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Fungal Endophytes - An Alternative Source of Bioactive Compounds from Plant Species for Prospective Applications – Review

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ABSTRACT

Plant derived compounds have a strong antagonistic activity on pathogenic microorganisms using tremendous natural bioactive compounds accumulated in different parts of plants. Limonoids are important group of metabolically altered triterpene in Meliaceae. Out of 300 limonoids known today, *Melia azedarach* (melianone, meliarachin, meliacine), *Melia dubia* (nimbin, meliacarpin) and *Azadirachta indica* (azadirachtin, nimbolide) contributes about one-third of limonoids. Endophytic fungi are plant symbionts that act as an elicitor for the production of secondary metabolites which serves as an excellent source of drugs for various ailments. It has a great potential to synthesize several novel bioactive compounds which paved a way for commercial exploitation of secondary metabolites for pharmaceutical and agricultural sectors. Many dominant endophytic fungi isolated from these plants includes *Colletotrichum* sp, *Trichoderma* sp, *Penicillium citrinum, Fusarium solani, Aspergillus* sp, *Nigrospora* sp and *Alternaria* sp which acts on human pathogenic microorganisms such as *Escherichia coli Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Candida albicans* common causative agents for Urinary Tract Infections (UTI) predominantly occurring in women. This review aims to delineate the overview on sources of limonoids present in the leaves and the endophytic fungi isolated from these leaves of Meliaceae. The isolated endophytic fungi from the leaves exhibited antagonistic activity on UTI causing pathogens which often leads to infertility among young women. Thus, the sources of limonoids and isolation of endophytic fungi can be enhanced by reinforcing the production of commercial bioactive secondary metabolites that can be substantially utilized by pharmaceutical and agricultural industries to safeguard human beings.

Key words: *Antagonistic activity, Symbiont, Urinary Tract Infection, Endophytic fungi, Elicitor*

Introduction

Medicinal plants are being used by mankind since many decades for several healing purposes. The thirst for knowledge about medicinal plants provoked the researchers to explore several novel compounds in the field of ethnobotany and ethnopharmacognosy (Gurib-Fakim, 2006). Plant-derived compounds containing tremendous natural bioactive compounds are found to be deposited in different parts of the plants such as the stem, leaf, flower, fruit and seed. These secondary metabolites exhibit a strong antagonistic activity on pathogenic microorganisms. About 95% of the globe's population approaches traditional systems of medicines like Unani, Ayurveda, homeopathy, and Siddha for their primary health care due to the presence of amalgamated phyto compounds repository within

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healthy medicinal plant extracts comprising high therapeutic values (Satyavati *et al*., 1987; Sandhya *et al*., 2006). The serious impact of anti-microbial resistance (AMR) pathogens has spurred researchers to discover extra productive novel drugs as an alternative source to safeguard human beings their (Mandal *et al*. 2014). Modification in the structural and functional mechanism of microbes strengthens its resistance potency which facilitated the evolution of antibiotic-resistant microbial strains such as Methicillin-Resistant *Staphylococcus aureus* (MRSA), Extended-Spectrum Beta-Lactamases (ESBL), *Klebsiella* ST258 and *Escherichia coli* ST131. These variations reduced antibiotic virulence against pathogens and led to frustration in the therapeutic drug formulations (Laxminarayan *et al*. 2013).

Endophytes are plant symbionts that act as an elicitor for the production of secondary metabolites by colonizing the internal parts of plant tissues for a specific period of their lifecycle without causing any negative effects on the host plants. Due to the distinctive acclimatization of the endophytic fungi in the host plant, the endophytic communities are triggered to synthesize the secondary metabolites of the host plant either partially (or) completely (Rajagopal *et al*., 2012; Ludwig Muller, 2015). This paved a way for the commercial exploitation of secondary metabolites for various medicinal, agricultural and pharmaceutical sectors (Strobel *et al*. 2004). Moreover, the bioactive compounds synthesized from endophytic fungi had less cytotoxic effects without any antagonistic activity in the eukaryotic host functioning mechanism (Alvin *et al*., 2014).

