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A summary of secondary metabolites and nanoparticles generated by filamentous fungi and their application in medicine

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***ABSTRACT* : Secondary metabolites, a kind of bioactive natural product (NP) generated by filamentous fungi, are briefly discussed in this review. Fungi generate compounds such as alkaloids, benzoquinones, flavonoids, phenols, steroids, and terpenoids, which have important roles in medicine and pharmacology. These chemicals are often employed as antioxidants, immunosuppressants, cholesterol-lowering medicines, and anticancer agents in addition to antibiotics for the treatment of microbiological infections. In this review also describe the imprtance of nanoparticles that produced by filamentous fungi.**

Keywords: secondary metabolites, nanoparticles, Antioxidant activity, Antimicrobial activity.

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I.INTRODUCTION

Many creatures, including fungi, bacteria, algae, plants, and animals, create small organic compounds known as secondary metabolites. Secondary metabolites are related to ecological or environmental interactions rather than fundamental growth, development, and reproduction, in contrast to primary metabolites, which actively take part in photosynthesis and respiration and are important to the survival of the species. Most secondary metabolites are categorized into several categories depending on how they were created, including terpenes, phenolic compounds, and alkaloids **(Conrado, Gomes, Roque, & De Souza, 2022; Macheleidt et al., 2016).**

The vast category of chemical substances produced by fungi known as secondary metabolites are employed in pharmaceuticals and medical treatments including Terpenes (such as glycosides, volatiles, and sterols), phenolic, (such as polyphenolic compounds, flavonoids, coumarins, lignans, stilbenes, tannins, and lignin), and compounds containing nitrogen (such as alkaloids and glucosinolates). They have a range of roles, and most of them are connected to the producing fungi's enhanced fitness in the environment, where they commonly engage in competition with other microbes or interaction with host plants. The number of SMs discovered in fungi is considerable **(Robey, Caesar, Drott, Keller, & Kelleher, 2021).**It is expected that just a portion of all those present in nature have been identified. Nowadays, filamentous fungi are regarded as a major source of important secondary metabolites. Its filamentous method of development allows for efficient substrate colonization and provides a significant surface to volume ratio that aids in nutrient absorption. They are utilised to create enzymes and tiny molecule substances like organic acids and antibiotics**(Devi et al., 2020).**

Bioactive metabolites produced by fungus include pigments, antioxidants, polysaccharides, enzymes, and antibiotics. Also take nutrition sources into consideration. There is a need to look for a solution for these disorders because of the growth in bacteria that are antibiotic resistant and diseases like cancer and inflammations. Fungi are regarded as a cheap and secure source for these treatments **(Alam, Agrawal, Verma, & agriculture, 2021).**

Natural antioxidants are essential for maintaining healthy and normal cell activity. These are substances that stop the beginning of oxidizing chain reactions, which reduces the oxidative stress linked to illness and aging. Creatures have developed defenses against the harm caused by free radicals by neutralizing them, however the quantity of antioxidant generated under usual circumstances is sometimes insufficient. Antioxidants from fungi are an established source that may be utilised to stop oxidative damage and, as a result, reduce its harmful effects on both people and animals **(Elnour, Mirghani, Musa, Kabbashi, & Alam, 2018).**During the routine metabolic processes of aerobic cells, the reactive nitrogen substance (RNS) or reactive oxygen substance (ROS) in the form of free radicals induce cellular destruction. Atoms or molecules having unpaired electrons in the outer orbital are known as free radicals. Asymmetry in the production of free radicals is a hallmark of oxidative stress, such as an excess of ROS or a reduction in natural antioxidant defenses**(Miller, Buettner, Aust, & Medicine, 1990).**

Many secondary metabolites produced by fungi, such as phenolic compounds, polyketides, steroids, terpenes, and flavonoids have been shown to have extra physiologically significant effects. These include antimicrobial, antiviral, and anti-inflammatory activities **(Abo Nahas et al., 2021; Bruce & Reviews, 2022; Rahman et al., 2022).**

Phytopathogenic bacteria and causal organisms that impact foods and people like *Salmonella typhimurium*, *Bacillus cereus*, *Listeriamonocytogenes*, *Staphylococcus aureus* and *Escherichia coli*, are becoming a more widespread public health hazard, causing a wide range of serious infections and even deaths worldwide. Because some fungal genera cause major plant and human illnesses, the demand for antimicrobial agents is increasing. Secondary metabolites are now good and safe agents that can cure these issues and get rid of these dangerous microbes while also playing a significant function as an anticancer, anti-inflammatory, antioxidant, and so on **(Jakubczyk & Dussart, 2020; Nwakanma, Njoku, Pharamat, & applications, 2016).**

Several scientists are currently very interested in nanoscience and nanotechnology because of its potential impact on many fields of science, including medical, energy, pharmaceuticals, industries, and so on **(Chavali & Nikolova, 2019).**

The study of developing novel materials at the nanoscale (between 1 and 100 nm) for a range of uses is known as nanotechnology **(Koo, 2019; Mobasser & Firoozi, 2016).**

Nanobiotechnology is a new field of nanotechnology which is the process of creating nano-sized particles with specialized functionalities by combining physical and chemical techniques with biological concepts. Physical and chemical methods of NP production can be replaced by nanobiotechnology at a lower cost **(Lee & Moon, 2020).**

