A Food Pyramid for Sub-Saharan Africa. Health Protection with Mushroom Nutraceuticals

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Abstract

In Sub-Saharan Africa, despite poverty, chronic hunger and food insecurity, traditional eating has been related to positive health outcomes and sustainability. There is little health research on diet quality based on what African people consume. The defining characteristics of the traditional African cuisine are the richness in herbs and spices, fermented foods and beverages, and healthy and whole ingredients used. However, as countries in this region become more economically developed, there is a shift to "modern" occidental foods rich in saturated fats, sugar and sweeteners. As a result, there are increased incidences of previously unreported ailments due to unbalanced diet. The regular practice of infinite international aid to the region to curb food insecurity has been unsustainable, ineffective and with no end in sight. Local increase in production and productivity is imperative. Protein rich foods in dietary guidelines enhance only those of animal or plant sources while rich protein sources such of mushroom, has been absent in these charts. This article considers the valorisation of traditional African foods and the importance of establishing an African Food-Based Dietary Guidelines (AFBDGs), an unprecedented Food Pyramid, along with the added emphasis on the potential of African mushrooms, which may play a role in shielding Sub-Saharan Africans against the side-effects of a western stylish diet and promote health. It enhances the preventive role of mushrooms in viral diseases and other disorders.

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Keywords: *food pyramid; African foods; mushrooms; viral diseases; nutritional guidelines*

1. Introduction

There is little health research on diet quality based on what African people consume. In Sub-Saharan Africa (SSA), comprising some 44 countries, despite poverty, chronic hunger, food insecurity, the trend to modernisation and introduction of new foods and eating choices, traditional eating has prevailed and considered positive in relation to health outcomes and sustainability.

The global food system is very complex and influenced by many different inputs, farming, economics, politics, environment, transport, storage, and consumers. These factors are aggravated in SSA, where notwithstanding its vast arable land is the second world region with the highest prevalence of malnutrition and a net importer of food [1]. The regular practice for the past decades of infinite international aid to the region to curb food insecurity has been unsustainable, ineffective and with no end in sight. However, there is a great potential to increase food production, productivity and reduce poverty and food insecurity in this region.

Malnutrition comprises over-nutrition and under-nutrition (wasting, stunting, and underweight), reflecting disproportions in intake of energy, proteins, essential fatty acids, phytonutrients, vitamins and/or minerals. It is frequent the concurrence of both under-nutrition and over-nutrition in the same population across the life course probably due to inadequate dietary intake or diseases, and inadequate nutrition is still one of SSA's primary concerns for enhanced human development [2]

In general, despite Africans smoking less and having more physical exercise than in developed countries, when food is available, the African diet rivals the healthy Mediterranean diet. However, in African urban areas, with the growing acceptance of “western” eating habits, one can expect more non-communicable diseases or chronic diseases (e.g. diabetes, cardiopulmonary diseases, cancer) for which African healthcare systems are unprepared [3].

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Among many possible initiatives to improve food and nutrition security in SSA, here we approach just two prophylactic steps against the onset of this trend to malnutrition, necessary to be established during childhood:

a) The creation and implementation of an African Food-Based Dietary Guideline that encourages sustainable dietary practices. Ideally, this guideline needs to be specifically designed for each of the main six African regions.
b) The incorporation of African indigenous foods into the existing diet; mushrooms, with proven major health benefits are detailed as functional foods.

Knowledge of what it is eaten is essential to dietetics and food science, as well as for biodiversity, agriculture production, and the food industry.

An overview of the African diet and the importance of establishing Food/Based Dietary Guidelines that apply to SSA are discussed. In addition, as known since ancient civilizations, it is emphasised the role of mushrooms as one of the most health-promoting foods on earth and a possible contributor to the African diet and well-being.

2. The African Diets

The diverse nature of African cooking has fantastic elements of different cultures – Arab, Black African, European, and Asian. Of particular note, African eating and drinking habits are significantly different in each African region.

Presently, there are some five to six main African regions and there are not many studies on food consumption patterns of the African people per country or among the 54 sovereign countries [4]. However, Africans, namely rural people in general, perform more physical exercise in their lives than people in developed countries. In addition, until recently, Africans, namely rural communities, do not eat much ultra-processed foods such as salty fatty packaged snacks, soft fizzy drinks, sweetened breakfast cereals, and instant noodles, which are nutritionally unbalanced [5].

The traditional African diet comprises more wholesome and healthful foods rather than pre-treated food (**Figure 1**). In general, the defining characteristics of the traditional African cuisine are the richness in herbs and spices, fermented foods and beverages, and healthy and whole ingredients used [6].

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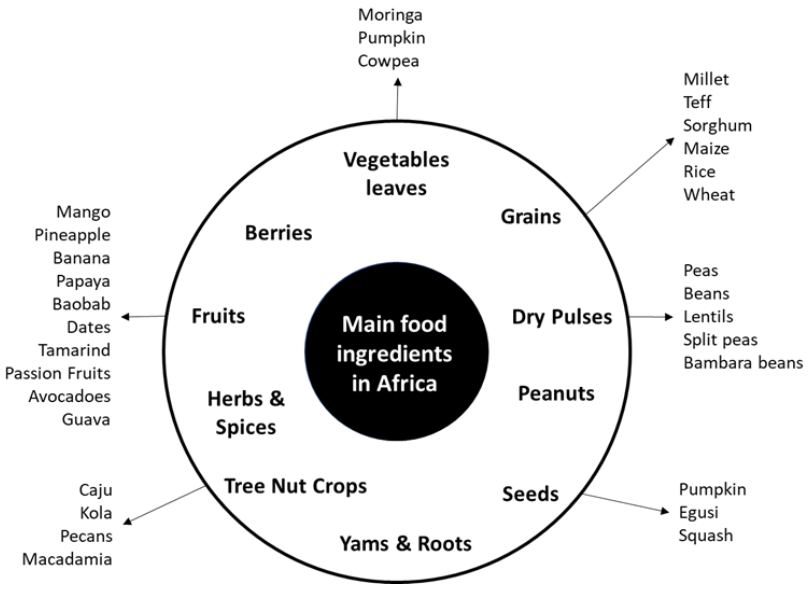

Figure 1. Main food ingredients in Africa.

In comparison with other continents, very little meat, fish and poultry is generally consumed in Africa [7]. It is considered that people in West Africa (Mali, Chad, Senegal and Sierra Leone) enjoy healthier diets than their counterparts in the United States, the United Kingdom, Japan or Canada [8].

Outlined in **Figure 2** are some select African high-nutrition foods "superfoods", worthy of this title, with high concentrations of essential nutrients such as phytonutrients, vitamins, minerals, enzymes and antioxidants, which have been identified, although no single food holds the key to good health or disease prevention.

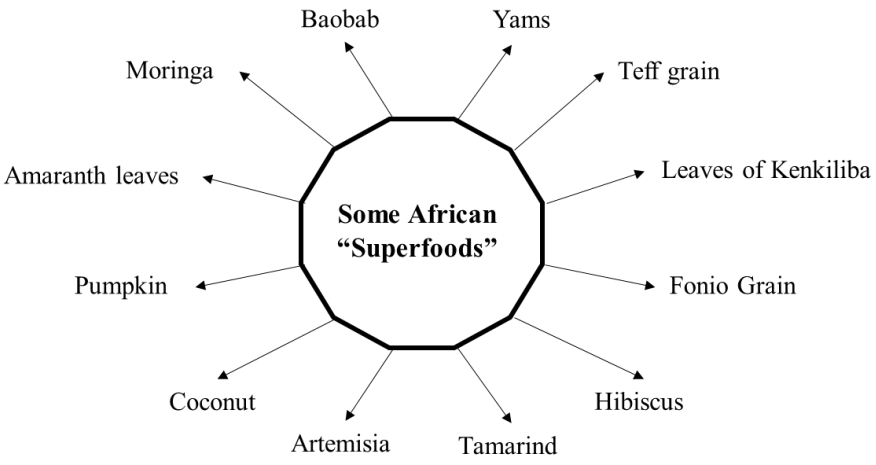

Figure 2. Some African high-nutrition foods "superfoods".

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Other foodstuffs with good nutrient counts and health properties comprise darky leafy greens, green tea, legumes/pulses, nuts and seeds, yoghurt, garlic, ginger, curcumin, avocado, sweet potatoes, seaweeds, baobab fruits, and mushrooms. Olive oil is also important but in northern Africa where Tunisia and Morocco are considered the largest producers in the world.

Meat, fish, seafood, and traditionally produced fermented dairy products (e.g., yogurt, cromwo, boeber, alouda, amasi, leite azedo) are often used as a garnish, prepared with cooking oil, tomatoes, onions, salt and spices, poured into a mash or porridge made from cereal or cassava flour. Beef, goat, chicken, eggs and mutton are quite expensive in Africa, so these foods are reserved for special days. However, fish and seafood are abundant in coastal regions and in many lakes.

Sustainable diets in Africa, including indigenous and traditional foods (**Figure 3**), must respect biodiversity and environmental impacts, contributing to production of affordable, nutritive, and social-cultural acceptable foods for present and future generations [9].

Figure 3. *Moringa leaves and tamarind fruit, widely used as food and for medicinal purpose.*

Most countries periodically review their multi-sectoral nutrition strategies and consider both more effective nutrition-specific intervention approaches (e.g. supplementation, fortification) and/or a shift to actions at the level of underlying causes (e.g. promoting optimal breastfeeding and complementary feeding, diet diversification). We have previously considered the issue of monotonous diet, lack of diversification, and fortification as a matter of business as much as science [10].

3. African Nutritional Guidelines

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Food-Based Dietary Guidelines are science-based suggestions in the form of instructions for healthy eating. Designed for information to customers and technical advisors, they must be suitable and relevant for each country, culturally appropriate and easy to implement. Moreover, they should be harmonious, comprehensible and unforgettable [11].

The human right to adequate food has cross-sectoral and multi-dimensional impacts but the present global food regulatory framework is confusing and limiting [12]. Many challenges still remain regarding the establishment of dietary guidelines integrating education, agriculture, health, environment and industry.

Nutritional guidelines around the world are presented in different configurations, exhibited as pyramids, plates, baskets, texts, circle graphs, diagrams, and tables, yet similar in terms of content, giving consumers a number of advised food groups and daily servings to maintain optimum health [13].

Many developed countries have established dietary guidelines, but implementation plans are often not comprehensive enough for consumers. In Africa, food-based dietary guidelines have been established in Benin, Kenya, Namibia, Nigeria, Seychelles, Sierra Leone, and South Africa.

The majority of SSA countries did not develop their own food pyramid [14] and, in general, the approach of the legal systems is broadly consistent with the International framework channelled through the Codex Alimentarius Commission since 1963 [15].

In African history, most rural life has been devoted for household production, procurement and preparation of foodstuffs, often low in nutrients, while food scarcity has constituted a major threat to survival. Unless the quality of food (i.e., safety and nutrient composition) that Africans eat is addressed, the continent will not be able to address under-nutrition and obesity-related diseases.

We have enhanced the fact that some 55 major nutrients are reasonably well characterized, and their required levels of intake calculated. However, the subject becomes quite complex when accounting for the active bioavailability of the dietary compound rather than the dose ingested [16]. Furthermore, the amount (over 25,000) of phytonutrients (e.g., flavonoids, phenolic acids, and glucosinolates) naturally occurring in plants are considered “lifespan essentials” for good health although not being

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fundamental for growth and development, this being one of the reasons to recommend nine servings of fruits and vegetables a day.

We have reviewed several national dietary guidelines throughout the world and noticed that with few exceptions, fermented foods and mushrooms are generally absent as a recommended category of food for daily intake in Food Guides, reflecting a failure to appreciate the benefits resulting from these foods [13].

Current food systems in African agriculture and animal production, are unsustainable with no diversification and no adequate integration of indigenous vegetables, being one of the greatest current threats to human health [17][18].

Africans eat starchy foods in the form of minimally processed or whole grains, legumes, beans, roots and yams, rather than refined starches and sugary products with the benefit of a high carbohydrate intake supplying 55-75% of total dietary energy [19]

The majority of African cuisines have a different starch base (sorghum, millet, maize, teff, rice, sweet potatoes, cassava, and yams) because they offer lots of calories. Starches are more filling, as they mislead the body and brain into feeling satiated [20]. Usually it is complemented with margarine or oil, supplying an extra source of energy but few essential nutrients where fried onions, garlic and tomatoes make a basic curried sauce [21]

Inadequate nutrition, whether associated with deficiency disorders or chronic diseases, is embedded in impoverishment and neediness [22]. In the poorer regions of SSA, micronutrient malnutrition exists wherever there is undernourishment due to food shortages, and it is likely to become common where diets lack diversity, even in conjunction with sufficient energy intake [23].

Food supplying proteins in dietary guidelines have been organized under the concept of being either animal or plant based while other rich protein sources, i.e., mushroom-derived, has been relatively neglected [24].

Below we propose a graphic design of a general Food Pyramid for Sub-Saharan Africa with inclusion of indigenous products **(Figure 4)**. It is an attempt since a sound or comprehensive African Food Guide Pyramid should be broader and include other information related to food safety, number of meals, amount of (un)refined foodstuffs, processing stages, access to potable water, food traditions, fermented food and beverages,

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salt and sugar consumption levels, methods of cooking, sociocultural habits and even creed and religious faiths. To note the specific inclusion of mushrooms as valuable food source of essential nutrients, namely protein and medicinal polysaccharides that have been in the past overlooked in dietary guidelines.

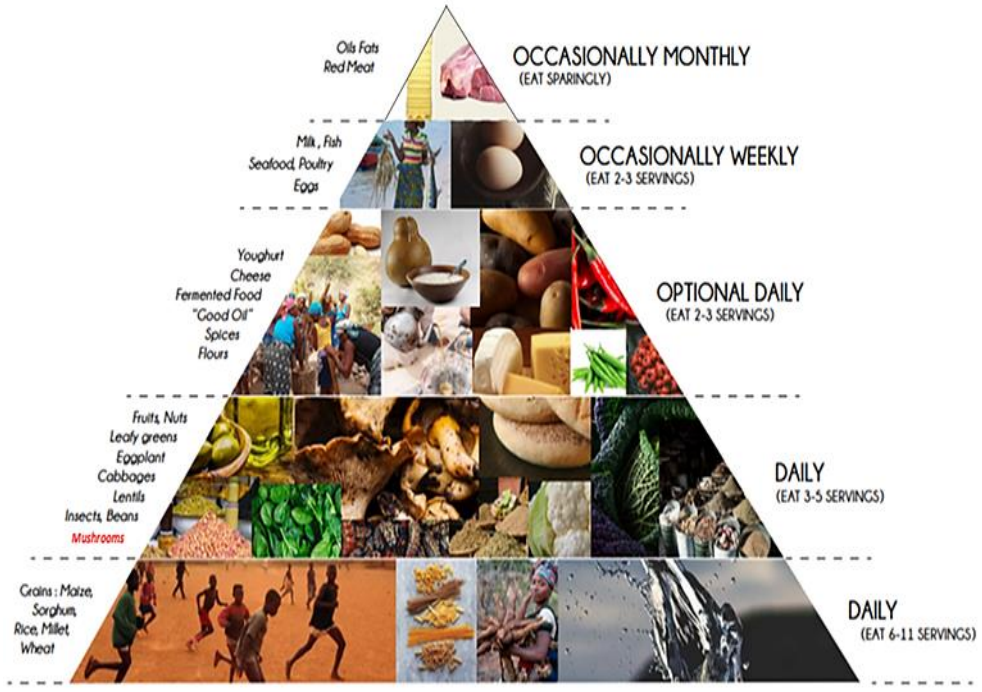

Figure 4. *The Sub-Saharan Africa Food Guide Pyramid. There are variations in amounts recommended from different food groups. A "serving size" is a standard amount of a food, such as a cup or a spoon, but they are not fixed recommendations. Recommended to drink a lot of water and teas, exercise physically daily, spare on salt, sweets, candies, processed foods, squash drinks, and fizzy beverages.*

The term "portion" means the amount of a food own selected for a refection or snack. A portion size can vary from meal to meal, depending on energy concentration, whereas "serving size" is a measured amount of food usually recommended by the food manufacturer or an external agent. There is room for all foods in a well-balanced, healthy diet, but some should be eaten less often and in smaller portions than others. Appropriate amounts eaten takes practice to land and depends on the individual.

