2004; Wang, Y. hua, 2021).

Pretrichodermamide A (**2**) shows antimicrobial activity against the human pathogenic bacterium *Mycobacterium tuberculosis*, with a minimum inhibitory concentration (MIC) value of 25 mg/mL (50 mM) (Harwoko et al., 2021). Chaetocochin C (**8**), chetomin A (**9**), chetomin C (**10**), and chetomin (**11**) have strong antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, and *Enterococcus faecium*, and antifungal activity against *Candida albicans* with MIC values of 0.12–9.6 μg mL^{-1} (Peng et al., 2019). Preaustinoid D (**16**) and dihydroxyneogrifolic acid (**17**) show moderate activity against *C. albicans* (MICs of 128 μg/mL), with the latter also exhibiting activities against *Bacillus subtilis* and *S. aureus*. Other compounds that have shown robust antibacterial activity include preaustinoid A1 (**18**), austin (**20**), and (S)-18, 19-dihydroxyneogrifolin (**21**) (Duan et al., 2016) (see Table 1 for details). Other compounds that have shown antifungal activities include (4S, 6S)-6-[(1S, 2R)-1, 2-dihydroxybutyl]4-hydroxy-4-methoxytetrahydro-2H-pyran-2-one (**34**), (6S, 2E)-6-hydroxy-3-methoxy-5-oxodec-2-enoic acid (**35**), LL-P880γ (**36**), LL-P880α (**37**), and ergosta-5,7, 22-trien-3b-ol (**38**) (Wu et al., 2016).

Emericellins A (**39**) and B (**40**) displayed moderate activities against three bacterial strains (*B. subtilis*, *Bacillus cereus*, and *E. coli*) with MIC values of 25–50 μg/mL (Pang et al., 2018a). Emericelactones A-D (**65**–**68**) showed moderate antimicrobial activities against two human pathogenic bacteria (*Micrococcus lysodeikticus* and *S. typhimurium*) with MIC values of 25–50 μg/mL (Pang et al., 2018b). Fusarubin (**75**), anhydrofusarubin (**72**) and bostrycoidin (**74**) exhibited highly significant activity against four tested pathogenic bacteria, including *Bacillus megaterium*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *E. coli* (Khan et al., 2018). The MIC value of fusaric acid (**98**) and dehydrofusaric acid (**99**) against *Acinetobacter baumannii* were 64 μg/mL and 128 μg/mL, respectively (Shi, S. et al., 2018). Drechmerin B (**42**) (Zhao, J. C. et al., 2018a) and fusaristerol A (**100**) (Chester et al., 2017) possessed significant antifungal activity toward *Candida albicans*, with MIC values of 12.5 μg/mL and 8.3 μg/disc, respectively. The antimicrobial activities of the methanol extract of the fungus *F. tricinctum* containing Ens (**90**) were tested against Gram-positive and Gram-negative bacteria and fungi (Zaher et al., 2015). Other compounds that have shown antibacteria activities include koninginin W (**60**), koninginin D (**61**), 7-O-methylkoninginin D (**62**), and koninginin A (**64**) (Wang, Y. L. et al., 2021).

Some endophytic fungal extracts have shown antibacterial activities. Valproic acid-treated fungal extracts (**106**) showed significant antibacterial efficiency against the bacteria *Pseudomonas aeruginosa*, *Shigella sonnei*, and *Streptococcus pyogenes* (Ameen et al., 2021). An ST9.1-EtOAc extract (**107**) had active fractions against methicillin-resistant *Staphylococcus aureus* (MRSA) with a MIC of 2.5 mg/mL and minimum bactericidal concentration (MBC) concentration of 50.0 mg/mL (Techaoei et al., 2020). An AP5-EtOAc extract (**112**) displayed pronounced antimicrobial properties against *S. aureus*, *E. coli*, and *Klebsiella* sp. with inhibition ratios of 53.04%, 61.23%, and 51.16%, respectively. However, it had only a low antibacterial activity against *Proteus vulgaris* and *Pseudomonas aeruginosa* with an inhibition ratio of 15.44% and 30.25%, respectively. In addition, it had the antifungal activity against *C. albicans* (Abdelgawad et al., 2022). Ethyl acetate extracts of *Colletotrichum coccodes* (**113**) and *P. capitalensis* (**115**) exhibited considerable antimicrobial activity against *S. aureus*, *E. coli*, *C. albicans*, and *P. aeruginosa* (Talukdar et al., 2021a; Talukdar et al., 2021b) (see Table 1 for details). High activities have been reported for EtOAc (**119**) and $CHCl_2$ (**120**) crude extracts of *Penicillium griseofulvum* MPR1 against *E. coli* with maximal inhibition zones of 45.5 and 41.0 mm, respectively (Amina et al., 2018). The ethyl acetate extract of *Arthrinium* sp. MFLUCC16–1053 (**121**) showed activity against *S. aureus* and *E. coli* with MIC values of 31.25 and 7.81 μg/mL, respectively (Pansanit and Pripdeevech, 2018).

