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Review

Precis. Nanomed. 2023, 6(3):1157-1180

Mushroom-Derived Nanoparticles in Drug-Delivery Systems – Therapeutic Roles and Biological Functions

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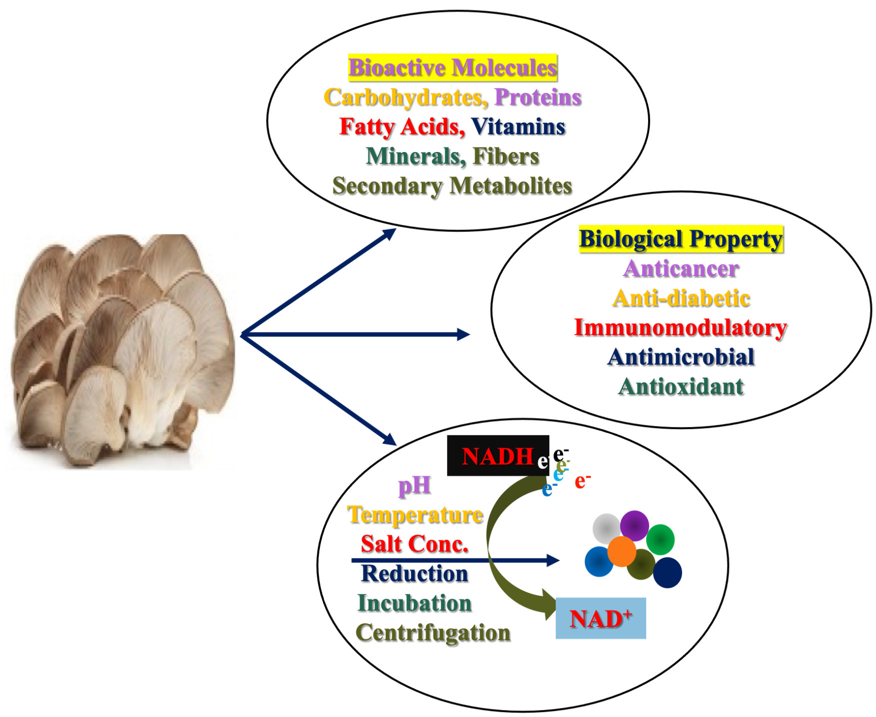
Submitted: August 1, 2023 Accepted: December 5, 2023 Published: December 11, 2023

Graphical Abstract:



Abstract:

In this era of globalization, there is a need for green synthesis of nanoparticles (NPs), which should lessen the tremendous energy consumption, the utilization of toxic compounds, and time, which can help save the environment from hazardous effects. Green synthesis attempts to utilize products from natural agents like plants and fungi because of their profound availability of bio compounds. The NPs derived from them exhibit anticancer, antibacterial, antimicrobial, antioxidant, anti-diabetic, and immunomodulatory

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properties because of their unique physical and chemical properties. These extraordinary properties make them promising agents in medicine and agriculture areas. The review has targeted the mushroom-derived NPs and bioactive compounds, including the nutritional content of mushrooms with their multipurpose properties, followed by encapsulation and delivery of the biotherapeutics. These NPs have found significant applications in advancing industrial and biomedical ventures. A complete understanding of the synthesis mechanism will help optimize the synthesis protocols and control the shape and size of NPs.

Keywords:

Biotherapeutics, green synthesis, mushrooms, antimicrobial, nanomedicine.

Purpose, Rationale, and Limitations

The production of nanoparticles [NPs] from chemical and physical synthesis may involve toxic byproducts and harsh conditions. Innovation and research in nanoparticle synthesis are derived from biomaterials that have gained attention due to their novel features, such as ease of synthesis, low cost, eco-friendly approach, and high water solubility. Nanoparticles obtained through macrofungi involve several mushroom species, i.e., *Pleurotus spp., Ganoderma spp., Lentinus spp.,* and *Agaricus bisporus*. It is well-known that macrofungi possess high nutritional, antimicrobial, anti-cancerous, and immune-modulatory properties. This article aims to discuss the different types of biological functions and bioactive constituents of mushrooms and their nanotherapeutic aspects for NP production via mushrooms. Nanoparticle synthesis via medicinal and edible mushrooms is a striking research field, as macrofungi act as an eco-friendly biofilm that secretes essential enzymes to reduce metal ions. The mushroom-isolated nanoparticles exhibit longer shelf life, higher stability, and increased biological activities. The synthesis mechanisms are still unknown; evidence suggests that fungal flavones and reductases have a significant role. Several macrofungi have been utilized for metal synthesis [such as Ag, Au, Pt, Fe] and non-metal nanoparticles [Cd, Se, etc.]. These nanoparticles have found significant applications in advancing industrial and bio-medical ventures. A complete understanding of the synthesis mechanism will help optimize the synthesis protocols and control the shape and size of nanoparticles. The review article mainly discusses the different types of biological functions and bioactive constituents of the mushrooms and their nanotherapeutic aspects as well.

Summary of Relevant Literature

Green nanotechnology is a probable substitute for toxic nanomaterials by the implementation of eco-friendly and less expensive procedures using live creatures and biomolecules. Several clinical trials have been set up to initiate and enhance this field of green nanomaterials and nanotechnology [1]. Nanomaterials extracted from bacterial culture and biomolecules procured from living organisms, like carbohydrates, proteins, and nucleic acids, are found to be operative composites. Such NPs enhance the treatment and inhibition of osteogenic diseases compared to physiochemically synthesized nanostructures, especially in the form of their improved cell adherence and proliferation and the capability of their action to counteract bacterial adhesion [2]. Macro fungi, like mushrooms or higher fungi, have been engaged for medicinal and agricultural purposes for a long time. They have also represented a new and successful resource of biologically important compounds that can serve as health accompaniments in diverse human infection circumstances. Mushrooms are an effective source of the distinctive molecule ergothioneine, an excellent source of crucial antioxidants that uplift the human immune system and health. It is also used as a preservative, promoting their consumption as functional foods [3]. Mushrooms are macrofungi cultivated on farms and can also be found in the wild. The oyster mushroom *Pleurotus* spp. is a medicinal mushroom that has anticancer, antioxidant, antitumor, antiviral, antibacterial, anti-diabetic, antihypercholesteremic, anti-arthritic, anti-yeast and antifungal activities. Much research has been conducted exhibiting the synthesis of NPs involving the numerous genera of edible mushrooms constituting innumerable bioactive materials with diverse natural actions. Various proteins and poly-saccharides in mushrooms have been utilized to synthesize intracellular and extracellular gold and silver NPs. The extracts obtained from medicinal mushrooms are highly stable, have a long shelf life, and have good water solubility and dispersion characteristics. Experiments with mushrooms have proven to be very promising green-chemical approaches to forming non-toxic, eco-friendly, and stable nanomaterials. NPs derived from macrofungi, including various mushroom species, such as *Agaricus bisporus*, *Pleurotus* spp., *Lentinus* spp., and *Ganoderma* spp. procure high nutritional properties in conjunction with beneficiary actions. Fungi have intracellular metal acceptance capability and maximum wall binding capacity; because of this, they have found high metal tolerance and bioaccumulation ability [4,5]. Shiitake mushroom extracts were found to prevent inflammasome formation in primary macrophages. [6] Many methods are being adapted to co-encapsulate multiple therapeutic agents within the same polymeric NP. Drug encapsulation is usually done either in the interior by direct encapsulation of drugs into the hydrophobic polymeric core of the nanoparticle or by attaching an additional function to the NPs, usually on the surface, to create a separate partition for drug loading, and incorporating drugs by covalent conjugation to the polymer molecules during their synthesis [7].

