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Bioprospecting of fungal endophytes from plants of the family Zingiberaceae and their pharmaceutical applications

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A B S T R A C T

Endophytic fungi are thought of as the hidden members of the microbial world that are widely recognised as a rich resource of potential chemical compounds with biological activities.The primary role of the bioactive substances produced by endophytes is to aid the host plants in withstanding abiotic and biotic stresses, which is ultimately beneficial to the survival of the host. Most of these endophytic fungi are from the Ascomycota, Oomycota, Zygomycota, and Basidiomycota groups.Research into endophytes has revealed that they have the potential to yield useful pharmaceuticals. Endophytic fungi are regarded as an under-utilized sourcethat hasn't been used enough to find new drugs and compounds. Endophytic fungi exhibit antibacterial, anticancer, immunomodulatory, antiviral, anti-diabetic, antioxidant, anti-inflammatory and other biological activities, which are being exploited for pharmaceutical application using biotechnological tools. The present review focuses on the biopharmaceutical potential of endophytic fungi from an important group of medicinalplant belonging to the family Zingiberaceace.

1. Introduction

Endophytes are described as polyphyletic groups of microorganisms which may be actinomycetes, bacteria or fungi (Kusari *et al*., 2012). Endophytic fungi (EF) are a group of fascinating host-associated fungal communities that thrive asymptomatically the internal tissues of healthy plants without causing any diseases to the host (Amirita *et al*., 2012). They colonise the host either as obligate associates or as facultative associates with lower and higher plants (Deshmukh *et al*., 2006). Endophytes communicate information to higher plants and have evolved biochemical pathways that produce novel bioactive substances. Therefore, they offer chances for discovering products and processes with medical and biotechnological applications (Bielecka *et al*., 2022). In recent years, accumulated research on endophytic fungi has revealed their wide-ranging ecological distribution, biodiversity and multidimensional interactions with host plants and other microbiomes in the symbiotic continuum (Alam *et al*., 2021).

It is believed that there are about one million different species of endophytic fungi that can be found in nature (Faeth and Fagan, 2002). According to Schultz, the endophytic fungi are mainly classified into three main ecological groups: (a) pasture or balansicaeousendophytic fungi; and (b) non pasture endophytic fungi; (c) mycorrhizal endophytic fungi (Faeth and Fagan, 2002).

Their affiliation can be compulsory or discretionary and does not, thus, cause direct damage to its host. Endophytes have dynamic relationship with its host plants, which include mutual relationship and antagonistic relationship**.** Plants primarily restrict endophyte growth and the endophytes undergo various mechanisms to steadily adapt into the living environment (Dudeja *et al*., 2012). In order to maintain a sustainable symbiotic association, a range of compounds are produced by the endophytes such as gibberellins, indoleacetic acid, alkaloids, isocoumarin derivatives, quinones, chlorinated metabolites, flavonoids, terpenoids, phenol and phenolic acids which facilitates the

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growth of the host plant and help them better survive in their environment. The presence of endophytes encourages plant nutrient absorption and thus contribute towards host plant's enhanced growth. Endophytes are considered as plant growth promoters by producing various broad range of phytohormones like auxins, gibberellins, IAA, cytokines etc. Besides plant growth, endophytes are known to induce growth in terms of increase in plant height, shoot diameter and shoot weight (Yates *et al*., 1997). Apart from plant growth factors, endophytes generate pharmaceutical agents which have biotechnological potential, like anti-tumor drugs (taxol), anti-fungal drugs (quercine), and various industrially important enzymes (Ting *et al*., 2008; Cao *et al*., 2004). Different enzymes are produced by endophytes include protease, amylase, pectinase, L-asparginase, chitinase, laccase, etc. Endophytes living inside medicinal or crop plants have confirmed the presence of most enzymes (Ayob *et al*., 2016).

During the past two decades, the endophytes are being explored for novel bioactive compounds. Various compounds generated via biosynthetic pathways belong to broad classes of compounds like phenols, tetralones, enniatins, steroids, isocoumarins. Endophytic organisms are actually a reservoir for the discovery of new compounds for development in medicinal and agricultural industries by producing various antibiotics, antioxidants, anti-parasitic and anti-cancer drugs. At present, main focus of exploring endophytes are the potential of these microorganisms in developing secondary metabolites. Since endophytic microbes may synthesis or even mimic the same substance produced by their host plants, bioprospecting of these microorganisms opens up avenues of discovering novel molecules (Venieraki *et al*., 2017).