In developing SSA countries, food deficiency distribution varies within its sub-regions and is exacerbated by systemic illness and parasitic diseases, intestinal infections, that decrease digestion, absorption and metabolism of nutrients [25][26].

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In SSA it is imperative the promotion of foods with a high ratio of micronutrients to energy content, diversifying food sources, moving away from the concept of food groups and adopt the use of local names for common foods and beverages. Each country, and probably individual region, must design specific Food Based Dietary Guidelines [27][28].

4. African Mushrooms

Mushrooms are vitally important to human life and of primary importance as global decomposers in most ecosystems and have been used in SSA since the Palaeolithic period (7000-9000 BC), where their application has been historically related to spiritualism [29].

Not attempting to be comprehensive here it is highlighted the potential and the current knowledge available on the nutraceutical value of African macrofungi underlining the global application of mushroom as dietary supplements in some major health concerns, also often used for innovative biotechnological, medicinal and ecological applications [30]. It does not underline their application in complementary folk medicine in this part of the world.

The tropical and subtropical regions of SSA are characterized by higher mushroom diversity compared to North Africa. Mushrooms (aboveground macrofungi) and truffles (subterranean macrofungi) are considered valuable foods in many cultures being rich source of different types of essential nutrients, and have been widely studied and reviewed [31][32].

It is clear that there is no single sector or actor that by themselves can establish food and nutrition security but there has to be a well-coordinated effort among them on a cross-sectorial approaches and multi-partner platforms [33]. The poor discovery, identification, and certification of edible and medicinal species of mushrooms in SSA retarded its use. There is a need for cooperative endeavours under a multi-institutional programme to seize the representative macro fungi species of SSA with a view to update their nutritional and health value [34].

Globally there are up to 3 million species of mushrooms, and as there is no single tool for their identification, only some 7% have been accurately classified [35]. There is a broad range of wild edible mushrooms but in Africa many remain poorly identified or unreported but with remarkable use in nutrition, as tonic and medicine [36][37].

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Presently in Africa wild mushrooms play a significant role in sustaining their livelihood but there are few ethnomycological reports and research on mushroom genetic resources, cultivation of undomesticated wild mushrooms, protection, and lineage improvement [38].

Mushrooms produce a vast set of extracellular carbohydrate-active enzymes and biological active molecules that degrade very complex compounds such as hemicellulose and lignin. The variety of enzymes is dependent on the habitat and specific substrates, so it differs among mushroom species and home ground [39].

Desert mushroom truffles have been used for thousands of years in Africa, include genera such as *Phaeangium Picoa*, *Terfezia, Delastreopsis, Balstonia, Delastria, Leucangium, Mattirolomyces, Tirmania*, and *Tuber* [40], and are of considerable interest for ecological reasons because of the low water input required for cultivation.

Various types of mushrooms and truffles (**Figure 5**) are considered as natural biota in the North Africa deserts [41][42] and in South Africa and Bostwana [43].

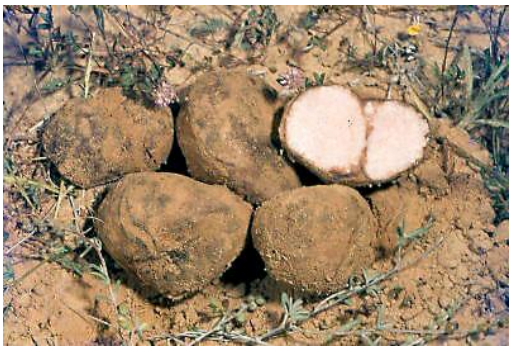

Figure 5. African desert truffles genus *Kalaharituber*

Mushrooms belonging to species of *Termitomyces, Pleurotus, Lentinus, Lenzites, Trametes, Ganoderma, Pycnoporus, Coriolopsis*, and *Calvatia* have been reported to be used in folk medicine in West Africa. Some popular wild edible and medicinal mushrooms in West Africa include *Schizophyllum commune, Lactarius sp., Chantarellus platyphyllus, Volvariella volvacea* and *Auricularia auricular-judae* [44][45].

Specific to Africa, there are more than 1000 species from the family Termitidae, constituting 95% of soil insect biomass [46]. Although they are wild, the African mushrooms, and particularly those species associated with termites (*Termytomyces*), are

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considered “superior” to all other mushrooms [47]. There are about a 30-40 mushroom species of *Termytomices* whose cap can reach 1 metre in diameter and most are highly valued as food (**Figure 6**)[48]. On the other hand, mushrooms of the species *Termitomyces, Agaricus, Boletus, Pleurotus, Cantharellus, Macrolepiota, Ganoderma*, and *Geastrum* have been reported in East and South Africa [32].

Figure 6. African *Termitomyces* mushroom.

The population on miombo dryland forest ecosystems rely directly on the woodlands for wood energy, food and nutrition. This region extends from East Africa (Burundi, Kenya, Tanzania, Uganda) to the Zambezian region (Angola, DR Congo, Malawi, Mozambique, Zambia, Zimbabwe) where most predominant mushrooms occurring include *Cantharellus* (15 spp.), *Lactarius* (incl. *Lactifluus*) (14 spp.), *Russula* (10 spp.), and *Amanita* (8 spp) [49].

Despite its millennial existence and its empirical knowledge, harvesting wild mushrooms is not a well-known concept in Africa due to the threat of being poisonous and sociological impacts (myth, culture and spirituality) [50][51], while commercial production does exist.

Mushroom cultivation is a lucrative agricultural process to produce proteins requiring compact space, temperate climate, high humidity, and waste organic substrates [52][53].

Table 1. Comparison of the most consumed mushrooms World-wide and in Africa [54].

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Most Consumed Mushrooms

World-wide	Africa
Agaricus bisporus	*Agaricus bisporus*
Lentinus edodes	
Pleurotus spp	*Pleurotus spp*
Auricula auricula	
Flamulina velutipes	
Volvariella volvacea	
	Termytomices genus

4.1 Bioactive elements of Mushrooms

Mushrooms feed on dead plant material fulfilling an essential role in the carbon cycle while harbouring numerous species with diversity of metabolites of nutraceutical and therapeutic significance [55].

Mushrooms are heterotrophic (do not perform photosynthesis) and reproduce through spores absorbing complex organic compounds from the environment as they are unable to synthesize their own organic matter [56]. The mycelia, which plays important roles as support and absorption of nutrients, rely solely on carbon obtained from other living organisms, i.e., plants, insects, and even other mushrooms, for growth.

There is abundant literature and we have described the nutraceutical value of some edible mushrooms and culinary-medicinal mushrooms, their biomass or extracts, which contain many low molecular bioactive components termed secondary metabolites since they are formed due to the enzymatic resections of primary metabolites (amino acids, sugars, vitamins) [57].

The most common metabolites in mushrooms include polyphenols, phenolic acids, quinones, coumarins, groups of flavonoids, stilbenes, hydrolysable and condensed tannins, terpenes and terpenoids, alkaloids, lectins, sterols, lactones, antibiotics, and metal-chelating agents all of which may activate the cell and humoral immunity hence increasing resistance to disease [58][59][60][61].

Mushrooms are well known to contain different bioactive polyphenolic compounds which act as effective antioxidants based on their excellent ability to scavenge free radicals and act as reducing agents [62]. These biological cell components and secondary metabolites

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on large number of mushrooms have been shown to affect the immune system of the human consumer [63][64].

Lignocellulose is the most abundant natural biopolymer on earth and its structure being so complex affects its biodegradation, a rate-limiting steps in the global carbon cycle [65]. Most species of mushrooms synthesize enzymes that may play important functions in the human organism. The vast list of enzymes in mushrooms include hydrolases, (gluco)amylase, pectinase, acid protease, endo-1,4-p-D-glucanase and 3-glucosidase, esterases, phenol oxidases, polyketide synthase, hemicellulases (glucuronoxylanase, arabinoglucuronoxylanase, and glucomannanase), the ligninolytic system, cell wall lytic enzymes (laminarinase, 1,4-β-D-glucosidase, β-N-acetyl-D-glucosaminidase, α-D-galactosidase, xylanases, β-D-mannosidase, acid phosphatase, laccase, lignin peroxidase, manganese peroxidase, polygalacturonase-pectinase, ribonuclease and many others [66][67].

Mushrooms can produce a high variety of extracellular enzymes, hidrolases breaking down polyssacharides and a ligninolytic system, which degrades lignin and opens phenyl rings, releasing compounds or remarkable nutritive value [68].

Hericium fruiting body contains polyphenol oxidases (PPOs), including tyrosinase and laccase, strong antioxidant substances [69]. By knocking out one of six PPO genes, reducing the enzyme's activity by 30%, the common white button mushroom (*Agaricus bisporus*) has been modified to resist browning and this is being cultivated and sold without further oversight and even approved by the US government [70]. *Hericium erinaceus* was only recently first reported in temperate forests of North Africa and known to have anti-peptic ulcer activity [71][72][73].

Several studies showed that *Pleurotus eryngii* and *Ganoderma lucidum* can produce laccases and this protein can confer activity against HIV by inhibiting the reverse transcriptase [74][75].

Superoxide dismutase (SOD) is also present in some mushrooms and its important physiological role is in the primary cellular antioxidant defence and its potential therapeutic use [76]. Proteolysis is an essential part of many physiological processes in all biota and basidiomycetes mushrooms are valuable sources of proteases used in defence mechanism of living organisms. and in biotechnological processes [77]. Multiple lectins produced by *Flammulina velutipes*, *Pleurotus ostreatus*, *Ganoderma carpense*, and

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many others, were shown to have potent inhibitory activity in the cell-free translation system and prevent or retard the spread of malignant cells, through mushroom ribosome inactivating proteins (velutin, α-sarcin, restrictocin, and mitogillin), characterized by the ability to irreversibly block protein synthesis [78][79].

In addition to the presence of enzymes, we have previously discussed [80] the significance of mushroom low-molecular-weight secondary metabolites (e.g. terpenes, steroids, anthraquinones and benzoic acid) which can regulate processes such as cell cycle regulation, apoptosis, autophagy, angiogenesis, metastasis, and signal transduction cascades which are associated with the development of cancer [81][82][61].

Nucleosides and nucleotides are components of native nucleic acids participating in the generation and storage of metabolic energy, synthesis of macromolecules and cell-cell communication through interplay with cell surface protein receptors, which may trigger changes inside the cell and thus the regulation of various physiological processes in the human body via the purinergic and/or pyrimidine receptors.

The purine nucleobases (adenine and guanine), pyrimidine nucleobases (cytosine, uracil, and thymine), nucleosides (uridine, guanosine, adenosine and cytidine), nucleotides and derivatives are common in mushrooms [83], and involved in a variety of enzymatic reactions either as substrates or as cofactors. The significance in the pathophysiology of diseases and therapeutic potentials of pyrimidine scaffolds as valuable medical applications is shown below **(Figure 7)**.

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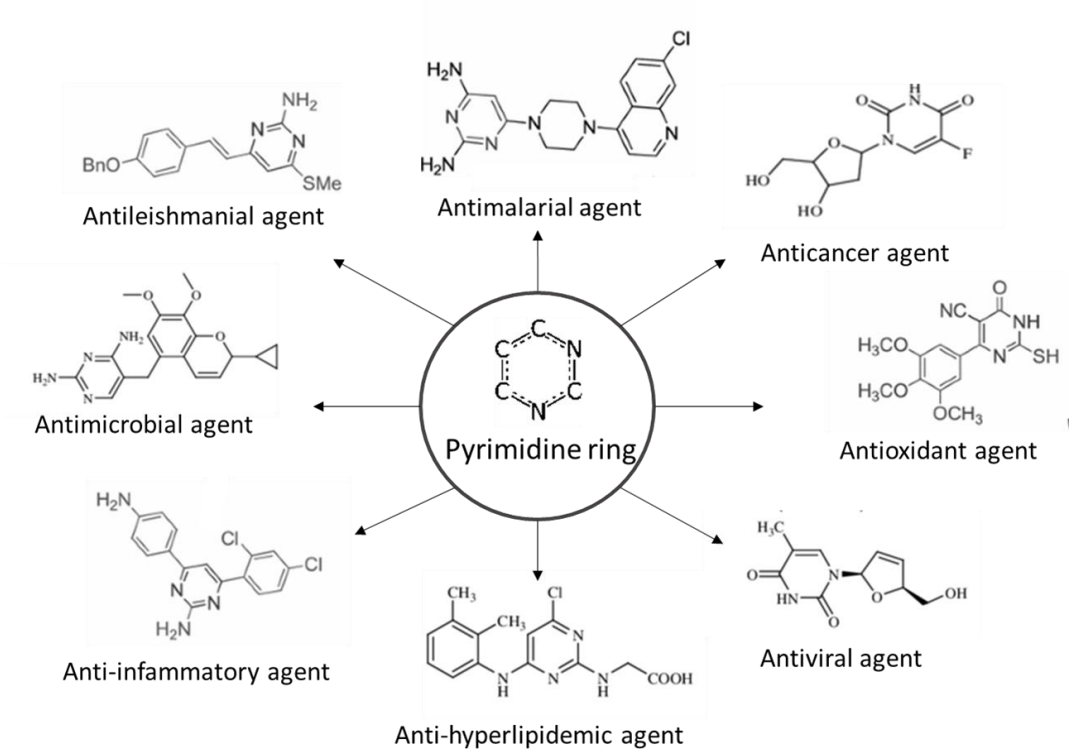

Figure 7. *Antimicrobial, antioxidant, antimalarial, anticancer, anti-inflammatory potential functions of pyrimidine derivatives* (Adapted from [84]).

From shiitake mushroom Lentinus edodes, the second most consumed in the world, it can be obtained lentinacin, a nucleoside compound well known to reduce total blood sugar and cholesterol [85]. DNA as well as novel genetically modified foods (GMOs) are composed of the same four nucleotides and consumption is considered safe since the likelihood of transfer and functional integration of DNA from ingested modified food by gut microflora and/or human cells is minimal cause mammalian cells have developed sophisticated methods to excise and destroy exogenous DNA [86]. Nevertheless, there is a practical daily safe limit of nucleic acid intake (ca. 2-4 g) in human adults [87].

5. Mushroom Nutrition and Host-Microbial Gut Interactions

The human gut is inhabited by a complex and metabolically active microbial ecosystem, a critical component of digestion and absorption. Some 57% of cells in the body are not human comprising our microbiota, mainly bacteria (60 species), unicellular parasites, yeasts, viruses, protists, fungi and archaea, divided between dominant species, more rare species, and transitory species, essentially residing in the skin and anaerobic bowel and living in harmony with the human hosts.

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Collectively, the trillions of microorganisms are called the microbiota, the microbiome being the collection of genomes from all the microbiotas. We know little about the factors framing the origin, evolution, and short- and long-term dynamics of gut microbiota composition and function [88].

Microbiota is established at birth, being a very stable system, while traveling through the birth canal and breastfeeding and this initial microbiota colonization process is crucial for the development [89], being affected if delivery is via caesarean section [90], while mothers' diet have a stronger association with microbiota than demographic characteristics [91]. At the moment of birth, a new microbial ecosystem is established in the child's gut, one that resides in that adult's gastrointestinal tract and sets the immune system for future life [92]. The dominant bacterial composition in healthy adults remains relatively stable and is influenced by long-term diet, with mushrooms playing a significant role.

