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Value-Added Secondary Metabolites from Microorganisms- A Concise Review

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Abstract: Microorganisms are an important source of a large number of bioactive compounds that have become a significant contribution to the production of drugs, chemicals, and biofuels. These secondary metabolites are organic compounds that are the maximum amount found by the extraction of microbes. With the advent of current knowledge in metabolic engineering, protein engineering, and synthetic biology which enable us to redesign microbial cellular networks and fine-tuning physiological capabilities that can be generating industrially viable strains for the production of natural value-added bioactive compounds. They are chiefly used in the biopharmaceutical industry owing to their potentiality to reduce infectious diseases in human beings and animals and thus increase the life expectancy and also microorganisms and their products inevitably play a significant role in sustainable agriculture development. In this chapter, we describe the recent progress on microbial factories for the synthesis of value-added products.

Introduction

Microorganisms are an important source of a large number of natural products which have shape significant contribution to almost every sphere of human, plant and veterinary life. Microbes have been known greatly for their possibility in the development of bioprocess technologies for unhindered production of food products and supplements to meet the increasing demand by continuously growing world population. Secondary metabolites from microbes are organic compounds which primarily used in the biopharmaceutical industry due to their ability to reduce infectious diseases in human beings and animals and thus increase the life expectancy and also their products certainly play a remarkable contribution in sustainable agriculture development [4].

Following the Business Communication Company (BCC), the total global market for microbes and microbial products was calculated near about $143.5 billion in 2014, and from 2015 to 2020, it can reach upwards to $306 billion at a compound annual growth rate (CAGR) of nearly 14.6 %. Among them, healthcare was the biggest end-user at about $100.4 billion in 2014 and assumed to increase over $187.8 billion by 2020 [27]. Advanced technologies for the production of microbial products are taking the place of synthetic production procedures for technical and economical advantages. These products include nutritional supplements such as vitamins and amino acids, organic acids, agriculturally important metabolites, enzymes, flavoring agents, coloring agents, and pharmaceutical products [15].

The coincidental discovery of antibiotic penicillin by Fleming in 1929 has drawn the attention of scientists to study the therapeutic role of microbial products for resisting life-threatening infections. Initially, almost all the chemical studies were done without planning as a result of less information about ethnopharmacology. In the early sixteen decades, enhance the necessity for drugs able to control new illnesses or resistant

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strains of microorganisms stimulated to search unconventional new sources of bioactive natural products. The microorganisms turned out to be an interesting field. In the seventeen decades, researchers attract bioactive compounds, and after that chemical ecology introduced new driving forces that are unorganized and also allow an extraordinary expansion of the whole field of natural product research. Now, it must be considered as a ''mature field'' [17].

The microorganisms are important as a source of valuable bioactive metabolites has accepted for more than half a century. For the result, over 120 of the most important medicines in use today (penicillins, cyclosporin A, adriamycin, etc.) are obtained from terrestrial microbes. At first, the expectable vast biodiversity of microorganisms might have been the reason for the interest in their study. Secondly, present in extremely large sphere of environment and thrive from abyssal zone to stratosphere (at heights up to 60 km) and in a wide range of temperatures ranging from arctic ice to boiling volcanoes [18,38].

Thirdly, microbes have been recognized considerably for their potential in the development of bioprocess technology and lastly, micro-organism-based methodologies do not constitute a major source of pollution. But, studies on microbes are detecting some unexpected prob-lems. First, the taxonomy of microbes are very poorly defined, so that binomial identi-fications are frequently uneasy to be carried out, and many papers describe metabolites isolated from numbered strains of otherwise partially or unde-fined organisms.

Secondary metabolites are produced at the end or near the stationary phase of growth which are not directly related to growth, development, and also reproduction of microorganisms. These products are largely involved in healthcare activities as antimicrobial agents, antiparasitic agents, antitumor, enzyme inhibitors and immuno-suppressive etc and also as plant growth stimul-ants, herbicides, and insecticides [14,19].

In this chapter, we are demonstrating the roles of microbial secondary metabolites in nutrition, healthcare, and agriculture with their current industrial status.

