



Review

Roles of endophytic fungi in medicinal plant abiotic stress response and TCM quality development

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ABSTRACT

Medicinal plants, as medicinal materials and important drug components, have been used in traditional and folk medicine for ages. However, being sessile organisms, they are seriously affected by extreme environmental conditions and abiotic stresses such as salt, heavy metal, temperature, and water stresses. Medicinal plants usually produce specific secondary metabolites to survive such stresses, and these metabolites can often be used for treating human diseases. Recently, medicinal plants have been found to partner with endophytic fungi to form a long-term, stable, and win-win symbiotic relationship. Endophytic fungi can promote secondary metabolite accumulation in medicinal plants. The close relationship can improve host plant resistance to the abiotic stresses of soil salinity, drought, and extreme temperatures. Their symbiosis also sheds light on plant growth and active compound production. Here, we show that endophytic fungi can improve the host medicinal plant resistance to abiotic stress by regulating active compounds, reducing oxidative stress, and regulating the cell ion balance. We also identify the deficiencies and burning issues of available studies and present promising research topics for the future. This review provides guidance for endophytic fungi research to improve the ability of medicinal plants to resist abiotic stress. It also suggests ideas and methods for active compound accumulation in medicinal plants and medicinal material development during the response to abiotic stress.

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1. Introduction

Medicinal plants are used for disease prevention and treatment originating from long-established practices of traditional medicine (Firenzuoli & Gori, 2007). After much ethnobotanical and ethnopharmacological studies, medicinal plants and their preparations have eventually become an integral part of mainstream medicine. Whether used directly or processed, medicinal plant quality is important; however, plant quality is affected by the environment, including sunlight, temperature, and moisture (Liu, Fang, Yang, Shang, & Fu, 2018; Liu, Ren, & Jeong, 2019; Omidi, Shams, Sahandi, & Rajabian, 2018). As sessile organisms, medicinal plants cannot escape the adverse environmental conditions of abiotic stress (Fig. 1), including heat, cold, and water stresses; nutrient deficiency; and excess of salt and toxic metals such as aluminum, arsenate, and cadmium (Cd) in soil (You & Chan, 2015). They experience the inhibition of growth and metabolism, eventually resulting in the decrease in active component content and plant biomass (He, Wang, & Hou, 2019b). These stresses often reach extreme levels and may even cause irreversible damage (Georgieva, Sárvári, & Keresztes, 2010), leading to restricted growth, serious injury, and death of the whole plant (Xie et al., 2019). Abiotic stress tolerance can be enhanced in medicinal plants by phytohormone stimulation (Kumar, Hazra, Datta, & Chattopadhyay, 2016), soil amendments (Kim, Khan, Waqas, & Lee, 2017; Liu et al., 2015), nanobiotechnological interventions (Bhavva et al., 2021), tissue

culture cloning (Chaturvedi, Jain, & Kidwai, 2007), and breeding of high abiotic stress-resistant varieties (Sallam, Alqudah, Dawood, Baenziger, & Borner, 2019). Although breeding and clone culture are effective methods with far-reaching significance and prospects, they are time-consuming, incur high costs, and have poor practicability.

Endophytic fungi play a crucial role in enhancing medicinal plant resistance to abiotic stress (Jia et al., 2016). These fungi inhabit a host plant during a certain period and do not cause obvious disease symptoms to the host plant tissue (Verma et al., 2021). They usually exist in various aquatic and terrestrial plants such as algae, herbs, shrubs, and conifers (Cosoveanu & Cabrera, 2018; Sarasan et al., 2017). At the organ level, endophytic fungi can thrive asymptotically in different healthy tissues of living plants above and/or under the ground (Jia et al., 2016). They are distributed in most plant tissues and can play an important role in varied physiological processes. *Serendipita indica* (basonym: *Piriformospora indica*), a beneficial endophytic fungus and fungal research hotspot, is able to colonize plant roots without causing any obvious disease symptoms, and it has beneficial effects such as stimulating metabolic activities, increasing plant hormone synthesis, and inducing stomatal closure (Qiang, Weiss, Kogel, & Schaefer, 2012). These effects help the host plant to resist cold, salt, and water stresses (Jiang et al., 2020; Nivedita et al., 2020; Tsai et al., 2020).

Recent studies are increasingly concerned with the outcomes of endophytic fungi and host medicinal plants sharing a reciprocal symbiotic relationship (Manganyi & Ateba, 2020). Medicinal plants have formed a relationship with microbes as a consequence of evolution (Field et al., 2019; Yan et al., 2019). On one hand, medicinal plants provide photosynthates and nutrition for endophytic fungi (Hadacek & Kraus, 2002). On the other hand, endophytic fungi improve secondary metabolism (Zhai et al., 2017), produce active ingredients (Ming et al., 2012), promote growth (Ye et al., 2020), and improve the ability to resist abiotic stress (Jia et al., 2016) in medicinal plants. However, studies have mainly focused on their metabolites and ignored their abiotic stress resistance, which also requires attention. Thus, we focused on whether endophytic fungi can improve host medicinal plant resistance to abiotic stress by regulating metabolites. Some metabolites of medicinal plants improve plant resistance to abiotic stress (Wang, Wang, Ma, Fu, & Gao, 2018; Xu et al., 2022); however, the role of endophytic fungi in this process has not been clarified.

In this review, we comprehensively describe the role of endophytic fungi in medicinal plants in abiotic stress response along with their mechanisms. We also summarize the conditions of abiotic stress experimental procedures and the distribution of effective endophytic fungi. Endophytic fungi in medicinal plants summarized here could promote secondary metabolite accumulation and medicinal material development in response to abiotic stress. Further research should focus on the medicinal compound activity on the host plant rather than their pharmacological activity in treating disease because plants usually metabolize secondary products for their survival. This review indicates that endophytic fungi have great potential in resisting abiotic stress and serves to guide the systematic research of medicinal plants under abiotic stress.

