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MEDICINAL MUSHROOMS AS A POTENTIAL SOURCE TO DEVELOP HEALTH ENHANCING BIOTECH-PRODUCTS

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Introduction

The search for natural sources of bioactive compounds (BAC) among biological organisms for development and formulation of novel health enhancing biotech-products (bio-pharmaceuticals, functional food, cosmeceuticals, etc.) are areas of major importance in modern biotechnology.

Fungi (mushrooms) are rich in proteins, carbohydrates, fibers, unsaturated fatty acids, vitamins, minerals and considered a very good dietary food. They are also regarded as sources of a wide range of bioactive molecules and enzymes with therapeutic activities [1, 7, 13, 14-16, 19]. However, fungal biodiversity is not completely disco-vered, yet. Only 82 000 species of an estimated 1.5 million fungi are known and approximately 14.000 mushroom species from 140.000 estimated species are described. Among them about 2000 species are safe and 650 species are possessing significant medicinal properties.

For millennia, mushrooms were valued by human-kind as edible and medicinal (anti-inflammatory, analgesic, blood-coagulating and wound-healing) resources. Most of the traditional knowledge about medicinal properties of mushrooms comes from the Far East. Anti-inflammatory, analgesic, blood-coagulating, wound-healing and other medicinal properties of mushrooms have long been recognized in China, Korea, Japan and Africa, as well as in Central and North American countries. Various cultures, especially in Mexico, use psychoactive *Amanita* and *Psilocybe* mushrooms in ancient religious and medical practices [8-10]. Western countries have just started to ponder the diversity and great potential of medicinal mushrooms.

Advancements in fungal biotechnology have extended from analysis of nutritional components and benefits to the search for natural BAC and enzymes in medicinal mushrooms that are used in medicine, food industry and cosmetology. Scientific data was documented that further investigation of fungal bioactive molecules will assist obtaining new preventive and curative biotech-products used in the treatment of immune system disorders, cancer, bacterial, viral and fungal infections, in regulation of blood glucose and lipids levels, etc. [8, 11, 14].

It is known, that several forms of chronic diseases, can, in part, be attributed to diet and arising from the awareness of the relationship between diet and disease has evolved the concept of "functional foods" [13]. The commercial mushroom biotech-products obtained from fruiting bodies and/or mycelia are largely consumable in the world market. They are not considered strictly pharmaceutical products (medicines), but represent a novel class of dietary food supplements (DSs) or functional food additives ("nutriceuticals"). They generally represent either dried mycelial biomass or fruiting bodies or their aqueous-alcoholic extracts [6, 19]. Mushrooms are also sold in dried forms as healthy food ("nutraceuticals"). Both "nutriceuticals" and "nutraceuticals" are foods that have a health-enhancing benefit.

The main groups of BAC of medicinal mushrooms and their therapeutic applications

The available information about bioactive metabolites, enzymes and biotechnological potential of medicinal mushrooms

suggests that they are promising biological organisms to develop health enhancing biotech-products [3, 13, 16-18, 20].

The major chemical groups of substances present in medicinal mushrooms are polysaccharides or β-glucans, terpenoids, steroids, phenols, glycoproteins, fatty acids lectins, statins and others. They have Immune-modulatory, antioxidant, genoprotective, antitumor, hypocholesterinemic, antidiabetic, hepatoprotective and other medicinal effects [1-3, 7, 11, 12, 19-21].

Fungal polysaccharides are most potent mushroom-derived substances with antitumor and immune-modulating properties. They are mostly present in cell wall with different types of glycosidic linkages, such as (1→3) and (1→6)-β-D-glucans. Glucans from medicinal mushrooms *Phellinus linteus, Ganoderma lucidum, Flammulina velutipes, Agaricus brasiliensis, Trametes versicolor, Schyzophillum commune* and *Hypsizygus marmoreus* are used to develop the antitumor and immune-modulating preparations [2, 19]. Fungal polysaccharide based antitumor biotech-products lentinan (from *Lentinula edodes*), schizophyllan (*Schizophyllum commune*), grifolan (from *Grifola frondosa*) and krestin (from *Trametes versicolor*) have been successfully used for the treatment of cancer in combination with chemotherapy [2].

