**Applications of Microbial Natural Products Lec. 5**

Over the years, the pharmaceutical industry extended their antibiotic screening programs to other areas. Since microorganisms are such a prolific source of structurally diverse bioactive metabolites, the industry extended their screening programs in order to look for microbes with activity in other disease areas. As a result of this move, some of the most important products of the pharmaceutical industry were obtained. For example, the immunosuppressants have revolutionized medicine by facilitating organ transplantation. Other products include antitumor drugs, hypocholesterolemic drugs, enzyme inhibitors, gastrointestinal motor stimulator agents, and other pharmacological activities.

1. Antibiotic

Of the 12,000 antibiotics known in 1955, filamentous fungi produced 22 % .The beta-lactams are the most important class of antibiotics in terms of use. They constitute a major part of the antibiotic market. Included are the penicillins, cephalosporins, clavulanic acid, and the carbapenems. Of these, fungi are responsible for production of penicillins and cephalosporins. It alkylates and inactivates the active-site nucleophylic cysteine of the ketosynthase enzyme of fatty acid synthetase by epoxide ring opening. Other properties that are desired in new antibiotics are improved pharmacological properties, ability to combat viruses and parasites, and improved potency and safety.

### Pharmacological Agents

Years ago, noninfectious diseases were mainly treated with synthetic compounds. As new synthetic lead compounds became extremely difficult to find, microbial products came into play. Poor or toxic antibiotics produced by fungi such as cyclosporin A or mycotoxins such as ergot alkaloids, gibberellins, zearelanone were then successfully applied in medicine and agriculture. This led to the use of fungal products as immunosuppressive agents, hypocholesterolemic drugs, antitumor agents, and for other applications.

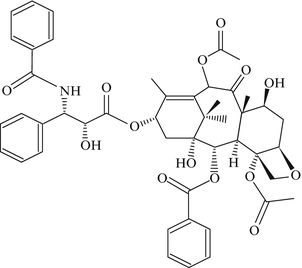
#### Hypocholesterolemic Agents

Only about 30 % of cholesterol in humans comes from the diet. The rest is synthesized by the body, predominantly in the liver. Many people cannot control their level of cholesterol at a healthy level by diet alone and require hypocholesterolemic agents. The statins form a class of hypolipidemic drugs, formed as secondary metabolites by fungi, and used to lower cholesterol by inhibiting the rate-limiting enzyme of the mevalonate pathway of cholesterol biosynthesis; i.e., 3-hydroxymethyl glutaryl-CoA (HMG-CoA) reductase. Inhibition of this enzyme in the liver stimulates low-density lipoprotein (LDL) receptors, resulting in an increased clearance of LDL from the bloodstream and a decrease in blood cholesterol levels. They can reduce total plasma cholesterol by 20–40 %. Through their cholesterol-lowering effect, they reduce risk of cardiovascular disease, prevent stroke, and reduce development of peripheral vascular disease/

#### Anticancer Drugs

Some of the anticancer drugs in clinical use are secondary metabolites derived from plants and fungi. Among the approved products are taxol and camptothecin.

Taxol (paclitaxel) was first isolated from the Pacific yew tree, Taxus brevifolia and later found to be a fungal secondary metabolite . It is a steroidal alkaloid .It inhibits rapidly dividing mammalian cancer cells by promoting tubulin polymerization and interfering with normal microtubule breakdown during cell division. The benzoyl group of the molecule is particularly crucial for maintaining the strong bioactivity of taxol. The drug also inhibits several fungi (species of Pythium, Phytophthora, Aphanomyces) by the same mechanism.

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**Fig.**  Chemical structure of taxol. The benzoyl group is located in the left side of the structure

#### Immunosuppressant Drugs

An individual’s immune system is capable of distinguishing between native and foreign antigens and to mount a response only against the latter. Suppressor cells are critical in the regulation of the normal immune response. The suppression of the immune response, either by drugs or radiation, in order to prevent the rejection of grafts or transplants or to control autoimmune diseases, is called immunosuppression.

Microbial compounds capable of suppressing the immune response have been discovered as fungal secondary metabolites. Cyclosporin A was originally discovered in the 1970s as a narrow-spectrum antifungal peptide produced by the mold, Tolypocladium nivenum (previously Tolupocladium inflatum) in an aerobic fermentation Cyclosporins are a family of neutral, highly lipophilic, cyclic undecapeptides containing some unusual amino acids, led to use in heart, liver, and kidney transplants and to the overwhelming success of the organ transplant field . Cyclosporin was approved for use in 1983. It is thought to bind to the cytosolic protein cyclophilin (immunophilin) of immunocompetent lymphocytes, especially T-lymphocyes. This complex of cyclosporin and cyclophilin inhibits calcineurin, which under normal circumstances is responsible for activating the transcription of interleukin-2. It also inhibits lymphokine production and interleukin release and therefore leads to a reduced function of effector T-cells.

#### Applications of Mycotoxins

Fungi produce poisons called mycotoxins, which, strangely enough, have been harnessed as medically useful agents. These agents (e.g., ergot alkaloids) caused fatal poisoning of humans and animals (ergotism) for centuries by consumption of bread made from grain contaminated with species of the fungus Claviceps. However, mycotoxins later were found useful for angina pectoris, hypertonia, serotonin-related disturbances, inhibition of protein release in agalactorrhea, reduction in bleeding after childbirth, and prevention of implantation in early pregnancy.Their physiological activities include inhibition of action of adrenalin, noradrenalin, and serotonin, as well as the contraction of smooth muscles of the uterus. Antibiotic activity is also possessed by some ergot alkaloids.

#### Inhibitors of Enzyme Activity

Enzyme inhibitors have received increased attention as useful tools, not only for the study of enzyme structures and reaction mechanisms, but also for potential utilization in medicine and agriculture. Several enzyme inhibitors with various industrial uses have been isolated from microbes. Among the most important are the statins and hypocholesterolemic drugs discussed previously. Fungal products are also used as enzyme inhibitors against cancer, diabetes, poisoning, and Alzheimer’s disease. The enzymes inhibited include acetylcholinesterase, protein kinase, tyrosine kinase, glycosidases, and others.

#### Pigments

The fungus is used to prepare red rice, wine, soybean cheese, meat, and fish. It is authorized in Japan and China for food use. There are 54 known Monascus pigments. They have an amazing number of activities: antimicrobial, anticancer, anti-mutagenesis, antidiabetes, anti-obesity, anti-inflammatory, cholesterol-lowering, immunosuppressive, and hypotensive .