A comprehensive review on fungal endophytes and its dynamics on Orchidaceae plants: current research, challenges, and future possibilities

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ABSTRACT
In the development of medicinally important Orchidaceae, the extent of fungal endophytes specificity is not presently very clear. Limited study has been available on natural products formed and its role on plant growth, defence mechanism by endophytes, and to characterize the chief treasure of bioactive molecules. Therefore, this review article presents an evaluation of the endophytes associated with Orchidaceae for physiology, metabolism, and genomics which have prominently contributed to the resurgence of novel metabolite research increasing our consideration of multifaceted mechanisms regulatory appearance of biosynthetic gene groups encoding diverse metabolites. Additionally, we presented the comprehensive recent development of biostrategies for the cultivation of endophytes from Orchidaceae and integration of bioengineered ‘Genomics with metabolism’ approaches with emphasis collective omics as powerful approach to discover novel metabolite compounds. The Orchidaceae-fungal endophytes’ biodynamics for sustainable development of bioproducts and its applications are supported in large-scale biosynthesis of industrially and pharmaceutical important biomolecules.

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Introduction
Orchidaceae is one of the largest and most important Chinese Orchidaceae medicinal families (COMFs) of plants, with over 28,000 identified species in about 763 genera species [1,2]. The chief genera from Orchidaceae families are Pleurothallis (over 1000 species), Dendrobium (over 1400 species), Epidendrum (over 1500 species), and Bulbophyllum (over 2000 species). Some species are inattentive only from Arctic and desert areas but are predominantly ample in the wet tropical regions of worldwide. However, numerous orchids are indigenously distributed and normally very uncommon. China country, with its trivial tropical zone and huge desert section, has relatively rare orchids. Orchidaceae seems to have experienced one significant hastening of net species variation in the orchidoids, with two other
accelerations in the higher epidendroids [3]. This speedy speciation with high COMFs species range is prospectively connected to the family’s focused pollination patterns, symbiotic relations with endophytic fungi, epiphytic environments colonization, and metabolism of crassulacean acid. Because of vital evolutionary and ecological consequence of orchids, investigation has long been showed on their biology and associations with diverse fungal endophytes [2].

All COMFs plants are well grown inside by varied endophytic microbial groups comprising fungi, bacteria, and Protista. The endophytes association with their Orchidaceae host plants is as a result of exceptional reworkings which permit the endophytes to correspond their development through their plant associations. These endophyte groups are accountable to likewise partial biosynthesis or wide-ranging of Orchidaceae host secondary metabolites (SMs) [4]. Annullohypoxylon, Alternaria, Colletotrichum, and Phaeosphaeriopsis which are recovered as endophytic fungi and their other natural capability to reside in the orchids are valuable for upcoming biotechnological purposes [5]. Most vulnerable orchids have inhabitants of <100 plants and their management is one of the key encounters faced by cultivators [6]. Determining influences disturbing the spatial dispersal and richness of endangered Orchidaceae plants is a chief encounter in existing protection biology [7]. Endophytes have shown a synergetic cooperation of fungus with their Orchidaceae family [8]. These symbiotic associations comparatively impact on soil rhizospheric nutrition and capability of plant [8,9]. Research investigations have explored that most of the Orchidaceae plants in landscape have a symbiotic bond with Orchidaceae-fungal endophytes (OFEs). OFEs live within the cells, corresponding to an epiphyte grown on the cell surface of the host plants [10].

OFEs can enhance plant growth, upsurge resistance on the way to disease triggering pathogens, defeat the weed, and improve tolerance capacity to biotic and abiotic stresses [11]. Furthermore, they are most potent to yield vast SMs (industrial important bioactive natural compounds) with pharmaceutical utilization [12]. Numerous endophytic fungi can deliver shield to the plant Orchidaceae by persuading defence system in Orchidaceae counter to an extensive pathogens range. The OFEs are recognized to yield an antimicrobial compound-like constituent that prevents the pathogen development and participate with most of the pathogens for nutrition and space [10]. Fungal endophytic biotechnology can be applied for the well-organized production of industrially, agriculturally, environmental, and economically imperative fungal products and products from plants. The balanced application of endophytes to employ the micro-biota, closely connected with plants, can benefit to the improved production of the agricultural products and amplified production of key novel metabolites in aromatic and medicinal plants, along with alteration to original bio-geographic areas through tolerance [4].

The study of these upcoming challenges and benefits will be useful to explore the role and function of fungal endophytes on Orchidaceae growth and appropriateness in their natural environment [13]. On the other hand, there is no critical comprehensive review published on this topic in the last 3 to 4 years. The purpose of this review article is to review the recent developmental investigation on OFEs, its dynamics on Orchidaceae, new insights towards endophytes becoming pathogenic to non-pathogenic or vice versa, production of SMs strategies along with genomics aspects, need, limitations, and challenges of current research trends which present the future outlooks. By the comprehensive evaluation analysis of OFEs, the novel and critical insights on physiological, genomics, and functional analysis of fungal endophytes on Orchidaceae provided the novel information which will be useful for overcoming from the growing challenges for Orchidaceae development.

**Orchidaceae-fungal endophytes (OFEs): distributions and specific characteristics**

The word ‘endophyte’ denotes to all microbes that inhabit internal tissues of host plants for completely or partially spending their life cycle. They cause imperceptible and asymptomatic contagion and live completely within the tissues of the host plant. Endophytes can cause no sign of disease indicators. Endophytes are potential biochemical synthesizers within the plants’ host and plants have been widely explored for their microbial endophyte’s accompaniment [4]. The OFEs occurrence allied by host Orchidaceae is exposed by examination of plant
tissues like stems, leaves, and roots tissues. Many fungal endophytes are silent pathogens and can occur as a consequence in plant-related symptoms after the plant is further down to aged or stress conditions. It has been proposed that fungal endophytes accomplish asymptomatic colonization through a stable neutral antagonism between virulence of fungal and its response to the defence plant part. The multilocus phylogenetic outline of inherited state reforms stated that OFEs have evolved after dynasties of parasites of insect and further got distinguished over an event of specific host kingdom jumps [14].