Mahogany family (Meliaceae) is grouped under evergreen tree species which includes 50 genera and 1400 species distributed throughout tropical and subtropical regions (Nakatani, 2001). *Azadirachta indica*, *Melia azedarach*, and *Melia dubia* are three tree species that are categorized under the Meliaceae family. Due to the presence of the triterpenoids compound, these trees are used for traditional healing purposes since eons ago for treating various health ailments. Triterpenoids are one of the largest groups among different phytocompounds with a vital combination of phytoconstituents that are used for resisting many phytophagous insects. These insects inhibit the growth of plants by hindering the production, quality and quantity that ultimately scale down in agricultural sectors (Grayer and Harborne, 1994). The modified triterpenes are interpreted as limonoids. The consequence of ring configuration and advanced chemical oxidization process is the characteristic features that emphasize the importance of limonoids which act as strong inhibitory compounds for various activities such as insecticidal, insect growth regulation, antifeedant, and provide restorative strength to living beings through its therapeutic antimicrobial properties (Paritala *et al.,* 2015).

Urinary Tract Infection (UTI) is a common disease that targets the lower urinary tract which includes the ureter, urethra, bladder, and kidney (Stamm and Norrby, 2001). The bacterium starts to colonize through massive replication in the bladder and enfeeble the urinary system (Jepson and Craig, 2007). Women are highly prone to UTIs than males due to unique gender factors like the shorter connection between the urethra and anal opening, due to hormonal fluctuations, and pH elevations in the urethra (Stamm and Raz, 1999). Inadequate medication may lead to miscarriage, premature births, morbidity and mortality in the perinatal period and additional obstacles during parturition (Warren *et al*., 1999).

Hence this review enlightens the boons of endophytic fungi invading the family Meliaceae and their effectiveness against harmful microbes, particularly UTI-causing pathogens and multi-drug resistant pathogenic organisms. Based on contemporary research, the current review focuses on the endophytes that are isolated from host plants for targeting pathogenic microbes. Scientists emphasize novel bioactive compounds obtained from endophytic fungi by modifying their culture condition which enhanced the isolation process into the simplest form. It is one of the ideal methods to isolate and extract numerous new endophytes from specific host species. This signifies that over-exploitation of medicinally important tree species for commercial purposes in pharmaceutical and agricultural sectors can be restored through endophytes, predominantly isolated from host species through slight alterations in *in-vitro* conditions and produce antibiotic enzymes which prevent harmful microbial colonization.

Mahogany family - Meliaceae

Meliaceae (or) Mahogany is a large family comprising 51 genera and 575 species with diverse remedial values (Yadav *et al*., 2015). The family includes several important tree crops and among those trees, *Azadirachta indica, Melia azedarach* and *Melia dubia* are

widely necessitated for timber production and extracted by-products for pharmaceutical purposes. The leaves of the family have characteristic features such as serrated margins with exstipulated and pinnate leaflets. The Meliaceae family produces a unique compound known as limonoids, a modified triterpene (Champagne *et al*., 1992; Taylor, 1981).

Azadirachta indica commonly called Neem (or) Indian lilac is a fast-growing, evergreen tree species that belongs to the family Meliaceae. It is widely distributed in tropical and semitropical regions like India, Pakistan, Nepal, and Bangladesh. It grows up to a height of about 20–23 meters, a diameter of 4-5 feet with an upright trunk. The phyllotaxy of *Azadirachta indica* has compound, imparipinnate leaves comprising 5–15 leaflets (Alzohairy, 2016). Limonoids, azadirachtin, nimbidol, nimbin, nimbolinin, nimbidin, salannin, gedunin, and quercetin (flavonoids) are the major phytoconstituents present in this tree species (Kokate *et al*., 2010; Hussain *et al*., 2011). In the earlier studies, polyphenolic flavonoids compounds such as ß-sitosterol and Quercetin were identified. Fresh neem leaf extract was processed, purified, and used for therapeutic purposes as these phytocompounds contain abundant antimicrobial properties that play a vital role in human health management (Alzohairy, 2016).

