Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

ISSN NO. 2320-5407

Article DOI:10.21474/IJAR01/7516
DOI URL: http://dx.doi.org/10.21474/IJAR01/7516

REVIEW

ENDOPHYTIC FUNGI: AS A POOL OF SECONDARY METABOLITES.

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Manuscript Info

Manuscript History

Received: 05 June 2018
Final Accepted: 07 July 2018
Published: August 2018

Keywords:-
Anticancer, Antimycotic, Antiviral, Antioxidant, Bioactive compounds, Endophytes.

Abstract

Endophytic fungi are the pool of secondary metabolites. Endophytes, microorganisms that reside in the tissues of living plants, are relatively unstudied as potential sources of novel natural products for exploitation in medicine, agriculture, and industry. Of the approximately 3,00,000 higher plant species that exist on the earth, each individual plant, of the billions that exist here, is host to one or more endophytes. There are many challenges in front of scientists for instance rise of new diseases, emergence of virus which are life threatening and management of complications occur after operation in patient with organ transplantation. This has led scientists to hunt for different natural sources that are safe and potent to meet the challenges of twenty first century. Endophytes possess different types of bioactivity, such as antibacterial, antiviral, anticancer and antifungal agents.

Introduction:-

Endophytes, which occupy a unique biotope with global estimation up to one million species, are a great choice to avoid replication in the study of natural products to assist in solving not only plant diseases but also human and animal health problems. 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 maximum number of natural drugs are produced by endophytes (Kaul*et al*., 2012). There are many pieces of evidence that bioactive compounds produced by endophytes could be alternative approaches for discovery of novel drugs. Stierle*et al*. (1993) were reported endophytic fungus as a sustainable alternative source of taxol. Natural products are adapted to a specific function in nature. Thus, the search for novel secondary metabolites should concentrate on organisms that inhabit novel biotypes. Endophytic fungi inhabit a biotype that is not well studied (Nithya and Muthumary, 2011).

Endophytic microorganisms are a significant reservoir of novel bioactive secondary metabolites including antimicrobial, antiinsect, anticancer, antidiabetic, and immunosuppressant compounds with their great potential applications in agriculture, medicine, and food industry (Kharwar*et al*., 2011). These bioactive compounds could be mainly classified as alkaloids, terpenoids, steroids, quinones, isocoumarins, lignans, phenylpropanoids, phenols, and lactones. World health problems caused by drug-resistant bacteria and fungi are increasing. Approximately 4000 secondary metabolites of fungal origin have been described to possess biological activities. The number of secondary metabolites produced by fungal endophytes is larger than that of any other endophytic microorganisms (Zhang *et al*., 2011). Most of the natural products from endophytic fungi are antimicrobial, anticancer agents,

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biological control agents, immunosuppressive agents, and other bioactive compounds by their different functional roles.