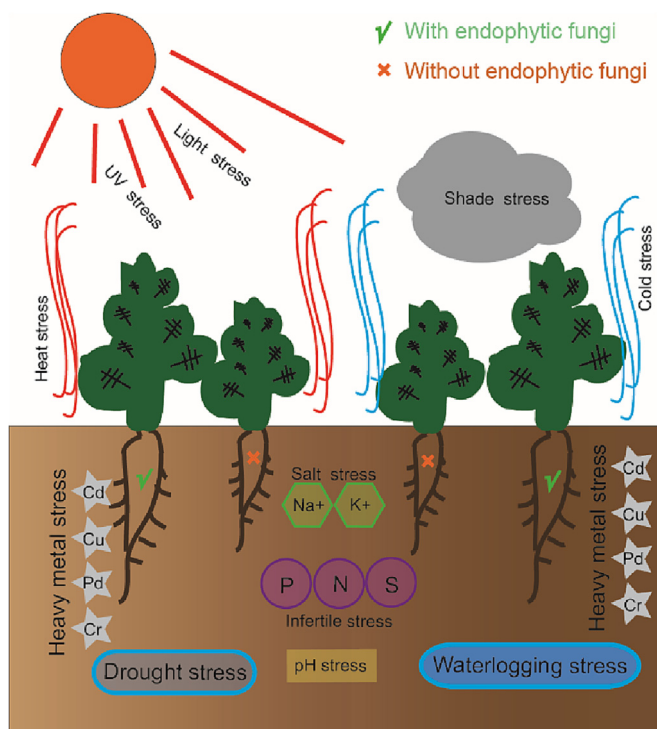


Fig. 1. Endophytic fungi enhance medicinal plant resistance to abiotic stresses.

2. Endophytic fungal response to abiotic stress in medicinal plants

2.1. Active metabolite accumulation

Secondary metabolites such as flavonoids, phytoalexins, phenylpropanoids, and carotenoids have been documented in stressed plants inoculated with microorganisms (Chukwuneme, Uzoh, Kutu, & Babalola, 2021; Koza, Adedayo, Babalola, & Kappo, 2022; Mohammadi et al., 2021). These secondary metabolites help plants tolerate abiotic stress by acting as antioxidants that scavenge reactive oxygen species (ROS) (Chukwuneme, Ayangbenro, & Babalola, 2021). Many active metabolites produced in response to abiotic stress in medicinal plants not only improve plant survivability but can also be used for medicinal purposes (Table 1). Co-inoculation of mycorrhiza and *P. indica* fungi had a synergic effect on the enhancement of essential oil in *Mentha piperita* L. in response to salt stress, which can be attributed to the role of fungi in mineral nutrient uptake (Khalvandi, Amerian, Pirdashti, & Keramati, 2021; Sirrenberg et al., 2007). Essential oil in *M. piperita* contains a high proportion of cytotoxic, antioxidant, and antimicrobial compounds with beneficial health effects such as antifungal effects, cancer prevention activities, and ROS scavenging activity (Khalvandi, Amerian, Pirdashti, & Keramati, 2021). It was reported that the inoculation of endophytes *Acrocalymma vagum* and *Fusarium acuminatum* could significantly increase glycyrrhizic acid content of host *Glycyrrhiza uralensis* Fisch. under drought stress, suggesting that the presence of endophytic fungi reduced the adverse effects of drought stress on the accumulation of plant active ingredients (He, Wang, & Hou, 2019b). In a co-cultured *Dendrobium officinale* Kimura et Migo system, endophytic *Cladosporium* sp. could promote the accumulation of active metabolite polysaccharides in the stem under heat stress by increasing relative chlorophyll content and photosynthetic rate, and reducing intercellular carbon dioxide concentration (Lu, 2018). Under drought stress, the co-inoculation of the endophytic strains *Microdochium majus*, *Meyerozyma guilliermondii*, and *Aspergillus aculeatus* in *Moringa oleifera* L. showed a significantly improved accumulation of secondary metabolites such as lipids, phenols, flavonoids, and proline in the plant. The finding supported the utilization of compatible endophytic fungi for establishing a tripartite mutualistic symbiosis in *M. oleifera* to alleviate the adverse effects of drought stress by strong antioxidant activities and specific active metabolite accumulation (Javed et al., 2022).

2.2. Medicinal material development

Medicinal plants in natural habitats often harbor ubiquitous endophytes, including some that are tolerant to abiotic stress and capable of stimulating plant growth (Jia et al., 2016; Wu et al.,

2021). Several studies have shown that the development of medicinal plant parts is closely associated with the presence of endophytic fungi in plant response to abiotic stress. It was reported that the inoculation of dark septate endophytes (DSE) *A. vagum* and *Paraboeremia putaminum* significantly increased organ biomass (e.g., total root length, surface area, and root branch number) of host *G. uralensis* under drought stress. Moreover, DSE inoculation significantly influenced the composition of soil mineral nutrients and microbial communities, indicating the possibility that DSE inoculation improved root development and nutrient absorption of host plants, altered soil microbiota, and contributed to plant growth and survival under drought conditions (He, Wang, & Hou, 2019b). Salt stress disrupted nutrient and water acquisition of *Aloe vera* plantlets, resulting in reduced growth and biomass. However, the interaction of *A. vera* with the endophytic fungus *P. indica* resulted in an overall increase in plant biomass, including an increase in the number of shoots and roots, which were also longer (Sharma, Kharkwal, Abdin, & Varma, 2016). The inoculation of endophytic *Cladosporium* sp. could promote stem development of host *D. officinale* in response to heat stress by increasing protective enzyme activity as well as soluble sugar and soluble protein content, and decreasing malonaldehyde accumulation (Lu, 2018).

