International Journal of Advanced Biochemistry Research

ISSN Print: 2617-4693
ISSN Online: 2617-4707
IJABR 2024; 8(1): 399-410
www.biochemjournal.com
Received: 07-10-2023
Accepted: 12-11-2023

Pradnya C Diwthe
M.V. Sc. Student, Department of Veterinary Pharmacology & Toxicology, Nagpur Veterinary College, Nagpur, Maharashtra, India

Dr. Alka Sawarkar
Assistant Professor, Department of Veterinary Pharmacology & Toxicology, Nagpur Veterinary College, Nagpur, Maharashtra, India

Dr. Swati Umap
Assistant Professor, Department of Veterinary Pharmacology & Toxicology, Nagpur Veterinary College, Nagpur, Maharashtra, India

Dr. AP Somkuwar
Professor and Head, Department of Veterinary Pharmacology & Toxicology, Nagpur Veterinary College, Nagpur, Maharashtra, India

Corresponding Author:
Dr. Alka Sawarkar
Assistant Professor, Department of Veterinary Pharmacology & Toxicology, Nagpur Veterinary College, Nagpur, Maharashtra, India

Endophytes and their therapeutic application

Pradnya C Diwthe, Dr. Alka Sawarkar, Dr. Swati Umap and Dr. AP Somkuwar

DOI: https://doi.org/10.33545/26174693.2024.v8.i1f.434

Abstract

The human population is increasing at an alarming rate, and a variety of health issues are popping up, such as the increase in the number of drug-resistant microorganisms and side effects of drugs. The natural therapeutic compounds produced by endophytic microbes have several potential applications in the pharmaceutical industry. Endophytes are "all organisms inhabiting plant organs that can colonise within plant tissues without causing apparent harm to their host." These symbiotic microorganisms live inside the different tissue parts of the plant, like nodules, roots, bark, leaves, and stems. Endophytes can be categorised as obligate and facultative. Facultative endophytes can survive in the soil, on the plant surface, inside the plants, and on artificial nutrients, and endophytes that inhabit inside plant tissues throughout their lifespan are called obligate endophytes. Endophytic microorganisms have a unique property to synthesise bioactive compounds hurting plant and human pathogens. These bioactive compounds are terpenoids, steroids, xanthones, phenols, perylene derivatives, quinines, furan diones, and terpenoids. Endophytes have discovered many bioactive compounds with insecticidal, antimicrobial, and anticancer properties in the last few years. Bioactive compounds produced by endophytes alone or in conjunction with host plants are eco-friendly and harmless for plants, animals, and humans. These are poorly investigated microorganisms; therefore, focus studies and trials are needed for specific applications of endophytes in antimicrobial resistance and drug discovery.

Keywords: Endophytes, secondary metabolites, therapeutic application, emerging potential

Introduction

Antimicrobial resistance (AMR) is a natural evolutionary process for microorganisms (bacteria, fungi, viruses, and parasites), which is sped up by the selective pressure caused by the widespread use and abuse of antibiotics (World Health Organization 2020) [111]. In hospitals, towns, and nations, there is ample evidence between the use of antibiotics and resistance. It is one of the main issues with public health, particularly in developing countries like India, where antibiotics are more readily available, and misuse of them increases the likelihood of resistance. The number of individuals around the world is growing at an alarming rate, and numerous new health problems are emerging. The global fight against the growing problem of antibiotic resistance depends on research on antibiotics and other microbial natural compounds. To solve this issue, developing new and potent drugs containing natural compounds is necessary. Traditional medicine has achieved significant use of medicinal plants to promote immunity and human health. Due to their ability to synthesise various therapeutic natural compounds, they have also been found to contain a broad spectrum of pharmacological properties (Akerele *et al.*, 1991) [3]. Asthma, skin conditions, respiratory, gastrointestinal, and urinary disorders, and several illnesses traditionally treated using various medicinal plants (Akerele *et al.*, 1991; Bajguz, 2007) [3, 8]. Depending on the plant species, soil type, and relationship with microbial communities, the presence and amount of these biologically active metabolites in medicinal plants may change (Morsy 2014; Faeth and Fagan 2002) [64, 31].

Endophytes are symbiotic microorganisms that survive inside the various plant tissues, such as nodules, roots, bark, leaves, and stems, without harming the entire plant or its constituent parts. Around 300,000 higher plants exist worldwide, each containing one or more endophytic microorganisms (Barkodia *et al.*, 2018) [12]. Endophyte is derived from the Greek terms Endon, which means "inside," and phyte, which means "plants." Entophytae is a name coined by the German botanist Heinrich Friedrich Link to designate a particular group of fungi that were partially planted parasites (Link, 1809) [56]. Bacteria and other microorganisms were later added to the definition of the term. Endophytic microorganisms were first identified under a microscope by De Bary in 1866 [25], who described them as "any organism that grows within plant tissues" (De Bary, 1866) [25].

Endophytes primarily invade the inside of plants through their roots and aerial parts, such as their leaves, flowers, stems, and cotyledons (Kobayashi *et al*., 2000) [53]. They can spread throughout the entire host plant body and are localised at the place of invasion (Hallmann *et al*., 1997) [39]. after invading, they remain in the host's cells, intercellular spaces, or vascular (tissue) system (Patriquin *et al*., 1978; Jacobs *et al*., 1985; Bell *et al*.,1995) [97, 45, 15]. Endophytes are known to produce a wide variety of natural compounds after resting in plant tissues, which could be a reliable and effective source of medicines. As a result, the pharmaceutical, agrochemical, and biotechnology industries all have great potential for natural compounds derived from endophytic bacteria (Findlay *et al*., 1997) [31].

Types of endophytic microorganisms

Most endophytic microorganisms associated with plants include fungi and bacteria (actinomycetes or mycoplasma). Endophytic bacteria live inside plant tissues and are essential for both preventing disease and promoting plant growth. Gram-positive and Gram-negative endophytic bacterial species have been found in various plants (Golinska *et al*., 2015) [35]. These include Pseudomonas, Acinetobacter, Agrobacterium, Bacillus, and others. Endophytic microbes most commonly belong to the phyla Actinobacteria, Proteobacteria, and Firmicutes (Zhao *et al*., 2011) [124]. Streptomyces is the most dominant endophyte that can synthesize bioactive metabolites (Holland *et al*., 2011) [41]. Mycoplasma species have also been found as endophytes that have a symbiotic relationship with some red algae, including Bryopsis pennata and Bryopsis hypnoides (Bhardwaj and Agrawal 2014) [17]. Endophytic fungi are divided into two groups: clavicipitaceous endophytes, which affect some grasses, and non-clavicipitaceous endophytes, which originate from asymptomatic tissues of nonvascular plants, including ferns and their allies, conifers, and angiosperms (Jalgaonwala *et al*., 2011) [46]. There are two primary categories of endophytic bacteria, i.e., facultative and obligatory. Obligate endophytes are those that live their entire lives inside the tissues of plants (Stoltzfus and de Bruijn 2000) [94], as opposed to facultative endophytes, which can thrive in the soil, on the surface of plants, inside plants, and on artificial nutrients (Baldani *et al*., 1997) [10]. Several plant species and plantlets from *in vitro* cultures have also been reported to have uncultivable endophytic bacteria. Facultative (cultivable) are extensively distributed in the plant kingdom and can be isolated from different plant species to investigate their potential to produce naturally occurring products of commercial importance.

Table 1: Some specific examples of endophytic microorganisms and their sources

Sr. No.	Endophytic microorganisms	Endophytic sp.	Source	References
1.	Endophytic Actinomycetes	*Streptomyces* sp. GT2002/1503	*Bruguiera gymnorrhiza*	Ding *et al*., 2010 [27]
		Streptomyces sp. Loyola UGC	*Dhatura stramonium* L	Christhudas *et al*., 2013 [23]
		Streptomyces sp. JQ92617	*R. densiflora*	Akshatha *et al*., 2014 [4]
2.	Endophytic Fungi	*Stemphylium globuliferum*	*Momordica charanti*	Pavithra *et al*., 2014 [73]
		Penicillium Oxalicum	*Cupressus Torulosa*	Bisht *et al*., 2016 [16]
		Alternaria tenuissima and *Diaporthe* sp	*Ocimum sanctum*	Kumar *et al*., 2014 [54]
		Aureobasidium pullulan	*Boswellia sacra*	Dompeipen *et al*., 2011 [29]
3.	Endophytic Bacteria	*Arthrobacter* sp. WWAT1, *Pseudomonas* sp. WYAT2, *Microbacterium* sp. WYAT3, *Psychrobacter* sp. WBAT4, *Enterobacter* sp. WWAT5, *Bacillus* sp. WBAT6, *Kosakonia cowanii* WBAT7, *Bacillus* sp. WBAT8, *Bacillus* sp. WBAT9, *Chromobacterium violaceum* WVAT6, *Serratia* sp.WPAT8 and *Burkholderia* sp. WYAT7.	*Artemisia nilagirica*	Ashitha *et al*., 2019 [57]
		Micrococcus endophyticus VERA1, *Bacillus megaterium* VERA2, *Pseudomonas chlororaphis* VERA3, *P. kilonensis* VERA4, *Stenotrophomonas pavanii* VERA5, *B. endophyticus* VERA6, *S. maltophilia* VERA7, *Pantoea ananatis* VERA8, *B. atrophaeus* VERA9 and *M. flavus* VERA10.	*V. anthelmintica*	Rustamova *et al*., 2020 [83]

Endophytes as a source of secondary metabolites

Endophytes synthesize various bioactive secondary metabolites with unique structural characteristics, including alkaloids, benzopyranones, flavonoids, phenolic acids, quinones, steroids, terpenoids, tetralones, xanthones, and many others. Such bioactive metabolites and a few other specialized metabolites are primarily produced by endophytic bacteria, fungi, and actinomycetes (Liarz *et al*., 2016; Patil *et al*., 2016; Yadav *et al*., 2017) [75, 70, 114]. endophytes synthesize secondary metabolites via three pathways: mevalonic acid, polyketide, and shikimic acid (Goyal *et al*., 2017) [37]. This article briefly reviews some significant groups of secondary metabolites with various biological activities. These include organic acids, terpenoids, alkaloids, terpenoids, phenols, and enzymes.