6.4. Antiviral compounds

Endophytic fungi isolated from MFH plants can produce different metabolites with antiviral activity and thus are considered sources of potential antiviral drugs. Such metabolites are less toxic and milder than traditional modern therapeutic drugs. This could open new paths for the future development of food supplements and nutritional products as alternative therapies for the prevention and treatment of infectious diseases (Patel, B. et al., 2021).

An ethyl acetate crude extract of *C. papendorfii* (**103**) showed an important antiviral effect against two viral pathogens, the human coronavirus HCoV 229 E and a norovirus surrogate, the feline coronavirus FCV F9 (Khiralla et al., 2020). Aspergillide B1 (**117**) and 3a-Hydroxy-3, 5dihydromonacolin L (**118**) showed the highest binding energy scores towards the main protease (M^{pro}) of COVID-19 at −9.473 and −9.386, respectively (El-Hawary et al., 2021).

6.5. Anti-inflammatory

Many researchers are now searching for biologically active metabolites that can inhibit the production of inflammatory mediators, with a focus on drugs of natural origin (Abdel-azeem and Khalil, 2019). Numerous studies have shown that metabolites produced by endophytic fungi of MFH plants have significant anti-inflammatory effects.

Piperine (**6**) has the least binding energy (−104.914) with the active site of efflux protein Rv1258c. In addition, compared to widely used non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, and diclofenac piperine (**6**) showed lower binding energy (−92.383) with the active site of prostaglandin synthesizing enzyme cyclooxygenase 2 (COX2), showing anti-inflammatory activity (Krishna et al., 2020). 1,3-dihydroxy-2,8dimethoxy-6-methylanthraquinone (**69**) reduces tumor necrosis factor (TNF-α)-stimulated reactive oxygen species (ROS), nitric oxide (NO), and prostaglandin E2 (PGE2), attenuates matrix metalloproteinase (MMP)-1 expression, and enhances collagen synthesis. Furthermore, it inhibits the expression of TNF-α-stimulated proinflammatory cytokine mediators, including inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), and proinflammatory cytokine interleukins (IL-1β), IL-6, and IL-8 (Fibroblasts et al., 2021). The addition of DGS1 (**79**) and DGS2 (**80**) significantly increased the levels of TNF-α, IL-6, and NO by activating the expression of TNF-α, IL-6, and iNOs genes, and had significant anti-inflammatory activity (Zeng, Y. J., Yang, Wu, et al., 2019a,b). The compounds in a JS0464-EtOAc extract (**111**) showed significant nitric oxide reduction activity in lipopolysaccharide-stimulated microglia BV-2 cells (Lee et al., 2017).

6.6. Anticancer

Cancer is a leading cause of death worldwide. It is speculated that there will be approximately 4.82 million and 2.37 million new cancer cases, and 3.21 million and 0.64 million cancer deaths in China and the US, respectively, in 2022 (Xia et al., 2022). The prevention and treatment of cancer have become important research fields. There are two traditional ways to obtain anticancer drugs: extraction from plants and chemical synthesis. However, due to the scarcity of plant resources and the tedious chemical synthesis pathways, there is increased research interest in identifying anticancer drugs from endophytic fungi (Wanwan et al., 2018).

