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FUNGI: A POTENTIAL SOURCE OF BIOPHARMACEUTICALS

Umar Farooq Gohar [1],*, Hamid Mukhtar [1], Amir Mushtaq [2], Ayesha Farooq [1], Farooq Saleem [3], Malik Asif Hussain [4] and Muhammad Usman Ghani [5]

[1]Institute of Industrial Biotechnology, Government College University, Lahore 54000, Pakistan,
[2]Ghulab Devi College of Pharmacy, Lahore 54000, Pakistan,
[3]Faculty of Pharmacy, The university of Lahore, Lahore, Pakistan,
[4]College of Medicine, University of Hail, Hail, Kingdom of Saudi Arabia,
[5]Pharmacy Department Jinnah Hospital Lahore, Pakistan.

*Corresponding Author: dr.mufgohar@gcu.edu.pk

ABSTRACT

This review is related to important antibacterial, antimycotic, antilipemic, immunosuppressive or immunomodulator and anti-tumor agents that occur naturally in various fungi, including marine fungi, endophytic fungi, soil fungi and environmental fungi. The purpose of this assessment is to show the drugs produced by fungi and the use of these drugs for pharmaceutical purposes. Right after the discovery of the first β-lactam antibiotic, penicillin, fungi have become the source of modern medicine including several important antibiotics to treat potentially deadly infections. With the discovery of new fungi and their fungal metabolites, began a new era in immuno-pharmacology and organ transplantation. The advancements and developments of medicines from natural products not only play a vital role in therapeutic applications of these active secondary metabolites but they also play a role in semi-synthetic modifications of natural products to improve their activity and to synthetically develop their structural imitations. So, it is concluded that the fungi are the potential source of the secondary metabolites and biopharmaceuticals.

Keywords: Marine-Derived Fungi, Fungal Metabolites, Natural Products, Anti-Cancer

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INTRODUCTION

The increasing number and worldwide distribution of resistant pathogens to antimicrobial drugs is potentially one of the greatest threats to global health, leading to health crises arising from infections that were once easy to treat. Infections resistant to antimicrobial treatment frequently result in longer hospital stays, higher medical costs, and increased mortality (Hay et al. 2018). Natural products are organic compounds formed by living organisms in response to external stimuli such as nutritional changes, infection and competition. Plants, animals, insects, fungi, bacteria and protozoans produce many biologically active natural products that have been isolated and used in pharmaceutical drug discovery and design (Rollinger et al. 2006).

The kingdom Fungi contains five noteworthy phyla that were established as indicated by their method of sexual reproduction. The five genuine phyla of fungi are the Chytridiomycota (Chytrids), the Zygomycota (conjugated organisms), the Ascomycota (sac parasites), the Basidiomycota (club organisms) and the lately described Phylum Glomeromycota (Carroll et al. 2011). Yeasts, molds, rusts, mushrooms, muck, puffballs, truffles, morels, and molds all belongs to Kingdom Fungi. More than 70,000 types of fungi have been discovered so far. Like plants and animals, fungi consist of an independent group. They live everywhere in the air, water, soil, and on land, or in plants and animals. Some of them are microscopic and some are macroscopic as much as reaches out for more than a thousand acres. The kingdom Fungi is a one regarding the most diverse amongst the groups of organisms on Earth and they are fundamental biological community agents that represent soil carbon cycling, plant, nutrition of plants and pathology. Fungi are in a wide assortment of sizes and forms and have great economic significance (Blackwell 2010).

There is a need to look new environmental specialties for capability of normal bioactive operators for numerous industrial, agricultural and pharmaceutical application; these must be certainly obtainable as well as eco-friendly, in the pursuit of new drugs, playing a vital role in the discovery of bioactive compounds. With this, bioactive compounds on a large scale has been obtained from different species including the micro-organisms such as fungi, bacteria and plants. For the treatment of certain diseases, bioactive compounds have been used (Aharwal et al. 2016).

Pharmaceutically, fungi have been a gold mine of leading compounds in antibiotic discovery. With the discovery of penicillin isolated from *Penicillium notatum* by Fleming in the autumn of 1928, which he reported in 1929,

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medicinal chemistry is revolutionized after a lengthy gestation period. In addition, the outburst of the Second World War amplified the urgency with which the study was carried on to success. The production of penicillin had been increased by 1940 and sufficient material was used for the first human trial in February of 1941, which resulted in a breakthrough in the treatment of bacterial infections. After the exciting discovery of penicillin, more attention of pharmaceutical companies and academic laboratories was laid on fungi as a basis of lead compounds. Thus, fungi became a dynamic source of drug discovery for the treatment of various diseases (Butler 2005).

Fungi are one of the most diverse life forms on this planet. After decades of research on fungal endophytes, it is now clear that they are unexceptionally present in all taxonomic groups of the plant kingdom, vegetation types (alpine to tropical), and ecological types (hydrophytes to xerophytes) in great diversity (Arnold et al. 2000; Persoh 2013). It became evident that endophytes are rich sources of bioactive natural products and many different agents have been isolated from these microorganisms with promising applications in development of natural drugs and other industrial products. According to Berdy (2005) more than 20,000 bioactive metabolites are of microbial origin. Fungi are among the most important groups of eukaryotic organisms (Fig. 1) that are well known for producing many novel metabolites which are directly used as drugs or function as lead structures for various bioactive products. The success of several drugs such as the antibiotic penicillin from *Penicillium sp.*, the immunosuppressant cyclosporine from *Tolypocladium inflatum* and *Cylindrocarpon lucidum*, the antifungal agent griseofulvin from *Penicillium griseofulv*um fungus, the cholesterol biosynthesis inhibitor lovastatin and statin from *Aspergillus terreus*, *Aspergillus fumigatus* and β-lactam antibiotics from various fungal taxa, has shifted the focus of drug discovery from plants to these microorganisms (Stadler and Keller 2008; Subhan et al. 2016; Ajdidi et al. 2020).

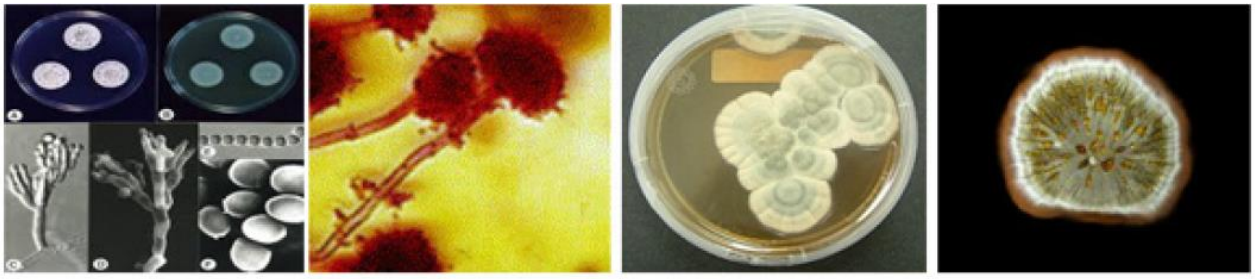

Fig. 1: Fungi, mycelium and thallus like bodies: A) *Penicillium griseofulvum*, B) *Penicillium chrysogenum,* C) *Penicillium citrinum* and D) *Aspergillus terreus* (Yousaf et al. 2019).

1. ANTIBIOTICS

Antibiotics are the substances being produced by the microorganisms and used to kill the pathogenic or infectious microbes in specific concentrations such as beta lactam antibiotics, chloramphenicol fusidic acid etc. Some important antibiotics produced by fungi and their mechanism of action has been shown in the Table 1.

Table 1: Antibacterial drugs produced by fungi

Drugs name	Inhibition Site	Fungi	References
Penicillin	Cell wall synthesis	*Penicillium chrysogenum*	Berdy (2005)
Cephalosporin	Cell wall synthesis	*Cephalosporium acremonium*	Berdy (2005)
Gentamicin	Protein synthesis	*Micromonospora purpurea*	Himabindu and Jetty (2006)
Fusidic acid	Protein synthesis	*Fusidium coccineum*	Dobie (2004)
Helvolic acid	Protein synthesis	*Aspergillus fumigatus*	Al-Fakih and Almaqtri (2019)
Patulin	Biofilm inhibition	*Aspergillus giganteus*	Al-Fakih and Almaqtri (2019)
Terric acid	Cell wall synthesis	*Aspergillus terreus*	Brian (1951)

1.1. Penicillin

Alexander Fleming in 1929 discovered the antibacterial consequence of penicillin. He mentioned that the agar plate streaked with *Staphylococcus aureus* had grown a fungal contaminant; he observed that the colonies of *Staphylococcus aureus* around that fungal contaminant were transparent due to cell lysis. Later, fungal contaminant was recognized to be *Penicillin notatum* and the antibiotic was named as penicillin which was effective again many Gram-positive bacteria (Ligon 2004). Fleming had given a major part of his career in discovering strategies for resolving wound diseases, and instantly perceived significance of fungal metabolites that is used to control the threshold level of microbes. Because of the instability, Fleming was unable to purify the compound even used crude

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he preparations from culture filtrates to control eye infections. Later, the two renowned British scientists, Mr. Florey and Mr. Chain, work together and figured out how to produce penicillin for a widespread use on an industrial level. Nobel Prize was also share among the three scientists for their work on penicillin (Diggins 1999). It is nevertheless a "frontline" antibacterial, however, the effectiveness of various penicillin resistance pathogenic bacteria has lower down the effect of it.