Terpenoids

There are 15,000–20,000 known structures in the terpenoid group. Its common origin is from mevalonate and isopentenyl pyrophosphate, and the lipophilic character of the structures sets it apart from other types of secondary metabolites. Chemically, terpenoids are typically cyclic unsaturated hydrocarbons connected to the fundamental isoprene skeleton with varying amounts of oxygen in the constituent groups. The number of isoprene structures and their carbon atoms in the molecules determine the nomenclature of terpenoids (Wagner and Elmadfa, 2003) [108]. Terpenoids consist of carbon isoprene units, which can be classified into monoterpenes, sesquiterpenes, and di-terpenes; it is known that endophytes stimulate plants to produce common terpenoid compounds known as phytoalexins as protection against plant diseases (Fu-kang *et al*., 2010) [134]. Reactive oxygen species (ROS) are produced in Atractylodes lancea by Pseudomonas fluorescens ALEB7B and the fungus endophyte Gilmaniella sp. AL12. This produces oxygenous sesquiterpenoids (Yuan *et al*., 2016; Zhou *et al*., 2016) [119, 126]. Recently, it was revealed that endophytic *Nemania bipapillata* produced botryane terpenoids from a red alga, chrysin, and Asparagopsis taxiformis, while endophytic *Chaetomium globosum* produced a flavone from Chaetomorpha media, a sea green alga (Medina *et al*., 2019; Kamat *et al*., 2020) [60, 50].

Alkaloids

In recent years, several alkaloids derived from endophytic fungi in plants have been identified to have excellent biological activities, such as antibacterial, insecticidal, cytotoxic, and anticancer properties. Endophytes include a variety of bioactive alkaloids, including ergot, parasite, loglines, and pyrrolizidine, which have promise as broad-spectrum insecticides and play significant roles in the food industry, medicine, and agriculture (Zhang *et al*., 2012) [121]. A naturally occurring chemical molecule called alkaloids mainly comprises basic nitrogen. They are produced through the decarboxylation of amino acids such as tryptophan, tyrosine, ornithine, histidine, and lysine. Endophytic Bacillus cereus, *Serratia liquefaciens*, Marmoricola sp. SM3B, *Bacillus thuringiensis*, *Bacillus licheniformis*, *Bacillus thuringiensis*, *Bacillus licheniformis*, Aranicola proteolyticus, and Acinetobacter SB1B are the potential alkaloid producers (Liu *et al*., 2015; Pandey *et al*., 2016) [57, 68]. Recently, it was discovered that endophytic Irpex lacteus and *Phaeosphaeria oryzae* produce isoindolinone alkaloid irpexine (Sadahiro *et al*., 2020) [85]. Meanwhile, endophytic *Phlegmariurus taxifolius* of the medicinal plant Huperzia serrata produces huperzine A (Cruz-Miranda *et al*., 2020) [24].

Phenols

The shikimate pathway produces a broad class of dietary secondary metabolites known as polyphenols and have several disease-preventing qualities (Vald'es *et al*., 2015; Lunardelli *et al*., 2016) [106, 59]. A new phenolic molecule produced by an endophyte like *Pestalotiopsis mangiferae*, for instance, has significant antibacterial and antifungal activity against B. subtilis, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Candida albicans (Subban *et al*., 2013) [95]. According to (Abdel Razek *et al*., 2020), endophytic Penicillium citrinum-314 from *Halocnemum strobilaceum* produces a novel phenolic alkaloid called 3-amino-5-(3-hydroxybutan-2-yl) -4-methylphenol.

Enzymes and organic acids

Specific enzymes produced from endophytes include acid and alkaline enzymes from *Aspergillus oryzae* and A. niger, neutral proteases from Aspergillus flavus and A. sojae, cellulase from *Trichoderma koningii*, diastase from *Aspergillus oryzae*, glucoamylase from Aspergillus niger and A. oryzae, lactase from S. lactis and *Rhizopus oryza* (Tiwari, 2015; Mishra *et al*., 2019) [103, 62]. Microbial organic acids can be utilized as taste enhancers, acidifiers, stabilizers, or preservatives in the food and feed industries. Colletotric acid is produced by *Colletotrichum gloeosporioides*, citric acid by Aspergillus Niger, fumaric acid by Rhizopus nigricans, gluconic acid by Aspergillus Niger, Itaconic acid by A. terreus and kojic acid by A. oryzae are among the organic acids produced by endophytic fungi and citric acid has also been produced by Yarrowia lipolytica and associated yeast species.

Therapeutic application of endophytes

Endophytes as sources of novel bioactive constituents with therapeutic potential applications. Both bacterial and fungal endophytes isolated from medicinal plants have the ability to produce novel bioactive compounds with various functional roles and pharmaceutically significant effects such as antibiotics, immunosuppressants, antioxidants, antiarthritic, antimicrobial, antidiabetic, anticancer, and anti-inflammatory activities could be utilised to address the need for new therapeutic agents to treat human diseases (Gunatilaka, 2006; Gouda *et al*., 2016) [38, 36]. These compounds are typically derived from natural sources or created by microbial production through fermentation or other microbial transformation (Berger, 2009) [13]. Due to its promising applications, biotransformation has been the approach that has been used the most frequently among these (Borges *et al*., 2009) [14].

Anticancer activity

The second greatest cause of mortality in the United States and a significant global public health issue is cancer. The pandemic of the coronavirus disease 2019 (COVID-19) adversely affected cancer diagnosis and therapy in 2020. Delays in diagnosis and treatment as a result of healthcare setting closures and COVID-19 exposure fear resulted in decreased access to care, which could cause a temporary decrease in cancer incidence followed by an increase in advanced disease and, ultimately, higher mortality. In 2020, it is estimated that there will be 19.3 million new cases of cancer worldwide (18.1 million excluding nonmelanoma skin cancer) and over 10 million cancer deaths (9.9 million excluding nonmelanoma skin cancer). With an expected 2.3 million new cases (11.7%), female breast cancer has surpassed lung cancer as the most often diagnosed malignancy. Lung (11.4%), colorectal (10.0%), prostate (7.3%), and stomach (5.6%) cancers are next in line. With an expected 1.8 million fatalities (18%), lung cancer continued to be the most common type of cancer. It was then followed by colorectal (9.4%), liver (8.3%), stomach (7.7%), and female breast (6.9%) cancers (Sung *et al*., 2021) [97]. Cancer is one of the world's leading causes of death, and the continuous interest in cancer research is not surprising.

Various naturally occurring anticancer chemicals have been extracted from many sources, including endophytes, demonstrating the success of cancer research efforts. The endophyte Metarhizium anisopliae, which colonizes the bark of the *Taxus brevifolia* tree, produces the diterpenoid Taxol ($C_{47}H_{51}NO_{14}$).

Due to its distinct mode of action, which blocks the depolymerization of tubulin molecules during cell division, it has drawn considerable attention as a potential anticancer agent (Schiff and Horwitz, 1980) [87]. According to recent research novel endophytic fungus, Epicoccum nigrum TXB502 from *Taxus baccata* was recently reported to produce Taxol (El-Sayed *et al*., 2020) [30], and endophytic fungus, *Hypocrea lixii* from *Cajanus cajan* to produce an anticancer drug called cajanol (Zhao *et al*., 2013) [125]. *Camptotheca acuminata*, an endophytic fungus that produces the potent antineoplastic chemical camptothecin ($C_{20}H_{16}N_2O_4$), is the precursor of anticancer agents, topotecan and irinotecan (Kusari *et al*., 2009) [128]. Some Actinomycetes taxa, including Actinomyces, Streptomyces, Mycolatopsis, Saccharopolyspora, and Micromonospora, have been found to produce metabolites having anticancer activity. For instance, the endophytic Streptomyces sp. strain BO-07 from *Boesenbergia rotunda* produces biphenyls (Taechowisan *et al*., 2017) [99]. It has been noted that the Streptomyces cavourensis strain YBQ59 from Cinnamomum cassia exhibits anticancer activities (Vu *et al*., 2018) [107].

