EGYPTIAN JOURNAL OF BOTANY (EJBO)

Endophytic *Fusarium* spp.: A treasure of natural products with promising biotechnological applications

Elham H. Amr[1], Noha M. Sorour[1], Ashraf S.A. El-Sayed[2], Marwa A.A.Fayed[3], Amera A. Abaza[1], Ashraf F. El-Baz[1]

[1]*Department of Industrial Biotechnology, Genetic Engineering and Biotechnology Research Institute, University of Sadat City, Egypt*
[2]*Department of Botany and Microbiology, Faculty of Science, Zagazig University, Zagazig, Egypt*
[3]*Department of Pharmacognosy, Faculty of Pharmacy, University of Sadat City, Sadat City 32897, Egypt*

MINI REVIEW ARTICLE

Endophytic fungi residing within plant tissues represent an underexplored reservoir of structurally diverse specialized metabolites. Among them, *Fusarium* spp. stand out for their capacity to biosynthesize a wide array of bioactive secondary metabolites (SMs). *Fusarium* spp. have been shown to produce antimicrobial, anticancer, nematicidal, antiviral, and other bioactive metabolites. Compounds exhibiting potent activity against pathogens including bacteria, fungi, and oomycetes offer leads for developing novel antimicrobials. Cytotoxic metabolites demonstrate activity against various cancer cell lines, holding promise as anticancer drug candidates. Nematicidal compounds could contribute to sustainable agriculture through eco-friendly nematode control. Antivirals active against diverse viruses may yield therapies for challenging diseases. Beyond these targeted activities, *Fusarium* metabolites also display antioxidant, anti-inflammatory, and other beneficial properties. Continued exploration of endophytic *Fusarium* metabolomes is warranted to fully understand their biosynthetic capacity. Isolating and characterization specialized metabolites through bioactivity-guided approaches can uncover new chemical scaffolds with applications in healthcare, agriculture, and industry. This review highlights the remarkable potential of endophytic *Fusarium* as a source of natural products (NPs) with applications across multiple sectors based on their documented metabolomic diversity.

Keywords: Anticancer, Antimicrobial, Antiviral, Endophyte, *Fusarium*, Nematicide

ARTICLE HISTORY
Submitted: November 16, 2024
Accepted: October 7, 2025

CORRESPONDANCE TO:
Ashraf S.A. El-Sayed
Department of Botany and Microbiology, Faculty of Science, Zagazig University, Zagazig, Egypt
Email: ash.elsayed@gmail.com

DOI: 10.21608/ejbo.2025.336801.3080

EDITED BY: Neveen Mahmoud Khalil

INTRODUCTION

Healthcare faces serious challenges from issues like drug-resistant infections, emerging viruses, and risks associated with transplants and cancer. Our ability to deal with these emerging threats is limited (Sharma et al., 2016). Natural products (NPs) represent a promising avenue to address this need. Only a small fraction of biodiversity has been explored for medicinal applications. Alkaloids, terpenes, and other SMs in plants, fungi, and marine organisms demonstrate complex activities that allow their survival. Some likely provide potent and selective effects relevant to human therapies (Bhardwaj & Agrawal, 2014). Several recent studies emphasize NPs' potential roles in drug discovery and development. They represent a source of novel chemical templates not found through synthesis alone. This diversity increases the chances of finding leads that avoid resistance or treat disease through new mechanisms (Wilson et al., 2020).

NPs are increasingly recognized for their significant contributions to drug discovery and development, serving as a rich source of novel chemical templates. Recent studies highlight their unique advantages over synthetic compounds, particularly in clinical success rates and biological activity. NPs and their derivatives have shown higher success rates in clinical trials, with a notable increase from 35% in Phase I to 45% in Phase III trials (Domingo-Fernández et al., 2024). This trend contrasts with synthetic compounds, which experienced a decline in success rates during the same phases (Domingo-Fernández et al., 2024). NPs inspired strategies, such as diversity-oriented and biology-oriented synthesis, facilitate the exploration of uncharted chemical spaces, leading to the discovery of novel bioactive molecules (Gagare et al., 2024). These strategies allow for targeted modifications that enhance biological activity, demonstrating the potential of NPs in developing effective therapeutics (Nakayama, 2024). Over 300,000 bioactive natural compounds exist, which can be classified according to their chemistry. Terpenoids and steroids, fatty acids and polyketide-derived substances, alkaloids, nonribosomal polypeptides, and shikimate compounds represent the major groups (Méndez & Salas, 2001). These NPs exhibit diverse bioactivities including antibacterial, antifungal, and anticancer properties. More than 10.000 NPS display biological activity, with over 8.000 possessing antibiotic or antitumor functions (Brusotti et al., 2014). Many NPs are of high clinical relevance as antibiotics, antitumor agents, and immunosuppressants. Additionally, growth promoters, insecticides, herbicides, and antiparasitics are important in veterinary medicine and agriculture.

Plants have long been recognized as a promising source of bioactive NPs for pharmaceutical applications. A wealth of biologically active compounds can be found in the plant kingdom, as only 10-15% of higher plant species have been investigated for their chemical constituents (Bisht et al., 2006). Unsurprisingly, plants are the source of about 25% of drugs approved by regulatory agencies like the FDA and EMA (Food and Drug Administration, European Medicines Agency). However, one limitation of isolation phytochemicals directly from plants is that nature only produces relatively small quantities. Recent research has highlighted that many plant-derived "natural" products are produced via microbial interactions. There is a growing understanding that significant numbers of NPs result from the biosynthetic activities of endophytic microbes inhabiting host plants or through host-microbe metabolic exchanges (Abdel-Razek et al., 2020). This realization has elevated the field of endophyte research, positioning it to advance natural product drug discovery and development approaches to the next level.

Approximately 23.000 SMs derived from microorganisms have been identified, with actinomycetes and fungi each contributing around 42% of these compounds (de Castro et al., 2020). A recent report from FDA underscores the importance of NPs in drug discovery, revealing that 38% of newly developed drugs are sourced from such compounds, with microorganisms contributing approximately 25% of this total. These findings accentuate the vital role of microorganisms as a sustainable avenue for novel drug development (Newman & Cragg, 2016). Microbial SMs, which include growth hormones, pigments, antibiotics, and antitumor agents, are not primarily utilized by microorganisms for their growth and development; however, they hold considerable promise for human health. These compounds have emerged as significant sources of life-saving pharmaceuticals, highlighting their importance in the ongoing quest for effective treatments for various diseases (Demain, 2014). Recent research has highlighted the growing interest in NPs derived from unexplored microbial sources, particularly microorganisms associated with plants (Ueoka et al., 2018). Notably, endophytic microorganisms have emerged as a significant focus of study, as they can produce bioactive compounds that may be similar to, or even identical to, those synthesized by their plant hosts. Studies indicate that these associated microorganisms can yield products with substantial therapeutic potential, thereby shifting the emphasis from traditional plant-based sources to microbial entities (El-Sayed et al., 2021, 2022; Abdelhamid et al., 2024). This approach not only enhances efficiency but also ensures a more sustainable source of high-value therapeutic compounds (Subbulakshmi et al., 2012).

Endophytes, derived from the Latin terms *endo* (inside) and *phytos* (plant), are organisms primarily fungi and bacteria that inhabit the internal tissues of plants. The concept of endophytic fungi was introduced in 1866, distinguishing them from pathogenic fungi based on their asymptomatic nature, meaning they do not harm the host plant (Bary, 1866; Wilson, 1995). These microorganisms can reside inter- and intracellularly within the healthy tissues of the host, including roots, seeds,

stems, and leaves, without causing observable disease symptoms (Tan & Zou, 2001). Endophytes engage in various types of symbiotic associations with plants, ranging from mutualism to parasitism. In mutualistic interactions, they produce beneficial metabolites that enhance plant resilience against biotic stresses, such as phytopathogens and herbivores, as well as abiotic stresses, including pollution and temperature fluctuations. Endophytes not only facilitate enhanced nutrient uptake and growth but also contribute to the production of bioactive SMs that can elicit growth-promoting effects and possess pharmacological properties (Zotchev, 2024). They are known to produce phytohormones and other bioactive compounds, including enzymes and pharmaceuticals, which hold promise for future applications in medicine and the agricultural sector (Parthasarathi et al., 2012). While endophytes may participate in the biosynthesis of plant products, they may also independently produce numerous substances of potential significance for modern medicine, agriculture, and the pharmaceutical industry (Adeleke et al., 2021).

With an estimated 300,000 plant spp. on earth, each plant harbors one or more endophytes, many of which exhibit host specificity. It is projected that there may be as many as one million distinct endophytic fungal taxa, indicating a hyper-diverse community (Strobel & Daisy, 2003). Endophytic fungi are classified into clavicipitaceous and non-clavicipitaceous groups based on taxonomy, evolutionary relationships, ecology, and host (Santangelo et al., 2015). Clavicipitaceous endophytes, often associated with grasses, maintain a mutualistic relationship with their hosts throughout their life cycles, developing in the intercellular spaces of aboveground plant tissues and propagating both horizontally and vertically, depending on the spp. (De Silva et al., 2016). In contrast, non-clavicipitaceous endophytes, such as *Fusarium*, *Colletotrichum*, *Phomopsis*, and *Xylaria*, are commonly found in most terrestrial plants and do not rely on their hosts to complete their life cycles (De Silva et al., 2016).

Fungal endophytes are recognized for their potential to produce a diverse array of bioactive compounds, making them significant sources of various natural drugs currently utilized in the treatment of antibacterial, antifungal, antiviral, antioxidant, anti-inflammatory, anticancer, and antidiabetic conditions (Boruah et al., 2024). Endophytic fungi synthesize metabolites from multiple structural classes, including alkaloids, terpenes, terpenoids, polyketides, xanthones, isocoumarins, flavonoids, lactones, phenolics, steroids, aliphatic compounds, quinones, peptides, and tetralones (Singh et al., 2021). These metabolites are produced through distinct biosynthetic pathways such as the shikimate pathway involving alkaloids and flavonoids (Peek & Christendat, 2015) and the TCA cycle yielding isoprenoids, polyketides, and terpenoids (Meena et al., 2019). Furthermore, they may serve as biocontrol agents (Poveda & Baptista, 2021), promote plant growth (Mehta et al., 2019), enhance nutrient solubilization in the rhizosphere, and activate systemic plant defenses against biotic (Poveda et al., 2020) and abiotic (Cui et al., 2021) stresses. *Fusarium* is a prominent genus of fungal endophytes, recognized for its vast species diversity and genetic variability. As one of the most dominant endophytic fungal genera globally, *Fusarium* exhibits remarkable adaptability, thriving on a variety of substrates and employing efficient dispersal mechanisms that influence its biology and interactions with surrounding organisms. This genus, which ranks third among endophytes, following *Aspergillus* and *Penicillium*, and is found in diverse habitats, including soil, plant debris, and various plant tissues (Singh et al., 2021). While *Fusarium* is often associated with plant pathogenicity, non-pathogenic endophytic species within this genus are equally significant due to their remarkable biosynthetic capabilities and a broad spectrum of biological activities (Zhang et al., 2023).

Fusarium spp. as endophytes and their various bioactivities-biotechnological applications

Fusarium spp. inhabit the roots of both cultivated and wild plants as intercellular endophytes, yet their role during the symptomless phase of infection remains equivocal defined. Many *Fusarium* spp. are pathogenic, causing significant diseases such as root, stem, and rot, which ultimately diminish crop productivity. Notably, *Fusarium verticillioides* and other species exhibit unique endophytic characteristics, sharing similarities with foliage endophytes of forage grasses, while also displaying hemibiotrophic behaviors (Zhang et al., 2023). The global distribution of *Fusarium* poses widespread problems, as numerous host plants are susceptible to infection by one or more species. Biotic and abiotic factors can shift the relationship between *Fusarium* and its host plants from a symptomless endophytic association to a hemibiotrophic and, subsequently, saprotrophic state, where the accumulation of mycotoxins raises health concerns for both animals and

humans (Zhang et al., 2023). Consequently, the production of mycotoxins can initiate infections from the symptomless root endophytic state. The dual characterization of *F. verticillioides* as both a pathogen and a symptomless endophyte highlights the complex interactions this species has with plants and suggests similar complexities may exist in other *Fusarium*-plant relationships (Bacon & Yates, 2006).

The genus *Fusarium*, comprising approximately 70 spp., exhibits significant variability in genetics, biology, and ecology, which in turn influences its secondary metabolism. These fungi have been isolated from a wide range of plant genera across diverse habitats**.** As endophytic microbes*,* *Fusarium* spp. may confer protection and survival advantages to their host plants through the production of a diverse array of chemically distinct and structurally unique secondary metabolites. These metabolites are known to display a remarkable spectrum of biological activities, including antimicrobial, anticancer, antiviral, antioxidant, antiparasitic, immunosuppressive, immunomodulatory, antithrombotic properties, and biocontrol capabilities against plant pathogens and nematodes (Toghueo, 2019). *Fusarium* is recognized as a prolific source of bioactive compounds, capable of producing over 100 unique secondary metabolites across various chemical classes. These classes include butenolides, alkaloids, terpenoids, cytochalasins, phenalenones, xanthones, sterols, diphenyl ether, and anthraquinone derivatives (Figure 1) (Singh et al., 2021). Recent metagenomic studies have indicated the potential for discovering novel species within the *Fusarium* genus, as several species remain unidentified. This underscores the significance of *Fusarium* as a valuable resource for new secondary metabolites with promising biological activities, which are essential for drug discovery (Figure 2).

Extensive research has led to the identification of 162 novel SMs, including polyketides, alkaloids, peptides, terpenes, and steroids. Among these, alkaloids have emerged as the most prolific chemical class produced by various *Fusarium* spp., followed by peptides and naphthoquinones (Wei et al., 2020). A comprehensive analysis suggests that 272 compounds qualify as unique bioactive entities within the genus, and the investigation of biosynthetic gene clusters (BGCs) analysis reveals untapped genetic potential for producing a diverse array of novel bioactive SMs (Toghueo, 2020). Despite the isolation of several species, many remain unidentified, yet they hold the promise of yielding metabolites with significant biological activities (Le et al., 2020; Liu et al., 2022). Recent advancements in bioinformatics have revealed a growing number of cryptic biosynthetic gene clusters associated with novel SM biosynthesis, which can be effectively activated through genome mining strategies (Zhang et al., 2022). Recent studies have highlighted a remarkable increase in the diversity of phytoconstituents isolated from various *Fusarium* spp., notably *F. chlamydosporum*, *F. proliferatum*, *F. solani*, and *F. oxysporum*. Between 1999 and 2010, only 15 compounds were identified, whereas from 2011 to 2016, this figure surged to 112, underscoring an expanding understanding of these fungi's SMs. This surge can be attributed to advancements in molecular identification techniques and a growing interest in their pharmacological potential (Shalapy & Kang, 2022; Ahmed et al., 2023). Notably, *F. oxysporum* and *F. solani* have demonstrated significant antibacterial and anticancer properties, with their metabolites proving effective against various pathogens (Alves et al., 2024). Given the complexity of *Fusarium* spp., continued research is imperative to fully elucidate their potential applications (Nikitin et al., 2023).

