Asian Journal of Pharmacology and Toxicology 02 (03); 2014; 01-16 ISSN: 2347-3886.

Asian Journal of Pharmacology and Toxicology

REVIEW ARTICLE

Received on: 18-02-2014
Accepted on: 02-03-2014
Published on: 10-03-2014

S T Shukla
Shree Dhanvantary Pharmaceutical Analysis & Research Centre,Kim, Surat-394110, India.
Email: sunilshukla01@ymail.com

QR Code for Mobile users

Conflict of Interest: None Declared !

Endophytic microbes: A novel source for biologically/pharmacologically active secondary metabolites

S T Shukla[1*], P V Habbu[2], V H Kulkarni[2], K S Jagadish[3], Aprajita R Pandey[4], V N Sutariya[1]

[1*] Shree Dhanvantary Pharmaceutical Analysis & Research Centre,Kim, Surat-394110, India.
[2] Soniya Education Trust's College of Pharmacy,Dharwad-580 002, India.
[3] Department of Agricultural Microbiology, University of Agricultural Sciences, Dharwad-580005, India.
[4] Percos India Private Limited New Delhi – 110092, India.

ABSTRACT

Endophytes, microorganisms that reside internal tissues of all plant species, are a proven source of novel organic natural molecules, presumed to emphasizing the frontiers of drug discovery. Next to the clinically acknowledged antineoplastic agent, taxol, endophyte research has yielded potential drug, given compounds with antimicrobial, antioxidant, antiviral, antidiabetic, anti-alzheimer's disease and immunosuppressant etc. These evidences arises a hope to combat incurable diseases, drug resistance, other challenges related to human health. The potential of finding new drugs that may be effective candidates for treating newly developing diseases in humans is great. This paper focuses particularly need for new useful compounds from endophytes, the recent role of new disease, recent scenario of screening approach for novel drug and their pharmacological interest. It also describes these compounds by different functions, including some examples that illustrate the potential for human use.

KEYWORDS: Endophytes, Secondary metabolites, Pharmacology, New drugs, Fungi, Bacetria.

Cite this article as:
S T Shukla, P V Habbu, V H Kulkarni, K S Jagadish, Aprajita R Pandey, V N Sutariya
Endophytic microbes: A novel source for biologically/pharmacologically active secondary metabolites.
Asian Journal of Pharmacology and Toxicology 02 (03); 2014; 01-16.

1. INTRODUCTION

Endophytes are the proved rich sources of natural compounds, showing a variety of pharmacological and biological activities. Mutualism interaction between endophytes and host plants may result in fitness benefits for both partners (Kogel et al. 2006). The endophytes may provide protection and survival conditions to their host plant, is postulated to be a 'balanced antagonism'. Moreover, the plausibility of horizontal gene transfer hypothesis to producing a variety of pharmacologically active substances which, once isolated and characterized, may also have potential for use in industry for medicine (Strobel et al. 2003; Staniek et al. 2008). Endophytic microbes seem to fit perfectly like natural 'warehouse', only a small part of which we have been able to tap into so far. Approximately 300000 plant species are unexplored on the earth, are host to one or more endophytes, and the presence of biodiversity endophytes in huge number plays an important role on ecosystems with greatest biological diversity, considering that only a small amount of endophytes have been studied, recently, several research groups have been motivated to evaluate and elucidate the potential of these microorganisms for production of active molecules (Strobel 2003; Strobel et al. 2003). Endophytes are chemical synthesizer inside plants, in other words, they play a role as a selection system for microbes to produce pharmacologically active substances with low toxicity toward mammalians (Strobel 2003; Owen et al. 2004). Newman and Cragg in 2007 presented a list of all approved agents from 1981 to 2006, from which a maximum number of natural drugs are produced by endophytes. Endophytes provide a broad variety of active secondary metabolites with unique structure, including alkaloids, glycosides, benzopyranones, flavonoids, phenolic acids, quinones, steroids, xanthones, terpenoids, tetralones, and others (Tan et al. 2001; Kaul et al. 2012). The intent of this review is to provide the insights for usefulness of endophytic compounds in respect to medical applications, to motivate the researchers against the health challenges and scientific research.

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 (Assiri et al. 2013). 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. 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 (Cowman et al. 2001). 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 (Nayyar et al. 2012). AIDS, since its discovery, it has caused nearly 30 million deaths as of 2009 (UNAIDS 2010). As of 2010, approximately 34 million people are living with HIV globally and still continuing (UNAIDS 2011). AIDS is considered a pandemic a disease outbreak which is present over a large area and is actively spreading (Kallings et al. 2008). However, the enteric diseases claim the most lives each year of any disease complex, and unfortunately, the victims are mostly children (Kogle et al. 2006).

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. 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' (Strobel 2006). 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. It can be sustain by modifications in parental structures of chemical moiety, that is good but these are temporary options, are causing resistances in bacteria and also reducing financial support towards natural product discoveries. Natural product discoveries needed collaborative research, are matter of long time investments and also keen interest of researcher.

How endophytic research can be beneficiary?

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 (Strobel 2003).
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 (Strobel 2003).
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 (Bicas et al. 2009).
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 compound (Priti et la. 2009).
5. There are many evidences that bioactive compounds produced by endophytes could be alternative approaches for discovery of novel drugs, Stierle and his co-workers were heralded as very significant hope of using the endophytic fungus as a sustainable alternative source of Taxol (Firakova et al. 2007).
6. There has been a monotonic increase in the number of US patents filed on endophytic fungi producing important metabolites with different biological activities (Priti et al. 2009).
7. The recent 'genomics revolution' has given momentum to considerable progress in the development of new technologies in bioscience, addressing specifically the arena of natural product biosynthesis from endophytes. Whole-genome sequence mining (Lautru et al. 2005) and genome scanning as an alternative approach, providing an efficient way to discover natural product biosynthetic gene clusters without having the complete genome sequence (Zazopoulos et al. 2003; Wilkie et al. 2001).
8. Applications of endophytes in pharmaceutical industries include cost effective drug production, endophytes as drug source help us to conserve biodiversity and drug resistance as they are an alternate source of drugs.
9. Recently the biotransformation process of endophytes have received big attention as biocatalysts in the chemical transformation of natural products and drugs, due to their ability to modify chemical structures with a high degree of stereospecificity and to produce known or novel enzymes that facilitates the production of compounds of interest (Pimentel et al. 2011).
10. Isolation of endophytic fungi from medicinal and other plants may result in methods to produce biologically active agents for biological utilization on a large commercial scale as they are easily cultured in laboratory and fermentor instead of harvesting plants and affecting the environmental biodiversity**.**

Novel natural products and the organisms that make them offer opportunities for innovation in drug discovery. Exciting possibilities exist for those who are willing to venture into the wild and unexplored territories of the world to experience the thrill of engaging in the discovery of endophytes, their biology, and potential usefulness

Anticancer Compounds from endophytic sources

Cancer is a group of diseases characterized by unregulated growth and spread of abnormal cells, which can result in death if not controlled (Bicas et al. 2008). It has been considered one of the major causes of death worldwide: An estimated 12.7 million new cancer cases with 7.6 million deaths (around 13% of all deaths) in 2008. If recent trends in major cancers are seen globally in the future, the burden of cancer will increase to 22 million new cases each year by 2030. This represents

an increase of 75% compared with 2008. (Ferlay et al. 2010;Taechowisan et al. 2012). The recent drugs for cancer treatments show nonspecific toxicity to proliferating normal cells, possess severe side effects, and are not effective against many forms of cancer (Gangadevi et al. 2008). Thus, the cure of cancer has been enhanced mainly due to diagnosis improvements which allow earlier and more precise treatments (Pasut et al. 2009). The anticancer properties of several secondary metabolites from endophytes have been investigated recently. Following, some examples of the potential of endophytes on the production of anticancer agents are cited. The diterpenoid "Taxol" multi-billion dollar compound produced by the yew plant has generated more believe and interest than any other new drug since its discovery (Gangadevi et al. 2008; Pasut et al. 2009). This compound due to its unique mode of action interferes with the multiplication of cancer cells, interrupting their growth and spreading. USFDA (United States Food and Drug Administration) has approved Taxol for the treatment of advanced breast cancer, lung cancer, and refractory ovarian cancer (Cremasco et al. 2009). Taxol was firstly isolated from the bark of trees belonging to Taxus family (*Taxus brevifolia*), its most common source (Wani et al. 1971). Nevertheless, these trees are rare, slow growing, and produce small amount of Taxol, which explain its high price in the market when obtained by this natural source (Gangadevi et al. 2008). Besides, in the context of environmental degradation, the plant source has limited the supply of this drug due to the destructive collection of yew trees (Guo et al. 2008). The isolation of Taxol-producing endophyte *Taxomyces andreanae* has provided an alternative approach to obtain a cheaper and more available product *via* microorganism fermentation (Stierle et al. 1993). Another important drug for cancer is the alkaloid "Camptothecin" a potent antineoplastic agent which was firstly isolated from the wood of *Camptotheca acuminata* Decaisne (Nyssaceae) in China (Wall et al. 1966). Camptothecin and 10-hydroxycamptothecin are two important precursors for the synthesis of the clinically useful anticancer drugs, topotecan, and irinotecan (Uma et al. 2008). The anticancer properties of the microbial products Camptothecin and two analogues (9-methoxycamptothecin and 10-hydroxycamptothecin) were already reported. The products were obtained from the endophytic fungi *Fusarium solani* isolated from *Camptotheca acuminate* (Kusari et al. 2009b). Many reports have described other Camptothecin and its analogues producing endophytes (Sweta et al. 2010; Rehman et al. 2008; Amna et al. 2006, Puri 2005). Since then, endophytes have been included in many studies purposing new approaches for drug discovery. "Phenylpropanoids" have attracted much interest for medicinal use as anticancer, antioxidant, antimicrobial, anti-inflammatory, and immunosuppressive properties (Korkina et al. 2007). Despite the phenylpropanoids belong to the largest group of secondary metabolites produced by plants, reports showed the production of such compounds by endophytes. The endophytic *Penicillium brasilianum*, found in root bark of *Melia azedarach*, promoted the biosynthesis of phenylpropanoid amides (Fill et al. 2010). Likewise, two monolignol glucosides, coniferin and syringin, are produced not only by the host plant, but were also recognized by the endophytic *Xylariaceae* species as chemical signals during the establishment of fungus-plant interactions (Chapela et al. 1991). Koshino and his coworkers in 1988 characterized two phenylpropanoids and lignin from stromata of *Epichloe typhina* on *Phleum pretense*. "Lignans" are other kinds of anticancer agents originated as secondary metabolites through the shikimic acid pathwayand display different biological activities that make them interesting in several lines of research (Gordaliza et al. 2004). Although their molecular backbone consists only of two phenylpropane units (C6-C3), lignans show enormous structural and biological diversity, especially in cancer chemotherapy (Korkina et al. 2007). Some well-known alkaloids first reported an endophytic fungus *Alternaria* sp. isolated from the phloem of *Catharanthus roseus* by Guo et al. that had the ability to produce vinblastine in 1998. Later, Zhang et al. (2000) successfully discovered an endophytic *Fusarium oxysporum* from the pholem of *C. roseus* that could produce vincristine. Yang et al. also found an unidentified vincristine producing endophytic fungus from the leaves of *C. roseus* in 2004. The aryl tetralin lignans, such as podophyllotoxin, are naturally synthesized by *Podophyllum*sps., they are clinically relevant mainly due to their cytotoxicity and antiviral activities and also valued as the precursor to useful anticancer drugs like etoposide, teniposide, and etopophos phosphate (Kusari et al. 2009a; Kour et al. 2008). Another study showed a novel fungal endophyte, *Trametes hirsute*, that produces podophyllotoxin and other related aryl tetralin lignans with potent anticancer and properties (Puri et al. 2006). Novel microbial sources of Podophyllotoxin were reported from the endophytic fungi *Aspergillus fumigatus* Fresenius isolated from *Juniperus communis* L. Horstmann (Kusari et al 2009a), *Phialocephala fortinii* isolated from *Podophyllum peltatum* (Eyberger et al. 2006), and *Fusarium oxysporum* from *Juniperus recurva* (Kour et al. 2008).A new compound "Ergoflavin" from ergochrome class was explained as anticancer isolated from an