Melia azedarach is also known as 'Persian lilac' (or) 'Chinaberry' (or) 'Pride of India' similar to neem with slight morphological and anatomical variations that are grouped under the family Meliaceae. It is a deciduous, evergreen tree that reaches a height up to 45 feet and a girth of around 5 feet. It is distributed throughout tropical and temperate regions like India, Japan, and China. The plant revives from seeds during monsoon in its natural habitat. The artificial propagation method can be carried out through plant cutting propagation. Phyllotaxy of *Melia azedarach* leaves is an alternate, usually bipinnate rarely tripinnate, 20 to 40 cm in length with a bright green dorsal surface, pale green ventral surface with 3 to 11 leaflet arrangement with serrated leaf margins. It exudes an unpleasant pungent odor when the leaves are smushed (Al-Rubae, 2009; Sultana *et al*., 2011). According to a literature survey, the phytochemistry of *Melia azedarach* leaves contain compounds like meliacin, quercetin, kaempferol, rutin, nimbinene, melianin, azaridine, lupeol, margosine, and beta-sitosterols (Taylor, 1984; Salib *et al*., 2008). Leaves contain ample amount of terpenoids and limonoids compared to other parts. Compounds like l-Cinnamoyl3-methacrylate-11-hydroxy meliacarpin, l-Cinnamoyl-3-acetyl-11-hydroxy meliacarpin, Deacetylsalannin, 1,3- Dicinnamoyl-l1-hydroxy-meliacarpin, α-Terpinene, α-Terpineol, Kaempferol-3-L-rhamnose-D-glucoside, Kaempferol-3-O-β-rutinoside and Rutin (Sharma and Paul 2013) are found to be present and also proved in previous research studies.

Melia dubia is also known as Malabar neem is a potent fast-growing native tree species of the Meliaceae family that grows rapidly in moist deciduous forests (Warrier, 2011). Though it is widely distributed in Australia and Asia, it has exuberant growth in the regions like Assam, North Bengal, Sikkim, Himalayas, Deccan, Western Ghats, and Northern Circars (Hasegawa *et al.,* 2010). Woods obtained from this tree species are commercially used as timbers as they have high resistant potency against pests, bugs, and worms damage. Thus these woods are widely used for making furniture products and for construction purposes (Suprapti and Hudiansyad, 2004). The tree reaches a height up to 20 meters with straightened crown, an erect round bole of 9 meters in length, and a girth of 1.5 meters (Saravanan *et al*., 2013). Leaf morphology includes 2-3 pinnate (hardly 1 pinnate), extended rachis length varying from 10 to 30 centimeters, swollen base, delicate, terete, with lepidote tomentose (Gopal *et al.,* 2015). With advanced agroforestry practices, this tree species can be cultivated even in an arid environment (or) in less irrigated regions (Singh *et al.,* 2021). The leaf essential oil predominantly contains oxygenated monoterpenes, monoterpenes camphene, α- pinene and β-pinene and also contains relatively less amount of compounds such as sesquiterpenes hydrocarbons, alkanes, phenylpropanoids, and sabinene (Nagalakshmi *et al.,* 2001).

Leaf Endophytes of the Mahogany Family

The fungal endophytes play a vital role in plant protection mechanisms through their inhibiting activities against phytopathogens through their bioactive secondary metabolites. The combination of bioactive compounds isolated from plant endophytes with conventional antibiotics (or) the independent role of phytocompounds obtained from fungal endophytes of plants hinders microbial colonization, amplification, and growth against UTI pathogens (Chutulo and Chalannavar, 2018). Specifically, the compound triterpenoids a terpenoid, derivative of squalene of the Meliaceae family have been extensively studied

