The Microbial Pharmacy: FDA Approved Medicines From Fungi

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Millions of patients with life threatening diseases are treated each year with medicines made by fungi. In fact, the medicinal value of fungal metabolites has been known for centuries; this is summarized in Table 1. From both a humanitarian view and from a market perspective, medicines produced by fungi are very valuable.

Records show that the earliest medicinal use of fungi recorded is red yeast rice, which was developed in China around 800 AD.[1] By cultivating a yeast (*Monascus purpurea*) in rice a pharmaceutically-active mixture of compounds is produced. Initially, this was carried out by people who were not mycologists.

Chemical analysis of red yeast rice products late in the 20th century showed that they contain a variety of organic compounds related to statins as well as Compactin, also known as Mevastatin®, the first statin approved by the US FDA for clinical use for the reduction of blood cholesterol levels in patients.[2] The Chinese claimed that red yeast rice had a variety of biological activities, including being useful to treat cardiovascular problems.[1]

The second historic and commonly used fungal product, although not at that time as a medicine in the strictest sense, are the psilocybin-containing mushrooms such as *Psilocybe mexicana,* which were used in religious ceremonies by the Aztec indians of Central America, and by other religions throughout the world.[3] Psilocybin has subsequently been evaluated clinically to address stress and related symptoms associated with terminal illness.[4]

In 1928 Alexander Fleming, a physician working at St Mary's hospital in London, observed the effect of penicillin, produced by *Penicillium notatum* which was a contaminant growing on a Staphylococcus containing Petri dish.[5] Penicillin (penicillin V was the first member of the penicillin family to be discovered) was subsequently isolated and characterized by a trans-Atlantic collaborative effort, which resulted in the first true antibiotic becoming widely available. Today penicillin yields from *Penicillium* are approximately 14,000 times higher than those initially observed by Fleming, and current yields in excess of 70 grams per liter of fermentation are claimed.[6,7] Through a variety of medicinal chemistry and fermentation approaches, hundreds of penicillins have been prepared and tested.

One semi-synthetic penicillin, amoxicillin, together with the *Actinomyces*-product clavulanic acid, is available as Augmentin® and used clinically for animal and human infection control. The antibiotic mixture works as follows; clavulanic acid overcomes the problem of antibiotic-resistant pathogenic bacteria producing an enzyme, beta-lactamase, which destroys the activity of penicillin. Clavulanic acid inactivates the beta-lactamase enzyme thereby protecting the penicillin and leaving the intact antibiotic able to produce the desired effect of killing the bacteria.

Cephalosporin, a second member of the beta-lactam antibiotic family, was discovered from a fungus, *Cephalosporium* isolated from a sewer outlet off the coast of Sardinia in 1948 by Italian scientist Giuseppe Brotzu.[8] The natural cephalosporin was never used clinically, but analogues were prepared with superior antibacterial activity. There have been multiple generations of cephalosporins, each with improved activity and applications.

A third clinically important antibiotic produced by fungi is the steroid fusidic acid. This compound is derived from the fungus *Fusidium coccineum,* and was developed in the early 1960s by the Danish drug company Leo Pharma.[9] It was introduced clinically for the treatment of Gram positive bacterial infections.

Shiitake mushrooms, which are native to East Asia, are cultivated worldwide for their health benefits. Shiitake mushrooms contain lentinan, a polysaccharide thought to be responsible for these health benefits. Lentinan has been studied extensively in the laboratory, and has been shown to be effective in enhancing the immune system.[10] It has also been shown to kill microbes and viruses.[11] Compounds from shiitakes have also been shown to lower cholesterol in laboratory studies.[12]

Ergotamine is a vasoconstricting ergot alkaloid from *Claviceps purpurea.* Ergotamine is used to treat migraine type headaches.[13] It was first isolated by Arthur Stoll at Sandoz (now Novartis) in 1918.[14] Use of this fungus medicinally began in the 16th century, when it was used to accelerate parturition.[15] Ergotamine is sometimes administered in combination with caffeine to treat migraine headaches.[16]

Lysergic acid was found from *Claviceps purpurea* in 1938.[17] Although not particularly active itself, lysergic acid diethylamide (LSD) is a highly potent CNS active compound producing hallucinations in those who take it. An account of the discovery of LSD by Albert Hofmann, who accidentally consumed LSD while preparing analogues of lysergic acid in the lab, is given in "LSD My Problem Child: Reflections on Sacred Drugs, Mysticism and Science." [18] The comments from his supervisor at the time, which addressed the accuracy of the reported amount ingested

with no mention of laboratory hygiene, together with a comment on potency, is a stark reminder of how things have changed in lab protocol over the past half century. What was considered as normal behavior in a lab in the 1940s would result in a scientist being ejected today.