Penicillin produced from *Penicillium chrysogenum* in 1941 become first used efficaciously to deal with a bacterial infection. Utilization of penicillin revolutionized the cure regarding pathogenic disease (Wong 2003). Numerous pathogenic bacteria ended up noticeably treatable, and new types of therapeutic mediation were viable. The concentration of active substance in penicillin was around 1 microgram for every ml of broth solution at that time when penicillin was first produced. Today enhanced strains and incredibly evolved fermentation techniques gives more than 700 micrograms for every ml of broth solution. Numerous closely related particles were present in the early broth. These particles are beta lactam rings melded to five-member thiazolidine rings, along a side chain (Kardos and Demain 2011) as also shown in Fig. 2. Chemical modification to the side chain may give somewhat unique properties to the compound. The natural penicillin's have a range of disadvantages. They are demolished by the acidity of the stomach, thus can't be taken orally, however it is injectable. They are highly delicate in conformity with beta lactamases enzyme, as evolved with the resistant bacteria, consequently lowering their efficiency (Ligon 2004).

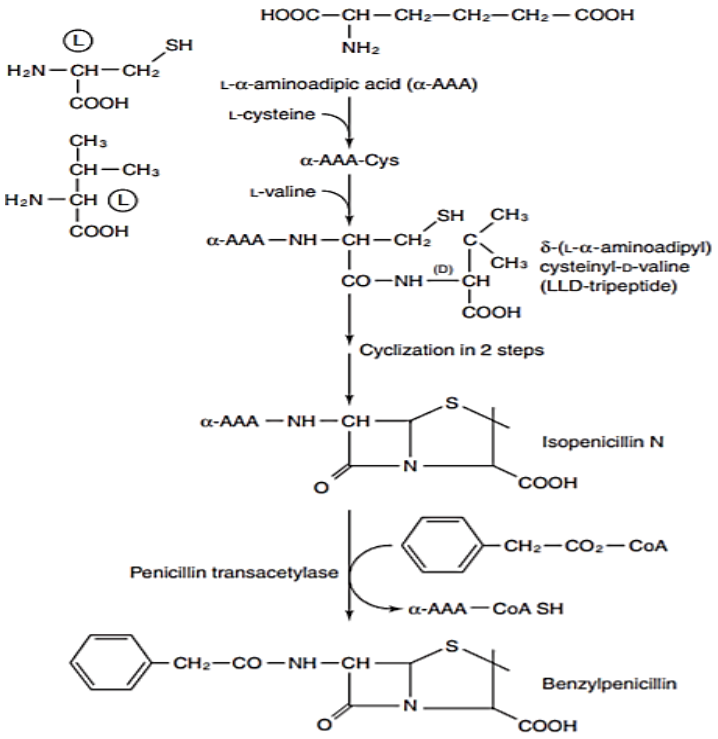

Fig. 2: Biosynthesis of Penicillin in *Penicillium chrysogenum* (Nigam and Singh 2014).

1.2. Cephalosporins

In 1948, an Italian scientist Giuseppe Brotzu isolated *Cephalosporium* from a sewer outlet off the coast of Sardinia (Bo 2000). The first classical example of β-lactam antibiotic is cephalosporin C which is obtained from a marine fungus, *Cephalosporium acremonium* (Blunden 2001). The natural cephalosporin was never used clinically, but analogues were prepared with better antibacterial activity. There have been multiple generations of cephalosporins, each with improved activity and applications. The mode of action of cephalosporins is very much alike to penicillins although their chemical structures differ due to which their antibacterial activity also differs. Cephalosporins also have beta lactam ring. The basic molecule (7-aminocephalosporanic acid) was produced by fungus *Cephalosporium acremonium*, hence the name cephalosporins (Khudyakova et al. 2004). Modification in the basic molecule give rise to in four generations of cephalosporins.

The first-generation include cefazolin, cephalothin, and cephalexin having a range of antibacterial activity and are operative against most *staphylococci* and *streptococci* in addition to penicillin-resistant *pneumococci*. The second-

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generation include cefamandole, cefaclor, cefotetan, cefoxitin, and cefuroxime have a broad-spectrum that consist more activity against additional species of gram-negative rods. In this manner, these antibiotics are effective against many coliforms. However, many strains of coliforms have developed resistance. The third-generation include ceftriaxone, cefixime, and ceftazidime are more susceptible against the gram-negative organisms as compared with the second-generation cephalosporins. Most *Enterobacter* species, *Hemophilus Influenza* and various species of *Neisseria* are sensitive against these drugs (El-Shaboury 2007). The spectrum of the fourth-generation cephalosporin i.e. cefepime is similar to that of third-generation drugs; however, the fourth-generation tablets are more resistant against β-lactamases (Chaudhry 2019).

1.3. Gentamicin

Gentamicin is extremely active drug that works against Gram-negative bacteria and *Mycobacterium tuberculosis*, produced by the genus *Micromonospora*. Gentamicin was introduced in the pharmaceutical market in 1971 (Chen et al. 2014). It is regarded as one of the essential antibiotics listed in World Health Organization. In recent time, gentamycin conjugates have been demonstrated for its anti-viral properties, in addition to its antibacterial properties (Himabindu et al. 2006). Gentamicin has also shown successful results when applied in agriculture (Stockwell and Duffy 2012).

Gentamicin has multiple components, in which gentamicin C complex is regarded as one of the major constituents which includes C-1, C-1a, C-2, C-2a, and C-2b (Boumehira et al. 2016), whereas, minor constituent of gentamicin includes gentamicin A, B, and X. For developing drugs against protozoa, the minor components of gentamicin had been used as a starting material (Hong and Yan 2012). The chemical structure of gentamicin includes a central diaminogenouscyclitol (2-deoxystreptamine (2DOS) 4,6- disubstituted exhibiting bit the secondary sugars garosamine and purpurosamine. To isolate gentamicin from soil for the very first time in New York, Two strains *M. echinospora* NRRL 2953 and *M. echinospora* NRRL 2985 were used (Piepersberg et al. 2007). One of the major complications in increased productivity of Gentamicin is thought to be the composition of the cell wall of *Micromonospora spp*, which prevents the release of gentamicin into the liquid media.

1.4. Fusidic Acid

Fusidic acid (FA) is an antibacterial drug produced from fungi *Fusidium coccineum*. Fusidic acid was produced by the fungus *Fusidium coccineum* on a medium containing (3RS,4R)-(2-^{14}C, 4-^{3}H)-mevalonic acid (MVA). The 6 ^{14}C atoms and 4 tritium atoms was shown by the obtained Fusidic acid (Yaohui et al. 2018). Fusidic acid is usually prescribed in microbial infection caused by methicillin-resistant *Staphylococcus aureus* strains (Curbete and Salgado 2015).

Fusidic acid is also used in the treatment of some other bacteria such as *Corynebacteria*, *Nocardia* and *Neisseria* Gram negative species. Fusidic acid acts by binding to the ribosome elongation factor G and prevents elongation of the polypeptide chain thereby inhibiting dissociation of the EF-G ribosome. FA is effective in prokaryotes due to the presence of only one elongation factor; however, eukaryotes have many other factors that are not suppressed by fusidic acid (Falck et al. 2006). Fusidic acid provides high anti-*staphylococcal* activity (Falagas et al., 2008). Two different strains of fungus *Fusidium coccineum* were used to study association between values of intracellular pH using the ^{31}P-NMR spectroscopy, the study concluded that the difference in intracellular pH is actually responsible for the action of enzymes in cells could be considered a factor for the cyanide-resistant respiration path function and, therefore, the production of fusidic acid in *F. coccineum* (Shipanova et al. 1995).

2. ANTIFUNGAL DRUGS

Fungi are the one of the notorious microorganisms as they can cause serious illness in humans and other organisms such Candidiasis, aspergillosis, ring worm etc. These fungal infections can be treated by the compounds produced by the fungi. Some of the important antifungal compounds, their source of production and mechanism of action has been shown in the Table 2.