for their antimicrobial activity against various gram-positive and gram-negative microorganisms. Chemical compounds synthesized from *Azadirachta indica* include azadirachtin, nimbolide, and nimbidine compounds, *Melia azedarach* includes melianone, meliarachin, and meliacine compounds, and *Melia dubia* includes nimbin, meliacarpin compounds are abundantly accumulated in different parts of the plant (Mwale *et al.,* 2020; Lin *et al.,* 2021). Based on species diversity and endophyte colonization, compared to other parts of plant tissues, leaf tissues are considered to be ideal for exploring fungal endophytes and the bioactive compounds isolated from these endophytes have wide applications in inhibiting different microorganisms causing adverse effects on human health. Based on the distribution, isolation, and colonization frequency of fungal endophytes, Tenguria and Khan (2011) reported that 85 endophytic fungi of 10 genera have been isolated from leaf tissue of *Azadirachta indica* with the fungal composition that includes ascomycetes (5.88%) with 5 *Chaetomium globosum* endophytes; coelomycetes (19.99%) with 14 *Pestalotiopsis* sps and 3 *Phoma* sps endophytes; hyphomycetes (68.2%) with 9 *Aspergillus flavus,* 8 *Aspergillus niger,* 6 *Alternaria alternata* (Fr.) Keissl, 4 *Fusarium* sps, 13 *Penicillium* sps, 18 *Trichoderma* sps, and 5 sterile mycelia endophytes. The *Trichomonas* sps, *Pestalotiopsis* sps, and *Penicillium* sps were found to be dominant. Antibiotic *Penicillium* sps acts efficiently by hindering microbial development. The frequency of endophyte occurrence was remarkably higher in the matured leaves than in tender leaves at the apical zones and high in the mid veins regions than in lamina tissue. The occurrence of foliar endophytes was influenced by the environmental factors, chemical compounds and type of host tissue, seasonal variations, and interaction between fungal endophytes (mycobionts) and the host tissue (phycobionts) (Von Halmschlager *et al*., 1993; Rodrigues, 1994; Chutulo and Chalannavar, 2018). Regarding isolation of endophytic fungus, a study was conducted. In this study, 16 fungal endophytes with 32.5% colonization frequency in the leaf tissues were identified in this research (Kanaga *et al*., 2018). A maximum repository of fungal endophytes was observed in the leaves than in roots, stems, flowers, and fruits. Some of the predominant endophytes obtained from leaves of *Melia azedarach* include *Aspergillus nidulans, Aspergillus flavus, Aspergillus niger, Aspergillus fumigatus, Alternaria alternata, Fusarium solani, Chaetomium* sps, *Curvulariafallax*, and *Cylindrocarpon lichenicola.* Among these endophytes, *Chaetomium* sps and *Aspergillus* sps were most dominantly present in the *Melia azedarach* leaves (Kanaga *et al.,* 2018). Abubakar (2016) isolated five endophytic fungi from *Azadirachta indica* leaf tissues and among those *Cladosporium* sps was predominantly present in the leaves with 11.3% colonizing frequency. A research study was conducted on 25 endophytic fungi isolated from leaves of *Melia azedarach* including four *Aspergillus flavus* (57.14%), five *Absidia repens* (71.42%), five *Aspergillus terreus* (71.42%), one *Chaetomium globosum* (14.28%), one *Alternaria* sps (14.28%), two *Curvularia* sps (28.57%), three *Fusarium solani* (42.85%), two *Humicola* sps (28.57%), one *Curvularia geniculata* (14.28%) and one *Melanospora* sps (14.28%) colonizing frequencies (Rani *et al*., 2020). Yang *et al*. (2012) isolated a unique glycolipid from the endophytic fungi, *Fusarium* sp. LN-11 from *Melia azedarach* leaves. This glycolipid is made of α, α-trehalose and unusual branched fatty acids. Major functions of trehalose include reserving carbohydrates, a strong protector and improving resistance during worsened environmental factors such as increased temperature and reduced dehydration. According to the investigator's assumption, the novel endophytic fungi *Fusarium* sp. LN-11 a supplementary glycolipid combined with other lipids may act as phytoalexins within plants. In an experimental study, about 75 plant segments of *Azadirachta indica* were used to analyze the endophytic fungi population and the total colonizing frequency of the endophytic fungi isolated from leaf segments was (20.65%). The endophytes and colonizing frequency obtained from leaf tissues of *Azadirachta indica* include six *Alternaria alternata* (28.57%), five *Aspergillus oryzae* (23.80%), three *Aspergillus fumigatus* (18.75%), three *Cladosporium cladosporioides* (15.78%) and two *Colletotrichum* sps (13.33%) (Qureshi *et al*., 2019). In a similar study, endophytic fungi from *Azadirachta indica* leaf and leaf with midrib tissues were isolated, identified and evaluated. Majority of genera were found to be hyphomycetes. *Alternaria* sps was most dominant followed by *Colletotrichum truncatum* and *Penicillium* sps with less frequency (Taware *et al*. 2017). In a research report, the fungal endophytes were isolated from leaves of *Melia azedarach* and the experimenter interpreted that among 720 leaf tissue segments, one species of *Nigrospora* and three species of *Aspergillus* belonging to hyphomycetes class were isolated. The

