REVIEW ARTICLE

Vitamin D_2-enhanced Mushrooms as Dietary Supplements and Nutraceuticals: A Nutritionally Sensible Trade-off for the Consumer

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ABSTRACT

Mushrooms have been prevalent in the human food supply for millenia largely due to their flavorful taste, robust nutritional value, and myriad medicinal properties. Dietary mushrooms are comprised of >12,000 species worldwide and ~20% of these are edible with many cultivated for human consumption. Many of the beneficial effects of dietary mushrooms and other fungi are purportedly due to a diverse, robust array of bioactive molecules, some of which are fungus-specific with these compounds reportedly exerting >200 different medicinal functions. One specific bioactive component of significant interest is the nutrient vitamin D_2, which can contribute to the daily vitamin D needs of humans. The increased research interest in dietary mushrooms as a source has occurred, in large part, to new biotechnological innovations that have generated ultraviolet-irradiated products with significantly enhanced vitamin D_2 (ergosterol) levels to amounts such that one serving may meet the daily dietary intake value for some individuals. Many argue that vitamin D_2 should not be considered part of a supplemental or nutraceutical regimen due to the considerable differences in absorption and metabolism between vitamin D_2 and D_3, the latter being the more bioactive form. However, dietary mushrooms contain myriad, diverse biologically active components such as fungus-specific antioxidant ergothioneine, and selenium, as well as multiple vitamin and minerals. As a result, many experts suggest a dietary intake of mushroom-derived vitamin D_2 as a wise choice for supplementation, although it may not be as bioavailable as vitamin D_3. The inclusion of such a wide array of bioactive nutrients and non-nutrients and a biologically meaningful contribution of vitamin D_2 to overall vitamin D daily values is a nutritionally sensible trade-off (in lieu of vitamin D_3). This is particularly important with the global prevalence of type 2 diabetes, hypertension, obesity, and cardiovascular disease given the purported association with vitamin D deficiency.

Key words: Dietary supplement, health, mushroom, nutraceuticals

INTRODUCTION

Mushrooms have been part of the human food supply for millenia largely due to their flavorful taste, robust nutritional value, and myriad medicinal properties. Dietary mushrooms constitute at least 12,000 species worldwide and approximately 20% of these are edible, although only a limited number (~35) is actually cultivated.[1-3] Many of the beneficial effects of dietary mushrooms and other fungi are purportedly due to a diverse, robust array of bioactive components, some of which are fungus-specific, with these compounds reportedly exerting >200 different medicinal functions. Examples of mushroom compounds include polysaccharides (β-glucans), dietary fibers (e.g., chitin), unsaturated fatty acids, terpenes, peptides, glycoproteins, alcohols, mineral elements, and antioxidants such as phenolic compounds, tocopherols, and ascorbic acid.[4-6] Edible mushrooms are also a rich source of

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some macronutrients (i.e., proteins) and micronutrients (i.e., vitamin and minerals), providing meaningful levels of B group vitamin (i.e., riboflavin and niacin), and the minerals selenium, potassium, copper, and zinc. Mushrooms contain little sodium (a contributor to hypertension in many) and are low-fat, with each 100 g serving containing only 2–8%, thus are a nutritious, low energy-dense food.[7]

Consumption of dietary mushrooms has been receiving considerable, renewed attention for many reasons related to improved health. As a food source that is neither fruit nor vegetable, but a fungus, mushrooms are replete with many nutritive and non-nutritive bioactive compounds.[8,9] They have been shown in numerous studies with diverse experimental models to exhibit antioxidant, free radical scavenging, antiviral, antibacterial, antifungal, hepatoprotective, neuroprotective, and antidiabetic effects [Table 1].[10,11]

