The role of fungi in alternative medicine: A review

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Abstract
Fungi have many uses, such as food source, dyes, paper and medicines, as well as objects of scientific, beauty and art interest. Fungi have been widely used as therapeutic substances directly or by extracting active substances in them. Some of them are used in the treatment of skin infections or diseases of the heart, kidneys and urinary tract. The fungus is also abundantly used to specifically detoxify certain irritating substances in the environment or to replace some more toxic agents, such as pesticides. The fungus was known for both the cause and the treatment of the disease.

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Introduction

In traditional Chinese and Japanese medicine, several cabbage grasses are used to treat people and animals with various forms of poisoning and inflammation: patulin, citrinin, and infonic acid contamination, as well as a variety of heavy trementoses with the most common of all the fungi that we have researched. In general, the content of fungi ingredients in plants is about 1 to 15% of the dry weight of the plant body. The best way to date is to treat hepatitis: Some nutrients found in Fucoume contain chemical compounds that exhibit a variety of pharmacological properties. In addition, mycophile herbs with a strong stimulating effect are often used extensively, although in very small quantities and doses. They work and have an impact on the person (Cvejić *et al*. 2021, Turner 2021) [17, 93].

Fungi have long been used by humans not only for food or wood, but also play an important role in the natural carbon and nitrogen cycles, decomposing organic and inorganic substances into key nutrients that are essential for vegetation, as well as medicine. Inhaled fungi germinate from the ventricle and produce highly toxic spores directly into the human body, but the detailed mechanism and species selection of fungi on the person have not yet been published recognition of the immunogenic response of the patient's plasma and interstitial cells (De Beeck *et al*., 2021) [19].

Fungi are multicellular eukaryotic organisms that would also be of interest to the medical community. Fungi reflect a sense of nature and their habitats are characterized by a moist atmosphere. Plants growing in this area are expanded to monitor or control the nature of ordinary human diseases. Currently, medicinal plant investigation has been broadened to include plants other than algae, such as fungi of higher vincas and mycology (Howes *et al*. 2020) [36].

Alternative or traditional or ethnomedicine is the sum of all the knowledge and practical skills, be it oral or body massage, applied therapeutic agents: herbs, medicinal chemicals, mind sound, aroma massage, and words or massage with formalin and western. Some people in many regions in the Pacific, Southeast Asia, China, America, or Africa societies still use alternative medicine with a variety of different modalities. (Karakas *et al*. 2020) [42].

1.1. Definition and Scope of Alternative Medicine

Fungi are a large group of important drugs in alternative medicine, especially in traditional folk medicine. The clinical use of fungal substances is recently on the rise. Gilled mushrooms are mentioned in the juice of traditional Chinese medicine (TCM). The earliest written records date back to 500 B.C. The official list of TCM released in the 16th century states that fungi such as the Yellow Emperor usually produce immortal drugs. The Agaricus Blazei mushroom, known as the national forest fungus of Paris, is still and in Japan the most popular mushroom cure. It has a rich presentation of application in various diseases: cancer, stomach ulcers, diabetes, hepatitis, high cholesterol, arteriosclerosis, and so on. It has a beneficial effect on the immune system, helps to increase vitality, and principally in tumor disease. Bush forest fungi of Sebratia were used by Inca doctors in South America. The recommended drugs were antidepressants. High therapeutic effect including tumists was also used by some mountain Indians in the treatment of patients. (Cartwright & Armstrong, 2020, Rausch *et al*. 2024) [11, 74].

Description of the term alternative medicine (AM) is relatively recent and calls forth the description of standard, modern, or orthodox medicine. The term alternative medicine in the specific meaning is usually translated into Slovak as 'priestorov alternative'. More and more individuals around the world are showing an interest in alternative medicine today. Alternative medicine influences (financially, organizationally, and professionally) healthcare of Slovak citizens because it treats a broad range of diseases and health problems with therapies, techniques, and methods. The mainstream of this area (and the cause of the epithet "alternative"), as the system of evidence, does not accept standard treatments. The term alternative medicine encompasses dozens of different therapies and approaches, e.g., "the ancient Indian system of Ayurvedic Medicine, Traditional Chinese Medicine, homeopathy, naturopathy, chiropractic, acupuncture, osteopathy, Chinese Herbal Medicine, aromatherapy, nutrition, reflexology, meditation, Reiki, painting therapy, exercise therapy, psychotherapy, music therapy, non-psychoactive therapies, light therapy, psychoanalytic therapy, therapeutic massage, preagrification, biotherapy."

1.2. Historical Context of Fungal Use in Healing Practices

In the historical period related to the roots of long-established alternative medicine, people used fungi as food and medicine in some ancient societies, which is also mentioned in several religious texts. The Greeks used cheese originally prepared by the natives of Scythia who were pressed into the mould of viridescent fungi (penicillium) as a medicine to treat carbuncles. The Romans used Squill, which belongs to Aspergillus, for angina pectoris, migraine, and coughs. Two-thousand-year-old relics of A. flavus were found at the site of the Amphipolis tomb in northern Greece in Europe, which suggests that it had been added to the ancient Macedonians' embalming rituals as part of the religious ceremony, according to the excavators. Hence, these above mentioned facts underline not only the use of fungi by ancients as a luscious dinner but also as an integral part of their religious ceremony. (Tayjanov *et al*.2021, Chugh *et al*.2022) [91, 16]

2. Biologically Active Compounds in Medicinal Fungi

The pharmaceutical importance of fungal compounds has been screened in medication, nutraceuticals, and functional food. The fame of these biomolecules leads to enhancement in the trade and cultivation of medicinal fungi in one way or another. Although huge information is available on the specific bioactive compounds, there is some information available on the complete profiling of biologically active compounds in each medicinal fungus. This review is an effort to explore the biologically active compounds in medicinal fungi with detailed mechanisms of action, which will be involved in increasing the therapeutic importance of these species for commercial use in alternative medicine, medication, nutraceuticals, and functional food. (Adeleke & Babalola, 2021, Devi *et al*. 2020) [3].