endophytic fungi growing on the leaves of an Indian medicinal plant *Mimusops elengi* family Sapotaceae (Deshmukh et al. 2009). "Secalonic acid D" a mycotoxin also belonging to ergochrome class, has shown potent anticancer activities. It was isolated from the mangrove endophytic fungus and observed high cytotoxicity on HL60 and K562 cells by inducing leukemia cell apoptosis (Zhang et al. 2009). Wagenaar and co-workers reported identification of three novel "cytochalasins", bearing antitumor activity from the endophyte *Rhinocladiella* sp. (Wagenaar et al. 2000). Extensive experiments identified these new compounds as 22-oxa-12-cytochalasins. "Torreyanic acid" is an unusual dimeric quinone isolated from the endophytic fungus *Pestalotiopsis microspora* from *T. taxifolia* and was proven to have selective cytotoxicity 5 to 10 times more potent in cell lines that are sensitive to protein kinase C agonists and causes cell death by apoptosis (Lee 1996). "Gliocladicillins A" and "B" were reported as effective antitumor agents *in vitro* and *in vivo*, since they induced tumor cell apoptosis and showed significant inhibition on proliferation of melanoma B16 cells implanted into immunodeficient mice (Chen et al. 2009). *Alternaria alternata*, an endophytic crude fungus fractions isolated from *Coffea Arabica* L., displayed moderate cytotoxic activity towards HeLa cells *in vitro*; in comparison with the dimethyl sulfoxide-(DMSO-) treated cells (Fernandes et al. 2009). Finally, many more other compounds with anticancer properties isolated from endophytic microbes were reported such as "cytoskyrins" (Brady et al. 2000), "rubrofusarin B" (Song et la. 2004), "phomoxanthones A" and "B" (Isaka et al. 2001), "photinides A-F" (Ding et al. 2009), and "(+)-epiepoxydon" (Klemke 2004).

Antimicrobial Compounds obtained from endophytes

Antimicrobial metabolites (Antibiotics) can be defined as low-molecular-weight organic compounds made by microorganisms to protect plant from outer invade, that are active at low concentrations against other microorganisms, and are the most bioactive natural products isolated from endophytes (Strobel et al. 2003, Guo et al. 2008). Endophytes are believed to carry out a resistance mechanism to overcome pathogenic invasion by producing secondary metabolites (Tan et al. 2001). So that, studies suggest a large number of antimicrobial compounds isolated from endophytes, belonging to several structural classes like alkaloids, peptides, steroids, quinines, terpenoids, phenols and flavonoids (Yu et al. 2010).

The novel antimicrobial metabolites from endophytes is now becoming an alternative option to overcome the increasing levels of drug resistance by human pathogens, the insufficient number of effective antibiotics against diverse bacterial species, and few new antimicrobial agents in development, probably due to relatively unfavorable returns on investment (Song et al. 2008). The antimicrobial compounds can be used not only as drugs for mankind but also as food preservatives in the control of food spoilage and food-borne diseases, a serious concern in the world food chain (Liu et al. 2008). The bioactive compound isolated from the culture extracts of the endophytic fungus *Xylaria* sp. YX-28 isolated from *Ginkgo biloba* L. was identified as "7-amino-4-methylcoumarin". The compound presented broad-spectrum inhibitory activity against several food-borne and food spoilage microorganisms and also suggested to be used as natural preservative in food (Liu et al. 2008). Many bioactive compounds, including antifungal agents, have been isolated from the genus *Xylaria* residing in different plant hosts, such as "sordaricin" with antifungal activity against *Candida albicans* (Pongcharoen et al. 2008); "multiplolides A and B" with activity against *Candida albicans* (Boonpong et al. 2001). Four antifungal "aliphatic compounds" were characterized from stromata of *E. typhina* on *P. pratense* (Koshino et al. 1989). Another strain F0010 of the endophytic fungus *Xylaria sp*. from *Abies holophylla* was characterized as a producer of "griseofulvin" ($C_{17}H_{17}ClO_6$), a spirobenzofuran antifungal antibiotic agent used for the treatment of human and veterinary animals mycotic diseases (Park et al. 2005). Cytosporone B and C were isolated from a mangrove endophytic fungus, *Phomopsis* sp. They inhibited two fungi *C. albicans* and *F. oxysporum* with the MIC value ranging from 32 to 64 $mg{\cdot}mL^{-1}$ (Huaug et al. 2008). Chaetomugilin A and D with antifungal activities were isolated from an endophytic fungus *C. globosum* collected from *Ginkgo biloba* (Qin et al. 2009). Chlorinatedmetabolites such as (−)-mycorrhizin A, (+)-cryptosporiopsin isolated from endophytic *Pezicula* strains were reported as strongly fungicidal and herbicidal agents, and to a lesser extent, as algicidal and antibacterial agents (Schulz et al. 1995). Likewise, two other new chlorinated benzophenone derivatives, "Pestalachlorides A" ($C_{21}H_{21}Cl_2NO_5$) and "B" ($C_{20}H_{18}Cl_2O_5$), from the plant endophytic fungus *Pestalotiopsis adusta*, proven to display significant antifungal activity against three plant pathogens *Fusarium culmorum, Gibberella zeae,* and *Verticillium albo-atrum* (Li et al 2008). The production of "Hypericin" ($C_{30}H_{16}O_8$), a naphthodianthrone derivative, and "Emodin" ($C_{15}H_{10}O_5$) believed to be the main precursor of hypericin, by the endophytic fungus isolated from an Indian medicinal plant, was reported. Both compounds demonstrated antimicrobial activity against several bacteria and fungi

(Kusari et al. 2008). An endophytic *Streptomyces* sp. from a fern-leaved grevillea (*Grevillea pteridifolia*) in Australia was described as a promising producer of novel antibiotics, "kakadumycin A" and "echinomycin". Kakadumycin A is structurally related to echinomycin, a quinoxaline antibiotic, and presents better bioactivity than echinomycin especially against Grampositive bacteria and impressive activity against the malaria parasite *Plasmodium falciparum* (Castillo et al. 2003). More than 50% of endophytic fungi strains residing in *Quercus variabilis* possessed growth inhibition against at least one pathogenic fungus or bacteria. *Cladosporium* sp., displaying the most active antifungal activity, was investigated and found to produce a secondary metabolite known as "Brefeldin A" ($C_{16}H_{24}O_4$), a lactone with antibiotic activity. Results showed brefeldin A to be more potent than the positive control in antifungal activity (Wang et al. 2007). Production of lipopeptide "pumilacidin", an antifungal compound, by *B. pumilus* isolated from cassava cultivated by Brazilian Amazon Indian tribes was described for the first time (de Melo et al. 2009). "Coronamycin", a novel peptide antibiotic produced by an endophytic fungi *Streptomyces* sp. isolated from *Monstera* sp., is active against *pythiaceous* fungi, the human fungal pathogen *Cryptococcus neoformans*, and the malaria parasite, *Plasmodium falciparum* (Ezra et al. 2004). The compounds "2-hexyl-3-methyl-butanodioic acid" and "cytochalasin D" were isolated from the endophytic fungus *Xylaria* sp. Isolated from *Brazilian Cerrado*, and presented antifungal activity (Cafeu et al. 2005). The polyketide "citrinin", produced by endophytic fungus *Penicillium janthinellum* from fruits of *Melia azedarach*, presented 100% antibacterial activity against *Leishmania* sp. (Marinho et al. 2005)..Among the 12 secondary metabolites produced by the endophytic fungi *Aspergillus fumigatus* CY018 isolated from the leaf of *Cynodon dactylon*, "fumigaclavine C", "fumitremorgin C", "asperfumoid", "physcion", and "helvolic acid" were shown to inhibit *Candida albicans* (Liu et al. 2004). Endophyte *Verticillium* sp. isolated from roots of wild *Rehmannia glutinosa* produced two compounds "2,6-Dihydroxy-2-methyl-7- (prop-1E-enyl)-1-benzofuran-3(2H)-one", reported for the first time, and "ergosterol peroxide" with good inhibition of the growth of three pathogens including *Verticillium* sp. (You et al. 2009). Other secondary metabolites with antimicrobial properties isolated from endophytic microbes were reported like "3-O-methylalaternin" and "altersolanol A" (Aly et al. 2008), "phomoenamide" (Rukachaisirikul et al. 2008), "phomodione" (Hoffman et al. 2008), "ambuic acid" (Li et al. 2001), "isopestacin", and "munumbicin A, B, C" and "D" (Castillo et al. 2002).