Polysaccharide glucuronoxylomannan (GXM) with anti-inflammatory and wound healing properties was isolated from submerged mycelium culture of *Tremella mesenterica* [21]. Healthy food obtained from biotechnologically cultivated mycelia of medicinal edible mushrooms *Hericium erinaceus* and *Tremella spp.* and from other natural components (medicinal plants, algae, etc.) posses antioxidant and immune-stimulating activity, helps maintain healthy cardiovascular function. Some mushroom species are able to decrease high glucose and lipid levels in blood and are recommended as neuro- and vasotonics, hepatoprotective and thrombolytic agents [11, 12]. Oyster mushrooms (species from genus *Pleurotus*) are potential producers of statins which have hypocholesterinemic activity [1, 7]. It was reported that consumption of mushroom dietary supplement plovastin (submerged mycelia of *P. ostreatus* and *P. eryngii* var. *ferulae)* significantly reduce blood cholesterol level.

Mushrooms are source of terpenoid compounds possessing cytotoxic, antifungal and antibacterial activities. Presently, antiviral agents against different viruses (Papilloma, H5N1, HSV-1, HSV-2, Hepatitis B, C, D, E, AIDS, etc.) are actively searching from different mushroom species (*Piptoporus betulinus*, *Fomitopsis officinalis, Coprinellus micaceus,* etc) to develop new class of mushroom based antiviral drugs [14].

Bioactive proteins lectins and hydrophobins of potential medicinal interest are so far described from mushrooms [17]. Lectins are carbohydrate-binding proteins with agglutinating properties that are wide-spread found in eukaryotes [15, 18]. The hydrophobins are most interesting candidates for various medical applications, such as increasing biocompatibility of medical implants addevices, immobilization of antibodies in a biosensor and stabilizing oil vesicles for drug delivery [13].

Other applications of mushroom based biotech-products

A new area of application of edible and medicinal mushrooms dietary supplements is formulation of balanced food for pets, particularly for dogs and cats. Except medicinal plants, vitamins, amino acids and many other ingredients such food additionally contains mushrooms polysaccharides obtained from mycelial biomass stimulating immune activity in animals.

Nutritive, anti-inflammatory, regenerative and antioxidant properties of mushrooms make their usage perspective in manufacturing of skin and hair care cosmetic products [6]. Fungal chitosan is also wildly used in cosmetology as an emulgatory, gel-forming, protective and anti-bacterial agent. Several species (*L. edodes, G. lucidum, Tremella spp.)* are currently proposed as highly active ingredients in world production of hair and skin care cosmetic products (Yves Rocher "Serum Vegetal de Shiitake" skin care line, *Tremella* cosmetic products, *Hypsizygus ulmarius* skin-care products developed by American company *Origins*, etc.).

Biotechnological production and cultivation of edible medicinal mushrooms

Mushroom cultivation is an intensive agricultural industry that produces more than 6 millions of tons a year. Introduction of new techniques and approaches in biotechnological cultivation of fruiting bodies resulting in 25 species being potentially cultivated. Among these most important cultivable edible medicinal mushrooms are

Lentinula edodes, Pleurotus ostreatus, Flammulina velutipes, Volvariella volvacea and *Ganoderma lucidum.*

Total commercial mushroom production worldwide has increased more than 15-fold in the last 25 years and continue increased constantly during the last decade. However, biotechnological production of fruiting bodies is a long-term process (1-2 months), whereas submerged cultivation of mycelium takes only several days. Mycelial cultures can be established and optimized for almost all known mushrooms species, whereas only a limited number (about 50 species) can be produced as fruiting bodies.