3. Role of endophytic fungi in abiotic stress response of medicinal plants

3.1. Salt stress

Salt stress refers to the loss of productivity of plants caused by cultivation in saline alkaline areas and/or irrigating with brackish and saline water (Morton et al., 2018). Na⁺ in saline water can directly bind to G-alpha interacting protein, C-terminus (GIPC) and regulate the entry of Ca²⁺ into the cytosol, which makes plants detect the salt stress signal (Zhao, Zhang, Song, Zhu, & Shabala, 2020). Salt stress inhibits the growth of medicinal plants by causing stomatal closure, producing hyperosmotic shock, inhibiting cell division, and influencing photosynthesis (Purakayastha, Mandal, & Kumari, 2017). Several studies suggest that endophytic fungi enhance salt stress resistance in host medicinal plants. *S. indica* makes up for the loss of plant roots caused by salt stress. When co-cultured with *S. indica* in salt stress experiments, the root length of *A. vera* increased by 36% under 100 mmol/L NaCl treatment compared with that without *S. indica* and no salt stress (Sharma, Kharkwal, Abdin, & Varma, 2016). Under 9 dS/m salt stress, *M. piperita* co-cultured with *S. indica* had 54.37% lower Na⁺ content than non-inoculated plants (Khalvandi, Amerian, Pirdashti, & Keramati, 2021). Soares et al. (2016) collected *Phragmites australis* subsp. *Australis* (Cav.) Trin. Ex Steud. grown in high-salinity areas and found that *Alternaria tenuissima*-Fi31 and eight other endophytic fungi isolated from

Table 1
Endophytic fungi in medicinal plants facilitating abiotic stress resistance through medicinal compounds.

Endophytic fungi	Plants	Medicinal compounds	Activities (or predicted activities)	Abiotic stress	References
<i>Serendipita indica</i>	<i>Aloe vera</i> L.	Total phenols, flavonoids, flavonols, aloin	Antioxidant and osmoprotectant	Salt stress	Sharma, Kharkwal, Abdin, & Varma, 2016
<i>Serendipita indica</i>	<i>Mentha piperita</i>	Menthol, menthyl acetate	Antioxidant	Salt stress	Khalvandi, Amerian, Pirdashti, & Keramati, 2021
<i>Fusarium acuminatum</i>	<i>Glycyrrhiza uralensis</i>	Glycyrrhizic acid	Osmoprotectant	Drought stress	He, Wang, & Hou, 2019b
<i>Paraboeremia putaminum</i>	<i>Glycyrrhiza uralensis</i>	Glycyrrhizin	Osmoprotectant	Drought stress	He, Wang, & Hou, 2019b
<i>Acrocalymma vagum</i>	<i>Glycyrrhiza uralensis</i>	Glycyrrhizin, glycyrrhizic acid	Osmoprotectant	Drought stress	He, Wang, & Hou, 2019b
<i>Cladosporium halotolerans</i>	<i>Dendrobium officinale</i>	Polysaccharides	Antioxidant	Heat stress	Lu, 2018

it have more than 72% growth promotion efficacy (GPE) in *Oryza sativa* L. under 120 mmol/L NaCl. This is an ideal example of a way to discover functional microbes. However, it is more meaningful to verify the role of endophytic fungi in the original host (Bibi et al., 2019; Soares et al., 2016). In addition, the concentration of Na⁺ can be used to measure the degree of salt stress for a clearer comparison.

3.2. Heavy metal stress

Excessive heavy metals in soil can cause oxidative stress and influence the structure and function of plant genes and proteins (Kim, Kim, & Kumar, 2019). Heavy metal stress also alters various biochemical processes of medicinal plants, including enzyme activity, oxyradical production, protein mobilization, and photosynthesis (Seneviratne et al., 2017). Under 400 mg/L CuSO₄ and Pb(NO₃)₂ solution stress, *Ocimum basilicum* L. inoculated with the common endophytic fungus *S. indica* can increase the root dry weight by 75% and reduce Cu²⁺ and Pb²⁺ content of the shoot by 23%; However, reducing the heavy metal content of plants can reduce the heavy metal damage to plants (Sabra et al., 2018). Pietro-Souza et al. (2017) collected *Polygonum acuminatum* Kunth. and *Aeschynomene fluminensis* Vell., two medicinal plants grown in soil with mercury (Hg) contamination, and found that *Massariosphaeria* sp. and eight other endophytic fungi isolated from medicinal plants could enhance dry biomass (average GPE 232%) of *A. fluminensis* when Hg concentration was 120 mg/kg, which was even more than the dry biomass of the control group (no inoculation, no Hg). When inoculated with *Glomerella truncata* and *Phomopsis fukushii*, the shoot length of the host *Solanum nigrum* L. was increased by 25% and 20%, respectively, under 25 mg/kg of Cd stress (Khan et al., 2017). Furthermore, when under 400 mg/kg of copper (Cu) stress, *Kandelia candel* (L.) Druce inoculated with *Purpureocillium* sp. A5 grew much better compared with non-inoculated plants (Gong, Liu, Liao, Song, & Zhang, 2017). However, there is a great loss in isolating endophytic fungi using only one culture medium, as the nutrients required by various strains are different. In experiments by Pietro-Souza et al., in addition to potato dextrose agar (PDA), malt extract and cornmeal media were used to isolate endophytic fungi (Pietro-Souza et al., 2017). Furthermore, the construction of heavy metal stress models was not uniform, and the model construction method unevenly affected the shoot dry weight of *O. basilicum* (Sabra et al., 2018).