Table 2. Antifungal drugs produced by fungi

Drug	Inhibition Site	Fungi	References
Griseofulvin	Centrosomal aggregation	*Penicillium griseofulvum*	Petersen et al. (2014)
Echinocandin	Cell wall synthesis	*Aspergillus nidulans*	Patil and Majumdar (2017)
Strobilurins	Fungal respiration	*Strobilurus tenacellus*	Balba (2007)
Humicolin	Germination of spores	*Aspergillus humicola*	Brian (1951)
Citrinin	Mycelial respiration	*Aspergillus terreus*	Brian (1951)

2.1. Griseofulvin

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Griseofulvin is a well-known antifungal compound obtained from filamentous fungi, *Penicillium griseofulvin* (Table 2) (Petersen et al. 2014). Multiple other species of fungi has also produced griseofulvin such as *P. urticae, P. raistrickii, P. raciborskii, P. kapuscinskii, P. albidum, P. melinii, P. brefeldianum Aspergillus versicolor* and *Nematospora coryli* (Nigam and Singh 2014). Griseofulvin is an antifungal agent having a broad range spectrum and is fungistatic rather than fungicidal and is used for the treatment of infections of the hair, skin and nails caused by fungi. Hence, interference with the function of microtubules and mitosis (Richardson and Warnock 2003).

Commercially, griseofulvin was presented in 1965 and was later on considered as an anti-cancer agent for the first time in 1973. Later, griseofulvin was found to initiate cell division as well as cell proliferation in HeLa cell line and inhibits the centrosomal aggregation in SCC-114 cell line. The suppression of centrosomal aggregation in SCC-114 cells was increased to 25-fold by synthetic analog GF-15. Furthermore, it was found that the combined therapy of griseofulvin and nocodazole (chemotherapeutic agent) enhanced the effectiveness of anti-microbial drug nocodazole and cancerous growth of affected mice (i.e COLO 205 tumors) is prevented (Petersen et al. 2014). Griseofulvin is produced commercially with mutant strains of *P. patulum, P. raistrickii*, or *P. urticae*. For attaining higher production methyl donors such as choline salts, methyl xanthate, and folic acid can be further added in the culture medium (Nigam and Singh 2014).

2.2. Echinocandins

Echinocandins are considered as a first-line agent for invasive candidiasis and candidemia. In 1970s, Ciba-Giegy, Sandoz and Eli Lilli separated the primitive echinocandin-type antimycotic (echinocandin B) from "*Aspergillus nidulans var. echinolatus*", "*Aspergillus nidulans var. roseus*" and *Aspergillus rugulosus* through fermentation (Emri 2013). The echinocandins contains caspofungin, micafungin, and anidulafungin which are the secondary metabolites, produced by ascomycotic fungi (Yue et al. 2015). Later, over 20 natural Echinocandins were isolated. The biosynthesis of the cyclic lipohexapéptidos occurs by non-ribosomal complex peptide synthase in different ascomycotic fungi. Their mode of action is unique; since the uncompetitive inhibitors of the β-1,3-glucan synthase complex is directed towards fungal cell wall. Currently three cyclic lipohiexapéptidos (micafungin, caspofungin and anidulafungin) are appropriate for use in clinics.

The echinocandins are narrow-spectrum antifungal agents that are limited to *Candida* spp. and *Aspergillus* spp. and there is slight difference amongst the individual drugs. All echinocandins have fungicidal effect against *Candida* spp.; but, in *Aspergillus* spp. these agents persuade abnormal morphologic hyphal growth instead of complete inhibition of growth thus considered as fungistatic (Falk et al. 2003).

In vitro, the echinocandins possess high activity against *C. glabrata, C. dubliniensis, C. albicans, C. tropicalis* and *C. krusei*. They show somewhat less activity against *C. guilliermondii, C. parapsilosis* and *C. lusitaniae* and MIC values are characteristically high for these pathogens than other *Candida* spp. Generally, they are very active against *A. fumigatus, A. flavus* and *A. terreus* (Asada et al. 2006). The echinocandins also show activity against *Pneumocystis jirovecii*. In vitro they also have modest activity against dimorphic fungi including *H. capsulatum, C. immitis* and *B. dermatitidis*, but still they are not considered to be clinically useful. The echinocandins have little or no activity against *C. neoformans, Fusarium* spp., *Trichosporon* spp. or zygomycosis (Uzun et al. 1997).

Echinocandin B (BCE), a fermentation product of *nidulans* and the starting point for the development of new antifungal drug anidulafungin. The ECB was discovered in 1974 as the first representative of the echinocandins. It is known as one of the natural cyclic hexapeptides having a side chain of linoleoyl. The ECB has shown a potent activity against *Candida tropicalis* and Candida albicans and in vivo activity has been demonstrated in an animal model of candidiasis. In recent decades, both the incidence and types of fungal infections that are severely damaging to human health have increased continuously, especially for immunosuppressed patients (Hof and Dietz 2009).

2.3. Strobilurins

The main natural strobilurins comprising strobilurin are strobilurins A and B, were initially isolated from *Strobilurus tenacellus* (Table 2), a basidiomycete mycelium. *Strobilurus tenacellus* is an edible agaric mushroom that is normally grown in degrading cones of Puru. These compounds do not show antibacterial actions that suppress the growth of multiple filamentous fungi and yeasts. The strobilurines is ß-methoxyacrylic acid derivate like Strobilurus, xerula, Oudemansiella, Crepidotus, Hydropus, Filoboletus, Mycena and Cyphellopsis and Bolinealutea an Ascomycete. They showed an effective fungicidal activity against phytopathogenic fungi, at a minimum concentration of 10^{7}-10^{8} M and could be used for the production of fungicides in the field of agriculture (Anke 1995).

The above agents produce their effects by inhibiting the respiratory system of the fungal cells. More specifically, they adhere to the bcl-segment of cytochrome of mitochondrial ubiquinol oxidation center, thereby inhibiting the electron transfer which results in inhibition of spore germination and mycelial growth (Dayan et al. 2009). Strobilurin can adheres to the ubiquinol-oxidation center (Qo-site) of the cytochrome bc1-enzyme complex (III complex), and is considered to be the most essential class of fungicides and inhibitors agriculture, a broad-spectrum antifungal activity and less toxicity to cells of eukaryotic cells (Liu et al. 2016).

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3. CHOLESTEROL-LOWERING DRUGS

Cholesterol is an important compound of the human metabolism. It is very important both structurally and functionally. The level of the cholesterol remains within certain limits. An increase cholesterol level leads to condition called hypercholesterolemia which can cause serious effects in the body. There are many drugs produced by the fungi that can reduce the increased level of cholesterol, some of them has been shown in the Table 3.

Table 3: Cholesterol-lowering drugs produced by fungi

Products	Mode of action	Fungi	References
Lovastatin	Prevent hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase	*Aspergillus terreus*	Tobert (1987)
Compactin		*Penicillium citrinum*	Chung (2001)
Statins	Inhibit HMG-CoA reductase	*Aspergillus terreus*	Subhan et al. (2016)
Lovastatin	Inhibit of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase	*Aspergillus terreus*	Boruta and Bizukojc (2017)
Itaconic acid	Conversion of cis-aconitate to itaconate by an enzymatically catalyzed decarboxylation		
Lovastatin	HMG-CoA reductase inhibitor	*Monascus purpureus*	Seenivasan et al. (2018)

Hypercholesterolemia is known to be hazardous for human health as it is delirious effect on heart. Thus, an effective way to control cholesterol level is to control de novo synthesis which is the main substance of the entire human body cholesterol. Hydroxymethylglutaryl-coenzyme is the enzyme which is firstly used in cholesterol biosynthesis and is inhibited by fungal secondary metabolites, statins (Rollini 2002). The mechanism associated with the control of cholesterol, makes statins reasonable for therapeutic purpose (Chong et al. 2001).

The statins are the largest selling class of drugs throughout the world. Sales for statins in 2005 were $25 billion (Endo 2010; Taylor et al. 2013). In addition to the ability to reduce the risk of cardiovascular morbidity and mortality, statins can also prevent and reduce the development of peripheral vascular disease (Maron et al. 2003).Various species of the genus *Monascus* and strains of *Aspergillus terreus* are involved in the synthesis of natural statins (Kimura et al. 1990). Synthesis of natural statins also involves other genera of filamentous fungi such as *Penicillin, Eupenicillin, Doratomyces, Hypomyces, Gymnoascus, Trichoderm and pleurotus* (Hosobuchi et al. 1993a). Lovastatin, an anti cholesterolemic drug was made available in the pharmaceutical market by the approval of United Stated Food and Drug Administration (Tobert 1987). Out of all the statins, mevastatin was the first drug discovered and named ML-236B (Endo et al. 1976b). It was separated in 1976 from a strain of *Penicillium citrinum* in (Endo et al. 1977). Later on, lovastatin was synthesized from genus *Monascus*17 strains, which includes particularly *Monascus. purpureus, Monascus. ruber, Monascus. vitreus, Monascus pilosus, and Monascus. Pubigerus* (Negishi et al. 1986).

