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The Synbiotic Role of Mushrooms: is Germanium a Bioactive Prebiotic Player? A Review Article

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Abstract *Background:* Mushrooms have been widely used as medicinal products. In developed countries, only in the past few decades, special attention has been given to dietary supplements as sources to improve health and wellness. *Aim of the study:* This review critically assessed the mode of action of mushrooms, their extracts and biomass, following our research on mode of action, efficacy and safety of mushroom nutrition. *Results:* The nutritional role of mushroom products, as indirect probiotics, as direct prebiotics or as both (synbiotics), is justified by their influence on the inflammation process and on the gut microbioma through their contents of β-glucans, enzymes, and secondary metabolites. A possible new concept is advanced, that ultra-trace elements (e.g. germanium) may play an eventual prebiotic complementary role on the mode of action of mushrooms. *Conclusion:* The special properties of mushrooms along with their minimal side effects make them ideal candidates for developing novel dietary supplements and therapies.

Keywords: *mushroom, microbiota, gut health, metalloid, bioactive compounds*

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1. Introduction

Fungi are a group of eukaryotic organisms that include yeasts, moulds and mushrooms, and are major decomposers in certain ecosystems and essential associates of many organisms. Recent estimates based on high-throughput sequencing methods suggest that as many as 5.1 million fungal species exist. Some 14,000 species of fungi can be considered as mushrooms, and at least 2,000 species have been identified as edible.

Mushrooms are appreciated for their nutritional value and health properties. Medicinal mushrooms, used for millennia as healing tools due to their acclaimed but unexplainable and peculiar impact on well-being, have only recently been the subject of scientific evaluation in the western world. Mushrooms are producers of bioactive molecules, phenolic and antioxidant compounds, valuable enzymes and substantial amount of dietary fibres with specific different therapeutic effects [1,2] and more than 120 remedial consequences of these molecules have been disclosed [3].

The term prebiotic was coined in 1995 [4] to describe the fact that non-digestible food ingredients have beneficial effects on the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already resident in the colon, and thus attempt to improve host health.

Prebiotics are non-digestible food ingredients, mainly fibrous polysaccharides that stimulate the growth of lactic acid bacteria and bifidobacteria in the gastro-intestinal tract and have a beneficial effect on the host by selectively stimulating the activity of these bacteria in the colon [5]. However, this definition would be more precise if, besides food, it referred to nutrients since organic trace mineral sources, such as proteinate and amino acid chelates, copper and zinc may also be considered as prebiotics [6,7].

Mushrooms are a source of potential prebiotic substrate and all mushroom species bioaccumulates prebiotic trace minerals copper and zinc [8]. As they contain many different polysaccharides such as β-glucans and hemicelluloses, mushrooms fulfil the potential for a new concept: a combination of synbiotic effect of targeted pre- and probiotic sources. Well studied mushroom polysaccharides, β-[1→3]-D-glucans [9] and their peptide/protein derivates (PSK and PSP, polysaccharide-peptide/protein complexes) and mucoproteins (formed by glycosaminoglycans covalently attached to core proteins), are essential prebiotics found to play a vital role in immunomodulation and antitumour activities [10,11,12]. β-glucans are glucose polymers absent in humans but constituents of plants and the cell wall of certain pathogenic bacteria and fungi [13].