Until now, OFEs, divided into 'clavicipitaceous and non-clavicipitaceous groups', have been found to ubiquitously colonize plants and have a profound impact on plant populations [14]. Based on Orchidaceae host colonization, transmission mechanism, and biological roles, the non-clavicipitaceous fungal endophytes have been distinguished into three key clusters: (i) the first cluster establishes in together above- and below-ground tissues of host plants; (ii) the second cluster is confined to above-ground tissues; (iii) the third cluster is restricted to below-pulverized tissues. Even though these clusters have a wide host ranging, the outline of host colonization tissues differs: (i) the first and third clusters broadly colonize the host tissues, while the second cluster shows extremely localized irregular colonizations; (ii) the second and third clusters are transmitted to host tissues horizontally, whereas the first cluster by both horizontally and vertically [15]. The latter cluster in particular has had growing attention in current years as a result of its taxonomic variety, that is, abundant fungal endophytes can be connected with a particular Orchidaceae species and its manifold functions including Orchidaceae growth speeding up, aptness, and stress acceptance, and the rich occurrence of OFEs symbiosis in mutually below- and above-ground tissues [14,16].

The style of colonization and penetration of OFEs and other pathogens in Orchidaceae evidenced that the OFEs are different from fungal pathogens. The OFEs entered from the stomata laterally in the cells of anticlinal epidermal and colonization are inadequate, localized along with intercellular in the shoots; on the other hand, the pathogen was entered directly from the cell wall and grown extracellularly. These variances of endophytes with reverence to fungal pathogens may not be able to cause disease to the host [10]. Hyde and Soytong [17] claimed that fungal endophytes grown at the above ground are host specific along with family or genus's specific. Schulz and Boyle [18] assumed that regardless of the life-cycle approach of the fungal endophytes, the disease does not become apparent till virulence of fungi and the host defence response are stable. Sieber [19] accused that the endophytic pathogen has been co-progressed with their plant species [15]. Diverse protocols may be annoyed for isolation of OFEs (Table 1). OFEs could be recovered using either solitary peloton or tissue (roots, stems, and leaves) segment protocol and they grew more slowly when bacteria is extant than if excluded. Some OFEs, however, are recovered using root segment as they did not formulate immense hyphal colonization. Furthermore, not all studies on OFEs used isolated fungal biomass as materials for its identification. Direct Internal transcribed spacer (ITS) deoxyribonucleic acid (DNA) sequencing from Orchidaceae tissues containing fungal DNA has also exposed for diversity of OFEs. Moreover, it is essential to highlight that although some OFEs-specific

### Table 1. Protocols for external tissue sterilization for Orchidaceae-fungal endophyte investigation.

| Orchids Segments                  | Standard Procedure                                                                 | Reference |
|-----------------------------------|-------------------------------------------------------------------------------------|-----------|
| **Root samples**                  | 5% solution ‘Domestos’ (20–30 min) – sterilized water                                | [92]      |
| Leave, stem, root samples         | Ethanol (75%) for 40 s, immersed in sodium hypochlorite 4% for 10 min and to end rinsed in sterilized distilled water (three times) | [93]      |
| **Root samples**                  | Surface sterilized in 70% (v/v) ethanol and 3% (v/v) H₂O₂ for 10 min, and afterward rinsed 3 times in sterilized distilled water | [94]      |
| Leave samples                     | Sodium hypochlorite (1%) for 1 min, then in ethanol (70%) for 1 min, rinsed 3 times with sterilized water | [89]      |
| **Root samples**                  | Surface sterilized in ethanol (75%) for 1 min, in 3% NaClO for 3 min, and rinsed in sterilized water three times | [95]      |
| Root samples                      | Sterilized by immersion in ethanol (70%) for 30 s and in sodium hypochlorite solution comprising 1% chlorine for 30 s | [96]      |
| Stems, leaves, and flowers        | Immersion in 75% ethanol for 30 s, 5% NaOCl for 30 s, 75% (v/v) ethanol for 30 s and then rinsing with distilled water | [97]      |
| Leaves                            | Surface sterilization and uncolonized dead tissue removed using sterile blade         | [98]      |
primers are available, they do not essentially amplify only fungal DNA [20].

**Relationships of fungal endophytes with Orchidaceae plants: occurrence, diversity, and transmission**

Orchidaceae are exceptional among all plants as their approach of nutrition involves straight and sometime obligate associations with fungi. Of more than 28,000 known species crossing 763 genera [1,2], over 200 OFEs genera have been investigated for their diversity, which are lower than 30% of the entire orchid genera. Orchidaceae with ornamental, horticultural, medicinal, and commercial applications have been considered for the occurrence of OFEs [20]. As to our information, OFEs have reflective effects on Orchidaceae ecology, capability, development, and even plant structural diversity [21]. The Orchidaceae seeds are miniature and comprise inadequate energy supply, and its colonization through a well-suited endophyte is vital for propagation in the optimum environments. The possible cooperation of OFEs has newly strained countless considering from both conservationists and horticulturists [22–24].

Modern research on OFEs has been focused in all trophic groups (i.e. photosynthetic, mycoheterotrophic, and mixotrophic) of all progress habits, from extremely diverse habitats (e.g. coniferous forests, rainforests, evergreen forests, wetlands, bamboo forests, swamps, botanical gardens, calcareous coastal plains, and greenhouses) in all continents except Antarctica. Some Orchidaceae occur in an inclusive habitats range, while others are endemic to certain regions. Perhaps, *Platanthera* minor cultivates in forests on hills and mountainous meadows at advancements 90–3000 m in China, Japan, and Korea. *Satyrium nepalense* is described to disperse from green hill slants at variable altitudes (600–4600 m) in India. On the other hand, *Ophrys benacensis* is grown only in north part of Italy and *Piperia yadonii* in North America. The epiphytic *Sarcocilhus parviflorus* orchid tolerates only with the presence of host *Backhousia myrtifolia* [20,25].

The OFEs transmission can be horizontal or vertical, after being the furthermore common and has been earlier studied. Vertical transmission occurs when the seeds are contacted through the endophyte and at that point transmitted to the host plant. This is the mechanism of transmission as a pasture OFEs. Horizontal transmission involves the formation of exterior spores and their airborne dispersal to infect many other hosts [26,27]. It occurs in the less specific species, usually those related with woody hosts and confined in certain tissues of the plants. On the other hand, the dispersion needs other biological agents, like insects (vectors) which support to spore fecundation and dispersal as in Epichloe festuca, and someplace the occurrence of Botanophila spp. (Antomiidae: Insecta) is related with the fungus and support to its reproduction (sexual) and spreading [28]. The details of isolated and identified endophytic fungi from different habitats are listed in Tables 2 and 3.