Others have shown mitigation of many chronic diseases, including cardiovascular disease (CVD), hypertension, cerebral stroke, and cancers through antiviral, antibacterial, antifungal, anti-inflammatory, hypolipidemic, antithrombotic, and hypotensive effects.[12-14] Dietary mushrooms, and purportedly mushroom-derived products, are also important immunomodulators that can "boost" the immune system.[1,15] In fact, mushrooms with immune-stimulating capabilities, namely, "immunoceuticals," are generally polysaccharides such as β-D-glucans and have been tested successfully in clinical trials with some clinical use.[19,20] Thus, similar to pharmaceutical agents, mushroom nutraceuticals and functional foods considered an emerging new superfood, when administered at therapeutic doses target and modulate biological processes, for example, intracellular signaling cascades that foster the development of disease. However, there continues to be a lack of complete knowledge between mushroom nutraceuticals and functional foods research and conveyance of information to the medical, nutritional, and dietetics communities that could assist with dietary recommendations. With more information from randomized clinical trials, these can be used in many stages of nutritional and/or medicinal therapies. As such, there is keen interest in developing functional foods, mushroom nutraceuticals (dietary supplements particularly with added value), and perhaps medications, although requiring pre-market FDA approval, from edible mushrooms.

BIOAVAILABILITY OF MUSHROOM COMPONENTS

The amount and the bioavailability of nutrients and non-nutrients primarily depend on the mushroom variety, agricultural practices, and also the form of the consumed compound (e.g., metabolite).[21,22] For example, basidiomycetes mushrooms contain biologically active compounds in fruit bodies, cultured mycelium, and cultured broth.[23,24] As a result, they might be used directly in the diet to elicit additive and synergistic effects of all the bioactive compounds, or specific parts or the whole mushrooms may undergo extraction to isolate and/or purify components with specific functions.[24-26] The antioxidant ergothioneine, in fact, is considered one of several essential longevity vitamin and proteins due to its biological activities.[27-29] The properties and mechanisms of many extracts and specific bioactive compounds such as the fungi-specific ergothioneine, from mushrooms, have previously been evaluated in different experimental models such as humans, human cell lines, animal models, and non-human cell lines.

EXTRACTING THE BENEFICIAL PROPERTIES OF MUSHROOMS

The industrial, laboratory extraction process of mushrooms can render many different products (from purified single chemicals to complex mixtures) with diverse functions and relative potencies depending on the conditions. Moreover, the mushroom species selected and/or the part of the mushroom (e.g., mycelium) dictate the type and amounts of bioactive compounds produced. For example, the most common extraction methods are based on aqueous (water and hot water) and alcoholic solvents.[25] Use of polar solvents such as ethanol or methanol produce fractions that

Table 1: Bioactivities and bioactive agents in three most commonly consumed dietary mushrooms*

Mushroom	Common name(s)	Bioactivity	Bioactive agent(s)
Agaricus bisporus	White button, cremini, portabella	Hypocholesterolemic, hypoglycemic, anti-aging, anti-cancer, anti-inflammatory, immunostimulatory	Lectin, fucogalactan, beta glucan(fibers),2-amino-3H-phenoxazin-3-one
Lentinula edodes	Shiitake	Antioxidant, anticancer, hypocholesterolemic, immunostimulatory, antimicrobial, antitumor, anti-inflammatory, anti-protozoal	Methanolic, ethanolic (mycelia) and water extracts, eritadenine, lentinan, oxalic acid, emitannin, heteroglycan
Pleurotus ostreatus	Oyster	Antioxidant, antitumor, antiatherosclerotic, hypocholesterolemic, immunostimulatory	Ethanolic and water extracts, lectin, lovastatin

*Ramos *et al*., 2019; Tinimundy *et al*., 2014; Mohamed and Farghaly, 2014[16-18]

are rich in polyphenols, terpenoids, lignans, and alkaloids, whereas aqueous extracts are rich in polysaccharides, proteins, peptides, lectins, and glycoproteins.[19] As one might surmise, phenolic compounds are more concentrated in organic extracts, thus exhibit higher antioxidant activities.[13,25,30,31] Aqueous extracts can elicit immunological responses, whereas polar solvents inhibit immune cell activity.[19] After a specific extraction process, the resultant fraction can be further isolated, processed, and/or purified to generate concentrated, novel chemicals and/or mixtures that may confer potential biological functionalities with some degree of functional specificity (e.g., antioxidant and immunostimulating).