Cervical cancer, the most common cancer in women worldwide, is usually prevented or treated with vaccines, radiation, chemotherapy, and short courses of therapy; however, chemotherapy drugs can destroy adjacent normal cells or change the nature of the cells, which can lead to undesirable sequelae (Anorlu, 2008; Siddharthar et al., 2014). To alleviate the side effects caused by chemically synthesized therapeutic agents, numerous researchers have explored new therapies using endophytic fungal metabolites. EPS (**81**), displays potential cytotoxicity against human cervical cancer (HeLa) with the proliferation of 33.10% (Mag et al., 2018). MM_2 (**82**) has the ability to inhibit HeLa with IC_{50} values of 39.21 μg/mL (Suhartati, 2020). The growth inhibition rates of crude extracts (**108**) of strain J-1 and J-3 on HeLa cells were 59.6% and 59.1%, respectively (Engel, 2019).

In addition to cervical cancer, breast cancer is one of the most common cancers among women, causing approximately 450,000 deaths worldwide each year (Cancer and Atlas, 2012). In our study, many compounds produced by endophytic fungi isolated from MFH plants showed significant inhibitory effects on breast cancer cells. For example, yamchaetoglobosin A (**1**) demonstrated cytotoxicity to human breast cancer MCF-7 cell lines with the inhibition ratio of 58% at a concentration of 40 μM (Ruan et al., 2017). Macrooxazole C (**5**) showed moderate anti-proliferative activities against MCF-7 cell lines with IC_{50} values of 0.29 mM (Ku et al., 2021). Chetoseminudin F (**7**), haetocochin C (**8**), chetomin A (**9**), chetomin C (**10**), and chetomin (**11**) displayed more potent cytotoxicity against human breast cancer MDA-MB-231 cell lines (Peng et al., 2019). Demethylchaetocochin C (**12**), chaetoperazine A (**13**), 4-formyl-N-(30-hydroxypyridin-20-yl) benzamide (**14**), and chetomin (**15**) inhibited the growth of MCF-7 and MDA-MB-231 (IC_{50} from 4.5 to 65.0 mM) (Wang, F. et al., 2019). Bipolahydroquinone C (**25**), cochlioquinone I (**26**), and cochlioquinones K–N (**28**–**30and 33**) showed cytotoxicity against MDA-MB-231 cells with IC_{50} values ranging from 5.5 to 9.5 μM (Long et al., 2019). Colletotrichalactones A and Ca (**45 and 47a**) displayed moderate to potent cytotoxic activities against MCF-7 cells with IC_{50} values of 35.06 and 25.20 μM, respectively (Bang et al., 2020). Beauvericin (**92**), enniatin B (**94**), enniatin H (**95**), and enniatin I (**96**) show antitumor activities against MCF-7 cell lines with IC_{50} values of 12.4, 12.22, 11.46, and 10.27 μg/mL (Shi, S. et al., 2018).

Some endophytic fungal extracts have shown antiproliferative activity, including the EtOAc extract of *C. papendorfii* (**103**) (Khiralla et al., 2020) and *Colletotrichum* sp. (**109**) (Line et al., 2016), they both reveal antiproliferative activity against the MCF-7 cell line.

Triple-negative breast cancer (TNBC) is a heterogeneous disease characterized by a lack of hormonal receptors and HER2 overexpression. It is the only breast cancer subgroup that does not benefit from targeted therapies, and its prognosis is poor (Prado-vázquez et al., 2019). Patients with TNBC are difficult to treat because of poor prognosis, limited treatment options, and resistance to multiple anticancer drugs. Therefore, the search for novel therapeutic agents to treat this complex malignancy is of great value (Razak et al., 2019). Secalonic acid derivative F-7 (**102**) possesses strong cytotoxic activity against TNBC cells, inducing mitochondrial damage and reactive oxygen species-mediated apoptosis, arresting the G1 phase of the cells in a dose-dependent manner. In addition, it causes significant microtubule disruption in TNBC cells, and restricts cell migration leading to concomitant increase in the expression of cleaved caspase and PARP (Farooq et al., 2020).

