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Review

Potentials of Endophytic Fungi in the Biosynthesis of Versatile Secondary Metabolites and Enzymes

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Abstract: World population growth and modernization have engendered multiple environmental problems: the propagation of humans and crop diseases and the development of multi-drug-resistant fungi, bacteria and viruses. Thus, a considerable shift towards eco-friendly products has been seen in medicine, pharmacy, agriculture and several other vital sectors. Nowadays, studies on endophytic fungi and their biotechnological potentials are in high demand due to their substantial, cost-effective and eco-friendly contributions in the discovery of an array of secondary metabolites. For this review, we provide a brief overview of plant–endophytic fungi interactions and we also state the history of the discovery of the untapped potentialities of fungal secondary metabolites. Then, we highlight the huge importance of the discovered metabolites and their versatile applications in several vital fields including medicine, pharmacy, agriculture, industry and bioremediation. We then focus on the challenges and on the possible methods and techniques that can be used to help in the discovery of novel secondary metabolites. The latter range from endophytic selection and culture media optimization to more in-depth strategies such as omics, ribosome engineering and epigenetic remodeling.

Keywords: fungal endophytes; secondary metabolites; extracellular enzymes; biotechnological applications; BGC activation

1. Introduction

The 21st century is distinguished by a huge increase in population growth, modernization and consumerism [1,2]. These engender multiple issues, especially those caused by massive industrial discharges and the excessive use of pesticides. Recently, scientific researchers have shed light on the importance of re-establishing an eco-friendly lifestyle [3–5].

Since ancient times, plants have been extensively used for health care and remediation [6,7]. In the 20th century, scientific researchers discovered that all plants on earth have harbored microbes since they first came into existence [8–11]. Plant–microbe interactions range from symbiotic to pathogenic [12,13]; in the symbiotic relationship, microbes are called 'endophytes'. Endophytes are conventionally known as microbes existing in all plant endospheric tissues (roots, shoots, fruits, leaves, flowers, seeds, etc.) without causing harmful consequences to the host plant [14–17]. These microorganisms are usually more abundant in roots and they can be transferred horizontally and vertically [18]. Particularly, endophytic fungi constitute an extremely large community, reaching up to three million species worldwide [19,20]. These eukaryotic organisms are known to harbor a large variety of secondary metabolites valuable to mankind, plants and the environment. They constitute an excellent substitute for exploring whole plants, thereby gaining time, facilitating the process of isolation and protecting the ecosystem [21,22]. The scientific community has approved the excellent roles of the fungal bioactive compounds in several vital fields including medicine, pharmacy, agriculture, industry and bioremediation. For instance, medicine improved exponentially with the discovery of the antibiotic penicillin [9,23], followed by the anticancer compound Taxol [24,25]. In addition, several industrial fields expanded rapidly after the discovery of numerous interesting extracellular enzymes produced by fungal endophytes [26,27]. In the present review, we will give an overview of plant–endophyte interactions; we will focus on secondary metabolites produced by endophytic fungi and their applications in several living sectors. Finally, we will cover the challenges and possible solutions in the discovery of novel bioactive compounds.

2. Endophyte–Host Plant Interactions

The endophyte–host interaction is often seen as a mutualistic symbiosis, whereby the host plant provides nutrition and protection to selected endophytes and they, in turn, promote plant growth (by producing matching or comparable compounds to the host plant) and enhance plant resistance to biotic (phytopathogens and herbivores) and abiotic (heavy metals, pollutants, temperature, etc.) stress factors [28–33]. Numerous studies have documented that the presence of endophytes is believed to influence several vital activities of the host plant, including plant growth promotion, defense responses against pathogen attacks and remediation against abiotic stresses [5,34].

Plant–endophyte interactions can become harmful in certain cases. There are two well-known ways for an endophyte to be or become a phytopathogen. The first way is the existence of wounds in the plant, allowing an indiscriminate penetration of microbial pathogens. The second way is plant atrophy or senescence, leading to the transformation of the endophytic microbe from a non-harmful to a harmful status due to its production of toxins engendering, in some cases, the mortality of the host plant [35]. Yan et al. [9] mentioned that an asymptomatic association between plants and their endophytic fungi is ensured by a balance between the antagonistic compounds produced by the endophytic fungi and the host plant (Figure 1).