This article discusses the mushroom-derived NPs used as different therapeutic agents and their profound properties.

Nature has its training protocols for manufacturing shrunken functional materials. Enhancing the perception of nanotechnology for the benefit and synthesis of silver NPs (Ag-NPs) with plant extracts can be attributed to the fact that it is eco-friendly, low in cost, and provides the greatest safeguard to human health. Synthesized silver NPs have a unique impact in the field of nanotechnology. Silver NPs mask various substantial pharmacological activities, and their cost-effectiveness provides an alternative to less effective drugs. Besides plant-mediated synthesis, particular importance has also been placed on the diverse bioassays exhibited by Ag-NPs [8]. Synthesis of silver NPs using *Ganoderma neo-japonicum*, a mushroom species, is a potential cytotoxic agent against human cancer cells [9]. Research activities in the context of nanotechnology have shifted towards environmentally friendly and economically supporting the increasing use of NPs in various industries. Nano synthesis, as part of bio-inspired protocols, provides reliable and sustainable methods for the biosynthesis of NPs by a wide range of microorganisms rather than current synthetic processes. Hence, this field is emerging speedily, and novel methodologies are constantly being invented to improve the properties of NPs. The mechanism of synthesis of metal NPs by different microbes and their applications in various agricultural areas to improve food security and crop production [10].

Bioactive properties of mushrooms:

Mushrooms are one of the most popular superfoods in the world, consumed by a large population in Asia for around two thousand years because of their great pleasurable flavor, medicinal properties, and inordinate textures [11]. In China and Japan, mushrooms like Lingzhi **(***Ganoderma lucidum*), shiitake (*Lentinus edodes*), and yiner (*Tremella fuciformis*) have been used for a long time and nowadays used as a superfood. Mushrooms have been conventionally employed as a medicinal agent because of their enormous healthy biological properties and various vital compounds [12,13]. Mushrooms contain different naturally active compounds like carbohydrates, proteins, fat, vitamins, and fibers and also possess rich sources of secondary metabolic compounds, including terpenoids, alkaloids, carotenoids phenolic, ceramide, and sterols [14]. Mushrooms contain fewer calories and fats, sodium ions, and cholesterol. Due to the presence of all these bioactive molecules, the nutritional value of edible mushrooms stands almost equal to that of meat and milk. All these bioactive elements in mushrooms as food and many other medicinal values make it one of the most popular foods in the world [15,16]. Mushrooms are not only used as a vegetable but also as a powder form of food product in pasta, patties, and snacks [15-17].

Carbohydrates

Carbohydrates are one of the most abundant bioactive molecules, playing an essential role after protein for proper cell function and growth. Mushroom is a versatile source of consumable carbohydrates [including trehalose, mannitol, glucose, glycogen, β-1-3 linked glucan, mannan, and chitin]. Polysaccharides derived β-glucan are believed to be one of the enormous groups of compounds present in mushrooms responsible for a vast range of healthy properties [18]. Among all the occurring bioactive compounds, carbohydrates β-glucan are responsible for various biological activities. β-glucan is a carbohydrate derivative β-1-3 linked biologically active heteropolysaccharides polymer composed of the glucose, mannose, galactose, and fructose subunits. β-glucans differ in molecular structure, degree, and chain length from species to species in the context of their biological activity [19]. They are considered biological response modifiers (BRM) that modulate the host immune system [20,21]. As an outcome of activating the host's immune system, these polysaccharides indicate substantial antiviral, antitumor, antimicrobial, and anti-diabetic activity. Nowadays, various polysaccharides with structurally diverse confirmations in their backbone have been isolated from different species of mushrooms. Mushroom-derived β-glucan has gained much therapeutic attention because of its antioxidative and hypolipidemic properties [22]. β-glucan has sufficient anti-diabetic properties to bind with bile acids, inhibiting cholesterol-bile micelle formation, as well as β-glucan has a diminished property of absorbing the endogenous cholesterol and its biosynthesis. β-glucan lowers the lipid deposition [hypolipidemic property] in the body to increase the removal of blood plasma cholesterol by low production and secretion of very-low-density lipoproteins in the blood circulation and enhances the heart functionality followed by lowering of the cardiovascular disease severity [22,23]. Mushroom-derived β-glucan also has a wide variety of therapeutic applications in cosmetics, biomedicine, and supplements [24].

Proteins

Proteins are one of the most important biological polymers the body requires and are considered the body's building blocks. Protein is made up of 20 amino acids in specific ratios and amounts that differ entirely from each other due to the presence of essential [synthesized by the body] and non-essential [body not synthesized including valine, lysine, methionine, leucine, isoleucine, threonine, histidine, and tryptophan, phenylalanine] amino acid [25]. All these non-essential amino acids have played a crucial role in the biosynthesis of functional proteins in the body. Thus, mushrooms have been considered an unimpeachable source of protein content. The mushroom proteins commonly contain all nine non-essential amino acids essential for body growth and development [26]. All these most widespread edible mushroom species, including *Agaricus bisporus, Lentinus edodes,* and *Pleurotus spp*, cultivated in various countries, have good protein [27]. The nutritional value of protein content in mushrooms is plentiful, higher than other vegetables, approximately double that of asparagus and cabbage, and much higher than that of apples and oranges, respectively. Mushrooms are an excellent protein supplement source for the body's growth and development for vegetarians who do not eat meat, fish, and eggs [28]. Due to all these bioactive properties, mushrooms are highly recommended by the Food and Agricultural Organization in malnutrition to lower the severity of the disease and serve as a highly active source of nutrition to fulfill health requirements. These mushrooms also have other major bioactive constituents, including peptides like lectins, laccases, and ribonucleases. Antibacterial and ribosome-inactivating proteins have greatly enhanced the biomedical properties of the mushrooms [29,30].