The bacteria species in the colon today are more or less the same as one had when aged six months old [93]. Molecules of the microbiota can mediate the critical balance between health and disease. Microbiota make up only about 1-3 percent of the body's mass, however, genetically the microbiome outnumbers the human genome by more than 150 times. And it is the combination of both human DNA and the microbiome gene complement of the gut, and their metabolisms, which makes us human [94][95][96].

The microbiota is ultimately associated with numerous features of normal animal and human physiology and metabolism, nutritional status, behaviour, and stress response [97]. Additionally, they can be a central or a contributing cause of health and many diseases [98].

Indeed, there is strong interaction between the human gut microbial metabolic pathways and host metabolism [99]. The differences in human genetics and microbiome composition and function, life and culture diversities and variation in environmental exposures affect the nutrient requirements with impact on human mood, distress, melancholy symptoms, cultural and social attitudes [100].

Mushrooms are neither plants nor insects but fungus with a unique role in Nature and Health. Mushrooms live in symbiotic relationship with other organisms (e.g. plants) to produce their own energy while supplying nutrients to the plants, and their role on the ecosystem is singular as they are the sole organisms on Earth performing the elimination

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of residues decomposing lingo-cellulosic dead matter and reincorporating on the life cycle [101][102].

The overall balance in the composition of the gut microbial community is important in ensuring homeostasis [103]. The processes through which microbiota drives its beneficial or harmful effects, controlling health, wellness and disease, remain largely unexplained, but include development of signalling molecules and identification of bacterial epitopes by both intestinal epithelial and mucosal immune cells [104][105].

The latest thinking presents this vast army of microbes as a vital component in furnishing and maintaining human health. Such is the microbiota's importance that it is now viewed by scientists as a “separate organ” with its own dynamic metabolic activity [106]. Human gut microbiota is actually directly linked to our brains which is explained by a network of neurons lining our guts that is so extensive some scientists have nicknamed it our "second brain" [107].

The most common anaerobic microorganisms that shapes the host immune system are *Bifidobacteria, Lactobacilli* and *Bacteroides*. The genera, *Prevotella*, *Ruminococcus* and *Bacteroides* (*Fibrobacter*), were shown to have reciprocal patterns of abundance, while little is known about variation across the world [92].

The gut associated lymphoid tissue is critical to maintaining normal digestive processes. Some 80 % of human immune system lies in the gastrointestinal tract and 20 % in the back of the mouth (e.g. amygdala) enhancing the fact that an optimal health starts in the gastrointestinal tract [108]. The connection between the gut, brain, and immune function explains why the intestinal health, food and dietary supplements ingested, can affect mental and neurological health, influencing mood and well-being, stress and anxiety [109].

Improper waste management is a common practice in Africa and has an adverse environmental impact and is unsafe for human health [110] Mushrooms have been used for several thousands of years for medicinal purposes, however their role on the regulation of gut microbiota is a new field and has not been sufficiently studied among the 2,000 species identified as edible [111].

The five key immune responses targeted by mushroom β-glucans involve the production of white blood cells, stem cell mobilization, neutrophil phagocytic capacity, production

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of reactive oxygen intermediates and help shift an overstimulated TH2 to a TH1 cell mediated immune response [112][113][114][115].

The array of gut microbiota profiles among SSA populations under different dietary practices and livelihoods is still extensively undetermined.

Food needs to cover the requirements of the human body and of the microbiota and there are significant racial difference in gut, vaginal, and skin microbiomes [116]. In the West people eat diets rich in protein and animal fats, thus have predominantly Bacteroides bacteria, while for those in Africa who consume more carbohydrates, especially rich in fibre, have the *Prevotella* species as the dominant bacteria [117]. In this context, gut microbiota from SSA people have different and specific profile which need to be studied in order to match and determine their nutrient requirements. Since most rural SSA family farmers operate traditional subsistence lifestyles, it is important to evaluate their microbiota profile and role as well as the widespread antibiotic use and general impact of industrialization [118]. This is actually possible by identifying and comparing the microbiome enterotypes in different countries or regions using 16S rRNA sequencing [119].

6. Anti-inflammatory Role of Mushrooms

Foods that may originate inflammation comprise processed carbohydrates such as white bread and pastries, fried chips, fizzy drinks, red meat, processed sausages, biscuits, desserts, and margarine. Inflammation is the body immune biological reaction to injury or disease. It is a protective mechanism where the blood flow raises to the area of tissue lesion or infection, a necessary part for recovery [120]. Inflammation is a beneficial reaction because it reveals the challenge of the body to infection; however, it is adverse because it destroys a lot of the fine cells in the process [121]. Evidence supporting the impact of specific foods on inflammation in the body is limited.

Some foods, mushrooms included, have the capacity to suppress inflammation, but it is unclear how often and how much is needed for this benefit. Following an anti-inflammatory diet one can fight off inflammation, however, although there is promising research for the impact of some foods there is no anti-inflammatory miracle food and although diet is crucial, it is not the single factor [122].

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African mushrooms such as *Pleurotus tuber-regium*, *Termitomyces* spp., *Pleurotus* spp., and *Agaricus* spp are rich in chitin which can be hydrolysed into glucosamine which is involved in the creation of molecules that protect joints from inflammation [123][124].

Some mushrooms act directly on inflammation. *Cordyceps synensis*, a mushroom that contains a nucleoside compound, cordycepin, that stimulates the production of interleukin 10, an anti-inflammatory cytokine [125].

Wild or cultivated mushrooms, fresh or as dietary supplements, have anti-inflammatory activity occurring through inhibition of NF-κB signalling, a protein complex that controls transcription of DNA, cytokine production and cell survival, and major transcription factor that regulates genes responsible for both the innate and adaptive immune response [126].

Poria cocos mushroom also contains triterpenes, which have been shown to improve inflammation and treat tumours [127]. Other mushrooms exert an anti-inflammatory effect less directly, by quenching damaging free radicals and counteracting oxidation. Chaga mushroom (*Inonotus obliquus*), for instance, has antioxidant activity, protecting cells against oxidative damage [128][129]. Oyster mushroom (*Pleurotus ostreatus*) has an antioxidant effect as well [130].

Consuming mushrooms does not necessarily show significant changes on induced inflammatory responses. The result is not surprising since it would certainly be harmful to strongly induce or suppress immune function following ingestion of a commonly consumed food. Mushrooms also have an effect on immune function, but that effect is evident only when the immune system is challenged [131].

Much of the active polysaccharides, water soluble or insoluble, isolated from mushrooms, can be classified as dietary fibres (i.e., β-glucan, xyloglucan, heteroglycan, chitinous substance) and their glycoprotein complexes [132].

The chemical nature of extracted β-glucan varies from different sources. Cereals and other food contain 2.5-4.5% β-glucans but these are not capable to control immune functions. However, mushroom β-glucans, which consist essentially of a (1,3)-β-linked with small numbers of (1,6)-β-linked side chains, can modulate the autoimmune mechanisms [133].

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These biological response modifiers (1,3)β-glucans, interact with intestinal cell wall, absorbed into the lymph fluid, where they recruit neutrophils and macrophages and trigger production of cytokines and stimulate immune function [134].

Biomass or an extract derived from the mushroom *Coriolus versicolor*, with potential immunomodulating and antineoplastic activities, has been shown to stimulate the production of lymphocytes and cytokines, such as interferons and interleukins, and may exhibit antioxidant activities [135][136].

Neuroinflammation is a specialized immune response that occurs in the central nervous system, linked to chronic neurodegenerative disorders (e.g. amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, Parkinson's disease, and particularly Alzheimer's) negatively affecting mental and physical functioning being characterised by synaptic dysfunction and a gradual loss of neurons from specific regions [137][138].

Mushrooms incorporate ergothioneine, which humans are unable to synthesise, a unique antioxidant, cytoprotective and anti-inflammatory derived from food histidine, but which accumulates to high levels in red blood cells and in many other tissues, functioning both as therapeutic and possibly as preventative agent of several diseases [139][140].

7. The Antiviral Role of Mushrooms

New viruses emerge all the time and mushrooms represent a vast source of bioactive molecules, which could potentially be used as antivirals. A virus is an infectious agent metabolically inert made up of a core of genetic material, either DNA or RNA, and an outer protein and lipid shell which can only replicate within a host cell organism. In some virus the nucleocapsid is covered by an external membrane, or envelope, which consists mainly of a phospholipid bilayer but also contains one or two types of virus-encoded glycoproteins [141].

Many of the common edible mushrooms and several mushroom dietary supplements are sources of natural bioactive compounds responsible for prevention and treatment of viral diseases through their improvement of human immunomodulation [142]. Furthermore, numerous previous studies have found many mushrooms exhibiting potential antiviral efficacy [143][144][145].

There are four mushrooms subjected to several clinical studies specifically for fighting viruses [146][147], but the following claims still considered unsubstantiated at least for

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Covid-19 prevention and treatment: **1)** *Ganoderma*: shown to kill the Influenza A virus, herpes, hepatitis and H1N1 strain of the Flu; **2)** *Cordyceps*: fighting the Influenza virus by boosting the body NK cell activity as well as other virus killing cytokines; additionally, it has been shown to decrease inflammation in chronic asthma and other lung diseases; **3)** *Maitake*: it has shown to actually stop the replication of the virus which would be very helpful in allowing the body to fight it off without getting to overwhelmed and prevent a lot of excessive damage; additionally, it also shows to boost the body supply of antiviral cytokines; **4)** *Shiitake*: ability in stopping the growth of the virus by preventing the entry into the cell; this mushroom has shown to be effective in fighting the herpes simplex virus, hepatitis C virus, HIV and the influenza.

Mushrooms fight viral infections and there are many studies on anti-viral activities of several mushrooms against herpes (HHV-causing skin infections) [148], West Nile (mosquito-borne disease) [149], Orthpoxviruses (variola agent) [150], influenza [151], hepatitis B [152], and human immunodeficiency (HIV) [153]. The most studied mushroom strains for producing antiviral bioactive compounds include *Coriolus versicolor, Lentinula edodes, Grifola frondosa, Ganoderma lucidum, Hericium erinaceus, Pleurotus ostreatus, Cordyceps sinensis, Laricifomes officinalis, Lenzites betulina, Rozites caperata, Daedaleopsis confragosa.* [154].

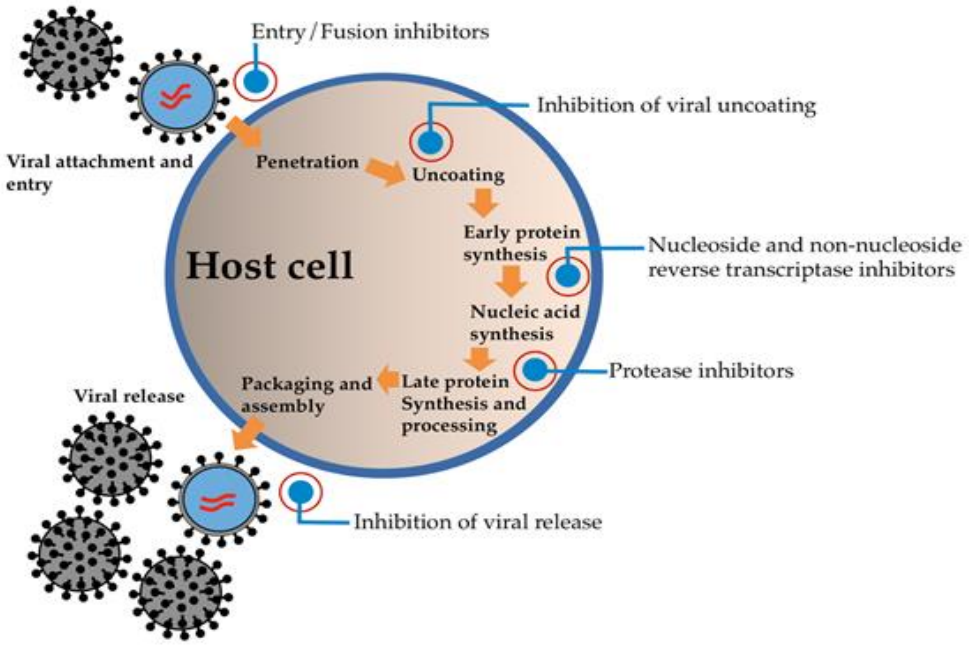

Figure 8. Major sites of antiviral drug action through inhibition of proteases necessary for replication, transcription, and maturation of viruses[142].

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People cannot avoid harmful germs and viruses but can become ill less often and with shorten periods if the immune system is strong. The objective of enhancing immunity is attractive, but the ability to do so has proved equivocal for several reasons. The immune system is precisely that, a complex network, not a single entity. There are no scientifically proven direct links between various lifestyle changes and enhanced immune function nevertheless one can boost the immune system by sleeping well in order to release protective cytokines, taking zinc [155], vitamins A, C, E [156], curcumin (turmeric) [157] as well as consuming mushroom supplements or fresh mushroom therefore preventing the chance of contracting viral diseases [158].

7.1 HIV/AIDS

We have previously reviewed this subject [159] and the pathogenesis of the disease is considered multifactorial. Nutrition is a fundamental part of a comprehensive package of care for people living with HIV/AIDS and mushrooms supply known bioactive molecules that may help patients [135]. To cushion the repercussion of the disease widespread, action taken must integrate all elements involved, including nutritional care [160]. To assess and reduce the severity of the complex interaction between HIV/AIDS and malnutrition have on each other, it is essential to forecast the evolution of the disease and the probability of morbidity and death toll [161].

Mushroom ß-glucans increases CD4 cells production and stimulates the immune system macrophages. Even when infected with HIV, the macrophages fight effectively and reduce HIV replication [162]. Several triterpenes from Ganoderma lucidum are active as antiviral agents against human immunodeficiency virus type 1 (HIV-1) [163].

Besides polysaccharides and triterpenoids displaying a variety of medicinal properties, mushrooms contain many antimicrobial factors which include lentinan, ganaderiol-F, ganoderic acid-ß, lucidumol, PSP, coprinol, campestrin, sparassol, armillaric acid, cortinellin and ustilagic acid [164][165][166]. These active compounds fight viruses in two major ways: **a)** they boost the immune system: directly (specific response) and/or through various factors of humoral and cellular immunity [167]; and **b)** attack the virus directly, which prevents the proliferation of viruses and can stop viral infections from developing [168].

Direct antiviral effects include inhibition of viral enzymes, synthesis of viral nucleic acids and adsorption or uptake of viruses [169]. Indirect antiviral effects are achieved by

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stimulating the immune response against the viral invasion and promoting biochemical factors, such as alkalinity, that discourage viral replication [170]. In many mushrooms, β-glucans, glycoproteins, melanins, terpenoids and nucleosides displayed antiviral activity [171].

The lymphotropic nature of the virus HIV-1, infects humans and the function of the lymph node is disrupted, and production of dendritic cells is increased and accumulation in lymph nodes, presenting exogenous microbial antigens [172].

Drug resistance to anti-HIV drugs is emerging, and many people infected with HIV have serious adverse reactions. Antiviral compounds from mushrooms (e.g., triterpenes, phenolic compounds, ergosterol peroxide, and purine derivatives) are strong biotherapeutics acting directly on the pathways of enzymatic system of the human host, regulating the interactions between viral and components of the human cell [173].

They may also act by inhibiting viral enzymes carried within the capsid and on the viral envelope, while some are only produced in the infected cell [174]. The antiviral compounds of mushrooms also may condition the virus genome intervening on the synthesis pathway of viral nucleic acids and its penetration of viruses into cells [175].