Antioxidant activity

Antioxidant substances protect cells from reactive oxygen species and free radicals, which can result in oxidative damage, cellular degeneration, and cancer. Most antioxidant substances have anti-inflammatory, antibacterial, anti-atherosclerotic, anti-carcinogenic, or antiviral activities that depend on concentration. Cancer, cardiovascular disease, atherosclerosis, hypertension, ischemia/reperfusion injury, neurological illnesses (Alzheimer's and Parkinson's diseases), rheumatoid arthritis, and aging are all considered to be ROS-linked diseases that can be effectively treated with antioxidants (Huang *et al*., 2007) [42].

Antioxidant metabolites are frequently produced by bacterial and fungal endophytes. for example, it has been found that the phenolic compound Graphislactone A, which was isolated from the endophytic fungus Cephalosporium sp., IFB-E001 that lives in *Trachelospermum jasminoides*, has antioxidant and free radical-scavenging properties *in vitro* (Song *et al*., 2005) [92]. Furthermore, it has been documented that the ethanolic extract from the endophytic Aspergillus fumigates of *Cajanus cajan*, which primarily contains luteolin, has antioxidant properties.

As evaluated by OH radical scavenging, DPPH, reducing power, xanthine oxidase inhibitory, and lipid peroxidation assays, the extract demonstrated significant antioxidant activity. Additionally, the extract significantly increased the expression of catalase (CAT), superoxide dismutase (SOD), and glutathione reductase (GR) activities in HepG2 cells and protect DNA from oxidative damage. Furthermore, flavipin, isolated from *Chaetomium globosum* CDW7, has been shown to have antioxidant properties; its concentration determined the antioxidant activity of the endophyte's crude extracts (Falade *et al*., 2021) [32].

Antidiabetic activity

Diabetes mellitus is one of the most common systemic diseases in the world, and it occurs when the body develops insulin resistance or fails to produce enough insulin. According to the World Health Organization, the number of people with diabetes mellitus of all forms has increased dramatically over the past few decades and is predicted to reach 629 million by 2045 (Agrawal *et al*., 2022) [2]. Various studies have revealed that certain endophytic extracts and chemicals have anti-diabetic properties. It has been reported that the endophytic Aspergillus awamori isolated from Acacia nilotica can produce an unidentified peptide with alpha-glucosidase and alpha-amylase inhibitory activities (Singh & Kaur 2016) [91]. The extract and the compounds "(S)-(+)-2-cis-4-trans-abscisic acid, 7-hydroxy-abscisic acid, and 4-des-hydroxyl altersolanol A" from Nigrospora oryzae hosted by *Combretum dolichopetalum* were reported to exhibit the ability to lower fasting blood sugar in mice with alloxan-induced diabetes (Uzor *et al*., 2017) [105]. L-783,281 is a non-peptidal fungal metabolite that was found in the fungus Pseudomassaria sp. It mimics insulin and can significantly lower blood sugar levels in mice models. L783,281 is a new therapy for the treatment of diabetes because, unlike insulin, it is not degraded in the digestive system (Zhang *et al*., 1999) [120].

Antimalarial activity

The antiplasmodial activity was reported in several endophytic isolates. The cyclodepsipeptide fusaripeptide A, derived from an endophytic fungus inhabiting Mentha longifolia, is one specific example of an antiplasmodial compound and remarkable anti-Plasmodium falciparum (D6 clone) activity was shown by fusaripeptide A (Ibrahim *et al*., 2018) [44]. Another study found that the substance 3-(2-Hydroxypropyl) benzene-1,2-diol, which was isolated from an endophytic fungal strain, had anti-plasmodial activity against the multidrug-resistant K1 clone when dihydroartemisinin was used as the standard drug (Sommart *et al*., 2008) [93]. Additionally, at 6.25 and 3.125 g/kg.b.wt, gancidin W, isolated from an endophytic bacterial strain (Streptomyces sp. SUK10) hosted by Shorea ovalis, displayed antimalarial activity against Plasmodium berghei PZZ1/100 *in vivo*, resulting in about 80% parasite growth suppression in male ICR mice strain.

Antiviral activity

The most curious microbes are viruses since they live both within and outside of their hosts. In essence, viruses need a host to reproduce or replicate, and during this process, they impact the host. The human body possesses defenses against viral invaders, but how effective they depend on the host's immune system, the size and nature of the virus, and other factors. Apart from influenza, herpes, dengue, etc., there has been a surge of viral infections over the past two decades, manifesting as major or minor outbreaks, epidemics, and pandemics, with SARS-CoV-2 being the most recent. One of the most likely ways to build up resistance to viral diseases is by getting vaccinated, but developing a promising vaccine takes a lot of effort. Viral disorders can also be treated with chemotherapy, which primarily targets the replication system of the virus inside the host. However, because of their underlying evolutionary process, they develop into drug-resistant varieties. Thus, treating these disorders becomes more challenging for clinicians.

Considering this concept, it is vital to investigate innovative chemical structures that are powerful and effective against viruses and may eventually be developed into therapeutic agents. Fungi have been widely recognised as the source of novel chemical compounds with various pharmacological properties, including antiviral activity, which is primarily measured using diverse vivo experiments. However, anti-viral drugs produced by fungal endophytes are a relatively recent discovery. Aconitum transsectum Diels' roots contain Alternaria solani, which has made a metabolite called 7-dehydroxyl-zinniol (23), with moderate anti-hepatitis B viral activity. The peel of *Puncia granatum* was used to isolate *Alternaria alternata* PGL-3, another endophytic isolate. With an ICso value of 17 g/mL, the ethyl acetate extract of the culture broth of this fungus demonstrated highly strong inhibition of HCV NS3/4a protease. It produced the chemicals alternariol (4) and alternariol-9-methyl ether (11). Therefore, these chemicals are responsible for *Alternaria alternata* PGL-3's anti-HBV (Patil and Maheshwari, 2021) [71].

Anti-Parasitic activity

Tropical diseases are caused mainly by pathogenic parasites that are vector- or non-vector-borne and are more common in people who live in unsanitary surroundings, have poor living situations, and are near animals. The estimated global prevalence of these tropical parasitic diseases is greater than 1 billion. Protozoans, helminths, bacteria, and viruses comprise the majority of harmful parasites in low areas. However, we should focus more on the parasitic diseases brought on by protozoans and helminths since they are more challenging to treat than diseases brought on by bacteria and viruses, which are more susceptible to vaccines. Producing vaccines for these parasitic organisms is challenging since they are difficult to cultivate in a lab, have a multicellular complex organisation, and complete their life cycle in many hosts. Small-molecule drugs are the best choice for treating these diseases. The variety of endophytic fungi found on tropical plants makes them the most significant source for screening and isolating compounds with anti-parasitic activity. In Trixis vauthieri, an Asteraceae plant from Brazil, Alternaria sp. UFMGCB 55 was seen as an endophyte and exhibited anti-trypanocidal properties. This endophytic isolate's bioactive extract was further isolated and produced the biphenyl tensin. Alternata P1210 made two chemicals, alternarlactones A and alternarlactones B, while living as an endophyte in the roots of the halophyte Salicornia sp. in Spain. Compounds revealed anti-parasitic efficacy against Plasmodium falciparum and *Leishmania donovani* (Shi *et al*., 2019) [89].

Antimicrobial activity

Metabolites with antibiotic action are low-molecular-weight organic natural compounds produced by microbes that are active against other microorganisms at low doses. Endophytes are believed to produce secondary metabolites as a defence mechanism against pathogenic invasion (Pimentel *et al*., 2011) [74]. Endophytes produce a variety of antimicrobial substances, including alkaloids, peptides, steroids, terpenoids, phenols, quinines, and flavonoids. Due to the growing resistance of human and plant diseases to currently available medications and chemicals, there is an urgent need for the identification of novel antimicrobials (Yu *et al*., 2010). The genus Xylaria has also been related to a variety of antifungal substances. Among them are sordaricins, which are effective against Candida albicans (Pongcharoen *et al*., 2008). The production of antimicrobial substances by numerous different endophytic bacterial and fungal species has also been reported, including 3-O-methylalaternin, altersolanol A, phomoenamide, phomodione, ambuic acid, isopestacin, and munumbicin A, B, C, and D. (Joseph and Priya, 2011; Pimentel *et al*., 2011) [49, 74] two new endophytes from *Panax notoginseng*, Fusarium sp. PN8 and Aspergillus sp. PN17 was discovered to produce saponins with antibacterial activity (Jin *et al*., 2017) [47]. Additionally, it has been observed that several endophytes of the species Bacillus, *Enterobacter asburiae*, Pseudomonas, Variovorax, Stenotrophomonas, Rhodococcus, Penicillium, and Alternaria exhibit quorum quenching activity by producing anti-quorum sensing chemicals such quercetin, catechin, phytolapicidin, baicalein, and naringenin against a variety of gram-negative and gram-positive bacteria (Rajesh and Rai, 2014a; Asfour, 2018; Parlet *et al*., 2019; Joo *et al*., 2021) [81, 6, 69, 48].