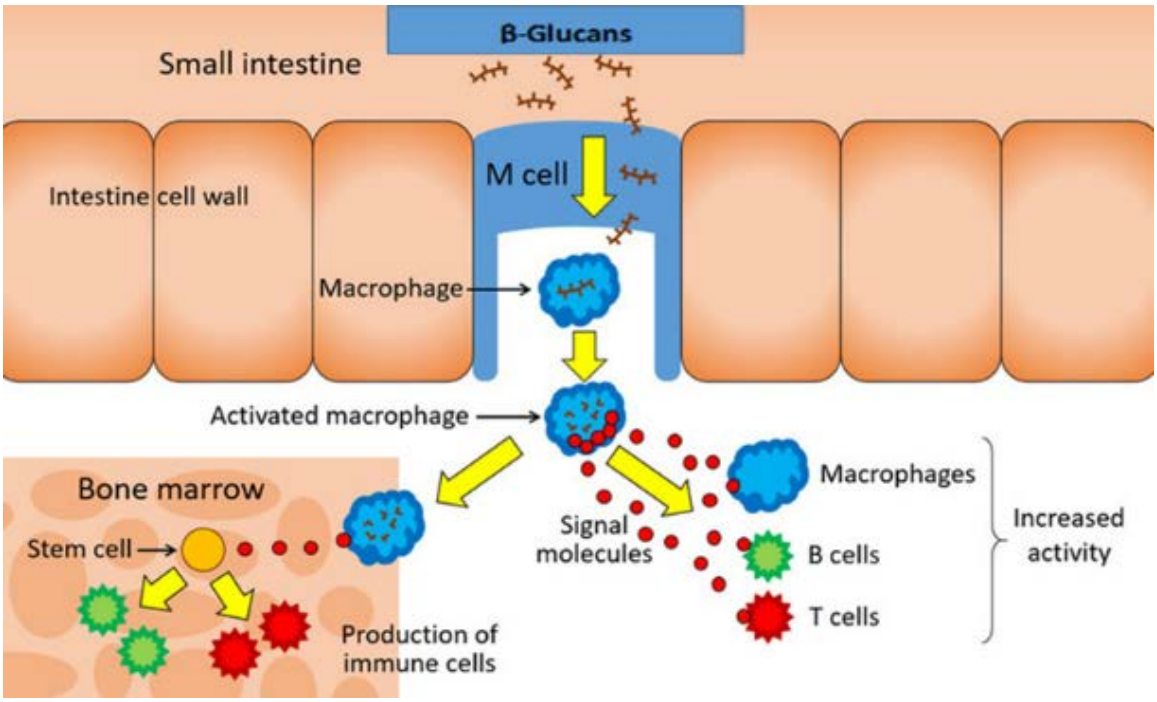

Figure 1. β-glucans, primarily in the ileum area through specialized M cells, increase host immune defence by activating complement system, enhancing and activating macrophages and natural killer cell functions. A large number of T cells, B cells, macrophages, and dendritic cells hover here and as the phagocytes engulf and digest antigen, they then present antigen markers to the T cells

They play a role in common colds, influenza, allergies, hepatitis, Lyme disease, ulcerative colitis, cancer, cholesterol, HIV, ear infections, aging, ulcerative colitis, Crohn's disease, diabetes, fibromyalgia, rheumatoid arthritis and multiple sclerosis [14,15,16,17], all through increase of the immune system function [18] (Figure 1).

Many of these compounds with carcinostatic activity [19], may be consumed as part of the normal diet and may have been modified/enriched in some way to provide health-giving benefits [20,21]. The nutritional role of mushroom products, extracts or biomass, as indirect probiotics, as direct prebiotics or as both (synbiotics), is presently justified by their influence on the inflammation process and on the gut microbioma through their content in fibre (β-glucans), enzymes, and secondary metabolites.

Although the underlying causes of inflammation and its role on harmful health effects remain largely unrevealed, it is clear that it contributes to several diseases. Nevertheless, the importance of chronic low-grade inflammation in older people on the onset of numerous unfavourable age-related conditions is now evident [4,22].

The role of β-glucans on oxidative stress, inflammation, immunological reactions and neurological impact has been demonstrated on many diseases [23]. All studies, mainly Asian, were based on the concept of the specific polysaccharide content. Here we advance the possible notion of metalloid germanium being responsible for mushroom mode of action.

2. Dietary Fibre and Inflammation

The unique property of mushroom polysaccharides to be non-digestible, increases their likelihood to be prospective prebiotics. Some findings provide insight into the mechanisms by which host-dietary fibre-microbe interactions establish immunological homeostasis in the gut and systemic autoimmunity [24,25].

People who eat diets high in fibre have lower circulating markers of inflammation in their blood. Host defence mechanism involves inflammation to eliminate pathogens from the site of infection, resolution and restoration of tissue homeostasis [26]. Inflammation, a defence mechanism that is vital to health, means how activated the immune system is and many different immune cells can take part in this process by releasing different substances, the inflammatory mediators [27,28,29].