7.2 Herpes virus

The Herpes Simplex Virus (HSV-1) co-evolved with humans for thousands of years in a constant, dynamic and endless dance where the pathogen is present at a high prevalence, affecting globally half of the human population [176][177].

While there are more than 100 known herpes viruses two strains occur in most of β-amyloid plaques of Alzheimer's Disease (AD), being their proteins two-thirds identical suggesting that this common virus may be a possible risk factor for AD showing some evidence that specific viral species directly contribute to a risk of developing AD [178]. The neurotropic virus can either remain in a dormant state, with occasional revitalization events, or eventually originate severe acute encephalitis, marked by aggravated neuroinflammation and extended neuroimmune activation, producing a life-threatening neurological disease [179]. HSVs alters host cell metabolism inducing antiviral mechanisms and reprograms cell death in non-immune cells, capable of inducing apoptosis in immune cells, the death of T cells, while allowing viral replication to occur

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in epithelial cells before uprising into the neural ganglia producing a latent infection [180].

Antiviral activity of the mycelia of higher mushrooms (*Pleurotus ostreatus, Fomes fomentarius, Auriporia aurea,* and *Coriolus versicolor*), against influenza virus type A (serotype H1N1) and herpes simplex virus type 2 (HSV-2) was determined to be effective [181].

7.3 Influenza Virus

Several mushrooms in natural form or as a food supplement are effective on preventing and treating a variety of viruses like the common cold and the flu virus. This is significant if it is considered the highly infectious nature and ability to mutations of these viruses. *Boletus edulis, Datronia molis, Calvatia gigantea, Laricifomes officinalis, Suillus luteus, Coriolus versicolor, Lentinus edodes, Lenzites betulina,* and *Piptoporus betulinus* were shown to be effective against the flu-causing influenza viruses [182][183].

7.4 Human papillomaviruses (HPVs)

In Portugal in 2008 the use of *Coriolus versicolor* biomass supplement for 1 year revealed a great efficacy, whether in the regression of the cervical dysplasia (LSIL), or in the disappearance of the High-Risk HPV. This dietary supplementation showed positive therapeutic impact, either in the reversion of LSIL (with High-Risk HPV+), or in those HSIL patients, who have undergone surgery, but experience continued High Risk HPV viral count [184].

This was subsequently replicated with active hexose correlated compound (AHCC), a fermented extract of cultured *Lentinula edodes* mycelia, administered for at least 6 months, with a 60% successful elimination of human papillomavirus (HPV) infections in women with positive PAP smears [185]. A recent study involving 42 patients showed that combination of administration of *Coriolus versicolor* biomass provided positive outcomes in cases of primary or recurrent genital warts [186].

Mushroom in extracts or biomass forms may be given as a complement in aggregation with surgery, chemo- or radiotherapy, with significant influence on NK cell activity when induced by the presence of a viral infection.

7.5 The Novel Coronavirus (SARS-CoV- 2)

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The interesting thing about this SARS-CoV-2 virus is the symptoms that can range from no conceivable symptoms, all the way to having severe cases of all major symptoms, lower respiratory tract infection with fever, dry cough, and dyspnea, spreading the virus. There are vast number of studies that have been done with mushrooms as a potential antiviral treatment but very few yet specifically with this new virus [187][188].

Recently, *Cordyceps sinensis* and *Cordyceps militaris* were claimed be effective agents for the prevention and treatment of COVID-19 by immunomodulating, reducing the proinflammatory cytokines, preventing lung fibrosis, improving tolerance to hypoxemia and inhibiting the viral enzymes [189].

In Norway *Agaricus blazei, Ganoderma lucidum, Hericium erinaceus,* and *Grifola frondosa* were considered to have preventive or curative effect against the severe lung inflammation and acute pneumonia that often complicates COVID-19 infection [190].

A recent study in Iraq showed that Ganoderma lucidum uptake on some hematological and immunological response in patients with Covid-19 had a great significant role in helping in the treatment of COVID-19 infections [191].

Mushrooms are the highest dietary source for the unique sulphur-containing antioxidant ergotheionine. This amino acid is a Generally Recognized as Safe (GRAS) product by FDA and gets into the food chain mainly through mushroom consumption. There is a recent study revealing ergotheionine potential beneficial role in SARS-CoV-2 cases [139]

The above claims must not be generalized to the recent SARS-CoV-2 infection [192] and the immediate priority is to harness innate immunity to accelerate early antiviral immune responses.

8. Antitumour Activity of Mushrooms

Usually, the causes of cancer are multifactorial, and include genetic, environmental and other risk factors. Recent meta-analysis of 213 studies, including 77 clinical studies, showed that *Ganoderma lucidum* or *Coriolus versicolor* mushrooms enhanced the efficacy and ameliorated their adverse effects, which lead to improved quality of life in cancer patients [193].

Mushroom lectins are a group of proteins/glycoproteins which can possess immunomodulating as well as direct cytotoxic activity toward tumor cell lines. In

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mushroom extracts and biomass there are also some anticancer hemolysing proteins [194], enzyme laccase [195], ribosome inactivating proteins [196], and ubiquitin-conjugated proteins which also display direct cytotoxic activity [197][198].

Polysaccharides of mushrooms have anti-tumour activity, which is associated with the immunostimulatory effect that they can exert, since they activate foreign body reactions from the immune system [199]. This anti-tumour activity is not caused by a direct cytotoxic effect but via activation of the innate immune system of the host. The mechanism of action is related to the presence of pattern recognition receptors that can recognize the polysaccharides as pathogen-associated molecular patterns (PAMPs), due to its high molecular weight [200].

Consequently, pro-inflammatory cytokines are produced in a cascade, including tumour necrosis factor alpha (TNF-α), members of the IL-1 family, which regulate immune homeostasis and the mechanisms against infections, in recognition of foreign cells and tumour cells [201].

Some structures of mushroom β-glucans are better adapted to specific receptors, which suggests a relationship between the structure and antitumour activity of polysaccharides and it was found that, mostly β-1,3-glucan, have the highest antitumour activity [202][203].

Triterpenes, the secondary compounds found in mushrooms, cause tumour cells to self-destruct (apoptosis) [204][205].

Polysaccharide extracts from *Hericium erinaceus* are active against liver cancer cells in vitro and in vivo [206][207]. The highest consumption of dietary mushrooms, including *Agaricus bisporus* and *Lentinula edodes*, is associated with a decreased risk of breast cancer in premenopausal women and postmenopausal women [208].

Maitake mushroom (*Grifola frondosa*) is one of the most popular edible medicinal mushroom. The natural killer (NK) cells, which have the ability to eliminate target cells without prior immunization, show important role in controlling viral infections and high cytotoxic activity in oncologic patients administered *G. frondosa* and significantly restrain tumour growth. This is achieved by increased release of TNF-α and IFN-γ from spleen and a significant boost in IFN-γ and TNF-α expressed in NK cells [112]. *Ganoderma tsugae* is another medicinal mushroom in which sixteen polysaccharides

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have been well investigated for anti-tumour effects on Sarcoma 180 (ascitic tumor) in mice [209].

9. Prebiotic Activity of Mushrooms

The interest in the gut microbiome and host interaction is increasing. The concept of prebiotic has been updated as "selectively group of nutrients that allow specific changes in the composition and/or activity in the gastrointestinal microbiota providing benefits upon host well-being and health" [210]. Prebiotics act as food for probiotics [211]. Furthermore, some health benefits of prebiotics, such as reducing glucose levels in the blood and improvement of the bowel function, have been medically proven and recognized by health authorities [212].

Endogenous β-glucans show better prebiotic properties than exogenous β-glucans. We have discussed the role of some bacteria Bacteroides (*B. ovatus, B. uniformis, B. capillosus*), *Prevotella, Ruminococcus, E. faecium, Streptococcus*, and *Clostridium* strains that are responsible for degradation of mixed linked β-glucans in the small intestine and in the hind gut [213].

Currently, inulin, fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), lactulose and polydextrose are recognized as the well-established prebiotics in the market but there is evidence that β-glucans can also be a source of long chain prebiotics [214]. Extracts of *Pleurotus ostreatus* and *Pleurotus eryngii* have a potential stimulator effect on the growth of probiotic bacteria [215]. Cosmopolitan strains of *Pleurotus* and *Cyclocybe* mushrooms, studied in terms of their prebiotic potential, exhibited a beneficial influence on the composition of gut microbiota of apparently healthy and elderly subjects [216].

The prebiotic effect of mushroom biomass (e.g. *Coriolus versicolor*) on human gut populations of total aerobes and anaerobes showed that dietary mushroom inclusion beneficially affected gut homeostasis performance and exerted changes in intestinal microbial communities [217].

10. Mushrooms and Neuroimmunology

When cells generate energy, they use oxygen and yield free radicals as a consequence of ATP generation by the mitochondria, a cell organelle that has a critical role in the development of neurodegenerative disorders [218]. The human body has various

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mechanisms to prevent oxidative stress by either yielding inner natural antioxidants (e.g., catalase, enzymes glutathione peroxidase, superoxide dismutase), or provided through foodstuffs and/or dietary supplements [219].

Neurodegeneration caused by disruptions of crucial homeostatic interactions between circulation and the brain may be mediated by microbial products that modulate the gut-brain axis causing neuro-inflammation and neuronal dysfunction [220].

Infection of the central nervous system may have different aetiologies causing inflammation of the brain (encephalitis). Neuro-inflammation can be caused by virus DNA/RNA infection which challenges the host immune system and continued exposure to the inflammatory mediators (e.g., cytokines, chemokines, and ROS) can result in neuronal dysfunction and degeneration [221].

People who incorporate mushrooms into their diets, even in small amounts (more than twice a week), seem to have a lower risk of mild cognitive impairment, usually preceding Alzheimer's disease [222]. Mushrooms contain many other substances whose exact role in brain health is not yet clear. These include β-glucan polysaccharides, hericenones, erinacines terpenoids, scabronines, isoindolinones, sterols and dictyophorines, a series of compounds that could contribute to the growth of nerve and brain cells [223]

Acetylcholine, a key neurotransmitter and the principal effector of the autonomic nervous system, is responsible for forming new connections and strengthening neural pathways in the brain [224] *Hericium erinaceus* (also called lion's mane) has been studied as a precursor of acetylcholine which have neuroprotective and anti-neurodegenerative properties. *H. erinaceus* mycelium shows great promise for the treatment of Alzheimer's and Parkinson's diseases [225].

We have previously discussed how abnormal redox homeostasis and oxidative stress causes diverse neuropsychiatric disorders and the immunomodulation role of mushroom biomass of *Coriolus versicolor* [226]. Presently the interest is to focus on mediator markers of oxidative stress and neuroinflammation in progressive neurodegenerative disorders and distinct configurations of chronic mental illness [227].

Oxidative stress and altered antioxidant systems have been considered an important factor underlying the pathogenesis of Alzheimer's disease. Brain inflammation has been linked

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to many diseases, including amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Parkinson's disease (PD) and, particularly, Alzheimer's disease (AD) [228].

We have previously discussed [213] the emerging role of lipoxinA4 and inflammasome in neurodegeneration and the potential therapeutic role of mushroom *Coriolus versicolor*. Integrated survival responses exist in the brain, which are under control of redox-dependent genes, called vitagenes, including heat shock proteins (HSPs), sirtuins, thioredoxin and lipoxin A4. Activation of LXA4 signalling and modulation of stress-responsive vitagene proteins could serve as a potential therapeutic target for AD-related inflammation and neurodegenerative damage [229][230].

Emerging mushroom nutraceuticals demonstrate potential as modulators of mitochondrial redox status and energy metabolism, capable of inducing beneficial outcomes on oncology [231]. Mushrooms through their powerful antioxidant characteristics, have the potential to protect neurons in mitochondrial dysfunctions associated aging and neurological disorders [232].

Food and beverages, macronutrients, micronutrients, or supplements, are the main source of energy for humans. Mitochondrial function is dynamic and controls intestinal epithelial stemness, essential characteristic of a stem cell, which is crucial for enabling tissue homeostasis and can be affected by diet as nutritional changes and can impact on mitochondrial structure, and affect energy metabolism [233][234][235].

Anxiety symptoms and disorders, more common than depression, are among the most common primary care challenges in medical practice. There are many evidence-based nutraceuticals and botanicals to treat these conditions. L-theanine is an amino acid (an analogue of amino acids L-glutamate and L-glutamine) found most in tea leaves and in mushrooms. It should be noted that health claims for L-theanine as a supplement are not recognized in the European Union but are approved by the FDA. But mushrooms as food containing L-theanine do not need any approval, becoming a functional food secondary component of medical treatment [236].

The ability of the brain to manage different challenges that arise across lifespan, makes it resilient to cognitive damage preventing dementia. Hippocampal adult neurogenesis has been considered to be a relevant contributor for brain cognitive reserve and brain plasticity [237].

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Coriolus versicolor, a common healthful mushroom, has been receiving increasing attention by its antitumoral, anti-inflammatory, antioxidant, antibacterial, and immunomodulatory properties, including in the hippocampus. Our data unveiled a so far unexplored neurogenic potential of *Coriolus versicolor* supplementation as a possible preventive strategy for different neurological conditions [136][230].

10.1 Role of Mushrooms in Autism

According to the World Health Organization, one child in 160 worldwide suffers from an autism spectrum disorder. Autism is more common in Africa than initially believed and it is a growing global public health concern. Most Africans are largely unaware of autism, a highly heritable neurodevelopmental disorder, often confused with witchcraft, curses or spells and demons, and children with autism in SSA tend to be diagnosed only around age 8, some 4 years later than worldwide.

Many African children with autism, more often boys than girls, are usually hidden away at home and the prevalence is unknown while only few clinicians have the skills or experience to identify the condition. Indeed, maternal and child mental health services have not been a priority since child mortality and malnutrition are more urgent concerns [238][239].

Autism Spectrum Disorder (ASD) is a disorder still very poorly understood, caused by genetic or environmental factors, first recognized in early childhood in the form of a multi organ system disability caused by impaired neurogenesis and apoptosis, impaired synaptogenesis and synaptic pruning or imbalanced excitatory-inhibition system [240].

Few studies with handful cases have been dealt in South Africa, Nigeria, Ethiopia and Kenya fostering the conviction that ASD is more severe in African children than elsewhere with up to 4% of children having the condition [241]. Recent epidemiological studies revealed possible important link between mycotoxin exposure and neurodevelopmental disorders with regard to ASD [242].

We have previously discussed dietary mushrooms and supplements which have specific effects on gastrointestinal inflammation in ASD patients. The most commonly used mushrooms as potent health-boosters, which may bring some hope to autistic children and families, include Chaga (*Inonotus obliquus*), Reishi (*Ganoderma lucidum*), Turkey Tail (*Coriolus versicolor*), Shiitake (*Lentinula edodes*), Lion's Mane (*Hericium*

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erinaceus), Cordyceps (*Cordyceps militaris*), and oyster mushroom (*Pleurotus giganteous*). They have shown beneficial to symptoms relating to anxiety and depression, related to both autism and attention deficit-hyperactivity disorder (ADHD) [243].

The therapeutic potential of *Hericium erinaceus* bioactive and bioavailable components that pass the blood-brain barrier has been demonstrated [244]. They act conditioning several functions including the triggering the production of nerve growth factor, the obstruction of the cytotoxicity of extracellular heterogeneous mixture of small peptides plaque deposits, and the shielding against neuron lysis [245].

Unlike neurons, neuroglial cells, the most abundant cell type in the brains, are involved in nutritional homeostasis, detoxification, and aging, providing nutrients and oxygen to neurons, or defend the nervous system from injury, playing a role in neuron synaptic function. Mushrooms could play a protective role against oxidative stress in glial cells. [246].

11. Concluding Remarks

While contemporary dietary patterns and production systems are changing in developed countries, aiming to reduce red meat and processed foods, in SSA priorities are different as traditional eating has been related to positive health outcomes and sustainability.