Endophytes as a source of antibiotics

Research on antibiotics and other microbial natural products is crucial in the global struggle against the escalating issue of antibiotic resistance. Finding new antibiotics to combat this issue is essential, and endophytes are one potential source of such antibiotics. Metabolites from microbial, plant, and animal life constitute natural products. These natural products are significant because they have traditionally served as sources of medicine. Natural products have frequently been used as sources for the lead compounds that gave rise to numerous synthetic drugs. Most endophytes produce various antibiotics; in fact, endophytes are one of the unexplored potential sources of new antibiotics. Some of the new antibiotics produced by endophytes include Ecomycins, Pseudomycins, Munumbicins, and Kakadumycins.

Ecomycins

The Ecomycins are a group of new lipopeptides that contain homoserine and β-hydroxy aspartic acid, two uncommon amino acids. Ecomycins are known to be produced by Pseudomonas viridiflava, an endophytic bacterium (Miller *et al*., 1998) [61]. One of the fluorescent Pseudomonads related to plants, this endophyte has been found in the tissues of numerous grass species. The three antifungal lipopeptides produced by P. viridiflava strain EB273 have been isolated and are only partially characterized as Ecomycins A, B, and C. Ecomycin A is the only one of these three compounds that are similar to amino acid composition with a known antibiotic syringotoxin (Ballio *et al*., 1990) [11]. Furthermore, research using the P. viridiflava strains EB274 (California, USA) and EB227 (Israel) of the same bacteria also produced antifungal lipopeptides with masses that are the same as those of Ecomycins B and C. (Harrison *et al*., 1991) [40] showed that these compounds had the ability to suppress the human infections Cryptococcus neoformans and Candida albicans.

Kakadumycins

These are peptide antibiotics synthesised (in culture) by the endophytic bacterium Streptomyces (NRRL30566) from the northern Australian Grevillea tree (*Grevillea pteridifolia*, also known as *Grevillea chrysodendron* R.Br.) (Castillo *et al*., 2003) [22]. Kakadumycin A and echinomycin, another quinoxaline antibiotic derived from Streptomyces and a potential anticancer drug, share chemical similarities. [53-54] Kakadumycin A is efficient against P. falciparum and shares the same antibacterial properties as Munumbicins (Waring and Wakelin 1994) [109]. Kakadumycin A is efficient against P. falciparum and shares the same antibacterial properties as munumbicins.

Pseudomycins

The Pseudomycins are a class of peptide antifungal chemicals derived from liquid cultures of the plant-associated bacteria Pseudomonas syringae. These lipopeptide antifungal peptides also contain non-conventional amino acids such as D- and L-diamino butyric acid, L-hydroxy aspartic acid, and L-chlorothreonine. The Proteobacteria Phylum's Pseudomonadaceae family includes the P. syringae. The four-membered pseudomycin family, which includes pseudomycin A as the main member, shows remarkable effectiveness against the human pathogen Candida albicans. Hydroxy aspartic acid, serine, arginine, lysine, and diamino butyric acid are all components of Pseudomycins A through C. Contrarily, Pseudomycin D is more complex than Pseudomycins A–C and has a molecular mass of 2401 Da. They are discovered to be distinct from the P. syringae antimycotics previously reported, such as syringomycin, syringotoxin, and syringostatins. They are efficient against certain pathogenic fungi that affect humans and plants, such as Candida albicans and Candida neoformans (Harrison *et al*., 1991) [40].

Munumbicins

The Munumbicins are a novel class of four bioactive compounds. Munumbicins A, B, C, and D are recently discovered antibiotics having broad-spectrum activity against bacteria, fungi, and a species of Plasmodium that cause plant pathology. These compounds were derived from a bacterium known as Streptomyces NRRL 30562 that was deposited in the Medi Peoria USDA National Laboratory. The Snake vine (*Kennedia nigriscans*), a medicinal plant indigenous to Australia's northern area, contains the endophytic bacterium. The munumbicins work against Gram-positive bacteria such as Staphylococcus aureus, Streptococcus pneumoniae, Bacillus anthracis, and Enterococcus faecalis (Castillo *et al*., 2002) [20]. A vancomycin-resistant strain of E. faecalis (VREF, ATCC 51299) and a methicillin-resistant strain of S. aureus (MRSA, ATCC 33591) are two Gram-positive bacterial strains that are frequently drug-resistant. A multi-drug resistant (MDR) acid-fast bacterium called Mycobacterium TB is susceptible to Munumbin B. The oddest thing about this situation is that only the MDR strain of M. tuberculosis was responsive to Munumbin B, whereas the drug-susceptible variant of this bacterium was less responsive. The munumbicins C and D are of particular interest since they are efficient against Gram-positive and harmful bacteria but also against the most pathogenic Plasmodium that causes malaria, Plasmodium falciparum. The most effective antimalarial medicine, chloroquine, was reportedly outperformed by Munumbicin D (Obianime *et al*.,2009) [67].

Xiamycins: The Xiamycins are an example of indolosesquiterpenes isolated from plant materials. They are newly discovered pentacyclic indolosesquiterpenes known as Xiamycin-A and its methyl ester-2, which were isolated from the endophyte Streptomyces sp. strain GT2002/1503 of the mangrove plant Bruguiera gymnorrhiza. It is interesting that Xiamycin-A has anti-HIV action that is only selective (Ding *et al*., 2010) [27]. (Ding *et al*., 2011) [28] reported the discovery of three new indolosesquiterpenes, Xiamycin B (1b), Indosespene (2), and Serpentine (3), in addition to the well-known Xiamycin A (1a), in the culture broth of Streptomyces sp. strain HKI0595, a bacterial endophyte of the common mangrove tree, Kandelia candle. According to their research, these Xiamycins are effective against various bacteria, including methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus faecalis.

Emerging potentials of endophytes

In this article, we highlight the newly discovered potentials of endophytes in the generation of bioactive substances with inhibitory effects on multi-resistant Staphylococcus aureus (MRSA), lipase, antibiofilm metabolites, nanoparticle biosynthesizers. Because most of these properties have only recently been revealed with relatively limited investigations, these traits are considered to be emerging in endophytes.

1. Production of anti-MRSA compounds

Staphylococcus aureus is a part of our natural microbiota, occasionally threatens human life as a pathogen, and is "a significant source of hospital and community-acquired infections" (Kim *et al*., 2020) [52]. S. aureus is among the most challenging pathogenic bacteria to treat, because of its morphological features of multiple drug resistance, which inhibit the efficiency of antibiotic therapy. However, recent research has identified bioactive substances that can stop MRSA from growing in endophytic bacteria. When extracted from the endophytic fungus Heritiera fomes, Pestalotia sp., oxysporone, and xylitol exhibited significant inhibitory action against six MRSA strains (Nurunnabi *et al*., 2018) [66].

2. Antibiofilm potential

Biofilms are defined as communities of microorganisms that are attached to a surface and play a significant role in the persistence of bacterial infections. In comparison to planktonic bacteria, bacteria within a biofilm are several orders of magnitude more resistant to antibiotics. No drugs targeting bacterial biofilms are currently being investigated in clinical trials (Rabin *et al*., 2015) [77]. Endophytic strains that have antibiofilm potential may be used in various biotechnological fields, such as antibiofilm therapies and biomedical applications (Rajesh and Rai, 2015b) [82].

(Rajesh and Ravishankar, 2014) [81] exhibited the antibiofilm potential of Bacillus firmus PT18 and *Enterobacter asburiae* PT39 isolated from *Pterocarpus santalinus* Linn. against Pseudomonas aeruginosa PAO1, which may be used for medical antibiofilm applications. In clinically important pathogens like Staphylococcus capitis 267 and S. haemolyticus 41 strains, Nocardiopsis sp., associated with Zingiber officinale, showed a dose-dependent biofilm suppression with >90% efficacy. As a result, the bioactive components from Nocardiopsis sp. extract would be good candidates for use in biomedical applications that target biofilms (Sabu *et al*., 2017) [84]. It has been reported that there are potential uses for antibiofilm produced by endophytes in the treatment of diabetic conditions. As an illustration, Alternaria destruens, hosted by Calotropis gigantea, simultaneously had alpha-glucosidase inhibitory potentials (Kaur *et al*., 2020) [51].

