EXPLORING THE ENDOPHYTIC FUNGI FOR BIOACTIVE METABOLITES: AN EMERGING PARADIGM

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ABSTRACT

Endophytes are ubiquitous in nature. Majority of plants harbour endophytes within various parts like roots, stem, leaves or seeds. Various fungal species live inside plants endosymbiotically. Endophytic fungi are known to be associated with number of medicinal plants, making them suitable candidates for bioprospecting. Endophytic fungi possess a storehouse of various bioactive metabolites with anti microbial, anti viral, anti cancerous or anti oxidant actions. Some of the endophytes yield compounds with immunosuppressant activities. These compounds generally originate from different biosynthetic pathways and belong to different categories like terpenoids, quinines, phenols, flavonoids, coumarins and steroids etc. In the present article, endophytic fungi associated with various medicinal plants have been reviewed for their bioactive metabolite production. A vast number of fungal species endophytic in various medicinal plants exhibit inhibitory actions against bacteria, fungi, viruses, parasites and free radicals. Endophytic fungi offer a plethora of biologically active metabolites which can serve as a potential to explore more of new drug formulations. These are the chemical reservoir of novel bioactive metabolites.With the help of latest techniques, desirable quality and quantity of various bioactive compounds can also be ensured. However, only a limited amount of efforts have been put in this direction, which otherwise show an enormous potentiality for further exploration. The present review was invisaged as an effort to provide an idea regarding the potentiality of endophytic fungi.

Key Words: Bioactive metabolites, Chemical reservoir, Endophytes, Medicinal plants, Therapeutic actions.

I.INTRODUCTION

World Health Organization (WHO) defines medicinal plant as " any plant in which one or more of its organ contain substances that can be used for therapeutic purposes or which are precursors chemo-pharmaceutical semi- synthesis." Ethnopharmacologists all over the world are fascinated by the fact that plants are invaluable resources for the valuable products [1]. According to an estimate by WHO , approximately 80% of the world population use plants in one form or other. Medicinal properties of the plants are attributed to the presence of certain bioactive compounds such as alkaloids, phenols, tannins, terpenes etc or some other secondary

metabolites. Endophytes are important component of plant microecosystem. Endophytes share an imperceptible relationship with host plant, in which these reside through out the life or for a brief period of life only. These include fungi, bacteria and some algae [2]. Endophytic fungi colonize all parts of the plants and have been isolated from different plant parts like roots, stem, leaves, flower, fruits or even dry seeds. [3]. Endophytes live endosybiotically and asymptomatically inside the plant parts either above or below the ground. It is estimated that over one million endophytic fungal species occur in nature. These fungi asymptomatically reside in the internal tissues of the host beneath the epidermal layer and colonize their via quiescent infection [4]. There is great biodiversity of endophytic fungi in the tropical as well as temperate zones, where approximately 300,000 tree species are found. Most of the trees have one or more endophytic fungi associated with them. Schultz classified endophytic fungi into three groups- mycorrhizae, balansicaeous or pasture and non-pasture [5].Endophytic fungi belong to ascomycetes and deuteromycetes. Over the years, some co-existing endophytes and their host plants have established a relationship with each other. Endophytes offer a plethora of advantages to the host with vast range of applications in agriculture and medicine. This mutual relationship proves to beneficial by improving quality and quantity of the crude drugs. There is increase in the surge of interest for endophyte isolation from various plant species.

II.IMPORTANCE OF BIOACTIVE COMPOUNDS AND NEED TO EXLORE RESOURCES:

Natural products are derived compounds present as some metabolite or their by product from the plants, animals or some microbes[6,7]. These are sources of novel bioactive compounds and have a profuse impact on modern medicine. About 68% of antibacterial compounds and 34% of of anti cancer compounds are either some natural product or their derivative[8]. Owing to these facts, there is a dire need to explore new and useful bioactive compounds to provide relief to the health aspect of human beings. Endophytes show a promising approach to explore effective bioactive metabolites from medicinal plants. The array of metabolites and other chemicals synthesized by endophytes endow plants with more resistance to nematodes, insects and livestock. Plants inhabited with endophytes grow at a faster pace due to synthesis of certain phytohormones and become compatible and dominate particular environment. Endophytic fungi produce more number of secondary metabolites than any other endophyte [9]. It is essential to understand relationship between endophytic fungi and their host plant, so that the medicinal properties of the host plant can be exploited to its full potential and applied for enhanced production of drugs from the plants. Fungal endophytes involve two transmission modes- horizontal and vertical. The former spreads by sexual and asexual spore transmission , while the latter transmits systemic fungus from plant to offspring via seeds [10]. Analytical data indicate that distribution and population structure of an endophyte is governed by a variety of factors like genetic background, age and environmental conditions. A large number of factors such as genotype of plant, its habitat, availability of nutrients in soil etc are responsible for the quantity and quality of crude drugs obtained from the medicinal plants. Apart from affecting the bioactivity of medicinal plants endophytic fungi also confer profound impacts on their growth , increasing their tolerance to abiotic as well as biotic stress factors. Our knowledge about the exact relationship

between fungi and their host plants is still very much limited. Proper understanding of the relationship between endophytic fungus and medicinal plants is of much significance to promote crude drug production.It can be achieved by manipulation of growth conditions or by adding particular endophytic fungus. It may also help to replace the traditional kind of manufacturing of drugs from natural medicinal plants by production of drugs using bioactivity of medicinal plants and endophytic fungi under cultural conditions[11,12].