Endophytic *Fusarium* spp. are recognized as important producers of industrially relevant enzymes through their symbiotic relationships with host plants. Proteases, lipases, cellulases, xylanases, and laccases represent some of the key enzyme classes synthesized. Proteases feature prominently due to applications across food processing, textiles, and detergent manufacturing, which collectively account for the majority of the global enzyme market (Mandal & Banerjee, 2019). Lipases aid in waste management and food processing through the hydrolysis of fats and oils (Ghosh et al., 2023). Cellulases and xylanases find widespread use in the pulp and paper industry (Shankar Naik et al., 2019). Laccases serve functions in textile dye degradation and various bioremediation strategies (Ghosh et al., 2023). Beyond industrial relevance, enzymes from endophytic *Fusarium* also offer opportunities to enhance sustainability across sectors like agriculture, biofuels, and environmental protection (Shankar Naik et al., 2019). Ligninolytic enzymes facilitate the conversion of lignocellulosic biomass into next-generation biofuels (Bhadra et al., 2022; Sorour et al., 2023). Their degradation capabilities also position certain enzymes as valuable tools for the bioremediation of pollutants (Ghosh et al., 2023; El-Baz et al., 2024).

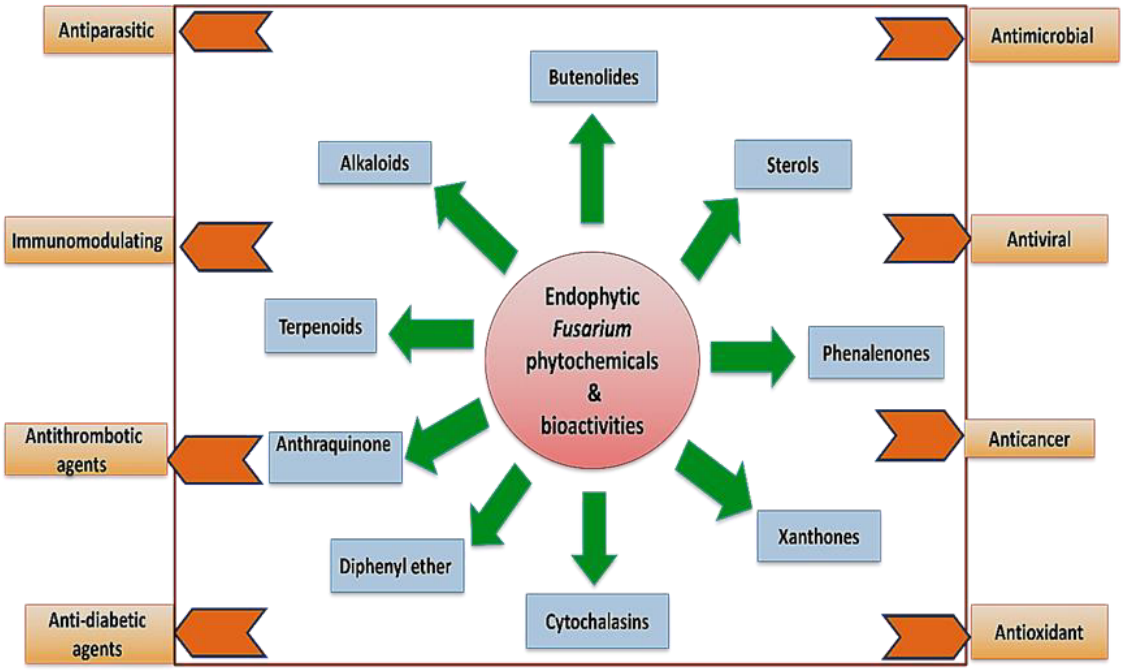

Figure 1. Endophytic *Fusarium* phytochemicals and bioactive metabolites

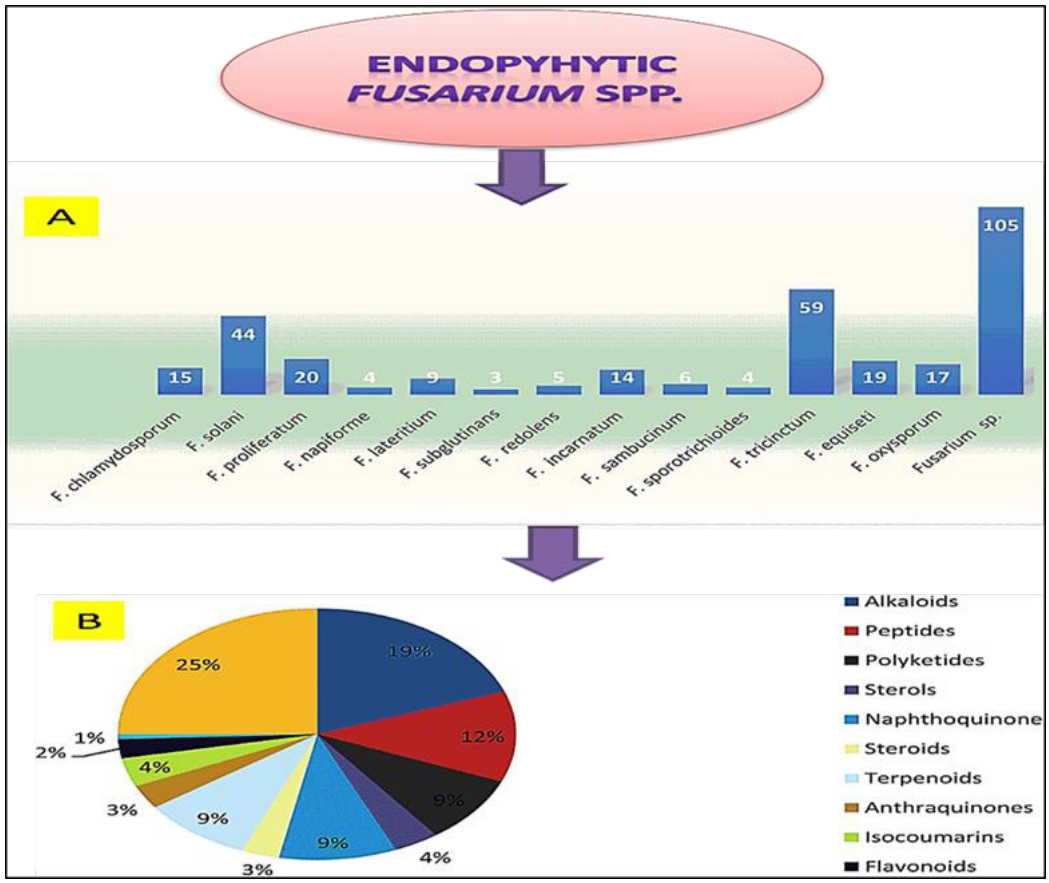

Figure 2. Number of bioactive compounds isolated from different endophytic *Fusarium* spp. (A), and secondary metabolite classes derived from the *Fusarium* genus (B)

Biotechnological and industrial applications of *Fusarium* spp.

In medicines

Over extended periods of observation, endophytic *Fusarium s*trains have demonstrated therapeutic potential through the production of a wide range of compounds used to treat serious maladies such as cancer, malaria, inflammation, and oxidative stress disorders. Specifically, fermentation of many *Fusarium* spp. has yielded medicines like camptothecin, vincristine, vinblastine, rohitukine, podophyllotaxin, and taxol which have applications in oncology (Toghueo, 2020). Additional anti-cancer drugs vinblastine and vincristine (Tung, 2002), the anti-viral podophyllotoxin (Nadeem et al., 2012), the anti-malarial compound camptothecin and its analogues (Ran et al., 2017), as well as the anti-inflammatory taxol (Li et al., 2009; Xiong et al., 2013) have been isolated from various *Fusarium* strains. These promising findings over several decades have encouraged continued exploration of *Fusarium's* drug-producing capabilities to sustainably manufacture such pharmacologically valuable compounds through microbial fermentation (Hidayat, 2016). Several bioactive compounds with pharmacological significance have been isolated from endophytic *Fusarium* strains in recent studies. Notably, the alkaloid huperzine A (HupA) was obtained from *Fusarium* sp. Rsp5.2, an endophyte of *Huperzia serrata*. HupA is a potent acetylcholinesterase inhibitor used to treat Alzheimer's disease, exhibiting an IC50 value of 2.849 ± 0.0026μg/mL (Le et al., 2020). These findings indicate that endophytic *Fusarium* strains continue to serve as promising sources of bioactive SMs with applications as pharmaceutical agents (Li et al., 2025).

- **Antimicrobial agents**

The growing threat of antimicrobial resistance among human pathogens underscores the urgent need to develop new anti-microbial agents. Standard antibiotics currently used in clinical settings are facing increased virulence and pathogenicity of many microbes as resistance escalates annually (El-Sayed et al., 2021). SMs isolated from endophytic microorganisms demonstrate potential as alternatives to conventional antibiotics, with various classes of compounds like phenols, piperazines, quinones, and quinolones exhibiting antimicrobial activity (Singh et al., 2024). Specifically, the *Fusarium* genus contains a diverse array of endophytic strains that have yielded a plethora of antimicrobial compounds belonging to structural groups such as alkaloids, peptides, steroids, quinines, terpenoids, phenols, and flavonoids (Yu et al., 2010). Several investigations have focused on identifying potent antimicrobial extracts from *Fusarium* endophytes that can be purified through chemical analysis to characterize novel active compounds.

Many endophytic *Fusarium* spp. have demonstrated the ability to produce a wide range of bioactive SMs with antimicrobial properties. Several studies have investigated crude extracts from fungi in the *Fusarium* genus isolated from various plant hosts. Several endophytic fungi, such as *F. oxysporum*, have been shown to produce potent antifungal compounds. For example, *F. oxysporum* produces 2,4-diacetylphloroglucinol, which has antibacterial and antifungal properties demonstrating potential as a new antibiotic (de Lamo & Takken, 2020; Aini et al., 2022; Bora & Devi, 2023). Additional studies have continued to explore the antimicrobial potential of endophytic *F. oxysporum* isolates. Similarly, the ethyl acetate extract of *Fusarium* sp. isolated from *Rumex madaio* was found to inhibit the growth of *S. aureus* (Bai et al., 2019). The crude extracts from various *Fusarium* endophytes contained compounds with antimicrobial properties, subsequent studies employed bioactivity-guided fractionation techniques to isolate and identify the specific pure responsible compounds were required. Shah et al. (2017) purified 3,6,9-trihydroxy-7-methoxy-4,4-dimethyl-3,4-dihydro-1H-benzo [g]isochromene-5,10-dione, 3-O-methylfusarubin, javanicin, and fusarubin from *Fusarium* spp. which demonstrated activity against various bacterial strains. While numerous studies have reported the isolation of bioactive SMs from endophytic *Fusarium* spp., some investigations have purified compounds lacking detectable antimicrobial activity (Amr et al., 2024).

- **Antiparasitic agents**

Due to the rapid spread of anti-drug resistance malaria parasites in recent years and the urgent need to fill the antimalarial drug development pipeline with new antiplasmodial agents for novel malaria therapy, natural sources continue to show promise in the discovery of lead compounds. Studies have demonstrated the potency of compounds derived from endophytic fungi. Fadiji & Babalola (2020) showed that the anti-malarial activity of two endophytic fungi, munumbicins E-4 and E-5, was twice as potent as the frontline

drug chloroquine. Given the success of NPs in providing past antimalarial drugs like chloroquine, screening natural sources remains a worthwhile pursuit that could lead to such discoveries.

While not many individual compounds from *Fusarium* species have been extensively evaluated for antiplasmodial properties, several studies indicate that endophytic *Fusarium* represents a promising source for antimalarial lead discovery, particularly against drug-resistant *Plasmodium falciparum* strains (Amr et al., 2024) . Extracts from diverse *Fusarium* isolates have demonstrated good potency against resistant parasite lines. Similarly, Toghueo et al. (2018) reported potencies ranging from 1.62-4.38µg/mL for extracts of *Fusarium* sp. N240 obtained from *C. odorata* against both drug-sensitive and resistant *P. falciparum* isolates. Additional studies provide further evidence of the promising potential of endophytic *Fusarium* spp. as sources of antiprotozoal compounds. Toghueo et al. (2019) found an ethyl acetate extract from *Fusarium* sp. AMst1, an endophyte of *Annona muricata*, demonstrated impressive antiplasmodial activity against multiple *P. falciparum* lines (IC50 1.16–1.43µg/mL).

Encouragingly, endophytic *Fusarium* also shows activity beyond malaria, possessing the potential for treatment of other important protozoal diseases. Beauvericin isolated from *Fusarium* sp. WC9 was found to potently inhibit *T. cruzi* with an IC50 of 2.43µM (Campos et al., 2015). Meanwhile, a moderate effect against *L. donovani* was demonstrated for the methanol extract of *F. tricinctum* obtained from *Hordeum sativum* fruits (Zaher et al., 2015). Additional promising leads have been uncovered from endophytic *Fusarium* species against leishmaniasis. Ibrahim and colleagues (2018) isolated two new compounds from *Fusarium* sp., an endophyte of *Mentha longifolia*, designated Integracides F and G, which exhibited anti-leishmanial activity with IC50 values of 3.74 and 2.53µg/mL, respectively against *Leishmania* species (Ibrahim et al., 2018). While these initial hits demonstrate only moderate inhibition, their simple chemical structures suggest opportunities for medicina chemistry optimization to improve drug-like properties and potentially yield preclinical candidates.

