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Diversity of endophytic fungi hosted medicinal ferns: Biotechnological potentials and possible applications

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ABSTRACT

Fern species belonging to the oldest vascular plants have been widely used as traditional medicines by indigenous communities especially in the humid regions of South East Asia for thousands of years. Fungal endophytic associations with ferns have been identified through various mechanisms, resulting in host ferns' resistance to adverse conditions or growth enhancement. The highest potential of fungal endophytes to produce bioactive compounds and their biological properties has prompted research into endophytes associated with fern species. The purpose of this review is to provide an overview of the endophytic fungi isolated from fern plants with medicinal properties and highlight their potential as natural sources of novel bioactive compounds for agricultural and therapeutic applications. Further research is needed to investigate these fungal endophytes colonizing medicinal ferns in different ecological niches.

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Introduction

Ferns as the second vascular plants are placed between lower and higher plants in pteridophytes and comprised more than 12000 known species (Schneider et al. 2004; Moran 2008). These earliest vascular plants are nonflowering and more similar to the seed-bearing plants (Prado & Sylvestre 2010). Ferns are abundantly distributed across tropical and subtropical ecosystems with high humidity, especially in Southeast Asia and the neotropical region (Jones & Luchsinger 1986; Winter & Amoroso 2003; Chin 2005; Mehltreter et al. 2010) and few species in Arctic and Antarctic regions (Mohr 2001; Smith 2014). Almost more than half of the fern species have been reported from China with 2600 species (Lu 2007), followed by India with 1200 species (Dixit 1984; Chandra 2000) and Malaysia with more than 1000 species (Parris & Latiff 1997).

Ferns are divided into four categories according to the purpose of their usage from rhizomes, stems, croziers, leaves, young fronds, and shoots including edible ferns, cattle bed ferns, ornamental ferns, and medicinal fern. Based on the survey of fern flora in Darjiling hills by Thapa (2016), different species in the genera of *Angiopteris*, *Diplazium*, *Deparia*, *Cyathea*, *Lygodium*, *Ophioglossum* and *Tectaria* have been categorized under

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edible ferns, species of *Dicranopteris lanigera*, *Dicranopteris taiwanseis*, *Diploterygium giganteum* and *Pteridium revolutum* under cattle bed ferns, and some species in *Cyathea*, *Davillia*, *Huperzia*, *Lycopodiella*, *Lycopodium*, *Nephrolepis* and *Selaginella* under ornamental ferns and some species in *Adiantum*, *Aleuritopteris*, *Equisetum*, *Lygodium*, *Nephrolepis*, *Pteris*, *Tectaria* and *Thelypteris* under medicinal ferns. There are many fern species which can be grown as ornamental plants in the genera of *Asplenium*, *Blechnum*, *Cyathea*, *Sphenomeris*, *Tectaria*, *Arachniodes*, *Huperzia*, *Angiopteris*, *Nephrolepis*, *Ophioglossum*, *Osmunda*, *Ceratopteris*, *Drynaria*, *Pyrrosia*, *Acrostichum*, *Adiantum*, *Pteris*, *Lygodium*, *Selaginella*, *Trigonospora*, *Vittaria* or even can be used in phytoremediation such as *Pteris vittate* and *Nephrolepis exaltata* (Ranil et al. 2015).

Fern application in medicine dates back more than 2000 years throughout the world in Europe, north and south America, Asia, and Africa (Murillo & Teresa 1983; Chin 2005; Benniamin 2011; Van Wyk & Wink 2017). Ethnomedicinal uses of ferns have been mainly documented in traditional medicine system in China (Chang et al. 2011) and other indigenous systems of medicine among other ethnic groups in the world (Pan et al. 2014). The highest diversity of fern species distributed in the Asian countries compared to other continents might be due to the large number of reports and surveys conducted in such regions indicating the popularity of herbal medicine and use of ferns in the traditional medicines in these regions. It is estimated that there are more than 400 medicinal fern taxa being distributed in 121 genera in 36 families with promising therapeutic values. *Culcita macrocarpa* C. Presl and *Blechnum eburneum* Christ. have been reported as near threatened and vulnerable plants, respectively (Muhammad et al. 2020) which might be due to overexploitation of resources, prevalence of invasive species, growth of cities, and forest fragmentation and loss of habitats for ferns (Paciencia & Prado 2005). Pteridaceae, Polypodiaceae, Dryopteridaceae, Aspleniaceae, Thelypteridaceae, and Cyatheacea are among of the most medicinally used families. Fern's taxa with potential uses are mostly founded in the genera of *Adiantum*, *Asplenium*, *Dryopteris*, *Equisetum* and *Pteris* to treat gastrointestinal ailments, stomach ailments, diseases related to accessory digestive organs and small or large intestine, skin issues, gynaecological and infertility disorders, respiratory diseases, urogenital diseases, and musculoskeletal disorder (Muhammad et al. 2020).

Pharmacological effects of fern plants are related to the production of diverse phytochemicals including alkaloids (Dong et al. 2012), flavonoids (Xia et al. 2014), polyphenols (Socolsky et al. 2012), terpenoids (Socolsky et al. 2007), and steroids (Ho et al. 2012). *Angiopteris evecta* as a member of Marattiaceae can be a valuable source of alkaloid, angiopteroside, flavonoid, monoterpenoid, polyphenol, saponin, steroid, triterpenoid and quinone which has anticancer, antiviral properties and can treat headache, wounds, broken bones, and fractures (Cambie & Ash 1994; Shil & Choudhury 2009; Baskaran et al. 2018). Phenols and flavonoids derived from *Asplenium nidus* (family Aspleniaceae) have anti-lice, antibacterial, antiviral activity and can be used for treatment of fever, mouth disorders, childbirth disorders, tuberculosis, chest pain, elephantiasis, skin disorders (Bourdy et al. 1996; Quattrocchi 2012; Pullaiah et al. 2017; Modolo & Foglio 2020). *Adiantum trapeziforme* (family Pteridaceae) contains compounds like ascorbic acid, peroxidase, polyphenol oxidase and shows antibacterial activity (Quattrocchi 2012). *Blechnum orientale* (family Blechnaceae) by having flavonoids, tannins, and terpenoids has a strong antioxidant and anticancer capacity (Ahmad & Ismail 2003; Lai et al. 2010; Singh & Singh 2012; Baskaran et al. 2018). Whole plants of *Ceratopteris thalictroides* (family Pteridaceae), especially leaves contain various bioactive compounds including alkaloids, phenols, flavonoids, saponins, and tannin which has been shown to have anti-inflammatory and anti-cancer effects and used for skin disease treatment (Baskaran et al. 2018; Joshi et al. 2019). Benzoic acid, flavonoids, and terpenoids reported from the roots of *Drynaria rigidula* (family Polypodiaceae) make this fern to be with potent anti-inflammatory and antiviral activities (Nugraha et al. 2013).