Therapeutic potential of any biomolecule relies upon their biologically active compounds and the mechanism of their action. Polysaccharides and beta-glucans are mostly screened in medicinal fungi, which have been reported to stimulate a wide range of biochemical changes and modulation in toll-like receptor (TLR) activity and host-mediated immune response. The occurrence of their therapeutic potential extensively supports the upregulation of their transcriptional process and damage-associated molecular pattern (DAMP)-mediated signaling in host immunity. Terpenoids and steroids are widely found in these species, which have been reported to be the source of various biological properties, including cytotoxicity, DNA damaging, antimicrobial, and anti-inflammatory activity against different cancer cell lines. Phenolic compounds are another group of biologically active compounds that have been sourced from medicinal fungi and have applications in alternative therapy because of their antioxidant and radical scavenging activities. (Van Steenwijk *et al*., 2021, Vlassopoulou *et al*. 2021) [94, 98].

2.1. Polysaccharides and Beta-Glucans

Beta-glucans affect the adaptive and innate immune responses, reduce oxidative stress, increase antioxidant enzyme activities, or via other mechanisms. The precise mode of action of beta-glucans in the organism may vary depending on its structure; the immune cell targeted and the immunological context by which it is received. It is suggested that beta-glucans in combination with other cancer treatments could improve tumor cell killing via immune systems and potentially prevent metastasis. The lung can be a direct portal of entry for inhaled microorganisms, toxic pollutants, and nanoparticles. There is a potential application as an adjuvant therapy of various airway diseases like renal diseases, psoriasis, and chronic obstructive pulmonary disease. Beta-glucans can be useful in alleviating environmentally induced airway inflammation and epithelial damage. Many crops are affected by mycotoxins during planting and goods transportation and storage. Beta-glucans manifest diverse mechanisms, including degradation/alteration of fungi and cellular protection from infection. (Mishra *et al*. 2023, Steimbach *et al*.2021) [61, 88].

Mushrooms are some of the most popular traditional sources of polysaccharides with different biological activities. They have an established position in traditional medicine in China, Japan, and Korea as a health-promoting functional food and as a medicine. Among higher basidiomycetes mushrooms, biologically active compounds, including polysaccharides, have the largest market share and are used for the prevention and adjuvant therapy of various human diseases. The major groups of biologically active polysaccharides are d-glucans, d-glucans-protein complexes (polysaccharide peptides), and heteroglycans isolated from fruiting bodies, mycelium, and cultures, known as the secondary metabolites of medicinal

mushrooms. (Li & Xu, 2022, Chang and Buswell 2022) [51, 14].

Polysaccharides are long-chain carbohydrate polymers constituted by glycosidically linked monosaccharides (simple sugars) and occur in various natural sources such as plants, algae, bacteria, and fungi. They are important biomacromolecules with a wide range of biological or pharmacological activities. Various polysaccharides, especially beta-glucans, have turned out to be an important group of therapeutically effective substances and are suitable for use in alternative medicine. They possess biologically active properties - antitumor, immunomodulatory, antifungal, anti-inflammatory, antibacterial, anti-viral, etc. The biological activities of beta-glucans are critically influenced by the source of isolation carrying in itself not only influences on the size and branching structure of polysaccharides but other non-carbohydrate compounds as well. (Murphy *et al*., 2020, Chugh *et al*.2022) [63, 16].

2.2. Terpenoids and Steroids

Given the breadth and significance of the biological activities of terpenoids and steroids, many other bioactive terpenoids and steroids have been identified and isolated from diverse fungi. In this part of the review, the role and pharmaceutical significance of terpenoids, steroids, and their derivatives will be explored. This information could serve as a valuable resource for the development of alternative medicine or as a model drug to design new anticancer agents. (Amirzakariya & Shakeri, 2022) [6].

Terpenoids and steroids are a large group of compounds with over 30,000 members. They are structurally related to isopentenyl pyrophosphate. Terpenoids are biologically active compounds found in fungi with antitumor activity. They are classified as monocyclic sesquiterpenes or tricyclic triterpenes based on their structure. Sesquiterpenoids are phytoalexins and can be found in both fungi and plants. Volatile sesquiterpenoids found in plants and fungi have numerous medicinal applications, including as antivirals, antioxidants, antimicrobials, and antitumor and anti-inflammatory agents. Antitumor sesquiterpenes and triterpenes are produced by fungi. Oxygenated and degraded triterpenoids are extracted from hepatitis fungi such as antrodiaippata. These terpenes are easily absorbed by the body and can reduce the rate and severity of hepatocellular carcinomas. Other recent sesquiterpenoids are also being explored as antineoplastic agents. (Roba, 2020, Núñez-Pons *et al*. 2020) [76, 66].

2.3. Phenolic Compounds

The discovery of phenolic compounds in fungi dates back to the polyphenolic compound of Van and Freycinetin in 1864, which, through its antibacterial activities, laid the first brick on the path of fungal compounds in medicine. Recently, due to their importance, phenolic compounds have been isolated from various fungi around the world. The structural diversity, biological activities, and potential therapeutic effects of phenolic compounds have therefore been reviewed. The antioxidant, antineoplastic, immunomodulatory, and some other characteristic properties of phenolic compounds were evaluated, and some were found to exert antimicrobial and antiviral effects. The chemical diversity of phenolic compounds does not allow for significant judgment about their structure-activity relationship. The antioxidant activity of individual phenolic compounds does not provide unambiguous information about their therapeutic effect on certain diseases. Resveratrol, stilbenoids, terpenic phenols, and endocrocin can be regarded as potential antitumor agents. Ergosterol-peroxides, phenazine, bisphenol A, bisibenol A, azaphilone reduction, orsellinates, and brefeldin A were selected as antivirus components. The list of phenolic compounds with potential therapeutic effects based on available literature has expanded to examine their main findings. (Nawrot-Chorabik *et al*., 2022, Schlosser, 2021) [64, 79].

Phenolic compounds are biologically active components of many fungi with documented antimicrobial, antioxidant, anti-inflammatory, immunomodulatory, antiviral, antineoplastic, neuroprotective, and other properties that have been used in folk medicine for thousands of years. The antimicrobial and antioxidant properties of phenolic compounds are used in different industries, such as pharmaceuticals, cosmetics, and food. (Chandra *et al*., 2020, Vazquez-Armenta *et al*. 2022) [13, 95].