Mushrooms have distinct nutritional and bioactive profiles and have been absent in all dietary guidelines despite its high biological value of its mycoprotein. There is limited information about the therapeutic and medicinal uses of mushrooms in Africa. Mushrooms complement the human diet with various ingredients not found or deficient in food items of plants and animal origin being considered an ultimate health food and prevention of various human diseases.

Recognizing mushrooms as good sources of nutraceuticals, in nutrient balancing, strengthening human immune system, enhancing natural body resistance, and lowering proneness to disease with little scope of toxicity or overdose, along with their minimal side effects, make them ideal candidates for developing novel dietary supplements and therapies. While mushrooms as food or biomass supplements are fully acceptable in the diet, their extracts must be evaluated differently as they are considered medicinal pharmanutrients.

It should be enhanced that it is unlawful to advertise that a non-food product can prevent, treat, or cure human diseases unless there are competent and reliable scientific evidence, including, when appropriate, well-controlled human clinical studies to evaluate the efficacy and assess their safety in toxicity trials.

Disclosure of Conflicting Interests

All authors declare no conflict of interests.

Bibliography

1. Dodo KM. Understanding Africa's Food Security Challenges. In: *Food Security in Africa [Working Title]*. ; 2020. doi:10.5772/intechopen.91773

2. Asongu SA, Odhiambo NM. Environmental degradation and inclusive human development in sub-Saharan Africa. *Sustain Dev*. **2019**;*27*(1):25-34. doi:10.1002/sd.1858

3. Forouzanfar MH, Afshin A, Alexander LT, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. **2016**;*388*(10053):1659-1724. doi:10.1016/S0140-6736(16)31679-8

4. Kearney J. Food consumption trends and drivers. *Philos Trans R Soc B Biol Sci*. **2010**;*365*(1554):2793-2807. doi:10.1098/rstb.2010.0149

5. O'Keefe SJD, Li J V., Lahti L, et al. Fat, fibre and cancer risk in African Americans and rural Africans. *Nat Commun*. Published online 2015. doi:10.1038/ncomms7342

6. Oniang'o RK, Mutuku JM, Malaba SJ. Contemporary African food habits and their nutritional and health implications. In: *Asia Pacific Journal of Clinical Nutrition*. ; 2003.

7. Nyadanu D, Lowor ST. Promoting competitiveness of neglected and underutilized crop species: comparative analysis of nutritional composition of indigenous and exotic leafy and fruit vegetables in Ghana. *Genet Resour Crop Evol*. Published online 2014. doi:https://doi.org/10.1007/s10722-014-0162-x

8. Imamura F, Micha R, Khatibzadeh S, et al. Dietary quality among men and women in 187 countries in 1990 and 2010: a systematic assessment. *Lancet Glob Heal*. **2015**;*3*(3):e132-e142. doi:https://doi.org/10.1016/S2214-109X(14)70381-X

9. Akinola R, Pereira L, Mabhaudhi T, et al. A Review of Indigenous Food Crops in Africa and the Implications for more Sustainable and Healthy Food Systems. *Sustainability*. **2020**;*12*:3493. doi:doi:10.3390/su12083493

10. Bell V, Barros AB, Fernandes TH. Food Fortification in Sub Saharan Africa: Science or Business? In: Fernandes TH, Ferrão J, Facknath S, eds. *Food and Nutrition Security in Africa*. Alcance Ed. Mozambique; 2020.

11. EFSA Panel on Dietetic Products Nutrition and Allergies (NDA). Scientific Opinion on establishing Food-Based Dietary Guidelines. *EFSA J*. **2010**;*8*(3):1460.

12. Vapnek J, Spreij M. Perspectives and guidelines on food legislation, with a new model food law. *FAO Legis Study*. Published online 2005.

13. Bell V, Ferrão J, Fernandes T. Nutritional Guidelines and Fermented Food Frameworks. *Foods*. **2017**;*6*(8):65. doi:10.3390/foods6080065

14. Fischer CG, Garnett T. Plates, Pyramids, Planet: Developments in National Healthy and Sustainable Dietary Guidelines: A State of Play Assessment.; 2016.

15. WHO, FAO. Understanding Codex. 5th Editio.; 2018.

16. Bell V, Ferrão J, Fernandes T. Nutrition, Food Safety and Quality in Sub-Saharan Africa. *EC Nutr*. **2017**;*9*(6):243-255.

17. Molina BP, D'Alessandro C, Dekeyser K, Marson M. Sustainable Food Systems through Diversification and Indigenous Vegetables. An Analysis of the Arusha Area.; 2020.

18. Ritchie H, Roser M. Environmental impacts of food production - Our World in Data. Our world in Data.

19. Vorster H. "Make starchy foods part of most meals": a food-based dietary guideline for South Africa. *South African J Clin Nutr*. **2013**;*26*(3):S28-S35. http://sajcn.co.za/index.php/SAJCN/article/view/743

20. Cisse F. African starchy foods, gastric emptying, and starch digestion in Malian stunted children. *Open Access Diss*. Published online 2014. https://docs.lib.purdue.edu/open_access_dissertations/247

21. Chastanet M, Chouin G, Lima D de, Guindeuil T. Towards a history of foodways in Africa before the 20th century. *Afriques*. **2014**;(05). doi:10.4000/afriques.1857

22. Tanumihardjo SA, Anderson C, Kaufer-Horwitz M, et al. Poverty, Obesity, and Malnutrition: An International Perspective Recognizing the Paradox. *J Am Diet Assoc*. **2007**;*107*(11):1966-1972. doi:10.1016/j.jada.2007.08.007

23. Ferrão J, Bell V, Fernandes T. Food and Beverage Fortification in Africa? *EC Nutr*. **2017**;*SI.01*:17-26.

24. Derbyshire EJ. Is There Scope for a Novel Mycelium Category of Proteins alongside Animals and Plants? *Foods*. **2020**;*9*(9):1151. doi:10.3390/foods9091151

25. França TGD, Ishikawa LLW, Zorzella-Pezavento SFG, Chiuso-Minicucci F, Da Cunha MLRSM, Sartori A. Impact of malnutrition on immunity and infection. *J Venom Anim Toxins Incl Trop Dis*. Published online **2009.** doi:10.1590/S1678-91992009000300003

26. Akombi BJ, Agho KE, Merom D, Renzaho AM, Hall JJ. Child malnutrition in sub-Saharan Africa: A meta-analysis of demographic and health surveys (2006-2016). Wieringa F, ed. *PLoS One*. **2017**;*12*(5):e0177338. doi:10.1371/journal.pone.0177338

27. Love P V. Developing and assessing the appropriateness of the preliminary food-based dietary guidelines for south africans. Published online 2002.

28. Maunder E, Steyn N. A spoonful of sugar helps the medicine go down! *South African J Clin Nutr*. **2012**;*25*(3):90-93. doi:https://doi.org/10.1080/16070658.2012.11734413

29. Samorin G. The oldest representations of hallucinogenic mushrooms in the world (sahara desert, 9000 – 7000 B.P.). *Integration*. **1992**;*2*(3):69-78. http://www.artepreistorica.com/2009/12/the-oldest-representations-of-hallucinogenic-mushrooms-in-the-world-sahara-desert-9000-–-7000-b-p/

30. Goldman GB GM, Gryzenhout M. Field Guide To Mushrooms & Other Fungi Of South Africa - eBook - WOOK. Struik, Capetown, South Africa.

31. Kalač P. A review of chemical composition and nutritional value of wild-growing and cultivated mushrooms. *J Sci Food Agric*. **2013**;*93*(2):209-218. doi:10.1002/jsfa.5960

32. Kinge TR, Goldman G, Jacobs A, Ndiritu GG, Gryzenhout M. A first checklist of macrofungi for South Africa. *MycoKeys*. **2020**;*63*(148). doi:10.3897/mycokeys.63.36566

33. Kasolo W, Chemining'wa G, Temu A. Neglected and Underutilized Species (NUS) for Improved Food Security and Resilience to Climate Change: A Contextualized Learning Manual for African Colleges and Universities. ANAFE, Nairobi; 2018.

34. Barroetaveña C, Toledo C V. The Nutritional Benefits of Mushrooms. In: *Wild Plants, Mushrooms and Nuts*. John Wiley & Sons, Ltd; 2016:65-81. doi:10.1002/9781118944653.ch3

35. Wedaralalage TCK, Jayawardena RS, Hyde KD. Hurdles in fungal taxonomy: Effectiveness of recent methods in discriminating taxa. *Megataxa*. **2020**;*1*(2):114-122. doi:10.11646/megataxa.1.2.2

36. Aryal KP, Poudel S, Chaudhary RP, et al. Diversity and use of wild and non-cultivated edible plants in the Western Himalaya. *J Ethnobiol Ethnomed*. **2018**;*14*:10. doi:10.1186/s13002-018-0211-1

37. Tibuhwa D. Folk taxonomy and use of mushrooms in communities around Ngorongoro and Serengeti National Park, Tanzania. *J Ethnobiol Ethnomed*. **2012**;*8*(1):36. doi:10.1186/1746-4269-8-36

38. Sitotaw R, Lulekal E, Abate D. Ethnomycological study of edible and medicinal mushrooms in Menge District, Asossa Zone, Benshangul Gumuz Region, Ethiopia. *J Ethnobiol Ethnomed*. **2020**;*16*(1):11. doi:doi:10.1186/s13002-020-00361-9

39. Kumla J, Suwannarach N, Sujarit K, et al. Cultivation of Mushrooms and Their Lignocellulolytic Enzyme Production Through the Utilization of Agro-Industrial

Waste. *Molecules*. **2020**;*25*(12):2811. doi:10.3390/molecules25122811

40. Trappe JM, Claridge AW, Arora D, Smit WA. Desert Truffles of the African Kalahari: Ecology, Ethnomycology, and Taxonomy. *Econ Bot*. **2008**;*62*(3):521-529. doi:10.1007/s12231-008-9027-6

41. El Enshasy H, Elsayed EA, Aziz R, Wadaan MA. Mushrooms and Truffles: Historical Biofactories for Complementary Medicine in Africa and in the Middle East. *Evidence-Based Complement Altern Med*. **2013**;*2013*:1-10. doi:10.1155/2013/620451

42. Wang S, Marcone MF. The biochemistry and biological properties of the world's most expensive underground edible mushroom: Truffles. *Food Res Int*. **2011**;*44*(9):2567-2581. doi:10.1016/j.foodres.2011.06.008

43. Morte A, Honrubia M, Gutiérrez A. Biotechnology and cultivation of desert truffles. In: *Mycorrhiza: State of the Art, Genetics and Molecular Biology, Eco-Function, Biotechnology, Eco-Physiology, Structure and Systematics (Third Edition)*. ; 2008. doi:10.1007/978-3-540-78826-3_23

44. Osarenkhoe OO, John OA, Theophilus DA. Ethnomycological Conspectus of West African Mushrooms: An Awareness Document. *Adv Microbiol*. **2014**;*04*(01):39-54. doi:10.4236/aim.2014.41008

45. Oyetayo O V. Medicinal uses of mushrooms in Nigeria: Towards full and sustainable exploitation. *African J Tradit Complement Altern Med*. **2011**;*8*(3):267-274. doi:10.4314/ajtcam.v8i3.65289

46. van Huis A. Cultural significance of termites in sub-Saharan Africa. *J Ethnobiol Ethnomed*. **2017**;*13*(1):8. doi:10.1186/s13002-017-0137-z

47. Mukiibi J. The nutritional value of some Uganda mushrooms. *Acta Hortic*. **1973**;(33):171-176. doi:10.17660/ActaHortic.1973.33.22

48. Zoberi M. Some edible mushrooms from Nigeria. *Niger F*. **1973**;(35):81-90.

49. Gumbo DJ, Dumas-Johansen M, Muir G, Boerstler F, Xia Z. Sustainable Management of Miombo Woodlands-Food Security, Nutrition and Wood Energy. FAO; 2018.

50. Kesel A Del, Malaisse F. Edible Wild Food: Fungi. In: Malaisse F, ed. *How to Live and Survive in Zambezian Open Forest (Miombo Ecoregion)*. Les Presses Agronomiques de Gembloux; 2010.

51. Rammeloo J, Walleyn R. The Edible Fungi of Africa South of the Sahara: A Literature Survey. Ministry of Agriculture, Administration of Agricultural Research, National Botanic Gardens of Belgium; 1993.

52. Tesfay T, Godifey T, Mesfin R, Kalayu G. Evaluation of waste paper for cultivation of oyster mushroom (Pleurotus ostreatus) with some added supplementary materials. *AMB Express*. **2020**;*10*(1):15. doi:10.1186/s13568-020-0945-8

53. Degreef J, Demuynck L, Mukandera A, Nyirandayambaje G, Nzigidahera B, De Kesel A. Wild edible mushrooms, a valuable resource for food security and rural development in Burundi and Rwanda. *Biotechnol Agron Soc Environ*. **2016**;*20*(4). doi:10.25518/1780-4507.13181

54. Piepenbring M, Maciá-Vicente J, Codjia J, Al. E. Mapping mycological ignorance – checklists and diversity patterns of fungi known for West Africa. *IMA Fungus*. **2020**;*11*(13). doi:https://doi.org/10.1186/s43008-020-00034-y

55. Camassola M. Mushrooms-The Incredible Factory for Enzymes and Metabolites Productions. *Ferment Technol*. **2013**;*2*(1). doi:10.4172/2167-7972.1000e117

56. Gupta A, Gupta R, Singh RL. Microbes and Environment. In Principles and Applications of Environmental Biotechnology for a Sustainable Future. In: *Principles and Applications of Environmental Biotechnology for a Sustainable Future*. ; 2017:43-84. doi:https://doi.org/10.1007/978-981-10-1866-4_3

57. Barros L, Cruz T, Baptista P, Estevinho LM, Ferreira ICFR. Wild and commercial mushrooms as source of nutrients and nutraceuticals. *Food Chem Toxicol*. **2008**;*46*(8):2742-2747. doi:10.1016/j.fct.2008.04.030

58. Tung Y-T, Pan C-H, Chien Y-W, Huang H-Y. Edible Mushrooms: Novel Medicinal Agents to Combat Metabolic Syndrome and Associated Diseases. *Curr Pharm Des*. **2020**;*26*(39):4970-4981. doi:10.2174/1381612826666200831151316

59. Chaturvedi VK, Agarwal S, Gupta KK, Ramteke PW, Singh MP. Medicinal mushroom: boon for therapeutic applications. *3 Biotech*. **2018**;*8*(8):334. doi:10.1007/s13205-018-1358-0

60. Dimitrijević M, Stankov Jovanović V, Cvetković J, et al. Phenolics, Antioxidant Potentials, and Antimicrobial Activities of Six Wild Boletaceae Mushrooms. *Anal Lett*. **2017**;*50*(10):1691-1709. doi:10.1080/00032719.2016.1242133

61. Rahi DK, Malik D. Diversity of Mushrooms and Their Metabolites of Nutraceutical and Therapeutic Significance. *J Mycol*. **2016**;*2016*:Article ID 7654123. doi:10.1155/2016/7654123

62. Al-Laith AAA. Antioxidant components and antioxidant/antiradical activities of desert truffle (Tirmania nivea) from various Middle Eastern origins. *J Food Compos Anal*. **2010**;*23*(1):15-22. doi:10.1016/j.jfca.2009.07.005

63. El Enshasy H. Immunomodulators. In: Hofrichter. M., ed. *The Mycota: A Comprehensive Treatise on Fungi as Experimental Systems for Basic and Applied Research. Industrial Applications*. Vol X. 2nd Editio. Springer; 2010:165-194.