Notable species like ginger and turmeric belonging to family Zingiberaceae has long been recognized as a potential cure for a variety of conditions, including cramps, digestive issues, arthritis, fever, cough, and cold (Ma, 2012). Zingiberaceae plants have been extensively researched in the scientific literature because of their antimicrobial, anti-apoptosis, anti-tumor, and anti-inflammatory and other biological activities, which can be attributed to the presence of several phyto-compounds in them (Karuppiah, 2012). Anti-microbial resistance (AMR) is a global health challenge on medicinal view point and there is a need for discovery of new antimicrobial compounds from natural sources. In this context, exploitation of fungal endophytes to synthesize novel antibiotics, especially the modified or somewhat similar with Zingiberaceae compounds has great prospect in medical application. The initial step for study about the biopotential of endophytic fungi is the isolation of some antagonistic fungal strains from non-symptomaticand healthy plant parts. Several researchers have successfully isolated and reported many fungal endophytes and evaluated their antibacterial potential. Antagonistic endophytic *Penicillium* sp. has been isolated from *Curcuma longa*, which exhibits inhibitory activity against human pathogenic bacteria such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (Rathod, 2013). The results of antagonistic activity of fungal strains towards examined pathogens were unique, demonstrating that fungal strains have varying capabilities in generating antimicrobial chemicals. Chemical compounds made by growing *Pestalotiopsis vaccinii* were thought to be new natural products made only by the strain itself (Wang, 2014; Wang, 2017). Research on application of fungal endophytes from the Zingiberaceae family is still in its infancy. However, earlier studies have revealed endophytic fungi (EFs) as new sources of bioactive chemicals with anticarcinogenic substances (Uzma *et al*., 2018). Therefore, the study of distribution, diversity, and biochemical properties of endophytes is a very important, which will help us to understand and improve plant fitness (Yuan *et al*., 2019). The present review provides a thorough explanation of the biological features of EFs from plants belonging to Zingiberaceae family, including their diversity, distribution, function along with pharmaceutical applications. Besides, the review also highlights the promising therapeutic uses and exhaustive pharmacological information of the species of Zingiberaceae.

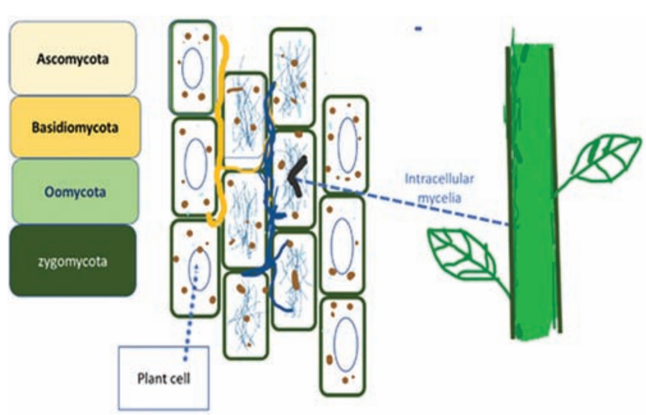

Fig. 1: Classification of endophytic fungi and their occurrence with in plant cell

2. Species and phytochemical diversity of family Zingiberaceae

The monocotyledonous family Zingiberaceae are comprised of a large number of medicinal, aromatic and ornamental plants, which are widely distributed throughout the tropical and sub-tropical regions of the world (Ghosh *et al*., 2013) with greater species concentration in Southeast Asia (Jantan *et al*., 2003). The family is comprised of over 1200 species under 53 genera (Kress *et al*., 2002). As many as 178 species under 22 genera are reported from North Eastern and peninsular region of India (Jain and Prakash, 1995).The members of Zingiberaceae are both perennial or annual rhizomatous herbs. These aromatic ethnomedicinally important plants are characterised by the presence of volatile oils and oleoresins. The important members under the family Zingiberaceae having medicinaluses belongs to the genus *Amomum, Curcuma, Alpinia Elettaria, Hedychium, Kaempferia* and *Zingiber* (Prabhu *et al*., 2010). In general, the rhizomes and fruits belong to this group of plant are aromatic and are used as tonic and stimulant. These multipurpose plant family are the rich sources of natural products and chemicals thatare already being utilized as spices, medicines, dyes, perfume and food.