3. Novel lipase inhibitor sources (LIs)

Obesity is a significant public health concern around the world, due to its link with various comorbidities, which sharply increases an individual's risk of "morbidity and mortality" in obese individuals (Falade *et al*., 2021) [32]. Furthermore, obesity is becoming more prevalent in a variety of developed countries. Several obese people are suffering frustration because of their repeated failures to lower their body mass index (BMI) through physical exercise. As a result, people are in serious need of effective drugs and weight loss strategies. It is exciting that LIs, which are intriguing alternative therapies for the treatment of obesity and overweight, maybe a good choice for such individuals. LIs function by decreasing the intestinal absorption of dietary lipids. This happens when LIs bind to lipase in a competitive manner to prevent the conversion of triglycerides to monoglycerides and fatty acids. Therefore, LIs have the potential to reduce weight in patients who are obese significantly and, as a result, lower the risk of comorbidities, including type-2 diabetes and cardiovascular disorders. Recent reports have suggested that endophytes are potential sources of novel LIs. A ginger endophytic actinobacterial strain produced secondary metabolites with promising pancreatic lipase inhibitory activity. Because the inhibition percentage (≈90%) was significantly higher than that of ginger extract (≈ 69%) and standard LI (orlistat), which had an approximate inhibition rate of 88%. The endophytic bacterial strain exhibited considerable substantial lipase inhibitory activity, which may be attributed to the presence of terpenoids, phenols, tannins, flavonoids, alkaloids, and saponins in the endophyte (Rahayu *et al*., 2019) [79]. Similarly, bioactive compounds from the endophytic fungus Phomopsis sp., cyclosporine B, and dothiorelone A, had outstanding lipase inhibitory efficacy as they had greater IC50 values than orlistat, which was used as the standard LI (Sheng *et al*., 2020) [88].

4. Nanoparticle synthesisers

Because of the extensive functionality, potential bioactivity, non-pathogenic nature, and enormous therapeutic utility of these particles, the biosynthesis of nanoparticles utilising both bacterial and fungal endophytic microorganisms has become an emerging frontier technology (Saravanan *et al*., 2020) [86]. Various endophytes have been used to synthesise silver and gold nanoparticles. These biosynthesised nanoparticles have a broad range of potential uses in nanomedicine due to their antibacterial, antifungal, antioxidant, antimicrobial, antidiabetic, anticancer, and photocatalytic degradation capabilities (Rahman *et al*., 2019) [80]. Silver nanoparticles are extensively used in biolabeling, antibacterial agents, catalysts, and sensors due to their unique optical, electrical, and magnetic qualities. Endophytic bacteria including Bacillus cereus, Bordetella sp., and Pseudomonas veronii obtained from the host plants Adhatoda beddomei, Piper nigrum, and Annona squamosa, respectively, have been used to synthesise silver nanoparticles that have been shown to exhibit antibacterial activity (Sunkar and Nachiyar, 2012; Thomas *et al*., 2012; Baker *et al*., 2015) [98, 104, 9]. The biosynthesis of the production of silver nanoparticles from endophytes and their potential uses in therapeutics has been a systematic review by (Rahman *et al*., 2019) [80]. Additionally, the endophytic bacterial extract Pantoea ananatis used to synthesise the silver nanoparticles showed notable antibacterial efficacy against Candida albicans and B. cereus which are resistant to conventional antibiotics (Monowar *et al*., 2018) [63].

5. Promising bioresources for developing NTDs therapeutics

Neglected tropical diseases (NTDs) are a diverse group of infectious diseases prevalent in over 140 countries' tropics and subtropics WHO (2012) [110]. Approximately 18 illnesses have been classified by the WHO as NTDs, which comprise several other diseases, including schistosomiasis, human African trypanosomiasis, leprosy, Buruli ulcer, Chagas disease, and leishmaniases.

According to the WHO, NTDs have an annual economic impact on developing countries of over one billion people. The WHO created a strategy to prevent, control, eliminate, and eradicate NTDs. It recommended preventative chemotherapy and the need to improve the management of NTDs as some of the significant approaches WHO (2021) [112]. Therefore, it is remarkable that active compounds from endophytes have demonstrated significant anti-leishmanial, antitrypanosomal, and schistosomicidal action (Brissow *et al*., 2017; Tawfike *et al*., 2019) [119, 102], which indicates that endophyte secondary metabolites are potential candidates for the control of NTDs. Endophytes, however, currently need to be explored in the development of prospective therapeutic candidates for the treatment of NTDs. Therefore, future research initiatives should focus on this direction because endophytes are promising bioresources for new natural bioactive substances for treating NTDs.

6. Drug development for coronavirus disease 2019 (COVID-19) Ongoing research aims to identify novel compounds that can block one or both CoV-2 proteins from competitively interacting with their target substrate. Docking of natural antiviral compounds found in Chinese medicinal plants tested against spike glycoprotein and 3CL exhibited some intriguing results (Zhang *et al*., 2020) [124]. As endophytic microorganisms are recognised for secreting secondary metabolites, endophytes from anti-COVID-19 medicinal plants can generate bioactive substances with promising CoV-2 protein inhibitory activity. Therefore, endophytes from medicinal plants with known antiviral effects can be investigated to isolate new drugs with SARS-CoV-2 spike glycoprotein and 3CL protease inhibitory action (Falade *et al*., 2021) [32].

Conclusion

Endophytes are under-explored superheroes, capable of synthesising secret chemicals that can be targeted against numerous disease-causing pathogens. Besides having wide therapeutic applications, focused studies and trials need to be conducted for their specific applications in Anti-microbial resistance and new drug discovery. The application of metagenomics combined with next-generation sequencing technologies is expected to open the numerous unexplored pools of antimicrobials secreted by yet uncultivated endophytic microbes. It is crucial to examine and emphasise the past achievements, ongoing research, and most recent advancements in research related to endophytic microbes to draw the research community's attention to this developing topic and potential exploitation of the available sources for their therapeutic purposes in numerous fields, such as the medical, pharmaceutical, food, and cosmetics industries.