MUSHROOMS AS FOOD AND DIETARY SUPPLEMENTS

US sales of mushrooms accounted for nearly $5 billion in revenue in 2017 and are projected to exceed $7 billion by 2020.[3] This increase is thought to be driven in large part by the notion that mushrooms will improve health and performance, as shown in numerous studies. As such, dietary supplements and nutraceuticals based on mushrooms are readily and widely available on the commercial market to consumers. These include (1) artificially cultivated fruiting body powders, hot water, or alcohol extracts of these fruiting bodies; (2) dried and pulverized products of the combined substrate, mycelium, and primordial (earliest stage of development) mushroom; (3) biomass or extracts from mycelium harvested from a submerged liquid culture grown in a fermentation tank or bioreactor; (4) naturally grown, dried mushroom fruiting bodies in the form of capsules or tablets; and (5) spores and their extracts.[23] The principal nutraceuticals found in mushrooms include (1) lipids, especially unsaturated fatty acids, for example, cis-linoleic and oleic; (2) vitamin, for example, vitamin E and vitamin C; (3) proteins, peptides, and amino acids, including lectins, leucine, and valine; (4) carbohydrates, especially polysaccharides.[23]

Most mushroom-derived preparations and substances are used as a novel class of "dietary supplements" or "nutraceutical" and have been given the term "mushroom nutraceutical" by Chang and Buswell.[32] This is a refined or partially refined extract or dried biomass from either the mycelium or the fruiting body of the mushroom, which is consumed in the form of capsules or tablets as dietary supplements. The intention is to mitigate, prevent, or regress an adverse condition or disease state, although not specifically marketed as such.[33,34] Due to the limited supply and high price of wild mushrooms, artificial cultivation has become a major source of many edible mushroom-based products on the market and potentially allows biotechnological innovation. There remains, however, a lack of information regarding the bioaccessibility (release from food or supplement matrix) and bioavailability (absorption and delivery to target tissues) of the compounds and possible interactions with the food matrix, prescription drugs, or nutrients. As a result, most of the mushrooms and their compounds are mainly consumed in natural form or in dietary supplements.

From a culinary perspective, functional foods can be biotechnologically modified to supplement the diet and increase nutrient density with the goal to increase nutritional value and fiber while maintaining low-calorie products. Many novel functional foods have significantly increased functionalities (e.g., pasting properties of wheat flour) with consequent increases in antioxidant, antimicrobial, antithrombotic, and hypocholesterolemic properties.[35] Moreover, beneficial effects also include decreased potential glycemic response, inhibition of food contaminants, avoidance of food deterioration, and protection from lipid peroxidation (rancidity). A particularly attractive and nutritionally useful biotechnological development has been the enhancement of vitamin D_2 in edible mushrooms and mushroom-derived products.

MUSHROOMS AND VITAMIN D

Vitamin D is crucial for bone health, muscle strength, and bone density, as well as for mitigating the risk of fracture, osteomalacia, osteoarthritis, and osteoporosis.[36] Relatively recently, it has been estimated that more than a billion individuals worldwide are vitamin D-deficient, with an estimated prevalence of 50%.[22] This is particularly alarming since vitamin D deficiency has been associated with CVD risk factors such as hypertension, dyslipidemia, and diabetes mellitus, as well as myocardial infarction, stroke, heart failure, and endothelial dysfunction.[37-39] Moreover, recent reports suggest that vitamin D supplementation could reduce the risk of influenza and COVID-19 infections (currently a pandemic) and deaths.[40] This could be due, in part, to the well-known role of vitamin D in modulating the immune system. This function has been shown to reduce the risk of numerous chronic diseases, including cancer, CVD, depression, and diabetes. As a result, it is vital to increase the intake of bioavailable and bioactive vitamin D to eliminate deficiencies.