India, traditionally known as 'the spice bowl of the world', is the largest producer, consumer and exporter of ginger. Ginger has rich cultivar and genetic diversity in India, and the cultivars are generally named after localities of occurrence or cultivation. More than 50 cultivars possessing varying yield and quality parameters are grown in India. Kerala holds maximum diversity of ginger followed by Himachal Pradesh and Assam (Ravindran *et al*., 2005). Disease-resistant and high-yielding ginger hybrids are the results of crop improvement programmes and Athira, Rajatha, Mahima, Suprabha, Suruchi, Suravi, Himagiri, Karthika, Varada are some popular varieties developed in India.

Endophytic fungi live in rhizomes of plants of ginger family and the metabolites that these fungi make may have an effect on the bioactivity of ginger extracts and the quality of the spice. These metabolites are not removed by washing, so they may also have an effect on human health. These metabolites are produced against host-specific phytopathogens and may demonstrate antibacterial, antifungal, cytotoxic, anticancer, antioxidant, and anti-inflammatory activities.

Though fungi are capable of colonising intercellular or intracellular regions of host plant, they are more likely to do so at the plant's roots than at its leaves or stems. Apoplastic fluid from the host is the primary nutrition supply for colonisation in aerial organs, allowing for healthy reproduction of EFs (Schulz *et al*., 2002). During an infection, fungi form three distinct types of interactions with their hosts: communalistic (non-beneficial/virulent endophytes), mutualistic (beneficial endophytes) and pathogenic (virulent pathogens). The nature of these interactions differs depending on the physiological status of the host plants or the specific conditions that they are exposed to. *Alpinia, Amomum, Curcuma, Elettaria, Hedychium, Kaempferia* and *Zingiber* are the interesting genera of Zingiberaceae which contain aromatic spice plants with very high medicinal values (Joy *et al*., 1998). Among them, few species are cultivated but majority of the species occur in the wild. Each of the above-mentioned genera are briefly discussed below.

2.1. Genus Alpinia

Alpinia Roxb. is the most widespread and largest genus belonging to subfamily Alpinioideae under the Zingiberaceae with about 230 species. Members of this genus are mainly distributed in India, Indonesia, Arabic gulf areas, Egypt, Malaysia, Japan, southeast Asia, the Pacific, Samoa, the Caroline Islands, Australia and northern New South Wales, China and Sri Lanka (Larsen *et al*., 1998; Smith, 1990). Most of the species grow in open and sunny places, low- to mid-elevation forests and brushwood. In India, the species of these genus are found in the Himalaya and Southern region of Western Ghats (Khare *et al*., 2007).These are perennial herbs with oblong-lanceolate leaves, tuberous root, greenish white flowers. (Gupta *et al*., 2010). While the rhizomes are source of essential oils (Jirawan *et al*., 2005), the young shoots and flowers are used as a spice (Arambewela *et al*., 2006) and condiments. In Asian countries, *Alpinia* species are used in cooking (*A. galanga*) and medicinal purposes (e.g., *A. officinarum* Hance). The plant is mostly used in the traditional system of medicine viz. Ayurveda, Unani, Chinese and Thai folk medicines (Yang *et al*., 1999). The active phytochemical constituents of these plants support medicinal and pharmacological properties.

2.2. Genus Curcuma

Curcuma is a genus with some 120 species occurring from Indochina, Malaysia, India, northern Australia and Thailand (Leong, 2007; Larsen, 1996; Maknoi, 2006). It is a genus of perennialherbs whose rhizomes are fleshy, aromatic and usually varies from light brown to different shades of yellow (Maknoi, 2007). India is the top producer of *Curcuma* rhizomes followed by Southeast Asia, Thailand, Central and Latin America, and Taiwan.

Many of its members have medicinal uses such as treating digestive disorders including dyspepsia and colic due to its anti-inflammatory, anti-viral, anti-bacterial, anti-fungal, and anti-oxidant properties. The anti-cancerous activity from extract of *Curcuma longa* is under trials. *Curcuma* is of great economic importance, with *Curcuma longa* as the top notched in the genus along with *C. amada*, *C. angustifolia* and *C. zedoria, C. caesia* are common species.