64. Mocan A, Fernandes Â, Barros L, et al. Chemical composition and bioactive properties of the wild mushroom: Polyporus squamosus (Huds.) Fr: A study with samples from Romania. In: *Food and Function*. ; 2018. doi:10.1039/c7fo01514c

65. Ruiz-Dueñas FJ, Martínez ÁT. Microbial degradation of lignin: How a bulky recalcitrant polymer is efficiently recycled in nature and how we can take advantage of this. *Microb Biotechnol*. **2009**;*2*(2):164-167. doi:10.1111/j.1751-7915.2008.00078.x

66. Nghi DH, Bittner B, Kellner H, et al. The Wood Rot Ascomycete Xylaria polymorpha Produces a Novel GH78 Glycoside Hydrolase That Exhibits α-l-Rhamnosidase and Feruloyl Esterase Activities and Releases Hydroxycinnamic Acids from Lignocelluloses. *Appl Environ Microbiol*. **2012**;*78*(14):4893-4901. doi:10.1128/AEM.07588-11

67. Hashimoto K, Kaneko S, Yoshida M. Extracellular Carbohydrate Esterase from the Basidiomycete Coprinopsis cinerea Released Ferulic and Acetic Acids from Xylan. *Biosci Biotechnol Biochem*. **2010**;*74*(8):1722-1724.

doi:10.1271/bbb.100299

68. Andlar M, Rezić T, Marđetko N, Kracher D, Ludwig R, Šantek B. Lignocellulose degradation: An overview of fungi and fungal enzymes involved in lignocellulose degradation. *Eng Life Sci*. **2018**;*18*(11):768-778. doi:10.1002/elsc.201800039

69. Kim S. Antioxidant Compounds for the Inhibition of Enzymatic Browning by Polyphenol Oxidases in the Fruiting Body Extract of the Edible Mushroom Hericium erinaceus. *Foods*. **2020**;*9*(7):951. doi:10.3390/foods9070951

70. Waltz E. Gene-edited CRISPR mushroom escapes US regulation. *Nature*. **2016**;*532*(7599):293. doi:10.1038/nature.2016.19754

71. Qin M, Geng Y, Lu Z, et al. Anti-Inflammatory Effects of Ethanol Extract of Lion's Mane Medicinal Mushroom, Hericium erinaceus (Agaricomycetes), in Mice with Ulcerative Colitis. *Int J Med Mushrooms*. **2016**;*18*(3):227-234. doi:10.1615/IntJMedMushrooms.v18.i3.50

72. Abdulla MA, Noor SM, Sabaratnam V, Abdullah N, Wong KH, Ali HM. Effect of culinary-medicinal lion's mane mushroom, Hericium erinaceus (Bull.: Fr.) Pers. (Aphyllophoromycetideae), on ethanol-induced gastric ulcers in rats. *Int J Med Mushrooms*. **2008**;*10*(4):325-330. doi:10.1615/IntJMedMushr.v10.i4.40

73. Jumbam B, Haelewaters D, Koch R, Al. E. A new and unusual species of Hericium (Basidiomycota: Russulales, Hericiaceae) from the Dja Biosphere Reserve, Cameroon. *Mycol Prog*. **2019**;*18*:1253-1262. doi:https://doi.org/10.1007/s11557-019-01530-1

74. Sun J, Chen Q-J, Cao Q-Q, et al. A Laccase with Antiproliferative and HIV-I Reverse Transcriptase Inhibitory Activities from the Mycorrhizal Fungus Agaricus placomyces. *J Biomed Biotechnol*. **2012**;*2012*:Article ID 736472. doi:10.1155/2012/736472

75. Xu L, Wang H, Ng T. A laccase with HIV-1 reverse transcriptase inhibitory activity from the broth of mycelial culture of the mushroom Lentinus tigrinus. *J Biomed Biotechnol*. **2012**;*2012*:Article ID 536725. doi:10.1155/2012/536725

76. Angelova M, Dolashka-Angelova P, Ivanova E, et al. A novel glycosylated

Cu/Zn-containing superoxide dismutase: Production and potential therapeutic effect. *Microbiology*. **2001**;*147*(6):1641-1650. doi:10.1099/00221287-147-6-1641

77. Sabotič J, Kos J. Microbial and fungal protease inhibitors—current and potential applications. *Appl Microbiol Biotechnol*. **2012**;*93*(4):1351-1375. doi:10.1007/s00253-011-3834-x

78. Perduca M, Destefanis L, Bovi M, et al. Structure and properties of the oyster mushroom (Pleurotus ostreatus) lectin. *Glycobiology*. **2020**;*30*(8):550-562. doi:10.1093/glycob/cwaa006

79. Olombrada M, Lázaro-Gorines R, López-Rodríguez JC, et al. Fungal ribotoxins: A review of potential biotechnological applications. *Toxins (Basel)*. **2017**;*9*(2):71. doi:10.3390/toxins9020071

80. Cruz A, Pimentel L, Rodríguez-Alcalá LM, Fernandes T, Pintado M. Health Benefits of Edible Mushrooms Focused on Coriolus versicolor: A Review. *J Food Nutr Res*. **2016**;*4*:773-781.

81. Kardideh B, Samimi Z, Norooznezhad F, Kiani S, Mansouri K. Autophagy, cancer and angiogenesis: Where is the link? *Cell Biosci*. **2019**;*9*(1):65. doi:10.1186/s13578-019-0327-6

82. Keller NP. Fungal secondary metabolism: regulation, function and drug discovery. *Nat Rev Microbiol*. **2019**;*17*(3):167-180. doi:10.1038/s41579-018-0121-1

83. Phan C-W, Wang J-K, Cheah S-C, Naidu M, David P, Sabaratnam V. A review on the nucleic acid constituents in mushrooms: nucleobases, nucleosides and nucleotides. *Crit Rev Biotechnol*. **2018**;*38*(5):762-777. doi:10.1080/07388551.2017.1399102

84. Kumar S, Narasimhan B. Therapeutic potential of heterocyclic pyrimidine scaffolds. *Chem Cent J*. **2018**;*12*(1):38. doi:10.1186/s13065-018-0406-5

85. Yang H, Hwang I, Kim S, Hong E-J, Jeung E-B. Lentinus edodes promotes fat removal in hypercholesterolemic mice. *Exp Ther Med*. **2013**;*6*(6):1409-1413. doi:10.3892/etm.2013.1333

86. Jonas DA, Elmadfa I, Engel K-H, et al. Safety Considerations of DNA in Food. *Ann Nutr Metab*. **2001**;*45*(6):235-254. doi:10.1159/000046734

87. Wu J-S, Yao G-S, Shi X-H, et al. Epigenetic Agents Trigger the Production of Bioactive Nucleoside Derivatives and Bisabolane Sesquiterpenes From the Marine-Derived Fungus Aspergillus versicolor. *Front Microbiol*. **2020**;*11*. doi:10.3389/fmicb.2020.00085

88. Leeming E, Johnson A, Spector T, Le Roy C. Effect of Diet on the Gut Microbiota: Rethinking Intervention Duration. *Nutrients*. **2019**;*11*(12):2862. doi:doi:10.3390/nu11122862

89. Du Toit A. Establishing the gut microbiota after birth. *Nat Rev Microbiol*. **2019**;*17*(11):647. doi:10.1038/s41579-019-0276-4

90. Shao Y, Forster SC, Tsaliki E, et al. Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth. *Nature*. **2019**;*574*(7776):117-121. doi:10.1038/s41586-019-1560-1

91. Tang M, Frank DN, Tshefu A, et al. Different Gut Microbial Profiles in Sub-Saharan African and South Asian Women of Childbearing Age Are Primarily Associated With Dietary Intakes. *Front Microbiol*. **2019**;*10*. doi:10.3389/fmicb.2019.01848

92. Rinninella E, Raoul P, Cintoni M, et al. What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. *Microorganisms*. **2019**;*7*(1):14. doi:10.3390/microorganisms7010014

93. Alsharairi NA. The Infant Gut Microbiota and Risk of Asthma: The Effect of Maternal Nutrition during Pregnancy and Lactation. *Microorganisms*. **2020**;*8*(8):1119. doi:10.3390/microorganisms8081119

94. Thursby E, Juge N. Introduction to the human gut microbiota. *Biochem J*. **2017**;*474*(11):1823-1836. doi:10.1042/BCJ20160510

95. Sender R, Fuchs S, Milo R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. *PLOS Biol*. **2016**;*14*(8):e1002533. doi:10.1371/journal.pbio.1002533

96. Qin J, Li R, Raes J, et al. A human gut microbial gene catalogue established by

metagenomic sequencing. *Nature*. **2010**;*464*(7285):59-65. doi:10.1038/nature08821

97. Leulier F, MacNeil LT, Lee W, et al. Integrative Physiology: At the Crossroads of Nutrition, Microbiota, Animal Physiology, and Human Health. *Cell Metab*. **2017**;*25*(3):522-534. doi:10.1016/j.cmet.2017.02.001

98. Sekirov I, Russell SL, Antunes LCM, Finlay BB. Gut Microbiota in Health and Disease. *Physiol Rev*. **2010**;*90*(3):859-904. doi:10.1152/physrev.00045.2009

99. Visconti A, Le Roy CI, Rosa F, et al. Interplay between the human gut microbiome and host metabolism. *Nat Commun*. **2019**;*10*(1):4505. doi:10.1038/s41467-019-12476-z

100. Zeisel SH. A Conceptual Framework for Studying and Investing in Precision Nutrition. *Front Genet*. **2019**;*10*. doi:10.3389/fgene.2019.00200

101. Hyde KD, Xu J, Rapior S, et al. The amazing potential of fungi: 50 ways we can exploit fungi industrially. *Fungal Divers*. **2019**;*97*(1):1-136. doi:10.1007/s13225-019-00430-9

102. Elenwo EN, Okere SE. Waste Re-Cycling using Edible Mushroom Cultivation. *J Appl Sci Environ Manag*. **2007**;*11*(3):153-156.

103. Belkaid Y, Harrison OJ. Homeostatic Immunity and the Microbiota. *Immunity*. **2017**;*46*(4):562-576. doi:10.1016/j.immuni.2017.04.008

104. Coleman OI, Haller D. Bacterial Signaling at the Intestinal Epithelial Interface in Inflammation and Cancer. *Front Immunol*. **2018**;*8*. doi:10.3389/fimmu.2017.01927

105. Kho ZY, Lal SK. The Human Gut Microbiome – A Potential Controller of Wellness and Disease. *Front Microbiol*. **2018**;*9*. doi:10.3389/fmicb.2018.01835

106. Yue B, Luo X, Yu Z, Mani S, Wang Z, Dou W. Inflammatory Bowel Disease: A Potential Result from the Collusion between Gut Microbiota and Mucosal Immune System. *Microorganisms*. **2019**;*7*(10):440. doi:10.3390/microorganisms7100440

107. Kim N, Yun M, Oh YJ, Choi H-J. Mind-altering with the gut: Modulation of the

gut-brain axis with probiotics. *J Microbiol*. **2018**;*56*(3):172-182. doi:10.1007/s12275-018-8032-4

108. Lazar V, Ditu L-M, Pircalabioru GG, et al. Aspects of Gut Microbiota and Immune System Interactions in Infectious Diseases, Immunopathology, and Cancer. *Front Immunol*. **2018**;*9*. doi:10.3389/fimmu.2018.01830

109. Qi X, Tester RF. Gut associated lymphoid tissue: Carbohydrate interactions within the intestine. *Bioact Carbohydrates Diet Fibre*. **2020**;*21*:100210. doi:10.1016/j.bcdf.2020.100210

110. Ferronato N, Torretta V. Waste Mismanagement in Developing Countries: A Review of Global Issues. *Int J Env Res Public Heal*. **2019**;*16*(6):1060. doi:doi:10.3390/ijerph16061060

111. Jayachandran M, Xiao J, Xu B. A Critical Review on Health Promoting Benefits of Edible Mushrooms through Gut Microbiota. *Int J Mol Sci*. **2017**;*18*(9):1934. doi:10.3390/ijms18091934

112. Del Cornò M, Gessani S, Conti L. Shaping the Innate Immune Response by Dietary Glucans: Any Role in the Control of Cancer? *Cancers (Basel)*. **2020**;*12*(1):155. doi:10.3390/cancers12010155

113. Smits SA, Leach J, Sonnenburg ED, et al. Seasonal cycling in the gut microbiome of the Hadza hunter-gatherers of Tanzania. *Science (80-)*. **2017**;*357*(6353):802-806. doi:10.1126/science.aan4834

114. Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. *Nature*. **2012**;*486*(7402):222-227. doi:10.1038/nature11053

115. De Filippo C, Cavalieri D, Di Paola M, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc Natl Acad Sci U S A*. **2010**;*107*(33):14691-14696. doi:10.1073/pnas.1005963107

116. Byrd D, Carson T, Williams F, Al. E. Elucidating the role of the gastrointestinal microbiota in racial and ethnic health disparities. *Genome Biol*. **2020**;*21*:192. doi:https://doi.org/10.1186/s13059-020-02117-w

117. Tomova A, Bukovsky I, Rembert E, et al. The Effects of Vegetarian and Vegan

Diets on Gut Microbiota. *Front Nutr*. **2019**;*6*. doi:10.3389/fnut.2019.00047

118. Hansen MEB, Rubel MA, Bailey AG, et al. Population structure of human gut bacteria in a diverse cohort from rural Tanzania and Botswana. *Genome Biol*. **2019**;*20*(1):16. doi:10.1186/s13059-018-1616-9

119. Allaband C, McDonald D, Vázquez-Baeza Y, Al E. Microbiome 101: Studying, Analyzing, and Interpreting Gut Microbiome Data for Clinicians. *Clin Gastroenterol Hepatol*. **2019**;*17*(2):218-230. doi:doi: 10.1016/j.cgh.2018.09.017

120. Chen L, Deng H, Cui H, et al. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget*. **2018**;*9*(6):7204-7218. doi:10.18632/oncotarget.23208

121. Punchard NA, Whelan CJ, Adcock I. The Journal of Inflammation. *J Inflamm*. **2004**;*1*(1). doi:10.1186/1476-9255-1-1

122. Minihane AM, Vinoy S, Russell WR, et al. Low-grade inflammation, diet composition and health: Current research evidence and its translation. *Br J Nutr*. **2015**;*114*(7):999-1012. doi:10.1017/S0007114515002093

123. Zhang P, Sutheerawattananonda M. Kinetic Models for Glucosamine Production by Acid Hydrolysis of Chitin in Five Mushrooms. *Int J Chem Eng*. **2020**;*2020*:1-8. doi:10.1155/2020/5084036

124. Salazar J, Bello L, Chávez M, Añez R, Rojas J, Bermúdez V. Glucosamine for Osteoarthritis: Biological Effects, Clinical Efficacy, and Safety on Glucose Metabolism. *Arthritis*. **2014**;*2014*:1-13. doi:10.1155/2014/432463

125. Steen E, Wang X, Balaji S, et al. The Role of the Anti-Inflammatory Cytokine Interleukin-10 in Tissue Fibrosis. *Adv Wound Care (New Rochelle)*. **2019**;*9*(4):184-198. doi: doi:10.1089/wound.2019.1032

126. Elkhateeb W, Daba G, Thomas P, Wen T-C. Medicinal mushrooms as a new source of natural therapeutic bioactive compounds. *Egypt Pharm J*. **2019**;*18*(2):88-101.

