Chapter 7
Fungal Secondary Metabolites: Biological Activity and Potential Applications

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7.1 Introduction

Fungi can be found in almost any type of habitat. They compete with other creatures in order to survive. Some of the fungi are detritivores, while others form interkingdom communities to obtain food and development (Willis et al. 2019). Fungi are remarkable organisms, and in order to survive (Devi et al. 2020b), they have developed many protective strategies as well as interactions, one of which is the production of different types of compounds known as secondary metabolites (Devi et al. 2020a). These compounds protect them against various invasive predators, parasites, and diseases (Calvo et al. 2002). Traditionally, fungi are considered to be as contaminants which infect the human surroundings and cause various diseases. Fungi are known for causing serious illnesses such as late blight of potato, caused by *Phytophthora* sp. essentially becoming responsible for the potato famine in Ireland, and rice blast leading to the famous Bengal famine of 1943 (Ul Haq et al. 2020). The damage was not limited to plants only, cattle poisoning with ergot (mold) body formed by the mycelium of *Claviceps* species, and mycotoxins are also caused due to fungi (Riet-Correa et al. 2013). Despite of having some negative impacts of members of fungal kingdom, it is a known that they carry a vast range of metabolites that can be helpful and could have medical, industrial, environmental, and agricultural applications (Goyal and Ramawat 2017; Kour et al. 2019b). The idea of harvesting secondary metabolites fascinates many biotechnologist and emerging companies. This idea can be dedicated to the discovery of penicillin by Alexander Fleming. Penicillin is a metabolite produced by *Penicillin chrysogenum*. This particular discovery has paved the path for consideration of fungi as useful organisms.

By using the same method, other antibiotics such as chloramphenicol and streptomycin were later isolated from various fungal species. In general, today *Saccharomyces cerevisiae* or commonly known as Baker's yeast is essentially used for food production, and the same fungi often act as genetic model for lab testing, and in that effect, mycological studies are in their own niche growing ever since. In addition, *Pichia pastoris* and *S. cerevisiae* are utilized for the biopharmaceuticals production (Berlec and Strukelj 2013). Today, we have established that fungi contain many beneficial primary and secondary metabolites ranging from alcohol, organic acids, antibiotics, vitamins, pigments, immunosuppressant and immunomodulatory agents, and economically important proteins and enzymes (Sanchez and Demain 2017). Some of the examples are antibiotic such as penicillin and immunosuppressant such as cyclosporine derived from *Penicillium fellutanum*, *Tolypocladium inflatum*, and many more (Anjum et al. 2012).

Nevertheless, benefits of fungi are not just limited to pharmaceutical industry, and fungi are being actively utilized as biofertilizer, as feedstocks for biofuel production, and also as human food for consumption (Azizan et al. 2016; Rana et al. 2019a; Rastegari et al. 2020a, b; Yadav et al. 2020a, b). Search for the novel compounds is of high demand in the pharmaceutical industry, and this has proven to be endless as nature holds an incomprehensible data bank of compounds. The requirement of novel compounds can be regarded to the fact that microbes infecting humans are ever evolving, which eventually makes the existing solutions ineffective. Exploring the compounds for medicine purposes has been a challenge ever since the beginning. But one thing that is essential to understand is that fungal kingdom might hold the answers to the problems, and a lot of studies are proving that fungal metabolites are pharmacologically important and can act as a potential solution in different domains such as anticancer, immunosuppressant, antidiabetic, immunoregulator, antimicrobial, and antifungal. Therefore, in this chapter, various fungal secondary metabolites and their applications have been discussed.

7.2 Fungal Classification

In 1969, Robert Whittaker published the five-kingdom classification which separated fungi from the plant kingdom and gave a separate position to fungi in the kingdom classification. Prior to that, a two-kingdom classification was proposed by Linnaeus, based on whether an organism has the ability to move or not was only classified into two groups of animals and plants. The five-kingdom classifications were more widely accepted and is still the way of classifying all the organisms. A considerable amount of traits were recognized that were neither of animal kind nor of plant type, and this prompted R.H. Whittaker to propose a separate kingdom for fungi. Traits such as chitin cell wall and absorptive mode of nutrition were different as compared to plants which do photosynthesis hence are autotrophs and have cellulose cell wall. On the basis of different phylogenetic evidences, fungal kingdom was further subdivided into six broad classifications (Fig. 7.1).

7.2.1 Basidiomycota

Basidiomycota is a monophyletic group having more than 31,000 species, and around one third of fungi belong to this phylum, such as mushrooms, toadstools, puffballs, jelly fungi, bracket fungi, rusts, and smuts (Taylor et al. 2014). The phylum gets its name from the club-shaped sexually produced spore known as basidiospore or basidium (Rivera-Mariani and Bolaños-Rosero 2012). Genetic and molecular studies show that there is large diversity present within this group that yet to be discovered. They play vital role in functioning of ecosystem at different levels and able to degrade different components in wood. Basidiomycota is further

Fig. 7.1 Classification of fungal kingdom

subclassified into three subphyla: Pucciniomycotina, Ustilaginomycotina, and Agaricomycotina. Pucciniomycotina appear as the most basal subphylum with highest support, with *Mixiaosmundae* branching at the base of subphylum Ustilaginomycotina and Agaricomycotina, both of them branch as sister subphyla and are monophyletic (McCarthy and Fitzpatrick 2017).

7.2.2 Ascomycota

The phylum computes of the largest phyla of fungal kingdom along with Basidiomycota. Its sexually produced spores are housed in a sac-like structure called as ascus. For the same reason, the group is often attributed as sac fungi. Presence of ascus/sac is the defining feature of Ascomycota. The phylum consists of cup fungi, morels, bakers, and brewer's yeast and truffles (Lutzoni et al. 2004; James et al. 2006). Further, it has major three subphyla: Taphrinomycotina,

Saccharomycotina, and Pezizomycotina. Many ascomycete yeasts, that is, Saccharomycotina, are connected with insects for dispersal, and the fungi provide enzymes, vitamins, and other resources to host insects however; the fungi do not harm the host insects (Vega et al. 2009). Taphrinomycotina are parasitic or saprobic on vertebrates and plants (Taylor et al. 2014). Pezizomycotina are the most ecologically and morphologically complex subphyla of ascomycota.

7.2.3 Zygomycota

The fungi belonging to this category have coenocytic hyphae. Mostly they grow on terrestrial terrains. Zygosporangia is the characteristic structure in which spores formed by the fusion of two hyphae are stored. They are an ecologically heterogeneous, paraphyletic, or polyphyletic assemblage of predominantly terrestrial organisms, which are generally placed near the base of fungal tree of life. They reproduce asexually via nonmotile endospores formed in sporangiola, sporangia, or merosporangia or by the formation of arthrospores, chlamydospores, and yeast cells, and they reproduce sexually by the formation of zygospores in zygosporangia. Species such as *Mucor* and *Rhizopus* are the major known examples of this class (Moore et al. 2011).

7.2.4 Oomycota

This class of fungal kingdom consists of water molds. The name is derived from sexually produced oospore, which is a result of contact between male antheridia and the female oogonia. Examples include late potato blight and sudden oak death. Due to few major similarities, the class is now classified along with brown algae (Goyal and Ramawat 2017).

7.2.5 Deuteromycota

This class is inclusive of fungi which are known only to have asexual form of reproduction or we are yet to discover their sexual reproduction. These are also known as imperfect fungi. Most of the members are analogous to either Basidiomycota or Ascomycota class. *Alternaria, Colletotrichum*, and *Trichoderma* are the ones which are included in this taxon (Goyal and Ramawat 2017).