Today, approximately 80% of mushroom biotech-products are taken from fruiting bodies either collected in the wild or grown commercially. In both cases, the resulting products are considerably diverse and unpredictable. The quality of fruiting bodies is strongly dependent on natural growth conditions and usually is *not constant with composition.* By contrast, biotechnological cultivation of mycelium allows to reduce it growth time and regulate metabolism to obtain a high yield of biomass and large amounts of desired BAC that are *constant with composition.*

Thus, the submerged biotechnological cultivation of mycelium has significant industrial potential and it is the modern approach for obtaining consistent and safe mushroom biotech-products.

Extensive research and development of biotechnological cultivation of mycelium has markedly increased owing to potential use of mushrooms in food, pharmaceutical and cosmetic industries. For this purposes study of biological characteristics and growth parameters of mycelium of perspective mushroom species are required to establish their biotechnological cultivation [4-6].

Safety and standardization of mushroom based biotech-products

It is commonly believed that many botanicals and mushrooms can be considered safe because of their long history of usage without toxicological effect. The main advantage of mushroom biotech-products with regard to safety (as opposed to herbal preparations) is that the mushrooms are cultivated commercially and not gathered in the wild.

Unfortunately, the standardization of mushroom healthy biotech-products is still in its early stage. The important problems of manufacturing such products are the lack of acceptable standards and specific protocols to assure its quality and insufficient understanding of their physiological effects.

Conclusion

Sustainable research in the fields of fungal biochemistry, molecular biology and biotechnology, as well as using improved screening methods (including genomics, proteomics and metabolomics) will assist further development and usage of mushroom based biotech-products with a positive global impact on human welfare and environmental conservation.

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SYNTHESIS OF POTENTIALLY BIOACTIVE 5-(5-MERCAPTO-4*H*-[1,2,4]TRIAZOL-3-YL)-3-ALKYL-4-METHYL-3*H*-THIAZOLE-2-THIONE DERIVATIVES

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In the last few decades the chemistry of 1,2,4-triazoles and thiazoles and also their mercapto- and thione-substituted systems have received considerable attention owing to their synthetic and biological importance. The 1,2,4-triazole and thiazole nuclei are associated with diverse pharmacological activities such as antibacterial, antiviral, anticancer, antitubercular, antifungal, hypoglycemic, antihypertensive, anti-inflammatory and analgesic [1-10, and references cited there]. There are known drugs, containing 1,2,4-triazole groups (Ribavirin, Anastrozole, Vorozole,Letrozole, Fluconazole, Intraconazole, Voriconazole, Triazolam, Alprazolam, Etizolam, Furacylin) and thiazole (Hemineurin, Famotidine, Nizatidine, Leucogenum, Cefotoxim, Ceftriaxon, Ceftazidime, Cefpirom, Aztreonam, Phthalazolum, Norsulfazolum, Nitazolum, Imiphosum). These heterocycles derivatives are significant in agrochemical industry as plant protecting and growth regulating materials. Among them there are 1,2,4-triazole herbicides (amitrole, cafenstrole, epronaz, flupoxam, amicarbazone, bencarbazone, carfentrazone, flucarbazone, ipfencarbazone, propoxycarbazone, sulfentrazone, thiencarbazone), fungicides (amisulbrom, bitertanol, fluotrimazole, triazbutil) and insecticides (isazofos, triazophos); thiazole herbicides (mefenacet, thiazopir, metabenzthiazuron, fenthiaprop, benazolin, benzthiazuron), fungicides (ethaboxam, isotianil, metsulfovax, octhilinone, thiabendazole, thifluzamide, flutianil, thiadifluor), insecticides (clothianidin, imidaclothiz, thiamethoxam, thiapronil, tazimcarb, thiacloprid) and others.

At the same time practical interest represents the synthesis of compounds with combination of two heterocycles, which can lead to the appearance of new physiological. In addition, at prolonged use of