Caffeic acid derivatives identified in the methanol extract of rhizomes of *Abacopteris penangiana* (family Thelypteridaceae) show antioxidant activity against neurotoxicity in mice (Fu et al. 2013). This medicinal fern has been traditionally used by Chinese locals for the treatment of blood stasis by promoting blood circulation, dampness, swelling in the tissues and inflammation (Administration Bureau of National Chinese Traditional Medicine, 1998 / Chinese Materia Medica). *A. penangiana* also contains flavonoids components with anti-inflammatory activity (Lei et al. 2011), cytotoxic activity (Fang et al. 2010), antioxidative activity (Zhao et al. 2007a, b), and neurotoxicity in PC12 cells by dopamine levels (Wei et al. 2013). *Macrothelypteris* is another genus in Thelypteridaceae with massive uses in Chinese medicine. Protoapigenone is a flavonoid compound isolated from *M. torresiana* with potential cytotoxicity against various tumor cells (Chang et al. 2008a,b). Other flavonoids and total polyphenols identified in this fern have been shown to be effective in renal protection, cancer chemoprevention and cancer inhibitory (Liu et al. 2011a, b, c; Chen et al. 2012a, b) and have diuretic and laxative properties (Mondal et al. 2018). *Polypodium leucotomos* as a tropical fern in Polypodiaceae is rich in polyphenol and can be used in traditional medicine with anticancer (Parrado et al. 2014), anti-inflammatory (Choudhry et al. 2014; Nestor et al. 2014), antioxidant, nootropic and immunomodulatory activities, cytokine suppression and leukotriene inhibition effects (Berman et al. 2016; Nestor et al. 2014). *Dicranopteris dichotoma* (family Gleicheniaceae) is a promising source of phytochemical such as diterpenes isolated from fronds led (Aoki et al. 1997; Li et al. 2006, 2007a), phenolic glycosides (Kuraishi et al. 1983). *Diplopterygium* is a medicinal herbaceous species in China containing various bioactive components such as diterpenoids, triterpenoids, phenolics, flavonoids, phytoecdysones, and ecdysteroids (Takemoto et al. 1973; Peng-Tao et al. 2009; Hu et al. 2011, 2014; Fang et al. 2013; Kong et al. 2023). *Ophioglossum* species (family Ophioglossaceae) are homoflavonoids enriched (Wan et al. 2012, 2013) distributed mainly across China (Mao 2010). The ferns *O. vulgatum* and *O. pedunculosum* have been shown to contain several flavonoids, glycerides, and amino acids (Wan et al. 2012; Clericuzio et al. 2012; Hu et al. 2016) with antioxidant, anti-inflammatory, antibacterial, and antimutation properties (Pietta 2000; Choi et al. 2001; Yoshizumi et al. 2001; Schroeterh et al. 2001). Various bioactive compounds including alkaloids, antheridiogen, phenols, flavonoids, and tannin have been identified from leaves, roots, and rhizomes of *Lygodium circinatum* (family Lygodiaceae), as an evergreen fern used for the treatment of snakebites, conjunctivitis, and eye problems (Ibrahim & Hamzah 1999; Baskaran et al. 2018). *L. microphyllum* is another species in the same fern genus which contains alkaloid, flavonoid, isoquersetin, and steroid with antioxidant and antimicrobial activities (Kuncoro et al. 2015, 2018).

What are endophytic fungi?

Several associations between plants and fungi have been occurred in different ecosystems (terrestrial, riparian, freshwaters, mangroves, marine, marshes, and coastal sand dunes). These interactions exhibit different lifestyles like biotrophy (parasitism-dependent), hemibiotrophy (initially biotrophic and then necrotrophic in a later stage), nectrotrophy (pathogens kill tissue and feed on dead or dying cells), endotrophy (mutualistic cause no harm to the host), and saprotrophy (live and feed on dead and decaying organic matter) (De Silva et al. 2016). The English term 'Endophyte' is derived from two Greek words "endon" meaning inside and "phyton" meaning plant (Abdel-Azeem & Salem 2012; Dutta et al. 2014; da Silva et al. 2022) which was firstly mentioned by De Bary in 1866 (Azevedo 1998) who defined them as any microorganism resides within plants without harming their hosts. Fungal endophytes have existed within terrestrial plants for more than 400 million years (Krings et al. 2007; Chadha et al. 2015) which colonize symptomless living plant tissues for at least part of their life cycle without causing adverse impacts to their host plants (Fouda et al. 2015) . The association between endophytic fungi and their hosts are one of the most important elements in plant micro-ecosystems that should have significant influences on the growth and development of host plants.

According to Azevedo (1998), endophytic fungi are distinct from phytopathogenic fungi that harm plants and epiphytic microorganisms that live on the surface of plant organs and tissues. These fungi are highly diverse, with an estimated one million species occurring in nature (Faeth & Fagan, 2002), and can thrive asymptomatically in different healthy tissues of living plants above and/or under the ground, including stems, leaves, and/or roots (Kusari et al. 2012a). While about 300,000 terrestrial host-plant species are distributed in temperate regions and tropical rainforests, only a few of these plants have been fully studied regarding their endophytic biology, providing opportunities for discovering novel fungal forms, taxa, and biotypes (Strobel & Daisy 2003; Gakuubi et al. 2021).

Fungal endophytes have been classified into three main ecological groups by Schultz: mycorrhizal, balansicaeous or pasture endophytic fungi, and non-pasture endophytic fungi (Faeth & Fagan, 2002). Based on phylogeny and life history strategies, fungal endophytes can be divided into two major groups: clavicipitaceous and non-clavicipitaceous. The latter group can further be classified into three functional groups based on their colonization patterns. The first group colonizes both above-ground and below-ground parts of plants (ascomycetes and basidiomycetes), while the second and third groups are limited to above-ground and below-ground parts, respectively. The diversity of the first non-clavicipitaceous group is localized, while the second (ascomycetes and basidiomycetes) and third (mycorrhizal and dark septate) groups have characteristics that enable them to colonize extensively across a broad range of host plants. For example, the second non-clavicipitaceous group can colonize over 20 species in a single tropical leaf (Arnold et al. 2003), while the third group (mainly dark septate endophytes, DSE) can colonize up to 600 plant species in broad geographic areas (Jumpponen 2001).

How endophytic fungi interact with their host plants?

Endophytic fungi establish different relationships with their host plants through mutualism, antagonism, and neutralism. The population structure of endophytic fungi is largely affected under varying ecological pressures e.g., the genetic background, nutrient level, and ecological habitats of host plants. In turn, it confers certain benefits such as induced growth, increased resistance upon attack by pathogens and/or herbivores (Rodriguez et al. 2009), as well as accumulation of bioactive components (Firáková et al. 2007). The bioactive compounds produced by endophytic fungi associated with host plants in a mutual interrelation are essential to increase the adaptability of both endophytic fungi and their host plants to biotic stresses: herbivore attacks, pests and phytopathogens (Azevedo 1998), and abiotic stresses: dry seasons, salinity, extreme temperatures, and others (Khare et al. 2018). These fungi can induce the production of various biologically active secondary metabolites, which can be utilized for medicinal purposes (Zhang et al. 2006; Firáková et al. 2007; Rodriguez et al. 2009). However, the colonization of these fungi is not accidental, as they are attracted by specific chemicals produced by the host plants. Additionally, the secondary metabolites produced by the host plant, such as saponin and essential oils can act as a resistance mechanism against pathogens. As a result, the secondary metabolites enhance barriers for the endophytic fungi colonization. To overcome this problem, endophytic fungi must secrete corresponding detoxifying enzymes such as cellulase, lactase, xylanase, and protease to break down these secondary metabolites before they enter the defense system of the resident host plants. Once in the host plant's tissue, the fungi can remain in a dormant state either for the entire life cycle of the host plant (neutral) or for a long period of time (mutually or antagonistically) until favorable environmental conditions or changes in the host plant's ontogenetic state allow them to thrive (Sieber 2007).