127. Nie A, Chao Y, Zhang X, Al. E. Phytochemistry and Pharmacological Activities of Wolfiporia cocos (F.A. Wolf) Ryvarden & Gilb. *Front Pharmacol*. **2020**;*11*:505249. doi:doi:10.3389/fphar.2020.505249

128. Staniszewska J, Szymański M, Ignatowicz E. Antitumor and immunomodulatory activity of Inonotus obliquus. *Herba Pol*. **2017**;*63*(2):48-58. doi:10.1515/hepo-2017-0013

129. Venturella G, Ferraro V, Cirlincione F, Al. E. Medicinal Mushrooms: Bioactive Compounds, Use, and Clinical Trials. *Int J Mol Sci*. **2021**;*22*:634. doi:https://doi.org/10.3390/ijms22020634

130. Dicks L, Ellinger S. Effect of the Intake of Oyster Mushrooms (Pleurotus ostreatus) on Cardiometabolic Parameters—A Systematic Review of Clinical Trials. *Nutrients*. **2020**;*12*(4):1134. doi:10.3390/nu12041134

131. Yu S, Weaver V, Martin K, Cantorna MT. The effects of whole mushrooms during inflammation. *BMC Immunol*. **2009**;*10*(1):12. doi:10.1186/1471-2172-10-12

132. Baeva E, Bleha R, Lavrova E, Al. E. Polysaccharides from Basidiocarps of Cultivating Mushroom Pleurotus ostreatus: Isolation and Structural Characterization. *Molecules*. **2019**;*24*(15):2740. doi:https://doi.org/10.3390/molecules24152740

133. Xiao Z, Zhou W, Zhang Y. Fungal polysaccharides. *Adv Pharmacol*. **2020**;*87*:277-299. doi: doi: 10.1016/bs.apha.2019.08.003

134. Vetvicka V, Vannucci L, Sima P, Al. E. Beta Glucan: Supplement or Drug? From Laboratory to Clinical Trials. *Molecules*. **2019**;*24*(7):1251. doi:doi:10.3390/molecules24071251

135. Habtemariam S. Trametes versicolor (Synn. Coriolus versicolor) Polysaccharides in Cancer Therapy: Targets and Efficacy. *Biomedicines*. **2020**;*8*(5):135. doi:10.3390/biomedicines8050135

136. Ferreiro E, Pita IR, Mota SI, et al. Coriolus versicolor biomass increases dendritic arborization of newly-generated neurons in mouse hippocampal dentate gyrus. *Oncotarget*. **2018**;*9*(68):32929-32942. doi:10.18632/oncotarget.25978

137. Stephenson J, Nutma E, van der Valk P, Amor S. Inflammation in CNS neurodegenerative diseases. *Immunology*. **2018**;*154*(2):204-219. doi:10.1111/imm.12922

138. Chen W-W, Zhang X, Huang W-J. Role of neuroinflammation in neurodegenerative diseases (Review). *Mol Med Rep*. **2016**;*13*(4):3391-3396. doi:10.3892/mmr.2016.4948

139. Cheah IK, Halliwell B. Could Ergothioneine Aid in the Treatment of Coronavirus Patients? *Antioxidants*. **2020**;*9*(7):595. doi:10.3390/antiox9070595

140. Borodina I, Kenny L, McCarthy C, Al. E. The biology of ergothioneine, an antioxidant nutraceutical. *Nutr Res Rev*. **2020**;*33*(2):190-217. doi:10.1017/S0954422419000301

141. Maginnis MS. Virus–Receptor Interactions: The Key to Cellular Invasion. *J Mol Biol*. **2018**;*430*(17):2590-2611. doi:10.1016/j.jmb.2018.06.024

142. Suwannarach N, Kumla J, Sujarit K, Pattananandecha T, Saenjum C, Lumyong S. Natural Bioactive Compounds from Fungi as Potential Candidates for Protease Inhibitors and Immunomodulators to Apply for Coronaviruses. *Molecules*. **2020**;*25*(8):1800. doi:10.3390/molecules25081800

143. McCarty MF, DiNicolantonio JJ. Nutraceuticals have potential for boosting the type 1 interferon response to RNA viruses including influenza and coronavirus. *Prog Cardiovasc Dis*. **2020**;*63*(3):383-385. doi:10.1016/j.pcad.2020.02.007

144. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The experience of clinical immunologists from China. *Clin Immunol*. **2020**;*214*:108393. doi:10.1016/j.clim.2020.108393

145. Roy BG. Potential of small-molecule fungal metabolites in antiviral chemotherapy. *Antivir Chem Chemother*. **2017**;*25*(2):20-52. doi:10.1177/2040206617705500

146. Geller A, Yan J. Could the Induction of Trained Immunity by β-Glucan Serve as a Defense Against COVID-19? *Front Immunol*. **2020**;*11*(1782). doi:https://doi.org/10.3389/fimmu.2020.01782

147. Lin B, Li S. Cordyceps as an Herbal Drug. In: Benzie I, Wachtel-Galor S, eds. *Herbal Medicine: Biomolecular and Clinical Aspects*. 2nd Editio. CRC Press/Taylor & Francis; 2011. https://www.ncbi.nlm.nih.gov/books/NBK92758/

148. Guidry CA, Mansfield SA, Sawyer RG, Cook CH. Resistant Pathogens, Fungi, and Viruses. *Surg Clin North Am*. **2014**;*94*(6):1195-1218. doi:10.1016/j.suc.2014.08.010

149. Wang S, Welte T, Fang H, et al. Oral Administration of Active Hexose Correlated Compound Enhances Host Resistance to West Nile Encephalitis in Mice. *J Nutr*. **2009**;*139*(3):598-602. doi:10.3945/jn.108.100297

150. Teplyakova T V., Kosogova TA. Antiviral Effect of Agaricomycetes Mushrooms (Review). *Int J Med Mushrooms*. **2016**;*18*(5):375-386. doi:10.1615/IntJMedMushrooms.v18.i5.10

151. Chunchao H, Guo J. A Hypothesis: Supplementation with Mushroom-Derived Active Compound Modulates Immunity and Increases Survival in Response to Influenza Virus (H1N1) Infection. *Evidence-Based Complement Altern Med*. **2011**;*2011*:1-3. doi:10.1093/ecam/neq037

152. He M, Su D, Liu Q, Gao W, Kang Y. Mushroom lectin overcomes hepatitis B virus tolerance via TLR6 signaling. *Sci Rep*. **2017**;*7*(1):5814. doi:10.1038/s41598-017-06261-5

153. Rodríguez-Valentín M, López S, Rivera M, Ríos-Olivares E, Cubano L, Boukli NM. Naturally Derived Anti-HIV Polysaccharide Peptide (PSP) Triggers a Toll-Like Receptor 4-Dependent Antiviral Immune Response. *J Immunol Res*. **2018**;*2018*:1-14. doi:10.1155/2018/8741698

154. Teplyakova T V., Psurtseva N V., Kosogova TA, Mazurkova NA, Khanin VA, Vlasenko VA. Antiviral Activity of Polyporoid Mushrooms (Higher Basidiomycetes) from Altai Mountains (Russia). *Int J Med Mushrooms*. **2012**;*14*(1):37-45. doi:10.1615/IntJMedMushr.v14.i1.40

155. Foster M, Samman S. Zinc and Regulation of Inflammatory Cytokines: Implications for Cardiometabolic Disease. *Nutrients*. **2012**;*4*(7):676-694. doi:10.3390/nu4070676

156. Jang I-S, Ko Y-H, Moon Y-S, Sohn S-H. Effects of Vitamin C or E on the Pro-inflammatory Cytokines, Heat Shock Protein 70 and Antioxidant Status in Broiler Chicks under Summer Conditions. *Asian-Australasian J Anim Sci*. **2014**;*27*(5):749-756. doi:10.5713/ajas.2013.13852

157. Catanzaro M, Corsini E, Rosini M, Racchi M, Lanni C. Immunomodulators Inspired by Nature: A Review on Curcumin and Echinacea. *Molecules*. **2018**;*23*(11):2778. doi:10.3390/molecules23112778

158. Guggenheim AG, Wright KM, Zwickey HL. Immune modulation from five major mushrooms: Application to integrative oncology. *Integr Med*. **2014**;*13*(1):32-44. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4684115/pdf/32-44.pdf

159. Fernandes T, Chaquisse E, Ferrão J. HIV and the Antiviral Role of Mushroom Nutraceuticals. *Adv Image Video Process*. **2020**;*8*(3):64-100. doi:10.14738/aivp.83.8650

160. World Health Organization. Essential Prevention and Care Interventions for Adults and Adolescents Living with HIV in Resource-Limited Settings / Coordinated by Kevin O'Reilly.; 2008.

161. Rose AM, Hall CS, Martinez-Alier N. Aetiology and management of malnutrition in HIV-positive children. *Arch Dis Child*. **2014**;*99*(6):546-551. doi:10.1136/archdischild-2012-303348

162. Maldonado S, Fitzgerald-Bocarsly P. Antifungal Activity of Plasmacytoid Dendritic Cells and the Impact of Chronic HIV Infection. *Front Immunol*. **2017**;*8*. doi:10.3389/fimmu.2017.01705

163. Lindequist U, Niedermeyer THJ, Jülich W-D. The Pharmacological Potential of Mushrooms. *Evidence-Based Complement Altern Med*. **2005**;*2*(3):285-299. doi:10.1093/ecam/neh107

164. Guo W-L, Guo J-B, Liu B-Y, et al. Ganoderic acid A from Ganoderma lucidum ameliorates lipid metabolism and alters gut microbiota composition in hyperlipidemic mice fed a high-fat diet. *Food Funct*. **2020**;*11*(8):6818-6833. doi:10.1039/D0FO00436G

165. Cao F-R, Feng L, Ye L-H, et al. Ganoderic Acid A Metabolites and Their Metabolic Kinetics. *Front Pharmacol*. **2017**;*8*. doi:10.3389/fphar.2017.00101

166. Zhang L, Gallo RL. Antimicrobial peptides. *Curr Biol*. **2016**;*26*(1):R14-R19. doi:10.1016/j.cub.2015.11.017

167. Florindo HF, Kleiner R, Vaskovich-Koubi D, et al. Immune-mediated approaches against COVID-19. *Nat Nanotechnol*. **2020**;*15*(8):630-645. doi:10.1038/s41565-020-0732-3

168. Rouse BT, Sehrawat S. Immunity and immunopathology to viruses: What decides the outcome? *Nat Rev Immunol*. **2010**;*10*(7):514-526. doi:10.1038/nri2802

169. Magden J, Kääriäinen L, Ahola T. Inhibitors of virus replication: recent developments and prospects. *Appl Microbiol Biotechnol*. **2005**;*66*(6):612-621. doi:10.1007/s00253-004-1783-3

170. Weber F. Antiviral Innate Immunity: Introduction. In: *Reference Module in Life Sciences*. Elsevier; 2020. doi:10.1016/B978-0-12-809633-8.21290-9

171. Ellan K, Thayan R, Raman J, Hidari KIPJ, Ismail N, Sabaratnam V. Anti-viral activity of culinary and medicinal mushroom extracts against dengue virus serotype 2: an in-vitro study. *BMC Complement Altern Med*. **2019**;*19*(1):260. doi:10.1186/s12906-019-2629-y

172. Lederman MM, Margolis L. The lymph node in HIV pathogenesis. *Semin Immunol*. **2008**;*20*(3):187-195. doi:10.1016/j.smim.2008.06.001

173. Jeong Y-U, Park Y-J. Ergosterol Peroxide from the Medicinal Mushroom Ganoderma lucidum Inhibits Differentiation and Lipid Accumulation of 3T3-L1 Adipocytes. *Int J Mol Sci*. **2020**;*21*(2):460. doi:https://doi.org/10.3390/ijms21020460

174. Cagno V, Tintori C, Civra A, et al. Novel broad spectrum virucidal molecules against enveloped viruses. Schang LM, ed. *PLoS One*. **2018**;*13*(12):e0208333. doi:10.1371/journal.pone.0208333

175. Raut JK. Mushroom: a potent source of natural antiviral drugs. *Appl Sci Technol Ann*. **2020**;*1*(1):81-91. doi:10.3126/asta.v1i1.30277

176. James C, Harfouche M, Welton NJ, et al. Herpes simplex virus: global infection prevalence and incidence estimates, 2016. *Bull World Health Organ*. **2020**;*98*(5):315-329. doi:10.2471/BLT.19.237149

177. Looker KJ, Welton NJ, Sabin KM, et al. Global and regional estimates of the

contribution of herpes simplex virus type 2 infection to HIV incidence: a population attributable fraction analysis using published epidemiological data. *Lancet Infect Dis*. **2020**;*20*(2):240-249. doi:10.1016/S1473-3099(19)30470-0

178. Mangold CA, Szpara ML. Persistent Infection with Herpes Simplex Virus 1 and Alzheimer's Disease—A Call to Study How Variability in Both Virus and Host may Impact Disease. *Viruses*. **2019**;*11*(10):966. doi:10.3390/v11100966

179. Duarte LF, Farías MA, Álvarez DM, Bueno SM, Riedel CA, González PA. Herpes Simplex Virus Type 1 Infection of the Central Nervous System: Insights Into Proposed Interrelationships With Neurodegenerative Disorders. *Front Cell Neurosci*. **2019**;*13*. doi:10.3389/fncel.2019.00046

180. Thaker SK, Ch'ng J, Christofk HR. Viral hijacking of cellular metabolism. *BMC Biol*. **2019**;*17*(1):59. doi:10.1186/s12915-019-0678-9

181. Vlasenko V, Vlasenko A. Antiviral activity of fungi of the Novosibirsk Region: Pleurotus ostreatus and P. pulmonarius (Review). Banaev EV, Belanova AP, Zaytseva YG, eds. *BIO Web Conf*. **2018**;*11*:00044. doi:10.1051/bioconf/20181100044

182. Eguchi N, Fujino K, Thanasut K, et al. In vitro Anti-Influenza Virus Activity of Agaricus brasiliensis KA21. *Biocontrol Sci*. **2017**;*22*(3):171-174. doi:10.4265/bio.22.171

183. Seo D, Choi C. Antiviral Bioactive Compounds of Mushrooms and Their Antiviral Mechanisms: A Review. *Viruses*. **2021**;*13*(2):350. doi:doi:10.3390/v13020350

184. Couto JS, Silva DP. Coriolus versicolor supplementation in HPV patients. In: *20th European Congress of Obstetrics and Gynaecology*. ; 2007. https://www.mycologyresearch.com/articles/coriolus-versicolor-supplementation-in-hpv-patients

185. Smith JA, Mathew L, Gaikwad A, et al. From Bench to Bedside: Evaluation of AHCC Supplementation to Modulate the Host Immunity to Clear High-Risk Human Papillomavirus Infections. *Front Oncol*. **2019**;*9*. doi:10.3389/fonc.2019.00173

186. Gincheva D, Gincheva V, Konova E. Effect of combined therapy polyhexamethylene biguanide and Coriolus-MRL on human papilloma virus (HPV) cervical and vulvar-related lesions. *IJMDAT*. **2020**;*3*:e220. doi:http://doi.org/ 10.32113/ijmdat_20201_220

187. Linnakoski R, Reshamwala D, Veteli P, Cortina-Escribano M, Vanhanen H, Marjomäki V. Antiviral Agents From Fungi: Diversity, Mechanisms and Potential Applications. *Front Microbiol*. **2018**;*9*. doi:10.3389/fmicb.2018.02325

188. Shahzad F, Anderson D, Najafzadeh M. The Antiviral, Anti-Inflammatory Effects of Natural Medicinal Herbs and Mushrooms and SARS-CoV-2 Infection. *Nutrients*. **2020**;*12*(9):2573. doi:10.3390/nu12092573

189. Kaymakci M, Guler E. Promising Potential Pharmaceuticals from the Genus Cordyceps for COVID-19 Treatment: A Review Study. *Bezmialem Sci*. **2020**;*8*(Supplement 3):140-144. doi:10.14235/bas.galenos.2020.4532

190. Hetland G, Johnson E, Bernardshaw S, Grinde B. Can medicinal mushrooms have prophylactic or therapeutic effect against COVID-19 and its pneumonic superinfection and complicating inflammation? *Scand J Immunol*. **2021**;*93*:e12937. doi:https://doi.org/10.1111/sji.12937