7.2.6 Microsporidiomycota

Microsporidiomycota are obligate intracellular parasite belonging to fungal kingdom. These are basically unicellular spore-producing fungi (Goyal and Ramawat 2017) and parasites of animals and protists. They are highly reduced in form and develop intimate association with certain parts of cells or organelles. *Encephalitozoon* are the human pathogens and infect kidneys, muscles, eyes, and sinuses. Not all of them are detrimental in nature; some of them also possess promising role in pest control without the use of pesticides.

7.3 Fungal Secondary Metabolites

The metabolites which are essential for growth and development are regarded as primary metabolites, while secondary metabolites are defined as those compounds which are not generally essential for the primary growth and development of an organism. Their absence often does not result in any observable phenotypic changes in the producing organism when grown in laboratory conditions. These small molecules possess important role in fungi such as defense and survival in external environment. These secondary metabolites are source of novel drug formulation. Studies prove that secondary metabolites act as antibiotics, antioxidants, antitumor, and antidiabetic agents. Bioassays of some of the compounds have also revealed their insecticidal properties. A large number of compounds have been isolated from fungi (Fig. 7.2).

7.3.1 Polyketides

Polyketides are the largest class among the fungal secondary metabolites. These compounds can be crystallized or can undergo reduction reaction, and they even undergo various step reactions and all this enables them to be a diverse group. The formation is by polyketide pathway in which condensation of acetyl-coenzyme A (CoA) and malonyl-CoA is catalyzed by type I polyketide synthases (Daley et al. 2017).

7.3.1.1 Aflatoxins

Aflatoxins are mycotoxin that are produced majorly by *Aspergillus* sp., and these species are able to produce an aflatoxin precursor sterigmatocystin, which is a carcinogenic compound. Aflatoxins are generally found in different agricultural commodities and are strongly regulated with different threshold limits depending on the

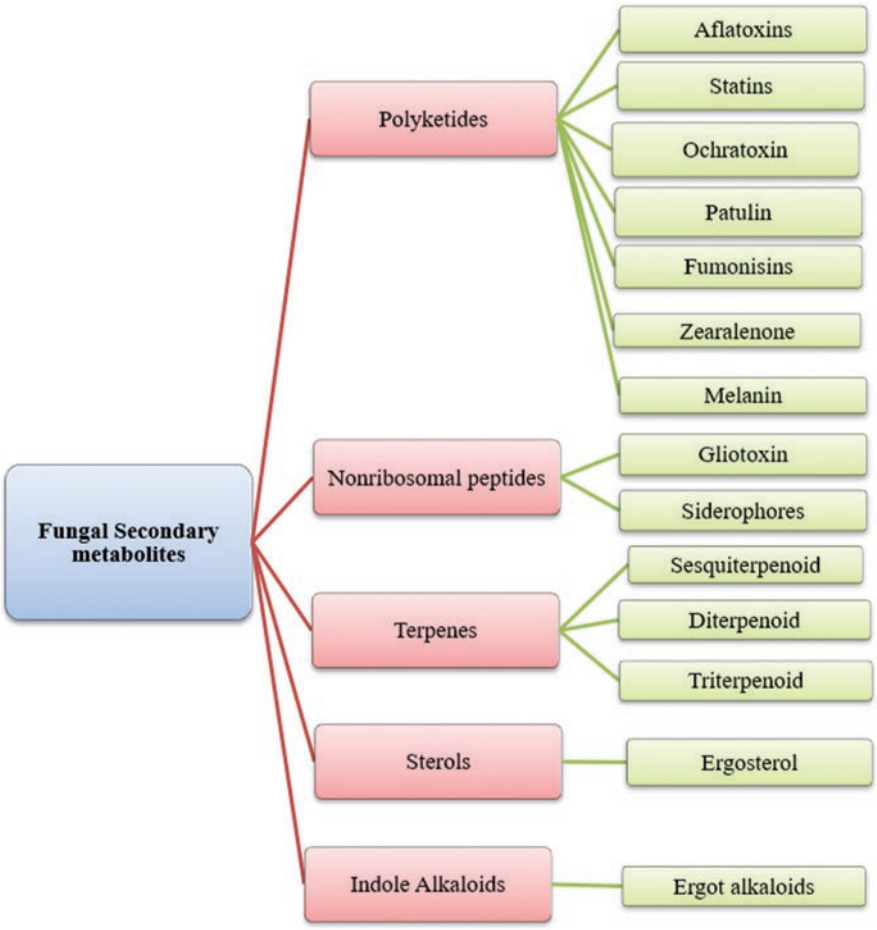

Fig. 7.2 Secondary metabolites of fungi

matrix (Pfliegler et al. 2020). *Aspergillus* sp. are particularly attracted to nuts and oils seeds, such as peanuts, walnut, corn, maize, and cotton seeds (Kumar et al. 2017). Aflatoxins are categorized as carcinogenic compounds as they include some of the most carcinogenic compounds ever isolated, such as B_1, B_2, G_1, and G_2. Among all, B_1 is the most toxic and carcinogenic obtained from *Aspergillus terreus*. Hepatitis B in conjugation with aflatoxin increases the probability of hepatocarcinogencity. They cause serious problems in human and animal, such as hepatotoxicity, teratogenicity, and immunotoxicity (Kumar et al. 2017). The toxic nature of these compounds links them to a number of diseases in both plants and animals. Illudin S isolated from *Omphalotus illudens* has the ability to glycolate the DNA, which makes it extremely toxic. Various aflatoxins producing species include *A.*

aflatoxiformans, *A. arachidicola*, *A. austwickii*, *A. cerealis*, *A. minisclerotigenes*, *A. mottae*, *A. pipericola*, and *A. texensis* (Pfliegler et al. 2020).

7.3.1.2 Statins

Statins are cholesterol-controlling compounds. One of the best studied compounds is lovastatin produced commercially using *A. terreus*. Statins usually show biological activity by influencing on 3-hydroxy-3-methylglutaryl-CoA reductase enzyme, which is essentially responsible for cholesterol formation. These are also referred as hypocholesterolemic agents. The inactivity of enzyme by statin lowers or nullifies the blood low-density lipoprotein cholesterol level (Adrio and Demain 2003).

7.3.1.3 Ochratoxin

Ochratoxin A is a mycotoxin produced by numerous fungal species such as *Aspergillus carbonarius, Aspergillus niger, Aspergillus ochraceus,* and *Penicillium verrucosum* (Bui-Klimke and Wu 2015). It was one of the first toxin that was discovered due to its capacity to infect human cells. It was isolated from *Aspergillus ochraceus*, but toxin is also found in other species such as *Aspergillus carbonarius* and *Penicillin verrucosum*. Toxin can also be found in grains such as corn, barley, oat, and wheat (Kolakowski et al. 2016). It is lethal to dogs, mice, pigs, and trout. It is an acute nephrotoxin, which causes necrosis in renal tubules and periportal liver cells. Other harmful effects include immunosuppression, embryo damage, and cancer induction (Bhalla 2019). Structurally, it is a pentaketide and derived from dihydrocourmarins which are similar to β-phenylalanine. The fungi species mainly invade plant products such as coffee beans, olives, grapes, nuts, and wines. Although ochratoxin A is a fat-soluble toxin and is not excreted, it can be transferred from animal sources too. If the fodder of animal is mold contaminated, it can build up in issues and circulatory system of animals.