Metal nanoparticle production has been shown using different chemical and physical methods. Because most of these processes are capital-demanding, poisonous, unfriendly to the environment, and have low productivity, today's nanotechnology requires a range of green approaches for NP synthesis. The plant extract, bacteria, fungus, enzymes, algae, and biodegradable polymers are among those under consideration. Biosynthesized NPs are finding key uses in medicine, particularly those linked to antibacterial activity, due to their amenability to biological functionalization **(Ahmed et al., 2022).**Fungi are one of the most fascinating extracellular sources for the creation of different nanoparticles employing green, secure, and environmentally friendly methods. Because of their tremendous secretion of proteins and other biomolecules, they have the highest productivity of any nanoparticle **(Ahmad et al., 2003).**Although bacterial biosynthesis of metal nanoparticles is common, fungal metabolite production is more advantageous owing to the huge surface area of fungal mats compared to other microorganisms**(Pantidos, Horsfall, & Nanotechnology, 2014).** Nanomaterials have sparked enormous interest in a different of biomedical fields, including anticancer, antibacterial, antioxidant, anti-diabetic, and anti-inflammatory actions, as well as medication transport and bioimaging applications **(Azharuddin et al., 2019).** Due to the ongoing desire for novel anticancer medications, chemotherapeutic research has focused on using metal nanoparticles as therapeutics against cancers due to their less harmful effect **(Olga et al., 2022).**

II. Secondary metabolites:

Secondary metabolites (SMs), usually referred to natural products, are small molecules whose primary activities have more to do with environmental communications than with basic growth and reproduction

(J. Bennett & Bentley, 1989; Bills & Gloer, 2017). The changeover from growth phase to stationary phase known as the idiophase is when organisms created secondary metabolites at the greatest rates. The producer organism can continue to develop without their synthesis, which is not necessary for growth, at least not in the near term. They are created by intracellular intermediates, and through certain metabolic pathways, these unique structures are compressed into more complex structures. Although not being necessary for the existence of the organisms, they carry out a number of different survival functions in nature. They are crucial for the economic and human health of our society. Among them are various compounds such as herbicides, agricultural fungicides, bio-insecticides, immunosuppressants, antiparasitics, antibiotics, cancer treatments, cholesterol-lowering drugs, and others**(Chadwick & Whelan, 2008)**. Antibiotics, signals to other species, or substances that impact the quantity of nutrients in the host tissues or soil are examples of SMs that fungi release. Similar to plants, fungi can have a wide range of SMs. Instead of being grouped together by species, fungus spread among themselves according to ecological characteristics.

These substantial physiological effects of low-molecular-weight metabolites are common. Quinine digitalis, morphine, and morphine are examples of plant secondary metabolites, whereas cephalosporin, ergotamine, penicillin, and statins are secondary metabolites found in fungi**(Nawrot-Chorabik, Sułkowska, & Gumulak, 2022)**.

2.1. Fungal secondary metabolites pathway:

Secondary metabolites (SMs) are a diverse group of compounds produced by fungi, that these organisms use them as a defense mechanisms. They categorized under four major chemical families: terpenoids, polyketides (PKs), hybrid non-ribosomal peptides/polyketides (NRP/PKs), and peptides (NRP/PKs). They have a wide variety of roles, and most of them are connected to the producing fungi's enhanced fitness in the environment, where they commonly engage in competition with microbes or interaction with the host plants. A large number of SMs have useful uses, such as in medicines or antibiotics, while some, called mycotoxins, are poisonous for humans.

These SMs come from four main different pathways **(Zaidman, Yassin, Mahajna, Wasser, & Biotechnology, 2005)** the methylerythritol-phosphate pathway, the shikimic acid pathway, the malonic acid pathway, and the mevalonic acid pathway. **(S. P. J. A. m. Wasser & biotechnology, 2011).** The plant secondary metabolites quinine, morphine, and digitalis, as well as the fungal secondary metabolites cephalosporin, statins, ergotrate, and penicillin are all important pharmaceutical products of these pathways. These methods are also used to create certain substances, including trichothecenes, aflatoxins, and ergot alkaloids, which may be harmful or beneficial may be poisonous or pharmacologically helpful **(N. P. Keller, Turner, & Bennett, 2005).**

The number of SMs discovered in fungi is considerable **(Robey et al., 2021)**, and it is assumed that only a subset of all those found in nature is known. SMs are made from main metabolic substrates from core metabolic pathways and primary metabolite pools, the most notable of which being acetyl-CoA, which is the precursor to polyketides (for example, aflatoxin) and the use of amino acids to create secondary metabolites (like penicillin) that are not ribosomal peptides and terpenoids (for example, carotene). Each SM biosynthesis route begins with a unique kind of enzyme and ends with the action of specialized tailoring enzymes, which introduce further changes to the molecules.

The processes and factors involved in the cellular regulation of the SM biosynthesis pathways in microorganisms have already been extensively discussed **(Brakhage, Schroeckh, & Biology, 2011; Deepika, Murali, & Satyamoorthy, 2016; Nielsen et al., 2019; Pfannenstiel & Keller, 2019)**.

