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Effects of Mushrooms and their Bioactive Substances on the Immune System in Cancer

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A B S T R A C T

Silver nanoparticles Despite enormous development in the field of drug development, cancer still remains elusive. Compromised immunity stands as a roadblock to the successful pharmacological execution of anti-cancer drugs used clinically currently. Recently some breakthrough cancer treatment strategy like nano-formulation, extracellular vesicles treatment, natural antioxidant therapy, targeted immunotherapy, gene therapy, thermal ablation and magnetic hyperthermia, and pathomics and radiomics has been developed and tested pre-clinically as well as clinically. However, clinical efficacy of such therapies is yet to establish and some are too costly to be utilized by patients from poor and developing countries. At this juncture, researchers are heading towards the search of medicines from natural sources that is higher safety margin and multitarget pharmacological efficacy compared to conventional treatments. Mushroom is used traditionally as food as well as drug since time immemorial due to its immunomodulatory effect which is loaded with proteins, low fat content and cholesterol. Mushrooms are recommended as one of the best vegetarian diets for immunosuppressed cancer and HIV/AIDS patients. Mushrooms are well-known for their anti-cancer activity that impacts hematopoietic stem cells, lymphocytes, macrophages, T cells, dendritic cells (DCs), and natural killer (NK) cells in the immune system. This comprehensive review article emphasizes on the molecular mechanisms of cancer genesis, conventional anti-cancer therapy as well as reported some significant breakthrough in anti-cancer drug development, anti-cancer activity of some selected species of mushrooms and their bioactive phytoconstituents followed by a brief discussion of recent anti-cancer efficacy of some metallic nanoparticles loaded with mushrooms.

Keywords: Anti-cancer, Mushroom, Immunomodulatory Nanomedicine, Gold nanoparticles

1. Introduction

The field of medicine and healthcare sector has advanced exponentially in the last two-three decades; however, the world is still fighting the menace of cancer. Approaches such as chemotherapy, radiotherapy, surgery, dietary as well as behavioral changes and the recent addition of immunotherapy have been developed to combat cancer where, many a times failure comes above success [1]. Although many forms of cancer are curable nowadays, however, cancer is still one of the tenth most leading cause of death worldwide of which death due to lung cancer and stomach cancer are placed at fourth and fifth position respectively [2]. Genomic instability, activation of proto-oncogene and inactivation of tumor suppressor gene, epigenetic instability, apoptosis, telomerase activity, and angiogenesis are some of the hallmarks of cancer genesis. Modern anti-cancer therapy is basically based on the modulation of these hallmarks of cancer. Despite augmented efficacy and survival, the modern anti-cancer therapy comes with various adverse effects of which compromised immunity comes in the forefront [3]. Researchers have been searching relentlessly for safer and alternative therapies that not only regulate the cancerous cells but also improve the immune system to fight cancer [4].

Nature has bestowed upon us with numerous natural resources for sustaining a healthy life and among many resources, mushroom is one such. Mushrooms are used as both food and medicines for thousands of years. Mushrooms are the fleshy and edible fruiting bodies of macrofungi from the basidiomycota and ascomycota group that are grown above the ground in soil or other substrates. Out of 1600 types of mushrooms worldwide, only 100 types are edible and only 33 types of edible mushrooms are cultivated around the world however, only three are commonly grown: white button mushrooms (Agaricus bisporus L.), oyster mushrooms (Pleurotus ostreatus L.), and paddy straw mushrooms (Volvariella volvacea L.) [5]. Mushrooms are hailed for their immune boosting properties and are regarded as one of the best diets for vegetarians and immunosuppressed persons such as cancer patients and persons suffering from HIV/AIDS [1]. Due to low-fat content and absence of cholesterol, many mushrooms are great sources of protein. Proteins such as laccases, lectins, ribosome inactivating proteins (RIP), fungal immunomodulatory proteins (FIP), ribonucleases, and other mushroom proteins with interesting biological activity have become attractive sources of natural anticancer, antimicrobial, antidiabetic, cardiovascular protective, hepatoprotective, antioxidative, and immunomodulatory drugs [6,7]. A systematic review of observational studies found that higher mushroom consumption was associated with lower risk of cancer, particularly breast cancer, owing to the antioxidants ergothioneine and glutathione [8]. Mushrooms are well-known for their ability to modulate the immune system, affecting hematopoietic stem cells, lymphocytes, macrophages, T cells, dendritic cells (DCs), and natural killer (NK) cells [9]. Mushrooms like *Lentinula edodes*, *Trametes versicolor*, *Grifola frondose*, *Hericium erinaceus*, *Fomes fomentarius* and many more are reported to exhibit potent anti-cancer efficacy in-vitro and in-vivo. The extract of *Agaricus blazei* Murill is reported to exert potent anti-leukemic effect