III.ENDOPHYTIC FUNGI-THE CHEMICAL RESERVOIR OF BIOACTIVE METABOLITES

Endophytes possess property to synthesize a variety of chemical metabolites [13]. The metabolites produced by various endophytic fungi can be exploited for cure of number of diseases. Unique structures and bioactive compounds synthesized by them provide the status of chemical reservoir of various bioactive compounds. Endophytic fungi with potential for bioactive compound production can be fermented on large scale to provide inexhaustible supply of bioactive compounds, thus can be exploited commercially. Bioactive compounds produced by endophytic fungi exclusive of those to their host are important to increase adaptability of both endophytic fungi and their host. In addition to improving tolerance to abiotic and biotic stress factors, these compounds can induce production of a plethora of known and novel bioactive secondary metabolites that can be exploited and employed as important medicinal resources. In co-evolution view, endophytic microbes improve resistance of host plants to adverse conditions by secretion of secondary metabolites.In the present paper, endophytic fungi and medicinal plants with reference to their bioactivity,and factors influencing their population structure and distributuion have been reviewed. It is hoped that this review may prove beneficial to make better use of this symbiotic association for getting better quality resources of medicinal plants.

IV.PHARMACOLOGICAL ACTIONS OF BIOACTIVE METABOLITES FROM ENDOPHYTIC FUNGI

Bioactive metabolites show a variety of activities, making them suitable for exploration of new and better drugs from the medicinal plants. Some of the pharmacological actions of the bioactive compounds are discussed below:

4.1 ANTI MICROBIAL ACTIVITY

Antimicrobial compounds are effective against other microbes in a little concentrations. Sesquiterpenes, diterpenoids and triterpenoids produced by endophytic fungi are mainly responsible for their anti microbial activity. A broad number of endophytic fungi exists in the rhizomes of *Paris polyphylla* var.*yunnaensis* ,a plant widely used in Chinese traditional medicines. Colletotric acid produced by *Colletotrichum gloeosporoides* endophytic in *Artemisia mongolica* exhibits antibacterial as well as antifungal property [14]. Antifungal property against *Candida albicans* and *Fusarium oxysporum* is reported to be shown by Cytosporone B and C produced by *Phomopsis* species [15]. *Penicillium* harboured by *Acrostic hum arena* exhibits anti bacterial

action against *Streptomyces aureus*[16]. Crude extract of secondary metabolites secreted by endophytic fungi isolated from various medicinal plants show a broad spectrum anti bacterial action. Among the isolated endophytic fungi, *Aspergillus, Curvularia, Chaetomium* and *Fusarium* show effectiveness against number of bacteria. The anti bacterial activity may be bactericidal or bacteriostatic. Similarly, *Phoma* species isolated from , *Fusarium Oxysporum, Rhizoctonia solani and Magnaporthe oryzae* (antifungal) *Xanthomonas compestris, X. oryzae* (antibacterial).

4.2. ANTI VIRAL ACTIVITY: Comparatively lesser number of bioactive compounds from endophytic fungi have been reported to show anti viral activities. The major limitation in the discovery of antiviral compounds of endophytic origin is probably lack of anti viral screening system in majority of bioactive compound discovery programs. Cytonic acid A & B have been isolated from an endophytic fungus *Cytonaema* sp. [17]. Anti viral activity of Hinnuliquinone isolated from endophytic fungus in leaves of oak trees (*Quercus coccifera*) have been reported against HIV-1 protease [Singh etal,2004]. Pestalotheol-C isolated from endophytic fungus *Pestalotiopsis theae* has been reported to show inhibitory action against HIV [18,19].

4.3. ANTI OXIDANT ACTIVITY

Certain unstable molecules called free radicals prove harmful as these cause number of degenerative diseases like Alzheimer' s disease. Antioxidants provide protection to the cells against free radicals. Due to only a handful of antioxidants recommended for clinical purposes, an urgency for the suitable antioxidants is there. *Pestalotiopsis microspora endophytic inside Terminalia morobensis* yields two important antioxidants known as Pestacin and Isopestacin [20].Similarly ,Graphislactone A was isolated from *Cephalosporin* sp., a fungi endophytic in *Tracheospermum jasminoides* and in vitro showed more potent antioxidant activity as compared to Ascorbic acid.[21]. A number of other endophytic fungi due to presence of phenolics and flavonoides in them can act as potential anti oxidants. *Chaetomium* sp. in *Nerium oleander* [22]; *Xylaria* sp. *Ginkgo biloba* [23].are among the few to be named here. Cajaninstilbene acid, another antioxidant has been reported from *Fusarium*,an endophyte of *Cajanus Cajun* [24].