Particularly in fungi, the SMs are categorized in accordance with the starting substrates they use (amino acids, acyl-CoA, carbohydrates, nucleotides, etc.), which are typically included in the last structure by specific enzymes such as polyketide synthases (PKSs), nonribosomal peptide synthases (NRPSs), terpene cyclases (TC), and dimethylallyl tryptophan synthases (DMAT) **(Brakhage et al., 2011; Deepika et al., 2016; N. P. J. N. R. M. Keller, 2019; Pfannenstiel & Keller, 2019).**

2.2. Filamentous fungi's secondary metabolites:

Nowadays, filamentous fungi are regarded as a major source of important secondary metabolites. Its filamentous method of development allows for efficient substrate colonization and offers an increased surface-to-volume ratio that aids in nutrient absorption. They are utilised to create enzymes and tiny molecule substances like organic acids and antibiotics**(Chávez, Fierro, García-Rico, & Vaca, 2015; Yu & Keller, 2005)**

An important class of microorganisms called filamentous fungi is capable of synthesizing a wide range of bioactive compounds known as secondary metabolites or natural products. **(Bills & Stadler, 2014; Calvo, Wilson, Bok, Keller, & reviews, 2002; Horgan, Murphy, & applications, 2017; Jansen et al., 2013).** Fungi create a variety of bioactive metabolites, including industrial enzymes, pigments, antibiotics, and antioxidants. Fungal products are significant sources of medicinal treatments, food ingredient, and nutrients **(Shankar, Sharma, & Biotechnology, 2022).**

Secondary metabolites are bioactive substances generated by several fungal species, most commonly fungi from the *Ascomycete, Pezizomycotina*, and several *Basidiomycete* subclasses, as well as *Kluyveromyces lactis***(Krause et al., 2018)**. *Penicillium, Aspergillus*, and other *Ascomycetes* fungi have produced the bulk of fungal-derived medicines, whereas *Basidiomycete* fungi and others may have produced less, at least in an industrial setting**(Bala, Aitken, Fechner, Cusack, & Steadman, 2011)**. Nevertheless, Aspergillus and Penicillium account for more than 35% of all identified fungal metabolites **(Berdy, 2005).**

Nearly all terrestrial and marine ecosystems have filamentous fungi present as free-living microorganisms, mutualisms, symbioses, and illnesses **(Blackwell, 2011; Li et al., 2021)**. This aggression is dependent on their ability to create a range of secondary metabolites, organic acids, and proteins that facilitate nutrient supply, cell proliferation known as hyphae, and a variety of specialised niche-specific activities like host tissue invasion, symbiotic relationships, eradicating competitive organisms, and mating.

Since the 20th century, the secondary metabolites of fungi have grown in importance**(N. P. Keller et al., 2005)**. Penicillin, the first antibiotic was first created by *Penicillium*, which started the antibiotic age**(J. W. Bennett & Chung, 2001; Raistrick, 1950)**. Nowadays, one of the most distinguishing traits of fungi is their extraordinary adaptive metabolism, which is demonstrated by the diverse variety of secondary metabolism in various species. There are thousands of compounds known as bioactive secondary metabolites that inhibit the development of human cancer cells as well as bacteria, fungi, viruses, protozoa, and worms. Moreover, it has been shown that a variety of other substances have biological properties including cytotoxicity, mutagenicity, immunosuppression, enzyme inhibitory, carcinogenicity, allelopathic, and others **(Pela, 2004)**.

As illustrations of how fungi are the source of both dangerous and advantageous substances, the discovery of penicillin, the first versatile antibiotic, and the aflatoxins poisoning incidence of the Turkey X illness are provided **(Nesbitt, O'kelly, Sargeant, & Sheridan, 1962; Quinn, 2013)**.

2.3. The Evolution of Secondary Metabolism in filamentous Fungi:

Via basic metabolic pathways and primary metabolism, secondary metabolites are created. Acetyl-CoAs are used to produce polyketides like aflatoxin and terpenes like carotene, while Penicillin and other non-ribosomal peptide secondary metabolites are made from amino acids. In contrast to genes that are required for the synthesis of a primary metabolite and are dispersed across the fungal genome, the genes that encode the metabolic enzymes to synthesise any secondary metabolite are organized in a continuous way as a biosynthetic gene cluster (BGC). Fungi's growth is greatly aided by secondary metabolites, which also have a direct impact on interactions with other species**(Bidartondo et al., 2011)**. "Gene clusters" are typically used to encode fungus metabolic pathways that are involved in ecological dynamics **(N. P. Keller, Hohn, & Biology, 1997)**. Genes that are physically close to chromosomes provide most of the regulators, enzymes, and transporters needed for the creation and dispersion of SMs. Just a small portion of fungal taxa often have specific gene clusters, however closely related species may also contain these clusters **(Gluck-Thaler & Slot, 2015).**

This gene clustering pattern demonstrates the evolution of gene transfer as well as rapid ageing, metabolic pathway loss, and reconfiguration. It seems that several SM gene clusters have been passed down between unrelated fungi. Future evolutionary, ecological, and pharmacological studies will concentrate on the gene clusters involved in secondary metabolism in fungus **(Campbell, Rokas, Slot, & evolution, 2012; Marcet-Houben, Gabaldón, & Biology, 2016)**.