- **Antiviral agents**

Endophytic fungi are recognized as a rich source of bioactive SMs with potential applications as antiviral agents (Lacerda et al., 2022). Several studies have evaluated *Fusarium* spp. for antiviral compounds given their proven ability to produce bioactive small molecules. Hawas and colleagues (2016) bioprospected the endophytic fungus *F. equiseti*, isolating multiple hits that demonstrated inhibition of the hepatitis C virus NS3/4A protease. Cyclo(L-Pro-L-Val) and griseoxanthone C showed good potency, while ω-hydroxyemodin and cyclo(L-Tyr-L-Pro) were the most potent inhibitors identified. More recently, Chang and colleagues (2023) reported the antiviral activities of two metabolites from *F. solani*, fusapyridon A and oxysporidinone, which inhibited Coronavirus HCoV-OC43 with low micromolar half maximal inhibitory concentration values of 13.33 and 6.65µM, respectively (Chang et al., 2023). Additional research has explored *Fusarium* compounds against other viral targets. Additionally, endophytic *F. oxysporum* has demonstrated considerable promise as a source of potent antiviral metabolites. Notably, Kılıç et al. (2021) reported that *F. oxysporum* produces compounds such as (1-benzyl-2-methoxy-2-oxoethyl)-2-hydroxy-3-methylbutanoate and various anhydride derivatives which exhibit strong inhibition of herpes simplex virus type-1 (HSV type-1), with impressive IC50 values as low as 0.312µM. These leads have been shown to function through mechanisms like inhibiting viral replication and assembly, as observed for glyantrypine-family alkaloids isolated from *F. oxysporum* that disrupt tobacco mosaic virus extension (Hao et al., 2022). Additionally, the diverse classes of SMs, including phenols and terpenoids, contribute to the antiviral efficacy of *F. oxysporum* (Lacerda et al., 2022).

- **Anticancer agents**

Cancer remains one of the leading causes of mortality worldwide. Endophytic fungi represent an alternative sustainable source for the production of the anticancer paclitaxel. Subsequent research has linked several other endophytic fungal species to paclitaxel production as well, including *Seimatoantlerium nepalense*, *Alternaria alternate*, and *Chaetomell araphigera* (Kousar et al., 2022). Camptothecin represents another naturally derived anticancer compound first isolated from an endophytic fungus. Specifically, *F. solani*, an endophyte inhabiting the bark of *Camptotheca acuminata*, was found to biosynthesize camptothecin (Li et al., 2017). Notably, camptothecin exhibited potent anticancer activity in preclinical assessments, though its clinical utility was limited by poor

solubility, stability, and toxicity issues. However, subsequent drug development efforts yielded derivative compounds like topotecan and irinotecan which were able to overcome these pharmacological shortcomings (Li et al., 2017). Despite ongoing challenges, research into the discovery of novel anticancer compounds from natural sources remains an active and important area of investigation. Several studies have demonstrated the cytotoxic potential of SMs produced by the fungal endophyte *F. oxysporum* against various cancer cell lines. Beauvericin and bikaverin, compounds isolated from the ethyl acetate extract of *F. oxysporum* inhabiting *Cylindropuntia echinocarpus*, exhibited cytotoxicity against the NCI-H460, MIA Pa Ca-2, MCF-7, and SF-268 cancer cell lines (Zhan et al., 2007, Gamal et al., 2024, Refaat et al., 2024).

Several other cytotoxic compounds with promising anticancer activities such as dihydronaphthalenone, 5-hydroxydihydrofusarubins A, and 5-hydroxydihydrofusarubins B have been isolated from endophytic *Fusarium* strains (Prajapati et al., 2024). In a related investigation, Wang et al. (2011) isolated nine additional metabolites from *F. oxysporum*, among which were (−)-4,6′- anhydrooxysporidinone, (+)-fusarinolic acid, gibepyrone D, and (2S,2′ R,3R,3′E,4E,8E)-1-O-D-glucopyranosyl-2-N-(2′-hydroxy -3′-octadecenoyl)-3-hydroxy-9-methyl-4,8-sphingadienine. Upon testing against prostate, pancreatic, and lung cancer cell lines, only beauvercin exhibited potent cytotoxicity, with IC_{50} values between 10.4 to 49.5µM against the three cancer types. In addition, Ibrahim et al. (2018) evaluated the in vitro cytotoxic potential of SMs produced by the endophytic fungus *Fusarium chlamydosporium* isolated from the medicinal plant *Anvillea garcinii*. In the first study, two compounds - Fusarithioamide A (1) and ergosta-7,22-diene -3β,5α,6β-triol (2) - were tested against various cancer cell lines including KB, BT-549, SK-MEL, and SKOV-3. While compound 2 demonstrated activity against all cell lines, compound 1 exhibited potent and selective cytotoxicity towards the BT-549 and SKOV-3 lines specifically. These studies collectively support the potential of *Fusarium* endophytes as sources of cytotoxic and anticancer compounds.

Subsequently, Ibrahim et al. (2018) isolated fusarithioamide B from the same fungal extract. Intriguingly, this metabolite displayed strong potency and selectivity against the BT549, MCF-7, SKOV-3, and HCT-116 cancer cell lines, with low IC_{50} values between 0.09-1.23µM. These findings indicate fusarithioamide A and B warrant further investigation as promising lead anticancer molecules, given their selective cytotoxic profiles. In particular, their potent inhibition of breast, ovarian, and colorectal cancer cell proliferation at sub-micromolar concentrations suggests they could serve as starting points for the development of novel cancer therapeutics. In related work, Kousar et al. (2022) highlighted that *F. oxysporum* supports the biosynthesis of the potent anticancer alkaloid vinblastine in *Cathranthus roseus* plants. Specifically, vinblastine exhibited strong cytotoxicity against leukemia and liver cancer cell lines, inhibiting growth at concentrations as low as 7.48µg/mL. Moreover, Mohamed et al. (2022) isolated a novel 1,4-oxazine-xanthone derivative called fusarioxazin and three sterols from an *F. oxysporum* extract associated with *Vicia faba* roots. Further evaluation revealed fusarioxazin possessed significant antibacterial activity against *S. aureus* and *B. cereus*, with MIC values of 5.3 and 3.7µg/mL. Notably, fusarioxazin displayed promising cytotoxicity toward colorectal, breast, and lung cancer cell lines, comparable to the clinical chemotherapeutic doxorubicin, with IC_{50} values between 1.8-3.2µL. These results indicate fusarioxazin warrants optimization as a lead for developing improved anticancer and antimicrobial therapeutics, highlighting the pharmaceutical potential of specialized metabolites from endophytic *F. oxysporum*.

- **Antioxidant and antiaging activities**

Endophytic fungi are recognized as producers of bioactive SMs with potential applications as antioxidants. the role of oxidative stress in diseases and the need for cost-effective options, further investigation of endophytic fungal antioxidants is warranted. Hamzah and colleagues (2018) reported the free radical scavenging activity of *F. lateritium* extract obtained from *Rhizophora mucronata*. Similarly, Bungtongdee et al. (2019) found an ethyl acetate extract of *F. oxysporum* from *Dendrobium lindleyi* flowers had high phenolic content and potent 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging. Furthermore, Bungtongdee et al. (2019) characterized an extract from *F. oxysporum* exhibiting strong antimutagenic effects, finding gibepyrone A, pyrrolo[1,2-a]pyrazine-1,4-dione, hexahydro-3-(2-methylpropyl) and indoleacetic acid as major constituents.

Beyond these targeted investigations, wider surveys have reported a diverse array of specialized metabolites from endophytic fungi, including borneol, corynesidones A and B, coumarin, 2,14-dihydroxy-7-drimen-12,11-olide, 5-(hydroxymethyl)-2-furanocarboxylic acid, isopestacin, lapachol, p-tyrosol, pestacin, phloroglucinol, tetrahydroxy-1-methylxanthone, tyrosol, and rutin which demonstrate antioxidant, anti-inflammatory and antitumor effects (Toghueo, 2020; Singh et al., 2024). These studies highlight endophytic fungi, such as *Fusarium* spp., as producers of bioactive metabolites with applications for chemoprevention of oxidative stress-related diseases.

- **Immunosuppressive and immunomodulator agents**

Immunosuppressive drugs are critically important medications for reducing rejection of transplanted organs and treating autoimmune diseases (Firestein et al., 2016). However, current therapeutic options for modulating the immune system like mycophenolate mofetil and cyclosporine often cause undesirable side effects such as hyperglycemia, osteoporosis, gastrointestinal issues, and more. As a result, there remains an urgent need to discover novel immunosuppressive agents with improved safety profiles. Endophytic fungi represent an underexplored source of specialized metabolites with potential immunomodulatory properties. Recent studies have shown that certain fungal SMs can activate or suppress immune responses through diverse mechanisms of action. Given their proven biosynthetic capacity and chemical diversity, exploring the metabolomes of endophytic fungi holds promise for delivering safer immunosuppressants and autoimmune therapeutics (El-Sayed et al., 2022, 2024).

Fungal endophytes are capable of synthesizing molecules that can modulate the immune system (Wang et al., 2019). For instance, Vasundhara et al. (2016) and Adeleke et al. (2021) reported the endophytic fungus *Fusarium subglutinans*, isolated from *Tripterygium wilfordii*, generates subglutinols A and B which exhibit immunosuppressive effects. Related research has also profiled the immunomodulatory activity of compounds derived from other endophytic sources (Adeleke et al., 2021). The endophytic *F. oxysporum* produces an array of bioactive SMs with notable immunosuppressive and immunomodulatory properties. Research has demonstrated these specialized metabolites can downregulate key immune signaling pathways. Woelflingseder et al. (2020) revealed the butenolide metabolite generated by *F. oxysporum* inhibits the NF-κB pathway in human colon epithelial cells, reducing pro-inflammatory cytokines like IL-1β and TNF-α. Additionally, the mycotoxins zearalenone and deoxynivalenol commonly synthesized by *F. oxysporum* have been shown to impair innate immune responses. Specifically, Feng et al. (2023) found these agents downregulate the TLR2/NFκB signaling cascade, an essential route for immune activation. These studies demonstrate *F. oxysporum* produces an array of specialized metabolites capable of immunosuppressive effects through targeting critical immune regulatory mechanisms like NF-κB. Elucidating the immunomodulatory properties of such fungal products provides insight into both their therapeutic potential and *Fusarium*'s interactions with host organisms (Feng et al., 2023).

- **Antithrombotic agents**

Currently, thrombolytic agents such as various plasminogen activators are the standard treatment but have significant drawbacks like high costs, gastrointestinal bleeding and immunogenic adverse effects (Shao, 2012). While several potential thrombolytic drugs have demonstrated efficacy in clinical testing (Han et al., 2010), new alternatives are still urgently needed. Microbial sources are particularly attractive for fibrinolytic enzyme discovery given their vast biodiversity, amenability to large-scale cultivation, and genetic tractability (Mander et al., 2011). In line with exploring microbes for antithrombotic agents, Wu et al. (2009) screened 1,075 endophytic fungal extracts and identified one from *Fusarium* sp. as the most potent. They subsequently purified a novel 28kDa single-chain fibrinolytic enzyme from this extract, exhibiting no sequence homology to other known fibrinolytic enzymes (Wu et al., 2009). In related work, Ueda et al. (2007) isolated a strongly fibrinolytic protease from *Fusarium* sp. BLB inhabiting *Hibiscus* leaves. This enzyme demonstrated not only protease activity across a wide pH range of 2.5-11.5 but also stability at high temperatures up to 50°C. Additionally, its N-terminal sequence was identical to previously reported proteases (Ueda et al., 2007). These fibrinolytic properties indicate potential for thrombosis treatment (Peng et al., 2005; Rovati et al., 2010).

- **Anti-diabetic agents**

Endophytic fungi inhabiting plant tissues have attracted research interest due to their ability to synthesize bioactive metabolites with antidiabetic properties. Several investigations have demonstrated endophytic fungal extracts lower blood glucose levels through antihyperglycemic and anti-lipidemic mechanisms. For instance, Ranjan et al. (2019) found the endophyte *Fusarium equiseti* associated with *Gymnema sylvestre* synthesizes the antidiabetic compound mycosterol. Mycosterol exhibits competitive inhibition of α-glucosidase and α-amylase, key enzymes involved in postprandial hyperglycemia. Additionally, Adeleke et al. (2021) reviewed evidence that various *Fusarium* spp. generate metabolites with anti-diabetic function. These findings highlight the promise of endophytic fungi as sources of multi-targeted antidiabetic therapies, offering natural alternatives or leads to help address the growing diabetes epidemic.

Plant biocontrol applications

- **Induction of plant defense system**

Several studies have demonstrated the ability of *Fusarium* endophytes to modulate plant physiology and defense responses upon infection by pathogens. Pappas et al. (2018) showed that inoculation of tomato plants with the root endophyte *Fusarium solani* strain K (FsK) before infestation by *Tetranychus urticae* spider mites altered the plant's defense gene expression profile (Pappas et al., 2018). The presence of *F. oxysporum* in *Hordeum vulgare* conferred resistance against virulent pathogens, with this effect positively correlated to increased production of phenolic metabolites in the plant (Schulz et al., 1999). This suggests endophytes can activate the host's defense response and stimulate antagonistic compounds that inhibit invading microbes. Van Bael et al. (2012) found endophytes not only elicit the host's response mechanisms but also promote the biosynthesis of antimicrobial SMs. These findings indicate *Fusarium* spp. show promise as biocontrol agents, naturally strengthening crop plants' defenses against pathogens

- **Improvement of plant resistance against abiotic stresses**

Endophytic *Fusarium* have been shown not only strengthen plant defenses but also enhance tolerance to abiotic stresses and promote overall growth. For example, Shah et al. (2019) demonstrated a *Fusarium* sp. endophyte from *Dendrobium moniliforme* roots promoted the growth and development of *Rhynchostylis retusa*. More broadly, studies have established the ability of *Fusarium* endophytes to aid plants under stressful conditions like salinity, as well as confer growth benefits to their hosts. Elucidating how endophytes prepare plants for stresses and boost yields could enable the development of enhanced bioinoculants.

SMs produced by *Fusarium* endophytes can directly stimulate plant growth and development. The concept of "mycovitalism," coined by Vujanovic & Vujanovic (2007) after observing positive impacts of *F. semitectum* on orchid seed germination, has gained acceptance in reflecting endophytes as vital plant symbionts. A growing consensus from recent research supports the holobiont conceptualization of plants, emphasizing their dependence on symbiotic microorganisms including endophytic fungi. *Fusarium* endophytes have been shown to enhance root growth, nutrient/water acquisition, and resistance to abiotic stresses like salinity and drought (Selosse et al., 2014; Wani et al., 2015). As reviewed above, *Fusarium* metabolites directly stimulate plant growth and accumulation of valuable compounds. This confirms *Fusarium* spp. as integral plant partners and validates efforts to leverage their stress mitigation and yield-promoting capabilities through bioinoculant applications.