References

1. Abdel Razek MM, Moussa AY, El-Shanawany MA, Singab ANB. A new phenolic alkaloid from *Halocnemum strobilaceum* endophytes: antimicrobial, antioxidant, and biofilm inhibitory activities. Chemistry & Biodiversity. 2020;17(10):e2000496.
2. Agrawal S, Samanta S, Deshmukh SK. The antidiabetic potential of endophytic fungi: Prospects as therapeutic agents. Biotechnology and Applied Biochemistry. 2022;69(3):1159-1165.
3. Akerele O, Heywood V, Synge H, editors. Conservation of Medicinal Plants. Cambridge University Press; 1991.
4. Akshatha VJ, Nalini MS, D'souza C, Prakash HS. Streptomycete endophytes from anti-diabetic medicinal plants of the Western Ghats inhibit alpha-amylase and promote glucose uptake. Letters in Applied Microbiology. 2014;58(5):433-439.
5. Aly AH, Debbab A, Proksch P. Fungal endophytes: unique plant inhabitants with great promises. Applied Microbiology and Biotechnology. 2011;90(6):1829-1845.
6. Asfour HZ. Anti-quorum sensing natural compounds. Journal of Microscopy and Ultrastructure. 2018;6(1):1.
7. Ashitha A, Midhun SJ, Sunil MA, Nithin TU, Radhakrishnan EK, Mathew J. Bacterial endophytes from *Artemisia nilagirica* (Clarke) Pamp., with antibacterial efficacy against human pathogens. Microbial Pathogenesis. 2019;135:103624.
8. Bajguz A. Metabolism of brassinosteroids in plants. Plant Physiology and Biochemistry. 2007;45(2):95-107.
9. Baker S, Kumar KM, Santosh P, Rakshith D, Satish S. Extracellular synthesis of silver nanoparticles by novel *Pseudomonas veronii* AS41G inhabiting *Annona squamosa* L. and their bactericidal activity. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2015;136:1434-1440.
10. Baldani J, Caruso L, Baldani VL, Goi SR, Döbereiner J. Recent advances in BNF with non-legume plants. *Soil Biology and Biochemistry*. 1997;29(5-6):911-922.
11. Ballio A, Bossa F, Collina A, Gallo M, Iacobellis NS, Paci M, *et al*. Structure of syringotoxin, a bioactive metabolite of Pseudomonas syringae pv. syringae. FEBS Letters. 1990;269:377-80.
12. Barkodia M, Joshi U, Rami N, Wati L. Endophytes: A hidden treasure inside plant. *IJCS*. 2018;6(5):1660-1665.
13. Berger RG. Biotechnology of flavours—the next generation. Biotechnology Letters. 2009;31(11):1651-1659.
14. Borges KB, de Souza Borges W, Durán-Patrón R, Pupo MT, Bonato PS, Collado IG. Stereoselective biotransformations using fungi as biocatalysts. Tetrahedron: Asymmetry. 2009;20(4):385-397.
15. Bell CR, Dickie GA, Harvey WLG, Chan JWYF. Endophytic bacteria in grapevine. Canadian Journal of Microbiology. 1995;41(1):46-53.
16. Bisht R, Sharma D, Agarwal PK. Antimicrobial and antidiabetic activity of a *Penicillium oxalicum* isolated from *Cupressus torulosa*. International Journal of Biotechnology and Biomedical Sciences. 2016;2(2):119-122.
17. Bhardwaj A, Agrawal P. A review fungal endophytes: as a storehouse of bioactive compound. World Journal of Pharmacy and Pharmaceutical Sciences. 2014;3(9).
18. Bosamia TC, Barbadikar KM, Modi A. Genomic insights of plant endophyte interaction: prospective and impact on plant fitness. In: Kumar A, editor. *Microbial Endophytes*. Woodhead Publishing; 2020. pp. 227–249.
19. Brissow ER, da Silva IP, de Siqueira KA, Senabio JA, Pimenta LP, Januário AH, *et al*. 18-Des-hydroxy Cytochalasin: an antiparasitic compound of *Diaporthe phaseolorum*-92C, an endophytic fungus isolated from *Combretum lanceolatum* Pohl ex Eichler. Parasitology Research. 2017;116(7):1823-1830.
20. Castillo UF, Strobel GA, Ford EJ, Hess WM, Porter H, Jensen JB, *et al*. Munumbicins, wide-spectrum antibiotics produced by *Streptomyces* NRRL 30562, endophytic on *Kennedia nigriscans*. Microbiology. 2002;148(9):2675-2685.
21. Campos FF, Rosa LH, Cota BB, Caligiorne RB, Teles Rabello AL, Alves TMA, *et al*. Leishmanicidal metabolites from *Cochliobolus sp.*, an endophytic fungus isolated from *Piptadenia adiantoides* (Fabaceae). PLoS Neglected Tropical Diseases. 2008;2(12):e348.
22. Castillo U, Harper JK, Strobel GA, Sears J, Alesi K, Ford E, *et al*. Kakadumycins, novel antibiotics from *Streptomyces sp.* NRRL 30566, an endophyte of *Grevillea pteridifolia*. FEMS Microbiology Letters. 2003;224(2):183-190.
23. Christhudas IN, Praveen P. Kumar & P. Agastian. Curr Microbiol. 2013;67:69-76.
24. Cruz-Miranda OL, Folch-Mallol J, Martínez-Morales F, Gesto-Borroto R, Villarreal ML, Taketa AC. Identification of a Huperzine A-producing endophytic fungus from *Phlegmariurus taxifolius*. Molecular Biology Reports. 2020;47(1):489-495.
25. de Bary A. *Morphologie und physiologie der pilze, flechten und myxomyceten*. Engelmann; 1866.
26. Devari S, Jaglan S, Kumar M, Deshidi R, Guru S, Bhushan S, *et al*. Capsaicin production by *Alternaria alternata*, an endophytic fungus from *Capsicum annum*; LC–ESI–MS/MS analysis. Phytochemistry. 2014;98:183-189.
27. Ding L, Münch J, Goerls H, Maier A, Fiebig HH, Lin WH, *et al*. Xiamycin, a pentacyclic indolosesquiterpene with selective anti-HIV activity from a bacterial mangrove endophyte. Bioorganic & Medicinal Chemistry Letters. 2010;20(22):6685-6687.
28. Ding L, Maier A, Fiebig HH, Lin WH, Hertweck C. A family of multicyclic indolosesquiterpenes from a bacterial endophyte. Organic & Biomolecular Chemistry. 2011;9(11):4029-4031.
29. Dompeipen EJ, Srikandace Y, Suharso WP, Cahyana H, Simanjuntak P. Potential endophytic microbes selection for antidiabetic bioactive compounds production. Asian Journal of Biochemistry. 2011;6:465-471.
30. El-Sayed ESR, Zaki AG, Ahmed AS, Ismaiel AA. Production of the anticancer drug taxol by the endophytic fungus *Epicoccum nigrum* TXB502: enhanced production by gamma irradiation mutagenesis and immobilization technique. Applied Microbiology and Biotechnology. 2020;104(16):6991-7003.
31. Faeth SH, Fagan WF. Fungal endophytes: common host plant symbionts but uncommon mutualists. Integrative and Comparative Biology. 2002;42(2):360-368.
32. Falade AO, Adewole KE, Ekundayo TC. Therapeutic potentials of endophytes for healthcare sustainability.

Egyptian Journal of Basic and Applied Sciences. 2021;8(1):117-135.

33. Findlay JA, Buthelezi S, Li G, Seveck M, Miller JD. Insect toxins from an endophytic fungus from wintergreen. Journal of Natural Products. 1997;60(11):1214-1215.
34. Fu-kang G, Chuan-chao D, Xiao-zhen L. Mechanisms of fungal endophytes in plant protection against pathogens. African Journal of Microbiology Research. 2010;4(13):1346-1351.
35. Golinska P, Wypij M, Agarkar G, Rathod D, Dahm H, Rai M. Endophytic actinobacteria of medicinal plants: diversity and bioactivity. Antonie Van Leeuwenhoek. 2015;108(2):267-289.
36. Gouda S, Das G, Sen SK, Shin HS, Patra JK. Endophytes: a treasure house of bioactive compounds of medicinal importance. Frontiers in Microbiology. 2016;7:1538.
37. Goyal S, Ramawat KG, Mérillon JM. Different shades of fungal metabolites: an overview. Fungal Metabolites. 2017;1-29.
38. Gunatilaka AL. Natural products from plant-associated microorganisms: distribution, structural diversity, bioactivity, and implications of their occurrence. Journal of Natural Products. 2006;69(3):509-526.
39. Hallmann J, Quadt-Hallmann A, Mahaffee WF, Kloepper JW. Bacterial endophytes in agricultural crops. Canadian Journal of Microbiology. 1997;43(10):895-914.
40. Harrison LH, Teplow DB, Rinaldi M, Strobel G. Pseudomycins, a family of novel peptides from Pseudomonas syringae possessing broad-spectrum antifungal activity. J Gen Microbiol. 1991;137:2857-65.
41. Hollants J, Leroux O, Leliaert F, Decleyre H, De Clerck O, Willems A. Who is in there? Exploration of endophytic bacteria within the siphonous green seaweed Bryopsis (Bryopsidales, Chlorophyta). PLoS One. 2011;6(10):e26458.
42. Huang WY, Cai YZ, Xing J, Corke H, Sun M. A potential antioxidant resource: endophytic fungi from medicinal plants. Economic botany. 2007;61(1):14-30.
43. Ibrahim SR, Mohamed GA, Ross SA. Aspernolides L and M, new butyrolactones from the endophytic fungus Aspergillus versicolor. Zeitschrift für Naturforschung C. 2017;72(5-6):155-160.
44. Ibrahim SR, Abdallah HM, Elkhayat ES, Al Musayeib NM, Asfour HZ, Zayed MF, Mohamed GA. Fusaripeptide A: new antifungal and anti-malarial cyclodepsipeptide from the endophytic *fungus Fusarium* sp. Journal of Asian Natural Products Research. 2018;20(1):75-85.
45. Jacobs MJ, Bugbee WM, Gabrielson DA. Enumeration, location, and characterization of endophytic bacteria within sugar beet roots. Canadian Journal of Botany. 1985;63(7):1262-1265.
46. Jalgaonwala RE, Mohite BV, Mahajan RT. A review: natural products from plant-associated endophytic fungi. J Microbiol Biotechnol Res. 2011;1(2):21-32.
47. Jin Z, Gao L, Zhang L, Liu T, Yu F, Zhang Z, Wang B. Antimicrobial activity of saponins produced by two novel endophytic fungi from *Panax notoginseng*. Natural Product Research. 2017;31(22):2700-2703.
48. Joo HS, Deyrup ST, Shim SH. Endophyte-produced antimicrobials: a review of potential lead compounds with a focus on quorum-sensing disruptors. Phytochemistry Reviews. 2021;20(3):543-568.
49. Joseph B, Priya RM. Bioactive Compounds from Endophytes and their Potential in. American Journal of Biochemistry and Molecular Biology. 2011;1(3):291-309.
50. Kamat S, Kumari M, Sajna KV, Jayabaskaran C. Endophytic fungus, *Chaetomium globosum*, associated with marine green alga, a new source of Chrysin. Scientific reports. 2020;10(1):1-17.
51. Kaur J, Sharma P, Kaur R, Kaur S, Kaur A. Assessment of alpha-glucosidase inhibitors produced from endophytic fungus Alternaria destruens as antimicrobial and antibiofilm agents. Molecular Biology Reports. 2020;47(1):423-432.
52. Kim SM, Escorbar I, Lee K, Fuchs BB, Mylonakis E, Kim W. Anti-MRSA agent discovery using Caenorhabditis elegans-based high-throughput screening. Journal of Microbiology. 2020;58(6):431-444.
53. Kobayashi DY, Palumbo JD. Bacterial endophytes and their effects on plants and uses in agriculture. In Microbial endophytes. CRC Press. 2000;213-250.
54. Kumar AS, Reddy GB, Kulal A. *In-vitro* studies on α-amylase, α-glucosidase and aldose reductase inhibitors found in endophytic fungi isolated from Ocimum sanctum. Current Enzyme Inhibition. 2014;10(2):129-136.
55. Liarzi O, Bucki P, Braun Miyara S, Ezra D. Bioactive volatiles from an endophytic Daldinia cf. concentrica isolate affect the viability of the plant parasitic nematode Meloidogyne javanica. PLoS One. 2016;11(12):e0168437.
56. Link HF. Observationes in ordines plantarum naturales. Dissertatio I. Mag Ges Naturf Freunde Berlin. 1809;3:3-42.
57. Liu Y, Liu W, Liang Z. Endophytic bacteria from Pinellia ternata, a new source of purine alkaloids and bacterial manure. Pharmaceutical Biology. 2015;53(10):1545-1548.
58. Liu SS, Jiang JX, Huang R, Wang YT, Jiang BG, Zheng KX, Wu SH. A new antiviral 14-nordrimane sesquiterpenoid from an endophytic *fungus Phoma* sp. Phytochemistry Letters. 2019;29:75-78.
59. Lunardelli Negreiros de Carvalho P, de Oliveira Silva E, Aparecida Chagas-Paula D, Honorata Hortolan Luiz J, Ikegaki M. Importance and implications of the production of phenolic secondary metabolites by endophytic fungi: a mini-review. Mini Rev Med Chem. 2016;16(4):259-271.
60. Medina RP, Araujo AR, Batista JM, Cardoso CL, Seidl C, Vilela AF, Silva DH. Botryane terpenoids produced by *Nemania bipapillata*, an endophytic fungus isolated from red alga Asparagopsis taxiformis-Falkenbergia stage. Scientific reports. 2019;9(1):1-11.
61. Miller CM, Miller RV, Garton-Kenny D, Redgrave B, Sears J, Condron MM, Strobel GA. Ecomycins, unique antimycotics from Pseudomonas viridiflava. Journal of Applied Microbiology. 1998;84(6):937-944.
62. Mishra R, Kushveer JS, Revanthbabu P, Sarma VV. Endophytic fungi and their enzymatic potential. In Advances in Endophytic Fungal Research. Springer, Cham. 2019;283-337.