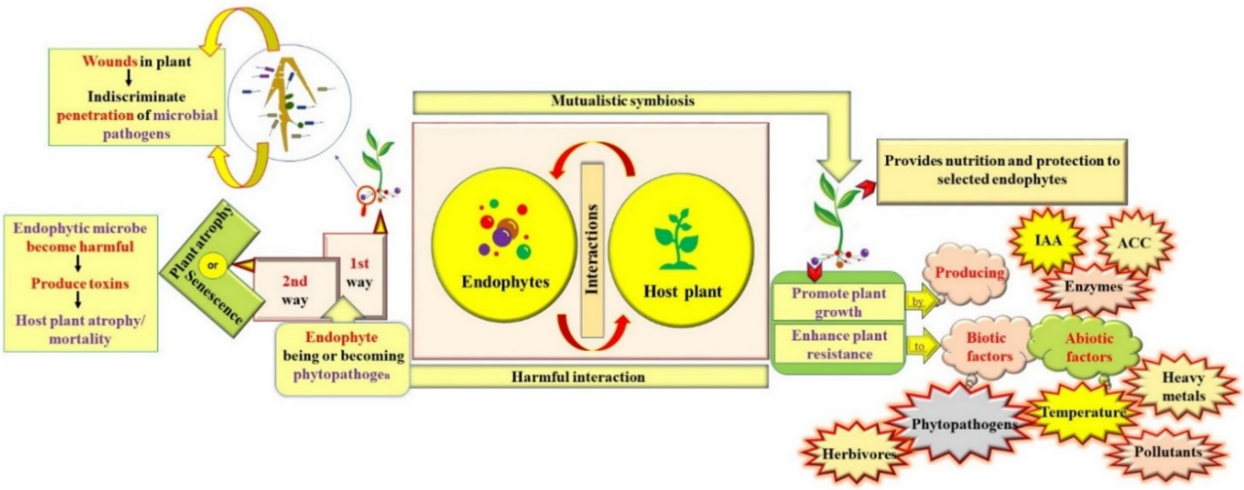

Figure 1. Interactions between fungal endophytes and host plants.

3. Processes of Isolation and Characterization of Endophytic Fungi

The percentage of cultivable microorganisms is only about 1% compared to the whole microbial community [36]. The process of isolation of cultivable fungal endophytes comprises multiple steps [37]. Briefly, the desired plant part(s) is/are washed thoroughly under running tap water, disinfected superficially with appropriate concentrations of ethanol and sodium hypochlorite or hydrogen peroxide and then washed multiple times with sterile distilled water to remove disinfectants. Afterward, the plant part(s) is/are cut into small pieces (5 mm average), which are spread on selective and non-selective growth media supplemented with antibacterial agents to avoid the multiplication of bacteria. The temperature of incubation is around 25 ± 2 °C [30,38,39]. The difference between endophytic and rhizospheric fungi is difficult to define. Thus, a supplementary step is always recommended: it comprises the incubation of the last washing water in a non-selective growth medium. The absence of fungal growth ensures a successful sterilization. Pure fungal isolates are obtained by sub-culturing the emergent hyphal tips, and then, they are stored in 20–30% glycerol solution either at -20 °C for short-term storage or at -80 °C for long-term storage [27,38]. The characterization and identification of fungal endophytes occur morphologically, biochemically and molecularly [22]. The molecular and genomic pathways enable the characterization of both cultivable and non-cultivable species. The most popular endophytic fungi belong to *Fusarium*, *Aspergillus*, *Penicillium*, *Trichoderma* and *Alternaria* genera [40–42]. In-depth studies of endophytic fungi enhance the knowledge of their potential for the production of novel effective secondary metabolites, which are also called bioactive compounds and natural products [4]. These microbial substances have diverse chemical structures and properties, which enable them to act in a beneficial way to host plants, the environment and humans in multiple fields [43–45].

4. History of Fungal Production of Secondary Metabolites

Bioactive secondary metabolites are natural organic and low-molecular-weight compounds synthesized by almost all microorganisms and used as a means of defense against external aggressions [46,47]. Particularly, secondary metabolites produced by endophytic fungi possess different interesting activities applicable in several fields [48,49]. Fungi have attracted scientific researchers since the discovery of the wonder antibiotic penicillin from *Penicillium notatum* fungus back in 1928 [50,51]. In 1993, Stierle et al. discovered another bioactive metabolite, Taxol (paclitaxel), from the endophytic fungus *Taxomyces andreanae,* inhabiting the *Taxus brevifolia* tree. This potent drug is mainly used for chemotherapy against cancer diseases [20,52,53]. These two lead compounds have paved the way towards exploring novel drugs from endophytic fungi. Such natural products are prominent, affordable, environmentally friendly and could be applied for commercial use [54]. The bioprospecting of bioactive compounds from fungal endophytes expanded in the 1990s and is still thriving. This is confirmed by hundreds of articles and patents describing novel or existing natural products and their possible applications in multiple domains [25,41,55]. Nowadays, studies have revealed that almost 70% of the existing bioactive compounds originate from microorganisms [52].