Endophytic isolates as antioxidant compounds

The importance of compounds bearing antioxidant activity lays in the fact that they are highly effective against damage caused by reactive oxygen species (ROSs) and oxygen-derived free radicals, which contribute to a variety of pathological effects, for instance, DNA damages, carcinogenesis, and cellular degeneration (Huang et al. 2007). Antioxidants have been considered promising therapy for prevention and treatment of ROS-linked diseases as cancer, cardiovascular disease, atherosclerosis, hypertension, ischemia/reperfusion injury, diabetes mellitus, neurodegenerative diseases (Alzheimer and Parkinson diseases), rheumatoid arthritis, and ageing (Valko et al. 2007). Many antioxidant compounds possess anti-inflammatory, antiatherosclerotic, antitumor, antimutagenic, anticarcinogenic, antibacterial, or antiviral activities in higher or lower level (Owen et al. 2000; Cozma et al. 2004; Halliwell et al. 1994; Mitscher et al 1996; Sala et al. 2002). Antioxidants are commonly found in medicinal plants, vegetables, and fruits. However, it has been reported that compounds from endophytes can be a potential source of novel natural antioxidants. Liu and coworkers (2007) evaluated the antioxidant activity of an endophytic *Xylaria* sp. isolated from the medicinal plant *Ginkgo biloba*. The results collected indicated that the methanol extract exhibited strong antioxidant capacity due to the presence of "phenolics" and "flavonoids" compounds among 41 identified compounds. Huang and coworkers (2007) investigated the antioxidant capacities of endophytic fungal cultures of medicinal Chinese plants and its correlation to their total phenolic contents. They suggested that the phenolic content were the major antioxidant constituents of the endophytes. "Pestacin" ($C_{15}H_{14}O_4$) and "isopestacin", 1,3-dihydro isobenzofurans, were obtained from the endophytic fungus *Pestalotiopsis microspora* isolated from a plant growing in the Papua New Guinea, *Terminalia morobensis* (Harper et al. 2003). Besides antioxidant activity, pestacin and isopestacin also presented antimycotic and antifungal activities, respectively. Pestacin is believed to have antioxidant activity 11 times greater than Trolox, a vitamin E derivative (Harper et al. 2003). Isopestacin possess antioxidant activity by scavenging both superoxide and hydroxy free radicals in solution, added to the fact that isopestacin is structurally similar to the flavonoids (Strobel et al 2002). Polysaccharides from plants and microorganisms have been extensively reported and considered as potent natural antioxidants (Chen et al. 2009; Kardosova et al. 2006; Luo et al. 2008; Sun et al. 2004). Liu and coworkers (2009a) reported, for the first time,

the capacity of endophytic microorganisms to produce polysaccharides with antioxidant. The bacterium endophyte *Paenibacillus polymyxa* isolated from the root tissue of *Stemona japonica* Miquel, a traditional Chinese medicine, produced "exopolysaccharides" that demonstrated strong scavenging activities on superoxide and hydroxyl radicals. "Graphislactone A", a phenolic metabolite isolated from the endophytic fungus *Cephalosporium* sp. IFB-E001 residing in *Trachelospermum jasminoides*, demonstrated to have free radical-scavenging and antioxidant activities *in vitro* stronger than the standards, butylated hydroxytoluene (BHT) and ascorbic acid, co assayed in the study (Song et al. 2005). For more detailed information on antimicrobial, antioxidant, and anticancer agents from microbial source, the references Firakova and coworkers (2007) and Newman and Cragg (2007) are recommended.

Endophytic immunosuppressive and immunomodulatory Compounds

Immunosuppressive drugs are used today to prevent allograft rejection in transplant patients, and in the future they could be used to treat autoimmune diseases such as rheumatoid arthritis and insulin-dependent diabetes. The endophytic fungus *Fusarium subglutinans*, isolated from *T. wilfordii*, produces the immunosuppressive but noncytotoxic diterpene pyrones subglutinols A and B (Klemke et al. 2004). Subglutinol A and B are equipotent in the mixed lymphocyte reaction (MLR) assay and thymocyte proliferation (TP) assay, with an IC50 of 0.1 μ*M*. In the same assay systems, the famed immunosuppressant drug cyclosporin A, also a fungal metabolite, was roughly as potent in the MLR assay and 104 more potent in the TP assay. Still, the lack of toxicity associated with subglutinols A and B suggests that they should be explored in greater detail as potential immunosuppressants (Klemke et al. 2004). Recently, *Colletotrichum dematium* isolated from *Pteromischum* sp. growing in tropical forest of Costa Rica produced novel antimycotic peptide collutelin A, also containing residues of Ile, Ser, Nmethyl- Val and beta-amino butyric acid in ratio of 3:2:1:1:1. Collutelin A exhibited strong immunosuppressive activity as it inhibited CD4 (+) T-cell activation of Interleukin 2 production; whereas cyclosporin A was moderate in same experiment (Ren et al. 2008). Although many other medicinal plants and their secondary metabolites have been screened for immunomodulatory activities, this activity is the first report for immunomodulatory activities of endophytic crude fractions from *Ocimum sanctum* Linn. This may be attributed the secondary metabolites of TRF-3 and TRF-6 which are yet to be explored (Madagundi et al. 2013).

Antiviral Compounds from endophytes

Another expanding use of products from endophytic fungi is the inhibition of viruses. Two novel human cytomegalovirus (hCMV) protease inhibitors, cytonic acids A and B, have been isolated from solid-state fermentation of the endophytic fungus *Cytonaema* sp. (Guo et al. 2000). It is apparent that the potential for the discovery of compounds having antiviral activity from endophytes is in its infancy. The main limitation to compound discovery to date is probably related to the absence of common antiviral screening systems in most compound discovery programs. "mellisol" and "1,8-dihydroxynaphthol 1-O-a-glucopyranoside" with activity against herpes simplex virus-type 1 (Pittayakhajonwut et al. 2005); An endophytic fungus *Pestalotiopsis theae* of an unidentified tree on Jianfeng Mountain, China, was capable of producing "Pestalotheol C" with anti-HIV properties (Li et al. 2008). The microbial flora characteristic of oak trees resulted in the isolation of a potentially valuable fungal specimen from the leaves of *Quercus coccifera*. This endophyte proved to be a synthesizer of Hinnuliquinone, a potent inhibitor of the HIV-1 protease (Singh et al. 2004). Four new Cyclohexadepsipeptides, Pullularins A–D, were isolated from the endophytic fungus *Pullularia* sp. BCC 8613. Pullularin A exhibited activities against the herpes simplex virus type 1and malaria parasite *Plasmodium falciparum* K1 (Isaka et al., 2007). Florke et al. (2006) reported anti-hepatitis C virus (HCV) activity of dihydroiso-coumarin *(*R)-(-)-mellein. It inhibits HCV protease with an IC50 value of 35 mM. This compound had been isolated from a number of endophytic fungi, such as *Pezicula livida*, *Plectophomella sp*., and *Cryptosporiop-sis malicoticis* (Krohn et al. 1997). A total of 81 Thai medicinal plant species collected from forests in four geographical regions of Thailand were examined for the presence of endophytic fungi with biological activity of 582 pure isolates obtained, 360 morphologically distinct fungi were selected for cultivation on malt Czapek broth and yeast extract sucrose broth, from which extracts were tested for biological activity. They also shown strong anti-viral activity against Herpes simplex virus type 1 was observed in 40 isolates (IC_{50} of 0.28–50 μg ml^{-1}) (Wiyakrutta et al. 2004). The aryl tetralin lignans, such as podophyllotoxin and its analogs showed antiviral and cytotoxicity activities and used as the precursor for many drugs for treatment cancer and viral infections, like etoposide, teniposide, and etopophos phosphate. Podophyllotoxin was found to produced by many endophytes: *Trametes hirsute, Aspergillus fumigates, Phialocephala fortinii,* and *Fusarium oxysporum* (Eyberger et al. 2006, Puri et al. 2006, Kour

et al. 2008, Kusari et al. 2009a). Arunpanichlert et al. (2010) investigated the secondary metabolites of endophytic fungus *Penicillium sclerotiorum*, and isolated the known compound (+)-Sclerotiorin. (+)-Sclerotiorin was evaluated for its inhibitory effect on human immunodeficiency virus HIV-1 integrase and protease, they found to exhibit anti-HIV-1 integrase and protease activities with IC50 values of 45.88 and 198.41μM, respectively. The endophyte *Phomopsis* sp., isolated from *Musa acuminata*, was found to produce hexaketide γ-lactones. Oblongolides Z, and 2-deoxy-4α-hydroxyoblongolide X showed anti-herpes simplex virus type 1 (HSV-1) activity and also having cytotoxic activity against KB, BC, NCI H187, and nonmalignant Vero cell lines (Bunyapaiboonsri et al. 2010). Pestaloficiols F-L (1-7), new isoprenylated chromone derivatives including one heterodimer (7), have been isolated from a endophytic fungus *Pestalotiopsis fici*. Compounds 1-3, 5, and 6 displayed inhibitory effects on HIV-1 replication in C8166 cells, whereas 4-7 showed cytotoxic activity against the human tumor cell lines HeLa and MCF7 (Liu et al. 2009b). One more novel compound, chlorinated pupukeananes possessing a unique spiroketal peroxide skeleton, named chloropupukeanolides A, were also isolated from endophytic *Pestalotiopsis fici* having same HIV-1 replication inhibitory action *in vitro* for C8166 cells with an IC50 value of 6.9 μM, and cytotoxic against human cancer cell lines HeLa, MCF-7 and MDA-MB-231 with IC50 values of 16.9, 15.5 and 15.9μM, respectively (Liu et al. 2010). Zhang et al. (2011) reported isolation of Emerimidine A, and B from culture of endophytic fungus *Emericella* sp., both of them showed moderate inhibition to Influenza virus H1 N1 with IC50 values of 42.07 mg/ml and 62.05 mg/ml respectively.