7.3.1.4 Fumonisins

Both *Fusarium verticillioides* and *Fusarium proliferatum* are the major producers of Fumonisins. It is a mycotoxin which predominantly infects maize, corn, and sorghum (Smith 2018). It is a cause of porcine pulmonary edema and equine leukoencephalomalacia. They are structurally similar to sphingosine, essential phospholipid in cell membrane. Fumonisins are 20-corbon aliphatic chain with two ester-linked hydrophilic side chains. Coincidently, the toxicity of the discovered fumonisins B1 and B2 is also a result of competition in phospholipid metabolism. The main concern in pharmacology is their carcinogenic, genotoxic, and teratogenic effects rather than acute effects (Smith 2018).

7.3.1.5 Zearalenone

The toxin is produced by various species of *Fusarium* sp., including *F. cerealis*, *F. crookwellense*, *F. culmorum*, *F. equiseti*, *F. graminearum*, and *F. semitectum* (Zhang et al. 2018). Zearalenone is a heat-stable compound, and hence, it is found in open-field growing crops majorly cereals. The production of toxin is usually preharvesting, but vague handling of crop can lead to postproduction of the toxin too. Unlike Ochratoxin, Zearalenone is rapidly metabolized in the animal body, and hence, it is less likely to be transferred from animals to humans (Binder et al. 2017). It causes reproduction and fertility disorders in mammals. The concentration in some cases plays an important role. In cow's milk, zearalenone can be found if the mold concentration on the fodder is extensive. The toxin F-2 was isolated, and structurally, it is a resorcylic acid lactone. Prior to this discovery, *Fusarium* sp. has been a major cause for many mycotoxic outbreaks. Zearalenone is also referred as mycoestrogen for its estrogen-like activity. It has been reported to stimulate the growth of breast cancer cells, though seldom it is administered in cases of hypoestrogenic syndromes.

7.3.1.6 Patulin

Patulin is a toxin produced by *Penicillium*, *Aspergillus*, and *Byssochlamys*. This toxin is most common in apple-made products such as juices, compotes, cider, and baby foods (Zhong et al. 2018). Grapes, oranges, pears, and peaches are also contaminated with patulin. Patulin has various biological activities in both animals and humans. It is neurotoxic, genotoxic, and immunotoxic to rodents while teratogenic to chickens. Patulin causes distortion of DNA and induces mutations in it. On cellular level, many abnormal pathways can be observed, such as production of reactive oxygen species, cell cycle arrest, caspase-3 activation, PARP cleavage, and subsequent apoptosis (Kwon et al. 2012). In human intestine and kidney, production of reactive oxygen species induces mitochondrial apoptosis and causes endoplasmic reticulum stress (Kwon et al. 2012).

7.3.1.7 Melanin

Melanin acts in a protective nature for the fungi. It is produced using two pathways: one is polyketide pathway with malonyl-CoA as the precursor and other uses diphenolic compounds such as 3,4-dihydroxyphenylalanine as precursor (Belozerskaya et al. 2015). Melanin protects the possessing species of the fungal kingdom from the UV radiations and essentially helps in proliferation and growth of the fungi. The open-field stress is reduced by the melanin by photoprotection approach (Cordero and Casadevall 2017). Albino mutants (i.e., lacking melanin) of the same species of fungi did not grow in the open fields. Resting spores of species such as *Aspergillus fumigatus*, *Aspergillus nidulans*, and *Wangiella dermatidis* consist of melanin,

which helps them to remain dormant and act as perennation agents. Melanin also partially acts as a defense against host immune system. Melanin absorbs ROS secreted by macrophages and neutrophils. The pigment is considered to be critical for pathogenicity of many species of fungal kingdom (Garvey and Keller 2010).

7.3.2 Nonribosomal Peptides

Nonribosomal peptides are secondary metabolites which are synthesized by multidomain enzymes called nonribosomal peptide synthetases without the requirement of cell ribosomal machinery. They are naturally synthesized by fungi and produced via mRNA-independent process. They consist of both proteinogenic and nonproteinogenic amino acids. *Tolypocladium niveum* produced an immunosuppressant cyclosporine which is administered to patients undergoing organ transplant. Nonribosomal peptides possess wide range of bioactivities and pharmacological properties.

7.3.2.1 Gliotoxin

Gliotoxin was found as a contaminant in the process of fumagacin production when it was extracted from *A. fumigatus*. Structurally, gliotoxin constitutes disulfide bridge across the piperazine ring and is characterized as dipeptide. This structural integrity of the toxin allows it to interact with other proteins via disulfide bridge linking to cysteine residues of the protein. This interaction leads to the formation of reactive oxygen species (ROS). The formation of ROS is mainly responsible for its toxicity. ROS generation releases cytochrome c and promotes mitochondrial apoptosis, caspase production leading to cell death. It is known for its immunosuppression activity. Immune response suppression can be seen in many fronts such as inhibiting NF-κB factor, thereby suppressing inflammatory and cytokine responses, inhibiting phagocytosis, and blocking mast cell degranulation. All these events suggest that gliotoxin possesses protective mechanism in *A. fumigatus* from host environment (Kwon-Chung and Sugui 2009).

7.3.2.2 Siderophores

Siderophores are mycotoxin with low molecular weight and considered to be highly coordinated with iron. There are three structural families of siderophores: fusarinines, coprogens, and ferrichromes (Yadav et al. 2020c). On basic level, almost all fungal siderophores are hydroxamate types with few exceptions to this generalization. The basic unit is N^{δ}-acyl-N^{δ}-hydroxyornithine, whose precursor is L-ornithine (Renshaw et al. 2002). Siderophores formation occurs through nonribosomal

peptide pathways. Role of siderophores is speculated in virulence of *A. fumigatus* as iron plays an important role in host–pathogenic interactions, and siderophores promote growth of hyphae in even iron-limiting environment (Garvey and Keller 2010). On the other hand, medically siderophores are being used to treat iron overload and aluminum overload conditions, although side effects come into play with the administration of these mycotoxins (Page 2019). They are also studied for anticancer properties in mice models and found to inhibit tumors in them. Actinides are elements which are mostly radioactive and carcinogenic, while siderophores enhances the excretion of actinides from body.

7.3.3 Terpenes

Terpenes are important bioactive metabolites produced by many fungi species. Structurally, terpenes are repetitive units of isoprene unit, both in linear and cyclic fashion. They are even categorized on the basis of number of isoprene units (C_5) present into diterpenes (C_{20}), hemiterpenes (C_5), monoterpenes (C_{10}), sesquiterpenes (C_{15}), sesterterpenes (C_{25}), triterpenes (C_{30}), and tetraterpenes (C_{40}). Diterpenoid, triterpenoid, and sesquiterpenoid are the terpenes which possess various biological activities. This group of compounds is structurally well diverse, and this fact can be pointed to the ability of the compounds to undergo various catalytic modifications such as glycosylation, cyclization, redox reaction, and alkylation. The production of terpenes is observed by mevalonic acid pathway. Gibberellins, carotenoids, indole-diterpenes, trichothecenes, and aristolochenes all are the examples of terpene class metabolites (Daley et al. 2017).