3.3. Water stress

Water stress can be divided into excess water stress (i.e., waterlogging or flooding) and water shortage stress (i.e., drought) (Wang & Komatsu, 2018). Excess water stress caused by soil waterlogging and/or submergence leads to oxygen deficiency in plants and severely suppresses their growth (Takahashi et al., 2018). Drought stress affects plant growth by marked reduction in water uptake. It lowers water potential, leads to osmotic stress (Santander et al., 2017), causes stomatal closure, damages chloroplast structure, and decreases photosynthesis-related enzyme activity (He, Zhang, & Tang, 2016). It also destroys fungi and makes pathogen infiltration easier (Lee, Lee, Bae, Seo, & Lee, 2014). Under drought stress (30% field water capacity), when co-cultivated with two endophytic fungi *A. vagum* and *P. putaminum*, *G. uralensis* was 3.7 and 3.9 times the height of the control plant (no inoculation, 30% field water capacity), and 1.1 and 1.3 times the height of the blank plant (no inoculation, 70% field water capacity), respectively (He, Wang, & Hou, 2019b). In contrast, when flooding stress was 80% of the soil moisture content, Pleosporales sp. CD-31 isolated from *Cynodon dactylon* (L.) Pers could increase the root fresh weight of the host by 1.67-fold (Zhao, 2016). However, there is no uniform

standard for model construction methods of either drought or waterlogging stress. Methods used to establish the water stress model include controlling field water capacity (He, Wang, & Hou, 2019b), controlling soil moisture content (Zhao, 2016), opening the culture container (Sherameti, Tripathi, Varma, & Oelmüller, 2008), and applying polyethylene glycol (Song, Liu, Cai, Sun, & Dai, 2011). These water control modes are inconvertible, and the severity of stress levels cannot be concluded from current literature, limiting the analysis of anti-water stress mechanisms. A unified standard is necessary to evaluate the degree of drought. A comprehensive drought index combined with medium water content and plant physiological state can meet our needs.

3.4. Temperature stress

Temperature stress refers to extreme temperatures, which can be divided into high temperature (i.e., heat) and low temperature (i.e., cold). Plants are continuously exposed to life-threatening stresses caused by extreme temperatures (Xia et al., 2015). Heat can reduce photosynthesis efficiency and increase stomatal conductance and transpiration rate (Si, Qiao, Jiang, Dong, & Liu, 2014), ultimately causing plant death. *Cladosporium halotolerans* isolated from *D. officinale* can significantly increase LT₅₀ (lethal temperature of 50%) of *D. officinale* from 49.8 °C (no inoculation) to 57.1 °C, and the dry weight of *D. officinale* also increased by 17% at 40 °C, which was more than the dry weight of the control group (no inoculation, 25 °C) (Lu, 2018). Cold stimulation of RGA1 caused an increase in Ca²⁺ influx, which makes plants sense the cold stress signal (Gong et al., 2020). Low temperature may cause vacuole damage, resulting in water shortage and plant death. Jain, Bhardwaj, Pandey, and Kumar (2021) isolated the endophytic fungi of *Arnebia euchroma* (Royle) I.M.Johnst., which is an endangered medicinal plant that grows naturally in extreme cold and arid environments in the Himalayas. These endophytic fungi can be used for improving tolerance in plants under cold stress. After inoculation with *Penicillium* sp. isolated from *Eucalyptus dunnii* Maiden, cold resistance was enhanced in hybrid *Eucalyptus*, and LT₅₀ of hybrid *Eucalyptus* inoculated with *Penicillium* sp. decreased from -2.45 to -5.16 °C (Xie et al., 2011). In addition, when *Achnatherum inebrians* (Hance) Keng seeds were divided into two groups—endophytic and non-endophytic fungi groups, *A. inebrians* with endophytic fungi had 16.9% longer roots and 62.5% more tillers than *A. inebrians* without endophytic fungi under 10 °C cold stress (Chen, 2011).

However, although LT₅₀ is a comparative evaluation criterion (similar to LD₅₀, ED₅₀, etc.), the stress sites were not uniform, such as at rhizosphere temperature (Zhou et al., 2015) or at ambient temperature (Lu, 2018). In addition, Zhou et al. (2015) screened endophytic fungi and found that *Curvularia crepinii* isolated from *Hedyotis diffusa* Willd. can withstand a high rhizosphere temperature of 50 °C for 4 d. *O. sativa* inoculated with *C. crepinii* showed a 60% survival rate, whereas plants not inoculated with *C. crepinii* died. Although *O. sativa* survival under high-temperature environments is important, we still hope to study the host *H. diffusa* because of its excellent clinical effect in the treatment of cancer.

3.5. Other stresses

In addition to these stresses, extreme environmental factors can constitute abiotic stress, such as light stress (i.e., shade or high light stress) and infertile soil stress (i.e., low phosphorus (P) or potassium content). Under 90% shade stress, endophyte–symbiotic *Poa alsodes* A. Gray had 140% higher total biomass compared with endophyte-free plants (Davitt, Stansberry, & Rudgers, 2010). When the endophytic fungus *A. vagum* or *P. putaminum* was inoculated, the plant total nitrogen (N) of *G. uralensis* significantly increased

by 40.8% and 24.5%, respectively; and the plant total P significantly increased by 18.2% and 36.4%, respectively (He, Wang, & Hou, 2019a). When cultured in 1/8 Hoagland nutrient solution, the dry weight of *D. nobile* inoculated with the endophytic fungus No. 37 increased by 2.2-fold, and the total N content increased by 9-fold (Gong, Li, Sun, Tang, & Yi, 2019). In addition, He et al. (2019a) found that the fermented residue of *G. uralensis* can increase plant biomass and N and P content, indicating that the endophytic fungi in *G. uralensis* play a positive role in nutrient utilization of the host. Acids, alkalis, ozone, and ultraviolet light are common abiotic stresses, but there are no reports about endophytic fungi increasing medicinal plant resistance to them.