III.Natural antioxidant from Filamentous fungi:

Free radicals can be scavenged from the human body by natural antioxidants present in filamentous fungus, such as nitrogen compounds like ascorbic acid, vitamins, and flavonols, and phenolic compounds like phenolic acids, tocopherol, and flavonoids. They are necessary for preserving health and avoiding chronic and progressive diseases including cancer, neurological problems, and Genetic damage **(Larson, 1988; Velioglu, Mazza, Gao, Oomah, & chemistry, 1998).**

It has been shown that a number of secondary metabolites and higher fungal enzymes guard against oxidative damage by preventing reactive oxygen species and free radicals **(Jones, Doyle, & Fitzpatrick, 2014).**

3.1. Oxidation stress:

Oxidation is a common mechanism used by living things to provide energy for biological processes **(Yang et al., 2002)**. Natural antioxidants are essential for maintaining healthy and normal cell activity. These are substances that stop the beginning of oxidizing chain reactions that prevents or slows the oxidative damage associated with ageing and illness. Creatures have progressed defenses against the harm caused by free radicals by neutralizing them, however the quantity of antioxidants generated normally is occasionally inadequate. Antioxidants from Fungi are a common source that may be utilised to stop oxidative damage and, as a result, reduce its harmful effects on both people and animals **(Miller et al., 1990)**. Any atom or molecule with unpaired electrons in its outer orbit is referred to be a free radical; they are frequently unstable and extremely active **(Gutteridge & Halliwell, 2000)**. During the routine metabolic processes of aerobic cells, the reactive nitrogen substance (RNS) or reactive oxygen substance (ROS) in the form of free radicals cause cellular disruption. Free radical production is out of balance under oxidative stress, as evidenced by an increase in ROS or a decrease in natural antioxidant defenses **(Miller et al., 1990).**

The usual metabolic functions of ROS in aerobic cells, such as death and development of the cell, are disrupted by oxidant signals. Cell toxicity results from this type of damage, which has negative effects on health **(Suzuki, Isobe, Morishita, & Nagai, 2010)**. Lipid peroxidation is the name of the attack by free radicals on mitochondria, which are typically their first target due to the lipid membrane's extreme sensitivity to ROS damage. Superoxide anions (O2), hydrogen peroxide (H2O2), and other new radicals are created when ROS interact with lipidic molecules. Then, these radical organizations interact with biological systems in a cytotoxic manner **(Barros, Ferreira, Queiros, Ferreira, & Baptista, 2007).** The link between antioxidant defenses and ROS generation is commonly used to describe the level of oxidative stress **(Suzuki et al., 2010)**. Many factors, such as the quantity of free radical molecules scavenged, what happens to radicals created by antioxidants, interactions with other antioxidants, and the physical properties and metabolism of antioxidant compounds, all affect free radical scavenging ability **(E. Niki & Noguchi, 2000; E. J. F. R. B. Niki & Medicine, 2010; Noguchi, Niki, & Medicine, 2000).** By neutralizing an active radical, an antioxidant molecule creates a stable non-radical outcome. One antioxidant-derived radical is created concurrently by the antioxidant. Another crucial element in the efficiency of antioxidants is where this radical goes**(E. Niki & Noguchi, 2000)**.

3.2. Natural antioxidant:

Free radicals and ROSs can be removed from the body by using natural products, particularly

Antioxidants found in fungus such as flavonoids, ascorbic acid, alkaloids, vitamins, carotenoids, and phenolic acids. They play a crucial part in preserving health and avoiding degenerative conditions including inflammation, cancer, neurological diseases, and Mutagenesis **(Doughari, 2012).** Antioxidants fall into two categories: artificial antioxidants and natural antioxidants. Natural antioxidants come from organic sources, including fungi, such as nitrogenous and phenolic chemicals, and this type are highly significant and used in food preservation. Rats are induced with cancer by artificial antioxidants like BHA and BHT, and thus, people may also be affected**(Ito, Fukushima, & Tsuda, 1985; Larson, 1988; Velioglu et al., 1998)**.

Phenolic compounds are hydroxylated aromatic substances containing one aromatic ring at least and one or more hydroxyl groups **(Apak et al., 2007)**. The amount and placement of hydroxyl groups, as well as the kind of replacement on the aromatic rings, all affect how antioxidant-active these compounds are **(Balasundram, Sundram, & Samman, 2006).** The most prevalent antioxidants that fungus make are polyphenolic chemicals. Flavonoids and phenolic acids are the most frequent of them, followed by ascorbic acid, tocopherols, and carotenoids.

There are 13 different types of flavonoids, and each one is broken down into a number of different chemicals, the two most prevalent of which are flavones and flavonols **(Bravo, 1998; Kris-Etherton et al., 2002).** The most often encountered derivatives of the two main categories of phenolic acids, hydroxycinnamic and hydroxybenzoic acid, are related compounds **(Ferreira, Barros, & Abreu, 2009)**. In contrast to hydroxycinnamic acid, which is usually connected to proteins, lignin, cellulose and in cell walls in addition to organic acids like quinic acids or tartaric, hydroxybenzoic acid is often found in complex structures like lignin and hydrolysable tannins **(Liu, 2004).** Flavonoids are the most prevalent antioxidant sub-group among phenolic compounds, which naturally form as byproducts of the shikimate and acetate pathways. Other phenolic substances include phenolic acids, phenyl propanoids, lignin, melanin, and tannins **(Bravo, 1998; Ferreira et al., 2009).**

Flavonoids, which are highly common in plants, fruits, and fungi and act as powerful free radical scavengers, can prevent cancer development, Mutagenesis, and cardiovascular disease and have additional physiologically essential impacts such as antimicrobial , anti-inflammatory, anti-allergic, antiviral and vasodilatory properties **(Wright, Johnson, & DiLabio, 201).**

