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ENDOPHYTIC FUNGI: A NOVEL SOURCE USED AS NATURAL THERAPEUTICS

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ABSTRACT

Endophytes are the microorganisms that exist in internal tissues of all plant species and are proven source of novel organic natural molecules, supposed to emphasizing the frontiers of drug discovery. Many researchers have proven that endophyte is a new and potential source of novel natural products for exploitation in modern medicine, agriculture and industry. Endophyte research has yielded various properties like antimicrobial, antioxidant, antiviral, antidiabetic, anti-alzheimer and immunosuppressant etc. This evidence arises a hope to combat incurable diseases, drug resistance, other challenges related to human health. endophytes belong to diverse structural classes, including: alkaloids, peptides, steroids, terpenoids, phenols, quinones, and flavonoids. The potential of finding new drugs that may be effective candidates for treating newly developing diseases in humans is great. Endophytes, found ubiquitous in all plant species in the world, contribute to their host plants by producing plenty of substances that provide protection and ultimately survival value to the plant. So far, a great number of novel natural products have been isolated from endophytes. These achievements would provide the opportunity to utilize endophytes as a new source for production of secondary metabolites.

KEYWORDS: Endophytes, fungi, antimicrobial, secondary metabolites, endophytic bacteria.

INTRODUCTION

Endophytic Fungi: A new way of generating natural compound is from endophytic fungi. Endophytic fungi are fungi that colonize living plant tissue without causing any immediate, obvious negative effects.[1] Mutualistic interaction between endophytic fungi and its host has generated a lot of interests regarding its broad potential in research. Several studies have shown that endophytic fungi are able to produce compounds that are similar to the secondary metabolites produced by its host. Hence, endophytic fungus has high potential as a new source of bioactive compound. Plant-bacteria associations have been studied for many decades. However, a complete understanding of the mechanisms utilized by plant growth-promoting bacteria had remained somewhat elusive, often making it difficult to take full advantage of these complex relationships to reproducibly improve the growth of plants in an applied setting. What is currently understood is that bacteria can positively impact plant growth and health while plants can "select "their micro biome in order to have beneficial bacterial colonizers, including those living within the plant tissues. To colonize the internal plant tissues, it has been proposed that bacterial endophytes have genomic differences compared to rhizosphere colonizing bacteria, although so far no definitive group of genes has been identified that is responsible for the endophytic lifestyle. Only some of those genes have been experimentally shown to be involved in endophytic colonization.[2]

The ability of diverse bacterial endophytes to promote plant-growth occurs as a consequence of either direct or indirect mechanisms. Direct promotion of plant growth occurs when a bacterium either facilitates the acquisition of essential nutrients or modulates of level of hormones within a plant. Nutrient acquisition facilitated by PGPB typically includes nitrogen, phosphorus and iron. Modulation of hormone levels may entail PGPB (Plant Growth-Promoting Bacteria) synthesizing one or more of the phy-tohormones auxin, cytokinin and gibberellin. In addition, some PGPB can lower levels of the phytohormone ethylene by synthesizing an enzyme, 1-aminocyclopropane-1-carboxylate (ACC) deaminase that cleaves the compound ACC, the immediate pre-cursor of ethylene in all higher plants. Indirect promotion of plant growth occurs when a PGPB decreases the damage to plants following infection with a phyto pathogen including some soil fungi and bacteria. This usually occurs by the inhibition of the pathogens by the PGPB. There are many endophytic fungus viz. Phaleria macrocarpa (P. macrocarpa) which is a native Indonesian plant has been used traditionally as herbal drink to treat many types of diseases such as cancer and diabetes.[3] Recent studies also showed that P. macrocarpa exhibited numerous different bioactivities.

This plant exhibited antioxidative, anti-inflammatory and cytotoxic activity.[4] Also proven that P. macrocarpa has anti-proliferative activity against two types of cancer cells (MDA-MB-231 and MCF-7 human breast adenocarcinoma cell lines).[5]

General Classification

Endophytic fungi mainly consist of members of the Ascomycota or their mitosporic fungi, as well as some taxa of the Basidiomycota, Zygomycota and Oomycot and Classification endophytic fungi and existence in plant cell. But there are also different ways of grouping fungal endophytes are suggested by the transmission mode in particular, and distinguished between the endophytes of the Clavicipitaceae (clavicipitaceous endophytes) and the rest (non-clavicipitaceous endophytes). Several studies have demonstrated that various fungal endophytic interactions ranging from mutualistic to antagonistic, depending on host and endophyte genotype, and environmental conditions.[6]