in human myeloid leukemia cells by increasing the secretion of a number of cytokines like IL-23 subunit of the IL-12 family, IL-1, monocyte chemoattractant protein-1 (MCP-1), granulocyte colony stimulating factor (G-CSF) [10]. Mushrooms contain numerous medicinally important bioactive compounds like polysaccharides, proteins, lipids, ash, glycosides, alkaloids, volatile oils, tocopherols, phenolics, flavonoids, carotenoids, folates, ascorbic acid enzymes, and organic acids [11]. Mushroom and its bioactive compounds demonstrated promising results in various stages of clinical trials of cancer. In a centrally randomized controlled clinical trial, polysaccharide k, extracted from the member of basidiomycetes, mycelia of *Coriolus versicolor* strain CM-101, showed potent efficacy by improving the survival of patients with curatively resected colorectal cancer [12].

The use of edible and medicinal mushrooms to synthesise nanoparticles has arisen as an interesting subject in the field of medical research as because mushroom-loaded nanoparticles are more stable, have a longer shelf life, and have more biological activity [13]. Recently, green synthesis of silver nanoparticles (AgNPs) utilizing crude extracts of B. edulis (BE-NPs) and C. versicolor (CV-AgNPs) mushrooms showed promising anti-proliferative effect against MCF-7, HT-29 and HUH-7 cell lines [14]. In another recent work of biofabricated gold nanoparticles (AuNPs) using the aqueous extract of the endophytic *Cladosporium sp*. isolated from *Commiphora wightii* showed enhanced apoptotic activity against breast cancer cell line MCF-7 [15].

In the following sections we have tried to emphasizes on the molecular mechanisms of cancer genesis, conventional anti-cancer therapy and reported some significant breakthrough in anti-cancer drug development, anti-cancer activity of some selected species of mushrooms followed by a brief discussion of recent anti-cancer efficacy of some metallic nanoparticles loaded with mushrooms. Overall, this review article will categorically discuss some important aspects of anti-cancer therapy using mushrooms and their bioactive phytoconstituents.

2. Methods

A thorough search for the scientific literature has been conducted for articles indexed with PubMed, Embase, Web of Science databases using keywords like ‘mushroom’, ‘cancer’, ‘immunomodulatory’ and ‘mushroom loaded nanoparticles’. For other related literature, cross- referencing searches were conducted. Results obtained with English language were used.

2.1 Molecular perspective of cancer genesis

Any one or a combination of chemical, physical, biological, and genetic insults to individual cells can cause carcinogenesis in a multicellular organism and results in altered neoplastic cell’s genome. Virtually every sort of mutation known has been used to demonstrate such genetic alterations, including transitions, transversions, deletions of varying sizes, chromosomal rearrangements, gene amplification, and insertional mutagenesis [16,17] (Fig. 1).