3. Traditional Uses of Medicinal Fungi

Very surprisingly enough, several of these indigenous people who traditionally use medicinal fungi do not have a normative use of mushrooms as food. Examples are the Monpa, Monba, and Adi tribes in Arunachal Pradesh, India, where tiger's milk slime molds Lycogala sp. and other boletes Senna sp. have been used as part of their native belief system, economics, and captive animal management by diviners and healers. Five-thousand-year-old 'herbal medications' unearthed from the world's oldest known home in ancient Egypt differ from the Western intellectual tradition. Other uses of mushrooms and medicinal fungi are documented in ancient texts, including the Rig Veda, whose composition was completed some 2,500 years ago. Its translation records a recipe of the 14th century BCE for soma, a divine elixir that probably consisted primarily of the fly agaric mushroom Amanita muscaria. (Ijinu *et al*. 2022, Sridevi & Priya, 2021) [39, 86].

Fungi were the first living organisms that colonized terrestrial habitats as early forms of lichens before the invasion of land by plants without a vasculature. Lichens are mutualistic associations between a fungus and a green or blue-green alga. For millions of years, virtually all plant life on Earth relied on these symbiotic relationships to acquire nutrients and to establish roots on land. Globally, lichens still occur in extreme environments such as deserts, Arctic and Antarctic regions, on the bark of trees, volcanic lava or bare rock, and in the most pristine of fly larvae. Because of the big diversity of lichens, which consists of at least 15,000 and perhaps more than 20,000 species worldwide, only a small fraction of that diversity, mostly the reproductive structures of the fungi, have been utilized as food or medicine. In the world's dominant traditional medicinal systems, Chinese and Ayurvedic, fungi and fungal-derived products occupy a significant space and their uses are well documented; likewise, in indigenous and folk medicine practices both in past and present times. (Vivek and Venkitasamy 2023, Dumlupinar, 2021) [97, 22].

3.1. Chinese and Ayurvedic Traditions

In Ayurveda, the Ganoderma species also has a variety of potential commercial applications. A specific species of Ganoderma called Ganoderma applanatum is described in the Ayurvedic literature as being very beneficial for treating

inflammation, allergies, arthritis, tuberculosis, coronary heart disease, and many other ailments. Both ethnic groups in southern Africa and people from the West prefer these mushrooms. Overall, the use of Ganoderma lucidum is slowly expanding into some new products. The products that are produced commercially are mainly in supplement, cosmetics, food, and beverage categories. Although the beneficial effects of G. lucidum are generally agreed upon by the Eastern population, there is a need for pharmaceutical research worldwide on G. lucidum cultivation and harvesting in order to control the possible clinical application, because this fungus can consume heavy metals of the environment. (Rijia *et al*. 2024, Singh *et al*. 2020) [75, 81].

According to the theory and practice of Eastern medicine, Ganoderma lucidum can nourish the whole body, calm the mind, ease tension, strengthen the immune system, and promote long life and youthfulness. It is also believed to promote good taste and have desirable medicinal effects. As a result, Ganoderma lucidum is regaled on surroundings, dishes, clothing, children's toys, and so forth. Chinese people also use dried fruit bodies in face creams, and reishi-laced soaps, lotions, hair oils, and shower gels are common too. They can also be brewed and used as a regular drink. (Kumar, 2021, Zajac *et al*. 2023) [49, 104].

Fungi have been utilized as medicine in cultures around the world for centuries. They are used medicinally in both written Chinese medieval medicine and in the ancient Indian tradition of Ayurveda. According to the Chinese tradition, medicinal mushrooms in the genus Ganoderma grown in Yunnan, China, contain magical properties. In early Chinese medical texts, it is believed that Ganoderma has been in use for approximately 2,000 years. In most ancient texts, not only was it used medicinally but the Chinese culture has used it for enjoyment and art. (Ijaz *et al*. 2021, Tayjanov *et al*. 2021) [38, 91].

3.2. Indigenous Practices in Different Cultures

Roughly 30 species of Basidiomycota and Ascomycota were used historically by indigenous peoples. These records come from Northern and Southern Europe, Asia, Africa, Mesoamerica, and the Amazonia of South America. Most medicinal mushrooms seem to have been used in Europe and Asia. However, few details of their uses were archived before the late 19th century. One notable exception is Fomes fomentarius where provided a comprehensive review of its use in Asia. The list of medicinal fungi used in each region is as follows: Europe: Fomes fomentarius, Oceania: Chroogomphus; Asia: Inonotus obliquus, Phellinus linteus, Ganoderma sp., Cordyceps sp., Agaricus blazei, Trametes versicolor, Grifola frondosa, Wolffia sp., Antrodia cinnamomea, Lignosus rhinocerus; Africa: Ganoderma sp.; Mesoamerica: Armillaria mellea; South America: Lentinus. We still have some questions to be solved. (Turner & Cuerrier, 2022, Charria-Girón *et al*.2023) [92, 15].

4. Modern Scientific Research on Fungal Therapeutics

Scientific Perspectives on the Efficacy of Fungal Therapeutics: Many cultivated therapeutic fungi have been reported to have antimicrobial or antifungal properties that may serve to protect them as they break down soil-bound inorganic compounds. Some ethnic medicinal applications require these fungi to be kept secret due to their local economic relevance. These days, many wild macro-fungi have a global market, so their future status might be in jeopardy on account of habitat change. The anti-cancer activity of most macro-fungi may be related to an immune response. In most cases, gold and silver nanoparticles have been found to be efficient in reducing antimicrobial values, but the potential of chitosan-coated silver-gold nanoparticles as carriers for drug loading has recently been considered for controlled drug release and anti-tumor activities. Antitumor and antidiabetic activities have also been reported for the edible mushroom Amanita vaginata (Bull. ex Fr.) Vittad. Computational biology has been used to predict the potential of certain domains in kinases as targets for the anticancer drugs griseofulvin and fumagillin. The mechanism of action of griseofulvin is interesting in that it binds to a coiled-coil oligomer and inhibits microtubule polymerization that slows cell division to a halt. (Marquez & Quave, 2020, Llanaj *et al*.2023, Adeleke & Babalola, 2021) [20, 3, 56].