Antioxidant activity mechanisms include: (i) metal chelation to inhibit the generation of reactive species by transition metals; (ii) radical scavenging activity against reactive oxygen and nitrogen species or against lipid peroxidising radicals; and (iii) interactions with other antioxidants. **(Apak et al., 2007; E. Niki & Noguchi, 2000).** The role of phenolic hydrogen in radical reactions, as well as the chemical substitutions contained in the structure, are what give phenolic antioxidants their stability and potency **(Hall, 2001).**

It has been claimed that polyphenols derived from natural origins can be used as antibacterial. Naturally occurring polyphenols stop microbial deterioration by preventing microbial development. Researchers showed that a polyphenolic substances' presence caused inhibit in the growth rate of the gram-positive bacterium *S. aureus*. The potential of tannins to reduce metal ions via precipitation or by structural means is believed to be harmful to bacteria, just as flavonoids can alter the permeability of bacterial cell membranes, may mediate the antibacterial effect of polyphenolic chemicals. An antimicrobially effective antioxidant derived from fungus may be a desirable source for storing food as well as a natural food supplement additive **(Kao et al., 2010)** .

IV. Extraction, purification and identification of secondary metabolites from filamentous fungi:

4.1. Extraction of SMs:

Three main techniques may be used to produce fungus biomass: solid state fermentation (SSF), submerged liquid fermentation (SLF), and static liquid culture. Solid state fermentation (SSF) microbes are grown on solid culture and in this method using agar with low water content and other supplements that aid the organism to grow and function properly. In contrast to filamentous fungi in static liquid culture, which form a mat of hyphae at the liquid's surface, submerged liquid fermentation (SLF) is the development of a microbe in a liquid media that has been agitated or swirled and in this methods don't using agar. The submerged fermentation happens in an aqueous liquid feeding medium and is most commonly used because it can control fermentation parameters including temperature, pH, dissolved oxygen, and other factors **(Srivastava et al., 2019).**

Submerged liquid fermentation has yielded a variety of bioactive compounds from filamentous fungi. Biomass produced in controlled submerged cultivations offers several benefits, including the ability to rapidly grow mycelia, early fruiting body development, and, most crucially, the capacity to modify the culture media to create active cultures of the highest quality and quantity**(Reshetnikov & Tan, 2001; S. P. Wasser, Sokolov, Reshetnikov, & Timor-Tismenetsky, 2000).** Metabolites including ergosterol, terpenoids, and polysaccharides are frequently developed using submerged liquid fermentation. In submerged culture, growth timing, growth factors, and nutrients needed for metabolism and growth have a significant impact on mycelial biomass production and bioactive polysaccharide synthesis **(Gregori, Švagelj, Pohleven, & Biotechnology, 2007; Kim et al., 2002; Lin, Wang, Lee, Su, & biotechnology, 2008).**

Techniques for cultivation and extraction are required to create bioactive compounds and biological activity from fungi effectively. The primary commercial aspect of filamentous fungal culture is the production of enzymes, antibiotics, organic acids, antioxidants, fatty acids, polysaccharides, plant growth regulators, pigments, mycotoxins, and alkaloids **(El-Enshasy, 2007).**

When secondary metabolites are created using any technique of culture, solvents are used to extract them. Organic solvents, such as ethyl acetate, chloroform, hexane or dichloromethane are frequently employed to extract metabolites from any culture procedures. There are approaches that have been optimized to provide a comprehensive description of SMs.

There are two techniques of extraction that are most frequently employed: ultrasonic-assisted extraction (UAE) and liquid-liquid extraction (LLE). In the (UAE) ultrasonic vibrations improve efficiency of extraction by cell disruption to facilitate chemical release into the solvents. (LLE) is used to separate the metabolites from the aqueous phase and transfer them to organic solvents for extraction**(Zahari, Chong, Abdullah, & Chua, 2020)**.

The Solid-Phase Extraction technique, which depends on a physical separation between the microbial biomass and the resin employed in solid-phase extraction, is an effective method for extracting SMs **(Mai et al., 2021)**.

A polar solvent, such as hot water, methanol, ethyl acetate, ethanol, or acetone, used alone or in combination to extract flavonoids or phenolic acids from fungi or plant materials **(Chen, Inbaraj, & Chen, 2011; Qian, Liu, & Huang, 2004; Robbins & chemistry, 2003).**

Because fungi have a lot of molecules in their mycelia, natural chemical isolation and separation is a labor-intensive process. These treatments are frequently required, and they are greatly influenced by the chemicals' volatility and stability. **(Sticher, 2008).** A variety of sample preparations, such as pre-purification and clean-up extraction techniques, such as filtration, precipitation, or thin layer chromatography, may be required before purification or analysis .These methods are beneficial because they enable the concentration of the desired active components while also permitting the selective removal of disruptive substances.

4.2. Purification of SMs:

Secondary metabolites can be purified using a variety of techniques following extraction to obtain the pure compound from mixture of compounds in the fungal extract. The compounds included in the crude extract are fractionated and purified using techniques including high-performance liquid chromatography (HPLC) ,thin layer chromatography (TLC), liquid chromatography (LC), column chromatography, gas chromatography , and supercritical fluid chromatography (SFC) **(Câmara, Martins, Pereira, Perestrelo, & Rocha, 2022; Tsao, Yang, Young, Zhu, & chemistry, 2003)**. The purification technique entails a multistep process that starts with extraction, moves on to pre-purification, and finally includes one or more chromatographic processes. Prior to organic solvent extraction and partitioning with water or supercritical CO2 to remove less polar or more polar compounds, or prior to purification by TLC and HPLC, the fresh or dry sample will be chopped up or ground to a powder. The purification process entails eliminating interference-causing chemicals from the crude extract using various solvents and any available chromatographic technique.