2.2 Genomic instability

Dynamic genetic alterations describe and promote cancer. Genomic instability is primarily responsible for the enormous number of structural defects found in cancer genomes. During the life cycle of cells, genomic instability refers to a heightened potential for changes in the genome. Modifications in nucleic acid sequences, chromosomal rearrangements, and aneuploidy are examples of these changes [18]. The exact etiology of chromosomal abnormalities is unknown. Certain environmental and occupational exposures, as well as cytotoxic medication therapy, have been proven to cause chromosomal abnormalities in various kinds of leukaemia. Chromosome rearrangements include reciprocal translocations, inversions, and insertions. There is strong evidence that these changes occur early in the carcinogenesis process, if not at all. Notably, some chromosomal rearrangements, such as the BCR-ABL1 fusion gene, act as sensitive indications in the evaluation of cancer therapy response [19]. Cell divisions in normal tissues are strictly controlled to prevent neoplastic transformation or tumorigenesis. The processes that retain genetic information, such as cell cycle checkpoints, DNA repair, transcription, replication, epigenetic regulation, chromatin remodeling, and chromosomal segregation during mitosis, are all involved in genomic instability [20]. The cell cycle is a series of well-ordered chemical activities that allow the cell to duplicate itself. The primary processes of the cell cycle are DNA replication and the segregation of replicated chromosomes [21]. The movement of a cell through the cell cycle is tightly regulated by vital regulatory proteins termed CDK (cyclin-dependent kinase), which prevent the commencement of a new cell cycle phase before the previous one has been completed. The CDKs are a group of serine/threonine protein kinases that are activated at certain phases during the cell cycle. They are made up of a catalytic subunit with low intrinsic enzymatic activity and a critical positive regulatory component termed cyclin. CDKs are regulated by several mechanisms, including the binding of activating cyclin subunits, inhibitory Cip or INK4 subunits, and phosphorylation [22].

A total of eight cyclins have been discovered. The cyclins D, E, A, and B come into action in order during each cell cycle. While cyclins activate CDKs, their inhibitors (CDKIs) repress them, giving the cell cycle a negative control. Many human cancers have CDKIs that have been mutated or repressed. Melanoma is caused by germline mutations in the p16 gene, for example: malignancies of the pancreas, glioblastomas, esophageal cancers, acute lymphocytic leukaemia (ALL), non-small-cell lung carcinomas (NSCLC), softtissue sarcomas, and urinary bladder cancers are all caused by somatically acquired inactivation or deletion of p16 [23,24]. Tumor suppressor genes code for the checkpoint control proteins. They inhibit cells from entering S-phase, preventing the replication of damaged DNA and, as a result, aberrant cell division. Tumor suppressor gene mutations are recessive yet inheritable. To produce aberrant cellular division, both copies must be knocked out. pRb, p53, APC, BRCA 1 and 2 are all involved in DNA repair, cell cycle regulation, and cell death (apoptosis) [25]. *2.3. Proto-oncogene and tumor suppressor gene*

A proto-oncogene is a normal gene that can become an oncogene through [30]. RNF20, a histone H2B ubiquitin ligase that has been demonstrated to mutations. In contrast, an oncogene is a gene that obtains a function or is reduce p53 function, accelerate cell motility, and promote cellular overexpressed abnormally, resulting in the conversion of a normal cell into a transformation in vitro, is silenced in breast and prostate malignancies [31].