5. Processes of Fungal Secondary Metabolite Production

Fungal endophytes are an abundant and natural treasury of drugs with simple and complex molecular structures. The operation of drug production is executed by the endophytic fungus and influenced by the host plant and by other competing endophytes. The biosynthetic pathways of secondary metabolites are manipulated by a group of arranged genes, named biosynthetic gene clusters (BGCs), encoding tandem enzymatic reactions [56,57]. The acyl-coenzyme A enzyme represents the initial point of synthesis of diverse classes of biomolecules including alkaloids, terpenoids, cyclohexanes, peptides, polyketides, flavonoids, hydrocarbons, steroids, monoterpenoids, xanthones, tetralones, quinones and several other compounds endowed with significant activities in vital fields of life [8,58–62]. The regulation of fungal BGCs occurs at the transcriptional and the epigenetic levels [23]. Transcriptional regulation ranges from cluster-specific regulators to global transcriptional complexes [63]. Keller [23] suggests that up to 50% of fungal BGCs contain a cluster-specific transcription factor recognizing palindromic motifs in cluster gene promoters. Epigenetic regulation occurs through DNA methylation and histone acetylation among other epigenetic mechanisms used to control gene expression. Epigenetic manipulation is actually an effective strategy for unlocking the chemical diversity encoded by fungal endophyte genomes [64].

6. Biotechnological Applications of Secondary Metabolites Produced by Endophytic Fungi

The trend of using biological (herbal and microbial) drugs encouraged the scientific community to prospect the natural products synthesized by endophytic fungi [65,66]. These endophytes produce unique compounds and also compounds similar to those produced by their host plants making them an easy alternative to plants to avoid ecological distortion [67]. The produced compounds may be directly or indirectly applied in several biotechnological fields such as medicine, pharmacy, agriculture, bioremediation and industry. Some of these natural products are discussed along with their functions in the following sections [9,68] (Figure 2).