Narrowing the diet, as often happens in old adults, can result in the shrinking of gut microbiome [30]. Diversity is the key and the microbiota of people on narrow diversity diets, such as in developing countries, may collapse. A change in diet in a short time modifies considerably the microbiota pattern, although it reverts rapidly as soon as the diet is discarded [31]. The majority (over 80%) of a person's gut microbiota is postulated to be transmitted from maternal microorganisms to offspring during gestation. New-born and child microbial colonization sets the stage for the adult microbiota; bacteria species in the colon at adult stage are more or less the same as when aged 6 months old [32,33].

We have previously studied the ability of mushroom diet or supplements to positively modulate inflammation as unresolved inflammatory process [34].

2.1. Gut Microbiota and Fibre

Most human major diseases have a physiological, environmental or lifestyle base, but it is likely that gut microbiota may interact and share the overall risk as they coevolve during their lifetime. Since the 50's, short chain fatty acids-SCFAs (acetic, propionic, butyric) are well known metabolites in ruminant and equine nutrition,

production and metabolism [35]. SCFAs activate intestinal gluconeogenesis via a gut-brain neural circuit [36], which can have beneficial effects on glucose and energy homeostasis [37,38].

The benefits, in humans, of consuming fibrous rich diets and how volatile SCFAs associated with these diets can improve the health of gut microbiota, have also been extensively studied [39,40,41]. Gut microbiota yields vitamins and exogenous fibre-degrading carbohydrases. The human body, by definition, does not produce vitamins (e.g. B group vitamins: riboflavin, folate and thiamine) nor enzymes able to degrade cellulose and hemicelluloses, which is accomplished by gut bacteria.

Another important role of gut microbiota is their interaction with xenobiotics (e.g. dioxins and polychlorinated biphenyls), including persistent organic pollutants and foodborne chemicals, which may disrupt microbial digestion and impact on host homeostasis [42,43]. It remains unclear how quickly and reproducibly gut bacteria respond to dietary changes.

3. The Prebiotic Role of Mushrooms

The balance of microbiota profile is crucial for human well-being, health and disease prevention [44,45]. Because of its resident microbiota, the human colon is one of the body's most metabolically active organs since colonic bacteria itself is considered to function as an organ [46]. However, due to the dynamic and complex nature of the human gut microbiota ecosystem it is difficult to understand the future microbiome composition [47,48].

Prebiotics are promising health compounds because they can regulate the structure and number of intestinal flora [49] (Figure 2). Mushrooms are rich in polyphenols and polysaccharides such as α-glucan, β-glucans, chitin, galactans, hemicellulose, mannans and xilans making them suitable for prebiotic use. But not all dietary carbohydrates are prebiotics and the most commonly used are FOS: fructo-oligosaccharides, GOS: galacto-oligosaccharides, XOS: xylo-oligosaccharide, fructans (e.g. inulin) [50].

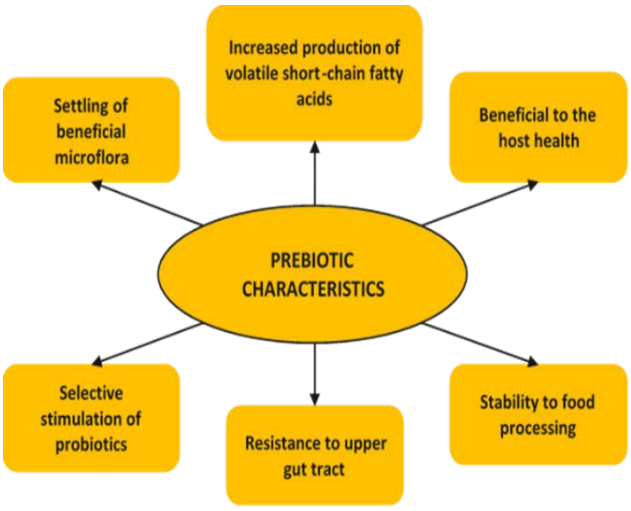

Figure 2. Prebiotic features on gut SCFAs production, on clusters of microbiota and eventual host benefits

The most frequently studied β-glucans obtained from mushrooms include lentinan from shiitake mushrooms *Lentinus edodes*, grifolan from *Grifola frondosa*, schizophyllan from *Schizophyllum commune*, SSG from *Sclerotinia sclerotiorum*, PSK (called also Krestin) and PSP (polysaccharide peptide) from *Coriolus versicolor*, and β-glucan called pleuran isolated from *Pleurotus ostreatus* [51,52].