**Orchidaceae shoots**

A wide range of Orchidaceae species surveyed composed of OFEs symbionts in foliar tissues [29]. Similarly, most of the monocots, orchids, normally have modest stem and leaves with corresponding veins, even though nearly Vanilloideae have reticulate venation. Leaves may be ovate, orbiculate, or lanceolate and very inconstant in proportions on the different Orchidaceae species. OFEs-inhabiting stems and leaves have excessive potential to progress various fungal endophytes’ symbiosis associations with various mycota through horizontal transmission into the Orchidaceae. Till date, many OFEs are recovered from shoot segments (leaves and stems) of the different Orchidaceae species in many publications [20,30,31]. The most common OFEs documented from shoot segments are *Habenaria radiata*, *Epipactis thunbergii*, *Chiloglottis sp.*, *Colletotrichum sp.*, *Cylindrocarpum sp.*, *Hypocrea sp.*, *Nigrospora sp.*, *Pestalotiopsis sp.*, *Alternaria sp.*, *Cercospora sp.*, *Lasiodiplodia sp.*, *Phyllosticta sp.*, *Chaetomella sp.*, *Sclerotinia sp.*, *Conocybe sp.*, *Gymnopus sp.*, *Hydopus sp.*, *Psathyrella sp.*, *Resinicium sp.*, and *Geopora sp.* These OFEs belong to diverse genus, for example *Sordariomycetes*, *Dothideomycetes*, *Leotiomyces*, *Agaricomycetes*, *Puccinomycetes*, and *Tremellomycetes* [20]. Recently, three OFEs are recovered and identified from threatened *Dendrobium aequum*. Stem parts are obtained from original plants from India, Kolli hills [32]. *Fusarium sp.* and
| Host plant (Orchidaceae) | Isolated taxa/OTU | References |
|--------------------------|-------------------|------------|
| Dendrobium nanum (India) | Root | Morphology, ITS | 2 [20] |
| Dendrobium nobile (Yunnan, China) | Root, stem, leaf | Morphology, ITS | 33 [20] |
| Dendrobium nobile (China) | Stem | Morphology, ITS | 1 [93] |
| Dendrobium nobile (China) | Stem, root, leaf | Morphology, ITS | 10 [93] |
| Dendrobium nobile (China) | Stem and root | Morphology, ITS | 5 [93] |
| Dendrobium nobile (China) | Root | Morphology, ITS | 2 [93] |
| Dendrobium nobile (China) | Stem, root, leaf | Morphology, ITS | 7 [93] |
| Dendrobium nobile (China) | Stem | Morphology, ITS | 3 [93] |
| Dendrobium nobile (China) | Root | Morphology, ITS | 2 [93] |
| Dendrobium nobile (China) | Root | Morphology, ITS | 2 [93] |
| Dendrobium nobile (China) | Stem, root | Morphology, ITS | 6 [93] |
| Dendrobium nobile (China) | Root | Morphology, ITS | 3 [93] |
| Dendrobium nobile (China) | Leave, stem | Morphology, ITS | 51 [93] |
| Dendrobium nobile (China) | Stem | Morphology, ITS | 2 [93] |
| Dendrobium nobile (China) | Leave, stem, root | Morphology, ITS | 62 [93] |
| Dendrobium nobile (China) | Leave, Stem | Morphology, ITS | 2 [93] |
| Dendrobium nobile (China) | Stem | Morphology, ITS | 1 [93] |
| Dendrobium nobile (China) | Stem | Morphology, ITS | 2 [93] |
| Dendrobium sinense (Hainan, China) | Root | Morphology, ITS | NA [95] |
| Dendrobium sinense (Yunnan, Guangxi, China) | Root | Morphology, ITS | NA [95] |
| Dendrobium sinense (Yunnan, Guangxi, China) | Root | Morphology, ITS | NA [95] |
| Dendrobium sinense (South China) | Root | Morphology, ITS | NA [95] |
| Dendrobium sinense (South China) | Root | Morphology, ITS | NA [95] |
| Dendrobium sinense (South China) | Root | Morphology, ITS | NA [95] |
| Dendrobium sinense (South China) | Root | Morphology, ITS | NA [95] |
| Dendrobium sinense (South China) | Root | Morphology, ITS | NA [95] |
| Dendrobium sinense (South China) | Root | Morphology, ITS | NA [95] |
| Dendrobium sinense (South China) | Root | Morphology, ITS | NA [95] |
| Dendrobium umbonatum (Guizhou, Yunnan, China) | Root | Morphology, ITS | 18 [20] |
| Dendrobium sinense (Thailand) | Leave | Morphology, ITS | 6 [97] |
| Epipactis thunbergii (four species) (Japan) | Root | ITS | 1 [20] |
| Eulophia zollingeri (three species) (Taiwan) | Root | NR | ITS | 1 [20] |
| Holcoglossum (nine species) (Yunnan, Guangxi, and Hainan, China) | Root | ITS | 15 [20] |
| Hygrochilus parishii (Thailand) | Leave | Morphology, ITS | 4 [97] |
| Orchis militaris (Italy) | Root | NR | ITS | 3 [20] |

(Continued)
Acremonium sp. are the most dominant isolates grown inside the D. loddigesii, which have shown higher assemblage and colonization in tissues [14].