A. Secondary metabolites from endophytes as antimycotic agents

Endophytic fungi are mitosporic and meiosporicascomycetes that asymptomatically reside in the internal tissues of plants beneath the epidermal cell layer, where fungi colonize healthy and living tissues. Their biological diversity is enormous, especially in temperate and tropical rainforests. The fungi are hosted in nearly 300,000 land plant species, with each plant hosting one or more of these fungi. Wagenaar*et al*., (2000) three novel cytochalasins have recently been reported from *Rhinocladiella* sp. as an endophyte on *Tripterygiumwilfordii*these compounds have antitumor activity and have been identified as 22-oxa-cytochalasins. *Muscodorvitigenus*, isolated from *Paullina paullinioides* yields naphthalene as its major product naphthalene, the active ingredient in common mothballs, is a widely exploited insect repellant.Worapong *et al*., (2001). *Muscodoralbus* is a newly described endophyticfungus obtained from small limbs of *Cinnamomumzeylanicum*. Daisy and Castillo, and Strobel*et al*.,(2002.) reported *M. vitigenus* shows promising preliminary results as an insect deterrent and has exhibited potent insect repellency against the wheat stem sawfly (*Cephuscinctus*). An interesting observation is that in the case of co-cultivation between *A. niger* and actinomycetes, an intimate physical interaction is required to activate silent gene clusters in *As. niger*(Schroeckh*et al*. 2009) Although the topic of volatile antibiotics would perfectly fit into the previous section, they have been put it under a separate heading because special techniques are required to detect these compounds. Because microbes in nature live in communities, growth of various fungi in co-culture with other organisms has been tested. Co-culture can indeed result in activation of silent gene clusters or in strongly increased expression (Ola *et al*. 2013; Wu *et al*. 2015b). Little-studied groups of fungi are considered to be potential sources of novel natural products for medicine and agriculture (Hormazabal and Piontelli, 2009). The function of invasive fungal infections has increased significantly during cancer organ transplantation, chemotherapy and bone marrow transplantation. Endophytes are presumably ubiquitous in plants, with populations dependent on host species and location. During long research only a few numbers of antifungal agents are available for the treatment of various life threatening fungal infections. The search for new antifungal agents to overcome the growing human problems of drugs resistance in microorganisms is growing. Ongoing global efforts to discover new compounds from EF of medicinal plants are yielding valuable results (Zhou *et al*., 2007). Compounds produced by EF are being recognized as a versatile arsenal of antifungal agents. Their anti-microbial activity is detected using air contact between the volatile-producing fungus and the target pathogen.

B. Secondary metabolites from endophytes as antiviral agent

Endophytes have also been studied for their antiviral activity, the emergence of multi resistance against existing drugs, and high cost of current therapies as well as the AIDS associated opportunistic infections, such as *Cytomegalo* virus and *Polyoma* virus needs essential antiviral agent. Cytonic acid A and B were recognized as human *cytomegalo* virus protease inhibitors from endophytic fungus *Cytonaema* Sp. isolated Bioprospecting for Microbial Endophytes and their Natural Products from*Quercus* Sp. (Guo*et al*., 2000). A novel quinine related metabolites *xanthoviridicatins* E and F was also produced by an endophytic*Penicilliumchrysogenum* able to inhibit the cleavage reaction of HIV-1 integrase. Fermentation of endophytic fungi with potential for bioactive compound production has several advantages like reproducible and dependable productivity. These endophytes can be grown on large scale in fermenters to provide inexhaustible supply of bioactive compound and thus can be commercially exploited. In order to optimize various biosynthetic pathways, changes in the culture conditions should be explored which leads to the production of derivatives and analogues of novel compounds (Goutam*et al*. 2014). Endophyticactinobacteria are examined to be a substitute to combat multidrug-resistant human pathogens as they serve as a latent source of novel antimicrobial compounds (Ravi and Vasantba. 2017).

C. *Secondary metabolites from endophytes as antioxidant compounds*

Natural antioxidants and might substitute synthetic antioxidants which produce many undesirable secondary effects. Antioxidants are the substances that when present in low concentrations compared to those of an oxidizable substrate significantly delays or prevents oxidation of that substance. Reactive oxygen species (ROS) produced during the cellular metabolism are essential for cell signaling, apoptosis, gene expression and ion transportation1. Phenolic and flavonoid compound seem to have an important role in stabilizing lipid peroxidation, associated with antioxidant activity Yanishlieva-Maslarova, (2001). Fungal endophytes are a store house of novel secondary metabolites including antibiotic, antioxidant, anticancer and immunosuppressant compounds (Strobel, 2002). Free radicals are reactive oxygen and nitrogen species which are generated by various physiological processes in the body. Uncontrolled generation of free radicals leads to attack on membrane lipids, proteins, enzymes and DNA causing oxidative stress and ultimately cell death. *Cephalosporium* sp., an endophytic fungus isolated from the root of *Trachelospermumjasminoides*produce a phenolic compound with strong free radical scavenging and antioxidant activity (Song *et al*., 2005).

