A COMPREHENSIVE REVIEW ON ECONOMICALLY IMPORTANT SECONDARY METABOLITES PRODUCED DURING PLANT FUNGUS INTERACTION

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Abstract : Pharmaceutical industry's demand for highly efficacious drugs has forced scientific community to find various alternative sources with potent secondary metabolites. The emergence of a more thoughtful approach by incorporating modern tools and techniques enabled the fungus-infected plants to become a novel source of new molecules/drugs and gained a unique position in the pharmaceutical industry. In this background a review on the topic from all available sources has been comprehended. The findings emerged from the review has shown that the plants infected by fungi produce an array of bioactive secondary metabolites with unique structures which include alkaloids, benzopyranones, flavonoids, phenolic acids, quinones, steroids, terpenoids, tetralones, xanthones, chinones, phenols, isocoumarins, benzopyranones, cytochalasins, enniatines and others. Most of the studies on secondary metabolites produced upon fungus infection revealed that they are very good antioxidants and have good pharmacological activities. They possess medicinal properties like hepatoprotection, anti-inflammation, immunomodulation, anticarcinogenicity, anti-infertility, etc. Apart from this the fungus-infected plants also produces certain secondary metabolites capable of synthesizing silver nanoparticles and these nanoparticles are good antioxidants with diverse pharmacological properties. The fungal infection provides protection to their host from insect, pest and herbivore attack. Upon infection by fungus, biomass production and mineral uptake increases. The fungus' infection improves the host's efficacy to tolerate drought, heat, salinity, etc. The review provides baseline data which is useful as a lead which often play a key role in the drug discovery and designing of novel drugs.

***Index Terms* - fungus-infected plants, secondary metabolites, antioxidants, pharmacology.**

I. INTRODUCTION

There is a general presumption that fungal infection causes a severe toxic effect on plants, animals, and humans. Customarily, the fungus-infected plants are not advocated in most of the health care systems especially the classical health traditions like Ayurveda. The benefits of fungus-infected medicinal plants are hardly explained in the traditional as well as modern medical systems. But we are now witnessing the entry of a new informational paradigm in the scientific validation of natural products. A more thoughtful approach by incorporating modern tools and techniques seems much more suited to confirm the efficacy and to obtain information that might lead to understanding the mode of action. The pharmaceutical industry's demand for highly efficacious drugs also forced the scientific community to find alternative sources like fungus-infected plants as a novel source of new molecules/drugs. The secondary metabolites produced by fungus has a unique position in the pharmaceutical industry (Alexander et al., 2013). In fact, the fungi that inhabit the tissues of living plants are an under-explored area of research. The fungus infected plants have been considered unique, and are viewed as an outstanding source of bioactive natural products. Upon infection, the plants synthesise an array of metabolites, many of which are bioactive. Plant fungus interaction is a complex system with the production of different classes of secondary metabolites that have immense utility, particularly from the therapeutic perspective. Since the fungus infection triggers numerous metabolic pathways in the plant with the production of diverse phytoconstituents, it has become essential to single out those concerned with therapeutic effect. Once the properties of the secondary metabolites are revealed, it would replace conventional molecules and ultimately enhance the health industry.

All plants in natural ecosystems are thought to be symbiotic with mycorrhizal and/or endophytic fungi (Rusty et al., 2008), and the very existence of the fungi infected plants has been known for over hundred years. The perennial rye grass *Lolium temulentum* infected with the fungus *Neotyphodium lolii,* was mentioned in the Old Testament or Hebrew Bible as undesirable (Kingsbury, 1964). Fungal infection modifies the chemical profile of the host and the fungi act as biotransformer or biocatalyst. During this event, it converts one or more compounds into other forms which may be either useful or harmful. The symbiotic association of plant and fungi seems to be extended from the level of simple contact to a highly sophisticated and complex genomic level interaction. During microbial association in plants, they are often organized and embedded within an extracellular polymeric substance matrix, termed as biofilms. Infections by biofilms are difficult to defend by plants because these structures are particularly resistant to most of the secondary metabolites produced by the plants. One of the regulatory mechanisms suggested to play a significant role in coordinating biofilm formation for many species is intercellular signaling or quorum sensing (Patricia and Arturo, 2012).

II. FUNGUS INDUCED SECONDARY METABOLITES

The fungal flora found on plants exerts their influence on the host plant's physiology. The host plants overcome the adverse effects of the infection by producing phytoalexins, and forms a complex system with a different class of secondary metabolites. Approximately 22,000 bioactive secondary metabolites from microorganisms have been described so far and about 8,600 of these are of fungal origin. Gosio (1896) discovered a crystalline fungal product mycophenolic acid from *Penicillium glaucoma* and the same is considered as the first microbial secondary metabolite discovered from microorganisms (Demain and Fang 2000).