Anti-inflammatory action of endophytic content

Anti-inflammatory refers to the property of a substance or treatment that reduces inflammation. Ergoflavin, a pigment from an endophytic fungus, growing on the leaves of an Indian medicinal plant *Mimosops elengi* Bakul. A dimeric xanthene linked in position 2, belongs to the compound class called ergochromes, ergoflavin showed good anti-inflammatory and anticancer activities (Deshmukh et al. 2009). 3-methylcarbazoles was obtained from culture of an endophytic Streptomyces sp. LJK109, isolated from the root tissues of *Alpinia galanga*. It was the major anti-inflammatory component, suppresses macrophage production of the inflammatory mediators NO, PGE2, TNF-α, IL-1β, IL-6 and IL-10 in a dose-dependent manner (Taechowisan et al. 2012). The methanolic extract of the endophytic mycelium from Rhizoctonia sp. showed remarkable anti-inflammatory activity using a murine model of paw edema in mice. **(**De barros et al. 2011). Recent studies showed that chronic inflammation might be contributed to inflammation-associated cancer. Nuclear factor kappa B (NF-κB) is known to regulate diverse cellular processes including inflammation, immune response, differentiation, proliferation, apoptosis and cancer. The role of NF-κB activation pathway in acute inflammation and cell-survival, as well as its sustained activation in several cancer cases has been reported. Linking inflammation to tumor promotion and progression, so interfering NF-κB activation, and targeting NF-κB in chronic inflammatory diseases could reduce cancer incidence. NF-κB inhibitors "11β-methoxycurvularin, 11α-methoxycurvularin, Trans-dehydrocurvularin, and 1-chloro-2,4-dihydroxy-5-methoxy-7-methylanthraquinone" have been isolated from culture of *Penicillium* sp., an endophyte isolated from Egyptian plant *Limonium tubiflorum*, with IC50 values ranging from 1.6 to 10.1 μM for isolated compounds (Aly et al. 2011). Cyclopeptolide antibiotic HUN-7293, pestahivin (77), was identified from Pestalotiopsis sp. RF5890 (Itazaki et al. 1995). Which was reported as a naturally-occurring inhibitor of inducible cell adhesion and a lead for a new class of potential therapeutics for the treatment of chronic inflammatory disorders or autoimmune diseases, potently suppressed cytokine-induced expression of VCAM-1 on human endothelial cells (Foster et al. 1994; Hommel et al. 1996).

Endophytic metabolites reported for Alzheimer's disease

Alzheimer's disease (AD), also known in medical literature as Alzheimer disease, is the most common form of dementia. There is no cure for the disease, which worsens as it progresses, and eventually leads to death. Huperzine A (HupA), a lycopodium alkaloid isolated earlier from *H. serrata*, has attracted intense attention since its marked anticholinesterase activity was discovered by Chinese scientists (Liu et al. 1986a; Liu et al. 1986b). HupA has been marketed in China as a new drug for Alzheimer's disease (AD) treatment and currently used in the USA as a supplement for preventing further memory degeneration (Zangara 2003). ZT-1, the semi-synthetic derivative of HupA, is being developed as anti-AD new drug candidate both in China and in Europe (Wang et al. 2010, Ma et al. 2007). The another reported work is endophytic *Chaetomium globosum* JN711454 metabolites were isolated from healthy leaves of Egyptian medicinal plant Adiantum capillus-veneris collected showing first time inhibitory activity against butyrylcholinesterase, one of neuro hydrolase enzymes that play a major role in development of Alzheimer's disease (Selim et al. 2013). Moreover, an intriguing endophytic metabolite was reported capable of stimulating the *Trk* family of

tyrosine kinase receptors, leading to the activation of multiple signalling cascades, culminating in neuroregenerative effects, including neuronal survival and neurite outgrowth (Wilkie et al. 2001).

Endophytic compounds cardiac related actions.

Denoting some curious facts, two indole alkaloids, fumigaclavine-C and fumitremorgin-C from the culture of *Aspergillus fumigatus* (strain No.CY018), an endophytic fungus harboring inside the leaf of *Cynodon dactylon*. These alkaloids claimed for vasorelaxant effects on isolated rat thoracic aortic rings due to the blockage of L-type voltage-dependent calcium channels, activation of ATP-sensitive potassium channels and inhibition of Ca^{2+} release from intracellular Ca^{2+} stores. Therefore the results demonstrate that fumigaclavine C from the endophytic fungus has a potential capacity in vascular protection and thus may have therapeutic use in protection against cardiovascular disease (Hsiao et al. 2006). Other interesting report endophytic fungi were isolated from Digitalis to screen them for glycosides as have been found in the plant itself. A total of 35 fungal endophytes were isolated and screened for the production of secondary metabolites. After preliminary analysis by thin layer chromatography and HPLC chromatograms revealed the five fungal cultures produce glycoside digoxin, thus providing a novel, alternative and eco-friendly source for the production of such a pharmaceutically important and valuable drug (Kaul et al. 2012). *Pestalotiopsis* species were most dominant endophytic species isolated from four medicinal plants including *Terminalia arjuna, Terminalia chebula, Azadirachta indica*, and *Holarrhena antidysenterica*. 32 *Pestalotiopsis* species isolated from different parts of the medicinal plants were selected for the study. Among them fungal extracts screened for antihypertensive assay, five (TA-37, TA-60, TA-102, TA-103, and TC-320) showed a more than 60% inhibition of angiotensin-converting enzyme (Tejesvi et al .2008).

Oral insulin mimetic effect compound from endophytes

A nonpeptidal fungal metabolite (L-783,281) was isolated from an endophytic fungus (*Pseudomassaria* sp.) collected from an African rainforest near Kinshasa in the Democratic Republic of the Congo. This compound acts as an insulin mimetic but, unlike insulin, is not destroyed in the digestive tract and may be given orally. Oral administration of L-783,281 in two mouse models of diabetes resulted in significant lowering of blood glucose levels. These results may lead to new treatments for diabetes (Zhang et al. 1999).

Anti-tubercular Compounds from endophytes

The World Health Organization (WHO) estimates that currently 50 million people are infected and 1500 people die each hour from tuberculosis worldwide. After emergence and spread of M. tuberculosis resistant strains to multiple drugs, the search for new antimycobacterial agents is timely (WHO, 2008). The globe recognized medicinal plants as repository for fungal endophytes with metabolites containing novel molecular structure and biologically active against various human pathogenic diseases for potential use in modern medicine. Endophytic fungi from *Garcinia* sp. are good sources for exploring the possibility of new antimycobacterial drugs. Extract of endophytic fungi isolated from Thailand *Garcinia* plant species exhibited inhibition against M. Tuberculosis (Wiyakrutta et al., 2004). Phomoxanthone A and B isolated from the endophytic fungus *Phomopsis* sp. from *Garcinia* sp. plant in Thailand exhibited significant activity against M. tuberculosis (Isaka et al. 2001). Four diterpenes and a nor-diterpenoid, possessing unusual carbocyclic skeletons, were isolated from the West Indian gorgonian *Pseudopterogorgia elisabethae*. The structures and relative configurations of novel metabolites elisabethin D, elisabethin D acetate, 3-epielisabanolide, elisapterosin A, and elisapterosin B were elucidated. The tetracyclic carbon skeleton of the elisapterosins were undescribed and constitutes a new class of C (20) rearranged diterpenes displaying strong in vitro anti-tuberculosis activity (Rodriguez et al. 2000). The endophytic mitosporic *Dothideomycete* sp. LRUB20 isolated from Thai medicinal plant *Leea rubra* produced dothideopyrones A–D (1, 3, 4, and 5) (pyrone derivatives) together, with seven known compounds, including questin, asterric acid, methyl asterrate, sulochrin, and eugenitin, 6- hydroxymethyleugenitin and cis, trans-muconic acid and 3-nitropropionic acid, asterric acid and novel compound 2 hydroxymethyl-3-methylcyclopent-2-enone (synthetically known) and cis-2-hydroxymethyl-3-methylcyclopentanone inhibiting Mycobacterium tuberculosis H37Ra (Chomcheon et al. 2005).

Many endophytic fungi containing antitubercular metabolite had been isolated from tropical region of Thailand viz., *Eutypella scoparia* PSU-D44 an endophytic fungi isolated from *Garcinia atroviridis* in Southern Thailand had two new pimarane diterpenes and two new cytochalasins compound (Pongcharoen et al., 2006, Phongpaichit et al., 2006), *Phomopsis* sp. PSU-D15 isolated from *Garcinia dulcis*, contained three new metabolites as Phomoenamide, Phomonitroester and Deacetylphomoxanthone B (Rukachaisirikul et al. 2008), Hydronaphthalenones and Dihydroramulosin with eight known compounds; (R)-mellein, cis-4- hydroxymellein, 8-dihydroramulosin , 6- hydroxyramulosin, griseofulvin, 3-(2-hydroxypropyl)

benzene-1,2-diol, desoxybostrycin and austrocortinin from endophytic fungi PSU-N24 isolated from *Garcinia nigrolineata*, showed antimicrobial, antimalarial and antimycobacterial activities (Sommart et al, 2008). *Cladonia arbuscula* endophytic fungi isolated from *Vaccinium myrtillus* and endophytes isolated from *Carlina vulgaris, Empetrum nigrum* and *Vaccinium vitis-idaea* showed inhibition against *M. tuberculosis* (Gordien et al., 2010). *Muscodor crispans* is being recently described as novel endophytic fungus of *Ananas ananassoides* (Wild Pineapple) grown in Bolivia having potential to inhibit drug resistant strain of *M. tuberculosis*. It has a mixture of volatile organic compounds (VOC's) as ester- propanoic acid, 2-methyl-, methyl ester; propanoic acid, 2-methyl-; 1-butanol, 3-methyl-;1- butanol, 3-methyl-, acetate; propanoic acid, 2-methyl-,2-methylbutyl ester; and ethanol (Mitchell et al. 2010).

Endophytic metabolites for Rare diseases

A rare disease, also referred to as an orphan disease, is any disease that affects a small percentage of the population. Most rare diseases are genetic, and thus are present throughout the person's entire life, even if symptoms do not immediately appear. Many rare diseases appear early in life, and about 30 percent of children with rare diseases will die before reaching their fifth birthday. Trypanothione reductase is an enzyme involved in the protection of *Trypanosoma* and *Leishmania* species come under rare diseases, are considered to be a validated drug target. The endophytic fungus Alternaria sp. (UFMGCB55) and *Cochliobolus* sp. (UFMGCB-555) were isolated from the plant *Trixis vauthieri* DC (Asteraceae), and *Piptadenia adiantoides* J.F. Macbr (Fabaceae) respectively, known to contain trypanocidal compounds. The isolated compounds cochlioquinone A and isocochlioquinone A are the first in its class to have shown TR inhibitory activity, opening new perspectives for the design of more effective derivatives to treat severe rare diseases (Campos et al. 2008; Cota et al. 2008). Zikmundova and coworkers (2002) reported an endophytic fungus isolated from the roots and shoots of *Aphelandra tetragona*, capable to transform benzoxazinones, 2-benzoxazolinone and 2-hydroxy-1,4-benzoxazin-3-one into new compound named as "3,4-dimethyl-2-(4-hydroxy-3,5-dimethoxyphenyl)-5-methoxy tetrahydrofuran", which showed trypanocidal activity similar to its natural corresponding precursor against the causative agent (*Trypanosoma cruzi*.) of Chagas disease.