The free radical scavenging ability of phenols is attributed to the occurrence of hydroxyl groups. Phenols and alkaloids were the major phytochemical constituents of endophytes in the study which supports the views of Huang *et al*., (2007).Preliminary phytochemical investigation of ethyl acetate extracts of endophytic fungi associated with *Eugenia jambolana*confirms the presence of alkaloids, phenols, flavonoids, saponins, and terpenes. Phenols and terpenes are the main chemical constituents responsible for reducing lipid peroxidation and hence act as primary and secondary antioxidants (Hajdu*et al*.,2007).There is 22% of endophytic fungi extract isolated from five *Garcinia*species plants exhibited antioxidant activities Phongpaichit*et al*.,(2007) Total antioxidant activities of the extracts were evaluated by phosphomolybdate method that is routinely used to evaluate the total antioxidant capacity of the extracts Silva *et al*.,(2007). The extract showed significant inhibition percentage. The consequence of accumulation of ROS includes the damage of DNA, RNA, proteins and lipids resulting in the inhibition of their normal functions. The abnormal functioning of these biomolecules can enhance the risk for cardiovascular disease, cancer, autism and other diseases (Song *et al*., 2010). Another antioxidant compound phenylpropanoid amide has been isolated from endophytic fungus *Penicilliumbrasilianum*that reside in *Meliaazedarach*Fill *et al*., (2010). This concept is supported by increasing evidence that oxidative damage plays a role in the development of chronic, age-related degenerative diseases, and that dietary antioxidants oppose this and lower risk of disease. Tianpanich *et al*., (2011) has evaluated radical scavenging activities of isocoumarins and a phthalate from the endophytic fungus *Colletotrichum*sp. Nitya*et al*., (2011) have reported total antioxidant activity of some endophytic fungi.The endophytic fungi of *Neriumoleander*L.and liverwort *Scapaniaverrucosa*were shown to have excellent antioxidant capacity (Zeng*et al*.,2011). Antioxidant activity of *Chaetomium*sp.isolated from wheat (*Triticumdurum*) was 38% by using the β-carotene/linoleic acid system oxidation (Sadrati*et al*.,2013). Ethyl acetate extract of *Aspergillusterreus*isolated from *Ocimum sanctum* exhibited 34.83% antioxidant activity with (14.96±0.07) mg/g GAE phenolic content (Sharma and Vijaya Kumar, 2013). Endophytes of *Salvadoraoleoides*, *Tabebuiaargentea*showed antioxidant potential in different assays (Govindappa*et al*., 2013). In this results, *Aspergillusterreus*showed 63% encouraging antioxidant activity having (41.2±0.40) mg/g GAE. Furthermore, the feasibility of access to plant bioactive compounds is challenged by the low levels at which these products accumulate in native medicinal plants, the long growth periods required for plant maturation, and the difficulty in their recovery from other plant-derived metabolites (Staniek*et al*., 2014). More than 51% of small molecule drugs approved between 1981 and 2014 were based on natural products, the rest being synthetic (Chen *et al*., 2016). With the increasing demand for herbal drugs, natural health products and secondary metabolites, the use of medicinal plants is growing rapidly throughout the world. However, we are facing the accelerated loss of wild medicinal plant species; one third of the estimated 50.000-80.000 medicinal plant species are threatened with extinction from overharvesting and natural anthropogenic habitat destruction (Chen *et al*., 2016). Antioxidants have become the topic of interest recently. The field of free radical chemistry is gaining more attention now a days. Free radicals are reactive oxygen and nitrogen species which are generated by various physiological processes in the body. Uncontrolled generation of free radicals leads to attack on membrane lipids, proteins, enzymes and DNA causing oxidative stress and ultimately cell death. These ROS are responsible for many degenerative human diseases like neurodegenerative disorders, cancer, Alzheimer's disease, ageing, Parkinson's disease, diabetes mellitus, atherosclerosis, and inflammatory diseases. Protection against free radicals can be enhanced by taking sufficient amounts of exogenous antioxidants. An antioxidant is a stable molecule which donates an electron to a rampaging free radical and terminates the chain reaction before vital molecules are damaged. Dietary antioxidants, including polyphenolic compounds, vitamin E and C are believed to be the effective nutrients in the prevention of oxidative stress related diseases. Fungal endophytes represent an abundant and dependable source of novel antioxidant compounds (Yadav*et al*., 2014). Lot of studies were conducted as antiviral, anticancer, antidiabetic and antimicrobial effects to test the potential effects of fungal endophytes, but very few scientists worked on their antioxidant capacity (Seemadhankhar*et al*., 2012). Srinivasan*et al*., 2010 was conducted antioxidant properties using EF *Phyllosticta*sp. which is isolated from medicinal plant *Guazumatomentosa*and also quantified phenol and flavonoid content. Antioxidant was screened (Zeng*et al*.,2011) with the 2,2'-azinodi(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) decolorization assay and 2,2'-diphenyl-1-picrylhydrazyl (DPPH) found this EF have potential novel source of natural antioxidants. Antioxidant was screened for EF in medicinal plants *Rhodiolacrenulata*, *R. angusta*, and *R. sachalinensis*(Cui *et al*., 2015). DPPH, FRAP, and Iron chelating activity are conducted using endophytes*Asperigillusniger* ,*Penicillium sp.* and *Trichoderma sp.* (Govindappa*et al*., 2013).