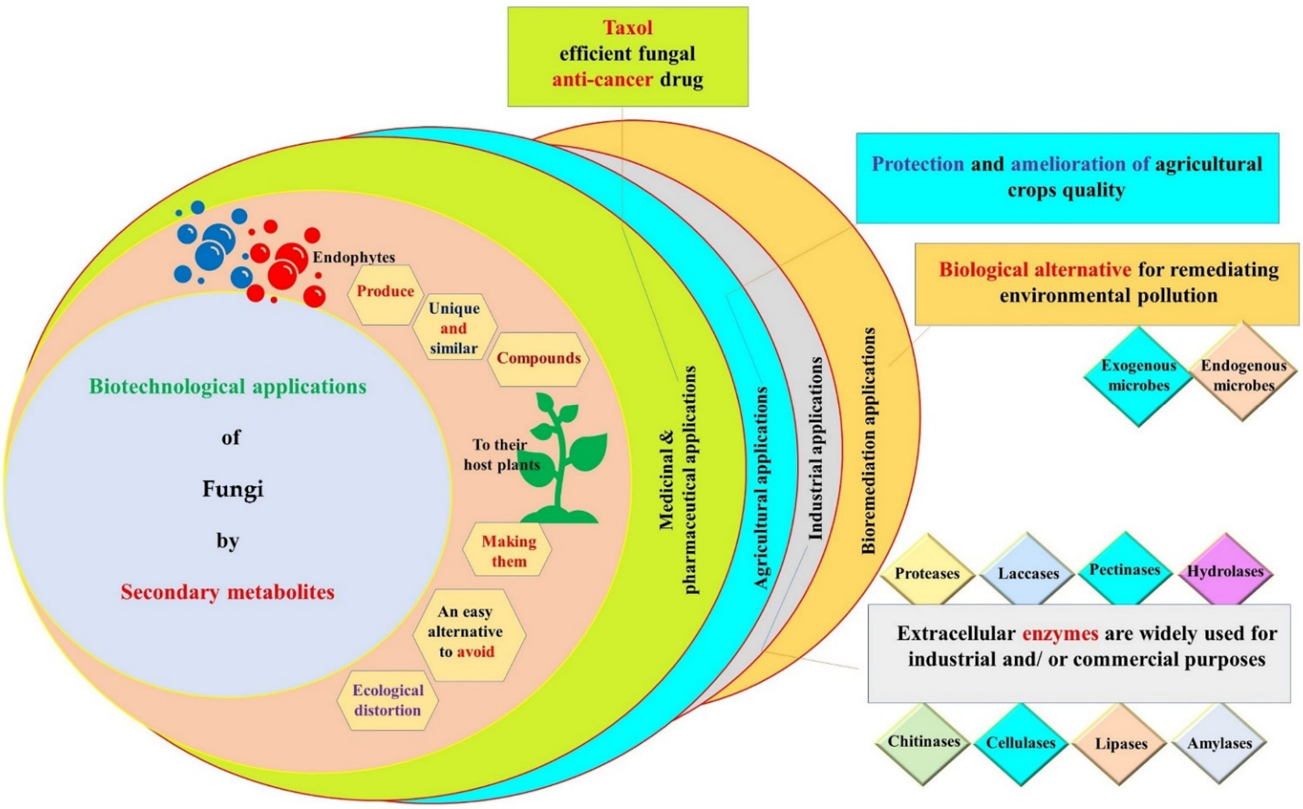

Figure 2. Biotechnological applications of secondary metabolites and enzymes produced by endophytic fungi.

6.1. Medicinal and Pharmaceutical Applications

Global human health is threatened by the development of various chronic and infectious diseases, the emergence of pathogens resistant to commercial antibiotics and the harmful side effects engendered by the prolonged utilization of chemical drugs [69,70]. These shortcomings require the search for novel bioactive compounds from natural sources, such as fungal endophytes, to develop new pharmaceutical drugs for human diseases [47,71,72]. For instance, cancer constitutes a major health problem despite the continuous development of new medicines [73]. It is a disease caused by abnormal cell division (leading to tumors), which could invade all human body parts and engender elevated mortality rates in humans all over the world. This harmful disease is reported to be the second leading cause of death in the world, behind cardiovascular disease [20]. For instance, Taxol is a clinically approved fungal anticancer drug blocking the proliferation and migration of cancer cells [71–75]. Various other biological compounds, such as antibacterial, antifungal, antidiabetic, immunosuppressant, antihypertension, antiviral, antiprotozoal, antiparasitic, antimutagenic, insecticidal, antioxidant, anti-inflammatory, anticancer, etc., were exhibited by endophytic fungi and constitute alternative biological remedies for several human diseases [76–83] (Table S1).

6.2. Agricultural Applications

The plant–endophytic fungi interaction is a mutual association helping plants to cope with both biotic and abiotic stresses [31,42,84,85], promoting plant growth by assimilating essential nutrients (potassium, nitrogen and phosphorus) and producing ammonia, siderophores, hormones (auxins, gibberellins and cytokinins) and enzymes [12,13,17,86]. Particularly, secondary metabolites produced by beneficial fungi play a very interesting role in protecting and ameliorating the quality and yield of agricultural crops [40,87]. In recent years, the biocontrol of plant diseases using beneficial endophytes and their secreted compounds has been studied intensively due to the endless benefits to plants, human health and the environment [88–90]. Table S2 in the Supplementary Materials contains examples of novel fungal secondary metabolites applied to improve and protect agricultural crops (Table S2).