The two primary dietary forms of vitamin D are D_2 (ergocalciferol), found in fungi (e.g., mushrooms, and yeast) and D_3 (cholecalciferol), found in animals [Table 2]. Interestingly, mushrooms can exhibit considerable concentrations of ergosterol, steroid alcohol, that can be converted to bioavailable, bioactive vitamin D_2 after exposure to ultraviolet (UV) irradiation up to concentrations higher than most natural food sources.[41] Exposure of fresh mushrooms to UV radiation, generating at least 10 μg D_2/100 g fresh weight, demonstrated that a 100 g serving (~1.5 cups raw) would provide 50–100% of the daily required vitamin D to consumers. In several human studies, individuals consuming mushrooms displayed significantly increased plasma

Table 2: Vitamin D_2 amounts in commonly consumed mushrooms

Mushroom	Common name	Serving size	vitamin D_2 (IU)
Agaricus bisporus	White button	1 cup (70 g)	2
Agaricus bisporus	Cremini	1 cup (72 g)	5
Agaricus bisporus	Portabella	1 cup (86 g)	9
Pleurotus edodes	Oyster	1 cup (86 g)	25
Lentinula edodes	Shiitake	4 mushrooms (15 g)	23
Lentinula edodes	Shiitake	20 mushrooms (75 g)	115
Grifola frondosa	Maitake	1 cup (70 g)	786

USDA national nutrient database for standard reference

concentrations of vitamin D, which remained largely stable during subsequent storage and cooking, after consumption of either of the three most commonly consumed mushrooms, including white button mushroom (*Agaricus bisporus*), oyster mushrooms, and shiitake mushrooms (*Lentinula edodes*).[22] These observations have led to widespread efforts to "biofortify" dietary mushrooms with vitamin D and provide these functional products commercially since UV-exposed fresh mushrooms will retain nutritionally relevant amounts of vitamin D_2 for at least 1 week. Others, however, have shown in the three most commercially purchased mushrooms (button, shiitake, and oyster) that exposure to UV-B and subsequent hot air-drying resulted in good retention of vitamin D_2 up to 8 months when stored in dry, dark conditions at 20°C in closed plastic containers.

Dietary UV-irradiated mushrooms contain vitamin D; however, it is in the form of vitamin D_2, ergocalciferol, not D_3. This is relevant because the two are not absorbed in the same manner and neither is technically the final fully bioactive form of vitamin D, namely, 1,25-dihydroxycholecalciferol, used in the body, but are chemical precursors. Previously, the assumption was that both D_2 and D_3 exhibited equal absorption and metabolic convertibility suggesting equivalent contributions to the daily value (DV), that is, 600 IU, for vitamin D. According to the FDA, 1 IU of mushroom vitamin D is the same as 1 IU coming from fish or dairy; however, studies have shown that 4 IU of synthetic vitamin D_2 is needed to equal the effectiveness of 1 IU of vitamin D_3 from cod liver oil. Subsequently, many additional studies suggested incongruity, but this has not been fully addressed. The concern is not that vitamin D_2 is not bioavailable and bioactive, it is merely posited that it is not equivalent to vitamin D_3, but this assertion may imply that it is not as effective or efficacious. As a result, there is currently divergence between clinical practice and expert advice regarding the most appropriate means of addressing vitamin D deficiency.[42] It may prove challenging and difficult to estimate one's daily consumption of vitamin D when the assumption is that a D_2 supplement, nutraceutical, or functional food of a given IU value has the same effect in the body as the equivalent IU amount coming from D_3. Whether from a fungus or an animal, however, both are good dietary sources and can help one reach the required intake for most of 600 IU.

There has been disagreement regarding the use of vitamin D_2 supplementation to meet DVs for vitamin D with some strongly advising against vitamin D_2, or ergocalciferol, stating that it should not be regarded as a nutrient suitable for supplementation or fortification.[43] However, vitamin D_2 (50 ug; 2000 IU) from mushrooms and mushroom-derived products has been as effective as purified supplemental vitamin D_2 in increasing and maintaining serum 25-hydroxyvitamin D_2 ($25(OH)D_2$) concentrations in humans. A 5-week study in adults with serum 25(OH) D (combined $25(OH)D_2$ and $25(OH)D_3$) concentrations <50 nmol/L showed that vitamin D_2 from the soup made from UV-B irradiated mushrooms improved vitamin D status as effectively as supplemental vitamin D_2.[44] Baseline serum 25-hydroxyvitamin D (25(OH)D) levels, a measure of vitamin D status, were not significantly different among the groups. The levels among the three groups gradually increased and plateaued at 7 weeks and were maintained for the next 5 weeks. After 12 weeks of vitamin D supplements, the levels were not statistically significantly different than those who ingested the mushroom powder. These results provide evidence that ingesting UV-irradiated mushrooms and contain vitamin D_2 is a good source of vitamin D that can improve the status of healthy adults. From a dietetics perspective, however, animal-derived vitamin D_3 may not be acceptable to vegetarians suggesting a source of vitamin D_2 may be preferred.