D. *Secondary metabolites from endophytes as antibiotics*

Antibiotics are used to treat bacterially infected animals but are also administered as a preventive measure. From an animal and human health perspective, Antibiotics are used to treat infections caused by bacteria and other micro-organisms. Traditionally, the term "antibiotics" is used to describe any substance produced by a micro-organism that is effective against the growth of another microorganism. Antibiotics are used to treat bacterially infected animals but are also administered as a preventive measure. Important group of antibiotics was introduced by Duggar,(1948) the tetracyclines, of which chlortetracycline, isolated from the soil bacteria *Strepromycesaureofaciens*, was the first . In the same year, David Gottlieb reported the isolation of a new broad spectrum antibiotic from the soil bacterium *Streptomyces venezuelae*called chloramphenicol (Carter *et al*., 1948).

Different antibiotics have different antibacterial mechanisms of activity. The main mechanisms of antimicrobial action inhibit the bacteria cell wall synthesis by covalently binding with penicillin-binding proteins (PBP), which catalyse the synthesis of peptidoglycan, the major component of the cell wall (Jovetic*et al*., 2010). Chloramphenicol binds to the active site of transfer ribonucleic acid (tRNA) and thus inhibits the protein synthesis at the ribosome (McCoy *et al*., 2011). The carbapenems are structurally very similar to the penicillins the sulfur atom has been replaced by a carbon atom and an unsaturation has been introduced. As a result the carbapenems possess the broadest antimicrobial activity amongst the ß-lactams Nordmann*et al*.,(2011). The most common carbapenems are imipenem, meropenem, ertapenem, doripenem and biapenem.

E. Secondary metabolites from endophytes as anticancer agents

Endophyte hold main position in drug discovery as it has antibiotic, antiviral and anticancer properties, due to their ability to produce chemical which can be used as drug. The discovery of novel antimicrobial metabolites from endophytes is an important alternative to overcome the increasing levels of drug resistance by plant and 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. For this reason, seeking new ways of obtaining Taxol is the key to protecting this limited resources and reducing the cost of drug theraphy with this end goal in mind, scientists all over the world are researching arras related to Taxol production including chemical synthesis, plant tissue cell culture microbial fermentation(Wang *et al*.,2007).In particular microbial fermentation has demonstrated that he isolation and identification of Taxol producing endophytic fungi is new and feasible approach to the production of Taxol (Sun *et al*.,2008).Presently, the development and utilization of Taxol producing fungi have made significant progress worldwide. Extensive research such as searching for paclitaxel producing endophytic fungi from Taxus species as well as from other related plant species, microbial fermentation processes and genetic engineering for improving paclitaxel production has been developed, and much progress has been achieved during the past two decades.