7.3.4 Sterols

Sterols are isoprenoid-derived molecules and major constituent of eukaryotic cell membranes. It is necessary for permeability, fluidity, and protein function. Therefore, they are required for growth of fungi. Ergosterol was discovered over 100 years ago in *Claviceps purpurea*. It has been considered as fungal sterol, and multiple pathways are involved in the formation of ergosterol. In some taxa, pathways are incomplete and, in some cases, result in the formation of other end-products. Ergosterol synthesis starts with acetyl-CoA and comprises of 20 steps (Alcazar-Fuoli et al. 2008). In a study two aromatic steroids were isolated from *D. concentrica*, that is, 19-norergosta-1,3,5,7,9,14,22-heptaene and 1-methyl-19-norergosta-1,3,5,7,9,14,22-heptaene (Qin and Liu 2004). Another study reported the presence of two steryl esters with a polyhydroxylated ergostane-type nucleus in *Tricholomopsis rutilans* (Wang and Liu 2005).

7.3.5 Indole Alkaloids

Alkaloids are the largest group which is of pharmacological importance. For indole alkaloids, tryptophan and dimethylallyl phosphate are the precursors, but sometimes, other amino acids are also used. The most widely studied group of indole alkaloids is ergot alkaloids. Initial findings suggested ergot alkaloids as toxins, but later other uses were also found. They are produced by *Claviceps purpurea* and its related species. Ergot alkaloids have the ability to induce abortion and promote uterine contractions (Schiff 2006). They also act as vasodilators which can reduce blood pressure by dilating the blood vessels. Ergots also inhibit noradrenaline and sclerotin. Fumigaclavines and fumitremorgens are also tryptophan-derived alkaloids synthesized by *Aspergillus fumigatus* (Goetz et al. 2011).

7.4 Function of Secondary Metabolites

The release of secondary metabolites aligns with either the fungal development or to counter any stress conditions including both biotic and abiotic stresses. These metabolites can change the course of development, survival, and interaction with other species both interkingdom and intrakingdom.

7.4.1 Protects from UV Damage

This functionality is usually devoted to the presence of a polyketide compound know as melanin. Melanin is a constituent part of spores and hyphae of the fungi. It is usually produced by either polyketide or l-3,4-dihydroxyphenylalanine pathway. Protection being the ecological role of melanin was seen in an albino mutant (i.e., lacking melanin) of *Cochliobolus heterostrophus*, which was unable to stand the sunlight and thus was not able to survive in open ground. However, other species which was having melanin in their spores was able to survive in the open ground. There are other metabolites which are also having the function of photoprotection. These compounds also protect the pathogenic fungi from the host immunity.

Melanin is a well-studied and widely used secondary metabolite in cosmetics, food coloring, human skin care products, and bioelectronics (Blachowicz et al. 2020). It is a brown-colored natural pigment localized in the cell wall of spores and hyphae of many fungi (Toledo et al. 2017). Melanin biosynthesis in fungus occurs through enzymatic or spontaneous polymerization of polyphenols, such as catechol, 1, 8-dihydroxy naphthalene (DHN), or dihydroxyphenylalanine (L-DOPA). The primary role of fungal melanization is microbial pathogenesis and protection against extreme environments, such as Arctic and Antarctic poles, high-temperature fluctuations in deserts, acidic pH, exposure to radiations, extraterrestrial conditions,

metal-polluted areas, oxidative stress, low moisture, nutrient availability, hypersaline waters, elevated osmotic pressure, and so on. The pigmented fungi exhibit resistance to radiotoxicity compared to their albino counterparts. Melanin is defense armor for fungus to tolerate and resist toxic conditions (Gómez and Nosanchuk 2003). A notable property of melanin is to interact with electromagnetic rays, acting as a photoprotective and energy harvesting agent. Electromagnetic radiations are potentially hazardous when exposed to the human skin depending on the duration of exposure. Ionizing radiations or electromagnetic radiations, including gamma rays, X-rays, and ultraviolet rays, cause skin damages such as erythema, tanning, skin aging, degeneration of skin cells, fibrous tissue, and blood vessels. Prolonged exposure of UV rays is responsible for most nonmelanoma and melanoma skin cancer. The UV-A rays (320–400 nm) permeate the dermis causing mutations in the DNA, premature aging of the skin (wrinkles, fine lines, freckles, and coarse skin), and suppresses immunity. The UV-B rays (280–320 nm) penetrate the epidermis, causing erythema and sunburn – a vital factor responsible for melanoma skin cancer. The high-frequency electromagnetic radiations generate intermediate free radicals from biomolecules such as DNA and proteins (Ikehata and Ono 2011). The free radicals or reactive oxygen species (superoxide anions, peroxides, hydrogen peroxide, and hydroxyl radical) have unpaired electrons making them highly unstable. The ROS damages the cellular structure and function in the epidermal and dermal regions of the skin by oxidizing the proteins, carbohydrates, and lipids. Melanin absorbs and dissipates photons from ionizing radiations and thus acts as a photo protectant or a natural sunscreen for human skin. The complex, unorganized structure of melanized fungi absorbs the entire UV region (UV-A, UV-B, UV-C) of the electromagnetic spectrum. The same properties of melanin that prevent oxidative damages in the human skin protect pathogenic fungi against the host defense mechanism.

7.4.2 Defensive Role

In the open fields, competition for food and survival is not only interspecies but also interkingdoms. Fungi have developed mechanisms, either direct or indirect to survive in the environment. The first ever direct functionality of the mycotoxin was illustrated by Alexander Fleming. Penicillin, an antibacterial, was produced by *Penicillin notatum* to kill the surrounding bacteria such as *Staphylococci* present in the culture. Later, penicillin was regarded as the wonder drug. *Beauveria bassiana*, another fungus, contains a toxic metabolite arsenal to kill insects. The species also fills the insect with antibacterial so curb down the microbial competition. *Aspergillus flavus* produces aflatoxin, which is considered to be a group of carcinogenic compounds which increases the ability of a fungi to fight and survive with insect proximity by 26 times. Bacterial–fungal interaction is also beneficial for fungi in a number of cases. Some examples include that the endosymbiont relation of *Burkholderia rhizoxinica* and *Rhizopus microspores* is responsible for rice seedling blight, which becomes worse once the microbial toxin rhizoxin enters into the plant

cells. Some other symbiont species also enhance the rhizoxin to increase its phytotoxicity to mutually benefit both organisms from the host. A complex gradient-depended effect is also seen with *Aspergillus*, where phenazine produced by *Pseudomonas aeruginosa* acts as an antifungal agent if present in high concentration, but within a certain concentration, phenazine is helpful to the fungi for sporulation (Macheleidt et al. 2016; Raffa and Keller 2019).

7.4.3 Protects from Toxic Natural Products

Fungi also need certain mechanisms to protect itself from toxins that are being produced by itself. That is where different self-protection strategies come in. The efflux pumps in GliA are important and provide protection from trichothecenes, cellular biosynthetic gene cluster intermediate transporters, detoxifying enzymes, and duplicate copies of target protein. Among all, duplicate copies are of high importance for human kind in drug discovery as the presence of duplicate function directly points toward a eukaryotic target. This is the main source of identification of many antifungal agents which are modified and used as an effective treatment for human invasive pathogens and pathogenic biofilms (Keller 2019).

7.4.4 Growth and Development

Although major development is coordinated by primary metabolites, some protective function is still depending on secondary metabolites which promote the development and reproduction of fungi. Fungi produce toxins such as fusarubins and furocoumarin which protect the sexual structures from predators and fungivores. Photoprotection of spores by melanin improves the chances of spore germination. Production of certain secondary metabolite inhibits other spore germination in the surrounding. This external behavior can be seen in *Penicillium* sp. (Calvo and Cary 2015; Keller 2019).