Another concern with food applications of mushroom phytochemicals (e.g., polysaccharides and vitamin D_2) is to determine the appropriate dose for bioactivity without adverse or toxic effects so that food, dietary supplement, or nutraceutical can be considered functional.[34] Although some of the most studied bioactive agents produced by mushrooms are already available and marketed as mushroom nutraceuticals, addition to food products in a purified form is in the initial stages of global commercialization. This is due to numerous production problems, including production economics (process of

combining various material and immaterial inputs [plans, expertise] to produce a product), quality standardization, and stable availability and authenticity of the source material. In addition, more clinical studies regarding the therapeutic effects and the effective doses of functional foods are needed for greater global commercialization.[34]

MUSHROOM DIETARY SUPPLEMENTS AND APPLICATION

Many commercial mushroom and mushroom-derived products have been successfully and safely marketed. For example, Lentinan (*L. edodes*), Concord Sunchih and Reishi Plus (*Ganoderma lucidum*), Grifon (*Grifola frondosa*), and didanosine (*Cordyceps militaris*) are available to the public as mushroom nutraceuticals and dietary supplements.[45] Notably, there have been clinical studies on the therapeutic effects of commercially available, mushroom-derived nutraceuticals, and dietary supplements. These include as examples *Agaricus blazei* extract, active hexose correlated compound (AHCC), Ganopoly®, Hispidin, Hispolon, Immune Assist™, and SX-Fraction®.[8] Although there is considerable therapeutic potential for mushrooms as a foundation for formulations, there are problems involving the preparation and subsequent marketing such as safety issues, better methods of standardization, regulatory issues, demonstration of efficacy, and elucidation of mechanisms of action.[23] In addition, there is a strong necessity of performing clinical trials for these nutraceutical products for widespread acceptance on the global market.[9]

To evaluate the efficacy of specific mushroom species for particular therapeutic purposes or to check safety concerns, there are many databases that are freely accessible, although with so many potential mushroom-derived products may be incomplete. When recommending mushroom supplements for consumption with the presence of a specific disease or condition, the health professional should be aware of potential interactions with medications (e.g., chemotherapy). Finding a high-quality mushroom supplement can be challenging. For example, some mushroom companies in the supplement industry are selling mycelium that is grown on rice or other grain mediums and may not disclose that this could pose an allergen risk.[46] In addition, some products sold as mushrooms will state "reishi mushroom" or "shiitake mushroom" on the label, but will actually be myceliated grain with negligible amounts of the actual mushroom or even none. Since many mushroom products, including supplements, are produced in other countries, it is imperative to test for authenticity, presence of contaminants or adulterants, purity, etc. The most effective current method for testing mushrooms is the analysis of beta-glucan content, the primary medicinal polysaccharide of mushrooms. The Megazyme test, which is now available in many laboratories, is an industry standard for testing mushrooms, although testing for total polysaccharide content can be used as well but with considerable uncertainty.[47] This is because the latter non-specific test will detect starch glucans also, thus contamination and/or adulteration, whether intentional or not, may produce a false positive or provide erroneously high analyte values. As a result, the consumer should consider the means of testing used to support an assertion of product efficacy or purity.