The establishment and evolution of mutualistic interrelations between fungi and plants can be attributed to several factors, including the ability of endophytic fungi to produce plant metabolites. They can sometimes secret bioactive compounds closely like their hosts (Kumar et al. 2017). In fact, some "plant metabolites" might be made by their endophytes (Kusari et al. 2012b). The similarity between phytochemical products from both endophyte and host can be explained by genetic recombination throughout evolutionary time (Tan & Zou 2001). Although the genetic mechanisms underlying the symbiotic relationship between plants and fungi are unknown, several hypotheses have been proposed regarding signaling mechanisms. For example, flavonoids, isoflavonoids, and phenolic compounds function as signaling molecules in the rhizosphere (Ryan et al. 2008), while stress-activated MAP kinase pathways are involved in mutualistic stability (Eaton et al. 2011).

Diversity and Distribution of endophytic fungi

Research has been conducted on the distribution and population structure of endophytic fungi in a plant species across wide geographical areas, such as terrestrial, semiaquatic, freshwater, and marine habitats. Similarly, fungal endophytes of various phototrophic organisms (forest trees, medicinal plants, mangroves, algae, seaweeds, vegetables, ferns, orchids, etc.) have been examined which among them, terrestrial plants have gained great attention in their interaction with endophytic fungi compared to aquatic environment (Sandberg et al. 2014).

Exploring medicinal plants for endophytic fungi is important for discovering new drugs. Traditional medicinal compounds and medicinal plants are a good starting point to investigate the potential of associated endophytic fungi. Many endophytic fungi in medicinal plants have promising biological activities and can produce value-added metabolites found in the plants through their involvement in promoting plant growth, tolerance to adverse conditions, providing nutrients and preventing invasion by herbivores (Zhao et al. 2011; Venieraki et al. 2017). There are also secondary metabolites such as the anticancer drugs, camptothecin, and podophyllotoxin and the bioinsecticide azadirachtin (Puri et al. 2006; Gurudatt et al. 2010) which can be co-produced by the host and endophytic fungi. Some hormones and anticancer drugs such as gibberellins and taxol can be synthesized independently by both the host and the endoparasite (Stierle et al. 1993; Bömke & Tudzynski (2009)). This ability of endophytic fungi or host plant species is the result of biochemical convergence or horizontal gene transfer (Venieraki et al. 2017; Taghavi et al. 2005).

Host genotype and environmental conditions are two main factors in the population of endophytic fungi (Tan et al. 2003). Results from the studies of Arnold & Lutzoni (2007) indicate that the population structure or distribution pattern of endophytic fungi is significantly associated with latitude as few species of fungal endophytes from many different classes of Ascomycota have been obtained from higher latitudes compared to a great number of species found in tropical latitudes. Another example is observed in the study by Hoffman & Arnold (2008) which examined in different host plants (*Juniperus virginiana*; *Platycladus orientalis*; *Cupressus arizonica*; *Platycladus orientalis*) resided in two geographic locations (North Carolina and Arizona) and suggested the importance of host geography and taxonomy in the formation of the endophytic community. In addition, the diversity of fungal species can be dependent on the geographical and seasonal factors (rainy or dry) as what observed in the research conducted by Collado et al. (1999), Jiang et al. (2013) and Souza et al. (2018). Population of endophytic fungi may vary according to the specific organs and plant tissues (root, stem, leaf, woody tissues) in which they colonize, as well as various stages of plant maturity (Sieber 2007; Jiang et al. (2013); Nascimento et al. (2015)).

Community composition and diversity of endophytic fungi is also variable dependent on the techniques employed to isolate and evaluate fungal species in plant tissues (Sun et al. 2011; Gamboa et al. 2002). These methods can be mainly categorized as direct and indirect. Direct methods involve sterilizing the surface of the plant and then conducting plating, histological studies using simple stains and fluorescent dyes, and microscopic analysis. Simple stains are helpful in locating the endophytic fungi within live plant tissues. Indirect methods include biochemical techniques that use structural components like chitin and ergosterol, immunological approaches that use fungal-specific antigen-antibody reactions such as radioimmunoassay (RIA), and molecular methods such as DGGE, RFLP, DNA cloning, ITS sequence analysis, pyrosequencing, DNA barcoding, RNA applications, and liquid chromatography-mass spectrometry (LC-MS).

What are the beneficial relationships conferred by endophytic fungi to host plants?

The production of metabolites in the interaction of plants-endophytic fungi is an important factor which occurs in five ways: (a) endophyte induces host metabolism, (b) host induces endophyte metabolism, (c) host and endophyte share and partially contribute to specific metabolic pathways, (d) host plants are able to metabolize products of endophyte origin and vice versa (e) endophytes are able to metabolize secondary compounds of host (Ludwig-Muller 2015). Endophytes not only produce bioactive compounds but also stimulate host plants for synthesizing or accumulation of more secondary metabolites (Jiang et al. 2013). This process increases the resistance of host plant and help it adapt more easily to its habitat (Gomes & Luiz 2018).

Endophytic fungi live inside plant tissues either all through their lives or during certain periods of their life cycles without causing obvious harm or morphological changes in the hosts, resulting in a balanced antagonism. During the colonization of these fungi in the intercellular or intracellular spaces of host tissues, various secondary metabolites are produced by the host plants which make them resistant to pathogens. Endophytes need to metabolize these secondary metabolites by their hydrolytic enzymes to break down such obstacles for a successful colonization before penetrating the defense mechanism of host plants (Dutta et al. 2014; Jia et al. 2016). The production of these secondary metabolites in the mutualistic interaction between endophytic fungi and their host can provide many advantages for the plants (Tanvir et al. 2017) like promoting growth of host plants and assisting them in nutrient uptake, increase of resistance potential to stresses.

Plant growth

Endophytic microorganisms can modify root morphology of their host and change nitrogen accumulation which results in the plant growth. They also have a critical role in the efficiency of water use by leaves through osmotic adjustment and stomatal regulation (Lata et al. 2018). Increasing the nutrient availability from soil, germination, photosynthesis, and competitive abilities in the host plants are the key components for the fitness and growth of a plant. These mechanisms can be significantly mediated by endophytic fungi as they increase the absorption of nutritional elements like macronutrients (N, P, K, Ca, Mg, S, C, O, H) and micronutrients (Fe, B, Cl, Mn, Zn, Cu, Mo, Ni) by the host (Aly et al. 2011). Fan et al. (2020) demonstrated that the genera of *Oidiodendron* and *Cladosporium* as dominant genera of endophytic fungi in root and stem of *Huperzia serrata* promote nitrogen uptake and plant growth. Production of phytohormones, hormones such as auxins and gibberellins, indole-3-acetic acid, indole-3-acetonitrile and cytokinins, are the other ways in which endophytic fungi enhance the fitness and growth of host plants (Luz et al. 2006; Jia et al. 2016).

Resistance to biotic & abiotic stress

The endophytic fungi were believed to trigger the defense systems of their host plants by producing secondary metabolites (e.g., enzymes and antibiotics), resulting in symbiotically conferred stress tolerance. By the endophytic colonization in a host plant, direct competition for habitat and nutrients can occur which inhibit the infection by plant pathogens (Zabalgogeazcoa 2008; Abo Nouh et al. 2021, 2024). Another mechanism in protecting the host plant against pathogens like insects and mammals, and the tolerance to biotic stresses was often linked to bioactive compounds produced by the endophytic fungi that had antimicrobial properties against pathogens (Gunatilaka 2006; Zhang et al. 2006). For example, botryosphaerin as a tetranorlabdane diterpenoid produced by endophytic fungus in the genus

Botryosphaeria isolated from *Huperzia serrata* showed Anti-nematicidal activity (Chen et al. 2019), thereby protecting the host plants from pathogen attacks, increasing their chances of survival. In another study, Jeon et al. (2019) demonstrated the biocontrol activity of *Amphirosellinia nigrospora*, an endophytic fungus isolated from the Cretan brake fern (*Pteris cretica*), against bacterial and fungal pathogens of tomato by producing a potent antimicrobial compound (oxygenated cyclohexanone).

