Health-Promoting Effects of Bioactive Compounds from Endophytic Fungi

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Plant endophytic fungi reside within the living tissues of plants, forming a unique symbiotic relationship. One of their defining features is their ability to exist within the plant for extended periods, often throughout the plant's life cycle. They colonize various plant tissues, including leaves, stems, and roots, and display remarkable adaptability to different environmental conditions. Unlike pathogens, they do not provoke an immune response from the host plant, allowing them to maintain a stealthy coexistence. Endophytic fungi have evolved diverse mechanisms to survive within the plant's internal environment. Some form specialized structures called "microsclerotia" or "sclerotia", which protect them from adverse conditions. Others produce secondary metabolites, including bioactive compounds, which contribute to their ecological success and their potential to influence plant health

Keywords: plant endophytic fungi ; bioactive compounds ; human health

1. Introduction

Endophytic microorganisms are commonly found on plants, especially perennial varieties. These microorganisms, which include both fungi and bacteria, occupy plant tissues for prolonged periods or specific phases of their life cycles [1]. Importantly, this colonization takes place without causing discernible harm or inducing visible changes in the physical appearance of the host plants. This intricate association has garnered attention due to its potential implications for plant well-being and development [2]. Endophytes are harmless microorganisms that live inside healthy plant tissues and protect them from diseases. They achieve this through strategies such as colonization, competition for nutrients, antibiotic synthesis, and resistance mechanisms [3]. Endophytic fungi not only safeguard plants but also enhance growth by producing phytohormones, bolstering stress resistance, and creating protective pesticides [4]. Due to their capacity to produce a variety of bioactive substances with a significant potential for enhancing human health, these mysterious microorganisms have carved out an intriguing habitat within the living parts of plants [2]. Scientists have found evidence of at least one type of endophyte in every plant examined so far [5]. These endophytes can take up residence in different parts of plants, including the stem, roots, leaves, inflorescences, fruits, seeds, and even in non-living parts such as dead plants [6]. The number of endophytes in a particular plant species can vary significantly and depends on factors such as the type of plant, its stage of growth, the density of the invading microorganisms, and the surrounding environmental conditions [7]. These fungi are ubiquitous and have the potential to produce a wide variety of bioactive molecules due to their inherent diversity, which includes a wide range of plant species.

Transitioning to the heart of this exploration, an in-depth analysis of the health-promoting properties exhibited by these bioactive compounds is embarked upon. Their potential as antioxidants, which are capable of neutralizing harmful free radicals and safeguarding cellular health, forms a critical cornerstone of their benefits [8]. At the same time, their anti-inflammatory properties hold promise for reducing chronic inflammatory conditions that are behind many health problems. The compounds' effectiveness as antimicrobial agents makes a significant contribution to the ongoing battle against drug-resistant pathogens, which further highlights their importance [9]. Moreover, their potential to combat cancer and modulate immune responses adds layers of complexity to their potential applications in health promotion [10].

2. Plant Endophytic Fungi and Their Bioactive Compounds

2.1. Definition and Characteristics of Endophytic Fungi

Plant endophytic fungi reside within the living tissues of plants, forming a unique symbiotic relationship that has captured the attention of researchers [11]. Endophytic fungi are organisms that inhabit the internal tissues of plants without causing any apparent harm or disease symptoms to their host. Unlike parasites or pathogens, they form a mutualistic association with the plant, from which both parties benefit [12]. This intricate relationship often involves the exchange of nutrients, signals, and metabolites, contributing to the overall health and resilience of the plant. These fungi possess distinct characteristics that set them apart from other microbial inhabitants [13]. One of their defining features is their ability to exist within the plant for extended periods, often throughout the plant's life cycle. They colonize various plant tissues, including leaves, stems, and roots, and display remarkable adaptability to different environmental conditions [14]. Unlike pathogens, they do not provoke an immune response from the host plant, allowing them to maintain a stealthy coexistence. Endophytic fungi have evolved diverse mechanisms to survive within the plant's internal environment [15]. Some form specialized structures called “microsclerotia” or “sclerotia”, which protect them from adverse conditions. Others produce secondary metabolites, including bioactive compounds, which contribute to their ecological success and their potential to influence plant health [16].