It is also interesting that fungi have been the source of two of the best known hallucinogens, both of which are currently, or have been, used in clinical trials to treat terminally ill patients.[19-22]

Cyclosporin A, a powerful immunosuppressant used following organ transplant to overcome the issues of organ rejection by the new host, was initially found from *Tolypocladium inflatum* as an anti fungal agent by Sandoz research workers.[23] Further *in vivo* evaluation showed it had immunosuppressive activity. Cyclosporin A is a cyclic peptide, MW 1202.61 grams/mol, and is biosynthesized by one of the largest enzyme complexes known. Current sales of cyclosporin are in excess of one billion dollars in the USA alone.[24] A number of semi-synthetic cyclosporins with significant biological activity including anti viral have been discovered.

There are a number of other microbial metabolites with immunosuppressive activity including mycophenolic acid which was first isolated from *Penicillium stoloniferum* over 100 years ago.[25] Mycophenolic acid inhibits purine biosynthesis and effects B and T lymphocyte proliferation.[26, 27] Mycophenolic acid, as the mofetil derivative, is marketed as CellCept® by Roche, and as the sodium salt Myfortic® by Novartis. It was approved by the FDA in 2000.

Statins are the most successful medicines in history as measured by the number of prescriptions filled and revenues generated. Worldwide sales are predicted to amount to 1 trillion dollars by 2020.[28] Approximately one in three people take a statin.[28]

The first statins to be discovered were Compactin and Mevacor, found from *Penicillium compactum* and *Aspergillus terreus* respectively. These compounds were initially discovered as cholesterol biosynthesis inhibitors and subsequently shown to affect hydroxymethylglutaryl coenzyme A reductase (HMG-CoA reductase). Medicinal chemistry has lead to the synthesis of a number of superior analogues which are currently on the market.

Pravastatin, a statin formed by the stereoselective microbial hydroxylation of Compactin, was discovered by Sankyo Pharma in the 1970s.[29] In the US, it is marketed as Pravachol® by Bristol-Myers Squibb. Sales of Pravachol® reached 1.3 billion dollars in the US in 2005.[30]

Cancidas®, also a cyclic peptide, was discovered from the fungus *Glarea lozoyensis* and developed by Merck in the 1990s.[31] Cancidas® represented a new class of antifungal agents that inhibit glucan biosynthesis.

The most recent fungal metabolite derivative to be introduced clinically is Fingolimod, also known by the trade name Gilenya® and marketed by Novartis. It was approved in 2011 for the treatment of multiple sclerosis.[32, 33] Fingolimod is a synthetic derivative of myriocin, a powerful immunosuppressant and a metabolite from *Isaria sinclairii,* a type of *Cordyceps*.[32, 33] *Isaria sinclairii* is the name of the anamorph, and *Cordyceps sinclairii*, which colonizes insects, is the name of the teleomorph. The culture broth of this fungus was used in traditional Chinese medicine as an "eternal youth" elixir.[32, 34]

In summary, the bioactivity of fungal metabolites has been known for at least 12 centuries and, based on contemporary research, has led to the development of some of the most important drugs of the 21st century.

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Table 1:

Compound	Derived Product	Producing Fungus	Application	Projected Annual Sales (2017)	Sales References	
Compactin	Mevastatin	Penicillium compactum	cholesterol lowering agent	never marketed		
Mevacor	Lovastatin	Aspergillus terreus	cholesterol lowering agent	$1 Billion	5	
Pravastatin	Pravachol	Penicillium compactum	cholesterol lowering agent	$1.3 Billion	9	US only
Penicillins	Penicillins	Penicillium notatum	bacterial infections	$8.2 Billion	1	global
Co-amoxiclav	Augmentin	(Actinomycetes)	bacterial infections	$1 Billion	6	global
Cephalosporins	Cephalosporins	Cephalosporium	bacterial infections	$9.9 Billion	1	global
Fusidic Acid	Fucidin	Fusidium coccineum	bacterial infections			
Psilocybin	Psilocybin	Psilocybe mexicana	terminal illness	never marketed		
Lysergic Acid	LSD	Claviceps purpurea	terminal illness	never marketed		
Cyclosporin A	Cyclosporin A	Tolypocladium inflatum	organ transplantation	$1 Billion	1	
Mycophenolic Acid	Myfortic, CellCept	Penicillium stoloniferum	organ transplantation	$306.8 Million	2	US only
Caspofungin	Cancidas	Glarea lozoyensis	fungal infections	$611 Million	3	
Fingolimod	Gilenya	Isaria sinclairii	multiple sclerosis	$2.5 Billion	4	
Shiitake mushrooms	Lentinan	Letinula edodes	cancer treatment and prevention, cholesterol lowering agent, immunostimulation, anti-infectious agent	$75 Million	7	shiitake and oyster US produced only
Ergot	Ergotamine	Claviceps purpurea	migraine headaches			
Strobilurins	Strobilurins	Stobilurus tenacellus	agricultural fungicides	$3.8 Billion	8	global

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