Hepatocellular carcinoma remains the fifth most frequently diagnosed cancer and is the second leading cause of cancer-related mortality globally (Xue et al., 2016). Conventional chemotherapeutic drugs have several disadvantages ranging from limited effectiveness, chemoresistance, treatment-related side effects such as nausea and vomiting, and toxicity to nontumor cells (Chopra et al., 2016; Gheena and Ezhilarasan, 2019). Therefore, the current trend of cancer research is the investigation of medicines of plant origin because of their affordability and accessibility with minimal or no side effects (Abu-darwish and Efferth, 2018; Fridlender et al., 2015; Shareef et al., 2016). Pleospyrone A (**48**), pleospyrones D-E (**51** and **52**), and a congener (**53**) were active against human hepatoma cell lines (HepG2) with IC_{50} values in the range of 1.26–47.5 μM (Lai et al., 2020). Chaephilone C (**54**) showed cytotoxicity against HepG2 cells with an IC_{50} value of 38.6 μM compared to camptothecin (32.3 μM) (Song, C. et al., 2020). Brefeldin A (**83**) and brefeldin A 7-O-acetate (**84**) have strong anticancer and antiviral effects and inhibit cell growth by inducing S-phase arrest in HepG2 cells, with an IC_{50} value of 0.024 μM (Xie et al., 2017). Pin (**88**) and PMG (**89**) significantly inhibit the adhesion and migration of HepG2 cells by blocking MMP-9 expression (Li, Q. et al., 2016). The TY5-EtOAc extract (**105**) induced apoptosis by increasing Bax and decreasing Bcl 2 and had a significant inhibitory effect on HepG2 viability in human hepatoma cells in a dose-dependent manner (Ty et al., 2018).

There are many other cancerous diseases such ovarian cancer, colon cancer, lung cancer, and lymphoma that require considerable chemical treatment (Markowitz et al., 2002; Minna et al., 2002; Mugnaini and Ghosh, 2016; Stewart et al., 2019). This can cause irreversible damage to the human body, while the biological activity of metabolites produced by endophytic fungi from MFH plants can effectively prevent these cancers without harmful effects. For example, epicorazine A (**3**) exhibited strong to moderate cytotoxicity against mouse lymphoma cells (L5178Y), human B-lymphoma cells (Ramos), and human acute T lymphoblastic leukemia cells (Jurkat J16) with IC_{50} values ranging from 1.3 to 28 mM (Harwoko et al., 2021). Epoxycytochalasin H (**4**) inhibits ovarian cancer cell A2780 viability, impairs mitochondrial function, activates mitophagy, and induces the mitochondrial apoptosis pathway (Xu, 2020). (4*S*, 6*S*)-6-[(1*S*, 2*R*)-1, 2-dihydroxybutyl]4-hydroxy-4-methoxytetrahydro-2H-pyran-2-one (**34**), (6*S*, 2*E*)-6-hydroxy-3-methoxy-5-oxodec-2-enoic acid (**35**), LL-P880γ (**36**), and LL-P880α (**37**) showed significant cytotoxic activities against human gastric cancer (MKN45), human colon cancer (LOVO), human carcinoma cells (A549), and human promyelocytic leukemia (HL-60) cell lines with IC_{50} values lower than 200 μM. All of these except LL-P880γ (**36**), as well as Ergosta-5,7,22-trien-3b-ol (**38**), show strong cytotoxicity against the human colon cancer (LOVO) cell line with IC_{50} values lower than 100 μM (Wu et al., 2016).

Shearilicine (**41**) exhibited cytotoxic activity against L5178Y and A2780 (Ariantari et al., 2019). The IC_{50} values for terpenoid-alkaloid (**43**) against human pancreatic cancer cells (Panc-1), human lymphoblastoid cells (NBT-T2), and human colon cancer cells (HCT-116) were 0.05, 0.75, and 0.05 parts per million (ppm), respectively. Furthermore, the IC_{50} values for sesterterpenoid (**44**) were 0.71, 0.30, and 0.67 ppm against these respective cell lines (Lut et al., 2021). GKK1032B (**55**) showed significant cytotoxicity against human osteosarcoma cell line MG63 with an IC_{50} value of 3.49 μmol L^{-1} (Na et al., 2022). Alternariol (**56**), alternariol-5-O-methyl ether (**57**), altenusin (**58**), and altertoxin II (**59**) exhibited cytotoxic activity against L5178Y with IC_{50} values of 1.7, 7.8, 6.8, and 6.2 μM, respectively (Orfali et al., 2017). Fusarubin (**70**) showed significant neuroprotective activity against glutamate-mediated HT22 (mouse hippocampal neuron cell) death (Choi et al., 2020).