isolated species with their colonization frequency include two *Aspergillus flavus* (6.6%), three *Aspergillus niger* (13.3%), one *Aspergillus* sps (16.6%), and one *Nigrospora* sps (3.3%) (Shekhawat *et al.,* 2010). Endophytic fungi like *Curvularia lunata* and *Geotrichum* sp. AL4 species were isolated from *Azadirachta indica* leaf tissues (Verma and Kharwar, 2006; Li *et al.,* 2007). Four fungal endophytes such as *Aureobasidium* sp. (AIL1), *Sodaria* sp. (AIL3), *Aspergillus* sp. (AIS1), and *Penicillium* sp. (AIS2) were identified and isolated from fresh leaf tissues of *Azadirachta indica* (Treasure *et al.,* 2020). In an investigation, total of 15 endophytic fungi of 10 genera were isolated from fresh *Azadirachta indica* leaf tissues and the dominant endophytes obtained from leaves with colonization frequency are *Trichoderma* (29.17%), *Pestalotiopsis* sp. (18.47%) and *Penicillium* (15.29%) other endophytes belonged to the classes hyphomycetes (58.2%), coelomycetes (89.99%), ascomycetes, and sterile mycelium (7.88%) (Aglave, 2018). Additional consideration also proved the endophytic fungal isolation from leaf tissues of *Azadirachta indica* which includes *Chaetomium globosum* (13.33%), *Colletotrichum* sp., (13.33%), *Phoma* sp., (13.63%), *Cladosporium cladosporioides* (15.78%), *Aspergillus fumigatus* (18.75%), *Fusarium* sp., (20.0%), *Aspergillus oryzae* (23.80%), *Aspergillus niger* (24.0%), *Penicillium* sp. (28.0%), *Alternaria alternata* (28.57%) and the most dominant sp with highest colonizing frequency is *Aspergillus flavus* (36.36%)(Qureshi *et al.,* 2019). A novel study was conducted on isolating and identifying the thermo tolerant endophytic fungi *Cladosporium* sp from *Melia dubia* leaf tissues and synthesis of the zinc nanoparticles from leaf tissue samples. Initially, the leaf segments were placed on potato dextrose agar medium (PDA) supplemented with streptomycin, incubated for two weeks and the temperature was maintained at 45±2 ^{0}C. After incubation for 2-3 weeks, individual fungal colonies were transferred to PDA. For zinc nanoparticles synthesis, the *Cladosporium* sp were grown aerobically in PDA and incubated at 25±2 ^{0}C, filtrate was then treated with zinc oxide solution and incubated at room temperature in dark. After UV-Visible spectroscopy analysis, SEM, X-RAY diffraction (XRD) studies and FTIR analysis the researchers concluded their work by revealing that among 200 leaf segments, a total number of seven thermo tolerant fungal endophytes which belong to 4 species have been isolated at 45^{0}C elevated temperature. The four species include 23 isolates of *Cladosporium* sp, 12 isolates of *Nigrospora oryzae*, 10 isolates of Sterile form I, and 5 isolates of Sterile form II. Thus the *Melia dubia* leaves were used for the first time for the inventive approach to screen thermo-tolerant endophytic fungi and for the zinc nanoparticles synthesize (Sri and Rajagopal, 2016).

Environmental Factors for Symbiotic Relationship

In nature, the synergistic relationship between host plants and endophytes plays an important role in the environmental community. Some salient features of endophytes include (a) specific endophytes are capable to secrete phytohormones which promotes the growth of host plants (Waqas *et al*., 2012) (b) secretion of bioactive compounds like alkaloids, triterpenes, diterpenes, isoflavonoids, and flavonoids increases the power of resistance in the host against biotic and abiotic stresses (Rodriguez *et al*., 2009) (c) Particular group of endophytes act as a repository for secondary metabolites of medicinally important plant species which are used for concoction drug formulations (Shwab and Keller, 2008). Production of bioactive compounds and interaction between host plants and endophytes requires specific factors, (1) temperature, (2) geographical location, (3) vegetation (factors required for endophytic fungi) (Suryanarayanan *et al*., 2005), and (i) growth, (ii) reproduction, (iii) spore germination and (iv) entire life cycle metabolic functions (factors required for the host). The endophytic fungi are restricted to specific host families and the genotypes of species (Dai *et al*. 2003; D'Amico *et al*. 2008).

Role of Terpenoids and Their Mode of Action in Microbial Inhibition

Mode of action as antibacterial and antifungal agents against various harmful human pathogens is achieved by targeting the structural conformation, the functions of bacteria and fungi and thereby inhibiting microbial development. (i.e.) antibacterial drugs targets and inhibits the formation of peptidoglycan, a rigid envelope that surrounds the cytoplasmic membrane of bacteria used for shielding bacterial cell wall (Ghannoum *et al.,* 1999). However, the antifungal drugs target ergosterol, an essential sterol present on fungal cell membrane that is required for different functions like membrane fluidity, integral membrane protein regulation, distribution, and cell cycle regulation (Bard *et al*., 1993; Gooday, 1995). Terpenes are considered the basic unit of plant secondary metabolites, which consists