**Orchidaceae roots**

OFEs located inside roots of Orchidaceae in the cortical or in the velamen tissues are cooperatively called as Orchidaceae root-associated fungal endophytes (ORAFEs). However, research focusing on ORAFEs normally ignore the strains occurred in the velamen due to which the profuse corky epidermis is usually known as an adaptive assembly for conservation [33]. Therefore, the roots cortical tissues are the chief target of numerous researches focusing on ORAFEs because it frequently anchorages fungal endophytes that may form network with the Orchidaceae as symbionts [34]. Roots of humid epiphytic Orchidaceae harbor various fungal genus, including mutualistic fungal root associates. The common endophytes of orchids could be a genus of Tulasnellaceae, Serendipitaceae, and Ceratobasidiaceae while Kottke et al. [35] stated Atractiellomycetes as forming mycelial with nearly Neotropical Orchidaceae. Besides mycorrhizal fungi, the roots of Orchidaceae are colonized by various fungal endophytes species [36–38]. Novotná et al. [36] observed the root-related fungal endophytes diversity such as Cyrtochilum myanthum, Stelis superbieni, and Scaphyglottis punctulate, using a species-dependent method. Ascomycota members are definitely dominant, such as Trichoderma sp. as the utmost common taxon. Basidiomycota (Polyporales and Agaricales) and Mucoromycota (Mortierellales and Umbelopsidales) members are also recovered. The potential fungi of Ceratobasidiaceae and Tulasnellaceae are recovered from S. superbieni and C. myanthum [36]. Harman et al. [39] stated that Trichoderma spp. have the capacity to colonize and nurture in relation to Orchidaceae roots [40]. The occurrence of fungal endophytes genera was also established in achlorophyllous roots of Orchidaceae Wullschlaegelia aphylla (Sw.) Rchb. f. from the rain forest of Caribbean region [41].

**New insights towards endophytes becoming pathogenic to non-pathogenic or vice versa**

Commensalism and mutualism denote the balanced phases of plant–microbe interactions. Commensalism delivers the advantage to the fungal endophyte by allowing an uninterrupted nutrient supply and existence without disturbing the host [42]. A steady state between the pathogen and its host plant is achieved when the pathogen resides in equilibrium with surrounding host tissues. This host–pathogen interaction moves toward an endophytic, commensal inter-relationship, and the plant harboring the pathogen remains asymptomatic. However, such plants can begin to show symptoms when there is a shift in this equilibrium, as for example, when there is a significant change in temperature, moisture, or humidity or when the plant is altered genetically for horticultural purposes. Environmental or genetic changes induced the visible disease symptoms because the pathogen re-establishes in its original parasitic form. The virulence expression of the pathogen is dependent upon the particular host environment. When the pathogen is isolated from an asymptomatic host and introduced into a new host, the strong pathogenic reactions may be observed [43]. Moreover, some plant–fungus combinations can give better insights into plant nutrition than other organisms. This is perhaps described by the evidences that some Orchidaceae plants are more dependent than others on the relationship, and that diverse endophytes have variable carbohydrates needs. To what range of nutritional inequity interrelation, the amplified genes appearance responsible for plants defence is not recognized and still challenges for forthcoming investigations. This is commonly the

### Table 2. (Continued).

| Host plant (Orchidaceae) | Habitat | Host segments | Isolation method | Identification method | Isolated taxa/OTU | References |
|-------------------------|---------|---------------|------------------|-----------------------|------------------|-----------|
| Pholidota pallida       | India   | Root, leaf    | SST              | ITS                   | 10               | [20]      |
| Pseudorchis albida      | The Czech Republic | Root | SST              | ITS                   | 66               | [20]      |
| Wullschlaegelia aphylla | France  | Root, rhizome | Single peloton   | ITS, 28S              | 11               | [20]      |

SST: Surface sterilized tissues; NA: Not available.
situation during the sprout’s germination of Orchidaceae when specific fungal endophytes colonize the seed rhizoids coat. When networking with positive non-photosynthetic Orchidaceae species, though, endophytes too may shift from a mutualistic to a parasitic symbiont [42]. Orchidaceae are extended green plants by two development arrangements: sympodial development, where a new shoot development from the deep-rooted shoot base; or monopodial development, with a solitary upward point on a non-terminal leaf. *Fusarium* strains are responsible for foliar as well as root illnesses on Orchidaceae and include *F. proliferatum*, *F. tricinctum*, and *F. subglutinans*. Some other Orchidaceae disease caused by pathogenic fungi are leaf spot by *Nigrospora oryzae* [44], wilt by *Fusarium oxysporum* [45], leaf spot by *Cladosporium cladosporoides* [46], blight and root rot by *Pythophthora capsica* [47], black spot by *Alternaria alternata* [48], anthracnose by *Colletotrichum gloeosporioides* [49], leaf spot by *Phyllosticta capitalensis* [50], and leaf spot by *Phoma multirostrata* [51]. It is very common to treasure more than one strain occurring at the similar place, causing parallel disease signs (Table 4 and Figure 1). Though, transition from pathogens to endophytes and vice versa may not necessarily be a long progression but can arise by mutation or deletion of a single gene. Even more rapidly, an endophyte can convert pathogenic by merely changing the growing conditions of the Orchidaceae which are also known as ‘conditional pathogens’ [30].

Commonly, fungal endophytes are realized as having function ranging from latent pathogens to mutualistic symbionts. Reliant on host genome type, some endophytic fungi may turn out to be pathogenic in stressed hosts [42], while they can be helpful in other conditions due to conditional pathogenic properties. Moreover, some host pathogens such as smuts are existing inside without symptoms in host Orchidaceae for several months. However, a large diversity of heterotrophic fungi exists inside the host tissues throughout their growth cycle and show no disease indications. Asymptomatic OFEs are ever existing in the plant tissues [52]. Most consideration has been highlighted on OFEs present in tissues [53,54]. Many scholars have exposed that they exist an inter- and intraspecific war and mutualistic symbiosis of other endophytes. These relations are additionally reported to disturb the diversity of the host community and species development [10].

Though, a very low percentage of OFEs are converted to pathogenic for their Orchidaceae plant at certain conditions, because their distinctive lifestyle is