According to Andrew and Hirano (1991), nearly 3, 00,000 plant species that exist on the earth seems to be infected with more than one million fungus species. The major class of compounds produced plant fungus interaction are alkaloids, benzopyranones, flavonoids, phenolic acids, quinones, steroids, terpenoids, tetralones, xanthones, chinones, phenols, isocoumarins, benzopyranones, cytochalasins, enniatines and others. These novel metabolites which are directly used as drugs or function as lead structures for synthetic modifications (Stadler and Keller, 2008, Mitchell et al., 2008, Tan and Zou, 2001). Most of these secondary metabolites are also very good natural antioxidants having a wide array of medicinal properties like hepatoprotection, anti-inflammation, immunomodulation, anticarcinogenicity, anti-infertility, etc.

III. ANTIOXIDANT ACTIVITY

Recent findings on the application of secondary metabolites produced during the plant fungus interactions show that the majority of secondary metabolites especially phenolic compounds are very good anti-oxidants and most of the secondary metabolites showed even better antioxidant activity than the conventional standards used for their investigation. The fungus *Cephalosporium* sp. infecting the plant *Trachelospermum jasminoides* produces a phenolic metabolite graphislactone A. On examining its antioxidant activity it displayed potent *in vitro* antioxidant and free radical-scavenging activity stronger than the standards, butylated hydroxytoluene (BHT) and ascorbic acid (Song et al., 2005). Pestacin, isopestacin, and 1, 3- dihydro isobenzofurans were obtained from the fungus *Pestalotiopsis microspore* isolated from the plant *Terminalia morobensis* growing in Papua New Guinea. A study on these compounds showed potent antioxidant activity (Strobel et al., 2002). Liu et al. (2007) have observed that the phenolic contents were the major antioxidant constituents of the endophytes. The methanol extract of the fungus *Xylaria* sp. isolated from the medicinal plant *Ginkgo biloba* exhibited strong antioxidant capacity due to the presence of “phenolics” and “flavonoids”. A study on the activity of the fungus infecting 29 traditional Chinese medicinal plants using RP-HPLC, LC-ES1 MS, and GC- MS has shown that the secondary metabolites produced during the plant fungus interaction are good antioxidants having anticancer, antimicrobial, immunosuppressant, anti-diabetic, anti-HIV properties etc. (Huang et al., 2008).

IV. ANTICANCER PROPERTY

Most of the fungus induced secondary metabolites show very good anticancer activity, some of them shows better activity than conventional standard drugs. The medicinal plant *Camptotheca acuminata* on infection with fungus *Fusarium solani* produces the compound camptothecin. This compound inhibits topoisomerase I, by binding and stabilizing the covalent complex of topoisomerase I -DNA, and thus exhibit anticancer activity (Kusari et al., 2011). Ergoflavin, a dimeric xanthene, belonging to the compound class called ergochromes which was described as a novel anticancer agent produced by fungi growing on the leaves of an Indian medicinal plant *Mimusops elengi* (Deshmukh et al., 2009). Crude extracts of the fungus *Alternaria alternata*, infected in the plant *Coffea arabica* L., displayed anti-cancer activity. The extract displayed moderate cytotoxic activity towards HeLa cells *in vitro*, when compared to the dimethyl sulfoxide treated cells (Fernandes et al., 2009). A quinone dimer, torreyanic acid was isolated from the fungus, *Pestalotiopsis microspora* infecting the plant *Torreya taxifolia.* The torreyanic acid was shown to possess 5 to 10 times more potent cytotoxicity in cell lines that are sensitive to protein kinase C agonists and causes cell death by apoptosis and shows its potency to be used as an anticancer drug (Lee et al. 1996). Studies on the infection of the fungus *Fusarium* sp. infecting on mangrove tree *Kandelia candel,* resulted in the identification of a new isoflavone, 5-O-methyl-2'-methoxy-3'- methylalpinumisoflavone. The pharmacological studies on the anticancer activity of the same, it was found that the compound inhibited the growth of HEp-2 and HepG2 cancer cell lines with IC50 values of 4 and 11^M, respectively, and has also shown anticancer activity (Huang et al. 2010). Eyberger et al. (2006) reported Podophyllotoxin in *Phialocephala fortinii* infecting host plant *Podophyllum peltatum* while Kour et al. (2008) reported the compound Podophyllotoxin in *Phialocephala fortinii* infecting the plant *Podophyllum peltatum.* Kusari et al. (2009) reported Podophyllotoxin in *Juniperusre curva* infected by *Fusarium oxysporum* which has shown anticancer properties. Secalonic acid D, a mycotoxin belonging to ergochrome class, is known to have potent anticancer activities. It was isolated from certain fungi infecting mangroves and it showed high cytotoxicity on HL60 and K562 cells by inducing leukaemia cell apoptosis (Zhang et al., 2009). Extract from the Chinese medicinal plant, *Actinidia macrosperma* infected with the fungus *Trichoderma citrinoviride* was tested for cytotoxic activity using the brine shrimp lethality assay and to assess the effect of fermentation broths on cancer cell proliferation, the MTT assay was also conducted. The study has shown that fungal extract can inhibit proliferation in a dose-dependent manner and the cytotoxic and antitumor activities against brine shrimp and five types of tumour cells was confirmed (Yin et al., 2012). The fungus *Aspergillus niger* infects the grass *Cynodon dactylon* and induces the production of a compound named xanthine oxidase, and the same have potent anti-cancer property (Song et al., 2004). The fungus *Taxomyces andreanae* infecting the plant *Taxus brevifolia* produces the anticancer drug Taxol (Stierle et al., 1993). *Nothapodytes foetida* infected with the fungus *Entrophospora infrequens* also produces camptothecin having anticancer activity (Amna et al., 2006).