Role of microbes in the healthcare industry

The most critical commitment of microbes to the pharmaceutical business is the improvement of anti-infection agents which were initially the results of microbial digestion; however, nowadays researchers able to produce more improved medications. Vaccine, an important towards the drug development, production usually requires culturing of huge amounts of bacteria. Steroids are also produced from microorganisms. Based on the principles of microbiology and human cell mechanisms pharmacists are allowed to discover antimicrobial drugs that would prevent an increasing number of communicable diseases. Recent days, utilization of antibiotics in a broad range, such as in chemotherapy, veterinary, plant pathology, food preservation, and in research laboratories. These components inhibit protein synthesis, cell wall formation, electron transport pathway, and nucleic acid synthesis [15]. Some of the microbial species have been noted for their ability to produce a variety of antibiotics. The total antibiotic consumption during 2000-2010 was grown by about 35 % (Table 1). The largest pro-ducer of antibiotics is the *Strepto-mycetes* [2,22,28,30,40]. Tetracyclines, the most extensively used broad-spectrum antibiotics, are utilized for the treatment of diseases caused by a wide range of micro-organisms including Gram-positive and Gram-negative bacteria, rickettsiae, chlamydiae, myco-plasma, and protozoan parasites [11]. Ciprofloxacin, another broad-spectrum antibiotic, is effective in the treatment of gastrointestinal infection, skin urinary tract infections, chancroid and bone infections, and gonorrhea [13]. Cephalosporins have a broader spectrum effect against infections and are less likely to be associated with anaphylactic reactions as compared to penicillin [3]. Carbapenems are used to treat most difficult Gram-negative infections and polymixins are used against multi-drug resistant infections like carbapenem-resistant Enterobacteriaceae. Besides, significant increases were also observed for monobactams, glycopeptides, cephalosporins, and fluoroquinolones for the same period. Now, using up of antibiotics in poultry, swine, and cattle against some infections and to stimulate animal growth overused the entire human therapeutic purposes [36].

Surgical removal, radiation, and chemotherapy are used for tumors treatment. Surgical methods and radiation therapy are inefficient to treat metastatic cancer and therefore, chemotherapy is predominantly helpful in the treatment of cancer that has spread to other parts of the body than origin site. Potential therapeutic targets revealed by the molecular genetics assessments of cancer biology. Many microbial metabolites have been studied for potent anti-cancer properties in healthcare after the discovery of the first anticancer agent, actinomycin by Wakesman and Woodruff [26].

Sirolimus from *Streptomyces hygroscopicus* Cyclosporine A from *Tolypcladium nivenum*, tacrolimus from *S. tsukubaenis*, mycophenolate mofetil from *Penicillium stoloniferum* and gliotoxin from *Aspergillus* and *Trichoderma* have been noted for their immunosuppressive activities and an important role in organ transplants [5,15,20,37]. Microbial α-amylase inhibitors are found from *Streptomyces corchorushii* and TAI-A and TAI-B from *Streptomyces calvus* TM-521 [34]. The clavulanic acid, inhibitor of β-lactamase and used to overcome antibiotic resistance, is derived from *Streptomyces clavuligerus* [1]. *Streptomyces toxytricini* is produced Lipstatin, a pancreatic lipase inhibitor, plays an important role in the treatment of obesity and diabetes [32]. Acarbose, a pseudotetrasaccharide, is produced by *Actinoplanes* sp. SE 50 and useful to reduce starch breakdown in the intestine and hence useful to treatment of type 2 diabetes mellitus diabetes in humans [16]. Protease inhibitors like antipain, leupeptin, and chymostatin have also found important applications in the treatment of AIDS, hepatitis, pancreatitis, and cancer. These protease inhibitors are produced by different species of the genus *Streptomyces* [6]. Most of these alkaloids are derived from the Claviceps sclerotium. Besides, the alkaloids have also been reported by other fungi including Aspergillus, Penicillium, and Rhizopus [25].