TLC is a quick, easy, and affordable process to determine how many ingredients are in a combination. By comparing the Rf of a chemical with the Rf of a known compound, TLC is also used to establish the identification of a component in a mixture. Other tests include spraying phytochemical screening reagents, which alter colour in accordance with the phytochemicals present in a crude extract, or by examining the plate under a UV light. This has also been employed to verify the identification and purity of isolated chemicals **(Sasidharan, Chen, Saravanan, Sundram, & Yoga Latha, 2011).**

In phytochemical extractions, HPLC is frequently used to improve the experimental setup and verify the purity of the isolated component. Used often and effectively for the research of polyphenolic compounds is the combination of columns and solvent system. In using HPLC, the purity level of the solute is taken into the greatest consideration when separating compounds by analytical HPLC, where crucial characteristics like resolution, sensitivity, and duration are taken into account. For final purification, however, it was necessary to use semi-preparative and preparative HPLC in the majority of situations, with a greater peak resolution power **(Hellstrom, Mattila, & Chemistry, 2008).**

4.3. Identification of SMs:

Identification of secondary metabolites by use of spectroscopic methods such as nuclear magnetic resonance (1H, 13C NMR), gas chromatography-mass spectroscopy (GC/MS), Fourier transform infrared spectroscopy (FTIR), mass spectrometry (MS) ,and X-ray diffraction (XRD) **(Grkovic et al., 2014; Ho et al., 2003; Lang et al., 2008; Wang et al., 2016; Zhang et al., 2017).**

Ultraviolet-visible (UV) spectra displaying unsaturation characteristic and the polyene or chromone of the secondary metabolites. Functional groups such carboxylic acids, carbonyls, hydroxyls, aliphatic bromo, esters, and silicon oxy compounds were detected in infrared (IR) spectra. By using gas chromatography-mass spectroscopy (GC-MS), it was easy to distinguish the isopropyl ester of elaidic acid, octadecenoic acids, and 2,3-dihydroxyl. For the purpose of finding unidentified chemicals and impurities in pharmaceutical goods, GC/MS analytical methods are highly helpful **(Adeyemo, Ja'afaru, & Adams, 2021)**.

Researchers said that (FTIR) is equally successful in the dereplication process as fingerprints, which are commonly utilised approaches for natural product dereplication. Current instruments help FTIR applications by being sensitive, having a small footprint, and producing a large amount of data. Dereplication of different analytical tools adds information about active structure class early in the separation phase and enables speedy identification of recognized compounds **(Grkovic et al., 2020; Grkovic et al., 2014)**.

Analytical techniques like NMR and X-ray diffraction (XRD) are used to describe the atomic-level of pure substances' molecules. The use of XRD in the medical industry has increased and may be taken advantage of, despite a number of limitations, including time requirements and the requirement for high numbers of crystalline samples **(Krishnan & Rupp, 2012; Zloh & DMPK, 2019)** .

V. Bio medicinal applications of filamentous fungi:

Fungi are a major source of pharmacologically diverse biomedicine natural products. It has been demonstrated that natural fungal products and isolated compounds have antibacterial, anticancer, antioxidant, anti-inflammatory, and antiviral activity, among many other health benefits**(Al-Fakih & Almaqtri, 2019).** People have employed plants and fungi as therapeutic agents for thousands of years; however, in recent years, the emphasis has shifted to extracts and refined biologically active compounds from these therapeutic agents for the creation of novel, effective medications.

Natural medicinal chemicals provide favorable health effects with unknown negative effects, and combinations are frequently employed for optimal benefit **(S. P. Wasser et al., 2000)**.

Due to bacteria's resistance to a variety of medicines, research on methods to prevent and treat bacterial infections has become important**(Signoretto, Canepari, Stauder, Vezzulli, & Pruzzo, 2012)**. Fungi are an inexpensive and reliable source of a wide variety of natural medicines ,that work against both gram-positive and gram-negative bacteria, including many food-borne pathogenic strains of bacteria **(Venturini, Rivera, Gonzalez, & Blanco, 2008)**, besides having an antifungal effect on mycelial fungi and yeasts **(Hearst et al., 2009; Jagadish, Krishnan, Shenbhagaraman, & Kaviyarasan, 2009)**. Moreover, numerous fungal species have demonstrated efficacy against viral, bacterial, and fungal infections that are resistant to treatments now being used, making them an alternate source of naturally occurring antimicrobial chemicals **(S. P. Wasser & Weis, 1999).**

5.1. Antibacterial activity:

In the past, most studies on the antibacterial effects of fungi have concentrated on the extraction of metabolites from filamentous fungi, with a very low amount of attention paid to liquid cultured mycelium **(Al-Fakih & Almaqtri, 2019).** Due to the antibacterial properties of both the liquid culture and the cultured mycelium, they have significant commercial potential **(Hatvani, 2001).** Antibacterial properties against a variety of bacteria are displayed by filamentous fungi. It has been discovered via research on several species that the increases of activity vary by strain **(Polishchuk, Kovalenko, & Cell, 2009).**

A variety of substances, mostly polysaccharides from fungus, show antibacterial activity**(Jong, 1991).**