Fatty acids

Fat content is very low in mushrooms compared to several other bioactive compounds [25-31]. The fat matter in different species of mushrooms differs from species to species as it ranges from 1.1 to 8.3% on a dry weight basis. The crude fat of mushrooms represents all classes of lipid compounds, including free fatty acids, monoglycerides, diglycerides, triglycerides, sterols, sterol esters, and phospholipids [32]. Mushroom chiefly has 70% unsaturated fatty acid compared to saturated fatty acid, which is very harmful to human health and results in high blood cholesterol [33]. Linoleic acid is also an important constituent of mushrooms and is present in sufficient amounts. These molecules make mushrooms a superb source in the healthy food category as they are an essential part of our diet [23,32-34].

Vitamins

Vitamins are essential for human health and diet as they are required in trace amounts for proper body function and growth. Mushroom is an excellent source of vitamins [35]. Vitamin B-complex vitamins in mushrooms are the most abundant, mainly thiamine [vitamin B1], riboflavin [vitamin B_2], [vitamin B_3] niacin, biotin, and various other vitamins like vitamin A, vitamin C, vitamin D, vitamin E [36]. Quantitative amounts of vitamins have been found, but most commonly, vitamin B containing thiamine content ranging from 0.35 mg in *Volvariella volvacea* to 1.14 mg in *Agaricus bisporus*, to 1.16, 4.80 mg in *Pleurotus* spp., and 7.8 mg in *L. edodes* (mg per 100 g dry weight of mushroom). In contrast, quantitatively fewer vitamins A, C, and D were found in mushrooms [37,38].

Minerals

The edible mushrooms are considered an excellent source of minerals, ions, and micro, macro, and trace elements, like Na^+, Mg^{++}, K^+, Ca^{++}, Cu^{++}, Fe^{3+}, Zn^{2+}, PO_4^{3-}, Mn^{3+}, Mo, Cd, etc. [37-39]. These minerals are essential for the human body's proper function, growth, and metabolism. Potassium ions are particularly abundant and have been found in nearly 45% of the total dry ash content K^+ ion. This essential mineral regulates blood pressure and makes the heart cells function correctly [38-40]. Concentrations of K^+, P, Na^+, Ca^{++}, and Mg^{++} ions mainly make up about 56 to 70% of the total ash content of the mushroom. The relative abundance of Na^+ is almost equal to the Ca^{++} present in approximately equal concentrations except in *Lentinus edodes,* in which Ca^{++} is present in extensive amounts [41]. Cu^{++} is present in higher amounts in species of *Pleurotus*. It assists the body in absorbing oxygen and enhances the synthesis of red blood cells [41]. Fungal mushrooms have almost all the heavy metals, which are chief contributors to making mushrooms a superfood (from an economic point of view) for human health. The zinc amount is highest in all species of *Pleurotus*. Besides all these ions, mushrooms also have a rich source of selenium ions. They act as antioxidants to protect the body from oxidative damage by free radicals by neutralizing and reducing the risk of cancer and other autoimmune destructive diseases [40-42].

Dietary fibers

Mushroom is considered an excellent and available source of dietary fiber ranging from 4 to 55% [dried matter] [23,24]. Mushroom-derived dietary fiber has shown different potential therapeutic uses in the gastrointestinal system. This insoluble dietary fiber regulates food movement throughout the digestive tract. Its gastronomic properties have been found to prevent constipation, diverticulosis, and other bowel syndromes. The therapeutic application of the soluble fibers is to absorb the water and become gel-like in consistency. These fibers bind with cholesterol, reducing the active cellular uptake and lowering total cholesterol levels in the blood. They play an important role in controlling diabetes [25]. Fungus-derived fibers also regulate the blood sugar balance by lowering the cellular uptake of carbohydrates. Feeding diabetic patients a high-fiber diet reduces daily insulin requirements and stabilizes blood glucose levels [38-40].

Other Bioactivities associated with the secondary metabolites

Additionally, the bioactive property of mushrooms has produced other natural compounds as secondary metabolites (alkaloids, flavonoids, saponins, tannins, anthraquinones, steroids, and polyketides). These organic compounds are structurally complex and often highly biologically active, showing a wide variety of biological functions [14,43,44].

Medical Use and Biological Functions of Mushrooms

The bioactive compounds of mushrooms possess excellent medicinal properties that provide a lot of attention in the medical, nanobiotechnology, pharmacology, and drug-delivery systems. Besides these fields, mushrooms have potential biological activity, including as an antibiotic, anti-diabetic, anticancer, antifungal, hypolipidemic, and immunomodulatory [40-45]. Oxidative stress is one of the most destructive processes, as it causes a lot of damage to the biological system. Mushrooms have a high level of flavonoids and other compounds that resist their harmful effect and defend against oxidative stress-induced diseases by lowering free radical generation. Moreover, mushrooms are rich sources of antioxidative vitamins and enzymes like glutathione peroxidases, superoxide dismutases, and catalases that protect and regulate the antioxidative defense system of the human body [46-48]. Another bioactive constituent of the mushroom is alkaloids, nitrogenous plant-derived secondary metabolites that perform various biological functions. It has been reported as a therapeutic agent in infectious diseases, including acquired immunodeficiency syndrome, cancer, and lung diseases [46,47]. Alkaloids are regulators of the Na^+ ion channels and antimicrobial activity, have immunostimulant properties, and induce cell death [44]. Mushrooms are also a good source of alkaloids that have anti-proliferating properties, which is why they are used to inhibit the growth of cancer cells [49,50]. Saponins are also an important part of the mushroom-derived secondary metabolites. It shows its myocardial protective function by inhibiting the sodium ion efflux by blocking the influx of concentration in the cells and subsequently activating the Na^+/Ca^{2+} anti-porter in cardiac muscles. An increase in Ca^{2+} influx through this anti-porter strengthens the contraction of heart muscles [51].