Compounds having antiparasitic activities are used to inhibit the growth and multiplication of parasite organisms that live on the body of humans and animals and can cause serious health problems including death of the host. Omura and coworkers noted eight compounds, which are produced as secondary metabolites by *Streptomyces avermitilis* and named as avermectins possessed activity against nemathelminthes and arthropods [35]. Polyether antibiotics, such as monensin, lasalocid A and salinomycin, produced by actinomycetes, are used to control poultry coccidiosis [33].

Role of microbes in food industry

Recently, a large number of fermented products are available for consumers among them a small proportion of these products are homemade, most of them are produced industrially (Table 1).

The common genus *Lactobacillus* converts sugars into lactic acid by fermentation. Milk contains a sugar called lactose, a disaccharide (compound sugar) having β-1, 4- glycosidic bond between galactose and glucose. Lactobacillus converts lactose of the milk into lactic acid which imparts the sour taste to curd [23]. *Streptococcus thermophilus, Lactobacillus acidophilus,* and bifidobacteria can also be used for the production of yogurt and it is commonly referred to as bioyogurt [24]. The production of cheese by strains of *Lactococcus lactis, Streptococcus thermophilus,* and *Lactobacillus* sp causes casein to coagulate slowly. This process is often assisted by the addition of the enzyme, chymosin (active ingredient in rennet). Chymosin removes negatively charged portion of casein that results in rapid aggregation of casein proteins [7]. Kefir, light alcoholic beverage, have varying and complex microbial composition which contain various species of yeasts, lactic acid bacteria, acetic acid bacteria, and mycelial fungi. Lactic acid bacteria contained in kefir are *Lactobacillus acidophilus,Lactobacillus fermentum, Lactobacillus helveticus, Lactobacillus casei, Lactobacillus kefiri, Leuconostoc mesenteroides, Lactobacillus parakefiri, Lactobacillus brevis* and *Lactococcus lactis*. Acetic acid bacteria include *Acetobacter aceti* and *Acetobacter rasens*; yeasts include *Candida lambica, Kluyveromyces marxianus, Saccharomyces exiguous* and *Torula kefir* [31,39]. Kumis, mild alcohol content as compared to kefir for mare's milk contains more sugars than other milks, made by spontaneous fermentation of lactose to lactic acid and alcohol. Strong kumis is produced by using *Lactobacillus bulgaricus* and *Lctobacillus rhamnosus,* whereas, *Lactobacillus* bacteria viz. *L. Acidophilus, L. Plantarum, L. Casei, L. fermentum* involve in the production of moderate kumis and light kumis is produced using *Streptococcus thermophilus* and *Streptococcus cremoris* [12]. *Saccharomyces cerevisiae* is used in baking and brewing industries for the production of wine, beer, ethanol, and also bread. *S. rouxii* is produced for the production of soy sauce. Chocolate is prepared with the help of microbes include yeasts and bacteria such as *Lactobacilli* and *Acetobacter*.

Role of microbes in agriculture industry

Halogenated, carbamate and organophosphorus compounds have been extensively utilized for the agriculture system for controlling the pests and as a result toxic effect on wildlife, human and domestic animals; chemical changes on undesired insects/pests on their predators, parasites, and contamination of groundwater [8,21,29]. Biopesticides include bio fungicides (*Trichoderma*), bioherbicides (*Phytophthora*), and bioinsecticides (*Bacillus thuringiensis, B. sphaericus*) are preferred over conventional pesticides due to