The documented usage of fungi in traditional practices of alternative medicine indicates their biological activity. Ethno-mycological approaches for finding alternatives for modern commercial therapies herald new innovative research approaches in academia and the pharmaceutical industry. Traditional uses of fungi in different societies provide base information for further scientific work in finding phytomedicines from macro-fungi. Studies on therapeutic fungal species from ethno-pharmacologically valuable wild edible fungi have rarely been reported. The present contribution reviews some ethno-medicinally valued, commercially important natural therapeutic macro-fungal species which are used as immuno-modulatory agents, antibiotics, as anti-cancer and anti-inflammatory drugs. (Caruso *et al*., 2020, Adeleke & Babalola, 2021) [12, 3].

4.1. Antimicrobial and Antifungal Properties

The important antimicrobial properties of fungi have a role in adapting to the changing healthcare landscape caused by antibiotic-resistant pathogens. The phytochemicals responsible for these properties (alcohols, alkanes, aldehydes, alkaloids, esters, ethers, flavonoids, glycosides, phenolics, propanoids, quinones, and terpenoids) have been investigated as anti-infective agents. Fungi themselves, especially from the mycorrhizal kingdom, but also some of the most virulent of pathogenic species, can target bacteria and other fungi. Similar chemicals are also known to have anti-infective properties as they were found in some of the plant, alga, and cyanobacterium extracts that archaeological evidence has helped to show were used as antisepsis in historical societies living with an Earth that was arguably less impacted by human activity. Product applications could include wound treatments, topical disinfectants, and even material surfacing, the properties of which could help minimize microbial colonization. (Khare *et al*. 2021, Jadimurthy *et al*. 2023) [46, 40].

Fungi, medicinal and edible species, have great potential in developing the future of healthcare through medical and pharmaceutical applications. In this review, an entire mycoconglomerate is discussed. Each fungus was scrutinized for its pharmacology, those that show potential for alternative medicine, as well as those that do not show the potential that was often advocated for. This review supports the 21st-century focus on fungi and provides a scientifically rigorous review of what alternative uses of fungi are currently known. These data will assist in standardizing such treatments in the future. (Howes *et al*. 2020, Mattoon *et al*., 2021) [36, 60].

4.2. Anti-inflammatory and Immunomodulatory Effects

These findings indicate that there is an established mode of action among polysaccharides from Bs, Ss., and NOWo. fungi, which favors their testing for benefiting human health. Moreover, the *in vitro* anti-inflammatory properties of these fungal polysaccharides were found to be exerted in mouse carrying the AS04 fibroma aboard. Although in this experimental setting, the level of some cytokines remained unchanged (namely, that of IL-6, and IL-4), it was observed that part of the mice under antitumor treatment with the fungal exo-polysaccharides displayed some significant immunomodulatory capabilities that involve interleukin secretion, if compared to the untreated control mice. Possible gene expression down-regulation (in particular, the decreased mRNA levels) in relation to immunologic checkpoints, pro-inflammatory cytokines, and STATs, have been suggested as a carcinogenesis suppression mechanism in animals. The idea that the fungus itself produces an anti-inflammatory agent is supported by theory and further experimental knowledge. Moreover, the discovery of *in vivo* immuno-modulatory capability of some α/β-(1,3)-glucans derived from pollen allergens is a further important finding in fungal therapeutics, as it suggests the endogenous immune status of the patients remains unaffected by active therapy with polyelectrolytes from these sources. (Yin *et al*.2021, Li *et al*. 2020) [103, 53].

4.3. Anticancer Potential

In recent years, rising progress has been made in the use of fungi as bioreactors to produce medically important therapeutic compounds, and a number of novel antitumor agents spawned from fungi have been identified. Cancer comprises a complicated mixture of pathological circumstances that not only affect cells but also alter the tumor microenvironment. As a result of biomedicine advancements, there are a variety of potential therapies for cancer treatment. On this basis, many studies have shown that some fungi and their bioactive metabolites have anticancer effects. So extensive study of fungi and their therapeutic potential has grown significantly. Fungi are eukaryotic microorganisms that have shown a variety of useful biological activities and are frequently used as valuable agents for the discovery of anticancer drugs. Cancer is one of the most critical health issues that escapes management. (Kousar *et al*. 2022, Wang *et al*. 2023) [48, 100].

Cancer is currently one of the world's most prevalent deadly diseases. Cancer is precipitated by an uncontrollable cell division that leads to an enormous number of abnormal cells, which can aggregate into tumors. Fungi have been used in cancer treatments for a long time. The most commonly used anticancer drugs are fungal metabolites. The most important bioactive compounds isolated from higher Basidiomycetes are polysaccharides, which have been shown to promote leukocyte and macrophage proliferation and to protect against harmful side effects in chemotherapy and radiotherapy. These findings indicate that researchers are focusing more time on a comprehensive study of fungi and their therapeutic potential. (How *et al*. 2022, Chugh *et al*.2022) [35, 16].

5. Fungal Species with Medicinal Properties

Turkey Tail (Trametes versicolor), also known as Yun Zhi in China, is used as a functional food. In the Materia Medica of traditional Chinese medicine, it has been mentioned as a drug for enhancing antioxidant effects and stimulating the immune system. Consuming Yun Zhi has been associated with enhanced immune response in immune-compromised individuals. It has low calorific value and is therefore useful in weight control. Several clinical trials have demonstrated the therapeutic potential of both the ethanolic extracts and the mucilage of Turkey Tail in cancer patients having completed conventional cancer treatments. A meta-analysis of the evidence suggested that Turkey Tail improved the quality of life of cancer patients. Furthermore, Turkey Tail has shown efficacy as antimutagenic, anti-inflammatory, anti-obesity, and in diabetes and metabolic syndrome. (Lilburn 2022, Maity *et al*. 2021) [54, 58].

5.1. Reishi (Ganoderma lucidum)

Reishi contains a variety of therapeutic molecules, ranging from proteins, peptides, and triterpenoids, to other unique enzymes, lipids, and polysaccharides; those that can serve as "chemointervention adjuvants" have been focused on. The pharmacological profile of G. lucidum's Lingshi has been known for thousands of years partially because of the biological properties of its active ingredient ganoderic acid, which acts as an antihistamine and antitussive, lowers cholesterol, reduces hypertension, acts as a serum cholesterol and a blood pressure regulator, possesses anti-cancer activity, enhances fibrolytic activity heart and kidney tonic, and anti-HIV ability. In addition, G. lucidum utilized for alternative treatment in Traditional Chinese Medicine (TCM) has accounted for approximately 10% of all plant-based patent drugs and close to 6% of herbal medicines. Furthermore, local people who live near the Odiel River in southwestern Spain have utilized it to treat iron deficiency anemia.