2.3. Genus Zingiber

The genus *Zingiber* is comprised of about 85 species of herbs mostly grown in Asia, Africa, central andsouth America (Sabulal *et al*., 2006). These plantae prefer moist, tropical conditions (Jayashree *et al*., 2015). Phytochemical investigation of the rhizomes of several *Zingiber* species has revealed that they possess various pharmacological and physiological effects due to the presence of bioactive compounds such as gingerols, shogaols, diarylheptanoids, phenylbutenoids, flavanoids, diterpenoids and sesquiterpenoids (Sivasothy *et al*., 2011). In addition, shogaols, dehydrated gingerol derivatives, are the predominant pungent constituents in dried ginger (Jiang *et al*., 2006).These plants are used as common ingredients in traditional medicines. The rhizomes have been used successfully to treat a variety of medical conditions, including gastrointestinal distress, motion sickness, vomiting, epilepsy, bronchitis, common cold, bruises, wounds, liver complaints, rheumatism, muscular pains, atherosclerosis, migraine headaches, high cholesterol, ulcers, and stomach discomfort (Shukla *et al*., 2007). Phenolic compounds in ginger root, especially gingerols, have been shown to have chemopreventive effects linked to their antioxidant and anti-inflammatory properties (Shukla *et al*., 2007).

2.4. Genus Hedychium

The genus *Hedychium* has 87 species, which have worldwide distribution (Plant list, 2010). *Hedychium spicatum*, found from Himachal Pradesh to Arunachal Pradesh, is useful in the treatment of liver complaints, fevers, vomiting, diarrhoea, inflammation, pains and snake bite.The rhizomes of *H. spicatum* are reported to harbour twenty-eight fungal strains and about 84% of endophytic fungi isolated belonged to the phylum Ascomycota. Endophytic fungal genera such as *Fusarium* and *Penicillium* were found to be common to all the plant parts. *Hansfordia biophila* is an endophytic fungus isolated from *Hedychium acuminatum* that produces tannin (Hastuti *et al*., 2018).

2.5. Genus Elettaria

The genus *Elettaria* is represented by few species of perennial herbs with rhizomes.They grow in India, Sri Lanka, Malaysia, and Indonesia (Wills, 1967). In India, the species are indigenous to the most southern tropical evergreen forests of the Western Ghats of India (Ravindran, 2002). Among them, Cardamom (*Elettaria cardamomum*), also known as Indian cardamom or small cardamom, has been used worldwide for culinary purposes and the older forms of medicine. Essential oils and other high-value antioxidant and gastroprotective bioactive metabolites from its fruits are primarily responsible for its unique aroma and function as a functional food as well as a nutraceutical and medicine (Hamzaa and Osman, 2012).

2.6. Genus Amomum

Amomum, another genus of Zingiberaceae, is represented by over 150 species, mostly in Asia and Oceania (Cai *et al*., 2021). They are perennial herbs with distichous leaves and elongating pseudo-stems (Syazana, 2018). Volatile oils, as one of the essential components of the genus *Amomum*, have been extensively studied. Till date, more than 160 non-volatile compounds have been isolated from this genus, including flavonoids, terpenoids, diarylheptanoids, *etc*. In China, India, Thailand and Nepal, 16 species of the genus *Amomum* are utilised in traditional medicine. Recent exploratory research on the pharmacological qualities of the *Amomum* species revealed their efficacy as anti-inflammatory agents (Jin *et al*., 2016), cure for stomach diseases (Kumar *et al*., 2014), cancer (Zhang *et al*., 2015), hepatopathy diseases (Kim *et al*., 2015) and malaria (Heilmann *et al*., 2001).

3. How endophytic fungi colonise within host plants

It is well established that endophytic fungus colonisation is not a random event and happens because of chemotaxis, or specialised molecules produced by the host plant. At the same time, different types of secondary metabolites like saponin and essential oils from medicinal plants, are made as a way to fight off pathogens which acted as barriers against the colonisation of endophytic fungi. To circumvent this, the endophytic fungi must secrete the corresponding detoxifying enzymes such as cellulases, lactases, xylanases and proteases for the degradation of these secondary compounds before they reach the defence systems of the host-plants. Once within the tissues of a host-plant, endophytic fungi assume a quiescent (latent) state, either for the entire lifetime of the host plant (neutralism) or for an extended period of time (mutualism or antagonism), until environmental conditions are favourable for endophytic fungi or the ontogenetic state of the host changes to the fungi's advantage (Sieber, 2007).