### Table 3. Available fungal endophytes from Orchidaceae plants.

| Name                  | References | Name                  | References |
|-----------------------|------------|-----------------------|------------|
| Acephala sp.          | [20]       | Nemania sp.           | [93]       |
| Alternaria sp.        | [20]       | Nemania sp.           | [95]       |
| Annulohypoxylon sp.   | [95]       | Nigrospora sp.        | [20]       |
| Annulohypoxylon sp.   | [95]       | Olpidium sp.          | [20]       |
| Aspergillus sp.       | [20]       | Paecilomyces sp.      | [20]       |
| Botryosphaeria sp.    | [93]       | Paraconiothyrium sp.  | [20]       |
| Botrytis sp.          | [20]       | Paraphoma sp.         | [99]       |
| Ceratobasidium sp.    | [100]      | Penicillium griseofulvum | [93] |
| Chaetomella sp.       | [20]       | Penicillium sp.       | [93]       |
| Chaetomiella sp.      | [20]       | Pestalotiopsis sp.    | [20]       |
| Cladophialaphora sp.  | [20]       | Pestalotiopsis lespedeae | [95]     |
| Cladosporium sp.      | [15]       | Pestalotiopsis microspora | [95]   |
| Clonostachys rosea    | [75]       | Pestalotiopsis olivacea | [95] |
| Colletotrichum sp.    | [75]       | Pestalotiopsis sp.    | [95]       |
| Colletotrichum sp.    | [20]       | Pestalotiopsis visiae | [93]       |
| Cosmospora sp.        | [20]       | Phaeosphaeria sp.     | [20]       |
| Curvularia sp.        | [20]       | Phialophora sp.       | [20]       |
| Daldinia sp.          | [20]       | Phomopsis amygdali    | [93]       |
| Didymella sp.         | [20]       | Phyllosticta capitans | [101]      |
| Dothideomyctes sp.    | [95]       | Phyllosticta sp.      | [20]       |
| Entorrhiza sp.        | [20]       | Pyrenochaeta sp.      | [99]       |
| Epulorhiza sp.        | [99]       | Resinicium sp.        | [20]       |
| Epulorhiza sp.        | [99]       | Rhizoctonia sp.       | [93]       |
| Exophiala sp.         | [20]       | Sclaphylgium sp.      | [20]       |
| Fusarium chlorodosporum | [95]   | Strumella sp.         | [20]       |
| Fusarium chlorodosporum | [93]   | Telephora sp.         | [20]       |
| Fusarium solani       | [93]       | Telephorus membranaceus | [77] |
| Fusarium sp.          | [93]       | Tolyposcladium membranaceae | [95] |
| Fusicosum sp.         | [20]       | Tolyposcladium memranaceus | [95] |
| Geotrichum sp.        | [20]       | Tolyposcladium infatum | [95]    |
| Gibberella sp.        | [20]       | Tolyposcladium sp.    | [95]       |
| Glacioalaphora sp.    | [20]       | Tolyposcladium sp.    | [95]       |
| Guignardia mangiferae | [93]       | Trichoderma chlorosporum | [93] |
| Helicopha sp.         | [20]       | Tulasnella calospora  | [96]       |
| Humicola sp.          | [20]       | Tulasnella calospora  | [6]        |
| Hypocrear sp.         | [20]       | Umbelopsis sp.        | [20]       |
| Hypoxylon fragiliforme| [95]       | Verticillium sp.      | [20]       |
| Hypoxylon sp.         | [93]       | Xylaria atrophaerica  | [95]       |
| Isaria farinosa       | [95]       | Xylaria berteri       | [95]       |
| Laccaria sp.          | [20]       | Xylaria primorskensis | [95]       |
| Lasiosphaeria sp.     | [20]       | Xylaria sp.           | [93]       |
| Macowanites sp.       | [20]       | Xylaria sp.           | [20]       |
| Nectria sp.           | [20]       | Xylariaeae sp.        | [95]       |
still undefined. The horizontally spread foliar OFEs are expressly enigmatic, as they infect only small parts of the leaves and accumulate enormously short biomass and subsequently in leaves-resonant minor patches of OFEs infections. For such fungal endophytes, it is tough to envisage a dominating function in the host, if any, assumed the minor influence of each infection. Overall, it is not well recognized whether these OFEs are metabolically dynamic throughout the intercellular contagion of the limited tissue area of the host. The sequenced genome of horizontally shifted OFEs advocates a non-invasive but energetic metabolism and reproduce the capability to exploit host nutrients accessible inside the intercellular position of the Orchidaceae plant [55]. The signaling biomolecules have not commonly shown the species specificity and a huge variety of those biomolecules have been reported in fungal endophytes. The discovery of quorum sensing biomolecule in the pathogenic fungal endophytes was a notable breakthrough to give more insights on OFEs relationship. Existence of quorum sensing biomolecule systems in fungal endophytes has exposed that lipids (oxylipins), alcohols (farnesol, tryptophol, tyrosol, and 1-phenylethanol), peptides (pheromones), acetaldehydes, and also some volatile complexes are dynamically involved in OFEs non-pathogenicity to pathogenicity or vice versa role as shown in Figure 2 [56].

**Current strategies for production of secondary metabolites**

The endophytic fungi have enormous possibility to synthesize several bioactive metabolites. Hence, it is needed to design suitable cultivation scheme for their marketable exploitation. The OFEs can be cultured using submerged (liquid) or solid-state fermentation (SSF). In both fermentations, the growth

| Causal fungal Endophytes | Study Area | Host plant (Orchidaceae) | Symptoms/Disease | References |
|--------------------------|------------|--------------------------|-----------------|------------|
| Alternaria alternata     | Zhejiang Province, China | Dendrobium officinale | Black spot | [48] |
| Cladosporium cladosporoides | Zhejiang Province, China | Dendrobium officinale | Leaf spot | [46] |
| Colletotrichum cymbicola | India | Cymbidium hybrid, Eria barnbosifolia, Eria emica, Cymbidium hybrid, Dendrobium fimbriatum, Bulbophyllum hirtum, Oncidium spacealatum, Coelogyne clava, Liparis longipes | Anthracnose | [89] |
| Colletotrichum clavipes | India | Cymbidium dendulum | Anthracnose | [89] |
| Colletotrichum gloeosporioides | Fujian, China | Dendrobium officinale | Anthracnose | [49] |
| Fusarium beigoniae | USA | Miltonia and Dendrobium | Leaf spot, peripheral necrosis on tissues with leaf sheath | [30] |
| Fusarium circinatum | USA | Dendrobium and Cymbidium | Leaf spot, leaf sheath, leaf blight and pseudobulb rot | [30] |
| Fusarium fraxinellum | Japan | Cymbidium | Leaf spot | [30] |
| Fusarium oxysporum | Korea, Malaysia, USA | Dendrobium and other orchids | Root rot, dry rot, stem rot, necrotic leaf spots | [30] |
| Fusarium oxysporum | Zhejiang Province, China | Dendrobium candidum | Wilt | [45] |
| Fusarium poae | USA | Cymbidium and Dendrobium | Leaf spot | [30] |
| Fusarium proliferatum | Malaysia, USA | Dendrobium | Root rot and stem rot | [30] |
| Fusarium solani | Malaysia, USA | Cymbidium, Dendrobium and Miltonia | Root rot and stem rot, Leaf spot, leaf blight, leaf sheath rot and pseudobulb rot, Foliar spot, foliar blight and pseudostem rot | [30] |
| Fusarium subglutinans | USA | Dendrobium | Leaf spot | [44] |
| Nigrospora oryzae | Zhejiang Province, China | Dendrobium candidum | Leaf spot | [51] |
| Phoma multirostrata | Zhejiang Province, China | Dendrobium officinale | Leaf spot | [47] |
| Phytophthora capsici | Guannan, China | Dendrobium candidum | Blight and root rot | [47] |
| Phytophthora palmivora | Thailand | Orchid plants | Black rot disease | [102] |
| Pythium ultimum | China | D. officinale | Leaf soft rot disease | [80] |
| Phyllosticta capitensis | USA | D. nobile | Leaf black sopts | [50] |
medium composition, pH, temperature, agitation and aeration, pCO$_2$ and pO$_2$ can be measured for the optimal formation of the desired end product [57]. It is well reviewed that these parameters distress the mycelial development and metabolite fusion in different fermentation types (Figure 3).

