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Fungi as chemical industries and genetic engineering for the production of biologically active secondary metabolites

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PEER REVIEW

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Comments

This is a really a valuable contribution for the new research in the field of fungal secondary metabolites. Because the author has compiled all the information in a very consistent manner. The authors have established a fine link that fungi is living organism but is used as chemical industries for the production of secondary metabolites, which I do believe is the real scientific contribution by naming fungi as chemical industries, that no one have ever used this term before for fungi.

Details on Page 867

ABSTRACT

Fungi is somewhere in between the micro and macro organisms which is a good source of producing biologically active secondary metabolites. Fungi have been used as tool for producing different types of secondary metabolites by providing different nutrients at different laboratory conditions. The fungi have been engineered for the desired secondary metabolites by using different laboratory techniques, for example, homologous and heterologous expressions. This review reported how the fungi are used as chemical industry for the production of secondary metabolites and how they are engineered in laboratory for the production of desirable metabolites; also the biosynthetic pathways of the bio-organic-molecules were reported.

KEYWORDS

Fungi, Natural products, Microbiology, Molecular genetics, Chemical biology

1. Introduction

Fungi survive in a wide ranging of habitats, such as in water, in land/soil, in air, and also in/on animals and plants, simply including both terrestrial and marine environments[1,2]. However, majority of them are terrestrial, living in/on soil or surviving on dead bodies of the multi-cellular organisms including both plants and animals, and are contributing to the natural recycling of the dead bodies into organic compounds. Besides, many of the terrestrial fungi are pathogenic to animals and plants, and potentially cause difficulty to cure fungal diseases[1-3].

The chemistry of fungi are a little more complex because they are structurally different from plants and animals but

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they have some patterns similar to plants and animals. For example, they decompose their foods using extra-cellular digestion, and then absorb the nutrients; whereas, they follow the same biosynthetic pathways for the synthesis of secondary metabolites like terpenes and polyketides using similar starting units[1,4].

By knowing that the fungi possess the same biosynthetic pathways like plants, the fungi became important to the scientists. They are also widely used as experimental model because they can be grown easily in the laboratory conditions *i.e.*, yeast[5,6].

2. Fungi as a source of natural products

Natural products are the organic compounds which have been produced as secondary metabolites by the living organisms. Almost all of the secondary metabolites possess biological importance. The secondary metabolites show different varieties of the structurally and functionally diverse group of natural products. The diversity has led them biologically active against various chronic diseases, rendering them important and valuable for the human being[7].

Natural products are the main source of drugs. According to one survey, about 61% (535 out of 877) naturally isolated chemical compounds have been developed into drugs in the entire world in 22 years (from 1981 to 2002). Seventy eight percent of antibacterial and seventy four percent of anticancer compounds are natural products[8]. Thus natural products offers a remarkable platforms for the development of front-line medicines[9].

Significant improvement and variation in the microbial natural products discovery is confined to the management of nutrient and environmental factors which encourage the biosynthesis of secondary metabolite. While the small changes in nutrient and/or environment have the ability to affect the quantity, quality and diversity of the secondary metabolites as fermentation products[10].

The natural products from any source have been classified as alkaloids, isoprenoids, non-ribosomal peptides and polyketides. All the groups differ from one another in their structures, functions and even in biosynthetic pathways.

2.1. Alkaloids

Alkaloids are the natural organic compounds mainly of plants origin. They have at least one basic nitrogen heterocyclic ring, possessing remarkable physiological activities in human. Alkaloids are divers in their function, because some stimulate central nerves system in human, some relieve pain, while some are toxic and others cause paralysis. Most of the alkaloids are colourless crystalline solids and a few are liquids. The solid alkaloids are soluble in lipids while the liquid ones are aqueous soluble. Coniine[11], graminutee[12], papaverine and quinine are some of the common alkaloids[13,14].

2.2. Isoprenoids

Isoprenoids (also called terpenes or terpenoids) are natural products that give proper odour or flavour to plants. Isoprenoids are the oils from plants that consist of a mixture of hydrocarbons (polyene) and their oxygenated derivatives. Isoprenoids is one of the largest group of natural products with approximately 25 000 known compounds[15,16].

Otto Wallach has received Noble Prize in 1910 for working with isoprenoids and assigning so called isoprene-rule that molecules of all isoprenoids are synthesized from two or more of the isoprene units joining into head-to-tail fashion[17]. Some of the common and well known isoprenoids from plants are camphor[18], isoprene[17], limonene[19], myrcene and vitaminute-A[20,21]; whereas, microorganisms may also synthesized some important isoprenoids such as aristolochene and gibberellin-GA4[22,23].

2.3. Non-ribosomal peptides

Non-ribosomal peptides are the natural products, which is an important class of secondary metabolites, mainly produced by microorganisms including actinomycetes, bacteria and fungi. Non-ribosomal peptides are produced by multi-domain and multi-modular enzyme called non-ribosomal peptides synthetase (NPRS)[24]. These secondary metabolites are bio-synthesized in the cytoplasm by cytosolic protein outside the ribosome[25,26]. Some common NRPS are bleomycin[27], cyclosporin-A and penicillin-G[28,29].

Non-ribosomal peptides are large multi-domain protein consisting of several modules (a group of domain or segments of the NRPS's polypeptide chain) which has the potential to join the building blocks (amino acid) together, forming a long peptide chain. The mechanism, which are involved in the bio-synthesis of polypeptide chain, are the selection of amino acid activation, and finally the condensation of amino acids. As the module is a group of domains, the chemistry of domain is very essential for the function of the module. The major domains that tie up the amino acids together are the adenylation domains (A-domains) serving as catalyst for the activation of substrate. The peptide carrier protein (PCP)-domain or thiolation domain, is an important domain because it is always activated by 4-phosphopantetheinyl-transferases to start its function. This domain is a bonding