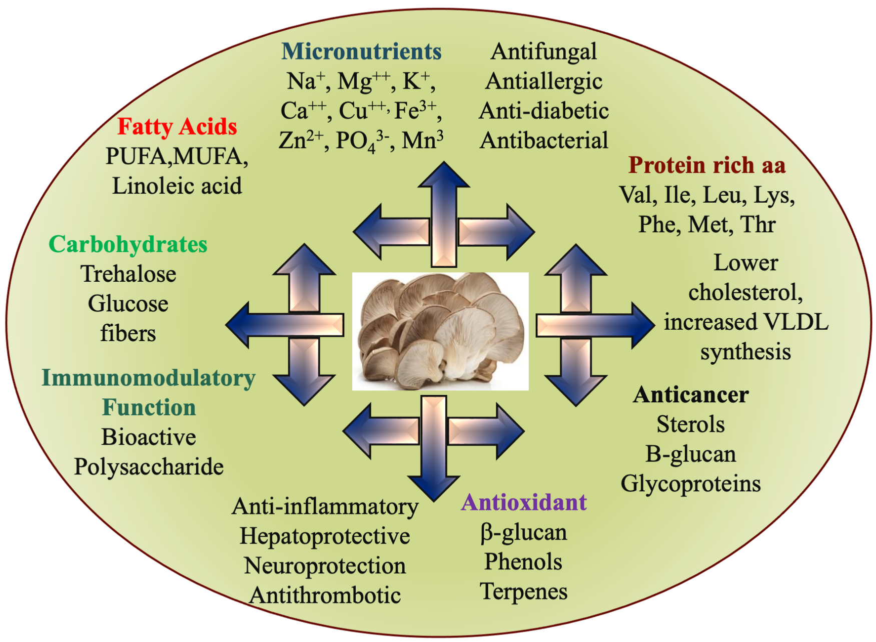

Figure 1. Immunotherapeutic roles and biological functions of mushrooms.

Antimicrobial properties

Microbial infection has become one of the main health issues worldwide because of its rapidly growing nature and ability to develop drug resistance against current therapies. The mushroom-derived metal NPs (MNPs) have a variety of shapes and sizes. Still, they are usually spherically shaped, and their size ranges from 5 to 50 nm depending upon the source of the mushroom species [4],[52]. These NPs have a variety of therapeutic applications, including strong antimicrobial activity against various types of microbes, like bacteria [including Gram-negative/positive] and fungi [34]. These NPs have been found to have strong immune protective, photodynamic effects that produce strong oxidative stress within the microbes through the direct physical contact of MNPs to bacterial membrane, resulting in the release of intercellular material, loss of cell membrane integrity, and cell death. MNPs (Ag-NPs, Au-NPs, ZnO-NPs) exhibiting bactericidal activity [53]-[54]. These NPs have a positive charge, and metal NPs are noncovalently bound to the negatively charged microbial cellular components (i.e., porins, peptidoglycans, and proteins, lipids) of the cell membrane via weak electrostatic interaction, leading to the damage of bacterial/fungi cell membrane, intercellular ionic leakage and, finally, cell inhibition by the generation of the reactive oxygen species and host defense against a variety of the microbes [55]. It was reported that mushroom-derived zinc NPs have antimicrobial activity. Biocompatible fabricated zinc NPs might be efficiently applied in the biomedical and food packaging fields [56,57]. The potential antimicrobial action of mushrooms against many food-borne bacteria, such as *Escherichia coli*, *Streptococcus faecalis*, *Bacillus subtilis*, *Micrococcus luteus*, and *Listeria* all are considered a boon for the food industry since these NPs overcome the problem of contamination of foodstuffs, and provide long time preservation without microbes' infection [58].

Anticancer properties

Apart from antibacterial and antioxidant activity, metal NPs derived from microfungi and other sources possess outstanding anticancer activity because of their profound ROS [reactive oxygen species] generation ability, which provides an excellent chemotherapeutic agent against cancer [49-59]. Various studies have shown that the mushroom-derived silver (Ag-NPs) NPs have dose-dependent toxicity against the different cancer cell lines (MDA-MB, A549, HeLa, K-562) [60]. Fabricated silver Ag-NPs derived from the *P. ostreatus* extract have also shown an anticancer effect against the HepG2 and MCF-7 adenocarcinoma cancer cell lines [61]. The mechanism of the action NPs induced cytotoxicity towards cancer cells attributes for forming cellular ROS species. These ROS are the highly reactive ROS that cause the oxidative damage of cellular proteins and DNA and subsequently induce the cancerous cell's mitochondrial dysfunction, apoptosis, necrosis, and cell death [61]. All these mitogenic activities of fungal-derived polysaccharides involve several mechanisms, such as the anti-proliferation of cancer cells and induction of apoptosis, regulating the immune system, and the anti-metastatic effects [62,63]. They regulate the activation of immune cells, macrophages, T lymphocytes, and natural killer (NK) cells; they secrete the various types of vasoactive inflammatory mediators and cytokines such as the tumor necrosis factor (TNF-α), γ interferon (IFN-γ), or 1β interleukin (IL-1β), among others and minimized the cancer progression and produce the cellular immunity against the wide variety of cancer [52].

Antioxidant property

In the biological system, excessive reactive free radicals are generated from various sources, possibly due to a poor diet, mental stress, smoking, or other ailments that cause extensive cellular damage. Mushrooms are an excellent source of bioactive polysaccharides with great antioxidant properties [64,65]. These polysaccharides can effectively clear free radicles and maintain the cell membrane and integrity by inhibiting lipid peroxidation and regulating oxidative stress. The mushroom-derived metal NPs have strong antioxidant properties because of glutathione, ascorbic acid, cysteine, tocopherol, polyhydroxy, and aromatic and phenolic compounds [66]-[67]. Zinc is one of the NPs that potently protects cells from oxidative stress and acts as an antioxidant. The ZnO-derived NPs, with the help of *P. djamor,* possess potent antioxidant properties. These NPs will be uptake by endocytosis and reduce the level of the free radical within the cell [68]. Two possible primary mechanisms for the antioxidant activity are the hydrogen atom transfer and the single-electron transfer mechanism. An excessive amount of the free radicals generated by oxidative stress could be neutralized by donating a hydrogen atom that includes total oxy-radical scavenging capacity assay, inhibition of induced low-density lipoprotein oxidation, oxygen radical absorbance capability, and radical-trapping antioxidant parameters. The single-electron transfer mechanism involves the reduction of compounds, such as radicals, metals, and carbonyls, by transferring one electron, including by changing the color when all this compound has reduced, such as Ferric Reducing Antioxidant Potential (FRAP), 2,2-diphenyl-1-picrylhydrazyl radical [69].