- **Pathogen biocontrol potential**

Preliminary data indicates certain *Fusarium* endophytes exhibit nematicidal activity. Continued exploration of these fungi could lead to the development of effective, eco-friendly nematode management solutions urgently needed by farmers worldwide. Optimizing endophyte-mediated nematode suppression represents a promising avenue for reducing crop losses from these pests in an environmentally responsible manner. Several studies have documented the ability of *F. oxysporum* isolates to inhibit various nematode parasites at different developmental stages (Waweru et al., 2014). Additionally, *F. moniliforme* strain Fe14 exhibited activity against *M. graminicola* (Le et al., 2016). This antagonism is thought to involve the production of antinematodal SMs. Similarly, chlamydosporin from *F. chlamydosporum* showed phytotoxic effects, while gibepyrone D, indole-3-acetic acid, 4- hydroxybenzoic acid and methyl 2-(4-hydroxyphenyl) acetate from *F. oxysporum*

162 displayed nematocidal properties (Toghueo, 2020). These studies support the development of *Fusarium* endophytes as biocontrol agents of plant-parasitic nematodes.

Biological activities of *F. oxysporum* as one of the most dominant endophytic *Fusarium* spp.

F. oxysporum is an endophytic fungus that has been isolated from various medicinal plants and shown to produce bioactive SMs with potential anticancer and antimicrobial activity (Kousar et al., 2022) (Figures 1, 2). Antioxidative and anti-aging agents were extracted from *F. oxysporum* such as cajaninstilbene acid inhabiting *Cajanus cajan* (Toghueo, 2020). *F. oxysporum* isolated from *N. foetida* was also found effective against *S. aureus*, *P. aeruginosa*, *E. coli*, and *C. albicans* (Musavi & Balakrishnan, 2014). *F. oxysporum* is also known to facilitate the vinblastine production by *Catharanthus roseus*, which demonstrates activity against leukemia and hepatocellular carcinoma cells (Kousar et al., 2022). Furthermore, this endophyte can synthesize the antifungal 2,4-diacetylphloroglucinol compound with potential antibiotic properties (de Lamo & Takken, 2020; Aini et al., 2022; Bora & Devi, 2023). *F. oxysporum* has been shown to produce an array of bioactive SMs with applications across agriculture and medicine. For example, the production of gibberellic acid, an important diterpenoid phytohormone, was maximized in an *F. oxysporum* isolate inhabiting *Coriandrum sativum* roots (Ben Rhouma et al., 2020). Wang et al. (2011) isolated a novel oxysporidinone analog alongside known metabolites like beauvericin from a *Cinnamomum kanehirae* endophyte that demonstrated activity against prostate, pancreatic, and lung cancer cell lines. Similarly, bikaverin from a *Cylindropuntia echinocarpus* isolate suppressed various cancer cell types and neovascularization (Toghueo, 2020).

- **Reported bioactivities of *F. oxysporum* metabolites**

F. oxysporum produces a wide array of SMs that exhibit diverse antimicrobial properties (Ibrahim et al., 2021). Many compounds demonstrate potent antibacterial activity against important human and plant pathogens. For instance, oxysporidinone inhibits various phytopathogenic fungi such as *Alternaria alternata* and *Venturia inequalis* (Breinholt et al., 1997). While (−)-4,6′-anhydrooxysporidinone exhibits moderate activity against *B. subtilis* and *S. aureus* (Wang et al., 2011). The mycotoxin fusaric acid possesses broad-spectrum antibacterial activity as well as strong antioomycete effects against *Phytophthora capsici* and *Phytophthora infestans* (Son et al., 2008). Beauvericin strongly impedes MRSA, *B. subtilis* and *Candida albicans* (Wang et al., 2011). Additionlly, naphthoquinone derivatives 8-O-Methyljavanicin and 8-O-Methylsolaniol display antibacterial activity against *S. aureus* and *S. pyogenes* (Baker et al., 1990). Bikaverin acts against phytopathogenic oomycetes and fungi such as *P. infestans* (Son et al., 2008). Additional compounds like the sesquiterpenoid and 1-Benzyl-2-methoxy-2-oxoethyl)-2-hydroxy-3-methylbutanoate inhibit important bacterial pathogens (Piska et al., 2020; Kılıç et al., 2021). These specialized metabolites highlight *F. oxysporum* as a promising source of novel antimicrobial agents.

Several compounds exhibit activity against various cancer cell lines, highlighting their promise in this therapeutic area. Fusarioxazin demonstrates significant cytotoxicity towards colorectal and breast cancer cell lines including HCT-116, MCF-7, and A549 (Mohamed et al., 2022). Enniatins H, I, MK1688 and beauvericin impair cell viability in lung, ovarian, and colorectal cancer models such as A549, SK-OV-3, SK-MEL-2, and HCT15 (Lee et al., 2008). Beauvericin also exhibits cytotoxic effects against melanoma, colorectal and central nervous system cancer cell lines (Zhan et al., 2007). Beyond individual molecules, other *F. oxysporum* metabolites show broad-spectrum anticancer properties. Bikaverin inhibits proliferation of non-small cell lung carcinoma and breast cancer cell line. 1-Benzyl-2-methoxy-2-oxoethyl)-2-hydroxy-3-methylbutanoate potently suppresses viability of breast, prostate and lung cancer models (Kılıç et al., 2021). *F. oxysporum* produces several metabolites with nematicidal properties against economically important plant-parasitic nematodes. Anhydrofusarubin, fusarubin, 8-O-methylfusarubin, and 3-O-methyl-8-O-methylfusarubin demonstrate varying degrees of activity against *Meloidogyne incognita* and *Rotylenchulus reniformis* (Kundu et al., 2016).

F. oxysporum has been shown to produce metabolites with antiviral properties. Compound 153 demonstrates activity against herpes simplex virus type 1, representing a potential candidate for developing antiviral therapies. Additionally, ergosta-5,8(14),22-trien-7-one,3-hydroxy-(3β,22E) inhibits the hepatitis C virus NS3 protease, indicating antiviral

potential against HCV (Yang et al., 2016). Beyond antimicrobial and cytotoxic effects, specialized metabolites from *F. oxysporum* also exhibit diverse bioactivities. Fusaricates A-G and 10-hydroxy-11-chlorofusaric acid induce phytotoxicity in barley plants (Wang et al., 2011; Yu et al., 2020). Cosmosporasides F–H demonstrate weak cytotoxic, antibacterial, and anti-inflammatory properties (Fu et al., 2022). Additionally, bikaverin protects against oxidative stress and attenuates hydrogen peroxide-induced neurotoxicity (Nirmaladevi et al., 2014).

- **Industrial and biotechnological applications of *F. oxysporum* enzymes**

Endophytic *F. oxysporum* produces an array of glycoside hydrolase enzymes with diverse industrial applications (Table 1). **β-Glucosidases** (BGL) enzymes catalyze the hydrolysis of aryl- and alkyl-β-glucosides, oligosaccharides, and diglucosides. BGL from *F. oxysporum* demonstrate high acid stability, making them well-suited for applications involving cellulose degradation under acidic conditions such as animal feed processing and fiber digestion enhancement (Zhao et al., 2013). **α-L-Fucosidases** (FUC) can be utilized as analytical tools for structural elucidation of complex carbohydrates due to their ability to cleave terminal fucosidic bonds in various biomolecules including oligosaccharides, glycoproteins, and blood group substances (Yano et al., 1985). *F. oxysporum* also secretes **α-D-galactopyranosidases** (GPase) hydrolyzes α-galactopyranosyl linkages at non-reducing ends of sugar chains. These enzymes can eliminate non-digestible oligosaccharides from legume products and soybeans to improve digestibility. α-D-galactopyranosidases could increase sucrose yields and quality in sugar refining operations (Katrolia et al., 2014). Moreover, their capacity to modify the physical properties of gum arabic positions them to improve formulations for coatings and emulsions. Overall, the diverse glycoside hydrolases produced by *F. oxysporum* offer opportunities to enhance processes in feed, food, analytical and other industries through biomass deconstruction capabilities.

Endophytic *F. oxysporum* produces **xylanases** that hold promise for several applications. As a group of enzymes that synergistically deconstruct the polysaccharide xylan, xylanases from *F. oxysporum* could facilitate ethanol production through saccharification of lignocellulosic biomass (Anasontzis et al., 2011). They may also enable sustainable industrial processing relying on xylan breakdown. Given the abundance of xylan globally, these enzymes represent useful tools for converting renewable plant polymers (Gómez et al., 2016). *F. oxysporum* also secretes **nitrilases** capable of converting nitriles to valuable amides and carboxylic acids (Chen et al., 2009). Such properties indicate potential utility in acrylamide and nicotinamide production, important precursors for various industrial polymers, pharmaceuticals and agrochemicals. The ability of this nitrilase to function robustly in industrial process environments expands its biotechnological applicability.

Cutinases are enzymes that break down cutin, a waxy polymer found in plants. Cutinases secreted by *F. oxysporum* facilitate the breakdown of cutin, enabling trans-esterification reactions for synthesis of compounds like butyl butyrate that use as flavors (pineapple flavor) (Nikolaivits et al., 2017). Moreover, cutinases offer eco-friendly biocatalytic degradation of polyethylene terephthalate (PET) and other synthetic polymers, representing a sustainable approach to plastic waste management (Dimarogona et al., 2015). *F. oxysporum* also synthesizes **lipoxygenase** (LOX), an enzyme that oxygenates polyunsaturated fatty acids and plays roles in inflammation and tumorigenesis (Mashima & Okuyama, 2015). *F. oxysporum* produces extracellular **laccases** with diverse applications. By catalyzing oxidation reactions while reducing oxygen to water, laccases from this endophyte could facilitate textile dye decolorization, pulp bleaching, organic synthesis and bioremediation/ detoxification processes. They may also assist with delignification, biofuel production from lignocellulosic feedstocks, and solubilization of brown coal (Kwiatos et al., 2018). Given these versatile functions, laccases represent useful tools for industries like textiles, paper, chemicals and energy. Additionally, *F. oxysporum* secretes **keratinases** capable of degrading keratin proteins present in hair, feathers and other keratinous materials. These enzymes offer an environmentally sustainable means of treating keratinous wastes generated from poultry and livestock industries, which are often disposed through landfilling or incineration (Preczeski et al., 2020). By converting these wastes into usable biomass through enzymatic breakdown, keratinases could help reduce agricultural waste streams while recovering value-added byproducts (Table 1).

Table 1. Endophytic *F. oxysporum* produces an array of enzymes with diverse industrial applications

Name of enzymes	Biological activities	Applications	References
Glycoside hydrolases • β-Glucosidases (BGL)	• Catalyze the hydrolysis of aryl- and alkyl-β-glucosides, oligosaccharides, and diglucosides. • Catalyzes the breakdown of terminal α-L-fucosidic bonds in various molecules, including oligosaccharides, glycoproteins, and blood group substances.	BGL from *F. oxysporum* shows high acid stability, making it a potential animal feed additive to enhance feed processing and fiber digestion. It could also be used in industrial applications requiring cellulose degradation at acidic pH.	(Ibrahim et al., 2021; Zhao et al., 2013)
• α-L-Fucosidases (FUC)	• It has remarkable roles in various bioprocesses, and it is used as a marker for hepatocellular carcinoma detection and structural analyses of complex natural products.	*F. oxysporum* produces FUC in large quantities. The enzyme can be utilized as an analytical tool for structural elucidation of complex carbohydrates and oligosaccharides	(Yano et al., 1985; Yamamoto et al., 1986; Moreti et al., 2013)
• α-D-Galactopyranosidases (GPase)	• Hydrolyzes α-galactopyranosyl linkages at non-reducing ends of sugar chains.	*F. oxysporum* produces GPases that could be used in several applications: • Eliminating non-digestible oligosaccharides in legume products and soybean • Improving digestibility of animal feed • Increasing yield and quality of sucrose in sugar refineries • Improving the physical properties of gum arabic, an industrially important polysaccharide used as a coating agent and emulsion stabilizer	(Katrolia et al., 2014; Maruta et al., 2017)
Xylanases	• Xylanases are a group of enzymes that work together to break down xylan, one of the most abundant carbohydrates on Earth.	*F. oxysporum* produces various xylanases that could be used for: • Ethanol production from lignocellulosic biomass • Sustainable industrial degradation of xylan	(Alconada & Martínez, 1994; Anasontzis et al., 2011; Dimarogona et al., 2012)
Nitrilases	• Microbial nitrilases are biocatalysts of remarkable organic importance in terms of nitrile conversion. • These enzymes convert nitrile compounds into amides and carboxylic acids, which have applications in various industries.	Nitrilase from *F. oxysporum* exhibits broad substrate specificity and optimal activity at industrially relevant temperatures and pH, making it potentially valuable for: • Acrylamide production • Nicotinamide production	(Chen et al., 2009; Bura Gohain et al., 2015)

Table 1. Cont.