These β-1,3-D-glucans are used as prebiotic dietary supplements, showing positive effects on the intestines and increasing the resistance of intestinal mucosa to inflammation [53,54]. Protein-bound polysaccharides, PSK and PSP, are extracts from mushroom *Coriolus versicolor* and have been the subject of extensive research by Asian scientists, being approved as nutraceuticals by Chinese and Japanese Food authorities [55].

The biological activity of these products is related to their immunomodulating properties, which enhance the body's defences against various forms of infectious diseases, including carcinostatic activity [56]. We have performed a safety assessment of *Coriolus versicolor* biomass as a food supplement which showed the absence of any remarkable adverse effects in rats [57].

4. The Indirect Probiotic Effect of Mushrooms

Probiotics have been used for as long as people have eaten fermented foods, i.e. dating from 7000 to 6600 BC. The beneficial effect of probiotics is mediated by multiple mechanisms of action such as resistance to low pH in the stomach, competitiveness to microbial species inhabiting the intestinal ecosystem, antagonistic activity towards pathogens (e.g., *Helicobacter pylori, Listeria monocytogenes, Clostridium difficile* and *Salmonella sp.*) [58,59].

Other possible functions include resistance to bacteriocins and acids produced by the endogenic intestinal microbiota and adherence and ability to colonise sites within the gut wall [60].

Lactobacillus, Bifidobacterium, Lactococus, Streptococcus, Bacillus, Enterococcus and yeast *Saccharomyces* are the most common probiotics and generally considered safe to consume. However, a good probiotic culture must be ingested continuously to have better effects [61].

Mushrooms (e.g. *Pleurotus ostreatus, Hericium erinaceus, Coriolus versicolor* and *Lentinus edodes*) can significantly modify intestinal flora composition by promoting the metabolism and proliferation of beneficial microorganisms such as *Lactobacilli* and *Bifidobacteria*, as well as by inhibiting pathogenic bacteria such as *E. coli*, *Clostridium* and *Salmonella* [62].

Mushroom ingredients have therefore an indirect probiotic role as they affect the type of microbiota. Gut bacteria feed on mushroom fibre such as β-glucans found in the cell walls of bacteria, fungi, yeasts, algae, lichens, and plants [63,64].

These polysaccharides act as prebiotics and are sometimes used as herbal medicine with multiple recognized clinical uses of mushroom β-glucans [65,66]. Bacteria feed on dietary fibre. If we do not feed bacteria, they feed off the host, more specifically off the mucus lining in the large intestine. Health-promoting gut microbes besides the production of useful SCFAs yield microcins, which are small protein molecules, retaining their biological activity and effectively improving health-promoting properties [67,68,69].

4.1. The Immunoceutical Role of Mushrooms

The immune system is a network of special cells, tissues, proteins, and organs that work together to protect the body from potentially damaging foreign invaders and disease. A lot remains unexplained about immune function and immune system misconceptions and myths are frequent, while industries take advantage to explore them. The idea of boosting immunity is tempting, but the capability to accomplish has proved deceptive for various reasons [29].

The immune system is precisely a system, not a single entity and it is highly individual and of complex nature, which is almost as specific to each individual as are fingerprints [70]. To function well, it requires stability, equilibrium and harmony and depends on age, lifestyle, and stress, exercise and diet although there are no scientific evidences of direct links between many lifestyle habits and variations of immune function. It is a fact that there are no medications to date that directly increase the activity of the immune system. Complementary or alternative products have been researched towards this objective [71].

Mushrooms seem to be a potential source for prebiotic compounds displaying immunomodulation and antitumour activity similar to those resulted from immune effector cells [72,73,74].