7.5 Biological Application of Fungal Secondary Metabolites

For the past few decades, scientists have tested secondary metabolites from over 10,000 fungal species for biological activity. There is an extensive history of using fungi folk medicine in Asian countries to promote health and longevity. Bioactive compounds from fungi offer vast and unexplored chemical compounds. The ability of fungi to acclimate to all niches of earth offers an understanding that the bioactive compound aids the survival of fungi. Decoding the biosynthetic gene clusters of fungi can help in finding unexplored bioactive compounds with beneficial

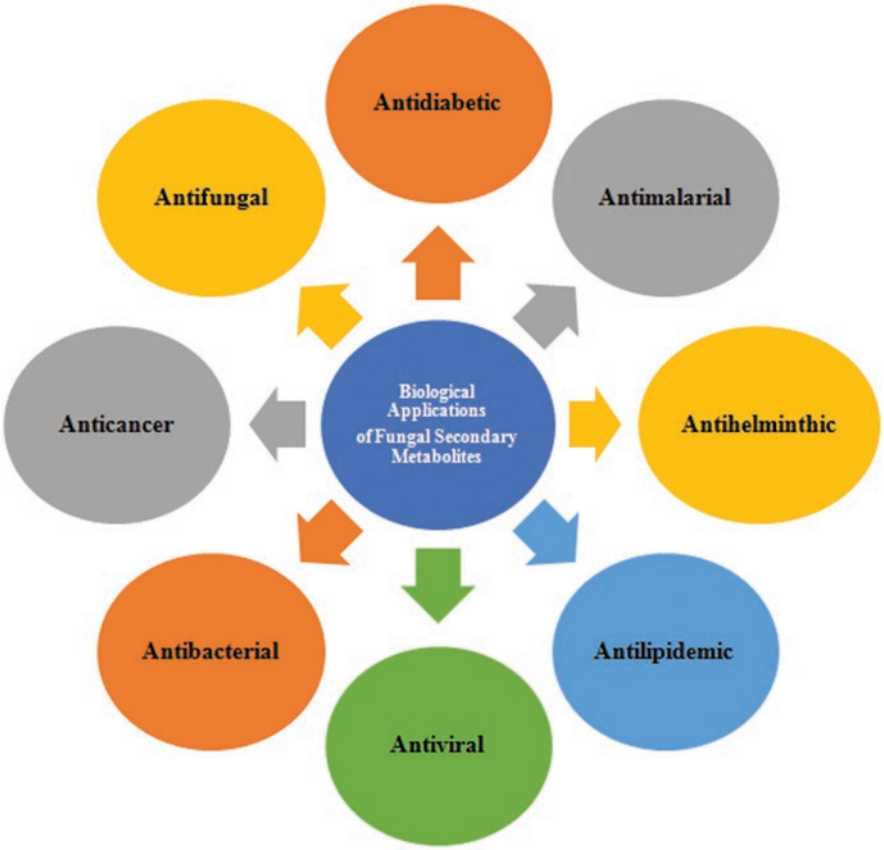

Fig. 7.3 Biological applications of fungal secondary metabolites

properties. Further investigation of bioactivity of secondary metabolites opened the gates of new era of antimicrobials from higher fungi. Pharmacological research of these bioactive compounds reveals that fungi possess various biological applications such as antibacterial, antiviral, antiprotozoal, antihelminthic, and antifungal activities. In recent decades, fungal secondary metabolites are being researched as potential leads in drug development, cosmetics, and crop protection in agriculture (Fig. 7.3).

7.5.1 Antibacterial Agents

The development of penicillin paved the way for development of antibacterial fungal metabolites. Penicillin is a bactericidal antibiotic that kills bacteria by inhibiting the action of enzyme transpeptidase, required for crosslinking of peptidoglycans in

the bacterial cell wall synthesis. In the late 1940s, a team of Oxford scientists under Howard Florey developed a way to mass-produce penicillin during the outbreak of the Second World War, but the drug yields were very low (Florey 1944). To overcome this challenge, researchers implemented a deep-tank fermentation method, which resulted in the production of over 600 billion units of pharmaceutical-grade penicillin per annum in 1945 during the Second World War. Ernst Chain, a German origin British biochemist along with Florey, discovered the chemical composition and therapeutic role of penicillin. In 1945, Howard Florey, Ernst Chain, and Alexander Fleming shared a Nobel Prize in Medicine for their work with penicillin. There are five types of naturally biosynthesized penicillin viz., penicillin G, penicillin K, penicillin N, penicillin O, and penicillin V. The discovery of β-lactam antibiotics such as cephalosporin, monobactam, and carbapenem followed the success of penicillin (Ingolia and Queener 1989). Cephalosporin isolated from the aerobic mold, *Cephalosporium acremonium*, forms a significant class of β-lactam antibiotics. There are four generations of cephalosporins which are grouped based on their antimicrobial activity (Mehta and Sharma 2016). The previous β-lactam drugs were short-range antibiotics effective against few gram-positive bacteria; however, the new generation of β-lactam antibiotics exhibits broad range of action and is effective against a wide range of pathogenic gram-negative bacteria. There are other classes of antibiotics derived from fungi that show antibacterial activity by following either of the mechanisms, that is, inhibiting protein synthesis; inhibiting nucleic acid and folic acid synthesis pathways; permeabilizing cytoplasmic membrane; and interfering with cellular processes (Silver 2011).

Fusidic acid isolated from *Fusidium coccineum* has antibacterial activity against *Mycobacterium tuberculosis*, *Neisseria* sp., *Nocardia* sp., *Staphylococcus aureus*, and penicillin-resistant and methicillin-resistant *Staphylococcus aureus* (Dobie and Gray 2004). Retapamulin, extracted from an edible mushroom *Pleurotus mutilins*, was the first pleuromutilin topical antibiotic developed by GlaxoSmithKline and sold under the trademark names Altabax and Altargo. Retapamulin is useful in the treatment of impetigo. Alamethicin, an ion channel-forming peptaibol antibiotic, was isolated from *Trichoderma viride* (Dotson et al. 2018). Ongoing studies have reported that several polyketides, peptides, and sterols extracted from fungi possess antibacterial properties, although their mechanism of action is yet to be deciphered.

7.5.2 Antifungal Agents

Fungal infections can be mild skin infections (mycosis), or they may have life-threatening implications, as seen in the cases of aspergillosis and candidiasis. The most common form of fungal infections includes skin and nail infections. About 40 types of fungi (typically *Trichophyton*, *Microsporum*, or *Epidermophyton*) can cause fungal skin infections (White et al. 2014). They lead to dry red itchy patches on the skin. Nail fungal infections, technically called onychomycosis, lead to thick, discolored, cracked nails. The cause of these infections is soil yeasts such as

Candida parapsilosis, *Candida guilliermondii*, and *Candida albicans*. In recent years, nondermatophyte molds, for instance, *Fusarium* spp., and *Onychocola canadensis* are being increasingly detected as the causative agent for fungal nail infections. It is difficult to find a cure for fungal infections, and at present, only a handful of antifungal agents are available. Fungi synthesize some antifungals as secondary metabolites for their existence. Griseofulvin is one of the first naturally synthesized antifungals from *Penicillium griseofulvum*. It is a fungistatic drug used in the treatment of hair, skin, and nail fungal infections. Griseofulvin inhibits mitosis of fungal cells by binding with tubulin and hinders microtubule function (Gupta et al. 2004). In the case of nail and hair infections, griseofulvin binds with keratin and makes it resistant to fungal invasions. Cerulenin, an antifungal antibiotic, derived from *Cephalosporium caerulens*, inhibits fatty acid biosynthesis in yeasts.