Anti-diabetic Properties

Mushrooms are considered excellent bioactive sources of food and energy for diabetic patients due to the presence of many nutraceuticals and biomedical properties. They contain very low cholesterol and fat and are an extremely rich source of protein, vitamins, and other essential minerals [23,39]. β-glucan is one of the most abundant polysaccharides in the bacterial, fungal, algal, and cell walls. β-glucans are heteropolysaccharide biopolymers that comprise a β-1,3 linked glucose chain exhibiting branches at certain sugar residues [18,19]. Other polysaccharides, such as galactan or mannan, lectin, lignin, polysaccharide-peptide, and protein complexes in mushrooms have also been found. The biological activities of the β-glucans depend upon various factors, including the type of monomer, glycosidic linkage type, and the number and positioning of branching [21,22,32]. All these structural differences in the glucan's polymer chain have strongly influenced the biological behavior of the mushroom. β-glucans have tremendous therapeutic potential in diabetes mellitus [24,32,70]. Mushroom-derived β-glucan has significant anti-diabetic properties to lower starch breakdown by inhibiting the functional, active role of the α- amylase and glucosidase enzymes that are mainly involved in regulating blood glucose levels in the body [76,77]. Likewise, mushrooms also have natural insulin-like active compounds and enzymes that help break down sugar or starch in foods, regulate glucose metabolism, and improve insulin resistance. *Agaricus bisporus* is one of the most common edible mushrooms in the world and contains certain other active compounds helping in the proper functioning of the pancreas, liver, and other endocrinal glands, thereby promoting the biosynthesis of insulin and other hormones.

Table 1: Anti-diabetic activity of bioactive compounds extracted from different mushroom species

Ref.	Species	Bioactive Compounds	Biological Functions
71	*Agaricus subrufescens*	β-glucans and enzymatically delivered oligosaccharides	Elevates insulin resistance in type 2 diabetes mellitus via increasing adiponectin concentrations, decreases blood glucose, and controls cholesterol levels and fatty acid breakdown.
72	*Sparassis crispa*	β-glucan	Enhanced wound healing in diabetic patients Increase in the migration of macrophages and fibroblasts, enhanced biosynthesis of type I collagen protein and adiponectin, regulates blood glucose levels, TAG, and Cholesterol
73	*Lentinus strigosus*	β-glucan heteropolysaccharides	Controls plasma glucose level, stimulates regeneration of pancreatic islets and causes the destruction of microvascular pancreatic islets.
71	*Phellinus baumii*	Exopolysaccharides [heteropolysaccharides and proteoglycans]	Lowers fasting blood glucose levels by 52.3 % compared to control. Amelioration of liver functions lowers fasting blood glucose levels, improves glucose tolerance and systemic insulin sensitivity.
74	*Inonotus obliquus*	Bioactive Terpenoid and sterol compounds	Anti-hyperglycaemic and anti-lipid peroxidative effects via decreasing blood glucose. Lower TAG, cholesterol, increased glutathione peroxidase activity. lower the levels of malondialdehyde, and increased the HDL, hepatic glycogen level
75	*Lentinula edodes*	Exo-polymer	Hypoglycaemic effects with lower levels of blood glucose, decreased levels of TAG and cholesterol.

They are vital to the body's metabolic functioning [78]. Most of the medicinal activity shown in the genus includes *A. subrufescens*, *Cordyceps sinensis*, *Ganoderma lucidum*, *Coprinus comatus*, *Poria cocos, Inonotus obliquus*, *Phellinus linteus*, *Pleurotus* spp, and *Sparassis crispa* which have hypoglycaemic effects on reducing blood glucose levels and anti-diabetic effects anti-inflammatory, hypocholesterolaemia effects [71]-[78].

Immunomodulatory properties

β-glucans are also considered BRM because they enhance the host immune system and, therefore, prevent and treat several common diseases and promote human health [32]. Mushroom has also been used in the treatment of diseases like cancer, cardiovascular problems, and viral and bacterial infections, which are among the most studied illnesses treated with polysaccharides from mushrooms, and the results show that these bioactive carbohydrates may be successfully used in their treatments [71,72]. β glucans are also used to modulate the immune response as it has lower cellular toxicity, low risk of adverse effects, and high immunostimulatory activity acting as an adjuvant to boost the immune response. Mushrooms are not only an active food source but also have a wide variety of pharmacologically active substances such as phenolic compounds, terpenes, polyketides, steroids, and vitamins that are recognized as excellent antioxidant compounds [11,14,17].

Nowadays, the mushroom has gained considerable attention in the scientific community due to their proven therapeutic potential against many diseases, including cancer. Mushrooms also exhibit an excellent immunomodulatory role in clinical practices. Immunomodulators are classified into three categories: immunoadjuvant, immunosuppressants, and immunostimulants [18,30,78]. Many natural compounds have demonstrated substantial immunomodulation. The plant-based natural compounds exhibit potent pharmacological and advantageous effects. Medicinal mushrooms are a significant source of natural immunomodulators [46,48,49]. The health advantages of mushroom products include anticancer, immune-stimulation, antioxidant, anti-hyperglycemic, anti-hypertensive neuroprotective, hepatoprotective, anti-diabetic, antifungal, antibacterial, and antiviral activities [70-79].

Table 2: Immunomodulatory actions of different species of mushrooms

Ref.	Species	Bioactive Accompound	Biological functions
80	*Pleurotus ostreatus*	heterogalactans, proteoglycan	Stimulates IFN-γ and IL-4 production and secretion
81	*Lentinus squarrosulus*	Heteropolysaccharide β Glucan	Stimulate the activation of the macrophage cells and the activation of the splenocytes and thymocytes.
82,83	*Pleurotus Florida*	[α-1-3, β1-6 glucan] and [α-1,6-glucan]	Promotes the macrophage cell activation and activation of the splenocytes and thymocytes.
78	*Agaricus blazei*	Glycoprotein, Heteroglycan, Glucomannan-protein complex, [β-1-3 glucan] and [β-1-6 glucan]	Stimulates macrophage cells, NK cells, dendritic cells, and granulocytes. Induction of [TNF-α], [IFN-γ], [IL-8] production and secretion.
84	*Ganoderma lucidum*	Ganoderan, Heteroglycan, mannoglucan, glycopeptide	Promotes the production and secretion of TNF-α, IL-1, IFN-γ and also activates the NF-κβ signaling.

They attributed their effects to different components, such as minerals, essential amino acids, dietary fiber, protein, peptide proteins complex, carbohydrate glycoproteins, lipopolysaccharides, and various plant secondary metabolites [15,17,18,32]. Out of them, few complex organic compounds have exhibited immunomodulatory effects. Mushrooms are an important source of different polysaccharides with immunomodulating activities. Most of these polysaccharides are homo glycans or hetero glycans, and they can combine with other proteins to make peptidoglycan or polysaccharide-protein complexes [41,43,85]. Glucans and specific proteins, including lectins, fungal immunomodulatory proteins (FIPs), ribosome-inactivating proteins (RIPs), ribonucleases, and laccases, among others, exhibit most of the biological function of mushrooms, specifically in terms of antitumor, immunomodulatory [71-86]. Immunomodulators play an essential role in the immunity enhancement of the individual against different diseases. [44,60-62]. The mushroom species also vary in their potential biological immunomodulatory activities depending on their core structures and fractional composition chemical modifications [18-21]. Mushroom-derived bioactive components can stimulate the individual's innate and adaptive immune system activities. The bioactive components, such as neutrophils, NK cells, macrophages, and cytokine expression, increase and stimulate the immune system. The secreted cytokines trigger the adaptive immune system via the elevation of B cells for antibody generation, followed by the stimulation of T-cell activation and differentiation to T helper [Th-1] and Th-2 cells, leading to the enhancement of the immunities [30,75,87].