2.2. Diversity of Endophytic Fungi in Different Plant Species

Endophytic fungi have established themselves as versatile inhabitants by finding their niche within the internal tissues of plants across various ecosystems [17]. They are not found in just one type of plant. They live in many different kinds of plants such as trees, bushes, grass, and small plants. These fungi can live in many different places such as forests, grassy areas, wetlands, and even underwater. This remarkable adaptability has led to their presence in diverse habitats, including forests, grasslands, wetlands, and even aquatic ecosystems [18]. Endophytic fungi exhibit a high degree of phylogenetic diversity and have been discovered in all terrestrial plants investigated to date. Among the most commonly isolated genera are Penicillium, Alternaria, Fusarium, Colletotrichum, Aspergillus, and Xylaria [19]. However, other studies have also identified genera such as Alternaria, Colletotrichum, Fusarium, Gibberella, Glomerella, Guignardia, Leptosphaerulina, Nigrospora, Phoma, Phomopsis, and Xylaria. It is important to note that the frequency of isolation of these genera can vary depending on factors related to the host plant, including its genotype, the specific tissue sampled, geographical location, plant age, and the season in which the sampling is conducted [20]. The distribution of endophytic fungi is not only influenced by the plant's taxonomy but also by its geographical location and environmental conditions. Different plant species harbor distinct endophytic communities, reflecting the intricate interplay between the fungi and their host plants [21]. Moreover, the surrounding soil, climate, and even the presence of neighboring plants can influence the composition and diversity of endophytic fungi within a given plant species. The diverse array of endophytic fungi is not merely a result of their passive colonization. It is a testament to the complex and dynamic relationship they share with their host plants [22]. The diverse functions that these fungi fulfill contribute to their distribution patterns. Some endophytic fungi assist their host plants by enhancing nutrient uptake, improving water efficiency, and mitigating stressors such as drought and pathogens [23]. In turn, the host plants provide a sheltered environment and access to essential nutrients, fostering a symbiotic exchange that fuels their coexistence [24]. The distribution and diversity of endophytic fungi also provide a glimpse into their potential applications. Different plant species may serve as reservoirs for unique bioactive compounds, offering a wellspring of possibilities for harnessing their health-promoting effects [25]. The diversity of endophytic fungi will emerge as a cornerstone, underscoring their significance in reshaping our understanding of wellness and healthcare paradigms.

2.3. Extraction and Identification of Bioactive Compounds from Endophytic Fungi

Endophytic fungi have emerged as a treasure trove of bioactive compounds that could revolutionize health and medicine. These fungi synthesize an array of molecules with potential health-promoting effects [26] that could pave the way for innovative healthcare interventions [27]. Utilizing a variety of extraction techniques, each one is tailored to the unique properties of the bioactive substances and the under-researched fungal strains [28]. Solvent-based methods, such as maceration and Soxhlet extraction, are commonly used to dissolve the compounds in organic solvents. Supercritical fluid extraction and microwave-assisted extraction offer alternatives that leverage the unique properties of the solvents used [29]. For extraction from culture liquid, ethyl acetate is the best solvent [30]. After the extraction process, the subsequent step involves isolating the bioactive compounds from the complex mixture obtained from endophytic fungi. Chromatographic techniques, including methods such as thin-layer chromatography (TLC) and high-performance liquid chromatography (HPLC), play a crucial role in separating this mixture into individual compounds based on their distinct physicochemical properties [31].

The isolated compounds are subjected to rigorous characterization and identification processes to elucidate their chemical structures and properties. Techniques such as nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) play a crucial role in unraveling the molecular structures of these compounds [32]. This phase is essential to validate the presence of bioactive compounds and understand their potential health-promoting properties. The journey from extraction to isolation is a testament to the complexity and potential of endophytic fungi and their bioactive compounds.

