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Chapter

Introductory Chapter: Secondary Metabolites - An Overview

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1. Introduction

The metabolism can be defined as the collection of all the biochemical reactions held in an organism. Metabolites are the intermediate products of metabolism. Metabolites have various functions, including fuel, structure, and signaling, stimulatory and inhibitory effects on enzymes, catalytic activity of their own, defense, and interactions with other organisms. A primary metabolite is directly involved in normal growth, development, and reproduction of the host cell. A secondary metabolite is not directly involved in those processes, but usually has an important ecological function [1]. Secondary metabolites are biochemical compounds with varied and sophisticated chemical structures, produced by strains of certain microbial, animal and by plant species. Products of secondary metabolism are that the metabolites are usually not produced during the phase of rapid growth (trophophase), but are synthesized during a subsequent production stage (idiophase). Herbal plants, animals, and microorganisms such as bacteria, actinobacteria, cyanobacteria, fungi, and algae attracted more attention in research that led to the discovery of secondary metabolites. The exploration of secondary metabolites from various resources subsequently led to the development of drugs for the treatment of human diseases of microbial origin. Routine screening of natural resources will introduce novel secondary metabolic products with high pharmaceutical value [2].

Secondary metabolites, complex group of natural metabolic products, serve as defense chemicals, quorum sensing metabolites in environmental interactions, symbiosis, transport of metals and solutes. And in doing so, they confer selective advantage of survival over competitors, though their absence does not compromise their vegetative growth [3]. Twenty-five percent of about 1 million natural secondary metabolites are biologically active. Plants contribute 60% of these metabolites, and microorganisms form the rest, among which fungi remain major (42%) producers of bioactive compounds [4, 5].

2. Taxonomy of secondary metabolites

There are five main classes of secondary metabolites such as terpenoids and steroids, fatty-acid-derived substances and polyketides, alkaloids, nonribosomal polypeptides, and enzyme cofactors [6].
2.1 Terpenoids and steroids

Terpenes are the polymers of five carbon isoprene units and considered as the biggest class of secondary metabolites. When terpenes get modified by different functional groups and oxidized methyl groups at various positions, they form terpenoids. Depending on the carbon units, terpenoids can be divided into monoterpenes, sesquiterpenes, diterpenes, sesterpenes, and triterpenes. They find use in the anticancer treatment, as fragrance agent in cosmetics, and as food flavoring agent [7].

Steroids are diverse class of secondary metabolites and play an important physiological and biochemical function in the living organisms in which they are found. They are lipophilic, low molecular weight and are derived from cholesterol, the family of steroids includes sterols, bile acids, a number of hormones (both gonadal and adrenal cortex hormones), and some hydrocarbons. A number of synthetic steroids are being extensively used as anti-hormones, contraceptive drugs, anticancer agents, cardiovascular agents, osteoporosis drugs, antibiotics, anesthetics, anti-inflammatories, and anti-asthmatics. Many plant-derived sterols known as phytosterols are also used as dietary supplement as they are able to lower cholesterol in human body and prevent cancer [8].

2.2 Fatty-acid-derived substances and polyketides

A fatty acid is the carboxylic acid with aliphatic chain and is a form of energy reserve in the body called fats. Derivatives of fatty acid have a wide variety of industrial application such as plastics, lubricants, and fuels; they include hydroxy fatty acids, fatty alcohols, fatty acid methyl/ethyl esters, and fatty alkanes [9]. Polyketides (PKs) are produced by the action of polyketide synthases (PKSs) in animals, plants, fungi, and bacteria. These biologically active secondary metabolites display a high structural diversity and find many applications in treatment of various acute and chronic diseases. Examples include antibacterial (erythromycin and tetracycline), antitumor (anthracycline and doxorubicin), antifungal (amphotericin and griseofulvin), antiparasitic (avermectin), and anti-cholesterol (lovastatin) drugs. The acetyl tranferase, ketosynthase, thioesterase, and other such domains constitute polyketides. Linkage of acyl-coenzyme A (CoA) on the acyl carrier protein (ACP) facilitates biosynthesis of polyketides with catalytic support from AT domain [10].