Endophytic fungi have been found to produce various antioxidant compounds that can enhance their host plants' tolerance to abiotic stresses such as drought, salinity and extreme temperatures, alkalinity, oxidative stress, and heavy metal toxicity (Herrera Carrillo et al. 2009; Torres et al. 2009; Abo Nahas 2023). Several studies have demonstrated an increase in the production of antioxidant compounds such as flavonoids and other phenolic antioxidants, alkaloids, and diterpenes in plants infected with endophytic fungi (Yadav et al. 2014; Bhardwaj et al. 2015; Mollaei et al. 2019; Xu et al. 2020a; Parthasarathy et al. 2020). Additionally, endophytic fungi with metal sequestration or chelation systems can increase their host plants' tolerance to heavy metals, allowing them to survive in contaminated soil (Weyens et al. 2009). Endophytic fungi can also regulate the biosynthesis of abscisic acid (ABA), a phytohormone that regulates stomatal closure in plants, thereby contributing to plant growth enhancement under salt stress conditions (Khare et al. 2018).

Endophytic fungi as major source of novel metabolite

Endophytic fungi can be considered as an alternative source of secondary metabolites for pharmacological studies because of their great potential in biosynthesizing some bioactive compounds which are useful in medicine, agriculture, and industries (Abdel-Azeem et al. 2016a, b, 2018, 2019; Balbool et al. 2018; Balbool & Abdel-Azeem 2020; dos Santos et al. 2021, 2022; Moubasher et al. 2022; Mohamed et al. 2022; Motlagh et al. 2023; Alghanem et al. 2023; Khader et al. 2024). Production of such compounds is primarily associated with three metabolic pathways (e.g., mevalonic acid, polyketide, and shikimic acid pathways). Diverse classes of such natural metabolites from fungal endophytes have been explored to exhibit a wide variety of biological roles including antibacterial compounds, antifungal compounds, anticancer compounds, antiviral compounds, cytotoxic compounds, anti-insect metabolites, pharmacological metabolites, secondary metabolites, volatile organic compounds, enzymes (Sridhar 2019). The anticancer drug Taxol ($C47H_{51}NO_{14}$) from *Taxomyces andreanae*, the fungal endophyte of the host species *Taxus brevifolia*, has become an important impetus for the study of natural products from biological source, mainly endophytes (Stierle et al. 1993). Other examples of anticancer compound Taxol were found in the taxol-producing endophytic fungi, *Pestalotiopsis microspore* (Strobel et al. 1996), *Taxodium distichum* (Li et al., 1996), *Seimatoantlerium tepuiense*, *Seimatoantlerium nepalense* (Bashyal 1999), *Tubercularia* sp. strain TF5 (Wang et al. 2006), *Phyllosticta spinarum* (Kumaran et al. 2008), *Bartalinia robillardoides* (Gangadevi and Muthumary 2008), *Metarhizium anisopliae* (Liu et al. 2009), *Pestalotiopsis terminaliae* (Gangadevi and Muthumary 2009), *Botryodiplodia theobromae* (Pandi et al. 2010) and *Fusarium redolens* (Garyali et al. 2013). It is widely accepted that the production of Taxol by *T. andreanae* was a result of genetic recombination caused by mutualism with the host species. This discovery has allowed for the protection of endangered and endemic plant species by providing an alternative source for drug extraction. Fungi are found in unique and often stressful environments, making them a valuable resource for discovering novel metabolites. Since then, research on the endophytic fungi clearly indicated that these microorganisms have the ability to promote the formation and accumulation of secondary metabolites that were only produced by host plants. Despite the assessment of endophytic fungi from angiosperms and gymnosperms for their value-added metabolites, other photosynthetic systems such as algae, bryophytes, mosses, and pteridophytes have been largely overlooked (Sridhar 2019). Due to labor intensive of the process of isolation and extraction of some metabolites with therapeutic properties from medicinal plants, efforts for natural-product research from endophytic fungi using in vitro cultivation and fermentation techniques have been a promising alternative natural source for different pharmaceutical, agriculture, and industrial applications (Sunkar et al. 2017).

Endophytic fungi associated with medicinal ferns

Despite several studies on the ferns which are capable of producing secondary metabolites with different pharmacological applications in treatment of disease, like cytotoxicity, hepatoprotective activity, antihyperglycemic activity, leishmanicidal activity, trypanocidal activity, anti-nociceptive activity, anti-inflammatory activity, immunomodulatory activity, and chemopreventive effects (Cao et al. 2017), there are few reports on the endophytic fungi associated with these group of antient plants (Asiandu et al. 2021) and sparce studies in which focus on identification and biodiversity of fungal endophytes in medicinal ferns with ability to synthesize a diverse range of bioactive compounds (Chen et al. 2015; Asiandu et al. 2019; Thi Minh Le et al. 2019). For example, fungal species in 9 genera of aquatic hyphomycetes, viz. *Alatospora*, *Anguillospora*, *Campylospora*, *Clavariopsis*, *Heliscus*, *Lunulospora*, *Pestalotiopsis*, *Tetrachaetum* and *Tetracladium* were isolated from roots of pteridophytes *Equisetum* sp., *Botrychium* sp. and some other ferns (Sati et al. 2009; Sati & Belwal 2005). In the study by Kumaresan et al. (2013) 40 fungal endophytes were isolated from five Pteridophyte species viz., *Adiantum* sp., *Gleichenia linearis*, *Lygodium flexuosum*, *Pteris* sp. and *Selaginella* sp. which were scattered in *Aspergillus*, *Aureobasidium*, *Botryodiplodia*, *Cladosporium*, *Colletotrichum*, *Drechslera*, *Fusarium*, *Penicillium*, *Pestalotiopsis*, *Phialophora*, *Phomopsis*, *Phyllosticta*, *Sporormiella*, and *Trichoderma*. The limited research on the fungal endophytes-ferns interaction (isolation, diversity, ecology, metabolites) has attracted the attention of researchers to discover new fungal species isolated from fern species and provide reviews on their metabolites with bioactive properties. Here, in this review, we summarized some other endophytic fungi isolated from medicinal ferns.

Adiantum spp.

Ramesha et al. (2020) reported *Nigrospora sphaerica* as endophytic fungus isolated from the healthy leaf segments of *Adiantum philippense*, as an ethnomedicinal fern which has medicinal properties to treat many diseases such as consuming sensation, erysipelas, epileptic fits, looseness of the bowels, bronchitis, coughing, and elephantiasis. A potent antimicrobial agent phomalactone was identified in *N. sphaerica* through TLC–bioautography and hyphenated spectroscopic techniques. This compound was known to have antifungal activity against *Aspergillus fumigatus* (Comai et al. 2003), nematocidal activity (Khambay et al. 2000), immunomodulating activity (Krivobok et al. 1994), insecticide activity (Krasnoff et al. 1994), and phytotoxic activity (Fukushima et al. 1998) and be effective against human and phytopathogenic bacteria and fungi. *N. sphaerica* can also produce some other antimicrobial compounds such as nigrosporolides (Harwooda et al. 1995), nigrosporins (Tanaka et al. 1997), lactones (Fukushima et al. 1998), epoxydons and pyrones, diterpenes, diketopiperazines (Cutler et al. 1991), and nigrosporolides (Zhang et al. 2009).