4.4. ANTI CANCER ACTIVITY

Taxol also known as Paclitaxel is a very potent anti cancer drug,isolated from the bark of *Taxus brevifolia*. It is quite effective against breast and ovarian cancer. Vincristine, a cytotoxic compound was isolated from endophytic mycelia sterilia inhabiting *Catharanthus roseus* [25].Endophytic fungus *Entrophospora infrequens* inhabiting *Nothapodytes foetida* is source of an alkaloid Camptothecin, a potent anti neoplastic agent [26,27]. Podophyllotoxin also possess anti cancer properties. It has been isolated from a number of endophytic fungi like *Trametes hirsute* [puri etal2006]; *Aspergillus fumigatus* [28] isolated from *Juniperus communis*; *Phialocephala fortini* isolated from *Podophyllum peltatum* [29] and *Fusarium oxysporum* from *Juniperus recurva* [30]. Ergoflavin ,an anti cancer compound was isolated from the leaves of *Mimosops elengi* [31]. Secalonic acid D another cytotoxic compound has been isolated from mangrove endophytic fungi [32].

4.5. IMMUNO-SUPRESSANT ACTIVITY

Immunosupressive drugs are used for the treatment of auto immune disorders and for the prevention of allograft rejection in case of organ transplantation. Intensive search for the suitable immunomodulatory compounds is going on to deal with the problems related to auto immune system. Endophytic fungi possess capability to synthesize compounds with immunosuppressive action. Cyclosporin A- an immunosuppressant has been isolated from endophytic fungus *Tolypocladium inflatum.* [33].Non – cytotoxic diterpene pyrones Subglutinol A& B were isolated from *Fusarium subglutinans* fungi inhabiting *Tripterygium wilfordii* [34]. Mycophenolic acid , an immunosuppressant used for treatment of auto immune disorders and prevention of rejection reaction in organ transplantation has been reported to be yielded by a number of endophytic fungi like *Aspergillus, Penicillium, Septoria, Byssochlamys* etc[35,36].

4.6. ANTI PARASITIC ACTIVITY

A variety of organisms live parasitically and may be pathogenic or non- pathogenic in nature. Pathogenic parasites are generally protozoans or helminthes. These cuase much harm to the health. Malaria, a tropical disease caused by a protozoan *Plasmodium* is extended to almost 40% of the global population. Out of various species, *P. falciparum* causing cerebral malaria is considered to be fatal one [37]. Major problem with most of the anti malarial drugs apart from their cost is resistance to the drugs over the period of time. Hence bioactive compounds with anti malarial properties seem to be the better choice. Phomoxanthones A&B produced by *Phomopsis* species show a remarkable anti malarial activity [38]. *P. archeri* endophytic fungus of *Vanilla albindia* produces Phomarcherins A-C, aromatic sesquiterpenes withanti malarial action [39]. *Leishmania* and *Trypanosoma* are other pathogenicprotozoans. Various endophytes as *Cochliobolus* sp.in *Piptadonia adiantoides* produce Cochlioquonone A against *Leishmania.* [40]. Ann analogue of Cercosporin produced by *Mycosphaerella* sp. inhabiting *Psychotoria horizontalis* has been reported to be effective against *Plasmodium falciparum,Leishmania* donovani and Trypanosoma *cruzi* [41].

V.CONCLUSION

Discovery of new chemical compounds play a significant role in the formulation of new and advanced drugs. Endophytic fungi offer a rich reservoir of bioactive compounds with wide range of therapeutic potential. These show potent, safe and cost effective results. Recently, keen interest has been shown by the scientists in this comparatively less explored arena. It has resulted in an inclination towards the exploration of endophytic fungi associated with various medicinal plants. Many bioactive compounds with antibacterial, anti fungal, anti viral, anti cancer and anti oxidant properties have been successfully isolated from number of endophytic fungi. Various reports indicate that number of fungi like *Aspergillus, Penicillium, Phomopsis, Septoria,, Cochliobolus* etc provide a large number of bioactive molecules used for various therapeutic purposes. *Phomopsis* spp. Isolated from different medicinal plants provide a large number of bioactive compounds[42,43,44]. With the help of latest technology like genetic engineering , various endophytic fungi can be manipulated in a better way to explore their therapeutic potential fully. Medicinal plants with endophytic fungi are indeed a hidden treasure

worth exploring. In the future also endophytic fungi hold a promising approach for the development of safer drugs with efficacy[45]. Exploring the endophytic fungi for a variety of bioactive metabolites is emerging as a paradigm with bright future prospects.There is dire need to tap more of unconventional resources , keeping safety issues and potency in mind at the same time.

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