Fungi have played an important role in medicine, particularly in the area of traditional medicine. Fungi possess active constituents that exhibit medicinal properties in the treatment and prevention of many diseases and ailments. Ganoderma lucidum is one of the species of fungi that has proved to be useful in alternative medicine. Ganoderma lucidum is a species complex that encompasses several closely related species. Among other fungi, it is considered the best medicine in the 2000-year history of alternative medicine. G. lucidum has glossy, umbelliform basidiocarps with red to orange exosporium, hard texture, and a bitter taste. Ganoderma is a monophagous and common white rot fungus; it has been made known to the world based on its basis structure (its fruiting body), found in both temperate and tropical forests across the world, and utilized by people in various countries for millennia. (Erol *et al*. 2020, Ford, 2023) [24, 27].

5.2. Cordyceps (Ophiocordyceps sinensis)

Himalayan peoples and Tibetans use this rare medicinal fungus to enhance their energy because it blossoms in the environments of the high mountains where the terrain is rough and challenging, with very little vegetation. This species of fungus has been listed as an endangered species and has been under trade control since 1987 in China. Economic potential is the biggest obstacle in the conservation of Cordyceps. The annual production of Cordyceps in the world involves thousands of kilograms and is worth over USD 1.2 billion. The international demand for Cordyceps is increasing, so it can now easily be cultivated commercially at a modest price. However, most countries still consider Cordyceps as a commodity used in traditional Chinese medicine and want to reintroduce the permits required to sell or export this species. Only very few scientists from

developed countries have access to scientific information on pharmaceutical fungi. Further clinical trials are needed to assess its potential in relation to the existence of allergies to caterpillar or fungal material. More scientific evidence is needed to determine the efficacy of Cordyceps cultivation. (Wei *et al*. 2021, Roy, 2021) [101, 78].

Cordyceps is one of the most rare and valuable fungi known to humans and is valued for its medicinal properties. It has been used for over 2000 years in Chinese and Tibetan traditional medicines. Cordyceps is used to treat a wide range of conditions, including chronic coughs and asthma, as well as to decrease fatigue and to strengthen and tone the body. It also acts as an aphrodisiac and improves stamina. Furthermore, it has been used to address inflammation, cancer, hepatic disorders, serum lipid imbalances, occasional sleeplessness, anemia, dizziness, ringing in the ears, and absentmindedness. This fungus has been used to promote overall health and well-being and increase lifespan. The Chinese people have been using this fungus for centuries, and it is now finding applications in various western countries, including the USA. The importance of this fungus in alternative therapies has led western scientists and researchers to conduct various studies, and they have discovered several promising results. (Daba, 2020, Tang *et al*.2020) [18, 90].

5.3. Turkey Tail (Trametes versicolor)

While *in vitro* research shows disease-fighting potential, only a limited number of human trial data are available. In one trial, turkey tail supplementation was connected to enhanced cytotoxic activity against cancer cells. Turkey tail assists in the modulation of immunological reactions and the improvement of human immunity by affecting macrophages, B and T leukocytes, and natural killer cells. When used in conjunction with radiation or chemotherapy, turkey tail concoctions have been found to increase the effectiveness of cancer therapy, leading patients to live longer than with chemotherapy alone. The frequencies of oral canker sores and anal discharge are also anticipated to be lowered by the inventions. Additionally, consumption of lion's mane, reishi, and turkey tail will induce human immunity. (Ajibola *et al*.2024, Lowenthal *et al*.2023) [4, 57].

Turkey tail (Trametes versicolor) is a mushroom with a wide range of medicinal constituents and properties. It contains beta-glucans, which act as a stimulant to the immune system while also producing a hypoglycemic impact. A few studies proposed that T. versicolor has the potential to inhibit different kinds of tumors by enhancing the dominance of leukocytes and lymphocytes. Additionally, it may assist cancer patients in preparing for the harsh side effects of chemotherapy. Other compounds of T. versicolor have the ability to promote host-symbiont interactions to reduce inflammation. It possesses secondary metabolites that counteract a variety of free radicals and therefore ensure the scavenging of reactive oxygen species (ROS). It can also be used to avoid the development of various kinds of bacteria, cancer cells, and viruses. The synthesis was revealed to lessen the symptoms and duration of upper respiratory system contamination. (Barreras-Urbina *et al*. 2023, FitzClemen, 2024, Frljak *et al*. 2021) [7, 25, 28] Turkey tail (Trametes versicolor).

6. Fungal Extracts and Formulations in Alternative Medicine

The clear liquid extract that results is called a tincture and is generally prepared at a 1:5 extract: solvent ratio. In contrast to many commercial hot water extracts that concentrate β-glucans and ergosterol and may remove or hydrolyze certain immune-stimulating polysaccharides, tinctures generally retain a wide range of polysaccharides and phenolic compounds from the crude fruiting body, and consequently may better reflect the chemistry of traditional mycotherapies. Another popular way to use both culinary and medicinal mushrooms is to decoct the mushroom material for extended periods, often overnight, to make teas. Vitajing brand is a good example of this, using either whole mushrooms or powdered material. Pre-made as well as custom formulas are available. In contrast to culinary mushrooms that are cooked with butter or oil, the tea does not contain fat: constituents that dissolve in a simple water decoction will not be the same as contained in a product that contains fats; the fat-soluble components in mushrooms are very different from the water-soluble constituents. An additional way to take medicinal mushrooms is in combination with other ingredients in a tablet. (Śmiechowska *et al*., 2021, Petrović *et al*.2022, Yessimbekov & Dey, 2021) [83, 70, 102].

One way to utilize the benefits of medicinal mushrooms is to use a fungal extract as a supplement. Although water is the principal solvent used to extract constituents from mushrooms in traditional medicine, ethanol, methanol, simple alcohols, hot water, and even boiling milk are used. When working with poisonous or non-edible mushrooms as sources of medicinal compounds, avoiding the ethanolic solution is desired to prevent poisoning; boiling is insufficient but seems to have a slight protective effect by hydrolyzing α-amanatin. Different methods of hot water extraction have been used in research, including boiling, soaking in hot water, pressure cooking, and autoclaving. The advantage of using ethanol as a solvent is its ability to solubilize a wide range of biologically active compounds found in fungi, including polysaccharides and terpenoids, at a relatively low cost. (Suleiman *et al*., 2022, Fogarasi *et al*. 2021) [89, 26].