of isoprene, a simple hydrocarbon molecule. The word terpene indicates the hydrocarbon molecule and terpenoid refers to a modified form of terpene (i.e.) by addition of oxygen. Isoprenoids are considered as building blocks to various metabolites such as sterols, carotenoids, turpentine, and phyto hormones. Globally, the aggravated antibiotic-resistant bacterial growth extensive studies and experiments are carried out by scientists emphasizing the importance of antimicrobial activities of terpenes (Zwenger and Basu, 2008). Though the action mechanism of terpenoids on fungal microbes has not been proved, researchers have reported the impacts of different terpenoid compounds such as geraniol, perillyl alcohol, linalool, and linalyl acetate act on fungal pathogens. These compounds alters the microbial cell functioning systems, by modulating mevalonate pathway (MP), cellular level fluctuation and their associated activities within eukaryotic cells, destabilization of the cell membrane, alters the membrane interconnected functions like cell signaling pathways, permeability, inhibits the G_1, S and G_2-M phases of the cell cycle which ultimately leads to cell death (Mo and Elson, 2004; Brehm-Stecher and Johnson, 2003; Rodrigues Goulart *et al*., 2004; Trombetta *et al*. 2005; Zore *et al*., 2011). Cinnamaldehyde showed its inhibition activity by changing the plasma membrane lipid profile in bacteria (Di Pasqua *et al*., 2006). Some compounds can fit into the lipid bilayer (or) with great affinity they can bind to it that incite structural alterations through permeability inflation that produced instability in maintaining bacterial homeostasis (Alvarez-Martínez *et al*., 2021). Terpenoids show their antibacterial actions through several mechanisms, including the depletion in biofilm development, modification in membrane fatty acids, protein coagulation, oxidative phosphorylation disruption, efflux pumps modulation, reduction in membrane integrity, elevation in membrane permeability, and impeding QS signaling (Bouyahya *et al*. 2022).

Urinary Tract Pathogens and their Consequences During Gestation

Urinary tract infections are the most commonly occurring infections in both males and females irrespective of their ages. The frequent occurrence of pathogens and their growth is more dominant during the time of pregnancy, premenopausal and postmenopausal conditions in women due to fluctuations in the hormone secretion and its distribution (estrogen deficiency). The bacteria induce urination frequency with severe pain along with cloudiness in the urine (Rajivgandhi *et al*. 2014). In addition to bacteria, the presence of salts, waste, and fluids intensifies the level of severity by entering and amplifying the urinary bladder (or) in renal regions (Flores Mireles *et al.,* 2015). Globally, 90% of the uropathogenic strains are gram-negative bacteria which often give rise to UTIs that originate in the gastrointestinal tract and then colonize in the genitourinary tract and some of the genus are, *Enterobacter, Enterococcus, Escherichia, Klebsiella, Proteus, Pseudomonas, and Staphylococcus* (Asmat *et al.,* 2021; Tchente Nguefack *et al.,* 2019; Almalki *et al.,* 2020; Wojno *et al*., 2020; Wiley, *et al.,* 2020). Among these gram-negative organisms such as *Proteus* sp, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* and gram-positive pathogenic bacterial strains such as *Staphylococcus* and *Streptococcus* sp. are causative pathogens responsible for UTI (Ahmed *et al.,* 2019). Multidrug resistance (MDR) microbes such as *Escherichia*, *Acinetobacter*, and *Pseudomonas aeruginosa* showed resistance to several antibiotic drugs in combination with UTI microbes leading to severe complications (Gallagher and MacDougall, 2022; Gastmeier, 2011). The colonization frequency of extended-spectrum beta-lactamase-producing *Escherichia coli* and Methicillin-resistant *Staphylococcus aureus* was found to be high and paved the way for pathogen transmission from mother to the neonate during gestation and after childbirth (Dammeyer *et al*., 2019). Due to numerous alterations in the mechanism of action such as modified (or) reduced antibiotic development, the MDR microbes could have occurred (Christaki *et al.,* 2020). If the condition is untreated, it may cause adverse conditions to the fetus and mother which leads to reduced birth weight, cystitis, pyelonephritis, and preterm delivery (Delzell Jr and Lefevre, 2000).