Corn steep liquor and maltodextrin, a low pace metabolizing nitrogen and carbon sources, produces lovastatin from the *Aspergillus terreus* fungi, and are found to produce better productivity (Sweetman 2009). In comparison to mevastatin and/or compactin production, test on multiple carbon sources were performed, and found fructose, maltose, glucose and glycerol effective for the production of compactin by *penicillium citrinium* (Chung 2001).

Slow metabolizing carbon sources were preferred over fast metabolizing substrates for the production phase, whereas the fast metabolizing substrates were used for the early growth. The carbon substrates and/or sources are essential for maintaining the pH level during the fermentation process. In contrast to nitrogen sources, various aspect of components has been studied including corn steep liquor, peptones, soyabean, meat extract, amicase, yeast extract, $NaNO_3$, fish meal, rice bran etc. (Endo et al. 1977; Ykema and Lindsay 2000). Among the nitrogen sources studied and tested, the yeast extract and corn steep liquor were found to show more part in the production of compactin, which is also known as mevostatin (Konya et al. 1998). The optimum temperature which is suitable for the mevostatin production is taken as 24–28°C (Bazaraa et al. 1998).

Statins are the blend of B-hydroxyacid and lactone. It is converted in vivo into respective β-hydroxyacid. The structural similarity of HMG-CoA with B-hydroxyaid form of statin results in the decreased cholesterol level, which is actually centered on competitive inhibition between the intermediate form of B-hydroxyacid and HMG-CoA form of statins, for the inhibition of HMG-CoA reductase (Gunde-Cimerman et al. 1993). The HMG-CoA reductase takes part in the conversion of HMG-CoA into mevalonate, the main precursor involved in the cholesterol biosynthesis (Alberts 1998). Lovastatin inhibits the production of mevalonate and acts as a competitive inhibitor of HMG-CoA. The affinity of intermediate form of HMG-CoA is less than the affinity of the statins, the Michaelis constant for the HMG-CoA substrate reaction is 4×10^{-6} M, while for lovastatin the inhibition constant of 6.4×10^{-10} M is determined (Arai et al. 1988).

Evidence suggested that statins decrease the manifestation of stroke through various mechanisms including the improved endothelial function, plaque stabilization as well as atherosclerosis progression. Moreover, the decrease of systolic as well as diastolic blood pressure has also been observed through a cold pressor test. This results in the

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vasodilation and lowers the blood levels (Furberg 1999; Ajdidi et al. 2020). The microbial production of statins has provided an excellent therapy for hypercholesterolemia and led to the synthesis of novel statins by chemical synthesis. The use of *A. terreus* to achieve these outcomes is an excellent example of the exploitation of a microbe for useful purposes (Subhan et al. 2016).

4. IMMUNOSUPPRESSIVE DRUGS

Immunosuppressant agents are the drugs that have ability to suppress or reduce, the strength of the body's immune system. Some of these drugs are used to make the body less likely to reject a transplanted organ, such as a heart, liver, kidney etc. Some of the important immunosuppressive agent produced by the fungi has been shown in the Table 4.

Table 4: Immunosuppressive drugs produced by various fungi

Immunosuppressive Drugs	Mode of Action	Fungi	References
Gliotoxin	Inhibit a number of thiol requiring enzymes	*Aspergillus fumigatus*	Coméra et al. (2007)
Mycophenolic acid (meroterpenoid)	Inhibition of inosine 5′-monophosphate dehydrogenase (IMPDH)	*P. brevicompactum*	Patel et al. (2016)
Cyclosporin A (nonribosomal peptide derivative)	Inhibition of calcineurin by making complex with cyclophilins A	*Tolypocladium inflatum*	Bushley et al. (2013)

4.1. Gliotoxin

Gliotoxin is a mycotoxin which is produced by various molds specie specifically the *Aspergillus fumigatus*. Gliotoxin is significant to show cast its immune-suppressive action. Gliotoxin is considered as an epipolythiodioxopiperazine (ETP) with the molecular mass of 326 Da, playing an important part in the virulence of *Aspergillus fumigatus* (Coméra et al. 2007). In a liquid medium with the 37 degrees temperature, *A. fumigatus* strains were incubated to measure the production of gliotoxin. Commonly, the Czapek Dox broth is used to measure the production of gliotoxin in a liquid medium. Once the cultivation has been done, mycelia were separated from the culture filtrates with the help of vacuum filtration (Cramer et al. 2006). The distinguished immunosuppressive properties of gliotoxin, it enables medical sciences to remove those immune cells responsible for the tissue rejection, via the ex- vivo treatment of tissues. Gliotoxin is considered to play an important role in the virulence of *Aspergillus fumigatus* because of its genotoxic, cytotoxic and apoptotic properties. Recent studies suggested that multiple genes, specifically the gli genes, are involved in the production of gliotoxin, for instance, *gliZ*gene, involved in the encoding of Zn_2Cys_6 binuclear transcription factor (Bok et al. 2006).

Gliotoxin has been proved to prevent the thiol requiring enzymes and as well to disrupt the NADPH oxidase activity to inhibit the respiratory bursts in the neutrophils. Gliotoxin mode of action is through the covalent interaction to the proteins (Tsunawaki et al. 2004). A multi gene collection encoder in *Aspergillus fumigatus* contains the enzymatic machinery which is responsible for the metabolism and biosynthesis of gliotoxin (Gardiner and Howlett, 2005). Gliotoxin induces the apoptotic cell death and contribute to the cause of the fungal infections through in vivo production. Gliotoxin also causes the cell shrinkage in filopodia through the significant re-assembly of the actin cytoskeleton (Coméra et al. 2007).

4.2. Mycophenolic Acid (MPA)

Mycophenolic acid can be produced by the solid-state fermentation using the fungus, *Penicillium brevicompactum* (Patel et al. 2016). Mycophenolic acid shows dual action, exhibiting the anti-microbial as well as immunosuppressive properties. Afterwards the solid organ transplantation, taking immunosuppressive procedures as the basis, mycophenolic acid is considered as an antiproliferative drug. To deliver its immunosuppressive properties, mycophenolic acid prevents the synthesis of inosine 5′-monophosphate dehydrogenase enzyme.

Mycophenolic acid inhibits the lymphocyte proliferation and subsequently prevents the precursor for the deoxyribonucleic acid synthesis, thereby blocking the immunoreactions. Mycophenolic acid gastrointestinal toxicity common signs include diarrhea, abdominal pain, and the mucosal changes such as the ulcers formation and the submucosal inflammation (Heischmann et al. 2017). Mycophenolic acid also exhibits the anti-viral properties, and are effective against multiple viruses, including the West Nile, chikungunya virus, yellow fever and as well as HCV (Fang et al. 2017).

4.3. Cyclosporin A

Cyclosporin A (CsA; CAS ID: 59865-13-3), is a distinguished immunosuppressive drug, which was firstly produced in the soil fungus, known as *Tolypocladium inflatum*. Cyclosporin A is considered as a drug which has transformed the organ transplantation to a lifesaving procedure. *Tolypocladium inflatum* is also known to produce some other bioactive secondary metabolities such as diketopiperazines, tolypin, efrapeptins and ergokonin-C

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(Bushley et al. 2013). Ciclosporin A antagonizes the activity of calcineurin, a calcium-dependent serine-threonine phosphatase that dephosphorylates and activates the transcription factor NF-AT (activated T-cell nuclear factor) to stimulate IL2 expression. Therefore, the dephosphorylation of NFAT is inhibited and, as a consequence, the proliferation of IL2-dependent T cells is suppressed. Further, cyclosporine A further interferes with the p38 and JNK signaling cascades (deMattos et al. 2000).

The beneficial effects of cyclosporin A are less specific in the long-term treatment process because of the greater number of side effects, such as neurotoxicity, hepatotoxicity, cytotoxicity and nephrotoxicity (deMattos et al. 2000, Thell et al. 2014). Cyclosporine A exhibits multiple distinguished characteristic, it is considered as greatly hydrophobic compound with at least 07 N-methylated amide nitrogen. The N-methylated amide nitrogen somehow favors the cis-peptide confirmation and also involved in the reduction of hydrogen bonds. For instance, it makes an inhibitory bond with peptidyl-prolyl cis-trans isomerase receptor family and as well with the cyclophilins, thereby considered as a powerful calcineurin blocker.

The depsipeptide sirolimus makes complex with the other immunophilins, for example, the FK506-binding proteins, and then this attaches to the mammalian target of rapamycin (mTOR) and prevents the serine–threonine kinase activity (Thell et al. 2014). To show cast its anti-viral and antifungal properties, Cyclosporine has also shown to weaken the immune response in insects. Cyclosporine is used in the organ transplantation as an immunosuppressant, and is considered as the first immunosuppressive drug that is involved in the T-cells immunoregulation, without showing the toxicity (Butler 2005), and is presently misused in tissue and the organ transplantation surgeries, to avoid rejection following the liver, heart, kidney and bone marrow transplantations. It increases the survival rates in patients with the organ transplantation (Dewick 2006).