2.3 Alkaloids

Plants are regarded as the oldest source of this natural occurring structurally diverse bioactive secondary metabolite. Some of the most widely recognized alkaloids, such as morphine, quinine, strychnine, and cocaine, are derived from plants. Alkaloids are small organic molecules containing nitrogen usually in a ring. In plants, they are mainly involved in defense against herbivores and pathogens. Rapid advances in molecular biology and metabolic engineering have led to discovery and synthesis of alkaloids also from microbes. Alkaloids can be classified according to their molecular weight, such as the indole alkaloids and isoquinoline alkaloids (each more than 4000 compounds). Other important groups include tropane alkaloids (~300 compounds), steroidal alkaloids (~450 compounds), and pyridine and pyrrolizidine alkaloids (respectively, ~250 and 570 compounds) [11].
2.4 Nonribosomal polypeptides

They come under the class of peptide secondary metabolites produced by microorganisms such as bacteria, cyanobacteria, fungi, and symbionts of higher eukaryotes. The nonribosomal peptides (NRPs) are synthesized by multidomain mega-enzymes named nonribosomal peptide synthetases (NRPSs), without the need for the cell ribosomal machinery and messenger RNAs. Their bioactivity and pharmaceutical properties can be evidenced by antibiotics (e.g., actinomycin, penicillin, cephalosporin, vancomycin), cytotoxics (e.g., bleomycin), and immunosuppressants (e.g., cyclosporines), which have found immense importance in the clinical industry [12].

2.5 Enzyme cofactors

The analysis of the cofactors is imperative in order to gain the understanding of the enzyme catalyzed reactions. Enzymes are proteins that catalyze vast repertoire of reactions found in nature. Generally the enzymes are composed 20 amino acid residues, but some may also require additional small molecules in the active site for the catalysis reaction to occur, these small molecules are known as cofactors. The cofactor can be a metal ion (e.g., Fe+) or small organic molecule [13].

3. Functions of secondary metabolites

3.1 Secondary metabolites as competitive weapons

The mechanism of natural defense has been evolved in microorganisms, and they achieve this by secretion of secondary metabolites. The best example could be the antibiotics, which can kill or inhibit the growth of competing microorganisms. Studies confirm that antibiotics are also involved in germination by stimulating spore formation, which can inhibit or stimulate spore formation. Formation of secondary metabolites and spores is regulated by similar factors. Thus the secondary metabolite slows down germination of spores until a less competitive environment and more favorable conditions for growth exist. It protects the dormant or initiated spore from consumption by amoebae and cleans the immediate environment of competing microorganisms during germination [1].

3.2 Secondary metabolites as metal transporting agents

Secondary metabolites act as metal precipitating or chelating agents in plants as the high bioaccumulation of the toxic trace metals can lead to abiotic stress that can cause oxidative damage to plant cells. Metal precipitation is achieved by low-molecular-weight compounds such as phenolics, amino acids, organic acids, and sugars as well as high-molecular-weight compounds such as mucilage and proteins in plants. In the rhizosphere or apoplastic space, the metals are excluded through chelation so as to avoid their entry into symplast. An example could be of the siderophores, which have high affinity for iron (Fe) and could solubilize ferric iron [14].

3.3 Secondary metabolites as agents for symbiotic relation with other organisms

In symbiotic relationship both the organisms are benefited from each other. The symbiotic association between soil fungi and roots is known as mycorrhizae.
Mycorrhizal roots can absorb much more phosphate than roots that have no symbiotic relationship with fungi. The fungi in turn protect the plant from damage by pathogens such as nematodes, *Fusarium*, *Pythium*, and *Phytophthera* by often using secondary metabolites such as antibiotics. Another example where the secondary metabolites mediate the symbiotic relationship is bacteria *Pseudomonas*, which act as plant growth-promoting bacteria, by colonizing the roots and producing antibiotics that limit the growth of other pathogenic bacteria as well as fungi [3].