4. Mechanisms

4.1. Enhancing resistance to osmotic stress

Osmotic stress, especially hyperosmotic stress, is the primary signal caused by salt, water, and temperature stresses (Zhu, 2016). Osmotic stress stimulates the cell membrane receptors OSCA1, HPCA1, and B4Raf, which make plants sense osmotic stress signals (Gong et al., 2020; Soma, Takahashi, Suzuki, Shinozaki, & Yamaguchi-Shinozaki, 2020; Zhao, Zhang, Song, Zhu, & Shabala, 2020). In response to osmotic stress, proline plays an important role as an osmoprotectant (Liang, Zhang, Natarajan, & Becker, 2013). For example, it stabilizes protein structure as a molecular chaperone, provides a buffer of cytosolic pH, and balances the cell redox status by accumulation (Verbruggen & Hermans, 2008). *S. indica* increased proline accumulation by 39.6% in *Medicago truncatula* Gaertn. by inducing *delta 1-pyrroline-5-carboxylate synthetase* gene expression under 250 mmol/L NaCl (Li et al., 2017).

In addition, endophytic fungi can function as osmoprotectants and promote host plant metabolite production (Xu et al., 2022), such as total soluble sugars (Ismail et al., 2018), soluble proteins (Song, Liu, Cai, Sun, & Dai, 2011), flavonoids (Bibi et al., 2019), and phenols (Sharma, Kharkwal, Abdin, & Varma, 2016). Interestingly, these compounds may play a greater role in medicinal plants than in other plants because of the well-known pharmacological activity determined by active compounds. In response to osmotic stress caused by drought stress, *G. uralensis* co-cultured with *A. vagum* increased the content of glycyrrhizic acid and glycyrrhizin by 46.6% and 33.3%, respectively, compared with non-inoculated plants (He, Wang, & Hou, 2019b). These compounds can form a water dispersion system to increase the osmolality of plants and contribute to the relief of differential osmolality. Endophytic fungi can increase the content of host active substances, and this effect persists even under osmotic stress. Thus, using endophytic fungi to increase the resistance of medicinal plants to abiotic stress not only ensures yield but also improves quality.

4.2. Improving oxidative stress resistance

Oxidative stress is one of the secondary stresses in plants. ROS overproduction and lipid peroxidation products in plants can be caused by nearly all abiotic stresses (Soumen, 2005), such as salt stress (Li et al., 2017), water stress (drought or flooding stress) (Tian, Bi, Zeng, Jiang, & Liu, 2015), and temperature stress (Liu et al., 2018; Lu, 2018). ROS and lipid peroxidation products are highly reactive and toxic, causing damage to proteins, lipids, and DNA, and ultimately resulting in oxidative stress (Gill & Tuteja, 2010). Antioxidant enzymes and reductive substances, including superoxide dismutase (SOD), peroxidase (POD), catalase (CAT), and ascorbate oxidase (AAO), play important roles in scavenging oxygen free radicals. *G. uralensis* inoculation with *F. acuminatum*

increased SOD activity by 60% under drought stress (30% field water capacity) (He, Wang, & Hou, 2019b).

In addition, some secondary metabolites induced by endophytic fungi, including phenols, flavonols, and polysaccharides, may play an antioxidant role in the plant body, regardless of their pharmacological activity in the human body (Jiang, Wang, Kang, Jiang, & Guo, 2020). In response to oxidative stress caused by heat, *Cladosporium* sp. BMP2947 and *C. halotolerans* improved polysaccharide content (intracellular and extracellular) by 1.43-fold and 1.72-fold in *D. officinale* (Lu, 2018), which may play an antioxidant role. In pharmacological research, polysaccharides have been considered active immunomodulatory components in *D. officinale* (Chen et al., 2021). Similarly, in response to oxidative stress caused by 300 mmol/L NaCl salt stress, *S. indica* can also increase the content of total phenols and total flavonols (emodin, chrysophanol, and quercetin) in *A. vera* leaf by 1.36-fold and 1.43-fold (Sharma, Kharkwal, Abdin, & Varma, 2016), thus increasing the pharmacologically active ingredients of *A. vera*.

4.3. Enhancing photosynthesis and phytohormone accumulation

Both phytohormone accumulation and photosynthesis are the main ways in which medicinal plants respond to abiotic stress (Balfagón et al., 2019; Ku, Sintaha, Cheung, & Lam, 2018). Therefore, enhancing photosynthesis and adjusting phytohormone accumulation are important ways for endophytic fungi to enhance medicinal plant resistance to abiotic stress. Endophytic fungi can influence the regulation of virtually all phytohormones, including jasmonic acid (JA) (Wani et al., 2017), salicylic acid (SA) (Ismail et al., 2018), indoleacetic acid (IAA) (Pietro-Souza et al., 2017), abscisic acid (ABA) (Ismail et al., 2019), and gibberellins (Waqas et al., 2012). *S. indica* can help the host against salt stress by producing plant hormones such as IAA (Shah et al., 2019; Sharma, Kharkwal, Abdin, & Varma, 2016). IAA produced by *Aspergillus* sp. A51 and *Massariosphaeria* sp. A19 may be beneficial to improve the resistance of *P. acuminatum* to 120 mg/kg Hg stress (Pietro-Souza et al., 2017). Besides, *A. flavus* (Ismail et al., 2019) and *A. japonicus* (Ismail et al., 2018) isolated from *Euphorbia indica* produced 95.0 and 63.11 µg/mL SA in culture filtrate, respectively. In addition, in the plant hormone system, JA, ABA, and SA have synergistic effects in resisting environmental stress (Wang, Song, Gong, Xu, & Li, 2020).