Cytokines and chemokines regulate individuals' homeostasis via cell differentiation, proliferation, apoptosis, inflammatory reactions, and immune responses. Cytokines are immunoregulatory glycoproteins that regulate the immune response and modulate the various types of immune cells for various functions. However, chemokines are small polypeptides that regulate immune cell migration and cell-to-cell adhesion and induce leukocyte activation. Functional pleiotropy and redundancy are the characteristic features of the generated cytokines.

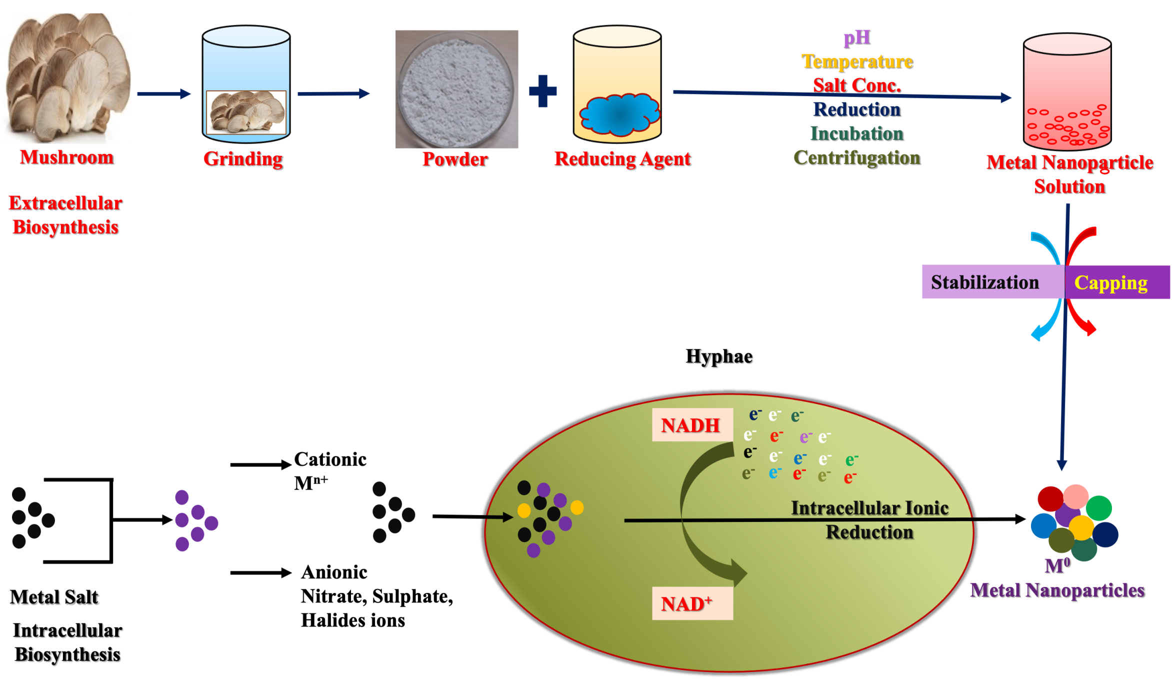

Figure 2. Biosynthesis of the mushroom-derived nanoparticles.

Biosynthesis and encapsulation of mushroom-derived NPs

Cytokines may act as a proinflammatory or anti-inflammatory factor, or both, depending on the local conditions and cellular interaction of the target cells [83,86-88]. TNF-α, IL-1β, IL-6, IL-15, IL-17, and IL-18 cytokines exhibited an inflammatory response, whereas IL-4, IL-10, and IL-13 showed anti-inflammatory potential. The productions of tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6], [IL-1], and interferon-γ [IFN-γ] cytokines production and secretion have also been upregulated in the presence of β-glucans by activating the macrophages cells [85,89,90. The high molecular weight of polysaccharides restricts them to direct penetration to the immune cells. Hence, the trigger process of polysaccharides in mushrooms involves different cell surface receptors, and their efficiency is profoundly affected by their binding affinity to the receptors. All these biological functions allow the mushroom to be used as a natural source of antioxidants and antimicrobial agents with high nutritional value and health benefits [60,91,92].

For the encapsulation of therapeutics, several methods, like extracts, essential oils, natural bioactive compounds, and varied matrices, have been developed [93-95]. The top-down methodology includes emulsification and emulsification-solvent evaporation, whether supercritical fluid techniques, inclusion complexation, coacervation, or nanoprecipitation, which are included in bottom-up methodologies. However, the mixture of each approach is commonly used. Hydrophilic and lipophilic, the nanoencapsulation technique has been used to encapsulate both. Microencapsulation could be divided into three types of techniques: chemical, physiochemical, and physiomechanical. The size of the bioactive compounds formed by microencapsulation is 1 μm to 1 mm. Many other encapsulation techniques are generally used, such as spray drying, ionic gelation, emulsification, and coacervation [95,96]. Spray-drying is a feasible process where bioactive compounds are united with the medium, followed by a spinning wheel for atomization of the mixture, which is filled into a spay dryer, after which the capsule is formed by contacting the atomized material and water, which is evaporated by hot air and capsules drop into the bottom and are collected from the dryer. It is also easy, inexpensive, and quick [97]. Another advantage is it can turn liquid feeds into powder form. [98]. Ionic gelation is an easy-going, effortless, organic solvent-free perspective for developing steady NPs [NP].

To provide charge density, communication between oppositely charged macromolecules and non-hazardous and multivalent material occurs, and the method depends on this principle. There are some disadvantages of this method, like large particle size, pH sensitivity, and high polydispersity, and the advantage is the high loading capacity [99-101]. The emulsification method depends upon alloyed structures, which include two aqueous phases [water-in-oil, W/O, oil-in-water O/W], aerosol formed by burning of one aqueous into another, and an adapted emulsifier acclimated for stabilization [102]. Coacervation is one of the oldest and most acclimated techniques. It has many applications in the food, ornamental, and pesticide industries [103]. It depends upon the dissociation of two liquid phases in a colloidal solution. Selecting an appropriate matrix is one of the most critical processes because matrix material has been affected by release profile, encapsulation efficiency, and the steadiness of the produced nanostructures [93]. Natural molecules have been applied as matrices to encapsulate a range of molecules.