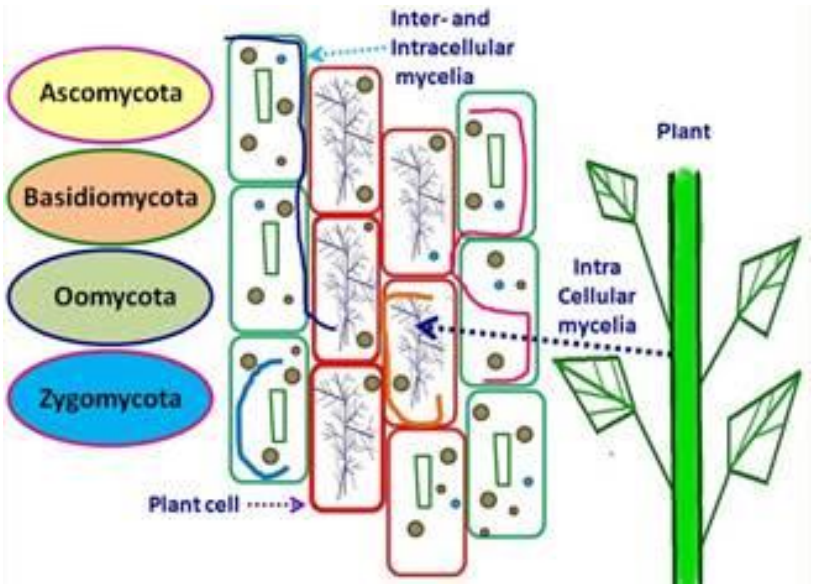

Figure 1: Classification of endophytic fungi and existence in plant cell

Challenges caused demands for new drugs

Challenges against human health are the development of resistance in infectious microorganisms (e.g., *Staphylococcus*, *Mycobacterium* & *Streptococcus etc.*) to present drugs and by the menacing presence of naturally resistant organisms. The even-more to the human population of new diseases and disease-causing agents such as Acquired immunodeficiency syndrome (AIDS), Swine flu (H1N1), Ebola, Crimean-Congo hemorrhagic fever, Lassa fever, Dengue fever, Chikungunya, severe acute respiratory syndrome (SARS) and Middle east respiratory syndrome coronavirus (MERS-CoV) diseases outbreak requires the

sequencing of some discoveries and development of new drugs to eradicate them. Not only to do for diseases such as AIDS require drugs that target them specifically, but new therapies are needed for treating subsidiary infections, causes weakened immune system.[7] Furthermore, others who are immune compromised (e.g., cancer and organ transplant patients) the tremendous rise in the incidence of fungal infections (opportunistic pathogens) such as *Aspergillus*, *Cryptococcus*, and *Candida*, which normally are not major problems these issues now thrown world's population all underscore our inadequacy to cope with these medical problems. In addition, more drugs are needed to efficiently treat parasitic protozoan and nematodal infections such as malaria, leishmaniasis, trypanomiasis, and filariasis. In India & other countries there is another demand for antimalarials because of the spread of drug resistance malaria. Moreover, malaria itself is effective in claiming lives each year than any other single infectious agent, the World Health Organization (WHO) has estimated that in 2010, there were 219 million documented cases of malaria. That year, between 660,000 and 1.2 million people died from the disease, with the exception of AIDS and tuberculosis. AIDS, since its discovery, it has caused nearly 30 million deaths as of 2009.[8] As of 2010, approximately 34 million people are living with HIV globally and still continuing. AIDS is considered a pandemic a disease outbreak which is present over a large area and is actively spreading. However, the enteric diseases claim the most lives each year of any disease complex, and unfortunately, the victims are mostly children. Sadly, the published breakthrough in exploiting the potential of the endophytic fungi as a source of important secondary metabolites by the pharmaceutical industries to obtain compounds of interest is still modest. To date there has been no one of the identified endophytic fungal isolates has had any industrial application as yet.[9] In 2002, Strobel who started it all said, 'efforts are underway by several pharmaceutical companies to determine the feasibility of making microbial taxol a commercial reality'. Eleven years later, we have no confirmation of taxol being commercially produced from its endophytic fungal source. Other drawbacks environmental degradation, loss of biodiversity, and spoilage of land and water also add to problems facing humanity, and each of these in turn can have health-related consequences. In this era discovery of new molecules really a tough job, financial support from governments & pharmaceutical industries are looking for immediate results for health problems.[10]

Plant selection[11]

It is important to understand the methods and rationale used to provide the best opportunities to isolate novel endophytic microorganisms as well as ones making novel bioactive products.