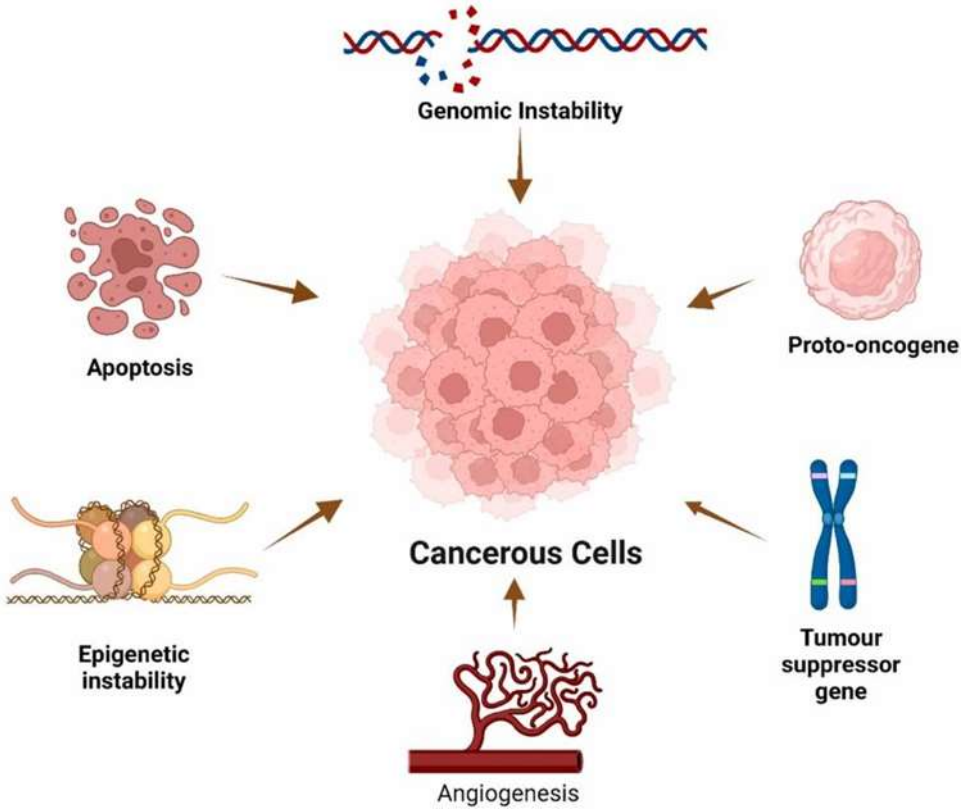

Fig. 1. Molecular perspective of cancer genesisFigure 1: Molecular perspective of cancer genesis. (Created with www.biorender.com)

cancer cell when it is mutated. Kinases also induce an increase in gene transcription. These kinases are known as transcription factors, and they frequently alter the G1/S transition, producing greater cyclin-CDK and lower inhibition during an inopportune phase of the cell cycle, such as SRC, RAS, MYC, and so on [25,26]. Chromosomal translocation, point mutations, and gene amplification are all examples of activation processes that lead to protooncogenes. According to the clonal hypothesis of oncogenesis, a tumor begins with a single cell.

Furthermore, there is a link between tumor formation and apoptosis (programmed cell death) suppression, resulting in cell immortality. Angiogenesis and angiogenic factors are expressed in tumors, suggesting that they may influence tumor creation and progression. Tumor- suppressor genes inhibit cancer growth while also promoting normal cell development. Neoplasms arise due to an increase in acquired and physical genetic changes in proto-oncogenes and tumor-suppressor genes, which serve as a target group in neoplasm cells [27].

2.3 Epigenetic instability

Epigenetic modifications-heritable alterations in gene expression induced by changes in chromatin structure rather than changes in DNA sequenceappear to be important elements in the etiology of cancer, according to mounting data. DNA methylation, covalent modifications of histones such as methylation, acetylation, phosphorylation, and ubiquitination, and noncovalent changes such as nucleosome location, are all examples of epigenetic alterations. Hundreds of genes are abnormally repressed or activated in malignancies due to alterations in DNA methylation or histone modifications at their promoters [28,29]. Overexpression of the histone H3 lysine 27 (H3K27) methyltransferase EZH2, which silences targets like the tumor suppressor p16INK4A, has been seen in a variety of tumors and is linked to tumor growth Epigenetic changes that mute tumor suppressor genes or activate oncogenes might eventually equal genetic mutations that achieve the same consequence during cancer initiation. Epigenetic modifications can imitate large-scale cytogenetic abnormalities seen in malignancies, in addition to replicating numerous point mutations. Colorectal cancer cells were studied to see if shared suppression of the entire 4 Mb stretch of chromosome 2q14.2 may be linked to worldwide histone H3K9 methylation and DNA hypermethylation [32]. While most malignancies have genomic instability, previously mysterious cancer-specific epigenetic alterations are now becoming more well recognized and are likely present in all tumors. As a result, it is probable that epigenetic changes are the primary causes of the onset and advancement of various malignancies [33].

2.4 Apoptosis

The total number of cells in multicellular organisms balances the cellgenerating effects of mitosis and the cell death triggered by apoptosis. Cancer can develop if this precise equilibrium is disrupted. Apoptosis is regulated by at least two genes associated with human malignancies, BCL2 and TP53. The most often altered gene in human cancer is TP53, reflecting its critical anticancer function [34]. By acting as cellular stress and DNA-damage sensor, p53 inhibits carcinogenesis. P53 gets stabilized in response to a variety of stressors, such as DNA damage, hypoxia, or proliferative signals, prompting cells

to enter cell cycle arrest or apoptosis [35]. p53 appears to induce apoptosis via transcription-dependent and transcription-independent processes that work together to ensure that the cell death pathway runs smoothly.