Edible mushrooms may be a potential source of natural antioxidants with free radical scavenging properties for application as a functional food ingredient. A large part of phenolic compounds (e.g. gallic acid) are associated with the presence of polysaccharides, and they are released in the colon following the fermentative actions [75].

On the onset of a common infection, the innate immune is promptly activated, through macrophages and neutrophils as the true maestros of resolution and regeneration, contributing crucially to the activation of adaptive immunity and controlling common infections [76].

Mushrooms play essential roles in innate and adaptive immunity, by enhancing the body's own use of macrophages, NK-natural killer cells and T-lymphocytes, rather than directly attacking any tumours [77,78]. The immune response regulation also affects anti-tumour properties. The immune response to β-glucans could be in part non-specific and determined by size rather than by chemical structure [79].

Mushrooms contain a mixture of β-1,3-glucan and β-1,6-glucan [80]. Macrophages in the mucous lining of the intestinal wall pick up the β-glucan particles through the β-glucan receptors. Absorbed through the intestinal cell wall into the lymph, they suffer macrophage phagocytosis and the immune function is activated [81,82].

5. Synbiotics

A synbiotic product is a combination of pro- and prebiotics as food ingredient or dietary supplement in a form of synergism, hence synbiotics, to enhance human and animal health. However, the FAO recommends that the term "synbiotic" be used only if the net health benefit is synergistic i.e. when one pre- or probiotic really increases the other's effectiveness [62].

The most common synbiotic is the combination of *Bifidobacterium* or *Lactobacillus* bacteria with FOS-fructooligosaccharides. A prebiotic compound must have the capacity not to be digested or absorbed in the small intestine neither by the host nor by bacteria, and pass into the caecum unaltered, where selectively it will be used by probiotics [83]. Long-term consumption of a synbiotic formulation with *Lactobacillus fermentum* (probiotic) and β-glucan from cauliflower mushroom *Sparassis Crispa* (prebiotic) prevented menopausal symptoms and improved the gut microbiota [84].

It is critical to recognize that there are an immense variety of probiotics with strain-specific effects, which makes it clear that extrapolations on benefits and harms cannot be made among available products [85].

5.1. Factors behind the Health Benefits of Mushrooms

Ginseng, aloe vera, broccoli, celery, comfrey, goji berry, chamomile, garlic, cumin, ginkgo, ginger, paprika, microalgae, seaweeds, shiitake mushrooms, green tea, watercress, leafy vegetables, and many other natural and fermented foods are regularly recommended by nutritional and healthcare practitioners. Their role as antioxidants is consensus despite the miscellaneous variety of proposed mechanisms of action [86,87,88].

For thousands of years, humans have turned to mushrooms that have mysterious abilities on healthcare. Some of 55 major nutrients and energy sources have been well described, however, thousands of other elements are consumed including over 100,000 phytonutrients and vast number of trace elements. Only in milk more than 600 fatty acids have been identified.

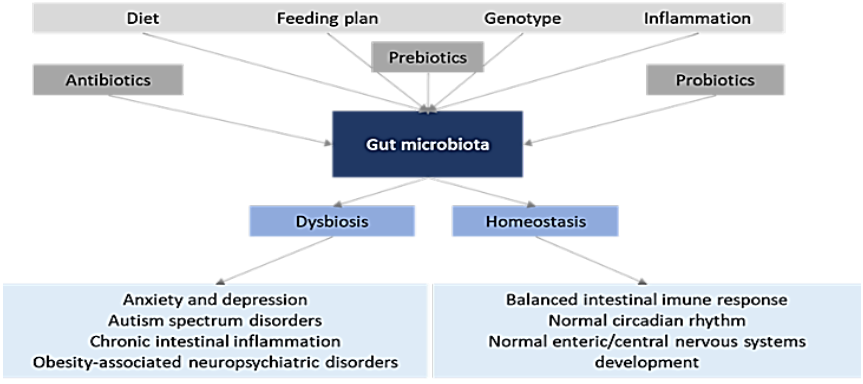

Figure 3. Gut microbiota may be affected by many factors. Immune homeostasis, counteracting dysbiosis, is achieved and maintained due in part to the extensive interplay between the gut microbiota and host mucosal immune system

This is the reason for encouraging food diversity as being the most adequate way of balancing nutrient and micro- and ultra-trace nutrient intake. Therefore, caution must be taken when pinpointing factors and mode of action when reporting the beneficial impact of any foodstuff (Figure 3).