Photosynthesis is a plant basic life activity and the basis of all life; the higher the photosynthetic efficiency, the better plants grow, irrespective of abiotic stress. Endophytic fungi can increase the content of chlorophyll and regulate chlorophyll fluorescence parameters to promote photosynthesis. *S. indica* can make up for the loss of chlorophyll caused by heavy metals to resist heavy metal stress (Shahabivand, Parvaneh, & Aliloo, 2017), increase Fv/Fm against salt stress (Khalvandi, Amerian, Pirdashti, & Keramati, 2021), and increase chlorophyll a-b binding protein against water stress (Ghabooli et al., 2013). In addition, *A. vagum* increases the stomatal conductance of *G. uralensis* under drought, which may be regulated by hormones and affect the net photosynthesis rate (He, Wang, & Hou, 2019b).

4.4. Assisting in ion transport

Reducing the absorption of heavy metals by plants is essential, and endophytic fungi can induce the specific distribution of heavy metal ions in different plant parts. Endophytic fungi can release active substances to complex heavy metals to reduce their levels in plants. To decrease metal phytotoxicity, *Massariosphaeria* sp. A19 and *Colletotrichum* sp. P42 can secrete siderophores to chelate Hg (Pietro-Souza et al., 2017) and *Purpureocillium* sp. can secrete acidic compounds to chelate Cu (Gong, Liu, Liao, Song, & Zhang,

2017). Interestingly, *A. fumigatus* can transform highly toxic hexavalent chromium (Cr) to non-toxic trivalent Cr through an enzyme to reduce heavy metal poisoning in plants (Bibi et al., 2018). However, combining *A. fumigatus* or the enzyme with nanomaterials can produce efficient biotransformation composites, which is essential to the treatment of Cr pollution. Therefore, the enzyme production mechanism of *A. fumigatus* and enzyme structure must be studied in detail for industrial applications.

5. Future perspectives

Environmental conditions conducive to growth, development, and metabolism improve the quality and increase the yield of medicinal plants, whereas extreme environmental conditions or abiotic stresses have serious negative effects on medicinal plant

quality and yield (Patel & Franklin, 2009; Yang et al., 2018). Endophytic fungi resistant to abiotic stress have become a hot topic in recent plant research, but studies are not systematically arranged. This review focused on the accumulation of active compounds and medicinal material development in medicinal plants during their response to abiotic stress, as well as collated the endophytic fungi involved in medicinal plant abiotic stress response (Table 2) and their underlying mechanisms (Fig. 2).

Medicinal plants synthesize and accumulate a vast array of structurally diverse small molecules known as secondary metabolites. The diversification of several secondary metabolite classes and their corresponding biosynthesis pathways in plants is driven by microbes and insects (Dixon, 2001). *Colletotrichum tofieldiae* (Ct), an endophytic fungus in natural *Arabidopsis thaliana* (L.) Heynh., was found to transfer the macronutrient phosphorus to

Table 2
Endophytic fungi and their mechanisms that enhance host resistance to abiotic stresses.

Stress types	Endophytic fungi	Experiment plants	Mechanisms	References
Salt stress	<i>Piriformospora indica</i>	<i>Aloe vera</i> L.	Scavenged DHHP free radicals	Sharma, Kharkwal, Abdin, & Varma, 2016
	<i>Alternaria tenuissima</i> -F131, <i>Arthrinium arundinis</i> -F16, <i>Paraphaeosphaeria michotii</i> -F121, <i>Phomopsis</i> sp.-F126, <i>Purpureocillium lilacinum</i> -F141, <i>Septoriella hubertusii</i> -F14, <i>Phomopsis mali</i> -F115, <i>Bipolaris buchloes</i> -F110 <i>Serendipita indica</i>	Rice	Increased resistance to salt stress	Soares et al., 2016
	<i>Cochliobolus</i> sp.	Okra	Reduced MDA, Produced salinity stress reliever	Lanza, Haro, Conchillo, & Benito, 2019 Bibi et al., 2019
	<i>Piriformospora indica</i>	<i>Medicago truncatula</i>	Reduced MDA, Drained Na ⁺ , Expressed defense genes, Accumulated proline	Li et al., 2017
Heavy metal stress	<i>Serendipita indica</i> <i>Aspergillus fumigatus</i> ML43, <i>Rhizopus</i> sp. CUC23, <i>Penicillium radicum</i> PL17 <i>Fusarium proliferatum</i> FBL1 <i>Glomerella truncata</i> , <i>Phomopsis fukushii</i>	<i>Ocimum basilicum</i> <i>Lactuca sativa</i> L.	Reduced absorption and transfer Converted Cr-VI to Cr-III, Reduced absorption and transfer	Sabra et al., 2018 Bibi et al., 2018
		<i>Solanum nigrum</i> L.	Increased chlorophyll content	Khan et al., 2017
Heavy metal stress	<i>Purpureocillium</i> sp. A5	<i>Kandelia candel</i>	Produced Cu-chelating ligand, Reduced absorption	Gong, Liu, Liao, Song, & Zhang, 2017
	<i>Massariosphaeria</i> sp. A19 <i>Colletotrichum</i> sp. P42 <i>Piriformospora indica</i>	<i>Aeschyromene fluminensis</i> Vell. <i>Helianthus annuus</i> cv. Zaria	Produced siderophores	Pietro-Souza et al., 2017
		<i>Chrysanthemum morifolium</i>	Increased chlorophyll and proline content, Reduced transfer	Shahabivand, Parvaneh, & Aliloo, 2017
Water stress	<i>Botrytis</i> sp. <i>Chaetomium globosum</i> <i>Piriformospora indica</i>	<i>Hordeum vulgare</i> L.	Reduced MDA, Increased SOD, POD, and PAL activities	Song, Liu, Cai, Sun, & Dai, 2011
	<i>Acrocalymma vagum</i> <i>Paraboeremia putaminum</i>	<i>Glycyrrhiza uralensis</i> <i>Glycyrrhiza uralensis</i>	Enhanced photosynthesis, Activated the methyl cycle, Increased APX, 2-Cys Prx, carbonic anhydrase, and ROS activities	Ghabooli et al., 2013
	<i>Fusarium acuminatum</i> <i>Piriformospora indica</i>	<i>Glycyrrhiza uralensis</i> <i>Arabidopsis</i>	Increased POD activity, Reduced MDA Increased SOD and CAT activities, Reduced MDA	He, Wang, & Hou, 2019b
			Increased SOD and CAT activities Enhanced photosynthesis, Upregulated phospholipase D δ , CBL1, and HAT gene expression	Sherameti, Tripathi, Varma, & Oelmüller, 2008
Temperature stress	Endophytic fungi of <i>Achnatherum inebrians</i>	<i>Achnatherum inebrians</i>	Increased TPX content, Upregulated antioxidant-related enzyme gene expression	Chen, 2011
			Increased antioxidant enzyme activity and content of free proline	Liu, 2016
Temperature stress	<i>Cladosporium</i> sp. BMP2947, <i>Cladosporium halotolerans</i>	<i>Dendrobium officinale</i> Kimura et Migo	Enhanced photosynthesis, Increased SOD, POD, and CAT activities, Increased soluble sugar and protein content, Reduced MDA	Lu, 2018
	<i>Aspergillus japonicus</i> EuR-26	Sunflower	Increased CAT and AAO activities, Reduced ABA, Increased soluble sugar and protein content	Ismail et al., 2018
	<i>Aspergillus flavus</i>	Sunflower	Increased CAT and AAO activities, Reduced ABA	Ismail et al., 2019
	<i>Curvularia crepinii</i>	Rice	Increased resistance to heat stress	Zhou et al., 2015