V. ANTIMICROBIAL PROPERTY

The fungus infecting on the plant induces the production of the compounds having diverse activity and some of them have shown good antimicrobial property on pharmacological screening. The fungus *Chaetomium globosum*, infecting on the plant *Ginkgo biloba* induces the production of Chaetomugilin A and D. The pharmacological studies on these compound revealed the antimicrobial property of the chaetomugilin A and D. (Qin et al., 2009). The compound citrinin is produced during the infection of the fungus *Penicillium janthinellum* on *Melia azedarach and* this compound has very good antibacterial property. The fungus *Chaetomium globosum* infecting the plant *Hypericum perforatum* induces the production of the compound Hypericin and the same has shown good antiviral property on pharmacological screening (Kusari et al., 2008). A potential compound paeciloxocin A was isolated from the fungus *Paecilomyces* sp. infecting on the mangroves. On examination of its pharmacological activities the compound inhibited the growth of microbial pathogen *Curvularia lunata* and *Candida albicans showing good* antimicrobial property (Wen et al. 2010). The fungus *Aspergillus flavus* and *Curvularia lunata* infects the medicinal plant *Kigelia africana* (Lam) Benth. It was assessed that the fungus infected leaf extracts for antibacterial activity against three standard pathogenic bacterial strains *Bacillus subtilis*, *Staphylococcus aureus*, and *Escherichia coli* and exhibited *in vitro* inhibition of bacterial growth (Al-Mahildris et al., 2013).

VI. Silver nanoparticles

Certain medicinal plants on infection with the fungus produces certain secondary metabolites capable of synthesizing silver nanoparticles (Gade et al., 2010). Most of these silver nanoparticles are also very good antioxidants and also having diverse pharmacological properties. Biological synthesis of nanoparticles is an efficient, environment-friendly and simple process. The fungus *Aspergillus clavatus* infecting stem tissues of *Azadirachta indica* was isolated and challenged with 1 mM $AgNO_3$ solution and the activity of fungus induced the production of silver nanoparticles (Verma et al., 2010). *Aspergillus clavatus* infecting *Azadirachta indica, Penicillium* infecting *Centella asiatica, Pestalotia* sp infecting *Syzygium cumini* and *Amylomyces rouxii* infecting the plant *Phoenix dactylifera* could produce silver nanoparticles of size 5-7 nm, 10-25 nm, 100 nm, and 10-40 nm respectively (Rekha et al., 2013). The silver nanoparticles showed efficient antimicrobial activity because of their unique physical and chemical properties. Manju et al. (2013) have reported that several fungi like *Fusarium oxysporum*, *Fusarium acuminatum*, *Penicillium fellutanum*, *Aspergillus clavatus, Fusarium solani, Aspergillus niger, Alternaria alternate,* etc. isolated from different hosts have been successfully used for the synthesis of silver nanoparticles.