Although mushrooms have been reasonably described for their β-glucans content they are not the cure-all that some people and firms claim, and why they work so well in several health problems is still under research and debate.

Indeed, no specific food has been acknowledged by scientists and government regulatory authorities as providing a health benefit.

6. Trace and Ultra-trace Minerals and Metalloids

Less than five decades ago many essential minerals were believed to be irrelevant to human metabolism and health and are now considered vitally important. While some metals, e.g., Fe, Co, Mo, Mn, Ni, Se, V and Zn, are essential nutrients for bacterial growth, microbiota interacts and processes metals and metalloids. Hence, since the 70s, bioinorganic chemistry or microbial biogeochemistry dedicated studies on microbial metabolism of inorganic elements.

It is an understanding that individual classes of metabolites cannot be considered in isolation and there are chemical links between different metabolites or chemical structures. Copper and Zinc, which are essential bio-elements, are well bio-concentrated by mushrooms in fruit bodies. Comprehensive studies on bio-concentration of heavy metals (Ag, Al, Ba, Ca, Cd, Co, Cu, Fe, Hg, K, Mg, Mn, Na, Rb, Sr, and Zn) and consumer exposure to mushrooms reveal the importance of Cu and Zn and the natural cycling of these metallic elements in forest ecosystems [89].

The challenge for prebiotic chemistry is to clarify the connections between the various chemical substructures of life and explaining how they can fit together to establish the convolutions that lead to life [90].

Nucleic acids act as informational molecules playing a crucial role in modern biology. A non-enzymatic process through a mineral catalyses the RNA oligomer formation; copper operates as a prebiotic catalyst by interacting with ribonucleotides [91,92,93].

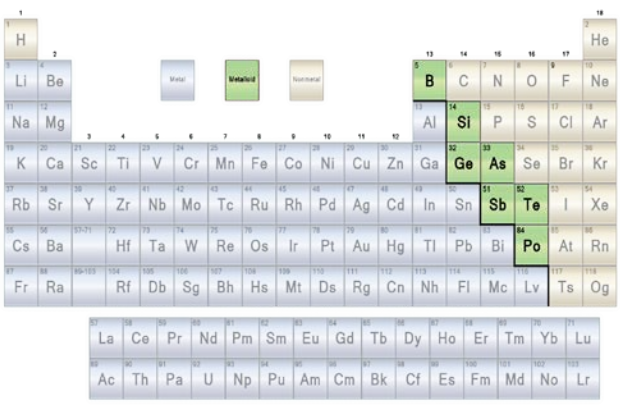

Figure 4. Metalloids in the Periodic Table

The following elements are generally classified as metalloids: boron (B), silicon (Si), germanium (Ge), arsenic (As), antimony (Sb), tellurium (Te), and polonium (Po) (Figure 4). The elements to the upper right of this line display increasing non-metallic behaviour. The elements to the lower left of the line display increasing metallic behaviour.

Metalloids encompass a group of biologically important elements ranging from the essential and beneficial to the highly toxic. Genetic evidence has demonstrated a crucial role for specific major intrinsic proteins (MIPs) in metalloid homeostasis thus suggesting that they could be potential pharmacological targets [94].

The second-most abundant element in the earth's crust and the third most abundant trace element in human body is silica (the oxide form of silicon), an essential trace mineral for bone density and key ingredient in collagen creation [95]. Studies on bioactive beneficial trace elements such as metalloids (e.g. germanium, silica) in foods, plants and mushrooms are scarce and little understood; while it has been suggested that they are essential elements they also have recognised oxic effects [96,97,98].

In humans and other mammals the role of metalloids (if any) is less well defined despite being a common dietary trace element 20-50 mg silicon/day is ingested by adults in western populations [99]. Silicon is inert and until recently was suggested not to take part in any chemical or biological interactions while in higher plants silicon is up taken and accumulated [100] and interaction with bio-molecules is possible [101].