In the case *Taxomycesandrenae, Pestalotiopsismicrospora, Alternaria*sp, *Fusariumlateritium, F.solni, F.mairie* and *Perconia*sp were screened to have the ability to produce Paclitaxel and its derivatives(Chakravarthi*et al*.,2008).This early work set the stage for a more comprehensive examination of the ability of other Taxus species and other plants to yield endophytes producing taxol. Developing new anticancer drugs with a higher potency and specificity against cancer cells has therefore become an important goal in biomedical research and concern for the medical fraternity. 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).

The anticancer drugs show nonspecific toxicity to proliferating normal cells, possess enormous side effects, and are not effective against many forms of cancer. Thus, the cure of cancer has been enhanced mainly due to diagnosis improvements, which allow earlier and more precise treatments. The rediscovery of known secondary metabolites that are typically produced under standard in vitro conditions has been an under-standable consequence of such an approach Scherlach and Hertweck (2009). The importance of compounds bearing antioxidant activity lies 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. These free radicals occur in the body during an imbalance between ROS and antioxidants. Hence, the role of antioxidant is necessary and important to balance the antioxidant status that would reduce the pathological conditions induced by free radicals. Fungi are remarkably a diverse group including approximately 1.5 million species, which can potentially provide a wide variety of metabolites such as alkaloids, benzoquinones, flavonoids, phenols, steroids, terpenoids, tetralones, and, xanthones and taxol, also known as paclitaxel,a chemical substance of tetracyclicditerpene lactam was first isolated from the bark,roots and branches of western coniferous tree *Taxusbrevifolia* Zhou *et al*.,(2010).Traditional methods of extracting taxol from the bark of Taxus species are inefficient and environmentally costly. Aly*et al*., (2010) isolated the bioactive metabolites and showed different biological activities that metabolites antitumor, herbicide, antimicrobial, antimalarial, and antileishmanial. Gayathri*et al*., (2010) pointed out theemergence of antibiotic resistance among pathogenic microorganisms limits treatment options.