Furthermore, p53's apoptotic activity is carefully regulated, and the result of p53 activation is impacted by a succession of quantitative and qualitative events [36]. The role of apoptosis in tumor formation was proven by the cloning and characterization of the bcl2 oncogene.

According to research, bcl2 promotes cell viability by preventing programmed cell death (apoptosis) [37]. Furthermore, Bcl-2 overexpression increased lymphoproliferation and accelerated c-Myc-induced lymphomagenesis in transgenic mice [38]. In mammalian cells, at least 15 Bcl-2 family member proteins have been identified, including proteins that induce and resist apoptosis. The Bcl-2 protein family regulates cell death largely by direct binding interactions that govern mitochondrial outer membrane permeabilization (MOMP), which results in the irreversible release of intermembrane space proteins, caspase activation, and apoptosis [39]. *2.6. Telomerase activity*

Telomeres are protective structures that cover both ends of the chromosome in humans. They are made up of lengthy, repeating TTAGGG sequences that are linked to a number of telomere-binding proteins. Telomeres guard chromosomes against end-to-end fusion, recombination, and degradation, all of which can result in cell death [40]. In human cells, telomerase suppression and/or short telomeres are thought to be a natural evolutionary mechanism for fighting cancer; they act as a powerful barrier to tumor transformation and inhibit uncontrolled cell proliferation. Oncogenesis is based on the endless multiplication of malignant cells, which is achieved in most cases via telomerase activation [41]. High telomerase activity is seen in cancer cells, allowing them to proliferate forever. In 85–95% of malignancies, telomerase is active [42]. Telomerase reverse transcriptase (TERT) is a gene that encodes the enzyme telomerase, which is responsible for telomere production. Telomerase activity permits cancer cells to replicate indefinitely. TERT is expressed in 85–95% of human malignancies, despite the fact that it is normally repressed in practically all somatic cells [43]. TERT expression is upregulated in tumors by a variety of genetic and epigenetic mechanisms, including TERT promoter mutations (mostly C228T or C250T), changes in TERT pre-mRNA alternative splicing, TERT amplification, epigenetic modifications through TERT promoter methylation, and/or disruption of the telomere position effect (TPE) machinery [44].

2.5. Angiogenesis

Angiogenesis is when existing blood arteries are used to create new ones to supply malignant development. The "angiogenic switch" is the start of this process, in which tumors gain the potential to grow and spread beyond their primary location [45]. The vascular endothelial growth factor (VEGF) family, in particular, has been found and defined as part of a broad network of signaling molecules and receptors involved in the control of angiogenesis. The VEGF family includes the growth factors VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF) [46]. Hypoxia regulates VEGF expression, providing a feedback mechanism to compensate for diminished tissue oxygenation by developing new blood vessels. Hypoxia regulates VEGF production through the HIF family of proteins, enhancing VEGF gene transcription [47]. Other factors (e.g., p53 expression) and cytokines such as epidermal growth factor (EGF) and transforming growth factor-beta (TGF-beta) may also boost VEGF production through a variety of methods [48].