Invasive fungal infections are life-threatening in immune-compromised patients. Healthy individuals can breathe in air with *Aspergillus* spores and remain unaffected. In case of immune-compromised individuals, spores of *Aspergillus* can cause aspergillosis. *Aspergillus* infections result in allergies and infections in lung and other organ. Similarly, *Candida* is present on the skin, mouth, throat, gut, and vagina without affecting a healthy individual. *Candida* can be precarious when it grows out of control or enters the bloodstream or internal organs. Fungal pathogens such as *Candida albicans* and *Aspergillus* can also cause hospital-acquired infections such as bloodstream infections, ventilator-associated pneumonia, urinary tract infections, and surgical site infections (Khan et al. 2017).

Echinocandins are the precursor leads of semisynthetic antifungal drugs against systemic infections such as aspergillosis and candidiasis. These drugs act by noncompetitively inhibiting the enzyme 1,3-β-D-glucan synthase required for the synthesis of fungal cell wall component β-glucan polymers. Echinocandin B isolated from *Aspergillus nidulans* was the first drug lead of class echinocandin (Denning 2002). Echinocandin B is the precursor of semisynthetic antifungals caspofungin (cancidas), anidulafungin (Eraxis), and micafungin (Mycamine). These three agents are approved by the FDA to treat candidemia, invasive candidiasis, and esophageal candidiasis. Echinocandins are administered with other groups of antifungals in combination therapy to cure aspergillosis. For instance, anidulafungin is used in combination with voriconazole to treat *Aspergillus* infections (Jeans et al. 2012).

Caspofungin is an intravenous drug used in empirical therapy of fungal infections in febrile patients with neutropenia and therapy of aspergillosis where patients are intolerant of conventional antifungal drugs (Shalhoub et al. 2014). Micafungin is used in the treatment of candidemia, candida peritonitis, and esophageal candidiasis. Micafungin is the only FDA-approved echinocandin drug for the prophylaxis of *Candida* infections in hematopoietic stem cell transplantation patients (Shalhoub et al. 2014). Pneumocandins are a closely related group of echinocandins isolated from *Zalerion arbicola* which are effective antifungals against *Candida* sp. and *Pneumocystis carinii* (Patil and Majumdar 2017).

7.5.3 Anticancer Agents

Scientists have examined the cytotoxic activity of fungal metabolites in the past few decades. Although these secondary metabolites were used since ages, their antitumor activity has been decoded in the past few years. For instance, in ancient China, Reishi, a medicinal fungus, served as a folk medicine to promote health and longevity, but in recent years, researchers have pointed out its antitumor mechanisms as well. The polysaccharide peptide (GI-PP) from Reishi is a potent angiogenetic and induces cell apoptosis by reducing the expression of Bcl-2 (antiapoptotic protein) and elevating Bax (proapoptotic protein) (Wachtel-Galor et al. 2011). A high dose of GI-PP alleviates the expression of vascular endothelial growth factor, and this explains the mechanism of antitumor activity of GI-PP. *Ganoderma lucidum*, a medicinal mushroom, has been demonstrated with apoptotic, antiproliferative properties. *G. lucidum* suppresses the migration of PC-3 cells, a highly invasive prostate cancer cell (Sohretoglu and Huang 2018). The water extract of *G. lucidum* was studied extensively compared to its alcohol extract. *G. lucidum* promoted the synthesis of $CD5^+$, $CD4^+$, and $CD8^+$ T lymphocytes (Lin 2005). In horses, *G. lucidum* was observed to elevate the production of specific antibodies. The alcohol extract of *G. lucidum* induced apoptosis in MCF-7 breast cancer cells in a dose- and time-dependent manner (Wu et al. 2012). The underlying mechanism is still not known, but the hypothesis suggests that it may be due to an increased expression of pro-apoptotic Bax protein. Another antineoplasmic metabolite isolated from *G. lucidum* is a triterpenoid, lucidenic acid N. It is a potent cytotoxic metabolite against Hep G2 cells, with an IC50 value of 2.06×10^{-4} μM (Wu et al. 2001).

Maitake glycan, isolated from *G. frondosa*, is an SFDA-approved drug, clinically used to treat cancer, polycystic ovary syndrome, and impaired glucose tolerance (Rossi et al. 2018). The bioactive component of maitake glycan is β-glucan or the d-fraction composed of β-(1 → 6)-glucan main chain with β-1,3 branches as opposed to β-(1 → 3)-glucan as main chain with β-1,6 branches in the β-glucan of other fungi with antitumor properties (Rossi et al. 2018). Maitake glycan inhibits tumor growth by cell apoptosis via notch1/NF-B/p65-mediated caspase pathway, activating immune cell and regulating the production of cytokines. Paclitaxel is a potent drug for chemotherapy medication to treat pancreatic cancer, ovarian cancer, breast cancer, cervical cancer, lung cancer, and Kaposi's sarcoma (Singla et al. 2002). The WHO has included it in the World Health Organization List of Essential medicines. Initially, paclitaxel was derived from *Taxus brevifolia*; in 1993, researchers discovered paclitaxel in an endophytic fungus that inhabited in the Pacific yew, and, since then, it has been found in several endophytic fungi. In 2001, the National Institute for Health and Care Excellence approved the use of paclitaxel in the treatment of non–small-cell lung cancer, first-line and second-line treatment of ovarian cancer, and treatment of advanced breast cancer where anthracyclic chemotherapy fails. Paclitaxel is a cytoskeletal drug that targets tubulin. It stabilizes the microtubule polymer and prevents the spindle configuration of chromosomes in the metaphase, thus blocking the progression of mitosis. This triggers cell apoptosis at the mitotic

checkpoint. Poricoic acid G, isolated from *Poria cocos*, showed cytotoxic properties against leukemia HL-60 cells (Ukiya et al. 2002). Experimental cancer drugs that target the enzyme farnesyl transferase to inhibit the activity of Ras protein in cancer cells such as 11,11′-dideoxyverticillin A, andrastin A, barceloneic acid A, and barceloneic acid B were isolated from marine *Penicillium* sp (Jin-Ming 2006). Other antitumor cytoskeletal drugs targeting tubulin include vinblastine and vincristine. Both these drugs are included in the World Health Organization List of Essential Medicines. Vinblastine was isolated from the endophytic fungi *Curvularia verruculosa* from the leaves of *Catharanthus roseus*. Fungal vincristine from *Eutypella* sp.-CrP14 was isolated from *Catharanthus roseus* (Kumar et al. 2013). These drugs are used in chemotherapy medication to treat small-cell lung cancer, acute lymphocytic leukemia, acute myeloid leukemia, Hodgkin's lymphoma, and neuroblastoma.