Reported other pharmacological actions from endophytes

Endophytic fungi are also known as producers of diverse metabolites of pharmacological interest. Endophytic mycelium from Rhizoctonia sp. also shows **antinociceptive** activities rather than anti-inflammatory in mice **(**De barros et al. 2011) and other important denotation for a **neuroleptic** compound production from endophytic fungi by the steriosective kinetic biotransformation process. Thioridazin a penothiazine used for the treatment of schizophrenia and other psychiatric disorders, Thioridazin is transformed to thioridazine-2-sulphoxide, which undergoes subsequent oxidation to sulphones (thioridazine-2-sulphon), both metabolites considered pharmacologically active (Borges et al. 2007). A novel enzyme from endophytic bacterium *Paenibacillus polymyxa* EJS-3 was showed a significant **anticoagulant** effect *in-vitro* method, isolated from tissues of *Stemona japonica* (Blume) Miq, a Chinese traditional medicine (Lu et al. 2010). Endophytic crude extract from *Ocimum sanctum* Linn shown **hepatoprotective** effect and antioxidant on rat model (Shukla et al. 2012; Madagundi et al. 2013). Yang et al. (2010) investigated an endophytic *Phomopsis* sp., isolated from the stem of the mangrove tree *Excoecaria agallocha* and reported isolation of Phomopsis-H76 A, B and C from culture filtrate. Phomopsis-H76 A was found to induce **formation of ectopic vessels** in the **subintestinal vessel plexus (SIV)**, whereas Phomopsis-H76 C was found to **inhibit blood vessel formation.** An endophytic *Streptomyces* sp. (AC-2), isolated from a traditional Chinese medicine plant *Cistanche deserticola* Y. C. Ma, produced **tyrosol**. This compound can **promote an increase of intracellular cAMP** special on GPR12 transfected cells, such as CHO and HEK293, might be a new possible ligand for GPR12 (Lin et al. 2008). RES-1214-1 and RES 1214-2, being non-peptide **endothelin antagonists**, were isolated from Pestalotiopsis sp., are selectively inhibited ET-1binding to endothelin type A receptor (ETA receptor) with IC50 values of 1.5 and 20 μM, respectively (Ogawa et al. 1995). The endophytic fungi were isolated from leaves, root and stem of *Calotropis gigantea, Azadirchta Indica, Ocimum tenuifloram* and *Lantana camara* reported producing **Tyrosinase**, a known enzyme for the **production of melanin**, which is distinguished for the hydroxylation of a monophenol and conversion of o-diphenol to o- quinone. This enzyme is essential for pigmentation, important factors in wound healing and primary immune response (Zaidi et al. 2013). Zhou and his co-workers (2004) screened a few **diosgenin**-producing endophytic fungi from *Paris polyphylla* var. *yunnanensis.* diosgenin is used for the commercial **synthesis of cortisone, pregnenolone, progesterone,** and other steroid products (Cao et al. 2007). Endophytic fungi isolated from *Vinca minor*

produce **vincamine**, which is used in the pharmaceutical industry as a **cerebral stimulant and vasodilator** (Yin et al. 20011). An endophytic fungus from *Hypericum perforatum* that produces **hypericin**, which shows **antidepressant activity**, is due to the **inhibition of reuptake of certain neurotransmitters** and also has some **affinity for NMDA receptors** (Kusari et al. 2008).

CONCLUSION:

Endophytes have proven to be rich sources of novel natural compounds with a wide-spectrum of pharmacological active compounds with potential for exploitation in a wide variety of medical, agricultural, and industrial arenas. Endophytes are a poorly investigated group of microorganisms that represent secondary metabolites having an immense impact on modern medicine, since about 40% of prescription drugs are based on them. Most of the plants resist invading plant pathogens in part through the production of antimicrobial compounds; in some cases these compounds may be the product of the plant's associated microorganisms. Screening such plants for endophytic isolation yielded novel and interesting microbes. This provided a lead-directed approach in screening endophytes from medicinally used plants, as a source for new therapeutic leads. But, the problems facing the future of endophytes biology and natural product discovery are environmental degradation, loss of biodiversity, the rapid diminishment of rainforests and disappearance of medicinal plants, which hold the greatest potential resource for acquiring novel microorganisms and their products. Research priority has increased towards endophytes, as desertion of any plant species will also diminish the entire suite of associated potential endophytes. Thus we can say that, empowering biological research for natural products is crucial option to fight against the various life-threatening diseases along with various industrial applications.

ACKNOWLEDGMENT

The authors are thankful to the Principal, Soniya Education Trust's College of Pharmacy, Dharwad, for providing the necessary digital library facilities for study. We thanks to Department of Agricultural Microbiology, University of Agricultural Sciences, Dharwad, is also acknowledged for providing library facilities during the study. And also thanks full to Shree Dhanvatary Pharmacy College, & Shree Dhanvantary pharmaceutical Research Centre's managing authority to motivate us for research work.

2. REFERENCES

1) Aly AH, Edrada-Ebel R, Wray V et al. (2008) Bioactive metabolites from the endophytic fungus *Ampelomyces* sp. isolated from the medicinal plant *Urospermum picroides*," Phytochemistry 69(8):1716–1725.
2) Aly AH, Debbab A, Clements C, Ebel RAE, Orlikova B, Diederich M, et al. (2011) NF kappa B inhibitors and antitrypanosomal metabolites from endophytic fungus *Penicillium* sp. isolated from *Limonium tubi-florum*. Bioorganic and Medicinal Chemistry 19:414–421.
3) Amna T, Puri SC, Verma V et al. (2006) Bioreactor studies on the endophytic fungus entrophospora infrequens for the production of an anticancer alkaloid camptothecin. Canadian Journal of Microbiology 52(3):189–196
4) Anti-tuberculosis drug resistance in the world: Fourth global report (2008) The World Health Organization/International Union against Tuberculosis and Lung Disease (WHO/UNION) Global project on Anti-tuberculosis Drug resistance Surveillance 2002-2007). Geneva (WHO/HTM/TB. 2009.422).
5) Arunpanichlert J, Rukachaisirikul V, Sukpondma Y, Phongpaichit S, Tewtra-kul S, Rungjindamai S, et al. (2010) Azaphilone and isocoumarin derivatives from the endophytic fungus *Penicillium sclerotiorum* PSU–A13. Chemical and Pharmaceutical Bulletin 58:1033 1036.
6) Assiri A, McGeer A, Perl TM, Price CS, Al Rabeeah AA, Cummings DAT, et al (2013) Hospital outbreak of Middle East Respiratory Syndrome Coronavirus. N Engl J Med. doi/full/10.1056/NEJMoa1306742
7) Bicas JL, Barros FCC, Wagner R, Godoy HT, Pastore GM (2008) Optimization of *R*-(+)-*α*-terpineol production by the biotransformation of *R*-(+)-limonene. Journal of Industrial Microbiology and Biotechnology 35(9):1061–1070
8) Bicas JL, Dion´ısio AP, Pastore GM (2009) Bio-oxidation of terpenes: an approach for the flavor industry. Chemical Reviews 109(9):4518–4531
9) Boonphong S, Kittakoop P, Isaka M, Pittayakhajonwut D, Tanticharoen M, Thebtaranonth Y (2001) Multiplolides A and B, new antifungal 10-membered lactones from *Xylaria Multiplex*. Journal ofNatural Products 64(7):965–967
10) Borges KB, Borges WDS, Pupo MT, Bonato PS (2007) Endophytic fungi as models for the stereoselective biotransformation of thioridazine. Appl Microbiol Biotechnol 77;(3):669-674 DOI 10.1007/s00253-007-1171-x
11) Brady SF, Singh MP, Janso JE, Clardy J (2000) Cytoskyrins A and B, new BIA active bisanthraquinones isolated from an endophytic fungus. Organic Letters 2(25):4047–4049
12) Bray F, Jemal A, Grey N, Ferlay J, Forman D (2012) Global cancer transitions according to the Human Development Index (2008-2030): a population based study. Lancet Oncol doi:10.1016/S1470-2045(12)70211-5
13) Bunyapaiboonsri T, Yoiprommarat S, Srikitikulchai P, Srichomthong K, Lumyong S (2010) Oblongolides from the endophytic fungus *Phomopsis* sp. BCC 9789. Journal of Natural Products 73:55–59
14) Cafˆeu MC, Silva GH, Teles HL et al. (2005) Antifungal compounds of *Xylaria* sp. an endophytic fungus isolated from *Palicourea marcgravii* (Rubiaceae). Quimica Nova 28(6):991–995.
15) Campos FF, Rosa LH, Cota BB, Caligiorne RB, Rabello AL, Alves TM et al. (2008) Leishmanicidal metabolites from Cochliobolus sp., an endophytic fungus isolated from Piptadenia adiantoides (Fabaceae). Plos Negl Trop Dis 2(12):e348. doi:10.1371/journal.pntd.0000348. Epub 2008 Dec 16.
16) Cao X, Li J, Zhou L, Xu L, Li J, Zhao J (2007) Determination of diosgenin content of the endophytic fungi from *Paris polyphylla* var. *yunnanensis* by using an optimum ELISA. Natural Product Research and Development 19:1020-1023.