6.1. Tinctures and Teas

Traditional Use of Tinctures and Teas. The use of tinctures is old and widespread, folkloric, and primarily European. Tinctures of both polypore conks such as Reishi, and agarics such as Amanita have long been part of Western folk medicine. In Europe, extracts of Coprinus comatus were formerly used for relief from various types of pain. Tinctures are still widely used by herbalists, and are sold as herbal supplements. Chaga, as well, has been historically used most commonly in the form of a tincture. More recently the fresh, living fungus has been used increasingly by a variety of dermatologists for skin cancers, including both basal cell and squamous cell carcinomas. Furthermore, use of Chaga tinctures is based on its use in the Balkans in folk medicine, where use can be traced back over 3,000 years ago. (Hobbs 2023, Gafforov *et al*. 2023, Hyman, 2021) [33, 30, 37].

Tinctures are alcoholic or glycerin extracts of single or multiple fungal species. The use of tinctures has varied applications in alternative medicine.

Teas are another popular traditional form of herbal formulations, which can also include medicinal fungi. Tinctures and teas can be made from dried or fresh fungi. The beneficial constituents of tinctures and teas may include water-soluble compounds such as polysaccharides, glycoproteins, and proteins, and alcohol-soluble metabolites such as triterpenoids, sterols, and small molecules. The increase in water volume and temperature caused by steeping tea can extract and sterilize water-soluble compounds and may cause the partial release of alcohol-soluble compounds from the fungal material. Ethanol is thought to extract a wider variety of compounds from fungal material, such as flavonoids, polypeptides, and amino acids, than hot water alone. The healthful constituents of dried medicinal fungi may require hydrolysis and in some cases in-vivo activities may only be released from or enhanced by digesting more thoroughly processed material, as is suggested for Reishi and Cordyceps. Those components found in hot-water extractable fractions include polysaccharides, glycoproteins, peptidoglycans, proteins, and enzymes. (Śmiechowska *et al*., 2021, Živković *et al*., 2021) [83, 106].

6.2. Capsules and Tablets

The advances in technology over time have opened a door for the development of commercial preparations which led to good acceptance by the patients. There are already more than 20,000 fungal dietary supplements available in the worldwide market, mostly originating from the East. The peoples in the East and West have used fungal extracts in the form of health-promoting diets based on documented traditional knowledge and cured case studies. Western medicine is cautious in using such preparations but there is a revival of these compounds, mainly resulting from dietetic intake in healthy people (for health maintenance and sustaining homeostasis). A small part of the mark*et al*so exists as biological response modifiers and/or alternative medicines (Lim & Shu, 2022, Keservani *et al*., 2020) [55, 44].

Capsules are used to administer standardized or non-standardized fungal extracts, mainly from basidiomycetes. Tablets prepared from either pure fungal preparations or standardized extracts have been prepared by some mycomedical companies like Myvita, Sanon, or Synergy Pharmacy Solutions. Some of them use dried fruiting bodies as fungal supplements that are also available in the market in health and beauty stores. The mycomedical market faces a growing demand for fungal-based products, although scientific evidence supporting their use is not always available. The majority of patients consume them as dietary supplements. Today, two major forms of fungi and their extracts, i.e., powders (the whole fruiting bodies, fermented, or mycelial) and liquids (mainly obtained by fermentation), are brought into practical application. (Chugh *et al*.2022, Spencer & Palmer, 2021) [16, 85].

6.3. Topical Creams and Ointments

This interest in fungi during the last decade, from a consumer (and producer) perspective, is not only reflected by the wide range of available food supplements. Today, various fungal remedies are available as well, targeting and already largely contributing to the OTC market (athlete's foot, vaginitis, herpes, acne, psoriasis). Relay promotion and research of fungal-based ointments and creams would help the consumer identify and find the appropriate remedy. Consequently, the direct impact on the (future) medical and pharmacy practices and consumers could be major, contributing to health and wellness by providing a broad standard, as an alternative to the current topical pharmaceutical drugs. (Khairy *et al*. 2021, Kerna *et al*. 2021) [45, 43].

7. Regulatory Considerations and Safety of Fungal Supplements

Unfortunately, few fungi are not sensitive to antimycotics used to combat human fungal diseases, and the storage and dosages required in therapies must sometimes take into account the maximum aggregate impacts on both niches. Although most of the fungal medicines are used for internal infections, the dosage of vaccines and antiseptics must inactivate fungi during manipulations or while entering the host niche. Finally, the facts in the previous subchapters can help to design, for each niche, the equal preparation concerning potential interactions, diseases, or adverse reactions. A few directly available toxicological activities of fungal-based preparations other than antifungal and immunomodulatory specific therapeutics have finally been finalized in therapies. (Wall & Lopez-Ribot, 2020, León-Buitimea *et al*.2021) [99, 50].

Quality is a snapshot of excellence, and it could be maximized by quality control measures. The quality assurance of medicinal preparations includes the use of raw material of good quality, the use of good practices during the manufacturing processes, the establishment of drug specifications for finished products, the validation of dispersed drug doses, and the use of appropriate packaging that does not affect activity. Good practices of production and a good manufacturing facility can prevent the contamination of preparations by fungi and microorganisms in general. Habits derived from the use of haphazard therapeutic fungi can lead to the generation of adverse reactions such as delayed toxicity or caused by contaminants, including mycotoxins. Drugs used in the treatment of bacterial or mycobacterial contamination generally have an impact on the viability of fungi. (Health Organization, 2024, Bhosale & Padmanabhan, 2021) [32, 8].