**Submerged (liquid) fermentation and solid-state fermentation**

Submerged development of OFEs has assumed a lot of consideration for the development of medicinally treasured metabolites. Fermentative development of bioactive products from endophytic fungi is low costly, nonstop, and environmentally sustainable. The key advantages of liquid cultivation comprise of higher mycelial growth and active metabolites production in a quicker period. Cultivation temperature has a reflective effect on mycelial biomass and metabolite harvest in submerge batch cultures of fungal endophytes. Upsurge in the temperature constrains fungal development and that appears to be accountable for reduced metabolite biosynthesis in the submerge batch cultures [58]. The production medium pH has countless impact on mycelium and metabolite development in case of OFEs like *Penicillium microspore* and *Athelia rolfsii* strains. It has been noted that mycelium formation and metabolite concentration show a diverse trend with the upsurge in the production medium pH. The well-adjusted proportion of the nitrogen and carbon sources is also accountable for steadying the pH of the medium [58]. In SSF, it has

![Figure 1. Common Orchidaceae disease symptoms on leaves caused by pathogenic/conditional pathogenic fungi.](image-url)
many other advantages comprising of higher produces, reduced catabolite suppression, and improved product steadiness. Research laboratory-type SSF has been described for SMs development using OFEs. Furthermore, the fermentation progression is further energy effective, eco-friendly (less contaminating), and requires less and modest downstream processing stages and procedures [59].

**Metabolism to genomics for production**

Pathway-specific regulatory proteins of fungoid SMs gene groups are frequently determined inside or directly together to the specific gene cluster. Characteristically, these proteins regulate the countenance of the complete gene cluster. They are not articulated under cluster noninducing situations. Thus, overexpression of their coding genes is an informal way to trigger the transcription of altogether pathway-precise genes. The benefit of this method is the supervision of only a solitary, relatively minor gene and the opportunity for both specific and ectopic addition of the overexpression concept. Stimulatively, recent data exposed that overexpression of a solitary pathway-precise regulator can also chief to the stimulation of supplementary, distantly situated, SMs gene groups [60]. The fungi alcohol dehydrogenase supporter and glycerinaldehyde-3-phosphate dehydrogenase promoter supporters were effectively applied to overexpress pathway-precise regulatory genes. As a consequence, novel mixtures were recovered and the product produces of known compounds were amplified [14]. A number of
supporters are obtainable for the protein’s over-expression in filamentous fungus [38,61,62].

In *Trichoderma* strain, numerous genes are portion of huge biosynthetic gene clusters encompassing core enzymes, for example nonribosomal peptide synthetases, polyketide synthases (PKSs), or cyclases/terpene synthases, addition enzymes (like cytochrome P450s, methyl transferases, and oxidoreductases, etc.), and, in other incidence, transporters and transcription genes aspects [63,64]. Six extra genomes (the mycotrophic *Trichoderma harzianum*, *Trichoderma asperellum*, *Trichoderma parareesei*, *Trichoderma gamsii*, and the devious human pathogens *Trichoderma citrinoviride* and *Trichoderma longibrachiatum*) were afterward supplementary to the public records [65]. The fungal SMs biosynthesis often involves exclusive and uncommon biochemical paths. These may be, to some extent, wide-ranging to yield higher substances’ diversity from only limited key precursors that are resultant from primary metabolism [66]. *Trichoderma*-resultant SMs encompass non-ribosomal peptides for example siderophores, diketopiperazines, and peptaibiotics identical to gliovirin, gliotoxin, polyketides, pyrones, terpenes, and isocyanate metabolites [65,67].

Comparable to other fungal strains, the appearance of SMs-connected genes in *Trichoderma* spp. is recognized to be measured by connections with pH signaling, the velvet-intricate proteins, and other (micro) organisms. Atanasova et al. [68] deliberate the transcriptomic rejoinders of *T. atroviride*, *T. reesei*, and *T. virens* to the occurrence of *R. solani*. Two PKSs were amongst the genes encouraged in *R. solani*, *T. atroviride* and *T. solani*, *T. reesei* connections, while in *T. virens* completely genes in the synthesis group of gliotoxin were up-controlled. *T. atroviride* additionally presented of the lipoxygenase genetic factor for an up-regulation supposed to be complicated in 6-PP biosynthesis scheme [69], and in *T. arundinaceum*, development in co-culturing through *B. cinerea* led to improved expression stages of the novel ‘Tri’ biosynthetic genetic factor [70,71].

**Industrial importance of endophytes for sustainable development**

In species that critically rely on symbioses for completion of their life cycle, spatial distribution outlines and co-occurrence may be powerfully depending on the spatial symbiont circulation. This may be principally true for Orchidaceae as their seeds require to associate with suitable fungal endophytes to achieve germination and successive development to a seedling [72]. Fungal endophytes may encourage the growth of Orchidaceae by activating rhizosphere soil nutrients. Impact on changes or amounts of SMs is also designated. All together, they are supposed to be a bioactive compounds resource that shields the Orchidaceae from soil pathogens [36]. Symbiotic sustainable orchid germination has been developed by a widespread and valuable method for seed propagation predominantly where species are required for reintroduction of co-cultivation system [73,74]. Some of the important OFEs dynamics for sustainable developments (Figure 4) are as follows.