63. Monowar T, Rahman MS, Bhore SJ, Raju G, Sathasivam KV. Silver nanoparticles synthesized by using the endophytic bacterium Pantoea ananatis are promising antimicrobial agents against multidrug resistant bacteria. Molecules. 2018;23(12):3220.
64. Morsy N. Phytochemical analysis of biologically active constituents of medicinal plants. Main Group Chemistry. 2014;13(1):7-21.
65. Nithya K, Muthumary J. Secondary metabolite from *Phomopsis* sp. isolated from Plumeria acutifolia Poiret. Recent Research in Science and Technology. 2010;2(4).
66. Nurunnabi TR, Nahar L, Al-Majmaie S, *et al*. Anti-MRSA activity of oxysporone and xylitol from the endophytic fungus *Pestalotia* sp. growing on the Sundarbans mangrove plant Heritiera fomes. Phytother Res. 2018;32(2):348–354.
67. Obianime AW, Aprioku SJ. Comparative study of Artesunate, ACTs and their combinants on the spermatic parameters of the male guinea-pig. Nigerian Journal of Physiological Sciences. 2009;24(1).
68. Pandey SS, Singh S, Babu CS, Shanker K, Srivastava NK, Kalra A. Endophytes of opium poppy differentially modulate host plant productivity and genes for the biosynthetic pathway of benzylisoquinoline alkaloids. Planta. 2016;243(5):1097-1114.
69. Parlet CP, Kavanaugh JS, Crosby HA, Raja HA, El-Elimat T, Todd DA, Horswill AR. Apicidin attenuates MRSA virulence through quorum-sensing inhibition and enhanced host defense. Cell reports. 2019;27(1):187-198.
70. Patil RH, Patil MP, Maheshwari VL. Bioactive secondary metabolites from endophytic fungi: a review of biotechnological production and their potential applications. Studies in natural products chemistry. 2016;49:189-205.
71. Patil RH, Maheshwari VL (Eds.). Endophytes: Potential Source of Compounds of Commercial and Therapeutic Applications. Springer Nature; 2021.
72. Patriquin DG, Dobereiner J. Light microscopy observations of tetrazolium-reducing bacteria in the endorhizosphere of maize and other grasses in Brazil. Can J Microbiol. 1978;24:734-42.
73. Pavithra N, Sathish L, Babu N, Venkatarathanamma V, Pushpalatha H, Reddy GB, Ananda K. Evaluation of α-amylase, α-glucosidase and aldose reductase inhibitors in ethyl acetate extracts of endophytic fungi isolated from antidiabetic medicinal plants. International Journal of Pharmaceutical Sciences and Research. 2014;5(12):5334-41.
74. Pimentel MR, Molina G, Dionísio AP, Maróstica Junior MR, Pastore GM. The use of endophytes to obtain bioactive compounds and their application in biotransformation process. Biotechnology research international; 2011.
75. Pongcharoen W, Rukachaisirikul V, Phongpaichit S, Kühn T, Pelzing M, Sakayaroj J, Taylor WC. Metabolites from the endophytic *fungus Xylaria* sp. PSU-D14. Phytochemistry. 2008;69(9):1900-1902.
76. Prabpai S, Wiyakrutta S, Sriubolmas N, Kongsaeree P. Antimycobacterial dihydronaphthalenone from the endophytic *fungus Nodulisporium* sp. of Antidesma ghaesembilla. Phytochemistry Letters. 2015;13:375-378.
77. Rabin N, Zheng Y, Opoku-Temeng C, Du Y, Bonsu E, Sintim HO. Biofilm formation mechanisms and targets for developing antibiofilm agents. Future medicinal chemistry. 2015;7(4):493-512.
78. Radji M, Sumiati A, Rachmayani R, Elya B. Isolation of fungal endophytes from Garcinia mangostana and their antibacterial activity. African Journal of Biotechnology. 2011;10(1):103-107.
79. Rahayu S, Fitri L, Ismail YS. Endophytic actinobacteria isolated from ginger (Zingiber officinale) and its potential as a pancreatic lipase inhibitor and its toxicity. Biodiversitas Journal of Biological Diversity. 2019;20(5).
80. Rahman S, Rahman L, Khalil AT, Ali N, Zia D, Ali M, Shinwari ZK. Endophyte-mediated synthesis of silver nanoparticles and their biological applications. Appl Microbiol Biotechnol. 2019;103(6):2551-2569.
81. Rajesh PS, Rai VR. Quorum quenching activity in cell-free lysate of endophytic bacteria isolated from *Pterocarpus santalinus* Linn., and its effect on quorum sensing regulated biofilm in Pseudomonas aeruginosa PAO1. Microbiol Res. 2014a;169(7-8):561-569.
82. Rajesh PS, Rai VR. Purification and antibiofilm activity of AHL-lactonase from endophytic Enterobacter aerogenes VT66. International Journal of Biological Macromolecules. 2015b;81:1046-1052.
83. Rustamova N, Wubulikasimu A, Mukhamedov N, Gao Y, Egamberdieva D, Yili A. Endophytic bacteria associated with medicinal plant Vernonia anthelmintica: diversity and characterization. Current Microbiology. 2020;77(8):1457-1465.
84. Sabu R, Soumya KR, Radhakrishnan EK. Endophytic *Nocardiopsis* sp. from Zingiber officinale with both antiphytopathogenic mechanisms and antibiofilm activity against clinical isolates. 3 Biotech. 2017;7(2):1-13.
85. Sadahiro Y, Kato H, Williams RM, Tsukamoto S. Irpexine, an isoindolinone alkaloid produced by coculture of endophytic Fungi, irpex lacteus and *Phaeosphaeria oryzae*. Journal of Natural Products. 2020;83(5):1368-1373.
86. Saravanan A, Kumar PS, Karishma S, Vo DVN, Jeevanantham S, Yaashikaa P, George CS. A review on biosynthesis of metal nanoparticles and its environmental applications. Chemosphere. 2020;128580.
87. Schiff PB, Horwitz SB. Taxol stabilizes microtubules in mouse fibroblast cells. Proc Natl Acad Sci USA. 1980;77(3):1561-1565.
88. Sheng SL, Li YP, Xiang HY, Liu Y, Wang YD, Kong LP, *et al*. Histone deacetylase inhibitor induced lipase Inhibitors from endophytic *Phomopsis* sp. 0391. Rec Nat Prod. 2020;14:42-47.
89. Shi YN, Pusch S, Shi YM, Richter C, Maciá-Vicente JG, Schwalbe H, Bode HB. (±)-Alternarlactones A and B, Two Antiparasitic Alternariol-like Dimers from the Fungus *Alternaria alternata* P1210 isolated from the halophyte *Salicornia* sp. J Org Chem. 2019;84(17):11203-11209.
90. Shweta S, Gurumurthy BR, Ravikanth G, Ramanan US, Shivanna MB. Endophytic fungi from Miquelia dentata Bedd., produce the anti-cancer alkaloid, camptothecine. Phytomedicine. 2013;20(3-4):337-342.