Different interactions have been developed between endophytic fungi and their host plants through a distinct fungus-host interaction during the lengthy period of co-existence and evolutionary processes: (i) a continuum of mutualism, (ii) antagonism, and (iii) neutralism. The genetic background, nutrient level, and ecological habitats of medicinal host plants are thought to be pressure-choice factors on the population structure of endophytic fungi, which in turn confer some kinds of benefits, such as induced growth, increased resistance to disease, and/or herbivores, as well as accumulated bioactive components (Firakova *et al*., 2007). For this reason, the mutual relationship between endophytic fungi and their host plants might impose specific effects on the formation of particular types of bioactive substances which have been explored for human benefits. To the best of our knowledge, there has been very little research on the commercialization of fungal endophytes isolated from Zingiberaceous plants.

4. Diversity of endophytes associated with the plants of the family Zingiberaceae

Endophytic fungi associated with different species of Zingiberaceae have been isolated from meristems, leaves, roots, stems, rhizomes by different workers. Generally, they are isolated by surface sterilization followed by culturing them from either crushed tissue extract or culturing through plant tissues on suitable media (Hata *et al*., 2008). Members of family Zingiberaceae have been explored for a diverse group of endophytic fungi. Eleven fungal strains have isolated from *Curcuma longa* plant by Septiana (2017). About 33 fungal isolates have been isolated from six species of Zingiberaceae viz. *Zingiber officinale*, *Curcuma domestica, Kaempferia rotunda, Curcuma xanthorrhiza, Curcuma mangga* and *Curcuma zedoaria* (Praptiwi *et al*., 2016).

Members of 10 fungal genera have been reported from *Alpinia officinarum* by Shubin *et al.* (2014). Endophytic fungi such as *Trichoderma* sp., *Mycelia sterilia*, *Penicillium* sp., *Alternaria* sp., *Penicillium* sp., *Fusarium* sp., *Aspergillus* sp., *Bipolaris* sp. and *Nigrospora* sp. have been isolated from *Hedychium coronarium* by Uzma *et al.* (2016). Similarly, species of *Colletotrichum, Fusarium, Bipolaris, Pithomyces, Mucor, Alternaria, Mycelia, Rhizopus, Cladosporium* are reported from *Hedychium flavescens* (Uzma *et al*., 2016). Bussaban *et al*. (2001) reported occurrence of *Eupenicillium crustaceum*, *Fusarium* spp., *Glomerella* spp., *Phomopsis* spp., *Phyllosticta* spp., *Pyricularia* spp., *Talaromyces flavus*, taxa of Xylariaceae, *Mycelia sterilia* from *Amomum siamense.*

5. Isolation of endophytic fungi from species of Zingiberaceae

Surface sterilization is the most needed technique which is used for the isolation of endophytic fungi from ginger family. Surface sterilized by immersing in 70% ethanol for 1 min. Then rinse the samples three times with sterile distilled water and soak them again in hypochlorite solution (NaOCl) 0.5% for 5 min and again rinse them in sterile water for six times. Allow the samples to become surface-dry by putting them on sterilized filter paper for 12 hours and it should be carried out in biosafety cabinet (Hallmann *et al.*, 2006). Place all the sterilized segments of each plant part on PDA containing chloramphenicol antibiotic (0.5 g/l) or streptomycin to inhibit the bacterial growth. Seal the Petri dishes with parafilm to prevent desiccation of the medium and incubate them in dark at 28 °C for 7-21 days. Continuously monitor the fungal growth. When the fungi grow out from the plant organ, then cut the hyphal tip arising from the fungal colony and transfer them to fresh PDA to enhance the normal sporulation for better identification. Every precaution should be practiced while performing the endophytic fungal isolation, as there are many chances of existence of epiphytic fungi during isolation.

Fungal identification was accomplished by observing their morphological characteristics. Besides, PCR and DNA sequencing are novel techniques employed to identify endophytic fungus. Identification of fungal endophytes can best be accomplished by amplification of Internal Transcribed Spacer (ITS) regions, which are repeating units of DNA encoding ribosomal RNA.