A specific rationale for the collection of each plant for endophyte isolation and natural-product discovery is used. Strobel and Daisy discussed the following methods of selection:

(i) Plants from unique environmental settings, especially those with an unusual biology, and possessing novel strategies for survival are seriously considered for study.

(ii) Plants that have an ethnobotanical history (use by indigenous peoples) that are related to the specific uses or applications of interest are selected for study. These plants are chosen either by direct contact with local peoples or via local literature.

(iii) Plants that are endemic, that have an unusual longevity, or that have occupied a certain ancient land mass, such as Gonwanaland, are also more likely to lodge endophytes with active natural products than other plants.

(iv) Plants growing in areas of great biodiversity also have the prospect of housing endophytes with great biodiversity. Just as plants from a distinct environmental setting are a promising source of novel endophytes and their compounds, so too are plants with an unconventional biology.

Isolation of Endophytes[12-14]

Endophytes can be isolated from various plant parts such as seeds, leaves and stems. The collected plants for studying endophytic communities should look apparently healthy and disease free plant, i.e. they do not display any visual symptoms of diseases, in order to minimize the presence of plant pathogenic and saprobic species, and to prevent the isolation of localized pathogenic endophytic microorganisms. The most important step for the isolation of endophytic fungi that reside in plant tissues is surface sterilization and the plant parts under investigation should be cut into small pieces to facilitate sterilization and isolation processes. Isolated Endophytic fungi from medicinal plants more likely exhibit pharmaceutical potentials. Plant endophytic fungi have been found in each plant species examined and it is estimated that there are over one million fungal endophytes existed in the nature. The secondary metabolites produced by endophytes associated with medicinal plants can be exploited for curing diseases.

Rajagopal and Suryanaryanan in 2000 isolated five endophyes from the leaves of Neem. Of these, four were sterile forms and one was *Fusarium avenaceum*. The result showed that colonization frequency percentage of endophytes was significantly higher in the monsoon season (49.6%) than during the dry seasons (24.3%).

Suryanarayanan and Rajagopal in 2000 isolated 963 isolates belonging to 36 fungal species from the bark tissues of ten tropical forest trees. Of these, four were Ascomycetes, one belonged to Coelomycetes and eleven were Hyphomycetes rests were sterile mycelia forms.

Raviraja in 2005 reported on the fungal endophytes in five medicinal plant species from Kudremukh Range Western Ghats of India. He isolated 18 species of endophytic fungi from bark, stem and leaf segments of five medicinal plant species growing within Kudremukh rang. pe in the Western Ghats of India. The dominant species were *Curvularia clavata, C. lunata*, *Callescens and F. oxysporum*. The higest species richness as well as frequency of colonization of endophytic fungi was found in the leaf segments rather than the stem and bark segments of the host plant species. The greatest number of endophytic fungal species were found within Callicarpa tomentosa (11 species), whereas *Lobelia nicotinifolia* harbored the lowest number of fungal endophytes (5 species). The study provides evidence the fungal endophytes are host and tissue specific to minimize the presence of plant pathogenic and saprobic species, and to prevent the isolation of localized pathogenic endophytic microorganisms. The most important step for the isolation of endophytic fungi that reside in plant tissues is surface sterilization and the plant parts under investigation should be cut into small pieces to facilitate sterilization and isolation processes.

Beneficiaries of Endophytes

1. There is growing awareness that the bioactive constituent profile of medicinal plants can be profoundly influenced by endophytic infection. Endophytes are microorganisms (typically fungi or bacteria) that infect plant tissues, often engaged in interactions with their hosts. These microbes can produce bioactive compounds themselves as that of plant producing, or can alter the metabolite profile produced by the plant. There is a great deal of variability in the type of bioactive compound that they producing, there are ample of possibilities to produce some novel kind of medicines, that will give break through results against some incurable diseases.

2. The pharmacological and medical concerns of new drugs are the toxicity of these prospective drugs to human tissues. Since the plant tissue where the endophytes exist is a eukaryotic system, it would appear that the secondary metabolites produced by the endophytes may have reduced cell toxicity; otherwise, host tissue may die. Thus, the host itself has naturally served as a selection system for microbes having bioactive molecules with reduced toxicity toward higher organisms.[15]

3. Methods to obtain bioactive compounds include the extraction from a natural source, the microbial production *via* fermentation, or microbial transformation. Extraction from natural sources presents some disadvantages such as dependency on seasonal, climatic and political features and possible ecological problems involved with the extraction, thus calling for innovative approaches to obtain such compounds.