3. Anti-cancer therapy: *c*onventional and breakthrough

3.1. Nanomedicine

To overcome some of the drawbacks related to conventional therapies like poor bioavailability and low specificity, biocompatible nanoparticles are employed in cancer therapy [49]. Further, nanoparticles are highly specific and selective towards the target and release the drug in a controlled manner in response to a stimulus [50–55]. For example, a liposomal formulation named ThermoDox releases doxorubicin upon an increment in the temperature level [56]. However, inorganic nanoparticles are used in the diagnosis of cancer, for example, the small light-emitting semiconductor nanocrystals known as quantum dots with optical and electronic properties are highly sensitive and used for imaging and detection purposes. Additionally, they can act as a promising tool in theranostic applications when combined with active ingredients [57]. Recent studies have indicated that polyethylene glycol (PEG) coated quantum dots in conjugation to anti-human epidermal growth factor2(HER2) antibody are localized in specific tumor cells [58]. Because of the low toxicity, electrical and optical properties another metallic nanoparticles mainly gold nanoparticles have found application as a contrasting agent for photodynamic therapy, computed tomography, X-ray imaging, and photoacoustic imaging. A nanoshell named AuroShell that employs photodynamic therapy is used for the treatment of breast cancer [59–63]. Lipid nanoparticles on the other hand have the capacity to cross the blood brain barrier (BBB) and are considered to be good candidates for the treatment of brain tumor [64]. Another family of nanoparticles named as dendrimers are composed of repetitive branched unit of polymers and are highly versatile and find many applications in cancer therapy. For example, in the in vivo tumor models doxorubicin loaded poly-L-lysine (PLL) dendrimers were found to produce anti-angiogenic responses [65–67]. In the present time, a dendrimerbased formulation named ImDendrim coupled to imidazolium ligand is under clinical trial that is meant to treat inoperable liver cancer not responding to conventional treatment strategies [68].

3.2. Extracellular vesicles in the treatment of cancer

Exosomes are found to have their involvement towards the development and bidirectional spread of cancer between the tumor cells and the tissues surrounding the tumor. They also play a contributory role towards the development of a microenvironment that is required for the pre-metastatic and metastatic development of the tumor [69–72]. Thus, circulating vesicles find contributory role in the early diagnosis, investigation and follow up related

to cancer. Henceforth, exosomes are considered as an important and valid cancer diagnostic tool that can be either be utilized as nanosized drug carriers in the treatment of cancer or as anti-cancer vaccines [73]. In the current times, detection by the means of exosomes has been considered as one of the dependable tools that can be used in the preclinical practice of various cancer types [74]. In the patients with metastatic prostate cancer, exosomal androgen-receptor splice variant 7 mRNA (AR-V7 mRNA) has been exploited as a prognostic marker to overcome the resistance provided by the hormonal therapy [75]. However, in order to treat the patients suffering from colorectal cancer, long non-coding RNAs (LncRNAs), isolated from serum exosomes have been used and to differentiate between the different subtypes of lung cancer, multiple miRNAs have been used [76,77]. Further, exosome Glypican 1- positive (GPC1-positive) has been used to detect the presence of pancreatic cancer and to detect and predict the onset of liver metastasis circulating exosomal macrophage named migration inhibitory factor (MIF) has been employed. Urinary exosomes rich in multiple lipids have been approved as an indicator for prostate cancer [78–80].

3.3. Natural antioxidants in cancertherapy

Different phytoconstituents namely the quercetin, vitamins, berberine, carotenoids, flavonoids and curcumin have been analyzed in the in vitro *in vivo* studies describe their efficiency as pro-apoptopic and anti-proliferative agents that can be used as complementary therapies in the treatment of cancer [81– 83]. Curcumin, classified as a polyphenol and obtained from *Curcuma longa* is found to have anti-oxidant, anti-inflammatory and chemopreventive properties [84]. Studies have indicated their cytotoxic potential in different types of tumors like pancreatic, lung, hepatocellular carcinoma, brain and leukaemia producing no adverse effect to the normal cells at the calculated therapeutic doses [85]. However, the compound has poor water solubility, bioavailability, not very stable and is highly lipophilic in nature. In order to overcome the bioavailability related problems, various strategies and distinct carriers like micelles and liposomes have been designed and developed. Moreover, 23 clinical trials on curcumin have been completed and 24 trials are still under study [86–88]. An alkaloid compound named Berberine has been demonstrated for their efficacy in modulating numerous signaling pathway and acting as a chemo preventive agent against different tumor types [89,90]. Like curcumin, it also has poor solubility in water because of which newer nanotechnological approaches have been designed to allow its passage across [91–93]. Presently, one clinical trial has been completed on berberine and six trials are under study [94]. Another bioactive compound named quercetin classified as a polyphenolic flavonoid has been found to interfere different signaling pathways and interact with the cellular receptors proving its effectiveness towards various tumors like breast, prostate, liver, colon and lung cancers [95–98]. Currently, four clinical trials involving quercetin has been completed and seven trials are ongoing [99].