5. ANTICANCER DRUGS

Anticancer drug, also called antineoplastic drug, any drug that is effective in the treatment of malignant, or cancerous, disease. There are several major classes of anticancer drugs; these include alkylating agents, antimetabolites, natural products, and hormones. Mangrove associated fungi are also source of anti-cancerous substances (Deshmukh et al. 2018). The fungi have the potential to produce such type of anticancer drugs as shown in the Table 5.

5.1. Taxol

Taxol is widely known as an effective anti-cancerous drug obtained from certain fungi; however, initially it was confined to the bark of yew tree *Taxus brevifolia* (Fukushima et al. 1983). The clinical improvement of Taxol has been overdue as problems related to the production of sufficiently high amounts of taxol. This was understood 20 years after the fact that it was shown that Taxol was created in the same way by the organism *Taxomyces andreanea* and later included *Penicillium raistrickii* (Strobel et al. 1997). In 1990, Taxol was considered as an anticancer medication against an extensive variety of tumors and is the initial vital drug against malignancy (Kawada et al. 2010).

Table 5: Anticancer drugs produced by various fungi

Drugs/Metabolites	Mode of action	Fungi	References
Taxol	Induce G2/M cell cycle arrest	*Taxomyces andreanea*	Strobel (1997)
Scopularides A and B	Inhibit tumor cell lines	*Scopulariopsis brevicaulis*	Kumar et al. (2015)
Terrein	Inducer of apoptosis in breast cancer	*A. terreus*	Liao et al. (2012)
Brefeldin A	Inducer of apoptosis in leukemia	*P. brefeldianum*	Gnagi et al. (2019)
Asperlin	Induce G2/M cell cycle arrest	*A. nidulans*	He et al. (2011)
Sequoiamonascin A and B	Cytotoxicity against tumor cell lines	*A. parasiticus*	Stierle et al. (2003)
Norsolorinic acid	Induce Go/G1 cell cycle arrest	*A. parasiticusand A. nidulans*	Yamada et al. (2012)
Austocystin D	Inhibit growth of human colon carcinoma	*A. pseudoustus*	Wang et al. (2008)
Chloctanspirone A and B	Inhibit tumor cell lines	*P. chrysogenumor P. rubens*	Samson et al. (2011)
Chondrosterin	Cytotoxicity against tumor cell lines	*Chondrostereum spp.*	Li et al. (2014)
Penicimutanolone, penicimutanin A, penicimutanin B and Penicimutatin	Cytotoxicity against tumor cell lines	*Penicillium purpurogenum*	Fang et al. (2014)

In 1990, Taxol was considered an anti-cancer drug against a wide variety of cancers and is the first essential cancer drug. Taxol acts by capturing the cell cycle in the G2 / M stage and, furthermore, promotes apoptosis through a remarkable method of activity through the promotion and adaptation of the tubulin polymerization. Taxol has improved tubulin polymerization in an in vitro structure using bovine filtered bovine tubulin without GTP, which is

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typically required. These polymerized microtubules were therefore stable at low temperatures and calcium, conditions that depolymerize ordinary microtubules (Schiff et al. 1979).

Taxol has reassembled the microtubules of the cytoskeleton for several reasons. In the first place, the proliferation will be inhibited, secondly, the cells will not be able to migrate elsewhere, and thirdly, the huge microtubule bundles will be clearly visible (Schiff and Horwitz 1980). The characteristic of the treatment with Taxol is considered the stable formation of microtubule bundles and is observed first in patients with the condition of the white blood cells treated with the drug Taxol. Taxol is widely used in the treatment of pulmonary, ovarian, mammary and Kaposi's sarcoma. In addition to anticancer activity, taxol also has antifungal properties (Stierle et al. 1993).

The generic name of taxol is paclitaxel. The US Food and Drug Administration has approved two drugs for the treatment of cancer, which are semi-synthetic molecules derived from Toxol, namely cabazitaxel and taxotere (Golden et al. 2014). Cabazitaxel is effective in the treatment of hormone-insensitive prostate cancer, while Taxotere demonstrates its effectiveness in the treatment of breast cancer. The Food and Drug Administration has approved Abraxane as an essential first-line drug in patients with metastatic pancreatic adenocarcinoma, grouped with gemcitabine (Wani and Horwitz 2014).

5.2. Scopularides A and B

Scopulariopsis brevicaulis LF580 produces cyclodepsipeptides scopularides. This fungus was obtained from a marine sponge *Tethya aurantium* (Kumar et al. 2015). The basic media for the growth of *Scopulariopsis brevicaulis* was described by Wickerham naming Yeast Malt Peptone (YMP, containing 3 g yeast extract L^{-1}, 3 g malt extract L^{-1} and 5 g soy peptone L^{-1}) (Tamminen et al. 2014). Another medium that is a variant of Wickerham-solid medium, called WSP30 (with the composition as follows: 1% glucose, 0.5% soy peptone, 0.3% malt extract, 0.3% yeast extract, 3% NaCl) is used for the culture of *Scopulariopsis brevicaulis* (Kramer et al. 2006). The genomic DNA from *S. brevicaulis* was prepared using liquid nitrogen. The mycelium was frozen in liquid nitrogen, pulverized and incubated in equal volumes of lysis buffer (10 mM Tris-HCl, 1 mM EDTA, 100 mM NaCl, 2% SDS, pH 8.0). After centrifugation, the supernatant was treated with RNase and then with an equal volume of phenol / chloroform (1:1). The two cyclodepsipeptides scopularides A and B produced by *S. brevicaulis* LF580 are able to inhibit the growth of pancreatic tumor cell lines (Colo357, Panc89) and colon tumor cell line (HT29) (Yu et al. 2008). These data suggest that *S. brevicauli* strain LF580 is capable of producing potentially anti-cancer compounds, which imposes the immediate importance of characterizing the genes involved in the production of biologically active compounds. Brefeldin A, terrain and asperlin, are three polyketides, known to exhibit the anti- cancerous properties. Since 1935, *Aspergellius terreus* is known to produce Polyketide terrein (Zaehle et al. 2014).

5.3. Terrin

After it was discovered that the terrein prevents breast cancer from the onset of apoptosis with an IC50 estimate of 1.1 nM in the MCF-7 cells, the terrein is considered to be 100 times stronger than taxol. A dynamic site against hepatic and pancreatic cells HepG2 (IC50 66.8 µM) and PANC-1 (IC50 9.8 MU) was also discovered (Liao et al. 2012).

5.4. Brefeldin

Another antifungal polyketide was decoupled from *Penicillium brefeldianum* in 1958, known as Brefeldin which was for almost 40 years after the fact that it induces apoptosis in colon (HT-29), leukemia (HL-60 and K-582), breast cancer (MCF-7 and BC-1), cervical (KB) and HeLa), prostate (DU-145), and lung disease cell lines (SPC-A-1 and NCI-H187) (Gnagi et al. 2019).

5.5. Asperlin

In 1966, Asperlin produced by the fungi *Aspergillus nidulans* while in 2011, it was revealed that asperlin is involved in the reduction of proliferation of cells and it induces the G2/M cell cycle in the individual cervical carcinoma HeLa cells (He et al. 2011).

5.6. Sequoiamonascin A

Specific cytotoxicity was shown against two melanoma cell lines and six leukemic cell lines with an estimated (IC50) log10 development mean inhibition - 6.00. In addition, it shows the toxic properties against lung disease NCI-H460, breast cancer cells MCF-7 and nervous system (CNS) central lines of tumor cells SF-268 cells, in which growth of cells can be condensed to 1-2 % treating with 10 µM of AN sequence (Stierle et al. 2003).

5.7. Norsolorinic Acid

Norsolorinic acid is produced by two structures including the *Aspergillus nidulans* and *Aspergillus parasiticus*, having a tricyclic structure. Norsolorinic acid begin, in particular, the capture of the cell cycle in the phase G0 / G1-

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cell cycle period and begins MCF-7 promptly initiates apoptosis in breast tumor MCF-7 and bladder malignancy T-24 with IC50 estimations of 12.7 and 10.5 µm (Yamada et al. 2012).

5.8. Austocystin D

In 1974 Austocystin D was produced by fungus *Aspergillus pseudoustus* (initially mistakenly identified as *Aspergillus ustus*). Specific Austocystine D has been shown to suppress the development of tumor cell lines and human colon carcinoma LS174T cells in mice that express the multidrug protection related protein. Furthermore, this drug restrained various malignancy cell lines: U-87 (brain, GI50 4946 nM), SR (leukemia, GI50 16 nM), MCF-7 (breast, GI50 < 1 nM), MDA-MB-231 (breast, GI50 549 nM), SW-620 (colon, GI50 27 nM), PC-3 (prostate, GI50 3 nM), MX-2 (uterine, GI50 3358 nM) and HCT-15 (colon, GI50 42 nM) (Wang et al. 2008).