Scientific studies have investigated the anticancer activity of several anthracenedione derivatives, which was separated from the secondary metabolites of themangroveendophytic fungus *Halorosellinia*sp. and *Guignardia*sp. Zhang *et al*., (2010). Khan *et al*., (2012) Bioactive metabolites produced by endophytes are also of great interest for drug discovery. Antibiotic resistance genes, in addition to clinical pathogens are also present in environmental isolates, which are horizontally transferred to other microorganisms. Murthy *et al*. (2011) reported the antioxidant potential of methanolic extracts of the endophytes*Fusarium*, *Mucor,* and *Penicillium*spp. isolated from *Lobelianicotianifolia*.According to Kumar and Kaushik (2012), different biofungicide metabolites, such as alkaloids, terpenoids, steroids, isocoumarins and chromones, phenolics and volatiles isolated and characterized from endophytic fungi display antifungal activity against plant pathogenic fungi. These isolated compounds exhibited antifungal and antibacterial activity against pathogenic fungi *Fusariumoxysporum, Rhizoctoniasolani, Colletotrichumgloeosporioides*and *Magnaportheoryzae*as well as against two plant pathogenic bacteria *Xanthomonascampestris*and *Xanthomonasoryzae*(Wang *et al*. 2012). A polyketide compound (5-hydroxyramulosin) isolated from endophytic*Phoma sp*. of *Cinnamomummollissimum*was reported for inhibiting fungal pathogen *Aspergillusniger*(Santiago *et al*. 2012). Sesquiterpenes, diterpenoids and triterpenoids are the major terpenoids produced by endophytic fungi and possess antimicrobial activity. A natural antioxidant Cajaninstilbene acid has been reported from *Fusarium*an endophyte of Pigeon pea, *Cajanuscajan*(Zhao *et al*.,2012). An endophytic fungus *Phomopsis*spp.from*Mesuaferrea*has also also been reported for its antioxidant activity (Jayanthi*et al*.,2011). Fungal endophytes*Aspergillusniger*, *Penicillium spp. AndTrichoderma*spp. isolated from *Tabebuiaargentea*have been reported for their antioxidant potential (Govindappa*et al*.,2013).Song *et al*., (2012) reported the xylok B present in the *Xylaria*sp. which is contains antioxidant property. Desale and Bodhankar(2013) reported the antibacterial activity of endophytes from *Vitexnegundo*and *Vitexaltisimea*. The endophytic fungi may provide agrochemical agents, which may be used as an alternative to replace synthetic pesticides, considering the increasing incidence of chemical resistance in fungal pathogens and potential environmental and mammalian toxicities (Wang *et al*., 2013). *Phoma sp*. endophytic in *Saurauiascaberrinae*is known to produce Phomodione and was found to be effective at a minimum inhibitory concentration of 1.6 μg/ml against *Staphylococcus aureus*(Yadav*et al*.,2014). Umashankar*et al*. (2014) partially purified coumarins from fungal endophytes of *Dactylocteniumaegyptium, Crotalaria pallid* and *Cyanodondactylon*and then checked their antimicrobial activity against common bacterial and fungal pathogens. Cui *et al*. (2015) determined the antioxidant activity of 180 endophytic fungal strains from Alpine plants such as *Rhodiolacrenulata, Rhodiolaangusta*and *Rhodiolasachalinensis*by DPPH free radical scavenging assay. Ratnaweera*et al*. (2015) isolated and purified a bioactive compound equisetin from endophytic*Fusarium sp*. harbored in *Opuntiadillenii*and evaluated its antibacterial activity against three gram positive and two gram negative bacteria and also determined its Minimum Inhibitory Concentration (MIC) values. Ethyl acetate extract of endophyte*Nigropsora*spp. isolated from a medicinal plants *Ginkgo biloba, Lanneacoromandelica* and *Eugenia jambolana*possess significant DPPH radical scavenging activity (Yadav*et al*. 2014). A new α-tetralone derivative together with cercosporamide, β-sitosterol and trichodermin were reported to be produced by *Phoma sp*. endophytic in *Arisaemaerubescens*.Guru*et al*. (2015) is Endophytic*Phoma sp*. isolated from different medicinal plants has been reported to be a promising source of antimicrobial compounds. Total antioxidant capacity (TAC), reducing power assay and DPPH free radical scavenging assay. HUVEC, breast cancer MCF- 7 and MDA-MB-231, prostate cancer PC-3, pancreatic cancer LNCaP and human breast epithelial fR2 cells.Secalonic acid-D was found to inhibit cell proliferation of all the cancer cell lines in a dose and time dependent manner. Wang *et al*. (2016) isolated three new compounds,colletotrichones A-C from the endophytic fungus *Colletotrichum sp*. (BS4) harbored in the leaves of *Buxussinica*and assessed their cytotoxicity (*in-vitro*) on human acute monocytic leukemia cell line (THP-1).

Conclusion:-

This review explains the traditional importance of endophyteswith comparative view in modern medicine.All isolated chemical constituents as a promising antibioticentity. Theherbal formulations or purification of novel compound so as toovercome the obstacles in the path of discovery of pure herbaldrug. The use of the secondary metabolites of plants or microorganisms has gained substantial attention in the treatment of cancer. Endophytes have proven to be rich sources of novel natural compounds with a wide-spectrum of biological activities and a high level of structural diversity. The use of endophytesas biocatalysts in the biotransformation process of natural products assumes greater importance. However, the application of microorganisms by the food and pharmaceutical industries to obtain compounds of interest is still modest, considering the great availability of useful microorganisms and the large scope of reactions that can be accomplished by them.

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

Acknowledgment:-
Authors thanks to Principal and Management of AyyaNadarJanakiAmmal College, Sivakasi for providing facilities to do the present study.

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