7.5.4 Antiviral Agents

Fungal secondary metabolites which possess antiviral properties are grouped in two categories based on their mechanism of action, that is, biological response modifiers (BRMs) and viral inhibitors. BRMs are compounds that modulate the host defense system by acting on a therapeutic target in a pathogenic disease. Most of the antiviral metabolites from fungus are BRM. For instance, styrylpyrone compounds, hispidin and hispolon, isolated from *Inonotus hispidus* were observed to show antiviral activity against influenza virus type A (H1N1 and H3N2) and B (Awadh Ali et al. 2003). A retrovirus requires three enzymes for replication in a host, namely reverse transcriptase, integrase, and protease. Antivirals target these three enzymes to inhibit viral activity by blocking virus replication. Hispidin caps its phenolic group with methyl ether and inhibits the activity of enzyme integrase required for viral replication (Roy 2017). *Ganoderma pfeifferi*, a medicinal mushroom, is a source of many antiviral metabolites. Triterpenes, ganodermadiol, lucidadiol, applanoxidic acid G, ganoderone C, lucialdehyde B, and ergosta-7, 22-dien-3α-isolated *Ganoderma pfeifferi* have shown antiviral properties against influenza virus type A (Mothana et al. 2003). Another group of triterpene metabolites lanosta-7, 9(11), 24-trien-3-one, 15; 26-dihydroxy, and ganoderic acid Y isolated from *G. lucidum* inhibits the growth of enterovirus 71. The fruiting bodies from *G. lucidum* such as ganoderiol F and ganodermanontriol inhibit the action of HIV protease enzyme. The chloroform extract of fruiting bodies *G. colossum* also inhibits the activity of HIV protease enzyme and ceases viral replication (El Dine et al. 2008). Krestin is a protein-bound polysaccharide extracted from Basidiomycetes with anti-HIV properties. It was reported to inhibit the activity of reverse transcriptase enzyme of avian myeloblastosis virus (Maehara et al. 2012).

7.5.5 Antilipidemic Agents

Antilipidemic agents are cholesterol-lowering drugs that inhibit the synthesis of cholesterol or low-density lipoproteins (LDL), decreasing fat accumulation in plasma and preventing atherosclerosis and thrombosis. Statins are a class of drugs primarily used to inhibit the biosynthesis of cholesterol (Endo 2010). The first statin drugs, mevastatin isolated from *Penicillium citrinum* and lovastatin isolated from *Monascus ruber* or *Aspergillus terreus*, were fermentation products (Subhan et al. 2016). Static acid is structurally analogous to enzyme hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, required in the biosynthesis of cholesterol by mevalonate pathway. Thus, statins act as competitive inhibitors of HMG-CoA and inhibit the synthesis of cholesterol, reducing the total and low-density lipoprotein cholesterol levels, and prevent the risk of coronary heart diseases. In a study, effect of rosuvastatin was evaluated on Coronary Atheroma Burden, patients with preexisting heart disease, where 40 mg/day of rosuvastatin was administered. It was observed that the drug reduced the levels of LDL cholesterol and elevated the levels of HDL cholesterol, and this led to a regression in the atheroma burden (Aly et al. 2011). Statins help in decreasing the incidences of strokes by ceasing atherosclerosis progression, stabilizing plaque, and improving endothelial functions (Pinal-Fernandez et al. 2018).

7.5.6 Antihelminthic Activity

Parasitic nematode infections in humans, plants, and animals are a significant cause of concern. They result in grave economic losses of crops and livestock. *Ascaris lumbricoides* and the hookworms *Ancylostoma duodenale* are common nematodes that infect humans. In the late nineteenth century, an antihelminthic agent, PF1022A, was isolated from *Mycelia sterilia*. PF1022A is a cyclic octadepsipeptide composed of alternating L-D-L configuration of 4N-methyl-L-leucines, 2 D-lactic acids, and 2 D-phenyllactic acids. PF1022A was initially tested against the roundworm *Ascaridia galli* in chickens. An oral administration of 2 mg/kg of PF1022A in chickens proved to inhibit the growth of *A. galli* (Von Samson-Himmelstjerna et al. 2000). PF1022A is not cytotoxic and does not affect the growth of gram-positive or gram-negative bacteria or fungi. The antihelminthic activities of PF1022A have been reported against *Haemonchus contortus*, *Ostertagia ostertagi*, *Toxocara canis*, and *Trichostrongylus colubriformis* and the intestinal nematode *Angiostrongylus cantonensis*. Fujisawa Pharmaceutical Co. Ltd. (Japan) has synthesized a semisynthetic drug derived from PF1022A known as emodepside, which is used in combination with praziquantel and sold under the tradename Profender® to treat nematode infections (Krücken et al. 2012).

7.5.7 Antimalarial Agents

Malaria caused by a female *Anopheles* mosquito is a life-threatening disease prevalent in Asian and African regions. As per the World Malaria Report, there were 228 million cases in 2018. Codinaeopsin, a fungal secondary metabolite, has been tested for its antimalarial properties against *Plasmodium falciparum* (Kontnik and Clardy 2008). 7-hydroxy-3,4,5-trimethyl-6-on-2,3,4,6-tetrahydroisoquinoline-8-carboxylic acid and 2,5-dihydroxy-1-(hydroxymethyl) pyridin-4, two alkaloid extracts isolated from endophytic fungi, have been reported to possess antimalarial activities (Elfita et al. 2011). Other antimalarial metabolites from fungi such as efrapeptins, zervamicins, and antiamoebin are under research.

7.5.8 Antidiabetic Activity

Many fungal metabolites are tested for its antidiabetic activity. A medicinal fungus, *Poria cocos* or *Wolfiporia extensa* Ginns, traditionally known as china root, is used as a folk medicine in China to treat diabetes. The compounds dehydrotumulosic acid, dehydrotrametenolic acid, and pachymic acid were isolated from the chloroform extracts of *P. cocos* (Kim et al. 2019). These three extracts showed different levels of insulin sensitizer activity. Dehydrotumulosic acid exhibits hypoglycemic properties. An alpha-glucose inhibitor, Aspergillusol A, isolated from a marine *Aspergillus*, has alpha-glucosidase inhibition property (Ingavat et al. 2009). Other compounds such as ternatin isolated from mushroom suppress hyperglycemia (Kobayashi et al. 2012). Few fungal isolates were studied, which act as DPP-4, alpha-glucosidase, and alpha-amylase inhibitors.

7.5.9 Fungicides and Insecticides

Fungal pathogens are responsible for some of the most devastating crop infections. They destroyed about a third of food crops annually, causing grave loss of economy. As per the Food and Organization of the United Nations, in 2009–2010, fungi induced losses in five staple crops, namely rice, wheat, maize, potato, and soybean. Similarly, insects destroy farm produce and can lead to famine. Fungal bioactive metabolites can be used as fungicides and insecticides to mitigate the losses (Rana et al. 2019b; Singh et al. 2020; Yadav et al. 2020c).

Strobilurins are a class of fungicides derived from β-methoxyacrylic acid. These are isolated from the Basidiomycetes genera that include *Crepidotus*, *Cyphellopsis*, *Filoboletus*, *Hydropus*, *Mycena*, *Oudemansiella*, *Strobilurus*, and *Xerula* and an ascomycete *Bolinea lutea* (Cooper et al. 2020). Strobilurins are effective against phytopathogenic fungi at concentrations as low as 10^{-8} to 10^{-7} M and exhibit

minimal toxicity to mammalian cells (Cooper et al. 2020). Strobilurins prevent mycelial growth and spore germination by blocking the electron transport chain and suppressing fungal cell respiration. Strobilurins are single-target compounds, and thus plant pathogenic fungi have quickly developed resistance to them within 2 years of introducing them in the market. Nodulisporic A isolated from *Nodulisporium* sp. is an effective insecticide against fleas, where it blocks the glutamate-gated ion channel in invertebrates (Smith et al. 2000). Its analog N-tert-butyl nodulisporamide is administered orally to dogs and cats to control fleas and ticks. Kresoxim-methyl from BASF is another popularly used strobilurin fungicide available as mixture with other fungicides. For instance, to tackle fungal infection on cereals, kresoxim-methyl and fenpropimorph or epoxiconazole are used in combination, which are sold as Brio® and Allergo®, respectively (Aly et al. 2011). Azoxystrobin is a strobilurin fungicide from Zeneca registered for use on 55 crops in about 49 countries and marketed under the brand names Amistar® for cereals, Quadris® for grapevines, and Heritage® for turf (Camargos et al. 2016).