Rhizopus oryzae can be found as endophytes on *Adiantum capillus-veneris* and has been reported to be potentially used in crops including sunflower and soybean under thermal stress as they induced chlorophyll content, shoot and root lengths, fresh and dry biomass of crop plants (Ismail et al. 2020).

Asplenium nidus

Asplenium nidus as a member of *Aspleniaceae* was reported to produce bioactive flavonoids with tumoricidal, anti-bacterial, anti-oxidant activities (Jarial et al. 2018). Thus, the endophytic fungi isolated from the fern may act as a source of bioactive constituent. Some endophytic species isolated from *A. nidus* is presented in Table (1).

Botrychium spp.

Different species of *Botrychium* such as (*B. lanuginosum*, *B. lunaria* and *B. multifidum*) are widely used as herb and reported for treating various types of diseases in Nepal traditional medicinal system (Ojha & Devkota 2021). *Botrychium ternatum* distributed across China, Korea, and Japan can be used as folk remedies to heal some ailments like dizziness, headache, cough, and fevers. These therapeutic properties can be resulted from producing kaempferol glycosides, and four quercetin glycosides in this medicinal fern (Cao et al. 2017). *Phyllosticta capitalensis* has been isolated as an endophyte on *Botrychium* sp. in USA (Wikee et al. 2013). *Phyllosticta capitalensis* has been reported in producing compounds like meroterpene analogues and polyketides which has antimicrobial effects on a panel of human pathogens (Xu et al. 2019).

Dryopteris spp.

Dryopteris plants are members of *Dryopteridaceae* family and are rich in secondary metabolites, including glycosides, steroids, alkaloids, phenols, terpenes, flavonoids, and tannins which are responsible for biological activities like antibacterial, antifungal, nematicidal and antioxidant activities (Soare et al. 2012; Egorova et al. 2021; Valarmathi et al. 2023).

Hamayun et al. (2020) isolated *Aspergillus violaceofuscus* as an endophytic fungus from roots and leaves of *Dryopteris flix*. The effect of culture filtrate of *A. violaceofuscus* was studied on seedlings of *Glycine max* and *Helianthus annuus* and showed the enhancement in the total chlorophyll content, plant height and biomass of these crops under high temperature. The presence of secondary metabolites including flavonoids, phenolics, Indole-3-acetic acid (IAA) and salicylic acid (SA) in the CF of the endophytic fungus has assisted the host under abiotic stresses. Such resistance to heat stress occurs by improvement of lipids, proteins and sugar concentration, ROS scavenging antioxidant system like flavonoids, proline, phenolics, AAO and CAT in the agronomic crops, *H. annuus* and *G. max*. The similar results were achieved by Hamayun et al. (2021) from the endophytic fungus *Penicillium glabrum* isolated from the fern species *Dryopteris blanfordii* under thermal stress.

Elaphoglossum spp.

Elaphoglossum is a medicinal fern recently placed in the family Dryopteridaceae, containing many secondary metabolites such as the prenylated acylphloroglucinols, elaphogayanin A-B, elaphopilosin C- E, lindbergins A-F and yungensins A-F (Cao et al. 2017). Some endophytic fungi in different genera were isolated from the fern species *Elaphoglossum* sp. in Columbia. These endophytes were identified as *Phomatospora berkeleyi*, *Chrysosporium* sp., *Scopulariopsis candida*, *Verticillium* cf. *psalliotae* and *Phoma* sp. (Dreyfuss 1984).

In the study of mycorrhizal status of neotropical ferns by Lehnert et al. (2009), several dark septate endophytes (DSE) in Ascomycota were shown to colonize the roots of *Elaphoglossum* species (*E. engelii*, *E. erinaceum*, *E. glossophyllum*, *E. guamanianum*, *E. petiolosum*, *E. quitense*, *E. yatesii* and *Elaphoglossum* sp.) and were supposed to show mycorrhizal association similar to the ericoid mycorrhiza with the host.

Rojas-Jimenez and Tamayo-Castillo (2021) identified various fungal endophytes isolated from different parts of *Elaphoglossum doanense* in tropical forests of Costa Rica, including *Apioclypea* sp. (Amphisphaeriales), *Colletotrichum* (Glomerellales), *Ophioceras* (Magnaporthales), *Paramicrothyrium* (Microthyriales), *Annulohypoxylon* (Xylariales) and *Anthostomella* (Xylariales).

Equisetum spp.

The presence of dark septate endophytes (DSE) or fine root endophytes (FRE) was verified in the six species of *Equisetum* (*E. arvense*, *E. sylvaticum*, *E. fluviatile*, *E. hyemale*, *E. palustre*, and *E. telmateia*) by molecular and microscopic staining approaches. Several endophytic fungi were documented from the plant material of representatives in *Equisetaceae* family including DSE (approximately more than 80%), unidentified fungi from the order *Helotiales*, *Phialocephala fortinii*, *Cladophialophora chaetospira*, *Tetracladium* spp. and arbuscular mycorrhiza (AM) *Glomeromycotina*. Potential functional role of these endophytic fungi shows similarity to mycorrhizae by colonizing the plants when fungus–plant nutrient exchange occurs and DSE provides nutrient acquisition (^{15}N-enriched soil organic compounds) which in turn gain organic C compounds from plant photosynthesis (Giesemann et al. 2020).

Teratosphaeria sp. AK1128 is an endophytic fungal strain, classified in family Teratosphaeriaceae (Dothideomycetes, Ascomycota), and isolated from a stem of *Equisetum arvense*. This fungus is capable of producing ten bioactive compounds like naphtho-γ-pyrone dimers, teratopyrones A–C, naphtho-γ-pyrones (aurasperone B, aurasperone C, aurasperone F, nigerasperone A, and fonsecin), diketopiperazines (asperazine and isorugulosuvine) which among them, nigerasperone A showed cytotoxicity against certain cancer cell lines (human metastatic prostate cancer, human non-small lung cancer, (human central nervous system glioma, human breast cancer, human metastatic breast cancer, normal human lung fibroblast cells) (Xu et al. 2020b).

A freshwater hyphomycetes endophytic fungus, *Anguillospora longissimi*, was reported from the roots of the riparian plants *Equisetum* sp. in India. Its bioactivity (antimicrobial potential) was assessed with preliminary and secondary antibacterial assays and caused the growth inhibition of bacterial strains which is mainly because of the production of antibiotic substances by the fungus, suggesting *A. longissimi* as a source of natural products and secondary metabolites (Sati & Singh 2014). Similarly, *A. longissimi* was shown to potentially inhibit plant pathogenic fungi and its antagonistic activity was evaluated with well diffusion and dual culture techniques. The fungus was able to inhibit *Tilletia indica* (by maximum rate, 79.76%) and *Fusarium oxysporum* (by minimum rate, 35.73%) in dual culture method, and *Colletotrichum falcatum* (by maximum rate, 62.96%) and *Pyricularia oryzae* (by minimum rate, 17.85%) in well diffusion method (Singh and Sati 2020). In another study by Singh and Sati (2017), *A. longissima* was found to be a potent fungus for phosphate solubilization by production of the organic acids which can dissolve the mineral phosphate or act as chelating agents with iron (Fe) and aluminium (Al) ions associated with phosphate.