Cortinelin, a mycelial extract derived from strain of *A.fumigatus*, has been demonstrated to suppress the development of both gram-negative and gram-positive bacteria **(Hirasawa, Shouji, Neta, Fukushima, & Takada, 1999; Polishchuk et al., 2009)**. Extracts from mycelium of fungi have proven to be active against bacterial plant pathogens and species, including *Salmonella typhimurium, Bacillus cereus, Escherichia coli, Staphylococcus aureus, and Listeria monocytogenes,* which have an influence on foods and humans**(Pacumbaba, Beyl, & Pacumbaba Jr, 1999; Sakagami & Takeda, 1993).**

Determining if pure substances or fungi extracts have antibacterial properties, a variety of bioassays are frequently used. These include the technique of agar well diffusion, the agar disc diffusion method, the microdilution method, and a technique that incorporates the extract into the bacterial culture medium and counts bacterial colonies. The outcomes of antimicrobial activity are therefore stated in a variety of units. The agar disc diffusion technique is used to incorporate the extract into the discs in varying amounts. Each disc's clear or measured inhibitory zone, and the width of the inhibition zone represents the antibacterial activity (IZD)**(CLSI, 2012)**.

5.2. Antifungal activity:

Filamentous fungi generate a variety of antifungal chemicals that are presently used in pharmacology and medicine**(Bladt, Frisvad, Knudsen, & Larsen, 2013)**.

These chemicals are recommended as substitutes for antifungal medications for a number of reasons, including the fact that they interact with other medications and antimicrobial peptides and do not harm plant or mammalian cells. They also do not cause inflammation, are highly stable even in harsh environmental conditions, and do not cause plant or mammalian cell toxicity**(Pereira et al., 2013)**. The discovery of new antifungal agents is of tremendous importance because existing antifungal medications have demonstrated to be ineffective or hazardous in healthy patients **(Svahn et al., 2012)**.

5.3. Antiviral activity;

Viral infections call for extremely specialised treatments, contrasted with bacterial infections, which are managed with antibiotics. A few examples of antiviral processes are the production of viral nucleic acids, the inhibition of viral enzymes, and the adsorption and assimilation of viruses into human cells **(Polishchuk et al., 2009).**

Basidiomycetes polysaccharides can stop viral infections from spreading, and isolated fungal compounds, especially smaller molecules, have been shown to have the same effect **(Polishchuk et al., 2009)(Lindequist, Niedermeyer, Jülich, & medicine, 2005)**. The immunostimulatory capabilities of polysaccharides or other complex compounds may have a secondary antiviral impact **(Brandt, Piraino, & Chemotherapy, 2000).**

Basidiomycetes bioactive chemicals have antiviral effect against the herpes simplex virus (HSV) and the human immunodeficiency virus (HIV) **(S. P. Wasser & Weis, 1999).** Low molecular weight medications have so far proven to be quite efficient at reducing the replication of HIV-1 and HIV-2 protease **(El-Mekkawy et al., 1998).**

Several investigations have demonstrated that *Basidiomycete* glycoproteins and polysaccharides have antiviral impacts in both animals and humans. researches have also successfully shown that lectins from *Ascomycetes* to plant viruses have an inhibitory impact **(Sun, Zhao, Tong, & Qi, 2003)**.

5.4. Antitumor activity:

Many secondary metabolites of filamentous fungus were shown to be active against tumour cell lines **(Bladt et al., 2013) .**

Fungus species such as *Aspergillus*, *Penicillium*, and *Talaromyces* species serve as factories for producing antibacterial, antifungal, and anticancer medicines**(Chakraborty, Majumdar, & Bhowal, 2021).** Because of this, fungi are an essential source for identifying natural substances **(Hyde et al., 2019)**. The principal types of natural substance in filmentous fungi include polyketides, terpenoids, alkaloids, phenolic and flavinoid chemicals, many of which are biologically active and have anticancer action**(Bladt et al., 2013)**.

Since then, a number of fungi's secondary metabolites with low and high molecular weights have demonstrated anticancer activity. It has been demonstrated that fungi's metabolites can prevent tumour growth without harming the host **(Svahn et al., 2012)**.

VI. Nanotechnology:

Nanotechnology is the transformation of single atoms, molecules, or substances into nanostructures to produce materials and machines with unique features. Nanotechnology employs two primary strategies: The "bottom-up" strategy including rearrange of specific atoms and molecules into nanostructures. In the "top-down" method, smaller objects such as photonics applications in nanoengineering and nanoelectronics are built from bigger ones without being subject to atomic-level regulation **(Subramani, Elhissi, Subbiah, & Ahmed, 2019)**.

Several scientists have become interested in nanoscience and nanotechnology due to its potential impact on a wide range of scientific fields, including energy, medicine, the pharmaceutical industry, and others**(Cardoza, Nagtode, Pratap, & Mali, 2022)**.

Nanotechnology is the study of creating innovative materials at the nanoscale (1-100 nm) that may be incorporated into different fields **(Madkour, Madkour, & applications, 2019).**

6.1. Green nanotechnology:

Green nanotechnology refers to a clean, environmentally acceptable approach for synthesizing Nanomaterials that eliminate or reduce the usage of hazardous ingredients during the creation process **(Nasrollahzadeh, Sajjadi, Sajadi, & Issaabadi, 2019)**.