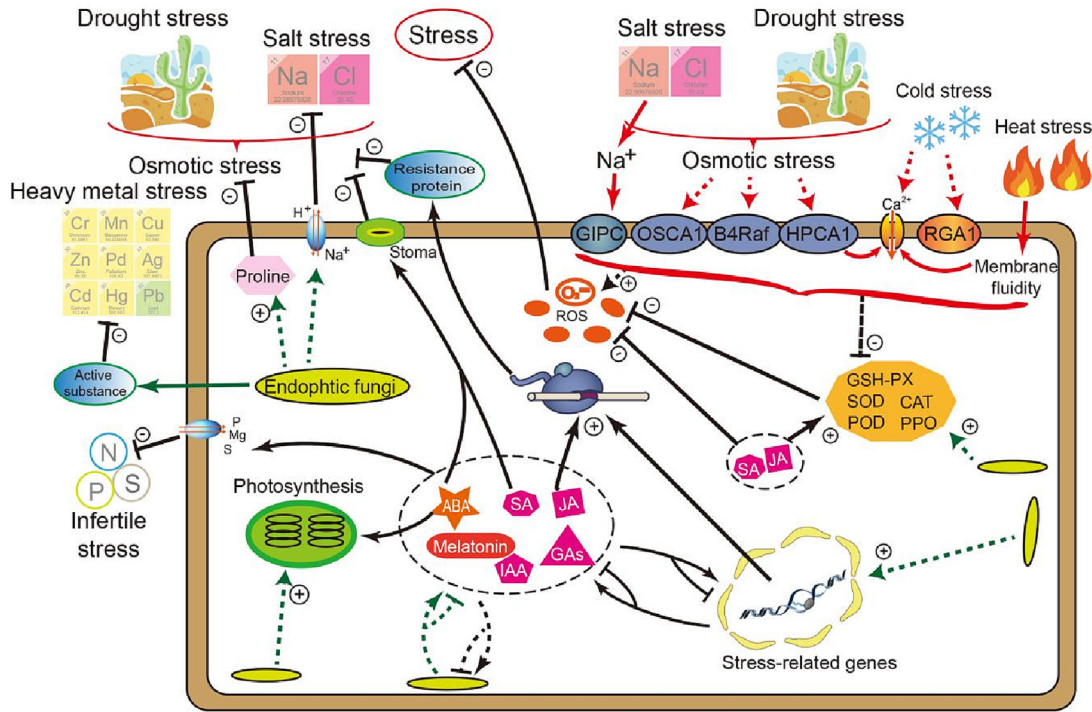


Fig. 2. Abiotic stress sensing and signaling, and regulatory mechanisms triggered by endophytic fungi in response to abiotic stress in medicinal plants. Salt stress activates G-alpha interacting protein interacting protein, C-terminus in the membrane via Na⁺. OSCA1, B4Raf, and HPCA1 are regulated by osmotic stress. Both cold and heat stresses regulate Ca²⁺ channels. Increase in reactive oxygen species (ROS) causes damage to plant cell. Endophytic fungi are resistant to abiotic stress by increasing antioxidant enzymes and proline, regulating phytohormones, and enhancing photosynthesis.

shoots, promote plant growth, and increase fertility only under phosphorus-deficient conditions. The host's phosphate starvation response system controls Ct root colonization and is needed for plant growth promotion (Hiruma et al., 2016). Endophytic fungi can increase the content of active compounds in medicinal plants, while also alleviating the damage caused to them under abiotic stress. We analyzed and summarized the families of endophytic fungi and medicinal plants (Supplementary Table 1), and their response mechanisms to different abiotic stresses (Fig. 3), which can provide guidance for medicinal plant studies on abiotic stress resistance. For example, endophytic fungi help the host resist salt stress by effecting antioxidant processes, osmotic systems, ion transport, active substances, and plant hormone systems. Therefore, in addition to studying oxidation systems and photosynthesis

(Sharma, Kharkwal, Abdin, & Varma, 2016), the effects of *S. indica* on *A. vera* can be studied on plant hormone systems, osmotic systems, active substances, and ion transport.