Huperziaceae

Huperzia serrata is considered as a medicinal plant in many western countries and China and is capable of producing bioactive compounds like lycopodium alkaloids with acetylcholinesterase (AChE) inhibiting activity (particularly huperzine A) (Liu et al. 1986; Ma & Gang 2004) which make this medicinal herb favorite to treat fever, schizophrenia, and myasthenia gravis (Skolnick 1997; Ma et al. 2007), blood disorders, muscle rupture (Thi Minh Le et al. 2019), contusions, strain, swelling (Jiang et al. 2014) and Alzheimer’s disease (Putri & Ariantari 2023).

Some fungal strains in the genera of *Alternaria*, *Fusarium*, *Trichoderma*, *Penicillium*, *Paecilomyces*, *Phoma*, and *Mucor* have been reported as endophytes from the stems, leaves, and roots of *H. serrata* in Vietnam

(Thi Minh Le et al. 2019). The presence of HupA in the methanolic extracts of strains was assessed by TLC, HPLC and NMR analyses and confirmed that *Penicillium* sp. LDL4.4 is a novel HupA-producing fungal strain which is able to produce notable amount of HupA, making it as a potent source to be used in the pharmaceutical industry to treat Alzheimer's disease, and suppress memory decline progress in patients. Other endophytic fungi in Huperziaceae family are able to produce HupA including genera of *Acremonium* (Wang et al. 2011, Li et al. 2007b); *Shiraia* (Wang et al. 2011, Zhou et al. 2010); *Aspergillus*, *Mycoleptodiscus*, *Leptosphaeria* (Wang et al. 2011); *Penicillium* (Wang et al. 2011), *Trichoderma* (Dong et al. 2014), *Colletotrichum* (Shu et al. 2014); *Blastomyces*, Botrytis (Ju et al. 2009); *Ceriporia*, *Hypoxylon* (Zhang et al. 2015).

Besides *H. serrata* as the major host plant species for inhabiting fungal endophytes, some other plants belong to the Huperziaceae family including *Phlegmariurus phlegmaria*, and *Phlegmariurus taxifolius* were assayed for their associated fungi which are promising Hup A producers. *Ceriporia lacerate*, *Colletotrichum gloeosporioides*, *C. boninense* and *C. guizhouensis*, *Hypoxylon investiens* and *Trichoderma harzianum* have been identified from *P. phlegmaria*, and *Fusarium* sp. was identified from *P. taxifolius* (Putri and Ariantari 2023).

Endophytic fungal community structures and diversity in different tissues of *H. serrata* plants was analyzed through Illumina-based high-throughput sequencing technology. The fungal operational taxonomic units (OTUs) were identified in seven phyla (Ascomycota, Basidiomycota, Chytridiomycota, Glomeromycota, Mortierellomycota, Mucoromycota, and Olpidiomycota) with Ascomycota and Basidiomycota as the dominant phyla, Dothideomycetes, Sordariomycetes, Eurotiomycetes, Tremellomycetes, Leotiomycetes, Agaricomycetes, Mortierellomycetes, Cystobasidiomycetes, Ustilaginomycetes, and Orbiliomycetes as predominant classes. Distribution of genera were tissue specific as genera of *Oidiodendron*, *Ilyonectria*, *Chloridium*, *Russula*, *Sebacina*, *Cladophialophora*, *Periconia*, *Pezicula*, *Roussoella*, *Scytalidium*, *Dactylonectria*, *Papiliotrema*, *Pochonia*, and *Verticillium* were mainly identified in the roots, the genera of *Cladosporium*, *Saitozyma*, *Pyrenochaetopsis*, *Claviceps*, *Cyphellophora*, and *Purpureocillium* in the stems, genera of *Phyllosticta*, *Serendipita*, *Devriesia*, and *Mortierella* in the leaves. Some genera were exclusive to the roots (*Botryosphaeria*, *Scytalidium*, *Idriella*) and stems samples (*Phialophora*, *Lecophagus*, *Clavaria*, and *Peniophora*). Among all 120 genera identified in the plant tissues of *H. serrata*, genera of *Cladosporium*, *Oidiodendron*, *Phyllosticta*, *Sebacina* and *PIlyonectria* were known as the dominant genera. The high richness and diversity of fungal endophytes in this medicinal herb *H. serrata*, indicating the plant as a potent source in the research program of various biological activities.

For example, in the chemical analyses of solid fermentation products of *Botryosphaeria* sp. P483, two new tetranorlabdane diterpenoids (botryosphaerins G and H) and seven known tetranorlabdane diterpenes (13,14,15,16-tetranorlabd-7-en-19,6β:12,17-diolide, botryosphaerin A, 3a,10b-dimethyl-1,2,3,3a,5a,7,10b,10c-octahydro-5,8-dioxa-acephenanthrylene-4,9-dione, acrostalidic acid, botryosphaerin B, LL-Z1271β and acrostalic acid) were identified which among them botryosphaerin H and 13,14,15,16-tetranorlabd-7-en-19,6β:12,17-diolide showed antifungal activity against *Gaeumannomyces graminis*, *Fusarium moniliforme*, *Fusarium solani*, *Fusarium oxysporum* and *Pyricularia oryzae* (Chen et al. 2015).

An endophytic strain *Bionectria* sp. Y1085 showed to produce some new metabolites like diketopiperazines and new polyprenol from the EtOAc extract of the endophytic fungus which was able to inhibit the growth of bacteria in the species of *Escherichia coli*, *Staphylococcus aureus*, and *Salmonella typhimurium* (Yang et al. 2019).

Yu et al. (2017) isolated *Chaetomium* sp. M453 from the branch of *H. serrata* in China and investigated its phytochemicals. The endophytic fungus was reported to produce four new steroids including three unusual C_{25} steroids, neocyclocitrinols E-G and 3β-hydroxy-5,9-epoxy-(22E,24R)-ergosta-7,22-dien-6-one in addition to some other known steroids. These chemicals were subjected for cytotoxicity and acetylcholinesterase inhibitory activities which among them only 3β-hydroxy-5,9-epoxy-(22E,24R)-ergosta-7,22-dien-6-one showed weak AChE inhibitory activity.

Penicillium chrysogenum MT-12 was screened for its bioactive secondary metabolites. It was able to produce some bioactive compounds including new polyketides and some of them were shown to have inhibitory effects on the lipopolysaccharide (LPS)-activated NO production in the RAW264.7 murine macrophage cells (Qi et al. 2017).

Pteris spp.

Pteris spp. was reported to produce various secondary metabolites, including pterosin-sesquiterpenoids (Pterosin F, Pterisemipol, Semipterosin A, Pteroside C, Q, S, T, U, W, X, (2R)-12-O-β-DGlucopyranosylnorpterosin B, 2R,3R-13-Hydroxypterosin L 3-O-βD-glucopyranos, Multifidoside A, B, C); *ent*-kaurane diterpenoids (Pterisolic acid A); flavonoids; benzenoids, and benzenoid derivatives; saponins; alkaloids; tannins and phenolic compounds (Gracelin et al. 2013; Cao et al. 2017). The endophytic fungi isolated from this fern can be used as alternative potential biological sources for some bioactive compounds.