Factors that determine the flux of silicon in the human body are poorly understood although the absorption and excretion is known not to be dependent on sex and age [102]. The oral exposure in humans to a small soluble molecule (orthosilicic acid, $Si\ [OH]_4$) of silicon did not provide any evidences on the balance of values of intake, excretion and exchange with the body Si pool [103].

The Panel on Food Additives and Nutrient Sources Added to Food of EFSA (European Food Safety Authority) evaluated the ch-OSA (choline-stabilized OrthoSilicic Acid) safety. The objective was to evaluate it as a silicon source and also its bioavailability. However, silicon safety itself, in terms of daily amounts that can be consumed and its classification as a nutrient, was outside the scope of the scientific opinion of EFSA [104].

There are few studies evaluating the safety, efficacy and bioavailability of the different existing chemical forms of silicon that use proper design, large number of volunteers and long follow-up period and much less is actually known on germanium [105].

6.1. The Case of Germanium

Germanium is present in all living plant and animal matter in micro-trace quantities and a comprehensive review of the metabolic distribution, physiological characteristics, biological functions, effects on immunity, germanium deficiency and germanium toxicity have been recently conducted in animals [106].

There are two general forms of germanium: organogermanium compounds, which are carbon-containing compounds (carboxyethyl germanium sesquioxide, spirogermanium, propogermanium, Ge-132); and

inorganic (non-carbon containing) germanium compounds (Ge, germanium citrate lactate, germanium dioxide) [107,108]. Elemental germanium is classified as inorganic which is present in all living plant and animal matter in micro-trace quantities [109].

The water soluble, highly stable, non-toxic organic germanium sesquioxide (Ge-132) is an ultra-trace metalloid or semi-metal used in Japan since 1967 but a novel water-soluble food supplement in the Western world [110]. Ge-132 is a synthesized form and is quite abundant in garlic and several other foods including mushrooms with significant potential for treating various human illnesses and promoting lifestyle. Since the elements of similar atomic number are biologically-essential trace elements (e.g. selenium), one might anticipate that germanium plays a role in human biochemistry.

Mechanisms by which bacteria dispose of metal pollutants and circumvent their toxic influence have major implications in environmental, medical, and biotechnological domains. This may include the bioremediation of waste sites, chelation therapy, and the production of unique metabolites. Although the concentration of heavy metals in fruiting body of mushrooms and their substrates is well studied, very little still is known on trace and ultra-trace elements and regular consumption of wild-growing mushrooms is discouraged [111].

The first reported study on germanium [112] referred that this metalloid occurs in high concentrations in certain medicinal plants, and that a synthetic derivative appears to have significant clinical efficacy, thus reopening the question of its biological essentiality. This report mentioned concentrations of germanium in foods and other biomaterials ranging from 0.1 to 1 ppm, corresponding to 0.1 to 1 μg germanium/g of food material, quite lower values later determined by others.

Very little information is available on the germanium content of food while well-known and widely used market products (e.g. garlic) have high levels of germanium (Table 1). The average daily intake of germanium for humans has been variously estimated to be from 1.5 to 0.4 mg/day [113].

Table 1. Germanium content in several foodstuffs [115,116]

Food	Ge content (ppm)
Processed food	
Scallops	0,008
Oysters	0,012
Frozen clams	0,023
Frozen shrimp	0,032
Raw clams	0,032-0,203
Canned tuna	3
Canned tomato juice	5
Baked beans	5
Unprocessed food	
Chlorella	76
Aloe vera	77
Comfrey	152
Edible climbing bell flower [*Codnopsis lancelata*]	239
Watercress (*Trapa japonica* Flerov)	239
Ginger	250
Ginseng	320
Garlic	754
Mushrooms	
Phellinus mushrooms	0,32-1,56
Coriolus versicolor	184-213
Coriolus cinnabarinus	800-2000

Despite the existence of an international standard [114], the method applied for determination of germanium in soil, food and water samples has been quite variable therefore the values recorded depend on the method of analysis, the reproducibility among laboratories and several other variables. The observed range of germanium levels varies significantly in the literature most probably due to different methodologies used.