4. There are reports that microbial endophytes mimic the bioactive compounds as produced by the plant itself thus making them a promising source of novel molecules. Hence, biotechnological techniques by using different microorganisms appear promising alternatives for establishing an inexhaustible, less time consuming, cost-effective renewable resource of high-value natural compounds.[16]

Antibacterial substances of endophytic origin

Emergence of multidrug-resistant (MDR) microorganism infections has generated considerable attention in recent decades. The problem of drug-resistant pathogens and infectious diseases are growing enormously. Antibiotic resistance is one of the greatest challenges facing modern medicine. New problems demand the discovered of novel antibiotics from fungal source. *Staphylococcus aureus* (MRSA) and Vancomycin-resistant *Enterococcus faecium* (VREF) have developed resistance toward current antibiotics. Antibiotics that lose their effectiveness for treating human disease through antibiotic resistance in this scenario old therapeutics must be replaced with new drugs .Metabolites produced from endophytes were reported to inhibit the growth of micro-organisms in host. The world recognized that fungal endophytes with novel metabolites biologically active against various resistant human pathogens.[17-18]

Antifungal activity[19]

Little-studied groups of fungi are considered to be potential sources of novel natural products for medicine and agriculture. The function of invasive fungal infections has increased significantly during cancer organ transplantation, chemotherapy and bone marrow transplantation. Endophytes are presumably ubiquitous in plants, with populations dependent on host species and location. During long research only a few numbers of antifungal agents are available for the treatment of various life threatening fungal infections. The search for new antifungal agents to overcome the growing human problems of drugs resistance in microorganisms is growing. Ongoing global efforts to discover new compounds from EF of

medicinal plants are yielding valuable results. Compounds produced by EF are being recognized as a versatile arsenal of antifungal agents.

Antiviral compounds[20]

The discovery of the potential antiviral compounds from EF is still in its infancy. There is only limited number of compounds reported as antiviral agents from fungal endophytes. The main limitation to antiviral compound discovery is most probably related to the absence of antiviral screening systems. Altertoxins was isolated from *Alternaria tenuissima* QUE1Se have HIV-1 virus activity. Several hundred endophytic fungal extracts were evaluated on HIV-1 replication in T-lymphocytes, and out of that four extracts are non-toxic and exhibited inhibitory with the range of 75% to 99% and out of three of these extracts were fractionated and fraction DB-2 completely inhibited HIV-1 replication at concentration that was also found it is not cytotoxic.

Anticancer substances[21-22]

Cancer is a group of diseases that can affect various organs of the body, and is characterized by the uncontrolled growth of abnormal cells and lead to death. It is a major cause of death worldwide. So far chemical inhibitors of carcinogenesis are mostly kinase inhibitors in the form of small molecules, antibodies and organic chemicals. The research and development of anticancer drugs is expensive which places a high financial burden on individual healthcare costs and government budgets. Medicinal plants are being reduced significantly due to over-harvesting, illegal exploitation and destruction of ecological habitat to conserve endangered medicinal plants and need to develop new alternative resources for harvesting anticancer compounds from plants. Anti-cancer drugs of natural products from EF are of are cheap and great value. The EF has been recognized as a possible useful source of bioactive secondary metabolites, especially in anticancer application. More than 60% of the anticancer and 70% of the antimicrobial drugs and compounds are currently in clinical use are natural products or natural product derivatives. There is an increase in need for a universal natural bioactive compound that can be used to suppress carcinogenic growth potential. Likewise, there are large numbers of anticancer agents produced by fungal endophytes inhabiting different medicinal plants.

Immune suppressive drugs[23]

Large number of novel immunomodulatory compounds has been isolated from endophytic fungi. Since long years intensive search is going for the identification of effective agents to

deal with immunological disorders related to mainly graft rejection and various other autoimmune diseases. The modulation of immune response with the aid of various bioactives in order to alleviate certain diseases is an active area of interest. There is a huge potential for production of these drugs from the alternative source and one of them could be endophytes. Microbial endophytes mimic the bioactive compounds as produced by the plant itself thus making them a promising source of novel compounds. *Entrophospora infrequens* isolated from *Nothapodytes foetida* (Wight) Sleumer and their chloroform (CEEI) and methanolic extracts showed delayed type hypersensitivity (DTH) reaction, and further screened for plaque forming cell phagocytic response and haemagglutination antibody titre (IgM and IgG).