6.3. Industrial Applications

Extracellular enzymes are the most common and searched compounds extracted from endophytic fungi for industrial and/or commercial purposes [9]. They include chitinases, cellulases, amylases, xylanases, pectinases, hydrolases, laccases, proteases, lipases, etc. [91,92]. Enzymes are used to degrade complex compounds into small ones that are easy to degrade or assimilate [93]. Various types of industries prefer using microbial hydrolytic enzymes due to their high stability, broad availability, cost-effectiveness and eco-friendliness [94,95]. For instance, protease dominates the global enzymes market and is responsible for hydrolyzing proteins and their derivatives into simple constituents (amino acids and oligopeptides). Fungal proteases are preferred for their high stability [92], and thus they are mostly used in pharmaceutical, therapeutic [26,96], food [97], detergent [98], waste management [99], leather and textile [100] industries. The cellulolytic enzyme is used to degrade cellulose and its related polysaccharides. It is applied in the human food, animal feed, agriculture, paper, laundry, wine and textile industries [101]. Xylanase works in synergy with esterase to hydrolyze xylan, which is a plant polysaccharide. Such organic carbon is mainly utilized in food-related industries (baking, drinking, etc.) [102,103]. In addition, it has been extensively documented that bacteria and fungi appear to be the dominant chitin decomposers due to the production of highly active and thermostable chitinase enzymes [104]. The application of chitinase is concentrated in seafood industries, since the catalyzation of chitin increases the nutritional benefits of seafood [105,106], human health improvements, due to its antioxidant, anti-inflammatory, antimicrobial and antitumor properties [107,108], and the biocontrol of phytopathogenic fungi and pests [109]. In addition, fungal pectinase is used to hydrolyze plant pectin. This enzyme is widely known in multiple industries for its versatile applications in fruit juice processing [110], breaking down pectin from agronomic and industrial wastes [111], textile industries [112], paper recycling [113] and many other applications [114]. Lipase is a serine hydrolase responsible for breaking down fats and oils; thus, it is essential in the food industry [115]. Lipases extracted from fungi are able to withstand extreme conditions [116]. Phytase enzyme is used to degrade phytates. It is especially used in the environmental, nutritional, and biotechnological fields [117,118]. Last but not least, amylase is responsible for converting starch into different types of sugars, and amylases originating from fungi are known to be thermostable: this is a redeeming feature for starch-producing industries [119]. Examples of endophytic fungal enzymatic applications in industries are illustrated in Table S3.

6.4. Bioremediation Applications

Natural source contamination is mainly caused by uncontrolled industrial discharges and anthropogenic activities [17], leading to the accumulation of recalcitrant pollutants, heavy metals, herbicides, pesticides, chlorinated products, etc. [120,121]. Bioremediation has arisen in the last two decades as a biological alternative for remediating environmental pollution [122,123]. It is based on the use of bacteria and fungi and their secreted compounds to degrade, transform or accumulate targeted pollutants, converting them into non-toxic compounds [124–126]. Bioremediation could occur by endogenous microbes living within the contaminated area [34], or by exogenous microbes (having high bioremediation capacities) induced artificially [27,127].

7. Challenges and Solutions to Improve Secondary Metabolite Discovery

Although the literature presents a wide variety of valuable bioactive compounds produced by endophytic fungi [127–129] (Tables S1–S3), it has been well established that researchers have discovered only a small portion of the real capacities of fungal endophytes. The major restrictions regarding this issue have been attributed to possible difficulties in microbial isolation/characterization and also BGC identification, the existence of cryptic BGCs, low stability or instability of fungal secondary metabolites expressed and/or the possible isolation of already known BGCs [130] (Figure 3). Depending on each situation, several methods could be used to solve issues and speed-up the discovery process, to decipher novel secondary metabolites contributing to the advancement of numerous vital fields [131,132]. Reportedly, numerous scientists have demonstrated the crucial role of advanced genetic, proteomic, metabolomic, bioinformatic and mass spectrometry tools to predict, understand and manipulate the biosynthetic pathways of natural products [133–136]. Other dereplication tools are applied to avoid the rediscovery of known compounds [137,138]. The challenge of a cryptic gene cluster's activation could be realized through numerous methods, starting from a good selection of the endophytic fungus by exploring extremophile crops in order to increase the chances of discovering novel noteworthy drugs [51,139]. Secondly, the optimization of the culturing conditions of the targeted endophytic fungi, by providing all essential nutrients and optimal growth conditions, is recommended [140–142]. The co-culture fermentation is another method based on the cultivation of two or more fungal isolates in the same culture environment to mimic the real growth environment. The association could be symbiotic or antagonistic; thus, it allows the production of novel compounds [143,144]. Heterologous expression is another important strategy based on the introduction of the predicted BGC into another potent host microbe to activate its expression. This method is recommended to allow the expression of the cryptic BGCs in native fungi and for biomass production of bioactive compounds [145]. Ribosome engineering is an approach well studied by Ochi [146,147] to create a fungal mutation aiming to improve cryptic gene activation, which allows the production of valuable bioactive molecules and antibiotics. Last but not least, the epigenetic remodeling technique helps in modifying the biosynthetic enzyme pathways to activate cryptic genes [148].