Pteris vittata was reported as a medicinal fern in the family Pteridaceae which traditionally used to treat abdominal pains, diarrhoea, flu (Li 2006) or wound tissues (Paul et al. 2020). The fern possesses some medicinal features such as antioxidant activity, radical scavenging activity or cytotoxic activity against K562 leukaemic cells (Chai et al. 2015, Kaur 2017). An endophytic fungus obtained from the fresh rachies of *P. vittata* was identified as *Echinosphaeria pteridis* (anamorph: *Vermiculariopsiella pteridis*) in the Western Ghats in southern India (Dhargalkar & Bhat (2009). *Diaporthe ueckerae* was another endophytic fungus isolated from the same fern in China (Gao et al. 2022) and showed to produce some known and undescribed cytochalasans such as ueckerchalasins A−E, 4′-hydroxycytochalasin J_3, cytochalasin H, cytochalasin J, cytochalasin J_1−J_3, longichalasin B, RKS-1778 , and phomopchalasin A which displayed antibacterial activity against *Staphylococcus aureus* (SA) and methicillin-resistant *S. aureus* (MRSA), selective activity against human carcinoma HeLa and HepG2. In the study conducted by Kumaresan et al. (2013), endophytic fungi in the genera of *Acremonium*, *Aspergillus*, *Aureobasidium*, *Botryodiplodia*, *Colletotrichum*, *Fusarium*, and *Phomopsis* were identified from *Pteris* sp. which among them, species in *Colletotrichum* found to be dominant genera.

Endophytic fungus *Emericella quadrilineata* was isolated from the fern species *Pteris pellucida* in some areas of North East India and showed effective properties in bioactivity assays (Goutam et al. 2014). Bacterial species such as *Staphylococcus aureus*, *Aeromonas hydrophila*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Shigella flexneri*, *Escherichia coli*, *Enterococcus faecalis* and *Morganella morganii* were used in antimicrobial assay and the highest inhibition was found in *Aeromonas hydrophila* and *Staphylococcus aureus* at rate of 22 and 18 mm, respectively. Moreover, antifungal activity was conducted using *Curvularia* sp., *Aspergillus flavus*, *Aspergillus niger*, *Alternaria alternata* and *Fusarium oxysporum*, *Corynespora* sp. with the highest inhibition percentage for two later species (66.52% and 60%, respectively). Methanol extract of the fungal strain was also found to exhibit a moderate antioxidant activity with Scavenging effect. Moreover, Goutam et al. (2016) isolated and identified the antibacterial compounds from the metabolites extracted from *E. quadrilineata* using gas chromatography mass spectroscopy (GCMS), Thin Layer Chromatography (TLC), C13NMR, H1 NMR and FTIR. Benzyl benzoate, benzaldehyde dimethyl acetal and benzoic acid were found to be as the dominant compounds with significant antibacterial activity. Benzyl benzoate was previously isolated from various plant extracts and played as spasmolytic (Rivero-Cruz et al. 2007), calmodulin inhibitor (Figueroa et al. 2009), tyrosinase inhibitors (Fang et al. 2011) and then reported to be effective to treat Angina pectoris and scabies (Robert & Babcock 1924, Gilman et al. 1980, Bachewar et al. 2009). Data from bioactive profile assay of endophyte *Emericella quadrilineata* and previous report of natural bioactive compounds in *Emericella variecolor* such as isoindolone (antiviral compound), varitriol (anticancer agent), varioxirane, dihydroterrian and varixanthone (antimicrobial agents) (Malmstrom et al.2002; Zhang et al. 2011a) have indicated the potential pharmacological importance of the endophytes in the genus *Emericella*.

Amphirosellinia nigrospora is an endophytic fungus belongs to the class Sordariomycetes in Ascomycota (Jeon et al. 2019) which was isolated from cretan brake fern (*Pteris cretica*). The fungus is able to produce oxygenated cyclohexanone ((4S,5S,6S)-5,6-epoxy-4-hydroxy-3-methoxy-5-methylcyclohex-2-en-1- one) as a remarkable antibacterial compound. The antimicrobial efficiency of this chemical was assayed against some phytopathogenic bacteria such as *Acidovorax avenae* subsp. *cattlyae*, *Agrobacterium konjaci*, *A. tumefaciens*, *Burkholderia glumae*, *Clavibacter michiganensis* subsp. *michiganensis*, *Pectobacterium carotovorum* subsp. *carotovorum*, *Pectobacterium chrysanthemi*, *Ralstonia solanacearum*, *Xanthomonas arboricola* pv. *pruni*, *Xanthomonas axonopodis* pv. *Citri*, *Xanthomonas euvesicatoria*, *Xanthomonas oryzae* pv. *oryzae* and against some phytopathogenic fungi such as *Botrytis cinerea*, *Cryphonectria parasitica*, *Collectotrichum coccodes*, *Fusarium graminearum*, *Magnaporthe oryzae*, *Pseudocercospora circumcissa*, *Raffaelea quercus mongolicae*, *Rhizoctonia solani* and *Sclerotinia homoeocarpa*. This compound was shown to has a significant antibacterial inhibitory for the bacterial wilt pathogen of tomato, *Ralstonia solanacearum* and its antifungal activity was observed severe in *M. oryzae* (Nguyen et al. 2019).

Selaginella spp.

Selaginella as a member of the family Selaginellaceae contains various secondary metabolites such as alkaloid, phenolic (flavonoid), terpenoid and disaccharide (trehalose) which made this fern valuable in traditional medication system (Setyawan 2011). Exploration of endophytic fungi isolated from the roots and leaves of *Selaginella tamariscina* in China led to identification of several fungal genera such as *Penicillium*, *Isaria*, *Aspergillus*, *Fusarium*, *Nigrospora*, *Didymella*, *Talaromyces*, *Tuberculina*, *Ceratocysts*, *Scytalidium*, *Phoma*, *Humicola*, *Kostermansinda*, *Colletotrichum* and *Pestalotiopsis* which among them *Chaetomium*, *Penicillium*, *Isaria* and *Aspergillus* showed the highest frequency (Zhang et al. 2019).

The pentaketide CR377 was derived from a *Fusarium* sp., which is an endophytic fungus residing within the stems of *Selaginella pallescens*. The plant was collected from the Guanacaste Conservation Area located in Costa Rica. When tested using an agar diffusion assay, the compound demonstrated antifungal properties against *Candida albicans*. The inhibition zone observed was similar to that of nystatin, which is a fungicide (Brady and Clardy 2000).

Anteaglonium sp. (Anteagloniaceae, Pleosporales, Pezizomycotina, Ascomycota) was reported as an endophytic fungus in *Selaginella arenicola*. Cytotoxic EtOAc extract of the culture of strain FL0768 was assayed to investigate the presence of bioactive compounds, leading to the isolation of 22 substances such as Anteaglonialides A−F, bearing a spiro[6-(tetrahydro-7-furanyl)cyclohexane-1,2′-naphtho[1,8-de][1,3]-dioxin]-10-one skeleton, three new spirobisnaphthalenes, palmarumycins CE1−CE3, nine known palmarumycin analogues, palmarumycins CP5, CP4a, CP3, CP17, CP2, and CP1, CJ-12,371, 4-O-methyl CJ12,371, and CP4, 4a(5)-anhydropalmarumycin CE2 (8a), and four known metabolites, O-methylherbarin, herbarin, herbaridine B, and hyalopyrone (Xu et al. 2015). In the following study on the same fungus (*Anteaglonium* sp. FL0768) by Mafezoli et al. (2018), some other secondary metabolites were produced which were identified as heptaketides, herbaridine A, herbarin, 1-hydroxydehydroherbarin, scorpinone, the methylated hexaketide 9S,11R-(+)-ascosalitoxin, ascochitine, palmarumycin CE4, palmarumycin CP4, and palmarumycin CP1.