Chitosan, an elite cationic polysaccharide, has various properties like antioxidant, lipid-lowering, antimicrobial activities, encapsulation potential, etc. The Food and Drug Administration classified this biopolymer as GRAS (Generally Recognized as Safe). Chitosan Nanocomposite Coatings are used for Food, Paints, and Water Treatment Applications[104]. The cationic attributes of chitosan lead beneath an acidic environment to the expansion of assorted forms, like nano/microparticles, emulsions, fibers, hydrogels, films, and membranes. It has been reported that in the form of a matrix, chitosan is used for the encapsulation of therapeutics. For example, *Camellia sinensis* encapsulated in water-soluble low molecular weight chitosan (CS) obtained from mushrooms by ionic gelation using tripolyphosphate (TPP) is effective in removing all the extracellular collagen caused by carbon tetrachloride (CCl4) in the hepatic fibrosis rat liver [105]. Another example is the encapsulation of bovine serum in chitosan of white mushroom containing hyaluronic acid (HA) coating of candle soot NPs (CSNP) and alginate coating of CSNP, which has an outcome of unlike surface chemistry HA–CSNPs less immunogenic HA–CSNPs adsorb anti-inflammatory proteins alginate–CSNPs adsorb proinflammatory [106].

Delivery of biotherapeutics

NPs are selected as transporters because of their ability to protect against degradation of solubility increases in the body, maintain delivery, and increase the chances of specific targeting being achieved by attaching NPs to selected antibodies. Several parameters are important in formulating NPs: the size, the surface charge, the release duration of the drug, and the encapsulation efficiency. In fact, for non-specific targeting of cancer cells, the size is essential for penetration and retention. According to Zhang, the size of a nanoparticle should be smaller than 150 nm [107]. In agriculture, nanomaterials can be used as smart delivery systems in various processes, particularly pest control and disease management. Targeting particular plant parts and releasing the active ingredients could act as "magical bullets."

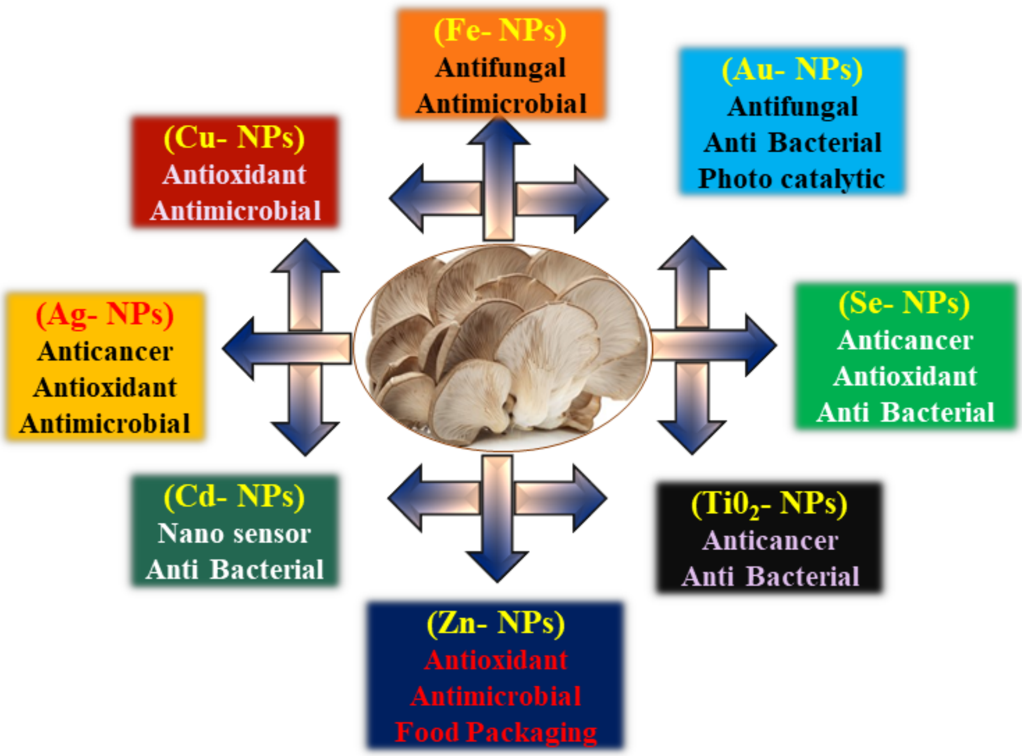

Figure 3: Mushroom-derived nanoparticles (MNPs) and their biological functions [1-6].

In contrast, nanocapsules can penetrate throughout the cuticles and tissues of adverse plants and are used for an efficient, consistent, and steady release of herbicides [108]. Polymers, defined as long chains of repeating structural units, have shown promise in recent years as drug transporters and have demonstrated some advantages over lipid vesicles. So, these polymeric NPs have been investigated to work as drug transporters to the target cancer cells.

Biocompatibility and biodegradability are the main properties of a polymer being effective as a drug carrier. Biocompatibility is the fundamental property used. It refers to any substance that belongs to the body for a long time without creating an immune response when used as a drug transporter. Biodegradability is the difference between polymers used for implantation and the ones used to encapsulate and deliver drugs.

Through hydrolysis, the polymer should be removed after the drug's delivery, the product should not be toxic, and the degradation time should not be too long or too short. Two conformations of polymeric NPs exist. The drug can be entrapped in the core formation by a polymer called a "nanocapsule," when entangled, the polymer chain forms a nanoparticle called a "nanosphere." The drug is present between the chains and is the most true conformation for the prepared NPs. Surface absorption is also an important factor [109]. For the delivery of therapeutics, the size of NPs is an essential factor. In biological applications, size and charge are important in structural and functional properties. For intercellular and intracellular delivery, particle size is an important factor. In the target organism, the interaction of particles with the protective cell membrane is enhanced by the smaller size. Therefore, the delivery of drug NPs size should be <100 nm. [110,111]. For the delivery of the drug, the particle should not be agglomerated and freely scattered. The property of agglomeration should be seen by HR-TEM and FE-SEM micrographs [112]. Another study has shown that a lectin-like protein derived from the mushroom *Agaricus bisporus* (LSMT) can penetrate the epithelial barrier of the intestine ex vivo. It is not toxic for prolonged oral administration in mice models in vitro [113]. Recently, another study has revealed its therapeutic role in the effective and convenient delivery of multidose COVID-19 vaccines. The mushroom-like structure allows the MILD (mushroom-inspired imprintable and lightly detachable microneedle) system to be easily pressed into the skin and record the vaccine counts *in situ*. This work used the inactivated SARS-CoV-2 virus-based vaccine loading MILD system-induced high antibodies against the SARS-CoV-2 receptor-binding domain *in vivo* without toxicity and damage. It's a novel delivery system promising to improve COVID-19 vaccination efficacy through its dual capabilities of vaccine delivery and *in situ* data storage. Thus, it possesses the great potential to help manage the COVID-19 pandemic. [114]. Another study has shown that using Agaricus bisporus wall material mannosyl erythritol lipid A (MEL-A) and coating chitosan liposomes with increased antioxidant capacity. It shown that mushroom chitosan-coated liposomes also have stronger antioxidant activity than commercial chitosan. Thus, these findings reveal that fungal chitosan-coated liposomes modified with MEL-A can be considered a promising delivery system with enhanced antioxidant effects for bioactive compounds [115]. The use of mushrooms is not limited. They will be used in various other biomedical applications to deliver functional food. Resveratrol (RES) is a common active factor in the functional food field, but poor water solubility and low bioavailability have limited its application. In this study, the novel NPs (RES-CBFMP NPs) using floral mushroom polysaccharide as the wall material have been developed for delivering RES, and RES-CBFMP NPs have shown good physicochemical stabilities, sustained gastrointestinal release kinetics, as well as improved antioxidant and anticancer activities in-vitro. This study may contribute to developing RES oral delivery systems and applying hydrophobic active molecules in the functional food field [116].