191. Al-jumaili M, Al-dulaimi F, Ajeel M. The Role of Ganoderma lucidum Uptake on Some Hematological and Immunological Response in Patients with Coronavirus (COVID-19). *Sys Rev Pharm*. **2020**;*11*(8):537-541. https://www.sysrevpharm.org/fulltext/196-1600985067

192. USA. Unsubstantiated Claims for Coronavims Prevention and Treatment - Carlin Creative Concepts LLC. Federal Trade Commission. Published 2020. https://www.ftc.gov/system/files/warning-letters/covid-19-letter_to_swro_carlin_creative_concepts_llc_0.pdf

193. Lam C, Cheng L, Zhou L, Al. E. Herb-drug interactions between the medicinal mushrooms Lingzhi and Yunzhi and cytotoxic anticancer drugs: A systematic review. *Chin Med*. **2020**;*15*:75. doi:https://doi.org/10.1186/s13020-020-00356-4

194. Ngai PHK, Ng TB. A hemolysin from the mushroom Pleurotus eryngii. *Appl Microbiol Biotechnol*. **2006**;*72*(6):1185-1191. doi:10.1007/s00253-006-0406-6

195. Matuszewska A, Stefaniuk D, Jaszek M, et al. Antitumor potential of new low molecular weight antioxidative preparations from the white rot fungus Cerrena unicolor against human colon cancer cells. *Sci Rep*. **2019**;*9*(1):1975. doi:10.1038/s41598-018-37947-z

196. Chan WY, Ng TB, Lam JSY, et al. The mushroom ribosome-inactivating protein lyophyllin exerts deleterious effects on mouse embryonic development in vitro. *Appl Microbiol Biotechnol*. **2010**;*85*(4):985-993. doi:10.1007/s00253-009-2048-y

197. Ivanova TS, Krupodorova TA, Barshteyn VY, Artamonova AB, Shlyakhovenko VA. Anticancer substances of mushroom origin. *Exp Oncol*. **2014**;*36*(2):58-66. https://pubmed.ncbi.nlm.nih.gov/24980757/

198. Cappadocia L, Lima CD. Ubiquitin-like Protein Conjugation: Structures, Chemistry, and Mechanism. *Chem Rev*. **2018**;*118*(3):889-918. doi:10.1021/acs.chemrev.6b00737

199. Roca-Lema D, Martinez-Iglesias O, Portela CF de A, et al. In Vitro Anti-proliferative and Anti-invasive Effect of Polysaccharide-rich Extracts from Trametes Versicolor and Grifola Frondosa in Colon Cancer Cells. *Int J Med Sci*. **2019**;*16*(2):231-240. doi:10.7150/ijms.28811

200. Jakopovic B, Oršoli´c N, Paveli´c S. Antitumor, Immunomodulatory and Antiangiogenic Efficacy of Medicinal Mushroom Extract Mixtures in Advanced Colorectal Cancer Animal Model. *Molecules*. **2020**;*25*:5005. doi:doi:10.3390/molecules25215005

201. Kany S, Vollrath JT, Relja B. Cytokines in Inflammatory Disease. *Int J Mol Sci*. **2019**;*20*(23):6008. doi:10.3390/ijms20236008

202. Yamanaka D, Takatsu K, Kimura M, et al. Development of a novel β-1,6-glucan–specific detection system using functionally-modified recombinant endo-β-1,6-glucanase. *J Biol Chem*. **2020**;*295*(16):5362-5376. doi:10.1074/jbc.RA119.011851

203. Han B, Baruah K, Cox E, Al. E. Structure-Functional Activity Relationship of β-Glucans From the Perspective of Immunomodulation: A Mini-Review. *Front Immunol*. **2020**;*11*:658. doi:doi:10.3389/fimmu.2020.00658

204. Jameel GH, AL-Ezzy AIA, Mohammed IH. Immunomodulatory, Apoptosis Induction and Antitumor Activities of Aqueous and Methanolic Extract of Calvatia Craniiformis in Mice Transfected with Murine Hepatocellular Carcinoma Cells. *Open Access Maced J Med Sci*. **2018**;*6*(7):1206-1214. doi:10.3889/oamjms.2018.275

205. Bryant JM, Bouchard M, Haque A. Anticancer Activity of Ganoderic Acid DM: Current Status and Future Perspective. *J Clin Cell Immunol*. **2017**;*08*(06). doi:10.4172/2155-9899.1000535

206. Wang X-Y, Zhang D, Yin J-Y, Nie S-P, Xie M-Y. Recent developments in Hericium erinaceus polysaccharides: extraction, purification, structural characteristics and biological activities. *Crit Rev Food Sci Nutr*. **2019**;*59*(sup1):S96-S115. doi:10.1080/10408398.2018.1521370

207. Blagodatski A, Yatsunskaya M, Mikhailova V, Tiasto V, Kagansky A, Katanaev VL. Medicinal mushrooms as an attractive new source of natural compounds for future cancer therapy. *Oncotarget*. **2018**;*9*(49):29259-29274. doi:10.18632/oncotarget.25660

208. Wong JH, Ng TB, Chan HHL, et al. Mushroom extracts and compounds with suppressive action on breast cancer: evidence from studies using cultured cancer cells, tumor-bearing animals, and clinical trials. *Appl Microbiol Biotechnol*. **2020**;*104*(11):4675-4703. doi:10.1007/s00253-020-10476-4

209. Rossi P, Difrancia R, Quagliariello V, et al. B-glucans from Grifola frondosa and Ganoderma lucidum in breast cancer: an example of complementary and integrative medicine. *Oncotarget*. **2018**;*9*(37):24837-24856. doi:10.18632/oncotarget.24984

210. Davani-Davari D, Negahdaripour M, Karimzadeh I, et al. Prebiotics: Definition, Types, Sources, Mechanisms, and Clinical Applications. *Foods*. **2019**;*8*(3):92. doi:10.3390/foods8030092

211. Ferrão J, Bell V, Chaquisse E, Garrine C, Fernandes T. The Synbiotic Role of Mushrooms: is Germanium a Bioactive Prebiotic Player? A Review Article. *Am J Food Nutr*. **2019**;*7*(1):26-35. doi:10.12691/ajfn-7-1-5

212. Guarino M, Altomare A, Emerenziani S, et al. Mechanisms of Action of

Prebiotics and Their Effects on Gastro-Intestinal Disorders in Adults. *Nutrients*. **2020**;*12*(4):1037. doi:10.3390/nu12041037

213. Bell V, Garrine C, Ferrão J, Calabrese V, Fernandes T. Effects of Nutrition on Neurology. *Open Access J Agric Res*. **2018**;*3*(9):1-6. doi:10.23880/oajar-16000199

214. Lordan C, Thapa D, Ross RP, Cotter PD. Potential for enriching next-generation health-promoting gut bacteria through prebiotics and other dietary components. *Gut Microbes*. **2020**;*11*(1):1-20. doi:10.1080/19490976.2019.1613124

215. Nowak R, Nowacka-Jechalke N, Juda M, Malm A. The preliminary study of prebiotic potential of Polish wild mushroom polysaccharides: the stimulation effect on Lactobacillus strains growth. *Eur J Nutr*. **2018**;*57*(4):1511-1521. doi:10.1007/s00394-017-1436-9

216. Mitsou E, Saxami G, Stamoulou E, Al. E. Effects of Rich in B-Glucans Edible Mushrooms on Aging Gut Microbiota Characteristics: An In Vitro Study. *Molecules*. **2020**;*25*:2806. doi:doi:10.3390/molecules25122806

217. Costa CM da SF. Evaluation of the prebiotic potential of coriolus versicolor-effect upon the human gut microbiota. Published online 2018. http://hdl.handle.net/10400.14/30621.

218. Kausar S, Wang F, Cui H. The Role of Mitochondria in Reactive Oxygen Species Generation and Its Implications for Neurodegenerative Diseases. *Cells*. **2018**;*7*(12):274. doi:10.3390/cells7120274

219. Lourenço SC, Moldão-Martins M, Alves VD. Antioxidants of Natural Plant Origins: From Sources to Food Industry Applications. *Molecules*. **2019**;*24*(22):4132. doi:10.3390/molecules24224132

220. Ma Q, Xing C, Long W, Wang HY, Liu Q, Wang R-F. Impact of microbiota on central nervous system and neurological diseases: the gut-brain axis. *J Neuroinflammation*. **2019**;*16*(1):53. doi:10.1186/s12974-019-1434-3

221. Suganya K, Koo B. Gut-Brain Axis: Role of Gut Microbiota on Neurological Disorders and How Probiotics/Prebiotics Beneficially Modulate Microbial and Immune Pathways to Improve Brain Functions. *Int J Mol Sci*. **2020**;*21*(20):7551.

doi:https://doi.org/10.3390/ijms21207551

222. Feng L, Cheah IK-M, Ng MM-X, et al. The Association between Mushroom Consumption and Mild Cognitive Impairment: A Community-Based Cross-Sectional Study in Singapore. Yu J-T, ed. *J Alzheimer's Dis*. **2019**;*68*(1):197-203. doi:10.3233/JAD-180959

223. Habtemariam S. The Chemistry, Pharmacology and Therapeutic Potential of the Edible Mushroom Dictyophora indusiata (Vent ex. Pers.) Fischer (Synn. Phallus indusiatus). *Biomedicines*. **2019**;*7*:98. doi:https://doi.org/10.3390/biomedicines7040098

224. Colangelo C, et al. Cellular, Synaptic and Network Effects of Acetylcholine in the Neocortex. *Front Neural Circuits*. **2019**;*13*(April):24. doi:https://doi.org/10.3389/fncir.2019.00024

225. Li I-C, Lee L-Y, Tzeng T-T, et al. Neurohealth Properties of Hericium erinaceus Mycelia Enriched with Erinacines. *Behav Neurol*. **2018**;*2018*:1-10. doi:10.1155/2018/5802634

226. Trovato A, Pennisi M, Crupi R, Al. E. Neuroinflammation and Mitochondrial Dysfunction in the Pathogenesis of Alzheimer's Disease: Modulation by Coriolus Versicolor (Yun-Zhi) Nutritional Mushroom. *J Neurol Neuromed*. **2017**;*2*(1):19-28. http://www.jneurology.com/articles/pneuroinflammation-and-mitochondrial-dysfunction-in-the-pathogenesis-of-alzheimerrsquos-disease-modulation-by-coriolus-versicolor.pdf

227. Khan A, Ikram M, Hahm JR, Kim MO. Antioxidant and Anti-Inflammatory Effects of Citrus Flavonoid Hesperetin: Special Focus on Neurological Disorders. *Antioxidants*. **2020**;*9*(7):609. doi:10.3390/antiox9070609

228. Novellino F, Saccà V, Donato A, et al. Innate Immunity: A Common Denominator between Neurodegenerative and Neuropsychiatric Diseases. *Int J Mol Sci*. **2020**;*21*(3):1115. doi:10.3390/ijms21031115

229. Calabrese V. Neuroinflammation and Mitochondrial Dysfunction in the Pathogenesis of Alzheimer?s Disease: Modulation by Coriolus Versicolor (Yun-Zhi) Nutritional Mushroom. *J Neurol Neuromedicine*. **2017**;*2*(1):19-28. doi:https://doi.org/10.29245/2572.942x/2017/2.942x/2017/1.1088

230. Scuto M, Di Mauro P, Ontario ML, et al. Nutritional Mushroom Treatment in Meniere's Disease with Coriolus versicolor: A Rationale for Therapeutic Intervention in Neuroinflammation and Antineurodegeneration. *Int J Mol Sci*. **2019**;*21*(1):284. doi:10.3390/ijms21010284

231. Ippolito L, Giannoni E, Chiarugi P, Parri M. Mitochondrial Redox Hubs as Promising Targets for Anticancer Therapy. *Front Oncol*. **2020**;*10*. doi:10.3389/fonc.2020.00256

232. Kushairi, Phan, Sabaratnam, David, Naidu. Lion's Mane Mushroom, Hericium erinaceus (Bull.: Fr.) Pers. Suppresses H2O2-Induced Oxidative Damage and LPS-Induced Inflammation in HT22 Hippocampal Neurons and BV2 Microglia. *Antioxidants*. **2019**;*8*(8):261. doi:10.3390/antiox8080261

233. Bajracharya R, Youngson NA, Ballard JWO. Dietary Macronutrient Management to Treat Mitochondrial Dysfunction in Parkinson's Disease. *Int J Mol Sci*. **2019**;*20*(8):1850. doi:10.3390/ijms20081850

234. Wesselink E, Koekkoek WAC, Grefte S, Witkamp RF, van Zanten ARH. Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence. *Clin Nutr*. **2019**;*38*(3):982-995. doi:10.1016/j.clnu.2018.08.032

235. Fontes A, Alemany-Pagès M, Oliveira PJ, Ramalho-Santos J, Zischka H, Azul AM. Antioxidant Versus Pro-Apoptotic Effects of Mushroom-Enriched Diets on Mitochondria in Liver Disease. *Int J Mol Sci*. **2019**;*20*(16):3987. doi:10.3390/ijms20163987

236. Williams J, McKune AJ, Georgousopoulou EN, et al. The Effect of L-Theanine Incorporated in a Functional Food Product (Mango Sorbet) on Physiological Responses in Healthy Males: A Pilot Randomised Controlled Trial. *Foods*. **2020**;*9*(3):371. doi:10.3390/foods9030371

237. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. **2020**;*396*(10248):413-446. doi:10.1016/S0140-6736(20)30367-6

238. Franz L, Chambers N, von Isenburg M, de Vries PJ. Autism spectrum disorder in sub-saharan africa: A comprehensive scoping review. *Autism Res*.

2017;*10*(5):723-749. doi:10.1002/aur.1766

239. Abdullahi A, Farouk Z, Imam A. Common mental disorders in mothers of children attending out-patient malnutrition clinics in rural North-western Nigeria: a cross-sectional study. *BMC Public Health*. **2021**;*21*:185. doi:doi.org/10.1186/s12889-021-10227-8

240. Hodges H, Fealko C, Soares N. Autism spectrum disorder: definition, epidemiology, causes, and clinical evaluation. *Transl Pediatr*. **2020**;*9*(S1):S55-S65. doi:10.21037/tp.2019.09.09

241. Zeliadt N. Why many autistic children in Africa are hidden away and go undiagnosed. The Independent. Published 2017. https://www.independent.co.uk/news/long_reads/autism-children-africa-hidden-diagnosis-autistic-mental-disability-a8106106.html

242. Adaku Chilaka C, Mally A. Mycotoxin Occurrence, Exposure and Health Implications in Infants and Young Children in Sub-Saharan Africa: A Review. *Foods*. **2020**;*9*(11):1585. doi:doi:10.3390/foods9111585

243. Bell V, Ferrão J, Chaquisse E, Manuel B. Role of Mushrooms in Autism. *Austin J Nutr Food Sci*. **2019**;*6*(September):0-8.

244. Chong P, Fung M-L, Kah K, Al. E. Therapeutic Potential of Hericium erinaceus for Depressive Disorder. *Int J Mol Sci*. **2020**;*21*:163. doi:doi:10.3390/ijms21010163

245. Li I-C, Chang H-H, Lin C-H, et al. Prevention of Early Alzheimer's Disease by Erinacine A-Enriched Hericium erinaceus Mycelia Pilot Double-Blind Placebo-Controlled Study. *Front Aging Neurosci*. **2020**;*12*. doi:10.3389/fnagi.2020.00155

246. Gebreyesus HH, Gebrehiwot GT. The Potential Role of Astrocytes in Parkinson's Disease (PD). *Med Sci*. **2020**;*8*(1):7. doi:10.3390/medsci8010007