Antioxidant Activity by Fungal Endophytes

Fungal endophytes that are isolated from leaves of *Azadirachta indica* have been investigated for the presence of bioactive constituents such as flavonoids, tannins, phenols, ascorbic acid, β-carotene and antioxidant activities (Kumaresan *et al*., 2015). In an research article the interpretations by the researcher revealed the presence of a natural antioxidant, cajaninstilbene acid (100.5±9.4) µg/g dry weight of mycelium from *Fusarium solani*, a fungal endophyte isolated from pigeon pea and this

Fusarium species was also isolated from neem leaves (Zhao *et al*., 2012). The *Alternaria alternata* (AE1), a fungal endophyte isolated from *Azadirachta indica* leaves showed strong antioxidant activity in assays such as DPPH free radical with IC50 – 38 µg/ml and superoxide radical scavenging activity with IC50 – 11.38 µg/ml (Chatterjee *et al*. 2019).

Antimicrobial Activities by Endophytic Fungus

The extracts from an endophytic fungus *Pestalotiopsis,* isolated from *Azadirachta indica* had a vital role in the bacterial growth of five different strains of bacteria such as *Bacillus subtilis, Escherichia coli, Pseudomonas fluorescens, Xanthomonas axonopodis*pv. *Malvacearum* and *Staphylococcus aureus* (Tejesvi *et al.,* 2008). The fungal endophyte *Alternaria* sp isolated from leaves of *Azadirachta indica* showed maximum inhibitory effect in chloroform extract (73.33 ± 8.50) and acetone extract (73.66 ± 6.02), minimum inhibitory concentration in the hexane extract (150 µg ml $^{-1}$) and acetone extract (120 µg ml $^{-1}$) and minimum fungicidal concentration in the hexane extract (430 µg ml $^{-1}$) and chloroform extract (300 µg ml $^{-1}$) against the human dermatophytes genus such as *Trichophyton* and *Microsporum* (Verma *et al.,* 2008). The cell-free filtrate of fungal endophytic *Aspergillus* sp., obtained through the isolation process from *Azadirachta indica* showed strong antibacterial activity against gram-positive bacteria such as *Streptococcus mutants* MTCC 497 (IZ 17.0 mm), *Streptococcus pyrogenes* MTCC 1924 (IZ 11.0 mm) *Bacillus subtilis* MTCC 121 (IZ 11.0 mm) and gram-negative bacteria such as *Pseudomonas fluorescens* MTCC 1748 (IZ 12.0 mm) and *Escherichia coli* MTCC 40 (IZ 18.0 mm). It also acts as antifungal action against *Candida glabrata* MTCC 3814 (IZ 13.0 mm) and *Candida albicans* MTCC 227 (IZ 24.0 mm) (Jain and Sharma 2014). Mycelial mats of endophytic fungi obtained from ethyl acetate neem leaves extract has been proved through several experiments for their antibacterial activity against gram-positive human pathogens such as *Bacillus subtilis*, *Bacillus cereus*, *Streptococcus pyogens*, and *Staphylococcus aureus* and gram-negative bacteria such as *Klebsiella pneumoniae*, *Escherichia coli*, *Proteus* sp., *Salmonella typhi* and *Pseudomonas* sp., (Selvi and Balagengatharathilagam, 2014). Isolation of fungal endophyte *Emericella* sp from *Azadirachta indica* leaves produced a bioactive compound named N-[(2S, 3aR, 6S, 7As)-6-acetamide-octahydro-1, 3-benzothiazol-2-yl] 2- (adamantan-1-yl) acetamide containing sulfur that strongly inhibited the growth of human fungal pathogen *Candida albicans* (Mittal *et al*., 2016). An endophytic fungus, *Penicillium* sp., isolated from leaves of *Azadirachta indica* showed an average range of antibacterial and antifungal activities. Maximum IZ was observed in *Staphylococcus aureus* (12.5 mm), *Klebsiella pneumoniae*, and *Proteus mirabilis* with IZ of 8.5 ± 0.5 mm each, *Salmonella paratyphi* with IZ of 10.5 mm, and *Escherichia coli* with IZ 9.5 mm respectively. Investigation on ethyl acetate extracts of *Alternaria alternata* AE1, an endophyte obtained from a leaf sample of *Azadirachta indica* showed more prominent results against gram-negative and gram-positive bacteria species with IZ of 11 mm (*Escherichia coli*), 12 mm (*S. aureus* and *S. typhimurium*) and 14 mm (*B.subtilis* and *Listeria monocytogenes*). The SEM study proved the action mechanism of the endophytic fungi against human pathogens by causing disruption in the bacterial cell wall structure that leads to rupturing of intracellular material such as protein, DNA, and potassium (K^+) ions and connecting end to end resulting in improper cell division. (Chatterjee *et al.,* 2019). The fungal endophytes such as *Cladosporium* sp, *Aspergillus* sp, *Muscodor* sp, *Ulocladium* sp, and *Alternaria* sp isolated from *Azadirachta indica* leaf tissues showed antimicrobial activity against various human pathogens like *Trichophyton* sp, *Hortaea werneckii*, *Candida albicans*, *Microsporum* sp and *Candida* sp (pink colony). Along with these endophytes *Penicillium* sp, *Trichoderma* sp, and *Fusarium* sp also inhibited the growth of *Candida* sp., *Trichophyton* sp., and *Hortaea werneckii* through leaves extract bioactive compounds obtained from various endophytic fungi colonization of respective host plant. Researchers interpreted their results that the secondary metabolites isolated from these endophytic fungi can be used for novel drug formulations against dermatophytes (Vasudha *et al.,* 2019). For the first time, innovatory anticestodal activity was proved in *Azadirachta indica.* The endophytic fungi *Pestalotiopsis* sp. from neem leaves strongly inhibited the growth of *Echinococcus granulosus* (hydatid cysts). The reports revealed that the scolicidal activity of this endophyte had occurred within 30 minutes of incubation with 97% mortality (Verma *et al.* 2013). The fungal secondary metabolites are produced by two endophytic fungi (Aln-L4 and Aln-L5) from ethyl acetate *Azadirachta indica* leaf extracts. The presence of aureonitol from Aln-L4 extract and cladosporin, scytalone, and citreoisocoumarinol