Future Perspectives

The mushroom mycelium and fruiting body were used as the necessary bio factors to synthesize metallic and non-metallic NPs *via* biochemical processes from aqueous extracts produced or purified to form such protein/enzyme and polysaccharides. These green chemistry methods synthesize myco-NPs such as Au-NPs, Se-NPs, CdS-NPs, Pa-NPs, Ag-NPs, ZnS-NPs, and Fe-NPs from different edible and therapeutic mushrooms; they are tested in 21% of industries and 79% of biomedical fields. Mushroom-based NPs are synthesized through the extracellular hyphae (~84%), or *via* the intracellular hyphae of mushrooms (~16%). For example, *Pleurotus* spp. were highly used (~38%) to make NPs, and silver NPs were the one often biosynthesized, around 64% of cases. Mushrooms have significant potential to synthesize metal NPs, with many applications. Mycogenesis is an efficient and suitable method for synthesizing various NPs with broad applications in many fields, such as textiles, agriculture, medicine, optics, cosmetics, and food.

Using mushrooms for NP synthesis has been a relatively new venture in nanotechnology. Therefore, interest has been taken due to many assets such as higher protein content in mushrooms, cost-effective nature, and downstream processing scale. The extra and intracellular reductases are significant in NP synthesis [117,119]. Mushrooms can be engineered to produce more enzymes involved in NP synthesis [120]. The different mechanisms involved in nanoparticle mycosynthesis using several macrofungi can help develop distinct synthesis strategies. It also allows us to modulate the size, shape, and production of NPs for their implementation in agriculture, medicine, and electronics [127]. The utilization of mushrooms to develop NPs has the advantages of downstream processing and easy handling. The synthesis of NPs *via* biological processes is relatively safe and inexpensive [121]. Its synthesis *via* mushrooms is widely applicable in many fields [128]. The formation of an innovative drug-delivery system for the particular site will be helpful in disease diagnosis. However, intelligent detection and biosensor system production will be beneficial to protect crops against pathogens and insects. Currently, the myco-nanotechnology techniques are still being developed. The implementation of NPs will continue to grow, but we still need to learn more about their toxicity, environmental accumulation, and impact on human health [122].

There is now hope that NPs can treat several severe human diseases, and in the future, it will open a new avenue in biomedical sciences. Besides, silver NPs would serve as a powerful solution to the current energy crisis by obtaining their uses as energy-driven machines [123].

The scientific literature also reveals several considerable works regarding the in-vitro studies of mushroom-based NPs, but little information is available about in vivo applications. Furthermore, additional examinations are required to elaborate on nanomaterial functions in the medicinal field. Although mushroom-based metal NP synthesis has a potentially broad-scale benefit, many challenges and limitations must be overcome before practical implementation [124]. More research is required to optimize several reaction steps to control better the shape, size, and monodispersity of NPs. NP stability is also a significant factor to consider. It is also essential to address the limitations of novel strategies in this research area [125,126]. The exact mechanism of mushroom-based NP syntheses is still not entirely known. So, more experimental trials are required to find a precise tool to recognize the responsible enzymes or proteins involved in the stabilization and reduction of NPs. This way, we can produce low-cost recovery techniques for commercially feasible processes [117].

Conclusions

In this review, we summarize the topical research based on mycosynthesized NPs. Many mushrooms are present in nature, and most can be unique species for nanoparticle synthesis. Elucidation of the mycosynthesis mechanism of significant metal NPs is needed to maintain a coherent approach. An in-depth understanding of these complicated biomedical processes of mushroom-based NP synthesis is a prerequisite for standard trials. The expansion of nanomedicine-based eco-friendly technologies plays a vital role in expanding biological applications. As green nanotechnology has advantages compared to traditional methods, recent research is being done considering our environment. Mycosynthesized metallic NPs, mostly silver, gold, and selenium NPs, show significant cytotoxic potential against several cancer cell lines. Besides, targeted drug delivery using NPs of edible mushrooms is being considered as a minimally invasive and novel drug application. Mushroom NPs may be considered in industries like inorganic NPs, carbon nanotubes, and waste treatment to absorb environmental toxins. Their use will expand upon current applications. NPs prepared from some of the mushroom species like *Agaricus bisporus* (button mushroom), *Pleurotus* (oyster mushroom), *Lentinus,* and *Ganoderma* are a few examples constituting uncommon nutritional, immune-modulatory, antibacterial, antifungal, antiviral and antimycobacterial properties. They also exhibit antioxidant and anticancer properties. In this review, it has been summarized that these green NPs can be used to control the release of site-specific drugs, encapsulate the drug, and prevent the degradation of molecular content by stabilizing them. Nanocarriers can be aggregated near the inflammatory marker sites of tumors because of advanced permeability and retention; hence, these hydrophobic biodegradable polymeric nanocarriers may provide a constant source of encapsulated therapeutic drugs at the disease location.

Acknowledgments:

The authors wish to acknowledge the Biosciences, Integral University, Lucknow department for providing the manuscript number IU/RD/2022-MCN0001639.

Conflict of Interest:

No authors declared a conflict of interest. For a signed statement, please contact the journal office at editor@precisionnanomedicine.com.

Quote this article as Pandey N, Ahmad F, Singh K, Ahmad S, Sharma R, Mushroom-Derived Nanoparticles in Drug Delivery Systems – Therapeutic Roles and Biological Functions**,** Precis. Nanomed. 2023, 6(4):1157-1180, https://doi.org/10.33218/001c.91083

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