**Natural compounds from Orchidaceae-fungal endophytes**

There is a very limited investigation on OFEs as sources of bioactive products of agricultural and pharmaceutical importance. Since then, a larger quantity of antibiotics were exposed towards the infectious disease treatments. Research on bioactive products for drug encounters is viable than other synthetic treatments, because of lesser harmfulness and broad-spectrum actions in less amount of multiple administration. Research on OFEs-based products is needed for continuous progresses in the screening procedure, extraction, separation, and structure understanding. Furthermore, various matters interrelated to large-scale stream of novel bioactive compounds should be addressed so as to assess their bioactivities to facilitate the new drug active biomolecules that could determine the existing OFEs data [10].

It is also reviewed that fungal endophytes have been extensively used as biosystem elicitors to excite the progress and metabolites production in Orchidaceae. Some investigators have used the mycelium extract, supernatant liquor, ethanol sediment, and protein polysaccharide fraction preparation from major OFEs, *Pestalotiopsis* sp., *Talaromyces* sp., and *Hypoxylon* sp. applied to host Orchidaceae. They have noticed the OFEs active constituent accountable.
for the improved biomass and bioactive ingredients in Orchidaceae (D. catenatum) [75].

OFEs possess biochemically exclusive potent bioactive molecules and show a numerous functions in the dominion of ecology and bioindustry. Plant science professionals have endorsed pioneer exploration of fungal endophytes for its various functions in different bioindustries. Therefore, a perception of environmental sustainability is interwoven toward the collaboration among endophytic fungi and their hosts Orchidaceae from a pharmaceutical’s viewpoint [76]. Fungal endophytes that produce the bioactive metabolites similar to their host compounds and impersonator the host interaction have also been recovered; e.g. paclitaxel (Taxol), camptothecin and its chemical analogs, ginkgolide azadirachtin, jasmonic acid, and so on. Though, isolation of potential endophytic fungi accomplished of producing metabolites from the host is always interesting as is presented in Table 5 [77].

**Fungal endophytes mediated plant protection and biocontrol of disease**

Research literature stated that endophytes can moderate the Orchidaceae defence organization diagonally to phytopathogens spectrum. The approach comprises either continuous targeting the phytopathogen and its lysis or by indirectly activating the Orchidaceae defence mechanism or growth advancement [76,78]. Macia-Vicente [79] stated that fungal

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**Table 5. Bioactive natural compounds from endophytic fungi.**

| Bioactive compounds | Endophytic fungi | Fermentation type and conditions | References |
|--------------------|-----------------|---------------------------------|------------|
| Mullein            | *Penicillium janczewskii* | Liquid culture: potato dextrose medium; 25°C; 23 days | [77]        |
| Gibberellins       | *Penicillium sp.* | ICI medium, 30°C for 10 days under dark environment, agitation at 200 rpm | [5]         |
| Penicillenols      | *Penicillium spp.* | Submerged culture: glucose yeast extract; 25°C; 15 days | [77]        |
| Pestacin           | *Penicillium microspore* | Submerged culture: M1D medium; 23°C; 35 days | [77]        |
| Pyrrocidine A and B| *Acremonium zeae* | Submerged culture: 25°C; 30 days | [77]        |
| Rhizoctonic acid   | *Rhizoctonia* | Solid state using grain–bran–yeast medium; 28°C; 40 days | [77]        |
| Taxol              | *Fusarium maire* | Basal medium culture: 25°C; 14 days | [103]       |
| Taxol              | *Aspergillus aculeatinus* | Liquid fermentation medium: 30°C; 8 days | [104]       |
| Taxol              | *Pestalotiopsis versicolor* and *Pestalotiopsis neglecta* | Modified liquid medium: 22°C; 21 days | [105]       |
| Taxol              | *Alternaria alternata* | Modified liquid medium: 30°C; 10 days | [106]       |
| Vincristine        | *Fusarium oxysporum* | Liquid culture: mineral medium; 25°C; 3–4 days | [77]        |
| Xylariaquinone A   | *Xylaria spp.* | Liquid culture: Malt extract medium for 5 weeks at 30°C under static environment | [77]        |
endophytes, *Pochonia chlamydosporia*, and *Fusarium equiseti*, are having a twofold antagonistic relation into the roots. They revealed that the pathogenic diseases in the plant hosts are condensed accompanied by an improved development.

The Orchidaceae can get various advantages over an association by endophytic fungi that indorse its development [80], expand counteraction against numerous stress [81], and protection from insects and diseases [76]. OFEs enhance that the deficiency resistance in Orchidaceae plant is an excessive advantage under dehydrated situations; the mechanisms differ from species to species. Drought pressure has caused a change stomatal behavior and osmotic regulation. Endophytic fungi like *Cryptosporiopsis* and *Colletotrichum* sp. could be active against phytopathogens, for example *Phytophthora capsici*, *Rhizoctonia cerealis*, *Pyricularia oryzae*, and *Gaeumannomyces graminis* [82].

OFEs exploit the mechanisms, for example antibiosis, mycoparasitism, and competition to moderate the pathogenic contagion by straight proliferating inside the host or indirectly via induced intrinsic resistance responses to the host. By being considerate of the outlines of host–fungal endophyte physiology and the inherent system to elaborate by exchanges between the pathogens, OFEs, and Orchidaceae, one can attract an elegant biocontrol database [76]. In some cases, the fungal development might occur in apoplastic fluid of the host. As a consequence, the tissues become re-enforced afterward endophytic diffusion, response as a defensive barrier against pathogens [83].