Table 1. Some microbes with their products and uses

Name of microbes	Products	Industry	Uses
Aspergillus niger	Lipase, Protease, Cellulose, Amylase	Dairy, Baking, Paper, Polymer, Detergent, Textile, Cosmetics, Leather, Healthcare, Beverages	Faster cheese ripening, Dough stability and conditioning pitch control, Polymerization control of lactones, skin care
Aspergillus oryzae	Lipase, Protease, Cellulose, Amylase	Dairy, Baking, Paper, Polymer, Detergent, Textile, Cosmetics, Leather, Healthcare, Beverages	Removal of dead skin, Dehairing, bathing, Protein stain removal, Biofilm removal, Restrict haze formation
Alteromonas sp.	Alteramide	Healthcare	Recover from carcinoma, DNA fragmentation
Bacillus subtilis	Laccase, Protease, Amylase	Textile, Cosmetics, Polymer, Paper, beverage, Healthcare	Non-chlorine Bleaching, Fabric dyeing, Hair dye, Polymerization of bisphenol A, Non-chlorine bleaching, Delignification, Detoxification
Bacillus sp	Cellulase	Textile, Detergents, Paper	Cotton softening, Denim finishing, Colour clarification, Deinking, drainage improvement
Candida antarctica	Lipase	Dairy ,Baking, Paper, Polymer, Detergent, Textile,	Pitch control, Skin care, Denimfinishing
Micromonospora marina	Thiocoraline	Pharmaceutical	Inhibit colon cancer, DNA replication
Penicillin funiculosum	Cellulase	Textile, Detergents, Paper	Cotton softening, denim finishing, Colour clarification, Deinking, Drainage improvement
Pseudomonas aeruginosa	Laccase	Textile, Cosmetics, Polymer, Paper, Beverage, Healthcare	Non-chlorine Bleaching, Fabric dyeing, Hair dye, Polymerization of bisphenol A

table 1. (continued).

Name of microbes	Products	Industry	Uses
Serraita sp	Protease	Polymer, Paper, Beverage, Healthcare	Removal of dead skin, Dehairing, Bathing, Protein stain removal, Biofilm removal, Restrict haze formation
Streptomyces antibioticus	Actinomycin D, Pentostatin	Pharmaceutical	Wilm's tumor in children, Hairy cell leukemia, Acute lymphocytic leukemia, Prolymphocytic leukemia
Streptomyces achromogenes	Streptozotocin	Healthcare	Pancreatic islet cell cancer
Streptomyces spp.	Bleomycin, Daunomycin, Mitomycin C, Mithramycin, Chromomycin A3, Amylase, Protease	Textile, Cosmetics, Polymer, Paper, Beverage, Healthcare, Pharmacetical	Non-chlorine Bleaching, Fabric dyeing, Hair dye, Polymerization of bisphenol A , Non-chlorine bleaching, Delignification, Detoxification, Inhibit Breast and urinary bladder cancer, Acute myeloid leukemia, acute lymphocytic leukemia, Neuroblastoma , Hodgkin's disease, Squamous cell carcinoma, Testicular cancer, Pleurodesi
Taxomyces andreanae	Taxol, paclitaxel	Healthcare	Inhibit breast cancer, Kaposi sarcoma, Microtubule depolymerization

biodegradable nature, high effectiveness, target specificity and less environmental risks [8].

Certain strains of *Bacillus subtilis, B. pumilus, Pseudomonas fluorescens, P. aureofaciens,* and *Streptomyces* spp. suppress plant diseases by outcompeting plant pathogens in the rhizosphere, producing anti-fungal compounds and promoting plant and root growth. They are exploited against a large number of plant pathogens including soft rots and damping-off [8,10].

The most common commercial fungal bio-pesticides applied in agriculture and forestry are *Trichoderma* spp. and *Beauveria bassiana. Trichoderma harzianum* is a potent antagonist of *Pythium, Rhizoctionia, Fusarium* and other soil-borne pathogens (Table 1). *Metarhizium anisopliae* and *Beauveria bassiana* are parasitic fungi found on many insect species. *Beauveria bassiana* has been proved effective in controlling crop pests such as aphids, thrips and whitefly pesticide-resistant strains. *Metarhizium anisopliae* is applied against spittlebugs on sugarcane as well as grassland and for the control of locust and grasshopper pests in Africa and Australia. Coniothyrium minitans is a mycoparasite applied against *Sclerotinia sclerotiorum* [9,10].

Conclusion

Some of the most important and widespread uses of microbes in the healthcare, mainly pharmaceutical industry, food industry, and agriculture industry. They are involved in the production of antibiotics and vaccines and the use of microorganisms in the recombinant DNA industry. However, there are a variety of other pharmaceutical agents derived from micro-organisms including vitamins, amino acids, dextrans, iron-chelating agents, and enzymes. Microorganisms as whole or subcellular fractions, in suspension or immobilized in an inert matrix are employed in a variety of assays. Pesticides from microbial origin have proved their significant potential in sustainable agriculture development.

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