Name of enzymes	Biological activities	Applications	References
Cutinases	• Cutinases are enzymes that break down cutin, a waxy polymer found in plants.	*F. oxysporum* produces cutinases that could be used in various applications: • Synthesis of flavor compounds, such as butyl butyrate (pineapple flavor), through trans-esterification reactions • Biocatalytic degradation of polyethylene terephthalate (PET) and other synthetic polymers, offering an eco-friendly approach to plastic waste management	(Legras et al., 1990; Dimarogona et al., 2015; Nikolaivits et al., 2017)
Lipoxygenase (LOX)	• LOX catalyzes the hydroperoxidation of polyunsaturated fatty acids like arachidonic and linoleic acids.	This enzyme plays important roles in physiological processes like inflammation and tumorigenesis. Further research could explore its potential in these areas	(Mashima & Okuyama, 2015; Ibrahim et al., 2018)
Laccases	• Laccases atalyze the oxidation of organic substrates while reducing oxygen to water.	*F. oxysporum* produces laccases with potential applications in several areas: • Textile dye decolorization • Pulp bleaching • Organic synthesis • Bioremediation and detoxification of environmental pollutants • Delignification • Biofuel production • Solubilization of brown coal	(Hämäläinen et al., 2018; Kwiatos et al., , 2018, 2020; Ibrahim et al., 2021)
Keratinases	• Keratinases are enzymes that break down keratin, a protein found in hair, feathers, and other animal tissues.	*F. oxysporum* produces keratinases that could be utilized for the **eco-friendly treatment of keratinous wastes**, such as chicken feathers and swine hair, which are often disposed of in landfills or incinerators.	(Preczeski et al., 2020)
Phospholipase B (PLB)	• PLB hydrolyzes phospholipids to produce fatty acids and phosphoglycerates.	*F. oxysporum* (PLB) has potential applications in the food and oil industries: • Production of beneficial phospholipid derivatives • Reduction of cholesterol content in food • Refining vegetable oils, particularly crude oil degumming	(Su et al., 2017; Liu et al., 2018)
Triosephosphate Isomerase (TPI)	• TPI is a glycolytic enzyme that catalyzes the interconversion of dihydroxyacetone-3-phosphate (DHAP) and glyceraldehyde-3-phosphate (GAP).	An essential enzyme for the survival and infectivity of this pathogenic fungus. Research could explore its potential as a target for antifungal drug development	(Wierenga et al., 2010)

F. oxysporum produces **phospholipase** B (PLB) with applications across the food and oil industries. By hydrolyzing phospholipids, this enzyme can generate beneficial derivatives and reduce cholesterol levels in foods. It also aids the refining of vegetable oils through crude oil degumming. These properties indicate potential commercial value (Su et al., 2017). F. oxysporum also secretes **triosephosphate isomerase** (TPI), a glycolytic enzyme essential for fungal survival and infectivity. TPI is a glycolytic enzyme that catalyzes the interconversion of dihydroxyacetone-3-phosphate (DHAP) and glyceraldehyde-3-phosphate (GAP) (Wierenga et al., 2010). Beyond secreted enzymes, *F. oxysporum* accumulates lipids including triacylglycerols suited for biodiesel feedstock (Sayeda et al., 2019). Also, they demonstrate ability to convert D-xylose and cellulose into ethanol, showing promise for biofuel production from lignocellulosic biomass (Xu et al., 2015). Phospholipase B and triosephosphate isomerase present industrial and pharmaceutical opportunities. Lipid accumulation provides a biodiesel platform, while cellulolytic activity positions this endophyte for next-generation cellulosic bioethanol schemes (Table 1).

- **Applications of metal nanoparticles produced by *F. oxysporum***

F. oxysporum has been shown to effectively synthesize silver nanoparticles (AgNPs) with promising antibacterial properties. AgNPs produced by *F. oxysporum* inhibit a wide range of human pathogenic bacteria, including multidrug-resistant strains of *E. coli, S. aureus,* and *K. pneumoniae* (Ahmed et al., 2018). They also impair *Streptococcus agalactiae*, an important cause of invasive disease. Incorporating these AgNPs into cotton cloth sterilizes the material against S. aureus, highlighting applications as medical textile antiseptics (Shati & Elsaid, 2020). Research further suggests combining AgNPs from *F. oxysporum* with antibiotics can result in additive or synergistic effects against antibiotic-resistant infections. Their capacity to augment standard drug therapies also provides opportunities to strengthen treatment of infections caused by resistant pathogens (Shati & Elsaid, 2020). *F. oxysporum* has also been employed for the eco-friendly synthesis of other nanoscale materials like platinum nanoparticles, cadmium/selenium (CdSe) and CdTe quantum dots which show promise in bioimaging, drug delivery, and bioelectronics due to their optical and electronic properties (Syed & Ahmad 2012, 2013; Yamaguchi et al., 2016). *F. oxysporum* likewise holds potential for sustainable production of metal oxide nanomaterials. *F. oxysporum* has also been used to bioleach fly ash, producing highly stable, fluorescent silica nanoparticles through a low-cost process (Bansal et al., 2007). Given the fungus's ability to synthesize nanomaterials from readily available raw resources, it shows implications for scalable, cost-effective nanomanufacturing with applications across industry and medicine. Continued studies optimizing *F. oxysporum*-mediated nanomaterial synthesis could make this a commercially viable green technology.

- **Production and biodegradation of bioplastics and bioplasticizers by *F. oxysporum***

Fusarium spp. has emerged as a significant player in bioplastic production, particularly through its ability to degrade synthetic polymers and produce biodegradable alternatives. This fungus can effectively interact with various plastics, such as polyethylene terephthalate (PET) and polycaprolactone (PCL), utilizing its enzymatic capabilities to break down these materials (Srikanth et al., 2022; Cognigni et al., 2023). Additionally, the biodegradation processes involving *Fusarium* spp. can yield valuable metabolites, enhancing the economic viability of bioplastic production (Ali et al., 2022).

Moreover, *Fusarium* spp. contribute to the microbial production of polyhydroxyalkanoates (PHAs), which are promising bioplastics due to their biodegradability and compatibility with existing plastic applications (Chawla et al., 2023). Beyond bacterial and algeal production of PHAs, *F. moniliforme*, a close relative of *F. oxysporum*, can synthesize PHAs when grown using sugarcane juice and ammonium ferrous sulfate as carbon and nitrogen sources, respectively (Jindal & Tiwari, 2013). While overall production costs remain high, this process demonstrates the techno-economic feasibility of fungal PHA synthesis using inexpensive agricultural residues. Thus, using renewable biomass, including low cost agricultural residues can facilitate economical production aligning with circular economy principles (Choi et al., 2023). Phthalic acid esters (PAEs) are a class of plasticizers and additives that have widespread industrial usage. PAEs such as diethylhexyl phthalate (DEHP) and dibutyl phthalate (DBP) are commonly used to improve the flexibility, workability and durability of plastics in numerous consumer

products like packaging, furnishings, medical supplies and building materials (Hu et al., 2016). Their characteristic properties including good insulation, strength and corrosion resistance have made PAEs economical and versatile for plastic manufacturing applications (Amr et al., 2024). However, the extensive use of certain PAEs like DEHP and DBP has raised environmental and health concerns due to their persistence and potential toxicity. While these compounds were initially thought to originate solely from industrial sources, it is now recognized that many organisms in nature including plants, bacteria, actinomycetes, fungi and animals are capable of synthesizing PAEs (Lee, 2000; Al-Bari et al., 2005; Adeyemo et al., 2024).

The natural occurrence of phthalate esters (PAEs) in diverse organisms has prompted a reevaluation of their status as environmental pollutants. While initially believed to solely result from industrial activity, it is now recognized that PAEs may be endogenously synthesized through microbial and plant secondary metabolism (Ortiz & Sansinenea, 2018). However, it remains unclear if environmental levels stem from natural production or accumulation from external sources (Thiemann, 2021). Biological evaluations of plant-derived PAEs have revealed activities like antitumor, antioxidant and antimicrobial effects, in addition to larvicidal properties, suggesting possible physiological roles (El-Sayed, 2012; Kdimy et al., 2023). Diethyl phthalate (DEHP) is primarily used as a plasticizer in polyvinyl chloride production for various industrial and medical applications, however it can easily leach into the environment from these sources (El-Sayed et al., 2015; Thiemann, 2021). As DEHP accumulates in plants, soils, water and sediments, continuous human exposure poses health risks (Kang et al., 2023). Biodegradation through aerobic microbial metabolism represents an attractive remediation strategy, as it facilitates complete mineralization of phthalate esters into benign byproducts (Boll et al., 2020). Dibutyl phthalate, is another bioactive ester. It acts as antimalarial, antibacterial, antifungal, antitumor, anticancer and herbicide. It is also employed as plasticiser in the manufacture of polyvinyl chloride and other plastics and as additive in the manufacture of ink. Indeed, the bioremediation potential of microorganisms for DEHP and related phthalates has been extensively explored in numerous studies (Ali et al., 2023; Sahoo & Kumar, 2023).

Endophytic *Fusarium* species have attracted research interest as producers of phthalic acid esters (PAEs), which exhibit diverse biological functions. These fungi are recognized to synthesize a wide range of SMs, with several studies identifying PAEs like diethyl phthalate and dimethyl phthalate in various endophytic *Fusarium* strains (Huang et al., 2021; Ahmed et al., 2023). PAEs have demonstrated allelopathic, antimicrobial and insecticidal properties beneficial to both plants and microbes through enhancing competitive abilities (Huang et al., 2021). A study by Hua (2010) characterized *Fusarium* sp. DMT-5-3 isolated from mangrove sediments, finding it could stepwise hydrolyze the ester bonds of dimethyl terephthalate (DMT) via intracellular esterases. This converted DMT first to monomethyl terephthalate (MMT) and then completely to terephthalic acid. However, with dimethyl isophthalate (DMI) as substrate these enzymes only partially hydrolyzed DMI to monomethyl isophthalate (MMI) without further metabolism. Further, the esterases exhibited higher activity intracellularly than extracellularly, and displayed high substrate specificity preferentially hydrolyzing DMT among tested dimethyl phthalate esters (DMPEs). Several studies have reported *Fusarium* spp. producers of bioactive phthalates. Bai et al. (2019) isolated dibutyl phthalate and beauvericin from the endophyte *Fusarium geni* inhabiting *Rumex madaio.* Both compounds demonstrated potent antimicrobial activity against *S. aureus*. Dibutyl phthalate was found as a predominant compound, highlighting endophytic *Fusarium* as natural sources of this bioactive phthalate. Recently, the first study about the biosynthesize of diethylhexyl phthalate (DEHP) by *F. oxysporum* was conducted by Amr et al. (2024). *F. oxysporum* isolated from *Polygala sinaicum*, is capable of synthesizing DEHP, its extracts demonstrated potent antimicrobial activity against a range of multi-drug resistant Gram-negative and Gram-positive bacterial pathogens (Amr et al., 2024). All previous findings highlight the dual role of endophytic *Fusarium* species in both producing and degrading PAEs, emphasizing their ecological importance and potential applications in bioremediation and pharmaceuticals.

CONCLUSION

Endophytic *Fusarium* spp. represent a treasure trove of NPs with diverse and promising biotechnological applications. Metabolites from *F. oxysporum* exhibit antimicrobial, cytotoxic, nematicidal and other effects, highlighting

opportunities for new therapeutics and agrochemicals. Its repertoire of industrially-applicable enzymes offers solutions for sectors such as feed, food, biofuel, and chemical processing through bioconversion capabilities. Nanoparticles (NPs) synthesized by *F. oxysporum* also hold value, such as AgNPs showing potent antibacterial properties against multidrug-resistant strains. The ability of these NPs to augment antibiotic therapies represents an approach to strengthen the treatment of resistant infections. Additionally, *F. oxysporum* shows potential for production and biodegradation of bioplastics and bioplasticizers. Further characterization and development of *Fusarium* spp. NPs, enzymes and other biomolecules are warranted to realize their commercial potential across pharmaceutical, agricultural and industrial applications. As a rich genetic resource, endophytic *Fusarium* spp. merit ongoing exploration to deliver novel product candidates and biotechnological solutions from sustainable, renewable sources.

Conflict of interest: The authors indicated no potential conflicts of interest.

Authors' contributions: All the authors are sharing equally on writing, and revision of this review article

Ethical approval: Not applicable.

REFERENCES

Abdelhamid, S.A., Abo Elsoud, M.M., El-Baz, A.F., Nofal, A.M., El-Banna, H.Y. (2024). Optimisation of indole acetic acid production by Neopestalotiopsis aotearoa endophyte isolated from *Thymus vulgaris* and its impact on seed germination of *Ocimum basilicum*. *BMC Biotechnology,* 24: 46.

Abdel-Razek, A.S., El-Naggar, M.E., Allam, A., Morsy, O.M., Othman, S.I. (2020). Microbial Natural Products in Drug Discovery. *Processes*, 8: 470.

Adeleke, B.S., Babalola, O.O., Glick, B.R. (2021). Plant growth-promoting root-colonizing bacterial endophytes. *Rhizosphere,* 20: 100433.

Adeyemo, O.M., Onilude, A.A., Oyinlola, K.A. (2024). Production, characterization of metabolites, and antimicrobial activity of *Streptomyces albospinus*-OY 44. *Savannah Journal of Science and Engineering Technology* 2: 041–051.

Ahmed, A.A., Hamzah, H., Maaroof, M. (2018). Analyzing formation of silver nanoparticles from the filamentous fungus Fusarium oxysporum and their antimicrobial activity. *Turkish Journal of Biology*, 42(1): 54-62.

Ahmed, A.M., Mahmoud, B.K., Millán-Aguiñaga, N., Abdelmohsen, U.R., Fouad, M.A. (2023). The endophytic *Fusarium* strains: A treasure trove of natural products. *RSC Advances*, 13: 1339–1369.

Aini, K., ELFITA, Widjajanti, H., Setiawan, A., Kurniawati, A.R. (2022). Antibacterial activity of endophytic fungi isolated from the stem bark of jambu mawar (Syzygium jambos). EBSCOhost, 23: 521.

Al-Bari, M.A.A., Bhuiyan, M.S.A., Flores, M.E., Petrosyan, P., García-Varela, M., Islam, M.A.U., (2005). *Streptomyces bangladeshensis* sp. nov., isolated from soil, which produces bis-(2-ethylhexyl) phthalate. *International Journal of Systematic and Evolutionary Microbiology,* 55: 1973–1977.

Alconada, T.M., Martínez, M.J. (1994). Purification and characterization of an extracellular endo-1,4-β-xylanase from *Fusarium oxysporum* f. sp. melonis. *FEMS Microbiology Letters,* 118: 305–310.

Ali, E.A.M., Abdel-Rahman, T.M.A., Ali, D.M.I., Gamal, A.-S.H. (2023). Fungal bioremediation of the plasticizer hazardous compound di-2-ethylhexyl phthalate (DEHP) in urine and blood bags. *Iranian Journal of Science,* 47: 673–682.

Ali, S., Zakarya, S., Khaled, S. (2022). Screening and optimisation of the biodegradation potential for low density polyethylene (LDPE) films by *Fusarium equiseti* and *Brevibacillus parabrevis*. *Biosciences Biotechnology Research Asia,* 19: 215–229.

Alves, R. de N.S., Borges, K.R.A., Silva, M.A.C.N. da, Teles, A.M., Alves, D., et al. (2024). Antioxidant, anticancer and antimicrobial activity of secondary metabolites from *Fusarium* species. *Observatorio de la Economía Latinoamericana*, 22: e4578–e4578.

Amr, E.H., Sorour, N.M., El-Sayed, A.S., Fayed, M.A.A. (2024). Isolation, identification and metabolic products assesment of some endophytes isolated from some Egyptian plants. Genetic Engineering and Biotechnology Research Institute, University of Sadat City.