VII. Pharmacological activities

The secondary metabolites produced as an outcome of plant fungus interaction are having a wide array of pharmacological activities like hepatoprotection, anti-inflammation, immunomodulation, anticarcinogenicity, anti-infertility, etc. The fungus *Pestalotiopsis theae* infecting an unidentified tree on Jianfeng Mountain, China, was capable of producing a compound pestalotheol C. It was also reported that fungus induced pestalotheol C compound have good anti-HIV properties (Li et al., 2008). A novel compound chaetoglobosin B was discovered from the fungus *Chaetomium globosum*, isolated from the leaf of endemic plant *Maytenus hookeri* distributed in areas of Yunnan, China. On conducting the pharmacological studies, the same showed potent antituberculosis activity (Ni et al., 2008). The fungus *Fusarium proliferatum* infecting *Dysoxylum binectariferum* produces an alkaloid rohitukine. Rohitukine is a chromane alkaloid and a study on the pharmacological activity reveals that the same possessing antiinflammatory, anti-cancer, and immunomodulatory properties. Flavopiridol a semi-synthetic derivative of rohitukine is also reported in the same infection (Patel et al., 2011). The fungus *Eupenicillium parvum* upon infection on the plant *Azadirachta indica* induces the production of a class of natural insecticides, azadirachtin A and B having antifeedant and insect growth-regulating properties (Souvik et al., 2012). *Another fungus Penicillium brasilianum*, found in the bark of *Melia azedarach*, promoted the biosynthesis of phenylpropanoid amides. It is also observed that the phenylpropanoid shows potent antioxidant, antimicrobial, anti-inflammatory, and immunosuppressive properties. (Fill et al., 2010). A nonpeptidyl fungal metabolite produced by *Pseudomassaria* sp. infecting an undetermined plant collected near Kinshasa, Democratic Republic of Congo showed potential anti-diabetic properties. Two mouse models of diabetes studies conducted by administering the fungal metabolites resulted in a significant lowering of blood glucose levels (Zhang et al., 1999). Mycophenolate, a product of *Penicillium brevicompactum* is important world over because of its high potential for preventing renal transplant rejection. The fungus *Fusarium subglutinans* infecting certain plants, producing two compounds Subglutinol A and B. The pharmacological studies of the same showed that, they can influence the immune system of animals. Subglutinol A and B are noncytotoxic diterpene pyrones, both the compounds have IC50 values of 0.1 ^M and were roughly as potent as the immunosuppressant drug cyclosporin A and it is recommended that these compounds could be used as immunosuppressant agents (Lee et al., 1995).

VIII. Fungus induced host benefits

The fungus infected plants have shown greater fresh and dry weights and the infection has also improved its drought tolerance. The fungal infection protect their host from insect, pest and herbivore attack due to the production of fungus induced secondary metabolites (Susanne et al., 2008). Fungus infection induces the plants to produce a certain class of alkaloids like ergovaline and lolitrem B which are responsible for its defense mechanism against insects and pests (Lyons et al., 1986). *Phialocephala fortinii* infecting the plant *Larix decidua* showed that the fungus infection causes the increase in the biomass production. It has also been noted that mycorrhizal associations increased the absorptive surface area of the plant due to extra-matrical fungal hyphae exploring rhizosphere beyond the root hair zone, which in turn enhanced water and mineral uptake. The protection and increased mineral uptake results in greater biomass production which is important for a successful remediation. The potentials of phytoremediation of metal-polluted soil can be enhanced by inoculating hyperaccumulator plants with mycorrhizal fungi is most appropriate for polluted sites (Hrishikesh et al., 2010). Some of the fungus infecting plants are capable of nitrogen (N) fixation, solubilization of phosphate, enhance uptake of phosphorus (P), production of siderophores, ACC deaminase, and plant hormones such as auxin, abscisins, ethylene, gibberellins, and Indole Acetic Acid (Firakova et al., 2007).

Allium cepa L. infected by the fungus *Glomus tunicatus* were more drought tolerant than non-infected ones (Nelsen et al., 1982). Upon the infection of an edible fungus, *Flammulina velutipes* increased iron and polyunsaturated fatty acid content in tomato by expressing a single gene encoding C-5 sterol desaturase (FvC5SD), ultimately it results in improved drought tolerance in tomato (Kamthan et al., 2012). The infection of fungus on some plants has shown that both partners are benefited to tolerate some undesired conditions. *Dichanthelium lanuginosum* growing on the geothermal soils of Yellowstone National Park was found to be colonized by the fungus *Curvularia protuberata.* It confers heat tolerance to the host plant, and neither the fungus nor the plant can survive separate from one another when exposed to heat stress >38 °C. (Redman et al., 2002). Dune grass, *Leymus mollis* is usually colonized by the fungus *Fusarium culmorum* and it confers salt tolerance to the host plant which cannot survive in coastal habitats without the habitat- adapted fungal infection (Rodriguez et al., 2008).