91. Singh B, Kaur A. Antidiabetic potential of a peptide isolated from an endophytic Aspergillus awamori. Journal of Applied Microbiology. 2016;120(2):301-311.
92. Song YC, Huang WY, Sun C, Wang FW, Tan RX. 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. 2005;28(3):506-509.
93. Sommart U, Rukachaisirikul V, Sukpondma Y, Phongpaichit S, Sakayaroj J, Kirtikara K. Hydronaphthalenones and a dihydroramulosin from the endophytic fungus PSU-N24. Chemical and Pharmaceutical Bulletin. 2008;56(12):1687-1690.
94. Stoltzfus JR, de Bruijn FJ. Evaluating diazotrophy, diversity, and endophytic colonization ability of bacteria isolated from surface-sterilized rice. In: The Quest for Nitrogen Fixation in Rice. International Rice Research Institute; 2000. p. 63-91.
95. Subban K, Subramani R, Johnpaul M. A novel antibacterial and antifungal phenolic compound from the endophytic fungus *Pestalotiopsis mangiferae*. Natural Product Research. 2013;27(16):1445-1449.
96. Sun JF, Lin X, Zhou XF, Wan J, Zhang T, Yang B, *et al.*, new alkenyl phenol and benzaldehyde derivatives from endophytic fungus *Pestalotiopsis* sp. AcBC2 isolated from the Chinese mangrove plant Aegiceras corniculatum. Journal of Antibiotics. 2014;67(6):451-457.
97. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249.
98. Sunkar S, Nachiyar CV. Biogenesis of antibacterial silver nanoparticles using the endophytic bacterium Bacillus cereus isolated from *Garcinia xanthochymus*. Asian Pacific Journal of Tropical Biomedicine. 2012;2(12):953-959.
99. Taechowisan T, Chaisaeng S, Phutdhawong WS. Antibacterial, antioxidant and anticancer activities of biphenyls from *Streptomyces* sp. BO-07: an endophyte in *Boesenbergia rotunda* (L.) Mansf A. Food Agric Immunol. 2017;28(6):1330-1346.
100. Tan QW, Gao FL, Wang FR, Chen QJ. Anti-TMV activity of malformin A1, a cyclic penta-peptide produced by an endophytic fungus Aspergillus tubingensis FJBJ11. International Journal of Molecular Sciences. 2015;16(3):5750-5761.
101. Tao YW, Lin YC, She ZG, Lin MT, Chen PX, Zhang JY. Anticancer activity and mechanism investigation of beauvericin isolated from secondary metabolites of the mangrove endophytic fungi. "Anti-Cancer Agents in Medicinal Chemistry. 2015;15(2):258-266.
102. Tawfike AF, Romli M, Clements C, Abbott G, Young L, Schumacher M, *et al*. Isolation of anticancer and anti-trypanosome secondary metabolites from the endophytic fungus Aspergillus flocculus via bioactivity guided isolation and MS based metabolomics. Journal of Chromatography B. 2019;1106:71-83.
103. Tiwari K. The future products: Endophytic fungal metabolites. J Biodivers Bioprospect Dev. 2015;2:2-7.
104. Thomas R, Jasim B, Mathew J, Radhakrishnan EK. Extracellular synthesis of silver nanoparticles by endophytic *Bordetella* sp. isolated from Piper nigrum and its antibacterial activity analysis. Nano Biomed Eng. 2012;4(4).
105. Uzor PF, Osadebe PO, Nwodo NJ. Antidiabetic activity of extract and compounds from an endophytic fungus Nigrospora oryzae. Drug Res. 2017;67(05):308-311.
106. Vald´es L, Cuervo A, Salazar N, Ruas-Madiedo P, Gueimonde M, Gonzalez ´ S. The relationship between phenolic compounds from diet and microbiota: impact on human health. Food Funct. 2015;6(8):2424-2439.
107. Vu HNT, Nguyen DT, Nguyen HQ, Chu HH, Chu SK, Chau MV, *et al*. Antimicrobial and cytotoxic properties of bioactive metabolites produced by Streptomyces cavourensis YBQ59 isolated from Cinnamomum cassia Prels in Yen Bai Province of Vietnam. Curr Microbiol. 2018;75(10):1247-1255.
108. Wagner KH, Elmadfa I. Biological relevance of terpenoids. Ann Nutr Metab. 2003;47(3-4):95-106.
109. Waring MJ, Wakelin LPG. Echinomycin: a bifunctional intercalating antibiotic. Nature. 1974;252(5485):653-657.
110. WHO. Accelerating work to overcome the global impact of neglected tropical diseases-A roadmap for implementation. WHO Press; 2012. Pp 1–22.
111. World Health Organization. Global antimicrobial resistance surveillance system (GLASS) report: early implementation 2020; 2020.
112. WHO. Control of neglected tropical diseases. World Health Organization; 2021. Retrieved from https://www.who.int/teams/control-of-neglected-tropical-diseases/overview on February 15, 2021.
113. Xu F, Zhang Y, Wang J, Pang J, Huang C, Wu X, *et al*. Benzofuran derivatives from the mangrove endophytic fungus Xylaria sp.(# 2508 Journal of Natural Products. 2008;71(7):1251-1253.
114. Yadav AN, Kumar R, Kumar S, Kumar V, Sugitha TCK, Singh B, *et al*. Beneficial microbiomes: biodiversity and potential biotechnological applications for sustainable agriculture and human health. J Appl Biol Biotechnol. 2017;5(6):4-7.
115. Yang H, Gao Y, Niu D, *et al*. Xanthone derivatives from the fermentation products of an endophytic fungus *Phomopsis* sp. Fitoterapia. 2013;91:189–193.
116. Ye Y, Xiao Y, Ma L, Li H, Xie Z, Wang M, *et al*. Flavipin in *Chaetomium globosum* CDW7, an endophytic fungus from Ginkgo biloba, contributes to antioxidant activity. Appl Microbiol Biotechnol. 2013;97(16):7131-7139.
117. Yu H, Zhang L, Li L, Zheng C, Guo L, Li W, *et al*. Recent developments and future prospects of antimicrobial metabolites produced by endophytes. Microbiol Res. 2010;165(6):437-449.
118. Yuan Y, Tian JM, Xiao J, Shao Q, Gao JM. Bioactive metabolites isolated from *Penicillium* sp. YY-20, the endophytic fungus from Ginkgo biloba. Nat Prod Res. 2014;28(4):278-281.
119. Yuan J, Sun K, Deng-Wang MY, Dai CC. The mechanism of ethylene signaling induced by endophytic fungus *Gilmaniella* sp. AL12 mediating sesquiterpenoids biosynthesis in Atractylodes lancea. Front Plant Sci. 2016;7:361.

120. Zhang B, Salituro G, Szalkowski D, Li Z, Zhang Y, Royo I, *et al*. Discovery of a small molecule insulin mimetic with antidiabetic activity in mice. Science. 1999;284(5416):974-977.
121. Zhang Y, Han T, Ming Q, Wu L, Rahman K, Qin L. Alkaloids produced by endophytic fungi: a review. Nat Prod Commun. 2012;7(7):1934578X1200700742.
122. Zhang SP, Huang R, Li FF, Wei HX, Fang XW, Xie XS, *et al*. Antiviral anthraquinones and azaphilones produced by an endophytic fungus *Nigrospora* sp. from Aconitum carmichaeli. Fitoterapia. 2016;112:85-89.
123. Zhang DH, Wu KL, Zhang X, Deng SQ, Peng B. In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. J Integr Med. 2020;18(2):152-158.
124. Zhao K, Penttinen P, Guan T, Xiao J, Chen Q, Xu J, *et al*. The diversity and anti-microbial activity of endophytic actinomycetes isolated from medicinal plants in Panxi plateau, China. Curr Microbiol. 2011;62(1):182-190.
125. Zhao J, Li C, Wang W, Zhao C, Luo M, Mu F, *et al*. Hypocrea lixii, novel endophytic fungi producing anticancer agent cajanol, isolated from pigeon pea (*C ajanus cajan* [L.] M illsp.). J Appl Microbiol. 2013;115(1):102-113.
126. Zhou JY, Yuan J, Li X, Ning YF, Dai CC. Endophytic bacterium-triggered reactive oxygen species directly increase Oxygenous Sesquiterpenoid content and diversity in *Atractylodes lancea*. Appl Environ Microbiol. 2016;82(5):1577-1585.
127. Zin NM, Baba MS, Zainal-Abidin AH, Latip J, Mazlan NW, Edrada-Ebel R. Gancidin W, a potential low-toxicity antimalarial agent isolated from an endophytic Streptomyces SUK10. Drug Des Devel Ther. 2017;11:351.
128. Kusari S, Zühlke S, Spiteller M. An endophytic fungus from *Camptotheca acuminata* that produces camptothecin and analogues. Journal of Natural Products. 2009 Jan 23;72(1):2-7.