Anasontzis, G.E., Zerva, A., Stathopoulou, P.M., Haralampidis, K., Diallinas, G., Karagouni, A.D., et al. (2011). Homologous overexpression of xylanase in Fusarium oxysporum increases ethanol productivity during consolidated bioprocessing (CBP) of lignocellulosics. *Journal of Biotechnology,* 152: 16–23.

Bacon, C.W., Yates, I.E. (2006). Endophytic root colonization by *Fusarium* species: Histology,

plant interactions, and toxicity. In: *"Microbial Root Endophytes*", Schulz, B.J.E., Boyle, C.J.C., Sieber, T.N. (Eds.), pp. 133–152. Springer, Berlin, Heidelberg.

Bai, X., Yu, R., Li, M., Zhang, H. (2019). Antimicrobial assay of endophytic fungi from Rumex madaio and chemical study of strain R1. *Bangladesh Journal of Pharmacology,* 14: 129–135.

Baker, R.A., Tatum, J.H., Nemec, S. (1990). Antimicrobial activity of naphthoquinones from Fusaria. *Mycopathologia*, 111:9–15.

Bansal, V., Syed, A., Bhargava, S.K., Ahmad, A., Sastry, M. (2007). Zirconia enrichment in zircon sand by selective fungus-mediated bioleaching of silica. *Langmuir,* 23: 4993–4998.

Bary, A. de (1866). "*Morphologie und Physiologie der Pilze, Flechten und Myxomyceten*". Engelmann.

Ben Rhouma, M., Kriaa, M., Ben Nasr, Y., Mellouli, L., Kammoun, R. (2020). A New endophytic *Fusarium oxysporum* gibberellic acid: Optimization of production using combined strategies of experimental designs and potency on tomato growth under stress condition. *BioMed Research International,* 2020: 4587148.

Bhadra, F., Gupta, A., Vasundhara, M., Reddy, M.S., (2022). Endophytic fungi: a potential source of industrial enzyme producers. *3 Biotech,* 12: 86. https://doi.org/10.1007/s13205-022-03145-y

Bhardwaj, A., Agrawal, P. (2014). A review fungal endophytes: As a store house of bioactive compound. *World Journal of Pharmacy And Pharmaceutical Sciences,* 3: 228–237.

Bisht, D., Owais, M., Venkatesan, K. (2006). Potential of plant-derived products in the treatment of mycobacterial infections. In: "*Modern Phytomedicine*", pp. 293–311. John Wiley & Sons, Ltd.

Boll, M., Geiger, R., Junghare, M., Schink, B. (2020). Microbial degradation of phthalates: Biochemistry and environmental implications. *Environmental Microbiology Reports*, 12: 3–15.

Bora, P., Devi, N.N. (2023). Exploration of the chemical constituents and its antioxidant, antibacterial activities of endophytic fungi isolated from the medicinal plant Dillenia indica. *Archives of Microbiology,* 205: 67.

Boruah, J.L.H., Das, D., Gogoi, P., Kumar, N., Borah, B., Borah, M., et al. (2024). Fungal endophytes as an alternative natural resource for the discovery of bioactive compounds of pharmacological importance. In: "*Endophytic Fungi: The Hidden Sustainable Jewels for the Pharmaceutical and Agricultural Industries*", pp. 57-78. Cham: Springer International Publishing.

Breinholt, J., Ludvigsen, S., Rassing, B.R., Rosendahl, C.N., Nielsen, S.E., Olsen, C.E. (1997). Oxysporidinone: A novel, antifungal N-methyl-4-hydroxy-2-pyridone from *Fusarium oxysporum*. *Journal of Natural Products,* 60: 33–35.

Brusotti, G., Cesari, I., Dentamaro, A., Caccialanza, G., Massolini, G. (2014). Isolation and characterization of bioactive compounds from plant resources: The role of analysis in the ethnopharmacological approach. *Journal of Pharmaceutical and Biomedical Analysis, Review Papers on Pharmaceutical and Biomedical Analysis,* 87: 218–228.

Bungtongdee, N., Sopalun, K., Laosripaiboon, W., Iamtham, S. (2019). The chemical composition, antifungal, antioxidant and antimutagenicity properties of bioactive compounds from fungal endophytes associated with Thai orchids. *Journal of Phytopathology,* 167: 56–64.

Bura Gohain, M., Talukdar, S., Talukdar, M., Yadav, A., Gogoi, B.K., Bora, T.C., et al. (2015). Effect of physicochemical parameters on nitrile-hydrolyzing potentials of newly isolated nitrilase of *Fusarium oxysporum* f. sp. lycopercisi ED-3. *Biotechnology and Applied Biochemistry,* 62: 226–236.

Campos, F.F., Sales Junior, P.A., Romanha, A.J., Araújo, M.S., Siqueira, E.P., Resende, J.M., et al. (2015). Bioactive endophytic fungi isolated from *Caesalpinia echinata* Lam. (Brazilwood) and identification of beauvericin as a trypanocidal metabolite from Fusarium sp. *Memórias do Instituto Oswaldo Cruz*, 110: 65–74.

Chang, S., Yan, B., Chen, Y., Zhao, W., Gao, R., Li, Y., et al. (2023). Cytotoxic hexadepsipeptides and anti-coronaviral 4-hydroxy-2-pyridones from an endophytic *Fusarium* sp. *Frontiers in Chemistry,* **10**, 1106869. Article ID: 1106869

Chawla, M., Narwal, S., Dhankar, R., Kalshan, S., (2023). Microbial production of bioplastics: An eco-friendly alternative. *Ecology, Environment and Conservation,* 29: 254–262.

Chen, J., Zheng, R.-C., Zheng, Y.-G., Shen, Y.-C. (2009). Microbial transformation of nitriles to high-value acids or amides. In: "*Biotechnology in China I: From Bioreaction to Bioseparation and Bioremediation*", Zhong, J.-J., Bai, F.-W., Zhang, W. (Eds.), pp. 33–77. Springer, Berlin, Heidelberg.

Choi, S.Y., Lee, Y., Yu, H.E., Cho, I.J., Kang, M., Lee, S.Y. (2023). Sustainable production and degradation of plastics using microbes. *Nature Microbiology,* 8: 2253–2276.

Cognigni, F., Temporiti, M.E.E., Nicola, L., Gueninchault, N., Tosi, S., Rossi, M. (2023). Exploring the infiltrative and degradative ability of *Fusarium oxysporum* on polyethylene terephthalate (PET) using correlative microscopy and deep learning. *Scientific Reports,* 13: 22987.

Cui, R., Lu, X., Chen, X., Malik, W.A., Wang, D., Wang, J., et al. (2021). A novel raffinose biological pathway is observed by symbionts of cotton *Verticillium dahliae* to improve salt tolerance genetically on cotton. *Journal of Agronomy and Crop Science,* 207: 956–969.

de Castro, I., Mendo, S., Caetano, T. (2020). Antibiotics from Haloarchaea: What can we learn from comparative genomics? *Marine Biotechnology,* 22: 308–316.

De Lamo, F.J., Takken, F.L. (2020). Biocontrol by *Fusarium oxysporum* using endophyte-mediated resistance. *Frontiers in Plant Science*, 11: 37.

De Silva, N., Lumyong, S., Hyde, K.D., Bulgakov, T., Phillips, A.J.L., Yan, J.Y. (2016). Mycosphere Essays 9: Defining biotrophs and hemibiotrophs.

Demain, A.L. (2014). Importance of microbial natural products and the need to revitalize their discovery. *Journal of Industrial Microbiology and Biotechnology*, 41: 185–201.

Dimarogona, M., Topakas, E., Christakopoulos, P., Chrysina, E.D. (2012). The structure of a GH10 xylanase from *Fusarium oxysporum* reveals the presence of an extended loop on top of the catalytic cleft. *Acta Crystallographica Section D*, 68: 735–742.

Dimarogona, M., Nikolaivits, E., Kanelli, M., Christakopoulos, P., Sandgren, M., Topakas, E. (2015). Structural and functional studies of a *Fusarium oxysporum* cutinase with polyethylene terephthalate modification potential. *Biochimica et Biophysica Acta (BBA) - General Subjects,* 1850: 2308–2317.

Domingo-Fernández, D., Gadiya, Y., Preto, A.J., Krettler, C.A., Mubeen, S., Allen, A., et al. (2024). Natural products have increased rates of clinical trial success throughout the drug development process. *Journal of Natural Products*, 87: 1844–1851.

El-Baz, A., Shetaia, Y., Abdelghani, D.Y., Abaza, A.A. (2024). Myco-remediation in industrial wastewater treatment. In: "*Trends in Biological Processes in Industrial Wastewater Treatment*", pp. 12.1-12.33. https://ioppublishing.org/contacts/

El-Sayed, M.H. (2012). Di-(2-ethylhexyl) phthalate, a major bioactive metabolite with antimicrobial and cytotoxic activity isolated from the culture filtrate of newly isolated soil *Streptomyces* (*Streptomyces mirabilis* Strain NSQu-25). *World Applied Sciences Journal*, 20: 1202–1212.

El-Sayed, O., Asker, M., Shash, S., Hamed, S. (2015). Isolation, structure elucidation and biological activity of Di- (2-ethylhexyl) phthalate produced by *Penicillium janthinellum* 62. *International Journal of ChemTech Research*, 8: 974–4290.

El-Sayed, A.S.A., Khalaf, S.A., Azez, H.A., Hussein, H.A., EL-Moslamy, S.H., et al. (2021). Production, bioprocess optimization and anticancer activity of Camptothecin from *Aspergillus terreus* and *Aspergillus flavus*, endophytes of *Ficus elastica*. *Process Biochemistry*, 107: 59–73.

El-Sayed, A.S.A., Zayed, R.A., El-Baz, A.F., Ismaeil, W.M. (2022). Bioprocesses optimization and anticancer activity of camptothecin from *Aspergillus flavus*, an endophyte of in vitro cultured *Astragalus fruticosus*. *Molecular Biology Reports*, 49: 4349–4364.

El-Sayed A.S.A., ElSayed A.I., Wadan K.M., El-Saadany S.S., Abd El-Hady N.A.A. (2024). Camptothecin bioprocessing from *Aspergillus terreus*, an endophyte of *Catharanthus roseus*: Antiproliferative activity, topoisomerase inhibition and cell cycle analysis. *Microbial Cell Factories*, 23(1): no. 15.

Fadiji, A.E., Babalola, O.O. (2020). Exploring the potentialities of beneficial endophytes for improved plant growth. *Saudi Journal of Biological Sciences,* 27: 3622–3633.

Feng, N., Zhong, F., Cai, G., Zheng, W., Zou, H., Gu, J., Yuan, Y., et al. (2023). *Fusarium* mycotoxins zearalenone and deoxynivalenol reduce hepatocyte innate immune response after the *Listeria monocytogenes* infection by inhibiting the TLR2/ NFκB signaling pathway. *International Journal of Molecular Sciences*, 24: 9664.

Firestein, G.S., Budd, R.C., Gabriel, S.E., McInnes, I.B., O'Dell, J.R. (2016). "*Kelley and Firestein's Textbook of Rheumatology*". Elsevier Health Sciences.

Fu, Y., Wu, P., Xue, J., Zhang, M., Wei, X. (2022). Cosmosporasides F–H, three new sugar alcohol

conjugated acyclic sesquiterpenes from a *Fusarium oxysporum* fungus. *Natural Product Research,* 36: 3420–3428.

Gagare, S., Patil, P., Jain, A. (2024). Natural product-inspired strategies towards the discovery of novel bioactive molecules. *Future Journal of Pharmaceutical Sciences*, 10: 55.

Gamal, A., Fikry, E., Tawfeek, N., El-Shafae, A.M., El-Sayed, A.S.A., El-Domiaty, M.M. (2024). Production and bioprocessing of Taxol from *Aspergillus niger*, an endophyte of *Encephalartos whitelockii*, with a plausible biosynthetic stability: Antiproliferative activity and cell cycle analysis. *Microbial Cell Factories,* 23(1): art. no. 78

Ghosh, U., Mathur, P., Chaturvedi, P., Sharma, C., Bhatnagar, P. (2023). Bioprospection of endophytic fungi for extracellular enzymes. In: "*Fungal Resources for Sustainable Economy: Current Status and Future Perspectives*", Singh, I., Rajpal, V.R., Navi, S.S. (Eds.), pp. 127–146. Springer Nature Singapore, Singapore.

Gómez, S., Payne, A.M., Savko, M., Fox, G.C., Shepard, W.E., Fernandez, F.J., et al. (2016). Structural and functional characterization of a highly stable endo-β-1,4-xylanase from *Fusarium oxysporum* and its development as an efficient immobilized biocatalyst. *Biotechnology for Biofuels,* 9: 191.

Hamzah, T.N.T., Lee, S.Y., Hidayat, A., Terhem, R., Faridah-Hanum, I., Mohamed, R. (2018). Diversity and characterization of endophytic fungi isolated from the tropical Mangrove species, *Rhizophora mucronata*, and identification of potential antagonists against the soil-borne Fungus, *Fusarium solani*. *Frontiers in Microbiology,* 9, 1707.

Han, S.M., Weaver, F.A., Comerota, A.J., Perler, B.A., Joing, M. (2010). Efficacy and safety of alfimeprase in patients with acute peripheral arterial occlusion (PAO). *Journal of Vascular Surgery,* 51: 600–609.

Hao, Y., Yu, M., Wang, K., Zhu, B., Wang, Z., Liu, Y., et al. (2022). Discovery of glyantrypine-family alkaloids as novel antiviral and antiphytopathogenic-fungus agents. *Pest Management Science,* 78: 982–990.

Hämäläinen, V., Grönroos, T., Suonpää, A., Heikkilä, M.W., Romein, B., Ihalainen, P., et al. (2018). Enzymatic processes to unlock the lignin value. *Frontiers in Bioengineering and Biotechnology*, 6: 20.

Hawas, U.W., Al-Farawati, R., Abou El-Kassem, L.T., Turki, A.J. (2016). Different culture metabolites of the Red Sea fungus F*usarium equiseti* optimize the inhibition of hepatitis C virus NS3/4A protease (HCV PR). *Marine Drugs*, 14: 190.

Hidayat, I., Radiastuti, N., Rahayu, G., Achmadi, S., Okane, I. (2016). Three quinine and cinchonidine producing Fusarium species from Indonesia. *Current Research in Environmental & Applied Mycology,* 6(1): 20-34.

Hu, A.-P., Liu, Y.-L., Shi, L.-K. (2016). Widespread occurrence of phthalic acid esters in raw oilseeds in China used for edible vegetable oil production. *Food Additives and Contaminants: Part A, Chemistry, Analysis, Control, Exposure and Risk Assessment*, 33: 1421–1427.