Antidiabetic activity[24]

The nature has provided abundant natural resources which can be explored for their medicinal uses. Diabetes, often referred to by doctors as diabetes mellitus, describes a group of metabolic diseases in which the person has high blood glucose (blood sugar), either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both. Nowadays diabetes is growing as important serious public health problem, particularly in developed countries as a major threat to global development. We need to find natural and effective antidiabetic drugs. Several researchers are investigated antidiabetic and hypolipidemic activity of EF isolated antidiabetic peptide from EF Aspergillus awamori from medicinal plant Acacia nilotica and its purified compound was further identified using HPLC.

Antiarthritis and Anti-inflammatory activities[25-28]

Historically, the best resources for novel scaffolds have always been natural products. Immune system of our body plays a crucial role, as an overactive immune system may lead to certain fatal disease like arthritis. Rhematoid arthritis (RA) is chronic, inflammatory, and systemic autoimmune disease, symptoms include pain, swelling, and destruction of cartilage and bone as a result of which permanent disabilities occur but the exact etiology is unknown. Nowadays, researcher shows a great interest in those finding medicinal agents that are derived from microbial source because of the currently available drugs are either have certain side effects or are highly expensive. Endophytic fungi *Talaromyces wortmannii* isolated from medicinal plant *Aloe vera* and further seperated as several pure substances and out of that component C showed potent anti-inflammatory activity and this ability was gained for this metabolite is due to inhibition of IL-8 release by blocking NF-κB and AP-1 activation. Compound Mutolide was isolated from the coprophilous fungus *Lepidosphaeria*sp.

(PM0651419) and showed good anti-inflammatory activity and in future it can be used as druggable candidate for the treatment of inflammatory diseases like RA. The primary purpose for such broad-based screening of endophytic fungi was to identify novel inhibitors of pro-inflammatory cytokines involved in various immunological pathways. Ergoflavin a pigment isolated from EF which is growing on the leaves of an Indian medicinal plant *Mimosops elengi* (bakul) showed good anti-inflammatory activity. Endophytes alternative to chemical comounds which are shown excellent anti-inflammatory and various biological activities.

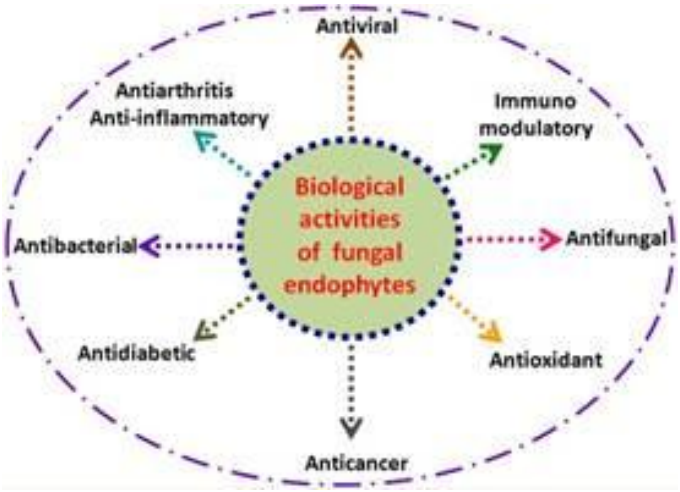

Figure 2: Biological activities of fungal endophytes.

CONCLUSION

Endophytic fungi can produce same or similar compounds originated from their host plants. Endophytic microorganisms are a huge reservoir of genetic diversity. Insights gained into endophyte-endophyte and plant-endophyte communication can be beneficial to biomedical community and the endophyte synthesized and secreted chemicals can be of importance to the society for the development of novel antibiotics against deadly pathogens. However, only a few numbers of antifungal agents are now available for the treatment of various life threatening fungal infections. There is an ongoing need for novel drugs that are highly effective in the treatment of cancer, drug resistant bacteria, and fungal infections. However, the application of microorganisms by the pharmaceutical and food industries to obtain different compounds of interest is still modest. Fungal endophytes represent an abundant and dependable source of novel antidiabetic compounds. There has been increasing interest in systematics, evolutionary biology, ecology and applied research of endophytic fungi. During the developments of modern biotechnology and taking advantage of genetic engineering,

metabolic technology and their better use to manipulate this important microbial resource, and to make benefit of mankind.

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