7.5.10 Immunosuppressants

Immunosuppressants are drugs that suppress the activity of the immune system. Immunosuppressive drugs are used to prevent rejection during organ transplantation and suppress allergic reactions, autoimmune disorders, and uncontrolled inflammation that might damage tissues and organs. Mizoribine (MZB), an imidazole nucleoside known by the generic name Bredinin, is an immunosuppressive drug isolated from fungus *Penicillium brefeldianum*. It is used in the treatment of lupus, IgA neuropathy, rheumatoid arthritis, and other rheumatic diseases. It is also used during renal transplantation, since compared to other immunosuppressive drugs, MZB is less toxic and has no drawbacks. MZB inhibits the synthesis of guanine nucleotide by inhibiting the activity of inosine monophosphate synthetase and guanosine monophosphate synthetase. It suspends DNA synthesis in S-phase of the cell cycle (Yokota 2002). Cyclosporine is a widely used class of immunosuppressants isolated from *Tolypocladium inflatum* (Yang et al. 2018). Using cyclosporine in organ transplantation surgery to prevent the rejection of bone marrow and in heart, kidney, and liver transplantation has been a revolutionary success, increasing the survival rates in transplant patients (Chinen and Buckley 2010).

Cyclosporines prevent cell apoptosis by binding with cyclophilin D, an integral part of mitochondrial permeability transition pore that regulates cell necrosis. This property of cyclosporines makes them the drug of choice in the treatment of neurodegenerative disease, cardiac hypertrophy, trauma, and ischemia–reperfusion injury (Yang et al. 2018). The binding of cyclosporine with cyclophilin D inhibits the activity of calcineurin, a protein phosphatase that activates T cells. Cyclosporines are the first class of nontoxic immunosuppressants that can selectively immunoregulate T cells (Yang et al. 2018). Gliotoxin, an anti-inflammatory drug, was isolated from fungal species such as *Aspergillus* sp. and *Gliocladium fimbriatum.* It is

an immunosuppressive drug that prevents apoptosis in neutrophils, eosinophils, granulocytes, macrophages, and thymocytes. Gliotoxin prevents an inflammatory response and release cytokines by inhibiting the activity of nuclear factor-κB (NF-κB) (Fraga-Silva et al. 2019).

7.5.11 Miscellaneous Activity

In traditional medicines, fungi have been used to cure several health ailments. *Cordyceps sinensis* was discovered 2000 years ago in China in the Qing dynasty. Ethnomedical reports suggest that *C. sinensis*, an aphrodisiac, has antioxidant properties and down regulates apoptotic genes (Shashidhar et al. 2013). *G. lucidum* has also been used as a folk medicine in China, Japan, and South Korea. Extracts from *G. lucidum* have shown immunomodulatory effects that impact cancer cells. Apart from this, *G. lucidum* extracts have antiviral, antibacterial, and antitumor agents. Endophytic fungi have long been used for sustainable agriculture by developing a symbiotic plant–microbe interaction (Singh and Yadav 2020; Verma et al. 2017). Endophytic fungi can produce bioactive secondary metabolites such as iron chelators, flavonoids, phenolic acids, steroids, alkaloids, coumarin, quinones, lignans, peptides, terpenoids derivatives, phosphate solubilizers, insecticides, and nitrogen fixation compounds, which benefit the plant host (Rao et al. 2020; Kour et al. 2019a; Rana et al. 2019c, 2020). For instance, endophytic fungi *Gliocladium catenulatum*, inhabiting in Cacao seedlings, releases bioactive metabolites that act as insecticides. Endophytic fungi *Fusarium solani* inhabiting *Rheum palmatum* synthesize rhein, a potent antimicrobial compound. Fungi are also used for biotransformation of steroids commercially as they are comparatively feasible than chemical methods. Fungal biotransformation of steroids includes reactions such as hydroxylation, dehydrogenation, and sterol side-chain cleavage. *Aspergillus* species are used in the preparation of rostanes by degrading the C-17 saturated side chain of the sterol. Fungi such as *yeasts, Candida,* and *Rhodotorula* are used in the production of industrially important products such as amino acids, ethanol, enzymes, recombinant protein insulin, and vitamins. Further source and application of fungal secondary metabolites have been mentioned in Table 7.1.

7.6 Conclusion and Future Prospects

Fungi are the microorganisms that can inhabit extreme environmental conditions and are a reservoir of bioactive secondary metabolites. Their commercial production is still at a slow pace, and alternative methods for upscaling are the need of hour. Fungal fermentation has a great scope for producing therapeutic proteins, enzymes, and recombinant proteins. The fermentation process needs to be optimized to increase the production yield and find an economical method to purify the

Table 7.1 Source and application of fungal secondary metabolites

Drug/drug lead	Source	Uses	Reference
Lucidenic acid N	*Ganoderma lucidum*	Anticancer drug	Wu et al. (2001)
Poricoic acid G	*Poria cocos*	Anticancer drug	Ukiya et al. (2002)
Psilocybin	*Psilocybe mexicana*	Psychedelic drug	Passie et al. (2002)
Mizoribine	*Fusarium subglutinans*	Immunosuppressant	Yokota (2002)
Ganodermadiol, lucidadiol, applanoxidic acid G	*Ganoderma pfeifferi*	Antiviral	Mothana et al. (2003)
Cephalosporin	*Cephalosporium acremonium*	Antibiotic	Schmitt et al. (2004)
Ganoderic acid β	*Ganoderma lucidum*	Antiviral	Li and Wang (2006)
Pravachol	*Penicillium compactum*	Antilipidemic	Endo (2010)
Fingolimod	*Isaria sinclairii*	Multiple sclerosis	Chun and Brinkmann (2011)
Endocrocin	*Aspergillus*	Immunosuppressant	Lim et al. (2012)
Asparaginase	*Penicillium digitatum*	Anticancer drug	Shrivastava et al. (2012)
Zhankuic acid A	*Antrodia camphorata*	Anticancer drug	Lee et al. (2012)
Lentinan	*Lentinula edodes*	Anticancer drug Antilipidemic	Ina et al. (2013)
Nigrosporin B	*Nigrospora*	Antibiotic	Wang et al. (2013)
Caspofungin	*Glarea lozoyensis*	Antifungal	Maiolo et al. (2014)
Anidulafungin	*Aspergillus*	Antifungal	Maiolo et al. (2014)
Mycophenolic acid	*Penicillium stoloniferum*	Immunosuppressant	Patel et al. (2016)
Lysergic acid	*Claviceps purpurea*	Psychedelic drug	Das et al. (2016)
Proliferin	*Aspergillus proliferans*	Antibiotic	Woappi et al. (2016)
PGG glucan	*Saccharomyces cerevisiae*	Antitumor	Bashir and Choi (2017)
SSG glucan	*Sclerotinia sclerotiorum*	Antitumor	Bashir and Choi (2017)
Polysaccharides	*Ganoderma lucidum*	Antitumor	Li et al. (2018)

end product. The biosynthetic gene clusters (BGCs) in fungi are untapped. Researchers must explore bioinformatics tools and techniques to study the fungal secondary metabolomes to capture, characterize, and synthesize bioactive metabolites. Current challenges in fungal secondary metabolite research include replicating the existing BGC cluster, expressing proteins from cryptic BGC, and identifying BGC from unknown genes. Investigations on genomic, proteomic, and metabolomic can help gather the knowledge necessary for the future development of fungal secondary metabolites on the industrial level.

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