Hua, L.Z. (2010). "*Degradation of Three Dimethyl Phthalate Isomer Esters (DMPEs) by Mangrove Sediment Fungi*". City University of Hong Kong.

Huang, L., Zhu, X., Zhou, S., Cheng, Z., Shi, K., Zhang, C., Shao, H. (2021). Phthalic acid esters: Natural sources and biological activities. *Toxins,* 13: 495.

Ibrahim, S.R.M., Mohamed, G.A., Al Haidari, R.A., Zayed, M.F., El-Kholy, A.A., et al. (2018). Fusarithioamide B, a new benzamide derivative from the endophytic fungus *Fusarium chlamydosporium* with potent cytotoxic and antimicrobial activities. *Bioorganic & Medicinal Chemistry,* 26: 786–790.

Ibrahim, S.R.M., Sirwi, A., Eid, B.G., Mohamed, S.G.A., Mohamed, G.A. (2021). Bright side of F*usarium oxysporum*: Secondary metabolites bioactivities and industrial relevance in biotechnology and nanotechnology. *Journal of Fungi*, 7: 943.

Jindal, P., Tiwari, D.P. (2013). Polyhydroxyalkanoates preparation by *Fusarium moniliforme* using sugarcane as substrate. *International Journal of Engineering Research,* 2. IJERTV2IS70421

Kang, J.S., Baek, J.H., Song, M.Y., Rehman, N.U., Chung, H.J., Lee, D.K., et al. (2023). Long-term exposure changes the environmentally relevant bis(2-ethylhexyl) phthalate to be a neuro-hazardous substance disrupting neural homeostasis in emotional and cognitive functions. *Environmental Pollution,* 324: 121387.

Katrolia, P., Rajashekhara, E., Yan, Q., Jiang, Z., (2014). Biotechnological potential of microbial α-galactosidases. *Critical Reviews in Biotechnology*, 34: 307–317.

Kdimy, A., Kim, S.J., Ali, Z., Khan, M.I.H., Tripathi, S.K., El Hajjaji, S., et al. (2023). Isolation of two plasticizers, Bis(2-ethylhexyl) terephthalate and Bis(2-ethylhexyl) phthalate, from *Capparis*

spinosa L. Leaves. *Chemistry & Biodiversity,* 20: e202300903.

Kılıç, G., Tosun, G., Bozdeveci, A., Erik, İ., Öztürk, E., Reis, R., et al. (2021). Antimicrobial, cytotoxic, antiviral wffects, and apectroscopic characterization of metabolites produced by *Fusarium oxysporum* YP9B. *Records of Natural Products*, 15(6): 547-567.

Kousar, R., Naeem, M., Jamaludin, M.I., Arshad, A., Shamsuri, A.N., Ansari, N., et al. (2022). Exploring the anticancer activities of novel bioactive compounds derived from endophytic fungi: Mechanisms of action, current challenges and future perspectives. *American Journal of Cancer Research*, 12: 2897.

Kundu, A., Saha, S., Walia, S., Dutta, T.K. (2016). Anti-nemic secondary metabolites produced by Fusarium oxysporum f. sp. ciceris. *Journal of Asia-Pacific Entomology,* 19: 631–636.

Kwiatos, N., Jędrzejczak-Krzepkowska, M., Strzelecki, B., Bielecki, S. (2018). Improvement of efficiency of brown coal biosolubilization by novel recombinant *Fusarium oxysporum* laccase. *AMB Express*, 8: 133.

Kwiatos, N., Jędrzejczak-Krzepkowska, M., Krzemińska, A., Delavari, A., Paneth, P., Bielecki, S. (2020). Evolved *Fusarium oxysporum* laccase expressed in Saccharomyces cerevisiae. *Scientific Reports,* 10: 3244.

Lacerda, Í.C. dos S., Polonio, J.C., Golias, H.C., (2022). Endophytic fungi as a source of antiviral compounds – A review. *Chemistry & Biodiversity,* 19: e202100971.

Le, H.T.T., Padgham, J.L., Hagemann, M.H., Sikora, R.A., Schouten, A. (2016). Developmental and behavioural effects of the endophytic *Fusarium moniliforme* Fe14 towards Meloidogyne graminicola in rice. *Annals of Applied Biology*, 169: 134–143.

Le, T.T.M., Hoang, A.T.H., Nguyen, N.P., Le, T.T.B., Trinh, H.T.T., et al. (2020). A novel huperzine A-producing endophytic fungus *Fusarium* sp. Rsp5.2 isolated from *Huperzia serrate*. *Biotechnology Letters,* 42: 987–995.

Lee, D.S. (2000). Dibutyl phthalate, an alpha-glucosidase inhibitor from S*treptomyces melanosporofaciens*. *Journal of Bioscience and Bioengineering,* 89: 271–273.

Lee, H.-S., Song, H.-H., Jeong, J.-H., Shin, C.-G., Choi, S.-U., Lee, C. (2008). Cytotoxicities of enniatins H, I, and MK1688 from *Fusarium oxysporum* KFCC 11363P. *Toxicon,* 51: 1178–1185.

Legras, J.L., Chuzel, G., Arnaud, A., Galzy, P. (1990). Natural nitriles and their metabolism. *World Journal of Microbiology and Biotechnology*, 6: 83–108.

Li, F., Jiang, T., Li, Q., Ling, X. (2017). Camptothecin (CPT) and its derivatives are known to target topoisomerase I (Top1) as their mechanism of action: did we miss something in CPT analogue molecular targets for treating human disease such as cancer? *American Journal of Cancer Research,* 7: 2350.

Li,Q-Z, Lin, F-C, Su, Z-Z (2025). Endophytic fungi—Big player in plant-microbe symbiosis, *Current Plant Biology,* 42: 100481

Li, Y.-C., Tao, W.-Y., Cheng, L. (2009). Paclitaxel production using co-culture of Taxus suspension cells and paclitaxel-producing endophytic fungi in a co-bioreactor. *Applied Microbiology and Biotechnology,* 83: 233–239.

Liu, Y., Li, M., Huang, L., Gui, S., Jia, L., Zheng, D., Fu, Y., et al. (2018). Cloning, expression and characterisation of phospholipase B from *Saccharomyces cerevisiae* and its application in the synthesis of l-alpha-glycerylphosphorylcholine and peanut oil degumming. *Biotechnology & Biotechnological Equipment*, 32: 968–973.

Liu, Y., Xu, M., Tang, Y., Shao, Y., Wang, H., Zhang, H. (2022). Genome features and antiSMASH analysis of an endophytic strain *Fusarium* sp. R1. *Metabolites*, 12: 521.

Mandal, S., Banerjee, D. (2019). Proteases from endophytic fungi with potential industrial applications. In: "*Recent Advancement in White Biotechnology Through Fungi, Diversity and Enzymes Perspectives*", Yadav, A.N., Mishra, S., Singh, S., Gupta, A. (Eds.), Volume 1, pp. 319–359. Springer International Publishing, Cham.

Mander, P., Cho, S.S., Simkhada, J.R., Choi, Y.H., Yoo, J.C. (2011). A low molecular weight chymotrypsin-like novel fibrinolytic enzyme from *Streptomyces* sp. CS624. *Process Biochemistry*, 46: 1449–1455.

Maruta, A., Yamane, M., Matsubara, M., Suzuki, S., Nakazawa, M., Ueda, M., et al. (2017). A novel α-galactosidase from *Fusarium oxysporum* and its application in determining the structure of the gum arabic side chain. *Enzyme and Microbial Technology*, 103: 25–33.

Mashima, R., Okuyama, T. (2015). The role of lipoxygenases in pathophysiology; new insights and future perspectives. *Redox Biology,* 6: 297–310.

Meena, H., Hnamte, S., Siddhardha, B. (2019). Secondary metabolites from endophytic fungi: Chemical diversity and application. In: "*Advances in Endophytic Fungal Research: Present Status and Future Challenges*", Singh, B.P. (Ed.), pp. 145–169. Springer International Publishing, Cham.

Mehta, P., Sharma, R., Putatunda, C., Walia, A., (2019). Endophytic fungi: Role in phosphate solubilization. In: "*Advances in Endophytic Fungal Research: Present Status and Future Challenges*", Singh, B.P. (Ed.), pp. 183–209. Springer International Publishing, Cham.

Méndez, C., Salas, J.A. (2001). Altering the glycosylation pattern of bioactive compounds. *Trends in Biotechnology*, 19: 449–456.

Mohamed, G.A., Ibrahim, S.R.M., Alhakamy, N.A., Aljohani, O.S. (2022). Fusaroxazin, a novel cytotoxic and antimicrobial xanthone derivative from Fusarium oxysporum. *Natural Product Research,* 36: 952–960.

Moreti, R., Perrella, N.N., Lopes, A.R. (2013). Carbohydrate digestion in ticks and a digestive α-l-fucosidase. *Journal of Insect Physiology,* 59, 1069–1075.

Musavi, S.F., Balakrishnan, R.M. (2014). A study on the antimicrobial potentials of an endophytic fungus Fusarium oxysporum NFX 06. *Journal of Medical and Bioengineering*, 2014: 162–166.

Nadeem, M., Ram, M., Alam, P., Ahmad, M.M., Mohammad, A., Al-Qurainy, F., et ak (2012). *Fusarium solani*, P1, a new endophytic podophyllotoxin-producing fungus from roots of *Podophyllum hexandrum*. *African Journal of. Microbiology Research,* 6(10): 2493-2499.

Nakayama, A. (2024). Studies on comprehensive total synthesis of natural and pseudo-natural products for drug discovery. *Chemical and Pharmaceutical Bulletin*, 72: 422–431.

Newman, D.J., Cragg, G.M. (2016). Natural products as sources of new drugs from 1981 to 2014. *Journal of Natural Products,* 79: 629–661.

Nikitin, D.A., Ivanova, E.A., Semenov, M.V., Zhelezova, A.D., Ksenofontova, N.A., et al. (2023). Diversity, ecological characteristics and identification of some problematic phytopathogenic *Fusarium* in soil: A review. *Diversity,* 15: 49.

Nikolaivits, E., Makris, G., Topakas, E. (2017). Immobilization of a cutinase from *Fusarium oxysporum* and application in pineapple flavor synthesis. *Journal of Agricultural and Food Chemistry,* 65: 3505–3511.

Nirmaladevi, D., Venkataramana, M., Chandranayaka, S., Ramesha, A., Jameel, N.M., Srinivas, C. (2014). Neuroprotective effects of Bikaverin on H_2O_2-induced oxidative stress mediated neuronal damage in SH-SY5Y Cell Line. *Cellular and Molecular Neurobiology,* 34: 973–985.

Ortiz, A., Sansinenea, E. (2018). Di-2-ethylhexylphthalate may be a natural product, rather than a pollutant. *Journal of Chemistry,* 2018: e6040814.

Pappas, M.L., Liapoura, M., Papantoniou, D., Avramidou, M., Kavroulakis, N., Weinhold, A., et al. (2018). The beneficial endophytic fungus *Fusarium solani* strain K alters tomato responses against spider mites to the benefit of the plant. *Frontiers in Plant Science*, 9: 1603

Parthasarathi, S., Sathya, S., Bupesh, G., Samy, R.D., Mohan, M.R., Kumar, G.S., et al. (2012). Isolation and characterization of antimicrobial compound from marine Streptomyces hygroscopicus BDUS 49. *World Journal of Fish and Marine Sciences*, 4(3): 268-277.

Peek, J., Christendat, D. (2015). The shikimate dehydrogenase family: Functional diversity within a conserved structural and mechanistic framework. *Archives of Biochemistry and Biophysics,* 566: 85–99.

Peng, Y., Yang, X., Zhang, Y. (2005). Microbial fibrinolytic enzymes: an overview of source, production, properties, and thrombolytic activity in vivo. *Applied Microbiology and Biotechnology*, 69: 126–132.

Piska, F., Teruna, H.Y., Saryono (2020). Terpenoid as antibacterial produced by endophyte *Fusarium oxysporum* LBKURCC41 from Dahlia variabilis Tuber. *Journal of Physics: Conference Series,* 1655: 012034.

Poveda, J., Baptista, P. (2021). Filamentous fungi as biocontrol agents in olive (*Olea europaea* L.) diseases: Mycorrhizal and endophytic fungi. *Crop Protection*, 146: 105672.

Poveda, J., Zabalgogeazcoa, I., Soengas, P., Rodríguez, V.M., Cartea, M.E., Abilleira, R., et al. (2020). Brassica oleracea var. acephala (kale) improvement by biological activity of root endophytic fungi. *Scientific Reports*, 10: 20224.

Prajapati, C., Kumar, D., Ambastha, V., Singh, S.K. (2024). Fungal endophytes as potential anticancer candidate over synthetic drugs: Latest development and future prospects. In: "*Endophytic Fungi: The*

Hidden Sustainable Jewels for the Pharmaceutical and Agricultural Industries", Singh, B.P., Abdel-Azeem, A.M., Gautam, V., Singh, G., Singh, S.K. (Eds.), pp. 27–56. Springer International Publishing, Cham, .

Preczeski, K.P., Dalastra, C., Czapela, F.F., Kubeneck, S., Scapini, T., Camargo, A.F., et al. (2020). *Fusarium oxysporum* and *Aspergillus* sp. as Keratinase producers using Swine hair from agroindustrial residues. *Frontiers in Bioengineering and Biotechnology*, 8: Article number 71.

Refaat, S., Fikry E., Tawfeek, N., El-Sayed, A.S.A., El-Domiaty, M.M., El-Shafae, A.M. (2024). Production and bioprocessing of epothilone B from *Aspergillus niger*, an endophyte of *Latania loddegesii*, with a conceivable biosynthetic stability: Anticancer, anti-wound healing activities and cell cycle analysis. *Microbial Cell Factories*, 23(1): art. no. 229.

Ran, X., Zhang, G., Li, S., Wang, J. (2017). Characterization and antitumor activity of camptothecin from endophytic fungus *Fusarium solani* isolated from *Camptotheca acuminate*. *African Health Sciences*, 17: 566–574.

Ranjan, A., Singh, R.K., Khare, S., Tripathi, R., Pandey, R.K., Singh, A.K., et al. (2019). Characterization and evaluation of mycosterol secreted from endophytic strain of Gymnema sylvestre for inhibition of α-glucosidase activity. *Scientific Reports,* 9: 17302.