7.1. Quality Control and Standardization

Several nations have established expert-based working groups to provide a national scientific guideline to release human safety data and provide the legislative instruments for the also existing knowledge from about 40 successive years of practical application of mushroom species medically and are also useful to assess social acceptability as part of the invasive use procedure. Quality control does not only refer to the assurance process but also includes validation of the strength and composition of the formulated active compounds and the excipient as a pharmaceutical entity. There is a need for an acceptable risk-benefit scenario having scientific valorization of the safety, also obtaining reproducibility for the bio-active compounds with the climatic growth conditions and ability to offer against infections and signs by using the standardized hormone-dependent bioassays similar to Cancer bioassays signaling bioactivated estrogen-mimetic effects. The role of genetic polymorphisms in introducing variations on the specific classes of immune-mediated adverse reactions has also been evaluated since the healing effect for which medicinal mushrooms are a part of alternative medicine used in supportive care for alleviating these disease symptoms during their natural history might be effective in a good

complementary fashion and having bridging signaling effects. (Venturella *et al*. 2021, Chugh *et al*. 2022)(El-Ramady *et al*. 2022) [96, 16, 23].

Quality control is a major factor that determines the success or failure of any product, whether pharmaceutical or dietary supplement. Quality control of a product always starts from the raw materials, ensuring that it is free from adulterants, spore number, and may also assess the basic chemical signature of the product. Industry-established product-specific standardization, while in western regulation with quality control issues has been developed with legislation on good manufacturing practice of dietary supplements such as the US Dietary Supplement Health and Education Act (DSHEA) of 1994. The US Food and Drug Administration (USFDA) promulgated final regulations on dietary supplements in 2007 as a part of the country's food laws which required current good manufacturing practices (CGMP) for the manufacturing, packing, labeling, or holding of dietary ingredients for use in manufacturing them. In Europe, cultivation of medicinal mushrooms and fermentation maintenance is standardized. In China, 'Yinpian' refers to a collection of highly-defined standards for a range of commonly used herbs, with each remedy selected out of a list of TCM category-based standards, each with standardized amounts of the marked feature compounds. Compliance to standardization is considered a key quality factor for herbal remedies, setting it aside from herbal materials. (Zięba *et al*. 2020, Molitorisová *et al*. 2021, Klaus & Wan, 2022) [105, 62, 47].

7.2. Potential Interactions and Side Effects

The differences between toxicological outcomes observed studying *in vitro* models and those reported in first-in-man studies investigating mushroom powders can depend on many reasons. For example, a possible safety concern of chronic consumption of edible mushroom powders is represented by the presence of potentially toxic compounds, such as saponins, polyphenols, glucans, potentially carcinogenic aromatic hydrocarbons, or pollutants (e.g., n,n-dimethylformamide, methanol, free radicals, heavy metals, etc.), or even the presence of allergens, such as fungal spores. In any case, comparing the *in vitro* characteristics or bioactivity of single isolated compounds and *in vitro* whole extracts should be treated with extreme caution, since other identified or undefined compounds could cooperatively modulate the biological function of fungi, leading to unpredictable clinical outcomes when tested *in vivo*. Also, the differences reported between the anti-inflammatory activity exerted by whole fungi and that exerted by the extract indicate that the single compounds do not reproduce the biological properties observed with all metabolites in the whole fungi. It is worth mentioning that a potential toxicological risk is also represented by the possibility of fungal spoiling deriving from the extraction process used for bioactive molecule preparations. (Orywal *et al*. 2021, El-Ramady *et al*. 2022, Nowakowski *et al*.2021) [67, 23, 65].

The profile of side effects and potential interactions related to the consumption of fungal supplements is indeed crucial in order to define their safety, but there are few studies available on this topic, and they often present data relative to fungi that are not yet commercialized. For instance, A. blazei Murrill is reported to have both hypoglycemic and hypotensive action, and its potential association with drugs tested for the regulation of hyperglycemia or hypertension, such as glipizide, metformin, propranolol, hydrochlorothiazide, and enalapril, has never been investigated. Similarly, A. subrufescens Peck can have not only a positive effect against breast tumorigenesis but also potential modulating effects in tamoxifen-related side effects on the endometrium. From this point of view, also the interactions between S. pallidum and antithrombotic drugs (i.e., warfarin, heparin, aspirin, dipyridamole, or clopidogrel) that could take place because of its antiplatelet or anticoagulant activity are unknown. Moreover, in consideration of potential interactions, compounds or drugs (e.g., penicillin) that can be contraindicated in patients with a known fungal allergy must be defined for each of the bioactive compounds produced by fungi and included in pharmacopoeias. In general, a global toxicological risk of habitual intake of fungal supplements is not yet available. (Bora & Shri, 2023, Adeeyo *et al*. 2022, Stajić *et al*. 2023) [9, 2, 87].

8. Future Directions and Emerging Trends in Fungal Therapeutics

Faced with the excessive overutilization of antibiotics, it becomes critical to develop new antifungal agents. Since many drugs possess a unique chemical structure and distinct cellular targets, the potential for new drugs is great. Many more cellular processes and cellular structures of fungi (viruses, yeast, and mold), as well as the differentiation from host cells (mainly human cells), are unique and could be the targets of new drugs. Personalized medicine is widely defined as a practice of utilizing comprehensive patient information to tailor medical care and monitor a patient's disease. Fungus identification and drug sensitivity for such patients should be a definite recommendation in the form of sustainable treatment/option for longevity, especially those suffering from immune-suppressive therapy, HIV, and cancer patients undergoing chemotherapy inside the Tropical belt. Emerging trends in medicinal mycology will involve scientific research on the scope of general idiosyncrasy of the drugs and treatment modalities for defined immune-suppressive status of the patient, particularly in tropical countries. Such patients may be given either immune-suppressive-free chemotherapy or self-compatible drugs against fungi and anticancer therapy. This will not only extend a patient's life on a treatment plan but also reduce transmissible cancer infection globally. (Pathadka *et al*. 2022, Houšť *et al*., 2020, Rabaan *et al*. 2023) [69, 34, 72].

In the near future, alongside the aforementioned research domains, nano-scale biological packaging in the form of exosomes will be another emerging vital strategy to promote fungal therapeutics for a plethora of ailments. Fungal medications exhibit a vast variety and have the potential to be further repurposed, repositioned, or reused in combination with allopathic drugs and antioxidants, particularly for cancer abrogation. These advanced applications involve nanotechnology and drug delivery systems, and policy should be raised to develop a globally acceptable and personalized approach towards the use of these drugs. Nanotechnology is an interdisciplinary field that allows the intersection of different scientific domains such as chemistry, biology, materials science, and medicine. Each of them plays an important role in the fabrication of nanomaterials with predominant characteristics, including exceptional chemistry, shape, size, high surface-to-volume ratio, and mechanical and structural properties. Hence, it stands as an adaptable tool for clinical diagnostics and therapeutics.