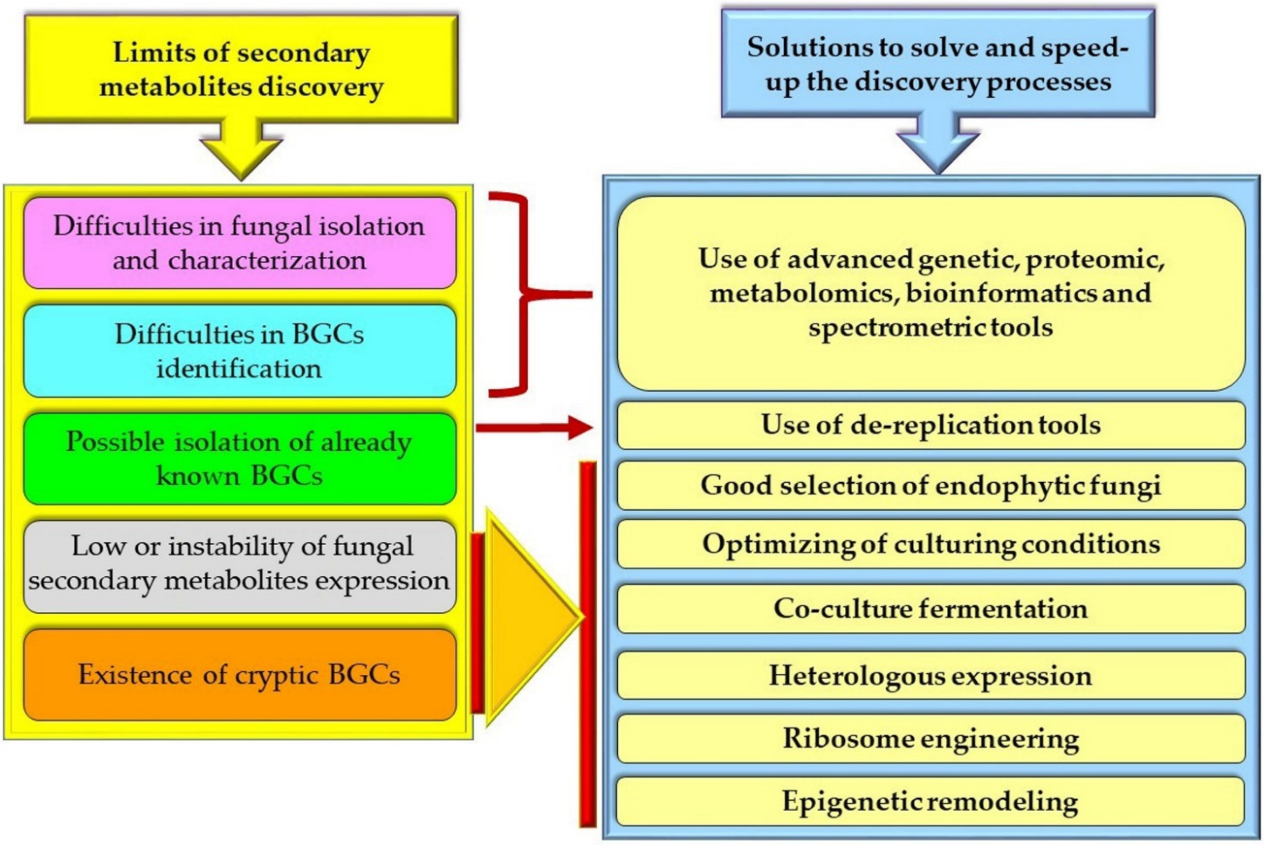

Figure 3. Limits and solutions helping in novel secondary metabolite discoveries.

8. Conclusions

This review highlighted the importance of secondary metabolites and extracellular enzymes extracted from fungal endophytes and their crucial contribution in resolving several human, animal and environmental issues. Thus, we started by describing the mechanisms of interaction between plants and endophytic fungi and their influence on the pathways and mechanisms of secondary metabolite biosynthesis. We also underlined the essential role of using suitable fermentation equipment, advanced analytical techniques and modern tools (omics, bioinformatics, ribosome engineering and epigenetic remodeling) to reveal the real potential of endophytic fungi in synthesizing valuable natural products. The future of research into fungal endophytes is full of interesting discoveries that are sorely needed to solve human and environmental problems in an eco-friendly and cost-effective way. Therefore, it is essential to accelerate the process of screening novel bioactive molecules and to improve the methodologies of large-scale production.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/f12121784/s1, Table S1: Medicinal applications of novel secondary metabolites produced by endophytic fungi, Table S2: Agricultural applications of novel secondary metabolites produced by endophytic fungi, Table S3: Industrial applications of extracellular enzymes produced by endophytic fungi.

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