17) Castillo U, Harper JK, Strobel GA et al. (2003) Kakadumycins, novel antibiotics from *Streptomyces* sp. NRRL 30566, an endophyte of *Grevillea pteridifolia*. FEMS Microbiology Letters 224(2):183–190
18) Castillo UF, Strobel GA, Ford EJ et al. (2002) Munumbicins, wide-spectrum antibiotics produced by *Streptomyces* NRRL 30562, endophytic on *Kennedia nigriscans*. Microbiology 148(9):675–685.
19) Chapela IH, Petrini O, Hagmann L (1991) Monolignol glucosides as specific recognitionmessengers in fungus-plant symbioses. Physiological and Molecular Plant Pathology, 39(4):289–298
20) Chen Y, Guo H, Du Z, Liu XZ, Che Y, Ye X (2009) Ecology-based screen identifies new metabolites from a Cordyceps-colonizing fungus as cancer cell proliferation inhibitors and apoptosis inducers. Cell Proliferation 42(6):838–847.
21) Chomcheon P, Wiyakrutta S, Sriubolmas N,Ngamrojanavanich N, Isarangkul D. Kittakoop P (2005). 3-Nitropropionic acid (3-NPA), a potent antimycobacterial agent fromendophytic fungi: is 3-NPA in some plants produced by endophytes? J Nat Prod 68:1103-1105
22) Cota BB, Rosa LH, Caligiorne RB, Rabello AL, Almeida Alves TM, Rosa CA, Zani CL. (2008) Altenusin, a biphenyl isolated from the endophytic fungus *Alternaria* sp. inhibits trypanothione reductase from *Trypanosoma cruzi*. FEMS Microbiol Lett 285(2):177-182 doi: 10.1111/j.1574-6968.2008.01221.x. Epub 2008 Jun 28.
23) Cowman AF, Duraisingh MT (2001) An old enemy, a new battle plan Perspectives on combating drug-resistant malaria. EMBO reports 2:77-79 doi:10.1093/embo-reports/kve032
24) Cozma LS (2004) The role of antioxidant therapy in cardiovascular disease. Current Opinion in Lipidology 15(3):369–371
25) Cremasco MA, Hritzko BJ, Wang NHL (2009) Experimental purification of paclitaxel from a complex mixture of taxanes using a simulated moving bed. Brazilian Journal of Chemical Engineering 26(1):207–218
26) De Barros BS, Da Silva JP, De Souza FJN, Agra IK, De Almeida BF, Albuquerque ED, et al. (2011) Methanol extract from mycelium of endophytic fungus Rhizoctonia sp. Induces antinociceptive and anti-inflammatory activities in mice. J Nat Med 65(3-4):526-31 doi: 10.1007/s11418-011-0534-x.
27) De Melo FMP, Fiore MF, deMoraes LAB et al. (2009) Antifungal compound produced by the cassava endophyte *Bacillus pumilus* MAIIIM4A. Scientia Agricola 66(5):83–592
28) Deshmukh SK, Mishra PD, Kulkarni AA et al. (2009) Anti-inflammatory and anticancer activity of ergoflavin isolated from an endophytic fungus. Chemistry and Biodiversity 6(5):784–789
29) Ding G, Zheng Z, Liu S, Zhang H, Guo L, Che YY (2009) Photinides A-F, cytotoxic benzofuranone-derived *γ*-lactones from the plant endophytic fungus *Pestalotiopsis Photiniae.* Journal of Natural Products 72(5):942–945
30) Eyberger AL, Dondapati R, Porter JR (2006) Endophyte fungal isolates from *Podophyllum peltatum* produce podophyllotoxin. Journal of Natural Products 69(8):1121–1124.
31) Ezra D, Castillo UF, Strobel GA et al. (2004) Coronamycins, peptide antibiotics produced by a verticillate *Streptomyces* sp. (MSU-2110) endophytic on *Monstera* sp. Microbiology150(4):785–793
32) Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr, accessed on day/month/year.
33) Fernandes MD, Silva TC, fenning LH et al. (2009) Biological activities of the fermentation extract of the endophytic fungus *Alternaria alternata* isolated from *Coffea arabica* L. Brazilian Journal of Pharmaceutical Sciences 45(4):677–685
34) Fill TP, da Silva BF, Rodrigues-Fo E (2010) Biosynthesis of phenylpropanoid amides by an endophytic *penicillium brasilianum* found in root bark of *Melia azedarach*. Journal of Microbiology and Biotechnology 20(3):622–629
35) Firakova S, Sturdıkova M, Muckova M (2007) Bioactive secondary metabolites produced by microorganisms associated with plants. Biologia 62(3):251–257
36) Flörke U, Krohn K, Zia-Ullah, Hussain H (2006) An orthorhombic modification of (R)-(-)-8 hydroxy-3-methyl-3,4-dihydro-1H-2benzopyran-1-one[(R)-(-)-mellein]. Acta Crystallographica E 62:03539–03541.
37) Foster CA, Dreyfuss M, Mandak B, Merngassner JG, Naegeli HU, Nussbaumer A, et al. (1994) Pharmacological modulation of endothelial cell-associated adhesion molecule expression: implications for future treatment of dermatological diseases. J Dermatol 21:847–854
38) Gangadevi V, Muthumary J (2008) Taxol, an anticancer drug produced by an endophytic fungus *Bartalinia robillardoides* Tassi, isolated froma medicinal plant, *Aegle marmelos* Correaex Roxb. World Journal of Microbiology and Biotechnology 24(5):717–724
39) Global Report Fact Sheet. *UNAIDS*. 2010. (07/07/10)
40) Gordaliza M, Garc´ıa PA, Miguel JM, Corral, Castro MA, G´omez-Zurita MA (2004) Podophyllotoxin: distribution, sources, applications and new cytotoxic derivatives. Toxicon 44(4):441–459
41) Gordien AY, Gray A, Ingleby K, Franzblau SG, Seidel V (2010) Activity of scottish plant, lichen and fungal endophytes extracts against *Mycobacterium aurum* and *Mycobacterium tuberculosis*. Phytother Res 24(5):692-698.
42) Guo B, Wang Y, Sun X, Tang K (2008) Bioactive natural products from endophytes: a review. Applied Biochemistry and Microbiology 44(2):136–142
43) Guo B, Dai J, Ng S, et al. (2000) Cytonic acids A & B: novel tridepside inhibitors of hCMV protease from the endophytic fungus *Cytonaema* species. J Nat Prod 63:602–604.
44) Guo B, Li H, Zhang L (1998) Isolation of the fungus producing vinblastine. Journal of Yunnan University 20:214-215.
45) Halliwell B (1994) Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? The Lancet 344(8924):721–724
46) Hasiao YM, Yong CS, Ying YM, Ji-hong J, Ren-xiang T, Lan L (2006) Endophytic fungle metabolites Fumifaclavine C causes relaxation of isolated rat aortic rings. Planta Med 72:387 392 doi: 10.1055/s-2005-916235
47) Harper JK, Arif AM, Ford EJ et al. (2003) Pestacin: a 1,3-dihydroisobenzofuran from *Pestalotiopsis microspora* possessing antioxidant and antimycotic activities. Tetrahedron 59(14):2471–2476.
48) Hoffman AM, Mayer SG, Strobel GA et al. (2008) Purification, identification and activity of phomodione, a furandione from an endophytic *Phoma species*. Phytochemistry 69(4):1049–1056
49) Hommel U, Weber HP, Oberer L, Naegeli HU, Oberhauser B, Foster CA (1996) The 3D structure of a natural inhibitor of cell adhesion molecule expression. FEBS Lett 379:69–73
50) Huang WY, Cai YZ, Xing J, Corke H, Sun M (2007) A potential antioxidant resource: endophytic fungi from medicinal plants. Economic Botany 61(1):14–30
51) Huang Y, Wang J, Li G, Zheng Z, Su ZW (2001) Antitumor and antifungal activities in endophytic fungi isolated from pharmaceutical plants *Taxus mairei, Cephalataxus fortune* and *Torreya grandis*. FEMS Immunology and Medical Microbiology 31(2):163-167
52) Huang Z, Cai X, Shao C et al. (2008) Chemistry and weak antimicrobial activities of phomopsins produced by mangrove