Selaginella delicatula was also reported as an endophytic fungal fern inhabiting *Shiraia* sp. in its leaves. Some bioactive compounds were obtained from the ethyl acetate extract of the strain BYJB-1 which led to the identification of one new benzophenone derivative (shiraone A), and seven known compounds (linchenxantone, 4-hydroxymellein, hypocrellin A, hypocrellin B, 9,11-dehydroergosterol peroxide, ergosteroal peroxide, and lactariolide I). The bioactivity properties of all chemicals were assayed against human hepatoma cell lines (HepG2 and SMMC7721) in cytotoxicity assay, and against MRSA and *E. coli* in antibacterial assays, indicating moderate cytotoxic activities of only two compounds 9,11-dehydroergosterol peroxide and ergosteroal peroxide against SMMC7721 cell line (Chen et al. 2022).

An endophytic fungus *Aspergillus ochraceous* was identified from *Setaginella stauntoniana* in China and several compounds such as semivioxanthin, 6-hydroxy-p-menth-4 (5)-en-3-one, flavacol , magnolin, preussin B, circumdatins D, isofucosterol, sclerotiamide, 3β-hydroxyergosta-8,24(28)-dien-7-one, and 3-O-β-D-glucopyranosyl stigmasta-5(6),24(28)-diene were isolated and purified by silica gel which showed antibacterial activity against *Bacillus subtilis* and inhibitory activity against acetylcholinesterase (Luo 2020).

Conclusion and Future prospects

Medicinal fern taxa as sources of diverse bioactive compounds have been reported to treat many diseases with strong potential in different biological activities such as antioxidant, anti-inflammatory, anti-microbial, anti-diabetic, anxiolytic, hepatoprotective, anti-aging, anticonvulsant, anticancer, insecticidal, etc. Evolution of mutualistic interrelations between fungal endophytes and their fern hosts and the discovery of bioactive substances originally produced by plants have opened the way to replace medicinal ferns with endophytic fungi due to their ability to grow fast and exhibit lower fermentation costs and easier managements. In this review, we increased awareness about the key roles of fungal endophytes in natural environments and their interaction with fern hosts in many domains. Several studies have been conducted on the endophytic fungi residing inside fern species in genera of *Huperzia*, *Phlegmariurus*, *Pteris*, *Adiantum*, *Dryopteris*, *Elaphoglossum*, *Selaginella*, *Equisetum*, *Botrychium* and *Diplazium*. On the contrary, in spite of many previously reports on the therapeutic activities of medicinal species in *Angiopteris*, *Blechnum*, *Ceratopteris*, *Macrothelypteris*, *Abacopteris*, *Polypodium*, *Dicranopteris*, *Diplopterygium*, *Helminthostachys*, *Ophioglossum*, *Lygodium*, *Stenoloma*, *Deparia*, *Dryoathyrium* and *Davallia*, there are no comprehensive or few researches for investigation of fungal endophytes associated with these medicinal ferns, which provides a huge gap and opportunities for exploration of the associated undiscovered fungal endophytes. Potential endophytic fungi isolated from lower plants can be used as promising alternatives which can produce various chemical compounds leading to drug discovery, biotechnological, agricultural, and industrial application.

Table 1: Endophytic fungi associated with medicinal ferns

Fern species	Fungal endophytes	Isolate Sources	Origin	References
Equisetum sp.	*Anguillospora longissima*	roots	India	Sati and Singh (2014); Singh and Sati (2017)
Equisetum arvense	*Teratosphaeria* sp.	stem	Western Alaska	Xu et al. (2020b)
Huperzia serrata	*seven fungal phyla*	roots, stems and leaves	China	Fan et al. (2020)
Huperzia serrata	*Botryosphaeria* sp.	unknown tissues	China	Chen et al. (2015)
Huperzia serrata	*Bionectria* sp.	unknown tissues	China	Yang et al. (2019)
Huperzia serrata	*Chaetomium* sp.	branch	China	Yu et al. (2017)
Huperzia serrata	*Penicillium chrysogenum*	unknown	China	Qi et al. (2017)
Huperzia serrata	*Alternaria*, *Fusarium*, *Trichoderma*, *Penicillium*, *Paecilomyces*, *Phoma*, and *Mucor*	stems, leaves, and roots	Vietnam	Thi Minh Le et al. (2019)
Huperzia serrata	*Cladosporium cladosporioides*	leaves	China	Zhang et al. (2011b)
Phlegmariurus phlegmaria	*Ceriporia*, *Colletotrichum*, *Hypoxylon*, *Trichoderma*	leaves	China	Zhang et al. (2015)
Phlegmariurus taxifolius	*Fusarium*	leaves, stems, and roots	Mexico	Cruz-Miranda et al. (2019)
Pteris vittate	*Echinosphaeria pteridis* (*Vermiculariopsiella pteridis*)	rachises	India	Dhargalkar and Bhat (2009)
Pteris sp.	*Acremonium* sp., *Aspergillus tereus*, *Aureobasidium* sp., *Botryodiplodia* sp., *Colletotrichum* spp., *Fusarium* sp., and *Phomopsis* sp.	shoots	India	Kumaresan et al. (2013)
Pteris pellucida	*Emericella quadrilineata* (*Aspergillus nidulans*)	leaves and stems	India	Goutam et al. (2014)
Pteris cretica	*Amphirosellinia nigrospora*	leaves, twigs and roots	South Korea	Nguyen et al. (2019)
Pteris vittate	*Diaporthe ueckerae*	leaves	China	Gao et al. (2022)

Table 1: Contd.

Fern species	Fungal endophytes	Isolate Sources	Origin	References
Selaginella tamariscina	*Penicillium*, *Isaria*, *Aspergillus*, *Fusarium*, *Nigrospora*, *Didymella*, *Talaromyces*, *Tuberculina*, *Ceratocysts*, *Scytalidium*, *Phoma*, *Humicola*, *Kostermansinda*, *Colletotrichum* and *Pestalotiopsis*	roots and leaves	China	Zhang et al. (2019)
Selaginella pallescens	*Fusarium* sp.	Stems	Costa Rica	Brady and Clardy (2000)
Selaginella inaequalifolia	*Xylariaceae*	leaves	Thailand	Okane et al. (2008)
Selaginella sp.	*Botryodiplodia* sp., *Colletotrichum* spp., *C. falcatum*, *Phomopsis* sp., *Phyllosticta* sp.	leaves and stems	India	Kumaresan et al. (2013)
Selaginella arenicola	*Anteaglonium* sp.	stem of the sand spikemoss	USA	Xu et al. (2015)
Selaginella delicatula	*Shiraia* sp.	leaves	China	Chen et al. (2022)
Selaginella stauntoniana	*Aspergillus ochraceous*	unknown	China	Luo et al. (2020)
Elaphoglossum sp.	*Phomatospora berkeleyi*, *Chrysosporium* sp., *Scopulariopsis candida*, *Verticillium cf. psalliotae* and *Phoma* sp.	leaves, stem, root	Columbia	Dreyfuss (1984)
Elaphoglossum spp.	dark septate endophytes (DSE)	Roots	Ecuador	Lehnert et al. (2009)
Elaphoglossum doanense	*Apioclypea* sp., *Colletotrichum*, *Ophioceras*, *Paramicrothyrium*, *Annulohypoxylon* and *Anthostomella*	leaves, petiole, branch, and root	Costa Rica	Rojas-Jimenez and Tamayo-Castillo (2021)

Conflict of interest

The authors declare that they have no conflict of interest.

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