3.4 Targeted therapy and immunotherapy in cancer

One of the major drawbacks associated with the conventional therapies of cancer is the low specificity towards cancer cell and acting both on the tumor and normal tissues leading to adverse drug effects. In order to achieve the specificity, nanoparticles were employed as these particles have the property of enhanced permeability and retention effect (EPR) towards tumor tissue [100]. This process of targeting is passive in nature that mainly depends upon the smaller size of nanoparticles but such targeting may result in the development of multiple drug resistance (MDR). Another mode of targeting known as active targeting can elevate the degree of uptake by the tumor cells by selecting specific receptors that are highly expressed on them [101,102]. For example, the receptors of biotin and folic acid are expressed highly on tumor cells and tissues and thus nanocarriers conjugating folic acid is used to target endometrial and ovarian cancer. Further, folic acid in conjugation with polyethylene glycol-poly (lactic-co-glycolic acid) nanoparticles incorporating drug docetaxel was found to enhance the cellular uptake of drug by human cervical cancerous cells [102–104]. A peptide named angiopep-2 binds to lipoprotein receptor-related protein-1 (LRP1) of the endothelial cells in BBB that is basically a low-density protein overexpressed in glioblastoma cancer cells and hence was found to be effective towards the treatment of brain cancer [105,106]. A combination of peptide bombesi in conjugation with poly (lactic-co-glycolic acid) (PLGA) nanoparticles incorporating docetaxel was used to target a peptide receptor releasing gastrin highly expressed on the cell surface of colorectal, ovarian, breast, prostate and pancreatic cancers [107,108].

3.5 Gene therapy towards the treatment of cancer

Research exploiting the treatment strategy of cancer led to the development of gene therapy that was found to be effective in treating cancer and many chronic diseases. Currently, around 2900 clinical trials incorporating gene therapy are under study, among which, around 66.6% trials are associated to cancer [109]. In the past few decades, the clinical application of various vectors carrying the tumor suppressor gene p53 was tested and evaluated of which ONYX-015 was tested against patients suffering from nonsmall cell lung cancer (NSCLC). The results of the study indicated a high degree of response when it was administered alone and in combination with chemotherapy [110]. A recombinant adenovirus named gendicine that carries the p53 wild-type gene in neck and head cancerous squamous cell was found to possess similar success rate when conjugated to radiotherapy [111]. Currently, researchers across the globe have shown great interest in approaches including the targeted gene slicing. Recently, RNA interference (RNAi) has been developed and established as a potential technology effective in both medical translation and basic research. The small interfering RNAs (siRNAs) are composed of double-stranded RNA and are capable of targeting the gene slicing approach [112]. RNA-induced silencing complex (RISC) is responsible for mediating the complete process intracellularly that cleaves the messenger RNA (mRNA) and interferes with the synthesis of protein [113].

3.6. Thermal ablation and magnetic hyperthermia in cancer therapy Biomedicine & Pharmacotherapy 149 (2022) 112901

Ablation of tumors by means of thermal energy incorporates a chain of techniques that either uses cold (hypothermia) or heat (hyperthermia) to destroy the cancer cells and tissues [114]. The necrosis of cell occurs at temperature below − 40 ◦C and at temperature greater than 60 ◦C. Hence, exposing the

neoplastic cells and tissues to a temperature ranging between 41 ℃ and 55 ℃ for a longer period of time was found to be effective towards their damage. Additionally, the sensitivity of cancer cells towards higher temperatures is much greater than that of normal cells [115]. The process of hypothermic ablation uses argon as the cooling agent that surrounds the tissue to a temperature of − 160 ℃ and forms ice crystals. Cooling initially results in the destruction of the cell membranes and then it completely kills the cell. However, thermal ablation using heat comprises of laser ablation, radiofrequency (RF) and microwave ablation [116]. These different kinds of lasers find their application depending upon the specific application. For example, in order to treat the internal organs, diode lasers (800–900 nm wavelength) and neodymium:yttrium-aluminium-garnet (Nd:YAG) lasers (1064 nm wavelength) are used as they exhibit a penetration depth of around 10 cm [117]. CO_2 lasers with a wavelength of 10,600 nm on the other hand are used to treat superficial treatments as they possess a penetration depth ranging from 10 μm to a maximum of 1 mm. However, laser ablation exhibits greater advantages like shorter treatment session, safety, higher efficacy and precision than the other ablation techniques in order to attain the same results [118,119]. *3.7. Recent innovations in cancer therapy: pathomics and radiomics*