IX. Discussion

From the review, it is obvious that scientific validation of these unexplored natural products will bring out potent herbal drugs/preparations for combating various conventional diseases to which a remedy is not available. Apart from that, replacing conventional modern medicaments with herbal preparations would also nullify the side effects of consuming conventional drugs which is one of the major issues faced by our health care industry. Even though it is an under-explored area of research, the fungus induced secondary metabolites have a unique position in the pharmaceutical industry.

Most of the studies on secondary metabolites produced upon fungus infection revealed that they are of very good antioxidants and have good pharmacological activities. Graphislactone A, Pestacin, isopestacin, and 1, 3- dihydro isobenzofurans were the major compound having potent antioxidant activity and the frequency of citation by the authors on these compounds appears to be very high. The anticancer secondary metabolites with high author citation frequency were Camptothecin, Podophyllotoxin, Taxol, Secalonic acid D, Xanthine oxidase, Ergoflavin, Torreyanic acid, and 5-O-methyl-2'-methoxy-3'-methylalpinumisoflavone. One interesting feature noticed was that the same economically important secondary metabolites were produced in the site of different plant fungus interactions. For instance, the anticancer compound Podophyllotoxin is seen produced in *Phialocephala fortinii* infecting host plant *Podophyllum peltatum* and also *Juniperusre curva* infected by *Fusarium oxysporum*. Likewise, many sources have also been reported for the isolation of another anticancer compound camptothecin. Another finding in this review was that the fungus can produce the same rare and important bioactive compounds as their host after infection. The anticancer drug camptothecin which was initially isolated from the wood of *Camptotheca acuminata* can now be isolated from the fungus *Fusarium solani* which is associated with the same plant. Hence based on the available data it is hypothesized that there must be a transfer of genes from host to the fungus which might be enabled the fungus to produce the host's secondary metabolites. Based on these findings it is recommended to use fungus infecting the medicinal plants as a source of active compounds and to preserve our biodiversity to some extent.

Various studies on the fungus induced metabolites for its pharmacological activities are underway. Some of the findings have shown significant efficacy of these compounds to compact diverse ailments. The compound pestalotheol C has shown good anti-HIV property, chaetoglobosin B has antituberculosis activity, Subglutinol A and B can act as immunosuppressant agents, alkaloid rohitukine and Flavopiridol has potent antiinflammatory, anti-cancer, and immunomodulatory properties. The fungus induced phenylpropanoid amides have shown potent antioxidant, antimicrobial, anti-inflammatory, and immunosuppressive properties. Mycophenolate, a product of *Penicillium brevicompactum* is important world over because of its high potential for preventing renal transplant rejection. The compounds Chaetomugilin A and D, citrinin, Hypericin, paeciloxocin were showed potent antimicrobial properties in various studies. Other findings emerged from this review were that compounds produced during plant fungus interaction can effectively use for the production of nanoparticles. These nanoparticles are also very good antioxidants and also having diverse pharmacological properties. As the biological synthesis of the nanoparticle is an efficient, environment-friendly and simple process the production of nanoparticles by using secondary metabolites produced from plant fungus interaction can be considered as an emerging area of research.

Additional findings emerged from this review is that fungus infection enables the host to overcome diverse stress conditions. Fungus infection increases biomass production, enhances water and mineral uptake, improves drought tolerance, increases the absorptive surface area which in turn increases mineral uptake, enables to overcome temperature stress, provides protection to host from insect, pest and herbivore attack, enable them to live in salinity. Many authors have reported that as the root surface area and mineral uptake increases, the fungus-infected plants can be used for phytoremediation in a far better way by artificially inoculating host with fungus. Fungus infection also confer the capabilities of nitrogen (N) fixation, solubilization of phosphate, enhance uptake of phosphorus (P), production of plant hormones.

X. Conclusion

Even though fungus induced secondary metabolites and its application is an under-explored area of research, the findings gleaned out of the present review points to the fact that additional class of secondary metabolites produced in fungus-infected plants possesses significant efficacy to be used in diverse research arena. Apart from the benefits in the health industry the author also suggests promoting the methodology of inoculating the plants with fungal spores which can enable the host to overcome various stress and can be used for phytoremediation. As the fungus are also capable of producing active compounds as in the host plant, it is also suggested to focus research on developing desired compounds from fungus instead of the host to protect our plant wealth. Ultimately the vast information accrued through this review can act as a good platform for innovative research and discovery of novel drugs.

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