In addition, anhydrofusarubin (**72**), 4-hydroxybenzaldehyde (**73**), bostrycoidin (**74**), and 3,5,9-trihydroxyergosta-7,22-diene-6-one (**77**) inhibited cell proliferation activity or activate apoptosis or necrosis in transformed kidney cells or kidney (renal) cancer cells (Khan et al., 2018). Fusaristerol A (**100**) displayed potent cytotoxic potential toward

HCT-116 with an IC_{50} value of 0.21 μM (Chester et al., 2017). Crude extracts of *Nigrospora sphaerica* (**110**) exhibited antiproliferative and anti-migratory effects on a solid tumor human glioma cell line (U251) and A549 (Maheshwari et al., 2018). Acremonidin E (**116**) inhibited melanin synthesis and activation of B16F10 and human melanoma cell line MNT-1 through downregulation of tyrosinase (Kim et al., 2019).

The inhibitory activities of these metabolites summarized above will facilitate the introduction of corresponding anticancer drugs for different cancers. Therefore, MFH plants are an important potential source of new anticancer drugs or precursors, providing a scientific basis and new ideas for the industrial production of such compounds.

7. Conclusion and perspectives

This review highlights the metabolites produced by endophytic fungi isolated from MFH plants that have been studied in recent years, as well as the activities of these compounds for the treatment of human diseases.

MFH plants are not only delicious foods for human consumption but their endophytic fungal metabolites also have a variety of beneficial bioactive properties. Recent studies have shown that endophytic fungi isolated from MFH plants can produce compounds with antioxidant, antimicrobial, anti-inflammatory and anticancer activities, which could enhance human immunity as well as improve human health, and are expected to become effective, safe and nontoxic therapeutic nutraceuticals for the prevention and treatment of diseases.

However, there are still some limitations in the development and utilization of these metabolites. To date, only 48.65% of MFH substances have been studied. In addition, only a small portion of the endophytic fungal resources have been extracted from MFH plants due to limitations associated with isolation and identification technologies. This could be improved using an effective combination of traditional isolation methods and modern advanced technologies, such multilocus sequence typing (MLST), metagenomics, and next-generation sequencing (NGS), thereby enriching the resource library of endophytic fungi.

Most studies on endophytic fungi from MFH plants have focused on their isolation and identification. The structures, compositions, and functions of metabolites produced by endophytic fungi from MFH are far from being explicit. In recent years, there has been great interest in the activity of such metabolites due to their biochemical diversity. The types of compounds consist mainly of alkaloids, terpenoids, polyketides, peptides, polysaccharides, quinones, esters, phenols, flavonoids, and steroids. The activities mainly include antioxidant, antimicrobial, anti-inflammatory, and anticancer activities. However, there is very little information regarding anti-disease mechanisms and medical applications, and more in-depth research is needed. Much of the work reported on bioactive endophytic fungi from MFH plants has remained at the experimental stage and has not been further applied in food or medicine. Effective active strains identified to be beneficial to humans should be further screened, with efforts to carry out large-scale fermentation and production of these strains.

Furthermore, studies on the mechanisms of endophytic fungal resourced-metabolites from MFH plants are not currently sufficient. More in-depth investigations using microbiology, bioinformatics, transcriptome analysis, reverse molecular docking, and network pharmacological technology are needed to scientifically understand their ecological roles and food and medical applications. Such studies would also provide new ideas for the development of such metabolites into mild, safe, and effective therapeutic nutraceuticals with preventive and therapeutic effects on inflammation and cancer.

CRediT authorship contribution statement

Jun Zhang: Data curation, Writing – original draft. **Yihui Zhu:** Data curation. **Jinping Si:** Supervision. **Lingshang Wu:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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