2.4. Bioactive Compounds of Endophytic Fungi

Endophytic fungi have emerged as a hopeful reservoir of innovative and environmentally friendly bioactive compounds, exhibiting minimal toxicity. Phytochemicals are classified based on their structural characteristics among bioactive metabolites. They encompass a wide range of biological properties, including antimicrobial, immunosuppressive, antiparasitic, antioxidant, anti-inflammatory, and anticancer effects, among others [33]. They surpass conventional antimicrobials in terms of efficacy, cost-effectiveness, and reduced susceptibility to microbial resistance. This presents a promising solution to the substantial challenges confronting public health systems. Moreover, from an economic perspective, the industrial utilization of fungal endophytes as a source of bioactive compounds holds significant potential for substantial benefits within the medical sector [8]. Metabolites derived from fungal endophytes, renowned for their antimicrobial properties, encompass a range of compounds, including altersolanol A, clavatol, chaetomugilin D, colletotric acid, enfumafungin, guignardic acid, hydroxy-jesterone, jesterone, pestacin, rutin, viridicatol, 2-hydroxyl-6-methyl benzoic acid, 7-amino-4-methylcoumarin, and xylarenone B, among others [2]. An exceptional endophyte found in Citrus nobilis, specifically Streptomyces spp. TQR12–4, has been documented to possess broad-spectrum antifungal capabilities, effectively targeting fungal pathogens such as *Colletotrichum* spp., *Geotrichum* spp., *Fungus* spp., and others [34]. Endophytes such as *Juniperus communis*, *Phialocephala fortini*, and *Trametes hirsute*, inhabiting the tissues of *Juniperus recurve* and *Podophyllum peltatum*, produce podophyllotoxin, a well-known biomolecule recognized for its anticancer attributes [35]. Extensive research has unveiled the diverse bioactivities exhibited by metabolites produced by various fungal endophytes. For instance, *Chaetomium* spp. and *Xylaria* spp., which are associated with the herbal plants *Nerium oleander* and *Ginkgo biloba*, have been identified as potent antioxidants [36]. Endophytes have demonstrated their potential for possessing antidiabetic properties. For instance, *Acacia nilotica* is known to host the endophyte *Aspergillus awamori*, which has been scientifically verified to produce bioactive compounds with efficacy against diabetes [37]. Certain metabolites produced by endophytic fungi have been documented for their effectiveness against various viruses, including the dengue virus, HIV, human cytomegalovirus, and influenza A (H1N1) virus. Additionally, two novel compounds, namely cytonic acid A ($C_{32}H_{36}O_{10}$) and cytonic acid B ($C_{32}H_{36}O_{10}$), have been synthesized by *Cytonaema* spp. and are reported to possess antiviral properties [33]. Subglutinol A and colutellin A have repeatedly demonstrated their potential as effective immunosuppressants for the treatment of various immunological disorders. These compounds have been extracted from fungi residing within plant tissues [38].

2.5. Plant and Endophytic Fungal Interactions

The connection between endophytic fungi and plants has evolved gradually, with specific adaptations from both the plant and the fungi. This relationship is intricate and varies depending on the specific fungus, plant species, or a combination of both [39]. There are two prevailing theories explaining the source of endophytes: Exogenous and endogenous. According to the endogenous theory, endophytes originate from plant chloroplasts and mitochondria, sharing genetic histories with their host plants. Conversely, the exogenous hypothesis proposes that endophytes enter their host plants through various means such as surface contact, induced channels, or root wounds [40]. Over time, endophytic fungi and their host plants have developed a range of associations, spanning from (i) mutualistic relationships to (ii) antagonistic ones, and even (iii) neutral interactions. Some fungal endophytes remain mostly inactive within their host tissues throughout the plant's life, a state referred to as neutralism. Others may remain dormant until environmental conditions become favorable, leading to either mutualistic or antagonistic interactions [41]. Endophytic fungi have evolved three distinctive modes of reproduction: Firstly, there is vertical transmission, also known as intercellular transmission, where infected plants pass on the fungal infection to their offspring through seeds or hyphae. An exemplar of this transmission method is *Neotyphodium* sp. Secondly, horizontal transmission, which is intracellular in nature, takes place when sexual spores from infected plants disperse to initiate infections, and this mechanism is employed by *Epichloe* spp. [42]. Lastly, there is a mixture transmission approach, which combines both vertical and horizontal transmission strategies. Vertical transmission is an asexual means of reproduction involving the transfer of intercellular hyphae from infected plants to non-plant hosts, initiating infection or germinating infected seeds. In contrast, horizontal transmission involves the development of infectious sexual spores that undergo the fungal sexual life cycle [33].

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