from Aln-L5 extract were found in the work of the discoverer (Nnanna *et al.*, 2018). A fungal endophyte, NM-LB 1 obtained from leaves of *Azadirachta indica* showed strong inhibitory activity with an IZD ranging from 2-3 mm against *Klebsiella pneumoniae* compared to positive controls Ciprofloxacin and Miconazole (Okonkwo Uzor *et al*., 2022). In a recent study, the five fungal endophytes which includes *AIE1, AIE2, AIE3, AIE4 &AIE5* isolated from segments of leaf blades and mid ribs of *Azadirachta indica* exhibited strong antimicrobial potency in the ethyl acetate crude extract against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa and Candida albicans*. *AIE1 and AIE2* showed low reverse transcriptase inhibition of 21% & 15% at maximum concentration of 1 mg/ml (Umurhurhu *et al*., 2023).

Conclusion

In this present circumstance, the need for primary health care increases gravely due to these emerging multi-drug resistant pathogenic microbes within the human community. The persistence of gestational UTI-causing pathogens increases miscarriages and premature births predominantly in young mothers.

Plants are a rich natural source that acts as a repository to synthesize secondary metabolites produced from different regions of plants which can be utilized to combat several human ailments. Phytocompounds derived from medicinal plants have powerful antipathetic activities against various gram-positive and gram-negative pathogens. Among numerous phyto compounds triterpenoids, a terpenoid derived from squalene has been proved to be an excellent source of an antimicrobial compound that targets and inhibits the growth of UTI pathogens through target checkpoints such as cell cycle arrest, modulating cell signaling pathways and terpenoids execute the therapeutic effects against helminthes infections and UTI. The species of Meliaceae including *Azadirachta indica*, *Melia azedarach*, and *Melia dubia* have ample amounts of bioactive secondary metabolites in different plant tissues such as root, bark, stem, leaf, flower and fruit. Endophytes are substantial natural compounds with extensive biologic activities which are colonized inside medicinal plant tissues. The constructed secondary metabolites are isolated from the endophytes has therapeutic potency which can fight against harmful pathogens. Numerous works of literature corroborated experimentally and proved that maximal endophytic fungal isolates were extracted from leaf tissues. The secondary metabolites were commercially exploited from these endophytes, as they have specific therapeutic properties for targeting the specific binding receptors of harmful pathogens, especially *Escherichia coli* and *Candida albicans* most frequently occurring pathogens, predominantly in females. Phyto compounds in drug discovery constrain the mode of action in the morbific pathogens thereby improving human health management.

Therefore this review aimed to delineate the overview of triterpenoids, bioactive phyto compounds which differs vastly from synthetic antibiotics and the process of isolating endophytic fungi from leaf tissues of Meliaceae family species. The extraction process of bioactive compounds from endophytes can be enhanced by reinforcing the production of commercially bioactive secondary metabolites that can be substantially utilized by pharmaceutical and agricultural sectors which can exert a profound effect to safeguard human beings.

Conflict of Interest

None

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