5.9. Chloctanspirone A and B

Chloctanspirone A and B are produced from *Penicillium rubens* or *Penicillium chrysogenum* (Originally published by mistake as *Penicillium terrestre*). These were the most important chlorinated form of sorbicillinoids that had been separated by a characteristic source and were the first to deal with their exceptionally interesting ring like structure. Chloctanspirone A is the most dynamic, simple yet preventive A-549 and HL-60 pulmonary tumor cell line of human cells with IC50 estimates of 39.7 and 9.2 µM. However, Chloctanspirone B is reasonably effective against similar cell lines. Surprisingly, there are two main precursors of terrestrols, L and K containing the epicenter, which separates the chloropanspirone A from B, were inactive. This focuses on the assumption that cyclohexenone residue affects the effect, but it is not the pharmacophore (Samson et al. 2011).

5.10. Chondrosterin

Chondrosterin was separated from the core tissue of the soft coral known as *Sarcophyton tortuosum*, and so is obtained from the species of *Chondrostereum*. At the point when this organism was refined in GPY (glucose 10 g/L, peptone 5 g/L, yeast separate 2 g/L, NaCl 23 g/L) fluid medium a metabolite, chondrosterin is obtained. This Compound displayed intense cytotoxic exercises against the tumor cell lines CNE-1 and CNE-2 with the IC50 estimations of 1.32 and 0.56 M (Li et al. 2014).

5.11. Penicimutatin, Penicimutatin A, Penicimutatin B and Penicimutanolone

Penicillium purpurogenum G59 is a marine derived fungus, and is responsible for the production of Penicimutatin, Penicimutanin A, Penicimutatin B and Penicimutanolone. Penicimutanolone, penicimutanin An and penicimutanin B repressed a few human malignancy cell lines (K562, HL-60, HeLa, BGC-823, and MCF-7) with IC50 esteems lower than 20 µM, compound penicimutatin likewise hindered the cell lines to some degree. Antitumor properties were examined by the MTT technique utilizing malignancy cell lines. Enacted optional metabolite production was investigated by different bioassays and HPLC-photodiode exhibit identifier (PDAD)- UV and HPLC-electron splash ionization (ESI)- MS (Fang et al. 2014).

Conclusion: Despite the large number of commercially available natural products and medicines derived from natural sources for various medicinal and agronomic applications, exhaustive research in this field is yet required to fulfill the mounting necessity for newer and improved stimuli for the medicines. Only a trivial part of the estimate of fungal biodiversity has been studied worldwide for obtaining bioactive agents. Still, the fungi have the capability to acclimate nearly all the corners of the earth and the ability to discover unknown species and obtain new bioactive metabolites from them is surprising. Discovering more widespread groups of fungal species and new methods for the enhancements in reproduction are still required. The efforts will simplify the chemical studies of fungal species for secondary metabolites, possibly addressing the urgent necessity for novel remedies worldwide.

ORCID

Umar Farooq Gohar https://orcid.org/0000-0002-4113-3067
Hamid Mukhtar https://orcid.org/0000-0002-7085-9887
Amir Mushtaq https://orcid.org/0000-0002-0959-0989
Ayesha Farooq https://orcid.org/0000-0003-1857-526X
Farooq Saleem https://orcid.org/0000-0002-8284-6442
Malik Asif Hussain https://orcid.org/0000-0002-8093-7631
M Usman Ghani https://orcid.org/0000-0003-1016-4650

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REFERENCES

Aharwal RP, Kumar S and Sandhu SS, 2016. Endophytic mycoflora as a source of biotherapeutic compounds for disease treatment. Journal of Applied Pharmaceutical Science 6: 242-254.

Alberts AW, 1998. Discovery, biochemistry and biology of lovastatin. The American Journal of Cardiology 62: 10-15.

Ajdidi A, Sheehan G and Kavanagh K, 2020. Exposure of *Aspergillus fumigatus* to atorvastatin leads to altered membrane permeability and induction of an oxidative stress response. Journal of Fung, 6: 42. doi:10.3390/jof6020042

Al-Fakih AA and Almaqtri WQA, 2019. Overview on antibacterial metabolites from terrestrial *Aspergillus spp*. Mycology 10: 191-209.

Anke T, 1995. The antifungal strobilurins and their possible ecological role. Canadian Journal of Botany 73: S940–S945

Arai M, Serizawa N, Terahara A, Tsujita Y, Tanaka M, Masuda H, Ishikawa S, 1988. Pravastatin sodium (CS-514), a novel cholesterol- lowering agent which inhibits HMG-CoA reductase. Sankyo Kenkyusho Nempo 40: 1-38.

Arnold AE, Maynard Z, Gilbert GS, Coley PD and Kursar TA, 2000. Are tropical fungal endophytes hyperdiverse? Ecological Letters 3: 267–274.

Asada N, Uryu H, Koseki M, Takeuchi M, Komatsu M and Matsue K, 2006. Successful treatment of breakthrough *Trichosporon asahii fungemia* with voriconazole in a patient with acute mycloid leukemia. Clinical Infectious Diseases 43: 39-41.

Balba H, 2007. Review of strobilurin fungicide chemicals. Journal of Environmental Science and Health 42: 441-451.

Bazaraa WA, Hamdy MK and Toledo R, 1998. Bioreactor for continuous synthesis of compactin by *Penicillium cyclopium.* Journal of Industrial Microbiology and Biotechnology 2: 192–202.

Berdy J, 2005. Bioactive microbial metabolites. The Journal of Antibiotics 58: 1-26.

Blackwell M, 2010. Fungal evolution and taxonomy. BioControl 55: 7-16.

Blunden G, 2001. Biologically active compounds from marine organisms. Phytotherapy Research 15: 89-94.

Bo G, 2000. Giuseppe Brotzu and the discovery of cephalosporins. Clinical Microbiology and Infection 6: 6-8.

Bok J, Chung D, Balajee S, Marr K, Andes D, Nielsen K, Frisvad J, Kirby K and Keller N, 2006. GliZ: A transcriptional regulator of gliotoxin biosynthesis, contributes to *Aspergillus fumigatus* virulence. Infection and Immunity 74: 6761-6768.

Boruta T and Bizukojc M, 2017. Production of Lovastatin and Itaconic acid by *Aspergillus terreus*: A comparative prospective. World Journal of Microbiology and Biotechnology 33: 34. doi: 10.1007/s11274-017-2206-9

Boumehira A, El-Enshasy HA, Hacène H, Elsayed Ea, Aziz R and Park EY, 2016. Recent progress on the development of antibiotics from the genus *Micromonospora*. Biotechnology and Bioprocess Engineering 21: 199-223.

Brian PW, 1951. Antibiotics produced by Fungi. The Botanical Review 6: 357-430.

Bushley KE, Raja R, Jaiswal P, Cumbie JS, Nonogaki M, Boyd AE, Owensby CA, Knaus BJ, Elser J, Miller D, Di Y, McPhail KL and Spatafora JW, 2013. The genome of Tolypocladium inflatum: Evolution, organization, and expression of the cyclosporin biosynthetic gene cluster. PloS Genetics 9: e1003496.

Butler MS, 2005. Natural products to drugs: natural product derived compounds in clinical trials. Natural Product Report 22: 162-195.

Carroll K, Funke G, Jorgensen J, Landry M and Warnock D, 2011. Manual of Clinical Microbiology: Taxonomy and Classification of Fungi, 10th Ed, ASM Press, Washington; pp: 1747-1755.

Chaudhry SB, Veve MP and Wagner JL, 2019. Cephalosporins: A focus on side chains and β-Lactam cross-reactivity. Pharmacy 7: 103.

Chen C, Chen Y, Wu P and Chen B, 2014. Update on new medicinal applications of gentamicin: Evidence-based review. Journal of Formosan Medical Association 113: 72–82.

Chong PH, Seeger JD and Frankin C, 2001. Clinically relevant differences between the statins: implications for therapeutic selection. American Journal of Medicine 111: 390–400.

Chung KJ, Lee JK, Park JW, Seo DJ and Lee SC, 2001. Method for producing pravastatin precursor, ML-236B. US Patent 6 204 032.

Coméra C, André K, Laffitte J, Collet X, Galtier P and Maridonneau-Parini I, 2007. Gliotoxin from *Aspergillus fumigatus* affects phagocytosis and the organization of the actin cytoskeleton by distinct signaling pathways in human neutrophils. Microbes and Infection 9: 47-54.

Cramer R, Gamcsik M, Brooking R, Najvar, L, Kirkpatrick W, Patterson T, Balibar C, Graybill J, Perfect J, Abraham S and Steinbach W, 2006. Disruption of a nonribosomal peptide synthetase in *Aspergillus fumigatus* eliminates gliotoxin production. Eukaryotic Cell 5: 972-980.