endophytic fungus *Phomopsis* sp. ZSU-H76. Phytochemistry 69(7):1604–1608

53) Isaka M, Jaturapat A, Rukseree K, Danwisetkanjana K, Tanticharoen M, Thebtaranonth Y (2001) Phomoxanthones A and B, novel xanthone dimers from the endophytic fungus Phomopsis species. J Nat Prod 64(8):1015-1018
54) Isaka M, Berkaew P, Intereya K, Komwijit S, Sathitkunanon T (2007) Antiplasmodial and antiviral cyclohexadepsipeptides from the endophytic fungus Pullularia sp. BCC 8613. Tetrahed, 63(29):6855-60.
55) Itazaki H, Fujiwara T, Sato A, Kawamura Y, Matsumoto Koichi (1995) Pestahivin and derivatives manufacture with Pestalotiopsis for HIV inhibitors. Japan Pat 07109299, CA, 123:110270d
56) Kallings LO (2008) The first postmodern pandemic: 25 years of HIV/AIDS. J Intern Med 263(3):218–43 doi:10.1111/j.1365-2796.2007.01910.x.PMID 18205765.
57) Kardosova A Machov´a E (2006) Antioxidant activity of medicinal plant polysaccharides. Fitoterapia 77(5):367–373
58) Kaul S, Ahmed M, Zargar K, Sharma P, Dhar MK (2012) Prospecting endophytic fungal assemblage of *Digitalis lanata* Ehrh. (foxglove) as a novel source of digoxin: a cardiac glycoside doi 10.1007/s13205-012-0106-0
59) Klemke C, Kehraus S, Wright AD, K¨onig GM (2004) New secondary metabolites from the marine endophytic fungus *Apiosporamontagnei*. Journal of Natural Products 67(6):1058–1063.
60) Kogel KH, Franken P, H¨uckelhoven R (2006) Endophyte or parasite—what decides? Current Opinion in Plant Biology 9(4):358–363
61) Korkina LG (2007) Phenylpropanoids as naturally occurring antioxidants: from plant defense to human health. Cellular and Molecular Biology 53(1):15–25
62) Koshino H, Yoshihara T, Sakamura S, Shimanuki T, Sato T, Tajimi A (1989) Novel C-11 epoxy fatty acid from stromata of *Epichloe typhina* on *Phleum pretense*. Agricultural Biology and Chemistry 53:2527–2528
63) Koshino H, Terada SI, Yoshihara T et al. (1988) Three phenolic acid derivatives from stromata of *Epichloe typhina* on *Phleum pretense*. Phytochemistry 27(5):1333–1338
64) Kour A, Shawl AS, Rehman S et al. (2008) Isolation and identification of an endophytic strain of *Fusarium oxysporum* producing podophyllotoxin from *Juniperus recurva*. World Journal of Microbiology and Biotechnology 24(7):1115–1121
65) Krohn K, Bahramsari R, Florke U, Ludewig K, Kliche-Spory C, Michel A, et al. (1997) Dihydroisocoumarins from fungi: Isolation, Structure elucidation, circular dichroism and biological activity. Phytochemistry 45:313–320.
66) Kusari S, Lamsh¨oft M, Spiteller M (2009a) *Aspergillus fumigates* Fresenius, an endophytic fungus from *Juniperus communis* L.Horstmann as a novel source of the anticancer pro-drug deoxypodophyllotoxin. Journal of Applied Microbiology 107(3):1019–1030
67) Kusari S, Lamsh¨oft M, Z¨uhlke S, Spiteller M (2008) An endophytic fungus from *Hypericum perforatum* that produces hypericin (2008) Journal of Natural Products 71(2):159–162
68) Kusari S, Z¨uhlke S, Spiteller M (2009b) An endophytic fungus from *Camptotheca acuminata* that produces camptothecin and analogues. Journal of Natural Products 72(1):2–7
69) Lautru S, Deeth RJ, Bailey LM, Challis GL (2005) Discovery of a new peptide natural product by *Streptomyces coelicolor* genome mining. Nature chemical Biology 1:265-269 doi:10.1038/nchembio731
70) Lee JC, Strobel GA, Lobkovsky E, Clardy J (1996) Torreyanic acid: a selectively cytotoxic quinone dimer from the endophytic fungus *Pestalotiopsis microspora.* Journal of Organic Chemistry 61(10):3232–3233
71) Li E, Jiang L, Guo L, Zhang H, Che Y (2008) Pestalachlorides A-C, antifungal metabolites from the plant endophytic fungus *Pestalotiopsis adusta*. Bioorganic and Medicinal Chemistry 16(17):7894–7899.
72) Li E, Tian R , Liu S, Chen X, Guo L, Che Y (2008) Pestalotheols A-D, bioactive metabolites from the plant endophytic fungus *Pestalotiopsis theae*. Journal of Natural Products 71(4):664–668
73) Li JY, Harper JK, Grant DM et al. (2001) Ambuic acid, a highly functionalized cyclohexenone with antifungal activity from *Pestalotiopsis* spp. and *Monochaetia* sp. Phytochemistry 56(5):463–468.
74) Lin ZJ, Lu XM, Zhu TJ, Fang YC, Gu QQ, Zhu WM (2008) GPR12 Selections of the metabolites from an endophytic Streptomyces sp. asociated with Cistanches deserticola. Arch Pharm Res 31:1108–1114
75) Liu F, Cai XL, Yang H, Xia XK, Guo ZY, Yuan J, et al. (2010) The bioactive metabolites of the mangrove endophytic fungus *Talaromyces* sp. ZH-154 isolated from *Kandelia candel* L. Planta Medica 76:185–189.
76) Liu J, Luo J, Ye H, Sun Y, Lu Z, Zeng X (2009a) Production, characterization and antioxidant activities in vitro of exopolysaccharides from endophytic bacterium *Paenibacillus polymyxa* EJS-3. Carbohydrate Polymers 78(2):275–281
77) Liu JS, Yu CM, Zhou YZ, Han YY, Wu FW, Qi BF, Zhu YL (1986a) Study on the chemistry of huperzine-A and huperzine-B. Acta Chimi Sin 44:1035–1040
78) Liu JS, Zhu YL, Yu CM, Zhou YZ, Han YY, Wu FW, Qi BF (1986b) The structures of huperzine A and B, two new alkaloids exhibiting marked anticholinesterase activity. Can J Chem 64:837–839
79) Liu JY, Song YC, Zhang Z et al. (2004) *Aspergillus fumigates* CY018, an endophytic fungus in *Cynodon dactylon* as a versatile producer of new and bioactive metabolites. Journal of Biotechnology 114(3):279–287
80) Liu L, Liu S, Niu S, Guo L, Chen X, Che Y (2009b) Isoprenylated chromone derivatives from the plant endophytic fungus Pestalotiopsis fici. J Nat Prod 72(8):1482-1486 doi:10.1021/np900308s.
81) Liu X, Dong M, ChenX, Jiang M, Lv X, Yan G (2007) Antioxidant activity and phenolics of an endophytic *Xylaria* sp. from *Ginkgo biloba*. Food Chemistry 105(2):548–554.
82) Liu X, Dong M, Chen X, Jiang M, Lv X, Zhou J (2008) Antimicrobial activity of an endophytic *Xylaria* sp.YX-28 and identification of its antimicrobial compound 7-amino- 4-methylcoumarin. Applied Microbiology and Biotechnology 78(2):241–247
83) Lu F, Lu Z, Bie X, Yao Z, Wang Y, Lu Y et al. (2010) Purification and characterization of a novel anticoagulant and fibrinolytic enzyme produced by endophytic bacterium *Paenibacillus polymyxa* EJS-3. Thrombosis Research 126:e349–e355
84) Luo D, Fang B (2006) Structural identification of ginseng polysaccharides and testing of their antioxidant activities. Carbohydrate Polymers 72(3):376–381
85) Madagundi S, Habbu P, Jagadish K S, Shukla S, Salagare M, Kulkarni V (2013) Free radical scavenging and *in vitro* immunomodulatory

activities of endophytic fungi of *Ocimum sanctum* Linn. Farmacia 61(2):330-343.

86) Ma X, Tan C, Zhu D, Gang DR, Xiao P (2007) Huperzine A from *Huperzia speciesan* ethnopharmacological review. J Ethnopharmacol 113:15–34
87) Marinho AMR, Rodrigues-Filho E, Moitinho MDLR, Santos LS (2005) Biologically active polyketides produced by *Penicillium janthinellum* isolated as an endophytic fungus from fruits of *Melia azedarach*. Journal of the Brazilian Chemical Society 16(2):280–283
88) Mitchell AM, Strobel GA, Moore E, Robison R, Sears J (2010) Volatile antimicrobials from *Muscodor crispans*, a novel endophytic fungus. Microbiol 156:270-277
89) Mitscher LA, Telikepalli H, McGhee E, Shankel DM (1996) Natural antimutagenic agents. Mutation Research 350(1):143–152
90) Nayyar GML, Breman JG, Newton PN, Herrington J (2012) Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. *Lancet Infectious Diseases* 12(6):48896 doi:10.1016/S1473-3099(12)70064-6.
91) Newman DJ, Cragg GM (2007) Natural products as sources of new drugs over the last 25 years. Journal of Natural Products 70(3):461–477
92) Ogawa T, Ando K, Aotani Y, Shinoda K, Tanaka T, Tsukuda E, et al. (1995) RES1214-1 and -2, novel nonpeptidic endothelin type A receptor antagonists produced by *Pestalotiopsis* sp. J Antibiotics 48:1401–1406
93) Owen NL, Hundley N (2004) Endophytes-the chemical synthesizers inside plants. Science Progress 87(2):79–99
94) Owen RW, Giacosa A, Hull WE, Haubner R, Spiegelhalder B, Bartsch H (2000) The antioxidant/anticancer potential of phenolic compounds isolated from olive oil. European Journal of Cancer 36(10):1235–1247
95) Park JH, Choi GJ, Lee HB et al.(2005) Griseofulvin from *Xylaria* sp. strain F0010, an endophytic fungus of *Abies holophylla* and its antifungal activity against plant pathogenic fungi. Journal of Microbiology and Biotechnology 15(1):112–117
96) Pasut G, Veronese FM (2009) PEG conjugates in clinical development or use as anticancer agents: an overview. Advanced Drug Delivery Reviews 61(13):1177–1188.
97) Pimentel MR, Molina G, Dion´ısio AP, Marostica MR, Pastore GM (2011)The use of endophytes to obtain bioactive compounds and their application in biotransformation process Biotechnology Research International 576286 doi:10.4061/2011/576286
98) Pittayakhajonwut P, Suvannakad R, Thienhirun S, Prabpai S, Kongsaeree P, Tanticharoen M (2005) An anti-herpes simplex virus-type 1 agent from*Xylariamellisii* (BCC 1005). Tetrahedron Letters 46(8):1341–1344
99) Pongcharoen W, Rukachaisirikul V, Phongpaichit S et al. (2008) Metabolites from the endophytic fungus *Xylaria* sp. PSU-D14. Phytochemistry 69(9):1900–1902
100) Pongcharoen W, Rukachaisirikul V, Phongpaichit S, Rungjindamai N, Sakayaroj J (2006) Pimarane diterpene and cytochalasin derivatives from the endophytic fungus Eutypella scoparia PSU-D44. J Nat Prod 69:856-858
101) Phongpaichit S, Rungjindamai N, Rukachaisirikul V, Sakayaroj J (2006) Antimicrobial activity in cultures of endophytic fungi isolated from Garcinia species. FEMS Immunol Med Microbiol 48:367-372
102) Priti V, Ramesha BT, Singh S, Ravikanth G, Ganeshaiah KN, Suryanarayanan TS , Uma RS (2009) Opinion :How promising are endophytic fungi as alternative sources of plant secondary metabolites? Current Science 97(4):477-478.
103) Puri SC, Nazir A, Chawla R et al. (2006) The endophytic fungus *Trametes hirsuta* as a novel alternative source of podophyllotoxin and related aryl tetralin lignans," Journal of Biotechnology 122(4):494–510
104) Puri SG, Verma V, Amna T, Qazi GN, Spiteller M (2005) An endophytic fungus from *Nothapodytes foetida* that produces camptothecin. Journal of Natural Products 68(12):1717–1719
105) Qin JC, Zhang YM, Gao JM et al. (2009) Bioactive metabolites produced by *Chaetomium globosum*, an endophytic fungus isolated from *Ginkgo biloba*. Bioorganic and Medicinal Chemistry Letters 19(6)1572–1574
106) Rehman S, Shawl AS, Kour A et al. (2008) An endophytic *Neurospora* sp. from *Nothapodytes foetida* producing camptothecin. Applied Biochemistry and Microbiology 44(2):203–209
107) Ren Y, Strobel GA, Graff JC, Jutila M, Park SG, Gosh S et al. (2008) Colutellin A, an immunosuppressive peptide from Colletotrichum dematium. Microbiol 154:1973-1979.
108) Rodriguez AD, Ramirez C, Rodriguez II, Barnes CL (2000) Novel terpenoids from the West Indian sea whip *Pseudopterogorgia elisabethae* Bayer. Elisapterosins A and B: rearranged diterpenes possessing an unprecedented cagelike framework. J Org Chem 65:1390-1398.
109) Rukachaisirikul V, Sommart U, Phongpaichit S, Sakayaroj J, Kirtikara K (2008) Metabolites from the endophytic fungus *Phomopsis* sp. PSU-D15. Phytochemistry 69(3):783–787
110) Sala A, Carmen Recio DM, Giner RM et al. (2002) Antiinflammatory and antioxidant properties of *Helichrysum italicum*. Journal of Pharmacy and Pharmacology 54(3):365–371
111) Schulz B, Sucker J, Aust HJ et al. (1995) Biologically active secondary metabolites of endophytic *Pezicula* species. Mycological Research 99(8):1007–1015
112) Selim KA, El-Beih AA, Abdel-RTM, El-Diwany AI. Biological Evaluation of Endophytic Fungus, Chaetomium globosum JN711454, as Potential Candidate for Improving Drug Discovery. Cell Biochem Biophys 2013 doi 10.1007/s12013-013-9695-4
113) Shukla ST, Kulkarni VH, Habbu PV, Jagadeesh KS, Patil BS, Smita DM (2012) Hepatoprotective and antioxidant activities of crude fractions of endophytic fungi of Ocimum sanctum Linn in rats. Oriental Pharmacy and Experimental Medicine 12(2):81-91 doi 10.1007/s13596-012-0061-7
114) Shweta S, Zuehlke S, Ramesha BT et al (2010) Endophytic fungal strains of *Fusarium solani*, from *Apodytes dimidiate* E. Mey. ex Arn (Icacinaceae) produce camptothecin, 10- hydroxycamptothecin and 9-methoxycamptothecin. Phytochemistry 71(1):117–122
115) Silva GH, Teles HL, Trevisan HC et al. (2005) New bioactive metabolites produced by *Phomopsis cassiae*, an endophytic fungus in *Cassia spectabilis*. Journal of the Brazilian Chemical Society 16(6):1463–1466
116) Singh SB, Ondeyka JG, Tsipouras N, Ruby C, Sardana V, Schulman M et al. (2004) Hinnuliquinone, a C2-symmetric dimeric non-peptide fungal metabolite inhibitor of HIV-1 protease. Biochem Biophys Res Commun 324:108-13.
117) Sommart U, Rukachaisirikul V, Sukpondma Y, Phongpaichit S, Sakayaroj J, Kirtikara K (2008) Hydronaphthalenones and a dihydroramulosin from the endophytic fungus PSU-N24. Chem Pharm Bull 56(12):1687-1690.
118) Song JH (2008) What's new on the antimicrobial horizon? International Journal of Antimicrobial Agents 32(4):S207–S213
119) Song YC, Huang WY, Sun C, Wang FW, Tan RX (2005) Characterization of graphislactone A as the antioxidant and free radical-scavenging substance from the culture of *Cephalosporium*