6. Biopharmaceutical potential of endophytic fungi from Zingiberaceae

Endophytic fungi are regarded as rich sources of numerous bioactive secondary metabolites and phytohormones that promote plant growth and enable plants to withstand biotic or abiotic stresses (Tan and Zou, 2001; Chadha *et al.*, 2014). Apart from the benefits to the host plant, the endophytes have also proved as an outstanding source of SMs and bioactive antimicrobial products**.** Endophytic fungi can biosynthesize some of the most important commercially exploited SMs, including antibiotics, anticarcinogenic, cytotoxins, insecticides, and allelopathic compounds (Schneider *et al*., 2008).They have a lot of commercial potential in the pharmaceutical, medical, agricultural, nutraceutical, cosmetic, flavour, and fragrance industries. This makes EFs an interesting topic for endophytism research (Hyde and Soytong, 2008).The potential of endophytic microorganisms as untapped resources for innovative drugs has aroused a great deal of attention (Strobel, 2002). The ginger species are well-studied for their biological properties such as anti-microbial, anti-oxidant, anti-tumor, antihyperglycemic, anti-hyperuricemic, anti-inflammatory, anti-larvae, anti-aging and functional properties as a topical medicine attributed to presence of alkaloids, flavonoids, glycosides, phenols, saponins, steroids, tannins, and terpenoids (Juwita *et al*., 2018).

Hypomontagnella monticulosa (Zg 15SU) isolated from *Zingiber griffithii* showed potent cytotoxic activity (Lutfia *et al*., 2021). Bioactive compounds such as a-cyclocitral, cembrene A, laurenan-2-one, sclareol, 2Z, 6E farnesol, cembrene, isocomene and α-curcumene obtained from endophytic fungi *Arthrinium* sp. (MFLUCC16-1053) account for their antimicrobial andantioxidant activities, which were isolated from *Zingiber cassumunar* (Pansanit *et al*., 2018). *Zingiber zerumbet* rhizomes harbour *Fusarium solani* and *F. oxysporum* which has antipythium activity (Keerthi *et al*., 2016). Similarly, the phenolic compounds produced by the fungal endophyte *Bipolaris specifera, Alternaria tenuissima, Aspergillus terreus, Nectria haematococca* and *Fusarium chlamydosporum* from *Zingiber nimmonii* have potential antioxidant properties (Das *et al*., 2017). *Eurotium* sp. isolated from *Curcuma longa* produces asparginase that has anticancer as well as antimicrobial properties (Jalgaonwala *et al*., 2010; Jalgaonwala *et al*., 2014). The anti-microbial and oxidant activity of 33 fungal isolates obtained from *Zingiber officinale, Curcuma domestica, Kaempferia rotunda, Curcuma xanthorrhiza, Curcuma mangga* and *Curcuma zedoaria* have been reported (Praptiwi *et al*., 2016). MM2 compound isolated from endophytic fungi *Aspergillus terreus* (RTN3) from young stems of *Alpinia chinesis* has shown potent anticancer activity and inhibitory effects on *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (Vo *et al*., 2020). The ability of endophytic fungus *Trichoderma afroharzianum* isolated from *Hedychium coronarium* in producing chitinase has been reported (Munir *et al*., 2019). The major bioactive compounds synthesized from endophytic fungi and their bioactivities are summarized below in Table 1.

Although the pharmacological activities of Zingiberaceae species have been extensively described, not much is known about bioprospecting of their endophytic microorganisms. Endophytic mycoflora are regarded as an exceptional pharmaceutical bioresource as they produce a wide range of substances known as secondary metabolites (Strobel, 2003). As bioactive compounds produced by endophytic community are believed to be regulated by the positive effect of plants, these plants with medicinal characteristics are regarded as a significant resource for studying fungal endophytes (Venkateswarulu *et al*., 2018). Endophytes have been found to be good sources of biologically active products that are interesting for certain health care uses (Strobel *et al*., 2001; Wiyakrutta *et al*., 2004). Apart from the benefits to the host plant, the endophytes have also proved as an outstanding source of secondary metabolites and bioactive antimicrobial products. Although there are many different endophytic fungi of documented pharmaceutical benefits isolated from family Zingiberaceae, we have complied a list of some of the most important ones in Table 1.

Table 1.

List of endophytic fungi isolated from plants of family Zingiberaceae showing their pharmaceutical and industrial activities.