Curbete MM and Salgado HRN, 2015. A critical review of the properties of fusidic acid and analytical methods for its determination. Critical Reviews in Analytical Chemistry 46: 352-360.

Dayan FE, Cantrell CL and Duke SO, 2009. Natural products in crop protection. Bioorganic and Medicinal Chemistry 17: 4022–4034.

deMattos AM, Olyaei AJ and Bennett WM, 2000. Nephrotoxicity of immuno-suppressive drugs: Long-term consequences and challenges for the future. American Journal of Kidney Diseases 35: 333-346.

Deshmukh SK, Gupta MK, Prakash V and Reddy SM, 2018. Mangrove-Associated Fungi: A Novel Source of Potential Anticancer Compounds. Journal of Fungi 4: 101. doi: 10.3390/jof4030101

Dewick PM, 2006. Medicinal natural products. A biosynthetic approach. Wiley, Baffins Lane.

Diggins FWE, 1999. The true history of the discovery of penicillin, with refutation of the misinformation in the literature. British Journal of Biomedical Science 56: 83–93.

Dobie D, 2004. Fusidic acid resistance in *Staphylococcus aureus*. Archives of Disease in Childhood 89: 74–77.

ISSN: 2708-7182 (Print); ISSN: 2708-7190 (Online)
Open Access Journal

El-Shaboury SR, Saleh GA, Mohamed FA and Rageh AH, 2007. Analysis of cephalosporin antibiotics. Journal of Pharmaceutical and Biomedical Analysis 45: 1-19.

Emri T, Majoros L, Tóth V and Pócsi I, 2013. Echinocandins: production and applications. Applied Microbiology and Biotechnology 97: 3267-3284.

Endo A, Kuroda M and Tsujita Y, 1976. ML-236A, ML-236B and ML-236C, new inhibitors of cholesterogenesis produced by *Penicillium citrinum*. Journal of Antibiotics 29: 1346–134.

Endo A, Kuroda M, Terahara A, Tsujita Y and Tamura C, 1977. Physiologically active substances and fermentative process for producing the same. U.S. Patent 4,049,495.

Endo AA, 2010. Historical perspective on the discovery of statins. Proceedings of the Japan Academy Series B Physical and Biological Sciences 86: 484–493.

Falagas ME, Grammatikos AP and Michalopoulos A, 2008. Potential of old-generation antibiotics to address current need for new antibiotics. Expert Review of Anti-Infective Therapy 6: 593–600.

Falck E, Hautala JT, Karttunen M, Kinnunen PKJ, Patra M, Saaren-Seppälä H, Vattulainen I, Wiedmer SK and Holopainen JM, 2006. Interaction of Fusidic Acid with Lipid Membranes: Implications to the mechanism of antibiotic activity. Biophysical Journal 91: 1787-1799.

Falk R, Wolf DG, Shapiro M and Polacheck I, 2003. Multidrug-resistant *Trichosporon asahii* isolates are susceptible to voriconazole. Journal of Clinical Microbiology 41: 911.

Fang S, Su J, Liang B, Li X, Li Y, Jiang J, Huang J, Zhou B, Ning C, Li J, Ho W, Li Y, Chen H, Liang H and Ye L, 2017. Suppression of autophagy by mycophenolic acid contributes to inhibition of HCV replication in human hepatoma cells. Scientific Reports 7: 44039.

Fang SM, Wu CJ, Li CW and Cui CB, 2014. A Practical Strategy to Discover New Antitumor Compounds by Activating Silent Metabolite Production in Fungi by Diethyl Sulphate Mutagenesis. Marine Drugs 12(4): 1788-1814.

Fukushima K, Arai T, Mori Y, Tsuboi M and Suzuki M, 1983. Studies on peptide antibiotics, leucinostatins. I. Separation, physico-chemical properties and biological activities of leucinostatins A and B. Journal of Antibiotics 36: 1606–1612.

Furberg CD, 1999. Natural statins and stroke risk. Circulation 99:185–188.

Gardiner DM and Howlett BJ, 2005. Bioinformatic and expression analysis of the putative gliotoxin biosynthetic gene cluster of *Aspergillus fumigatus*. FEMS Microbiology Letters 248: 241–248.

Gnagi L, Martz SV, Meyer D, Scharer RM and Renaud P, 2019. A Short Synthesis of (+)-Brefeldin C through enantioselective radical hydroalkynylation. Chemistry Europe 25: 11646-11649.

Golden EB, Formenti SC and Schiff PB, 2014. Taxanes as radiosensitizers. Anti-Cancer Drugs 25: 502–511.

Gunde-Cimerman N, Friedrich J, Cimerman A and Benicki, 1993. Screening fungi for the production of an inhibitor of HMGCoA reductase: production of mevinolin by the fungi of the genus *Pleurotus*. FEMS Microbiology Letters 111: 203–206.

Hay SI, Rao PC, Dolecek C, Day N, Stergachis A, Lopez AD and Murray C, 2018. Measuring and mapping the global burden of antimicrobial resistance. BMC Medicine 16: 78.

He L, Nan MH, Oh HC, Kim YH, Jang JH, Erikson RL, Ahn JS and Kim BY, 2011. Asperlin induces G_2/M arrest through ROS generation and ATM pathway in human cervical carcinoma cells. Biochemical and Biophysical Research Communications 409: 489-93.

Heischmann S, Dzieciatkowska M, Hansen K, Leibfritz D and Christians U, 2017. The Immunosuppressant Mycophenolic Acid Alters Nucleotide and Lipid Metabolism in an Intestinal Cell Model. Scientific Reports 7: 45088

Himabindu M and Jetty A, 2006. Optimization of nutritional requirements for gentamicin production by *Macromonospora echinospora*. Indian Journal of Experimental Biology 44: 842-848.

Himabindu M, Ravichandra P, Vishalakshi K and Jetty A, 2006. Optimization of critical medium components for the maximal production of gentamicin by *Micromonospora echinospora* ATCC 15838 using response surface methodology. Applied Biochemistry and Biotechnology 134: 143-154.

Hof H and Dietz A, 2009. Antifungal activity of anidulafungin, a product of *Aspergillus nidulans,* against *Aspergillus nidulans*. International Journal of Antimicrobial Agents 33: 285-286.

Hong W and Yan L, 2012. Identification of gntK, a gene required for the methylation of purpurosamine C-6' in gentamicin biosynthesis. Journal of General and Applied Microbiology 58: 349–356.

Hosobuchi M, Shiori T, Ohyama J, Arai M, Iwado S and Yoshikawa H, 1993a. Production of ML-236B, and inhibitor of 3-hydroxy-3- methylglutaryl CoA reductase, by *Penicillium citrinum*: improvement of strain and culture conditions. Bioscience, Biotechnolology and Biochemistry 57: 1414–1419.

Kardos N and Demain AL, 2011. Penicillin: the medicine with the greatest impact on therapeutic outcomes. Applied Microbiology and Biotechnology 92: 677-687.

Kawada M, Inoue H, Ohba SI, Masuda T, Momose I and Ikeda D, 2010. Leucinostatin A inhibits prostate cancer growth through reduction of insulin-like growth factor-I expression in prostate stromal cells. International Journal of Cancer 126: 810–818.

Khudyakova YV, Liukin MV, Smetina OP, Slinkina NA and Aleshko SN, 2004. Marine fungi as potential producers of antibiotics. Pacific Institute of Bioorganic chemistry of Far East Academy of Sciences, Vladivostok, Russia: 185.

Kimura K, Komagata D, Murakawa S and Endo A, 1990. Biosynthesis of monacolins: conversion of monacolin J to monacolin K (mevinolin). Journal of Antibiotics 43: 1621–1622.

Konya A, Jekkel A, Suto J and Salat J, 1998. Optimization of compactin fermentation. Journal of Industrial Microbiology and Biotechnology 20: 150-152.

Kumar A, Henrissat B, Arvas M, Syed MF, Thieme N, Benz JP, Sørensen JL, Record E, Pöggeler S and Kempken F, 2015. De Novo assembly and genome analyses of the marine-derived *Scopulariopsis brevicaulis* strain LF580 unravels life-style traits and Anticancerous Scopularide biosynthetic gene cluster. PloS One 10: 0140398.

Kumar MS, Jana SK, Senthil V, Shasshanka S, Kumar V and Sadhukhan AK, 2000. Repeated fed-batch process for improving Lovastatin production. Process Biochemistry 36: 363–368.

Kramer A, Labes A and Imhoff JF, 2016. phylogenetic relationship and secondary metabolite production of marine fungi producing the Cyclodepsipeptides Scopularide A and B. Marine Biotechnology 18: 466-474.