6.2. Activity and Function of Germanium

The therapeutic effects of organic germanium in a wide range of serious afflictions, have been reported [117,118]. The power of germanium is based on the fact that it increases oxygenation in the body tissues, considered more efficient than vitamin E, discharge accumulated hydrogen and washout of toxic heavy metals. It has also a potent antioxidant activity against hydrogen peroxide-induced oxidative stress although the oxygen modulation mechanisms not yet clear [119]. Oral Ge-132 intake increases plasma α-tocopherol levels by up-regulating α-tocopherol transfer protein [Ttpa] gene expression [120].

Just like selenium, inorganic germanium non-carbon containing compounds, i.e. germanium dioxide, germanium citrate lactate, and elemental germanium, are potentially toxic and should not be confused with organic germanium. Because of the possibility of contaminated organic germanium products on the market and several unclear and poor-quality scientific reviews, all types of germanium are currently thought of as unsafe. The high-purity synthetic organic complex of selenium is safe, with much lower toxicity than the inorganic form, and is used as a dietary supplement [53], being totally secreted intact from the body within 48 hours.

Organic germanium compounds are described as antioxidants and inhibiting the progress of cancer and AIDS and destroying cancer cells [121]. The organic germanium compound, Ge-132, has immune-modulating effects and is marketed as non-prescription drugs in Europe being recommended by the suppliers for AIDS and metastatic cancer disease [122]. The metalloid organic germanium may be a vital element for the ability of mushrooms *Ganoderma lucidum* and *Coriolus cinnabarinus* to fight cancer cells [55,123]. The combined effects of Ge-132 with *Lactobacilli* and oligosaccharide on the immune responses of mice suggest that this combination with a low concentration of Ge-132 stimulates the intestinal immunity [124,125].

The ingestion of Ge-132 promotes bile secretion [126] and significantly elevates the activities of hepatic superoxide dismutase (SOD) and catalase following herbicide paraquat ingestion. Data clearly demonstrated in rigorous scientific studies that Ge-132 may be useful as an antioxidant detox [127].

Direct use of bioactive phytochemicals from mushrooms (e.g. *Coriolus versicolor*) for gene vector development was studied to be used as a multi-therapeutic gene carrier for tackling cancers [128]. Besides the already well described and established role of these fibrous polysaccharopeptides, we advance with the possibility that other bioactive mushroom ingredients may be responsible for the mechanism of action on health benefits which have not been the subject of much research.

Although germanium supplements have been approved and used in Japan since the 70's, a proven safe and effective dose for organic germanium needs to be investigated [129] since there are reports demonstrating that dietary supplements of organic germanium may be toxic being evident that germanium products present a potential human health hazard [130,131,132,133].

There are some 2000 mushrooms identified as edible and a large number of the species are yet to be analysed for their nutraceutical/medicinal potential and the determination of germanium in botanical samples is necessary [134].

7. Concluding Remarks

Mushroom biomass and extracts are good choices for people with an already weakened immune system. They do not perform miracles neither do they have a specific role for each illness, rather, they support the immune system, assisting in preventing or mitigating the effects of a range of several ailments. However, dose setting, safety of use, and toxicological and clinical trials documenting the desired health effects are still necessary.

Current evidence does not support recommendations for or against single-nutrient or trace element supplementation. We have enhanced the need for a new field of research on the content of metalloids in mushrooms and plants with known beneficial health impacts. Only after a successful *in vitro* and *in vivo* testing on a wide statistical set of selected population groups and clinical trials, recommendations may be formulated.

There must be in future enlarged policies encouraging the development of common strategies and agendas, internationalisation of clusters among the Western world (EU and USA) with Asian scientific communities (China and Japan). Developing innovation, policy measures, scientific cooperation opportunities, while promoting competitiveness and understanding the huge difference on existing backgrounds among civilizations is necessary.

Conflicts of Interest

THF drafted and all authors contributed equally, and declare no conflict of interest and were not paid for the manuscript. No financing was involved.

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