Sl. No.	Host plant	Endophytic fungi	Chemical compound / Enzyme	Pharmaceutical activities / Industrial application	References
1	*Zingiber griffithii*	*Hypomontagnella monticulosa* Zg15SU	Sesterpenoid	Anticancer	Lutfia *et al*., 2021
2	*Zingiber nimmonii*	*Bipolarisspecifera, Alternaria tenuissima, Aspergillus terreus, Nectria haematococca* and *Fusarium chlamydosporum*	Phenolic compounds	Antioxidative	Das *et al*., 2017
3	*Zingiber cassumunar*	*Arthrinium* sp. MFLUCC16-1053	Bcyclocitral, 3Ecembrene A, laurenan-2- one, sclareol, 2Z, 6Efarnesol, cembrene, βisocomene and γcurcumene	Antibacterial and antioxidant activities	Pansanit *et al*., 2018

Sl. No.	Host plant	Endophytic fungi	Chemical compound / Enzyme	Pharmaceutical activities / Industrial application	References
4	*Zingiber zerumbet*	*Fusarium solani* and *F. oxysporum*		Antipythium activity	Keerthi *et al*., 2016
5	*Curcuma longa*	*Eurotium* sp.	Asparginase	Anticancer	Jalgaonwala *et al*., 2014
6	*Curcuma longa*	Fungal isolates	-	Antibaterial and antifungal	Jalgaonwala *et al*., 2010
7	*Alpinia calcarata*	*Cylindrocephalum* sp.	Amylase	-	Sunitha *et al*., 2012
8	*Elettaria* sp.	*T. harzianum* and *T. atroviride*	Antifungal enzyme	Antifungal	Munir *et al*., 2019
9	*Alpinia chinesis*	*Aspergillus terreus*	MM1	Anticancer	Vo *et al*., 2020
10	*Alpinia chinesis*	*Aspergillus terreus*	MM1	Antimicrobial against *Staphylococcus aureus* and Methicillin-resistant *Staphylococcus aureus* (MRSA)	Vo *et al*., 2020
11	*Elettaria* sp.	*Trichoderma harzianum*	-	Antagonistic activity	Munir *et al*., 2019
12	*Elettaria* sp.	*Trichoderma atroviride*	IAA production	-	Munir *et al*., 2021
13	*Hedychium coronarium*	*Trichoderma afroharzianum*	Chitinase	-	Munir *et al*., 2019
14	*Hedychium coronarium*	*Trichoderma afroharzianum*	-	Fusarium oxysporum	Munir *et al*., 2019
15	*Curcuma longa*	*Arthrobotrys foliicola, Cochliobolus kusano, Daldinia eschscholz, Fusarium oxysporum, Fusarium proliferatum, Fusarium solani, Fusarium verticillioides, Phanerochaetechrys osporium, Phaeosphaeria ammo philae*		Inhibit growth of thehistamineproducing bacteria	Septiana *et al*., 2017
16	*Zingiber officinale*	*Curvularia affinis*	-	Antimicrobial against *Fusarium oxysporum*	Ginting *et al*., 2013
17	*Zingiber officinale, Curcuma domestica, Kaempferia rotunda, Curcuma xanthorrhiza, Curcuma mangga* and *Curcuma zedoaria*	33fungal isolates	-	Anti-oxidant and antimicrobial	Praptiwi *et al*., 2016
18	*Hedychium coronarium*	Endophytic fungal strain	*Staphylococcus aureus*	Antimicrobial	Lutfia *et al*., 2018

7. Conclusion and future prospective

The current study shows that endophytic fungal metabolites are important targets for finding and making new drugs. Currently, the quest for novel biologically active metabolites from plant endophytes has broadened in light of the changing perspectives on medicinal substances and the rising demand for non-hazardous medications. We are losing the battle against therapeutic antimicrobial drugs due to development of resistance over the period of time. Endophytes, on the other hand, are a viable alternative since they contain an abundance of unique bioactive chemicals with virtually limitless potential biological activities. Numerous studies have reported novel, beneficial bioactive compounds exhibiting other biological properties, such as anti-diabetic, anti-inflammatory, antiprotozoal, anti-tuberculosis, insecticidal, immune-modulatory, antiviral, anticancer activities, anthelmintic, etc., that were successfully isolated from endophytic fungi. Since the turn of the century, endophytic fungi have been the subject of intense study in the pharmaceutical industry due to their abundance and pervasive distribution. Although bioactive chemicals and the usage of certain medicinal plants in traditional medicine have been extensively explored, little is known about the bioactivities of its associated endophytic fungus. Despite this, limited research has been conducted on the valuable bioactive compounds from endophytic fungi. Thus, the screening of endophytic mycoflora for the possible SMs synthesis can help in the establishment of their pharmaceutical functions for sustainable human health and effective against antibiotic resistance.

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