Li HJ, Jiang WH, Liang WL, Huang JX, Mo YF, Ding YQ, Lam CK, Qian XF, Zhu XF and Lan WJ, 2014. Induced marine fungus *Chondrostereum sp*. as a means of producing new sesquiterpenoids chondrosterins I and J by using glycerol as the carbon source. Marine Drugs 12: 167-175.

Liao WY, Shen CN, Lin LH, Yang YL, Han HY, Chen JW, Kuo SC, Wu SH and Liaw CC, 2012. Asperjinone, a nor-neolignan, and terrein, a suppressor of ABCG2-expressing breast cancer cells, from thermophilic *Aspergillus terreus*. Journal of Natural Product *75*: 630–635.

Ligon BL, 2004. Penicillin: its discovery and early development. Seminars in Pediatric Infectious Dieases 15: 52–57.

Liu M, Liu Y, Zhou S, Zhang X, Yu S and Li Z, 2016. Synthesis and antifungal activities of novel strobilurin derivatives containing quinolin-2(1H)-one moiety. Chemical Research in Chinese Universities 32: 600-606.

Maron DJ, Lu GP, Cai NS, Wu ZG, Li YH, Chen, H, Zhu JQ, Jin XJ, Wouters BC and Zhao J, 2003. Cholesterol-lowering effect of a theaflavin-enriched green tea extract: A randomized controlled trial. Alternative Medicine Review 163: 1448-1453.

Negishi S, Cai-Huang Z, Hasumi K, Murakawa S and Endo A, 1986. Productivity of monacolin K (mevinolin) in the genus *Monascus.* Fermention 64: 509–512.

Nigam PS and Singh A, 2014. Metabolic Pathways: Production of Secondary Metabolites - Fungi. Encyclopedia of Food Microbiology 2: 570–578.

Patel G, Patil M, Soni S, Chisti Y and Banerjee U, 2016. Production of mycophenolic acid by *Penicillium brevicompactum* using solid state fermentation. Applied Biochemistry and Biotechnology 182: 97-109.

Patil A and Majumdar S, 2017. Echinocandins in antifungal pharmacotherapy. Journal of Pharmacy and Pharmacology 69: 1635-1660.

Petersen AB, Rønnest MH, Larsen TO and Clausen MH, 2014. The chemistry of griseofulvin. Chemical Reviews 114: 12088–12107.

Persoh D, 2013. Factors shaping community structure of endophytic fungi-evidence from the Pinus-Viscum-system. Fungal Diversity 60: 55–69.

Piepersberg W, Aboshanab KM, Schmidt-Beißner H and Wehmeier UF, 2007. The Biochemistry and Genetics of Aminoglycoside Producers. In: Arya DP (ed), Aminoglycoside Antibiotics: From Chemical Biology to Drug Discovery. Wiley-Interscience, New Jersey, USA pp: 15-118.

Richardson MD and Warnock DW, 2003. Fungal Infection: Diagnosis and Management, 3rd Ed, Blackwell Publishing Ltd, Oxford pp: 70–72.

Rollinger JM, Langer T and Stuppner H, 2006. Strategies for efficient lead structure discovery from natural products. Current Medicinal Chemistry 13: 1491-1507.

Rollini M, 2002. Biosynthesis and biotechnological production of statins by filamentous fungi and application of these cholesterol-lowering drugs. Applied Microbiology and Biotechnology 58: 555-564.

Samson RA, Varga J, Meijer M and Frisvad JC, 2011. New taxa in *Aspergillus* section Usti. Studies in Mycology 69: 81–97.

Schiff PB and Horwitz SB, 1980. Taxol stabilizes microtubules in mouse fibroblast cells. Proceedings in National Academy of Science USA 77: 1561–1565.

Schiff PB, Fant J and Horwitz SB, 1979. Promotion of microtubule assembly in vitro by Taxol. Nature 277: 665–667.

Seenivason A, Venkatesan S and Panda T, 2018. Cellular localization and production of Lovastatin from *Monascus purpureus*. Indian Journal of Pharmaceutical Sciences 80: 85-98.

Shipanova I, Bartoshevich Y, Sibeldina L, Zaslavskaya P and Michtchenko A, 1995. Relationship between intracellular pH and antibiotic biosynthesis in *Fusidium coccineum*. Applied Microbiology and Biotechnology 43: 514-517.

Stadler M, and Keller NP, 2008. Paradigm shifts in fungal secondary metabolite research. Mycological Research 112: 127-130.

Stierle A, Strobel G and Stierle D, 1993. Taxol and taxane production by *Taxomyces andreanae*, an endophytic fungus of Pacific yew. Science 260: 214–216.

Stierle DB, Stierle AA and Bugni T, 2003. Sequoiamonascins A–D: Novel anticancer metabolites isolated from a redwood endophyte. Journal of Organic Chemistry 68: 4966–4969.

Stockwell VO and Duffy B, 2012. Use of antibiotics in plant agriculture. Revue Scientifique et Technique - Office International des Epizooties 31: 199–210.

Strobel GA, Torczynski R and Bollon A, 1997. *Acremonium* sp. —A leucinostatin A producing endophyte of European yew (*Taxus baccata*). Plant Science 128: 97–108.

Subhan M, Faryal R and Macreadie I, 2016. Exploitation of *Aspergillus terreus* for the Production of Natural Statins. Journal of Fungi 2: 13. doi: 10.3390/jof2020013

Sweetman SC, 2009. Cardiovascular drugs. Martindale: the complete drug reference, 36th Ed, Pharmaceutical Press, London, pp: 1155–1434.

Tamminen A, Kramer A, Labes A and Wiebe MG, 2014. Production of scopularide A in submerged culture with *Scopulariopsis brevicaulis*. Microbial Cell Factories 13: 89.

Taylor FC, Huffman M and Ebrahim S, 2013. Statin therapy for primary prevention of cardiovascular disease. JAMA 310: 2451-2452.

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Thell K, Hellinger R, Schabbauer G and Gruber CW, 2014. Immunosuppressive peptides and their therapeutic applications. Drug Discovery Today 19: 645-653.

Tobert JA, 1987. New developments in lipid-lowering therapy: the role of inhibitors of hydroxymethylglutaryl coenzyme A reductase. Circulation 76: 534–538.

Tsunawaki S, Yoshida LS, Nishida S, Kobayashi T and Shimoyama T, 2004. Fungal metabolite gliotoxin inhibits assembly of the human respiratory burst NADPH oxidase. Infection and Immunity 72: 3373-3382.

Uzun O, Kocagoz S and Centinkaya Y, 1997. In vitro activity of a new echinocandin, LY303366, compared with those of amphotericin B and fluconazole against clinical yeast isolates. Antimicrobial Agents Chemotherapy 41:1156-1157.

Wang CCC, Chiang YM, Kuo PL, Chang JK and Hsu YL, 2008. Norsolorinic acid inhibits proliferation of T24 human bladder cancer cells by arresting the cell cycle at the G0/G1 phase and inducing a Fas/membrane-bound Fas ligand-mediated apoptotic pathway. Clinical and Experimental Pharmacology 35: 1301-1308

Wani M and Horwitz S, 2014. Nature as a remarkable chemist: A personal story of the discovery and development of Taxol. Anti-Cancer Drugs 25: 482-487.

Wong J, 2003. Dr. Alexander Fleming and the discovery of penicillin. Primary Care Update for OB/GYNS 10: 124-126.

Yamada T, Jinno M, Kikuchi T, Kajimoto T, Numata A and Tanaka R, 2012. Three new azaphilones produced by a marine fish-derived *Chaetomium globosum*. Journal of Antibiotics 65: 413-417.

Ykema A and Lindsay JM, 2000. Nitrogen feed in statin fermentation. US Patent # US6165757A.

Yousaf M, Mammadova K, Baghirova S and Rahimova R, 2019. Biotransformation: A one pot method of novel pharmacological importance. Novel Approaches in Drug Designing and Development 4: 555645.

Yu Z, Lang G, Kajahn I, Schmaljohann R and Imhoff JF, 2008. Scopularides A and B, cyclodepsipeptides from a marine sponge-derived fungus, *Scopulariopsis brevicaulis*. Journal of Natural Product 71: 1052–1054.

Yue Q, Chen L, Zhang X, Li K, Sun J, Liu X, An Z and Bills G, 2015. Evolution of chemical diversity in echinocandin lipopeptide antifungal metabolites. Eukaryotic Cell 14: 698-718.

Yaohui G, Gaoqian W, Huiyun H, Hao G, Xinsheng Y and Dan H, 2018. Research progress in biosynthesis of fungal triterpenes and steroids. Chinese Journal of Organic Chemistry 38: 2335-2347.

Zaehle C, Gressler M, Shelest E, Geib E, Hertweck C and Brock M, 2014. Terrein biosynthesis in *Aspergillus terreus* and its impact on phytotoxicity. Chemistry and Biology 21: 719-731.