The synthesis of nanoparticles from various resources contributes to the medical, biomedical, and existence pharmaceutical sectors, as well as other critical items such as innovative materials, energy storage systems, electrical and optical displays, and so on**(Harish et al., 2022)**. There are several physical and chemical ways for preparing nanoparticles, but green chemistry or Nano biology synthesis has lately piqued the scientific community's interest in developing metal nanoparticles utilising living organisms such as fungi, bacteria, plants , and *actinomycetes***(Saravanan et al., 2022; Sikiru et al., 2022).**

Organic and inorganic nanoparticles (NPs) are the two different forms of NPs. Carbon, liposomes, dendrimers, hybrid, and compact polymeric NPs are examples of organic nanoparticles. Magnetic nanoparticles, noble metal nanoparticles like gold, copper, and silver, and semiconductor nanoparticles like titanium oxide and zinc oxide are examples of inorganic nanoparticles **(Boroumand Moghaddam et al., 2015)**. Several sectors, including medicine, pharmacy, agriculture, textiles, and antimicrobial uses, have exploited metal nanoparticles **(Begum et al., 2022; Morin-Crini, Lichtfouse, Torri, & Crini, 2019).**

6.2. Fungal nanoparticle production using green methods:

Nanoparticles are the end result of several physical, chemical, and biological processes, some of which are fresh and profoundly different.

The benefits of green NPs production by fungus include straightforward scaling up, quick processing of biomass, economic viability, and recovery of considerable surface distances with optimal mycelia growth**(Saravanan et al., 2021)**.

Metal nanoparticle production by bacteria is common, however manufacture by fungal metabolites is more advantageous because the vast Fungal mats' surface area in contrast to other microorganisms **(Dikshit et al., 2021)**. These properties make fungus more suitable for large-scale nanoparticle manufacturing. Intracellular synthesis involves incubating fungal biomass in the dark with a metal salt solution for a certain time, whereas extracellular synthesis involves treating fungal filtrates with the precursor solution and assessing synthesis **(Yadav et al., 2015)**. Because of the massive scale manufacturing, simple downstream processing, and economic feasibility, extracellular synthesis of NPs from the fungus is extremely valuable **(Aziz et al., 2015)**.

Temperature, metal ion concentration, pH, the concentration of extracts, concentration of raw materials, incubation duration, and reaction mixture are all essential environmental parameters impacting nanoparticle formation and fungus development. As a result, the optimization condition is not only necessary for healthy growth but also improves product yields**(Abd-Elsalam, 2022)**.

VII.Applications of metallic nanoparticles in biomedicine:

In many different industries, including medicine, pharmacy, agriculture, textiles, and antimicrobial activities, metal nanoparticles play a significant role **(Marouzi, Sabouri, & Darroudi, 2021; Salem & Fouda, 2021).**

Nanomaterials have sparked enormous interest in a variety of biomedical sectors, including anticancer, antibacterial, antioxidant, anti-inflammatory actions and anti-diabetic, in addition to medication transport and bioimaging applications **(Azharuddin et al., 2019)**. Due to the ongoing desire for novel anticancer medications, chemotherapeutic research has focused on using metal nanoparticles as therapeutics against cancers due to their less harmful effect**(Olga et al., 2022)**.

7.1. Antimicrobial activity of metallic nanoparticles:

Because of the existence of many types of microorganisms, air, water, and soil are contaminated, causing issues in living circumstances and causing problems in health care. Due to the growth of antibiotic-resistant illnesses, many researchers are interested in developing alternative antimicrobial agents, such as new medicines, metal nanoparticles and cationic polymers **(Nisar, Ali, Rahman, Ali, & Shinwari, 2019)**.

Inorganic metal oxide nanoparticles showed distinct antibacterial activity due to the released of reactive oxygen species (ROS) **(Happy et al., 2019; Singh et al., 2020).** ROS interacts with essential biological elements of microbial cells, including proteins, DNA, and phospholipids, which inhibits cell development and causes cell death **(Ahmadi Shadmehri, Namvar, & Sciences, 2020; Godoy-Gallardo et al., 2021)**. It could also be associated with how nanoparticles interact with cell surfaces, which influences the degree of cell membrane permeability. The nanoparticles subsequently enter the microbial cell, producing oxidative stress and cell death **(Gabrielyan, Trchounian, & Biotechnology, 2019)**. Scientists have previously investigated the effectiveness of NPs against hazardous food pathogenic bacteria such *S. aureus* and *E. coli***(Babayevska et al., 2022; Chandra et al., 2019; Schneider et al., 2021).**

Some filamentous fungi are resistant to the antifungal action of nanoparticles **(Żarowska, Koźlecki, Piegza, Jaros-Koźlecka, & Robak, 2019).** There are several methods by which nanoparticles might prevent the development of fungi, such as the generation of reactive oxygen species (ROS), the emission of metal ions, and the disruption of the microbial cell membranes permeability **(Cruz-Luna, Cruz-Martínez, Vásquez-López, & Medina, 2021; Nisar et al., 2019)**. ROS spreading is the most typical method. ROS may interact with key biological components such phospholipids, proteins, and DNA, causing growth inhibition and, eventually, cell death **(Kanaujiya, Kumar, Dwivedi, & Prasad, 2020)**.

VIII. Conclusion

Filamentous fungi are now thought to be a good source of many important substances (secondary metabolites) that interact in all fields, particularly medicine, and play a role in the treatment of cancer cells and as antioxidants, and when these substances are loaded on nanoparticles, they help to speed up and accurately treat the disease. Secondary metabolites are a low-cost source that can be created readily and spontaneously, making them a reliable supply for these therapies.

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