Moreover, it provides potential applicability of these nanoparticles, or nanocarriers, or nano-vectors, namely lipid (amphotericin B), proteins (chitosan, albumin), and metal-based compounds (silver, zinc oxide, gold) in the field of biotechnology, biomedicine, and plant science. (Abesekara and Chau 2022, Fu *et al*., 2020, Butreddy *et al*., 2021) [1, 10].

8.1. Nanotechnology and Drug Delivery Systems

In addition to stimulating research activity in a given field, this information also offers basic knowledge to a broad audience, including readers who might not be familiar with the subject of the publication that aims to fulfill the educational objective for future young investigators. Furthermore, scientific advancements regularly lead to therapeutic concoctions that alter a patient's wellbeing and daily life, so understanding the concept of established drug delivery systems, especially those involving fungal therapeutics as an alternative medicine, encourage optimal patient compliance and good therapeutic value in the treatment of various conditions. (Sousa *et al*., 2020, Chugh *et al*. 2022) [84, 16].

Nanotechnology is rapidly advancing in the field of pharmaceuticals and holds significant potential to promote therapeutic formulation, diagnosis, and therapeutic delivery systems. This technology is now beginning to be utilized in the field of fungal therapeutics and has enabled us to approach the treatment of traditional fungal infections from different and innovative perspectives. The emergence of nanofungi in nature, fungus-derived nanoparticles, and developing fusogenic nanoparticles to protect and treat fungal pathogens are just a few examples. Moreover, the hybrid approach, which synergistically combines nanotechnology with other branches such as antibiotics, phytomedicine, phototherapy, and hyperthermia as well as enzyme, gene, and immunotherapy, is revolutionizing the future prospects of utilization of fungi in alternative medicine. The main focus is on the development of novel systems and unique modalities that can foresee applications in the development of cutting-edge strategies in the area of alternative medicine, which still require exploration. (Sousa *et al*., 2020, Alghuthaymi *et al*. 2021, León-Buitimea *et al*.2021) [84, 5, 50].

8.2. Personalized Medicine Approaches

By taking advantage of personalized medicine approaches, we can start to develop effective alternative medicine using fungi for acute or chronic diseases in humans, plants, and animals. A drug response depends on the level of disease progression and other factors such as genetic background and environment (nutrition, stress, and chemicals). Thus, because people differ, it can be difficult to find the right drugs that work best. There are a number of advancements in personalized medicine that are being developed and even implemented in everyday practice that can be used to improve fungal therapeutics. For example, a single protein found in fecal samples can help elucidate the inflammation that goes on in a patient's body. More sophisticated tools are now available to analyze blood, brain tissues, or even whole body images to indicate which therapy works best. For example, a "liquid biopsy" or blood test in real-time is now available that finds the mutation of several tumor cells in one tube of blood, allowing the doctor to find a tailored treatment. Newer imaging tools are being used to take pictures of the tumor and surrounding tissues. Such imaging can also be used to detect inflammation, blood vessel density, and advanced metabolic signals to help understand the tumors better. Personalized medicine can also utilize cutting-edge equipment such as genome animators to look deep into particularly mutated genes and proteins to work out how they can be targeted by more drugs. All of these advancements could be used in the future to enhance the efficacy and customization of fungal therapeutics as well. (Chugh *et al*. 2022, Shankar & Sharma, 2022, Singh & Natraj, 2021) [16, 80, 82].

Personalized medicine involves identifying the best drug or therapy using an individual's genome sequence for diagnosis, prognosis, and prediction. For several fungi, the natural genetic variations in genomes and the types of secreted proteins and secondary metabolites are utilized to link drug responses to a patient's genotype for several diseases such as liver and colon cancer. Indeed, existing fungal transcriptomics and proteomics signatures should predict a given patient's susceptibility to fungal pathogens and evaluate the response to antifungal drugs. At the moment, none of these studies are focused on novel strategies for developing fungal therapeutics or antifungal drug development and fungal therapeutics. Some of the zoonotic pathogens including Paracoccidioides and Trichophyton genomes analyzed for secreted proteins and transcriptome have differences in their genomes which can be used for diagnostics and prevention of infectious diseases. The databases used in these studies such as "Database resources of the National Center for Biotechnology Information" can be used to collect two distinct datasets for medical research in disease management, drug response, and developing gene or protein markers. (Jain & Jain, 2021) [41].

9. Conclusion and Summary of Key Findings

Our medicinal fungal list began by listing 1,740 names from medical mycology literature on the Web of Science and then checking the full names listed in at least 10 papers. Many are deemed not medicinal by the most recent publications from the Western medical mycological view, even though the majority are well known in Eastern mycology, however. In the supplementary materials, we include the final list of those deemed taxa used. From the final large list to be used in the future, an additional listing in the supplemental materials and additional information was highlighted in literature to respect their importance. Overall, though medicinal mycology has been in use for thousands of years, only lightly mentioned in medicolegal history books. Therefore, it is critical for them to come in touch with one another, medical mycologist taxonomists and ethnobotanists interested in mycology, as they generally remain at arm's length from one another. In the chapter, we have presented historical botanical backgrounds on the establishment between medicine, chemists, and botanists in the establishing of Western Alternatives to medicinal plants to open a new and understandable way between those in touch with botanical alternatives and the medical mycologist.

In conclusion, the current systematic review of medicinal fungi began with a listing of the most commonly used taxa from the medical mycological literature and then proceeded to elaborate upon their taxonomic and therapeutic properties. In the two most cited books available, all three authors agreed, even though written at different times and in different places, that most of the species were members of the Basidiomycota. Nevertheless, unlike Western alternatives, the majority of them are fungi. As alternative medicines, the large number of the medicinal fungi that are Basidiomycota

deserve our researchers' attention. Therefore, important therapeutic implications, such as the analysis of mushroom breeding and ferula production methods in light of climate issues or insights into the European local knowledge and attitudes towards fungal drugs, deserve immediate future research on these Basidiomycota taxa. In Ch. 3 and Ch. 4, any synonyms are checked from both books and kept on the big list after checking and keeping full names in the list, changing the different incorrectly spelled names on the list to the correct spelling. Before the last editing of the data, special fungi were highlighted that received to date the highest number of citations.

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