Rovati, J.I., Delgado, O.D., Figueroa, L.I.C., Fariña, J.I. (2010). A novel source of fibrinolytic activity: *Bionectria* sp., an unconventional enzyme-producing fungus isolated from Las Yungas rainforest (Tucumán, Argentina). *World Journal of Microbiology and Biotechnology,* 26: 55–62.

Sahoo, T.P., Kumar, M.A. (2023). Remediation of phthalate acid esters from contaminated environment—Insights on the bioremedial approaches and future perspectives. *Heliyon*, 9: e14945..

Santangelo, J.S., Turley, N.E., Johnson, M.T.J. (2015). Fungal endophytes of Festuca rubra increase in frequency following long-term exclusion of rabbits. *Botany,* 93: 233–241.

Sayeda, A.A., Mohsen, S.A., Osama, H.E.S., Azhar, A.H., Saher, S.M. (2019). Biodiesel production from Egyptian isolate *Fusarium oxysporum* NRC2017. *Bulletin of the National Research Centre,* 43: 210.

Schulz, B., Römmert, A.-K., Dammann, U., Aust, H.-Jür., Strack, D. (1999). The endophyte-host interaction: a balanced antagonism? *Mycological Research,* 103: 1275–1283.

Selosse, M.-A., Bessis, A., Pozo, M.J. (2014). Microbial priming of plant and animal immunity: symbionts as developmental signals. *Trends in Microbiology*, 22: 607–613.

Shah, A., Rather, M.A., Hassan, Q.P., Aga, M.A., Mushtaq, S., Shah, A.M., et al. (2017). Discovery of anti-microbial and anti-tubercular molecules from Fusarium solani: an endophyte of *Glycyrrhiza glabra. Journal of Applied Microbiology,* 122: 1168–1176.

Shah, S., Shrestha, R., Maharjan, S., Selosse, M.-A., Pant, B. (2019). Isolation and characterization of plant growth-promoting endophytic fungi from the roots of *Dendrobium moniliforme*. *Plants,* 8: 5.

Shalapy, N.M., Kang, W. (2022). *Fusarium oxysporum* & *Fusarium solani*: Identification, characterization, and differentiation the fungal phenolic profiles by HPLC and the fungal lipid profiles by GC-MS. *Journal of Food Quality,* 2022: 4141480.

Shankar Naik, B., Abrar, S., Krishnappa, M. (2019). Industrially important enzymes from fungal endophytes. In: "*Recent Advancement in White Biotechnology Through Fungi*", Yadav, A.N., Mishra, S., Singh, S., Gupta, A. (Eds.), Volume 1, pp. 263–280. Diversity and Enzymes Perspectives. Springer International Publishing, Cham.

Shao, R. (2012). Screening of efficient thrombolytic strains and comparative analysis of methods for detecting thrombolytic activity. *Journal of Chongqing Normal University ,* 2012: 1–1

Sharma, D., Pramanik, A., Agrawal, P.K. (2016). Evaluation of bioactive secondary metabolites from endophytic fungus *Pestalotiopsis neglecta* BAB-5510 isolated from leaves of *Cupressus torulosa* D.Don. *3 Biotech,* 6: 210.

Shati, A.A., Elsaid, F.G. (2020). Biosynthesized silver nanoparticles and their genotoxicity. *Journal of Biochemical and Molecular Toxicology,* 34: e22418.

Singh, A., Singh, D.K., Kharwar, R.N., White, J.F., Gond, S.K. (2021). Fungal endophytes as efficient sources of plant-derived bioactive compounds and their prospective applications in natural product drug discovery: Insights, avenues, and challenges. *Microorganisms*, 9: 197.

Singh, B.P., Abdel-Azeem, A.M., Gautam, V., Singh, G., Singh, S.K. (2024). "*Endophytic Fungi: The Hidden Sustainable Jewels for the Pharmaceutical and Agricultural Industries*". Springer International Publishing, 348p.

Son, S.W., Kim, H.Y., Choi, G.J., Lim, H.K., Jang, K.S., Lee, S.O., et al. (2008). Bikaverin and fusaric acid from *Fusarium oxysporum* show antioomycete activity against Phytophthora infestans. *Journal of Applied Microbiology,* 104: 692–698.

Sorour, N., Herzallah, S., Alkhalaileh, N., Mamkagh, A., El-Baz, A., Shalaby, E., et al. (2023). Biofuel production by *Candida tropicalis* from orange peels waste using response surface methodology. *Slovak Journal of Food Sciences,* 17: https://doi.org/10.5219/1913

Srikanth, M., Sandeep, T.S.R.S., Sucharitha, K., Godi, S. (2022). Biodegradation of plastic polymers by fungi: A brief review. *Bioresources and Bioprocessing,* 9: 42. https://doi.org/10.1186/s40643-022-00532-4

Strobel, G., Daisy, B. (2003). Bioprospecting for microbial endophytes and their natural products. *Microbiology and Molecular Biology Reviews,* 67: 491–502.

Su, L., Ji, D., Tao, X., Yu, L., Wu, J., Xia, Y. (2017). Recombinant expression, characterization, and application of a phospholipase B from *Fusarium oxysporum. Journal of Biotechnology,* 242: 92–100.

Subbulakshmi, G., Thalavaipandian, A., Ramesh, V., Bagyalakshmi, B., Rajendran, A. (2012). Bioactive endophytic fungal isolates of *Biota orientalis* (L) Endl., *Pinus excelsa* Wall. and *Thuja occidentalis* L. *International Journal of Advanced Life Sciences (IJALS)*, 4: 9–15.

Syed, A., Ahmad, A. (2012). Extracellular biosynthesis of platinum nanoparticles using the fungus *Fusarium oxysporum*. *Colloids and Surfaces B: Biointerfaces*, 97: 27–31.

Syed, A., Ahmad, A. (2013). Extracellular biosynthesis of CdTe quantum dots by the fungus *Fusarium oxysporum* and their anti-bacterial activity. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy,* 106: 41–47.

Thiemann, T. (2021). Isolation of phthalates and terephthalates from plant material – natural products or contaminants? *Open Chemistry Journal,* 8: 1.

Toghueo, RMK. (2019). Bioprospecting endophytic fungi from *Fusarium* genus as sources of bioactive metabolites. *Mycology,*11(1): 1-21

Toghueo, R.M.K. (2020). Bioprospecting endophytic fungi from Fusarium genus as sources of bioactive metabolites. *Mycology,* 11: 1–21.

Toghueo, R.M.K., Sahal, D., Zabalgogeazcoa, Í., Baker, B., Boyom, F.F. (2018). Conditioned media and organic elicitors underpin the production of potent antiplasmodial metabolites by endophytic fungi from Cameroonian medicinal plants. *Parasitology Research,* 117: 2473–2485.

Toghueo, R.M.K., Kemgne, E.A.M., Eke, P., Kanko, M.I.M., Dize, D., Sahal, D., et al. (2019). Antiplasmodial potential and GC-MS fingerprint of endophytic fungal extracts derived from Cameroonian *Annona muricata*. *Journal of Ethnopharmacology,* 235: 111–121.

Tung, Y.C. (2002). A Preliminary study on the condition of the culture an isolate of endophytic fungus producing vincristine. *Journal of Chuxiong Normal University,* 6: 39–41.

Ueda, M., Kubo, T., Miyatake, K., Nakamura, T. (2007). Purification and characterization of fibrinolytic alkaline protease from Fusarium sp. BLB. *Applied Microbiology and Biotechnology*, 74: 331–338. `

Ueoka, R., Bhushan, A., Probst, S.I., Bray, W.M., Lokey, R.S., Linington, R.G., et al. (2018). Genome-based identification of a plant-associated marine bacterium as a rich natural product source. *Angewandte Chemie*, 130: 14727–14731.

Van Bael, S.A., Seid, M.A., Wcislo, W.T. (2012). Endophytic fungi increase the processing rate of leaves by leaf-cutting ants (Atta). *Ecological Entomology,* 37: 318–321.

Vasundhara, M., Baranwal, M., Kumar, A. (2016). *Fusarium tricinctum,* An endophytic fungus exhibits cell growth inhibition and antioxidant activity. *Indian Journal of Microbiology*, 56: 433–438.

Vujanovic, V., Vujanovic, J. (2007). Mycovitality and mycoheterotrophy: Where lies dormancy in terrestrial orchid and plants with minute seeds? *Symbiosis*, 44: 93–99.

Wang, Q.-X., Li, S.-F., Zhao, F., Dai, H.-Q., Bao, L., Ding, R., et al. (2011). Chemical constituents from endophytic fungus *Fusarium oxysporum. Fitoterapia,* 82: 777–781.

Wang, W.-X., Cheng, G.-G., Li, Z.-H., Ai, H.-L., He, J., Li, J., Feng, T., et al. (2019). Curtachalasins, immunosuppressive agents from the endophytic fungus Xylaria cf. curta. *Organic & Biomolecular Chemistry,* 17: 7985–7994.

Wani, Z.A., Ashraf, N., Mohiuddin, T., Riyaz-Ul-Hassan, S. (2015). Plant-endophyte symbiosis, an ecological perspective. *Applied Microbiology and Biotechnology*, 99: 2955–2965.

Waweru, B., Turoop, L., Kahangi, E., Coyne, D., Dubois, T. (2014). Non-pathogenic *Fusarium oxysporum* endophytes provide field control of nematodes, improving yield of banana (Musa sp.). *Biological Control*, 74: 82–88.

Wei, J., Chen, F., Liu, Y., Abudoukerimu, A., Zheng, Q., Zhang, X., et al. (2020). Comparative metabolomics revealed the potential antitumor characteristics of four endophytic fungi of *Brassica rapa* L. *ACS Omega*, 5: 5939–5950.

Wierenga, R.K., Kapetaniou, E.G., Venkatesan, R., (2010). Triosephosphate isomerase: A highly evolved biocatalyst. *Cellular and Molecular Life Sciences,* 67: 3961–3982.

Wilson, B.A., Thornburg, C.C., Henrich, C.J., Grkovic, T., O'Keefe, B.R. (2020). Creating and screening natural product libraries. *Natural product Reports,* 37(7): 893-918.

Wilson, D. (1995). Endophyte: The evolution of a term, and clarification of its use and definition. *Oikos*, 73: 274–276.

Woelflingseder, L., Adam, G., Marko, D. (2020). Immunosuppressive effect of the *Fusarium* secondary metabolite butenolide in human colon epithelial cells. *bioRxiv*, 2020-04.

Wu, B., Wu, L., Ruan, L., Ge, M., Chen, D. (2009). Screening of endophytic fungi with antithrombotic activity and identification of a bioactive metabolite from the endophytic fungal strain CPCC 480097. *Current Microbiology,* 58: 522–527.

Xiong, Z.-Q., Yang, Y.-Y., Zhao, N., Wang, Y. (2013). Diversity of endophytic fungi and screening of fungal paclitaxel producer from Anglojap yew, Taxus x media. *BMC Microbiology,* 13: 71.

Tan, R.X., Zou, W.X. (2001). Endophytes: A rich source of functional metabolites. *Natural Product Reports,* 18(4): 448-459.

Xu, J., Wang, X., Hu, L., Xia, J., Wu, Z., Xu, N., et al. (2015). A novel ionic liquid-tolerant *Fusarium oxysporum* BN secreting ionic liquid-stable cellulase: Consolidated bioprocessing of pretreated lignocellulose containing residual ionic liquid. *Bioresource Technology*, 181: 18–25.

Yamaguchi, T., Tsuruda, Y., Furukawa, T., Negishi, L., Imura, Y., Sakuda, S., et al. (2016). Synthesis of CdSe quantum dots using *Fusarium oxysporum. Materials*, 9: Corpus ID: 14274195

Yamamoto, K., Tsuji, Y., Kumagai, H., Tochkura, T. (1986). Induction and purification of α-L-fucosidase from *Fusarium oxysporum. Agricultural and Biological Chemistry,* 50: 1689–1695.

Yang, L.-Y., Lin, J., Zhou, B., Liu, Y.-G., Zhu, B.-Q., (2016). H1-A, a compound isolated from *Fusarium oxysporum* inhibits hepatitis C virus (HCV) NS3 serine protease. *Chinese Journal of Natural Medicines,* 14: 299–302.

Yano, T., Yamamoto, K., Kumagai, H., Tochikura, T., Yokoyama, T., Seno, T., et al. (1985). Purification and characterization of a novel α-l-fucosidase from *Fusarium oxysporum* grown on sludge. *Agricultural and Biological Chemistry,* 49: 3179–3187.

Yu, H., L., Z., Li, L., Zheng, C., Guo, L., Li, W., Sun, P., Qin, L. (2010). Recent developments and future prospects of antimicrobial metabolites produced by endophytes. *Microbiological Research,* 165: 437–449.

Yu, R., Li, M., Wang, Y., Bai, X., Chen, J., Li, X., et al. (2020). Chemical investigation of a co-culture of *Aspergillus fumigatus* D and *Fusarium oxysporum* R1. *Records of Natural Products*, 15: 130–135.

Zaher, A.M., Makboul, M.A., Moharram, A.M., Tekwani, B.L., Calderón, A.I. (2015). A new enniatin antibiotic from the endophyte *Fusarium tricinctum* Corda. *Journal of Antibiotics,* 68: 197–200.

Zhan, J., Burns, A.M., Liu, M.X., Faeth, S.H., Gunatilaka, A.A.L. (2007). Search for cell motility and angiogenesis inhibitors with potential anticancer activity: Beauvericin and other constituents of two endophytic strains of *Fusarium oxysporum. Journal of Natural Products,* 70: 227–232.

Zhang, H., Zhang, C., Li, Q., Ma, J., Ju, J. (2022). Metabolic blockade-based genome mining reveals lipochain-linked dihydro-β-alanine synthetases involved in autucedine biosynthesis. *Organic Letters,* 24: 5535–5540.

Zhang, H., Zeng, Y., Wei, T., Jiang, Y., Zeng, X. (2023). Endophytic *Fusarium* and allied fungi from *Rosa roxburghii* in China. *Mycosphere,* 14: 2092–2207.

Zhao, Z., Ramachandran, P., Kim, T.-S., Chen, Z., Jeya, M., Lee, J.-K. (2013). Characterization of an acid-tolerant β-1,4-glucosidase from *Fusarium oxysporum* and its potential as an animal feed additive. *Applied Microbiology and Biotechnology,* 97: 10003–10011.

Zotchev, S.B. (2024). Unlocking the potential of bacterial endophytes from medicinal plants for drug discovery. *Microbial Biotechnology,* 17: e14382.