### 3.4 Secondary metabolites as reproductive agent

Well-known sex hormones produced by fungi are trisporic acids, which are secondary metabolites of *Mucorales*. The trisporic acid was found in 1964 that caused enhanced carotene production in *Blakeslea trispora*. This was later shown to be the hormone that brought about zygophore production in *Mucor mucedo*. Zygophores (sexual hyphae) are produced when vegetative hyphae of the two mating types of these heterothallic organisms approach one another. Trisporic acids are produced from mevalonic acid in a secondary metabolic pathway of which the early steps are present in both (+) and (−) sexes. Since distinct late steps are absent in these sexes, both strains must meet and come in contact in order to complete the pathway that forms trisporic acid [15]. Similarly, a secondary metabolite, sirenin, is also involved in sexual reproduction in *Allomyces*, a phycomycete by working as a chemotaxic hormone that brings together the female and male gametes [16].

### 3.5 Secondary metabolites as differentiation effectors

Differentiation occurs during the development of an organism, which can be a morphological change or chemical change. Secondary metabolites released during this time bring about differentiation. Sporulation, which is the process of formation of spores from vegetative phase, is connected with production of antibiotics. This is supported by several evidences such as antibiotic production by all sporulating microorganisms, sporulation and antibiotic synthesis are induced by depletion of some essential nutrient, genetic links between the synthesis of antibiotics and the formation of spores and antibiotics are frequently inhibitory to vegetative growth of their producers at concentrations produced during sporulation [3].

### 3.6 Secondary metabolites as agents of communication between organisms

Cell-to-cell communication has been hypothesized to evolve first in the unicellular organisms long before the appearance of specialized (glands, neurons, immune cells, blood cells) cells. In microorganisms small secondary metabolites act as informational cues to regulate gene expression. Homoserine lactones (HLs) are synthesized from S-adenosylmethionine by many Gram-negative bacteria that diffuse and regulate their population density. HLs function in *Psuedomonas aeruginosa*, an opportunistic pathogen responsible for many hospital acquired infection. It uses two HL signaling systems, which combined to regulate over 300 genes. HL signaling could bring about drastic changes in gene expression affecting secondary metabolism, the elaboration of virulence factors, sporulation, and biofilm formation. Similar to this is *Vibrio cholerae* that uses autoinducers such as CAI-1 to terminate host colonization, halting biofilm formation and virulence factor expression. The signaling is also seen as a mechanism of pathogenesis in Gram-positive bacteria such as *Staphylococcus aureus*. During
infection when it enters the human body, it shows complex adaptive behavior that leads to changes in population density, time, and environment-specific. Part of this behavior is controlled by at least four two-component systems, one of which is the *agr* system, which uses a modified octapeptide in signaling [17].

4. Research on plants secondary metabolites

In the plant kingdom, more than 50,000 secondary metabolites have been discovered, and they exert a wide range of effects on the plant as well as other living organisms. Their functions involve induction of flowering, fruit set and abscission, maintenance of perennial growth or signal deciduous behavior. Many plant secondary metabolites act as antimicrobials and perform the role of attractants or, conversely, as repellents. They are used as herbs in the traditional medicine in many ancient communities as plant secondary metabolites have shown to possess various biological effects. Plant secondary metabolites are classified according to their chemical structures into several classes. The classes of secondary plant metabolites include phenolics, alkaloids, saponins, terpenes, lipids, and carbohydrates. They act as antibiotic, antifungal, and antiviral and therefore are able to protect plants from pathogens as well as serious leaf damage from the light because they contain important UV-absorbing compounds [18]. Further, secondary metabolites of plants also have ecological importance whereby they improve soil quality by influencing soil decomposition. Tannins and terpenes affect cycling of C and N by increasing N immobilization in the soil. They also defend plants from pathogens and diseases, attract pollinators, aid in seed dispersal, and help plants recover from injury [19].

5. Conclusion

Though numerically plants are largest contributors of secondary metabolites, unfathomed microbial metabolites of different ecological origin are treasure in store. The microbial biomolecules have several advantages over the metabolites of plant or animal origin, which finds many applications as briefed earlier. Microbial sources can be genetically modified to enhance the production of desired natural product by fermentation. The metabolic versatility makes microbes interesting objects for a range of economically important biotechnological applications. This book provides reviews and research articles on secondary metabolites of microbial, animal, and plant origin, which should benefit scientific community.
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References