**Nutrient cycling through host–endophyte interaction**

One distinguishing endophyte symbiosis feature is synergetic germination, where Rhizoctonias inhabit the reserve of fewer orchid seeds and deliver carbon (C) to the plant seedlings that nurture heterotrophically. Though, recent investigation advocates the opposite mechanism might take place that fungal carbon could essentially be provided through the fungi to mature orchids (Chlorophyllous) [84]. Though, fungal endophytes producing ample fruitbodies, which permit examination of isotopic loads, recently twisted out to have endophytic capabilities, for example in the Hygrocybe genus [84]. Though Rhizoctonias can support a germination, they may be impotent to favor the big need for the carbon of a mature orchid lacking of photosynthesis possibly because the carbon obtainability in the conjectured endophytic position may be too imperfect for such a carbon sink. The expansion of Orchidaceae plants is directly dependent on the existence of fungal allies because orchid seeds deficient of any nutrient reserves and propagation is only probable upon colonization through a well-matched fungus providing carbohydrates cycling. The emerging seedling remains reliant on fungal sugars for numerous years, an approach called mycoheterotrophy [85].
Need, challenges, and future possibilities of Orchidaceae endophytic fungi

The fungal endophytes have a profound influence on the growth, ecology, healthiness, assembly, and multiplicity of Orchidaceae communities. Hence, information about the diverse endophytic fungi related with orchid can deliver a better perception on the connections that arise in orchids’ ordinary habitats and in what way these fungi can support to orchid existence and variation [86]. One of the Orchidaceae-dominant challenges in facing ecology and preservation is the recognition of issues influencing the spatial delivery and richness of sporadic or endangered species. Moreover, little is identified about the physiological character and association degree or fungal specificity in the roots of orchids related with those of terrestrial classes [86].

On account of their multipart ecological exchanges with pollinators, fungal endophytes, and other animals, Orchidaceae are often the first biotic indicators of bionetwork decay. Many years may be desired for the reappearance of a level of environmental stability favorable to orchid perseverance, because of the dependency of orchids on fungal endophytes [87]. The extant information on fungal endophytes colonization of Orchidaceae roots does not offer an unambiguous representation, and the question ruins exposed as to whether these should be observed as orchid fungal endophytes [88,89]. Endophytic fungi relations would diverge from mycorrhizas by the nonappearance of a localized edge or particular hyphae, lack of biochemical transfer, and nonappearance of synchronized host fungus expansion, however these features are often tough to evaluate [90].

Morphological identification of OFEs to species or occasionally even genus position is not continuously probable. Many OFEs are not sporulate, even when sporulation encouraging methods are functional. Apart from the fungal nature, the morphological identification necessitates the investigators to have a good considerate of elementary fungal taxonomy and upright fungal cultures handlings. Morphological documentation may take additional time than molecular recognition, as endophytic fungi may need at least 3–4 weeks to sporulate. There are limitations to the old identification process of Colletotrichum sp. through morphology, as a result of the morphological traits’ plasticity [89]. Though, using morphological description to recognize fungal endophytes is a low-cost approach [20]. There are several disadvantages in relying on bioinformatics methods for classifying endophytes, including low value and misidentification of ITS sequences by GenBank. For example, Cai et al. [91] compared ITS sequences of ex-type specimens of Colletotrichum with the sequences in GenBank and reported that the majority of Colletotrichum ITS sequences in GenBank are wrongly labeled. Recently, some researchers advocated applying sequences of fungal ex-type for constructing phylogenetic backbone which may avoid improper identification [20].

OFEs have currently generated noteworthy attention in the microbial interaction between community as a result of their excessive possibility to donate the sighting of bioactive mixtures. It has been advised that the adjacent biological overtone between fungal endophytes and their host plants results in the generation of a huge number and multiplicity of bioactive molecules connected to epiphytes microbes. Furthermore, the symbiotic countryside of this association indicates that fungal endophytic bioactive complexes are less deadly to the cell, in place of biochemicals do not extinguish the eukaryotic mass structure. This is predominantly vital to the medical communal as probable drugs may not harmfully distress the human tissues [4]. Co-occurring of Orchidaceae species tends to inhabit diverse areas and associate with dissimilar fungi, signifying that OFEs may be unequally distributed inside the soil and, consequently, influence the above-the-ground spatial circulation of Orchidaceae [72]. Moreover, all the viable fermentations are routed by using monoculture axenic system, and endophytic fungi are never existing in the axenic stage in their normal ecological environments. The associated microbes such as endophytic bacteria, viruses, and numerous abiotic and biotic stresses are probable to disturb their metabolome in normal ecological position [77].

OFEs have many biotechnological future possibilities as natural metabolite producers should be measured when designing upcoming applications to save endangered Orchidaceae [5]. OFEs could be discovered as a treasure source of natural metabolites.
through potentially utilization of biotechnological approaches focused on the endangered form of Orchidaceae in the nearby future [5]. Fungal elicitors arranged from Orchidaceae-fungal endophytes may be used in the future as a booster for the in-vitro propagation of Orchidaceae, and many of these natural mixtures identified may be explored for their consequence on Orchidaceae germination [13]. Through advanced biotechnological invention, the novel and new potential fungal endophytes and their natural active compounds will give a new dimension for the understanding of role and function of endophytes and their elicitors on the development of plant and their products for industrial and pharmaceutical applications.

Conclusions and future insights

It is presently reviewed that generation of bioactive compounds by Orchidaceae and associated fungal endophytes is an indirect or direct result of complex and dynamic ecological interactions in nature. This review article exemplifies the complexity and multifaceted dimension of the OFEs interactions and selected functions that drive the (co-)evolution/culturing of OFEs' biosynthesis of pharmaceutically pertinent natural bioproducts. In the unremitting exploration for new drug sources, fungal endophytes from terrestrial Orchidaceae plants have been established to have the new dimensions for producing a battery of new natural bioproducts with wide spectrum of bioactivities and countless chemical multiplicities. It will be found to yield medically valuable constituents from OFEs which are exclusively recognized from their host plants (e.g. paclitaxel, dendrobine, and camptothecin) that overstate the view of using such OFEs as sustainable and low-cost bioresources for these substances.

The article provides the comprehensive information to understand the actual concept of expression of biosynthetic genes which is the most important challenge for sustainable production of desired OFEs metabolites. Furthermore, in their natural system, endophytic fungi are never existing in axenic stage. They are continuously connected with varied communities of endophytes. The nonappearance of comprehensive considerate with respect to identification, physiology, and biosynthetic gene expressions is a key coerce in the strategy of feasible bioprocess for gaining the pharmaceutically applicable high-worth bioproducts such as drugs and antibiotics with high impacts that subsequently help to begin an endophytic fungal-dependent Orchidaceae-sustainable strategies for the production of bioproducts.

Highlights

- The present review focused on the fungal endophyte’s dynamics on the Orchidaceae family plants.
- Critically analyzed OFEs for physiology, metabolism, genomics, and natural product development.
- OFEs are useful for Orchidaceae growth and sustainable development of bioproducts.

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