INCORPORATING MUSHROOMS INTO A HEALTHY DIET

Mushroom consumption has been positively associated with a higher intake of many nutrients, leading to better diet quality. As a result, health professionals should encourage frequent dietary consumption of a variety of mushrooms such as white button mushrooms. For example, one serving size of 84 g (3 ounces; ~1 cup fresh, sliced) is a good source (≥10% of the DV) of niacin, pantothenic acid, copper, and selenium, and an excellent source (≥20% of the DV) of riboflavin.[7] In fact, mushrooms contain significant amounts of vitamin B2 (riboflavin) and vitamin B3 (niacin). For example, 100 g (3 ½ ounces) of crimini contains 44 and 30% of your daily recommendation, respectively, and white button mushrooms have 36 and 30%, and oyster mushrooms have 32 and 39%. In the U.S., portobellos fortified with vitamin D are currently on the market. A three-ounce (85 g) serving provides 400 IU of vitamin D but may be considerably higher depending on production methods and mushroom variety. Dietary recommendations for adults <50 years of age are consumption of 400–1000 IU daily of vitamin D, demonstrating dietary mushrooms are a robust source that can meet DV. Moreover, if one consumes 100 g (3 ½ ounces or 1 1/3 cups) of button mushrooms a day, one will get nutrients as mentioned previously, for example, 70 g contains 1 g fiber, but also 3 mg of biologically active, fungus-specific ergothioneine. This correlates to 25 g of oyster, shiitake, or maitake mushrooms since they contain 4 times the amount. Collectively, numerous studies have demonstrated that dietary intakes of mushrooms, depending on genus and species, at levels of 25–100 g/day (1/3–1 cup sliced fresh) can lead to healthful outcomes.

CLINICAL STUDIES WITH MUSHROOMS

A number of preclinical and clinical human studies suggest that consumption of certain mushroom species, as either food or extracts or consumption of specific bioactive components from them, may reduce the risk of certain diseases via a range of health effects.[7,48] For example, the association of mushroom intake with breast cancer risk was determined in Korean female patients (n = 358) with breast cancer and cancer-free Korean control women (n = 360). The highest (11.37 g/d) versus the lowest (2.61 g/d) mushroom intake was associated with a lower risk of breast cancers among

premenopausal women with hormone receptor-positive status than those with hormone receptor-negative tumors compared with the lowest quartiles of intake. In a study with analysis of mushroom consumption data collected in a single 24-h recall with the U.S. adults (≥19 years) from 2001 to 2010, the data revealed that mushroom consumers had a lower risk of being overweight/obese and exhibiting metabolic syndrome. In a small (n = 54) 4-day crossover design intervention study in healthy overweight or obese adults, energy intake from mushroom meals was less than half the energy consumed from meat meals consumed in a laboratory setting. Moreover, energy intake was only partially compensated over 4 days (11.4 ± 12%), with no differences in ratings of hunger, satiety, or palatability between the mushroom and meat groups. Daily intake of calories and fat was lower in the mushroom groups. In a randomized controlled trial, participants (n = 30) treated with a shiitake-extract oral mouth rinse (2 rinses with 10 mL for 30 s at a 1-min interval twice daily) exhibited a more favorable plaque index than those treated with a water placebo. Moreover, the gingival index was improved for the mushroom group compared to a placebo or a gingivitis mouthwash. Decreases in total and specific oral bacterial pathogen counts were also observed for both the mushroom extract and the gingivitis mouthwash compared to the placebo group. Collectively, there are numerous human clinical trials that have focused on diverse beneficial actions of mushrooms and/or mushroom-derived compounds.

SUMMARY

Mushrooms can potentially be remarkably effective and efficacious, but many products suffer from ongoing limitations, including lack of standardized manufacturing, validation of purity and authenticity, and insufficient clinical trials to validate health claims and/or assertions. As a result, provision of information about mushroom-derived dietary supplements and mushroom nutraceuticals from medical, dietetics, and nutritional professionals should be based on the most current, peer-reviewed information available regarding appropriate selection, proper use, etc. Due to considerable therapeutic potential, dietary supplements and mushroom nutraceuticals may have a plethora of applications for maintenance and promotion of health and life quality of consumers. More than 600 human clinical trials involving dietary mushrooms have been conducted and published demonstrating health benefits. Moreover, several potentially efficacious mushroom compounds have proceeded through phases I, II, and III clinical studies and are being used successfully throughout parts of the world to treat various chronic diseases.

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