sp. IFB-E001, an endophytic fungus in *Trachelospermum jasminoides*. Biological and Pharmaceutical Bulletin 28(3):506–509

120) Strobel G (2006) Harnessing endophytes for industrial microbiology Current Opinion in Microbiology 9:240–244
121) Strobel G, Ford E, Worapong J, et al. (2002) Isopestacin, an isobenzofuranone from *Pestalotiopsis microspora*, possessing antifungal and antioxidant activities. Phytochemistry 60(2):179–183
122) Staniek A, Woerdenbag HJ, Kayser O, (2008) Endophytes exploiting biodiversity for the improvement of natural product-based drug discovery. Journal of Plant Interactions 3:75-98
123) Stierle A, Strobel G, Stierle D (1993) Taxol and taxane production by *Taxomyces andreanae*, an endophytic fungus of Pacific yew. Science 260(5105):214–216
124) Strobel GA (2003) Endophytes as sources of bioactive products. Microbes and Infection 5(6):535–544
125) Strobel G, Daisy B, Castillo U, Harper J (2004) Natural products from endophytic microorganisms. Journal of Natural Products 67(2):257–268
126) Strobel G, Daisy B (2003) Bioprospecting for microbial endophytes and their natural products. Microbiology and Molecular Biology Reviews 67 (4):491–502
127) Sun C, Wang JW, Fang L, Gao XD, Tan RX (2004) Free radical scavenging and antioxidant activities of EPS2, an exopolysaccharide produced by a marine filamentous fungus *Keissleriella* sp. YS 4108. Life Sciences 75(9):1063–1073
128) Taechowisan T, Chanaphat S, Ruensamran W, Phutdhawong WS (2012) Anti-inflammatory effect of 3-methylcarbazoles on RAW 264.7 cells stimulated with LPS, polyinosinic-polycytidylic acid and Pam3CSK. Advances in Microbiology 2:98-103 doi:10.4236/aim.2012.22013
129) Tan RX, Zou WX (2001) Endophytes: a rich source of functional metabolites. Nat Prod Rep 18(4):448–459
130) Tejesvi, MV, Kini KR, Prakash HS Subbiah V, Shetty HS (2008) Antioxidant, antihypertensive, and antibacterial properties of endophytic Pestalotiopsis species from medicinal plants. Canadian Journal of Microbiology 54(9):769-780.
131) Uma SR, Ramesha BT, Ravikanth G, Rajesh PG, Vasudeva R, Ganeshaiah KN (2008) Chemical profiling of *N. nimmoniana* for camptothecin, an important anticancer alkaloid: towards the development of a sustainable production system," in bioactive molecules and medicinal plants, K. G. Ramawat and J. Merillion, Eds, Springer, Berlin, Germany, pp 198–210
132) UNAIDS 2011 pg. 1–10
133) Valko M, Leibfritz D, Moncol J, Cronin MTD, Mazur M, Telser J (2007) Free radicals and antioxidants in normal physiological functions and human disease. International Journal of Biochemistry and Cell Biology 39(1):44–84
134) Wagenaar MM, Corwin J, Strobel G, Clardy J (2000) Three new cytochalasins produced by an endophytic fungus in the genus *Rhinocladiella*. Journal of Natural Products 63(12):1692–1695
135) Wall ME, Wani MC, Cook CE, Palmer KH, McPhail AT, Sim GA (1966) Plant antitumor agents. I. The isolation and structure of camptothecin, a novel alkaloidal leukemia and tumor inhibitor from *Camptotheca acuminate*. Journal of the American Chemical Society 88(16):3888–3890
136) Wang FW, Jiao RH, Cheng AB, Tan SH, Song YC (2007) Antimicrobial potentials of endophytic fungi residing in *Quercus variabilis* and brefeldin A obtained from *Cladosporium* sp. World Journal of Microbiology and Biotechnology 23(1):79–83
137) Wang YA, Zeng QG, Zhang ZB, Yan RM, Wang LY, Zhu D (2010) Isolation and characterization of endophytic huperzine A-producing fungi from Huperzia serrata. J Ind Microbiol Biotechnol doi 10.1007/s10295-010-0905-4
138) Wani MC, Taylor HL, Wall ME, Coggon P, McPhail AT (1971) Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. Journal of the American Chemical Society 93(9):2325–2327.
139) Wilkie N, Wingrove PB, Bilsland JG, Young L, Harper SJ, Hefti F, Ellis S, Pollack SJ. (2001) The non-peptidyl fungal metabolite L-783,281 activates TRK neurotrophin receptors. J Neurochem 78:1135-1145
140) Wiyakrutta S, Sriubolmas N, Panphut W, Thongon N, Danwisetkanjana K, Ruangrungsri N, Meevootisom V (2004) Endophytic fungi with anti-microbial, anti-cancer and anti-malarial activities isolated from Thai medicinal plants. World J Microbiol Biotechnol 20:265-272. doi 10.1023/B:WIBI.0000023832.27679.a8
141) Yang J, Xu F, Huang C, Li J, She Z, Pei Z, Lin Y (2010) Metabolites from the mangrove endophytic fungus *Phomopsis* sp. (#zsu- H76). European Journal of Organic Chemistry 5:3692–3695.
142) Yang X, Zhang L, Guo B, Guo S (2004) Preliminary study of a vincristine producing endophytic fungus isolated from leaves of *Catharanthus roseus*. Chinese Traditional and Herbal Drugs 35:79-81.
143) Yin H, Sun YH (2011) Vincamine-producing endophytic fungus isolated from *Vinca minor*. Phytomedicine 15;18(8-9):802-805 doi: 10.1016/j.phymed.2011.01.005. Epub 2011 Feb 18.
144) You F, Han T, Wu JZ, Huang BK, Qin LP (2009) Antifungal secondary metabolites from endophytic *Verticillium* sp. Biochemical Systematics and Ecology 37(3):162–165
145) Yu H, Zhang L, Li L et al. (2010) Recent developments and future prospects of antimicrobial metabolites produced by endophytes. Microbiological Research 165(6):437–449
146) Zaidi KU, Mani A, Ali AS, Ali SA (2013) Evaluation of Tyrosinase Producing Endophytic Fungi from *Calotropis gigantea, Azadirachta indica, Ocimum tenuiflorum* and *Lantana camara.* Annual Review & Research in Biology 3(4)
147) Zangara A (2003) The psychopharmacology of Huperzine A: an alkaloid with cognitive enhancing and neuroprotective properties of interest in the treatment of Alzheimer's disease. Pharmacol Biochem Behav 75:675–686
148) Zazopoulos E, Huang K, Staffa A, Liu W, Bachmann BO, Nonaka K, et al. (2003) A genomics-guided approach for discovering and expressing cryptic metabolic pathways. Nat Biotechnol 21:187–190
149) Zhang B Salituro G, Szalkowski D, Li Z, Zhang Y, Royo I, et al. (1999) Discovery of a Small Molecule Insulin Mimetic with Antidiabetic Activity in Mice. Science 284(5416):974-977 doi:10.1126/science.284.5416.974
150) Zhang G, Sun S, Zhu T, Lin Z, Gu J, Li D, Gu Q (2011) Antiviral isoindolone derivatives from an endophytic fungus *Emericella* sp. associated with *Aegiceras corniculatum*. Phytochemistry 72:1436–1442.
151) Zhang L, Guo B, Li H, Zeng S, Shao H, Gu S, Wei R (2000) Preliminary study on the isolation of endophytic fungus of *Catharanthus roseus* and its fermentation to produce products of therapeutic value. Chinese Traditional and Herbal Drugs 31:805-807.
152) Zhang YZ, Tao LY, Liang YJ et al. (2009) Secalonic acid D induced leukemia cell apoptosis and cell cycle arrest of G1 with involvement of GSK-3δ/β-catenin/c-Myc pathway. Cell Cycle 8(15):2444–2450
153) Zhou L, Cao X, Yang C, Wu X, Zhang L (2004) Endophytic fungi of *Paris polyphylla* var. *yunnanensis* and steroid analysis in the fungi. *Natural Product Research and Development* 16: 198-200.
154) Zikmundova M, Drandarov K, Bigler L, Hesse M, Werner C (2002) Biotransformation of 2 benzoxazolinone and 2-hydroxy-1,4-benzoxazin-3-one by endophytic fungi isolated from *Aphelandra*

tetragona. Applied and Environmental Microbiology 68(10):4863- 4870