Endophytic fungi can promote the metabolism of medicinal plants. It was found that the endophytic fungal elicitor could rapidly induce specific gene expression in medicinal plants, resulting in the activation of specific secondary metabolic pathways and the accumulation of active ingredients (Zhai et al. (2017)). However, after summarizing the mechanism of endophytic fungi improving the abiotic stress of medicinal plants, we found that fungal elicitors also play a role in combating abiotic stress, which can improve the content of active components in medicinal plants. Thus, active components with special properties may help medicinal plants resist abiotic stress; for example, phenolic compounds have

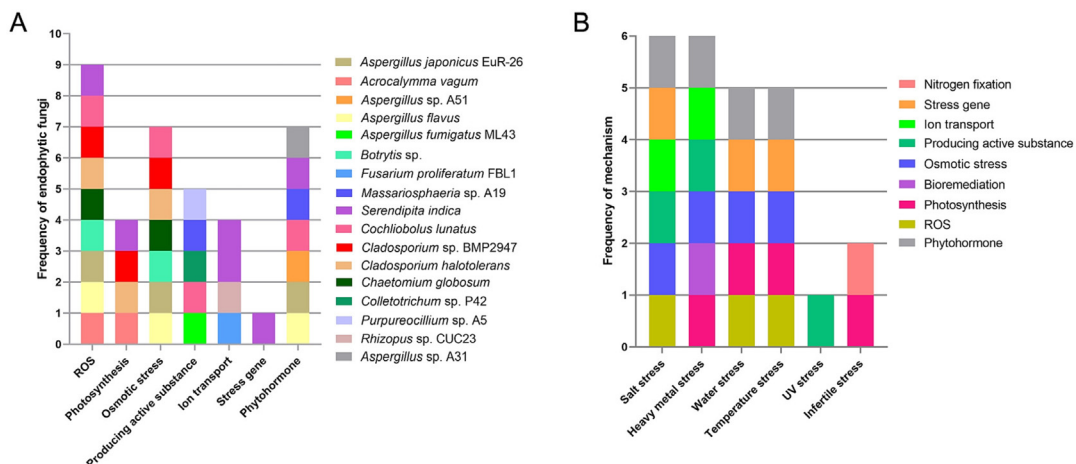


Fig. 3. (A) Frequency of each mechanism of abiotic stress resistance induced by endophytic fungi in medicinal plants. (B) Resistance mechanisms to each abiotic stress induced by endophytic fungi in medicinal plants.

antioxidant effects, organic acids form complexes with heavy metals, and general compounds can increase intracellular osmotic pressure and alleviate osmotic stress. The accumulation of secondary metabolites induced by endophytic fungi can stimulate the development and use of secondary metabolites and promote the quality development of traditional Chinese medicine (TCM). Because endophytic fungi can improve the quality of medicinal materials in an environment-friendly way, it is important to fully exploit endophytic fungal resources. A large number of microorganisms have been commercialized for TCM quality improvement and use against abiotic stress. This can be attributed to their ease of handling and endospore-forming ability that facilitates efficient colonization (Koza, Adedayo, Babalola, & Kappo, 2022). Efficient isolation of endophytic fungi is the most important step to fully utilize endophytic fungal resources. Isolation using only PDA medium is usually considered incomplete (Pietro-Souza et al., 2017), and using various media (Soares et al., 2016) or adding plant tissue to the medium (Nemr, Khalil, Sarhan, Abbas, & Hegazi, 2020) can improve the isolation rate.

In addition to common mechanisms, He et al. (2019b) found that the endophytic fungi *A. vagum*, *P. putaminum*, and *F. acuminatum* increase host resistance to drought stress by affecting the rhizospheric environment and its microorganisms. Thus, endophytic fungi and the rhizosphere may constitute a closely related whole, and a change in medicinal plant characters will affect the whole soil microbial community, not a certain strain. Therefore, studying the synergy of the overall function of mixed strains, key microbial communities, or even the whole microbial community will be of immense value. Microorganism–plant interaction is currently under intense investigation. As far as model plants and crops are concerned, many molecular mechanisms have been studied, including targets and receptors at the gene or protein level. Although meaningful, there are still some deficiencies in molecular studies of medicinal plants. The *Arabidopsis thaliana* genome is different from medicinal plant genomes and cannot be readily correlated with medicinal plant phenotypes. It can only be used for simple correlation or in pure molecular biology research, thus reducing its significance in medicinal plant research. Of course, this is because of less information and low splicing quality of the whole genome of medicinal plants. Based on retrieval data, we found that medicinal plant genome research accounts for only 4.12% of overall plant genome research, which limits the establishment of high-quality genetic transformation systems and hinders the study of endophytic fungi to improve medicinal plant resistance to abiotic stress. In the coming decades, we recommend several priority topics for additional research: (1) studies on the effects of endophytic fungal communities in medicinal plant TCM quality development and abiotic stress response; (2) deep analysis of plant and fungal genes expressed during the transition of rhizospheric microbes into the endophytic lifestyle; (3) tripartite “plant-fungal-bacterial” symbioses that potentially generate synergistic effects on medicinal plant; (4) development of innovative approaches for the separation and cultivation of endophytic fungi to investigate the effects of unculturable endophytes on medicinal plants; (5) genetic manipulations of functional endophytic fungi to give them additional beneficial functions in medicinal plant abiotic stress response.

CRedit authorship contribution statement

Jiahao Zhang: Writing – original draft. **Jiemiao Lu:** Visualization. **Yichun Zhu:** Visualization. **Xiaoxia Shen:** Data curation. **Bo Zhu:** Writing – review & editing. **Luping Qin:** Validation.

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

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.chmed.2023.02.006>.

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