The current scenery of efficient cancer therapy depends upon surgery and radiotherapy that can be achieved by inserting a radioactive source locally at the desired site to obtain a distinct irradiation or by employing an external source of beam. Newer innovations into the field have resulted in the development of image-guided radiotherapy (IGRT) whereby best amount of radiation can be set during the treatment of the patient. Also, intensitymodulated radiotherapy (IMRT) was introduced that can generate different intensities and help reduce the doses to be received by healthy tissues and hence overcoming the adverse effects. Two new innovative and promising tools namely pathomics and radiomics are based on collecting image features quantitatively from pathology and radiology screenings as prognostic and therapeutic indicators of disease [114,120,121]. Pathomics is based on the characterization and generation of tissue images possessing high resolution [114,122,123]. However, radiomics on the other hand is associated with the quantification of tumor properties at high throughput level obtained after the analysis of medical images [124–126]. Presently, 50 clinical trials involving radiomics are under study and a few trials have been already studied [68].

4. Selected medicinal mushrooms with anti-cancer activity

Mushrooms are well-known for their ability to complement chemotherapy and radiation therapy by alleviating cancer-related adverse effects such as nausea, bone marrow suppression, anaemia, and decreased resistance. Antitumor drugs and other bioactive compounds have recently been discovered in several mushrooms. Mushrooms contain many essential chemicals including polysaccharide-protein complexes, agaritine, ergosterol, selenium, polyphenols, and terpenoids. Numerous bioactive compounds, including antitumor drugs, have been isolated from diverse mushrooms in recent years. Polysaccharides, proteins, lipids, ash, glycosides, alkaloids, volatile oils, tocopherols, phenolics, flavonoids, carotenoids, folates, ascorbic acid enzymes, and organic acids are important bioactive components found in mushrooms [11]. Apart from their medicinal characteristics, these chemicals are considered biological response modifiers (BRMs). *In vitro* and in vivo studies support mushroom chemicals' medicinal properties. Tumors and other disorders are targeted by these chemicals. These are cytotoxic to cancer cells and enhance the immune system by activating lymphocytes, NK cells, and macrophages, increasing cytokine production, reducing cancer cell growth, boosting apoptosis, and blocking angiogenesis (Table 1). These chemicals interact with intestinal cells, the frontline of the intestinal immune system, triggering an immunological response and producing.

An inflammatory response if necessary [128]. Mushroom poly-saccharides and polysaccharide-protein complexes are key sources of immunomodulatory and anticancer drugs. The immunoceuticals from more than 50 mushroom species have been tested in vitro, in vivo, and on human malignancies. Extract of Chaga mushrooms (CME) had a significant cytotoxic effect on 4T1 breast cancer cells, and the possible mechanism was concluded to be induction of autophagy rather than apoptosis or necrosis [129]. Results observed from different studies provide strong evidence that the medicinal fungus of the A. blazei Murrill species, has several bioactive compounds that participate in the tumoricidal and anticarcinogenic activity [130]. A study conducted in androgen-dependent prostate cancer cell lines (LNCaP and VCaP) and a patient-derived xenograft (PDX) tumor showed that White button mushroom (WBM) (Agaricus bisporus) intake affects prostate cancer by interfering with the androgen receptor (AR) signaling axis [131]. Polysaccharide-protein complexes such lentinan, schizophyllan, polysaccharide-K, polysaccharide-P, active hexose correlated compounds (AHCC), and maitake D fraction are examples. These phytochemicals are found in Ganoderma lucidum, Ganoderma tsugae, Schizophyllum commune, Sparassis crispa, Pleurotus tuberregium, Pleurotus rhinoceros, Trametes robiniophila Murill, Coriolus versicolor, Lentinus edodes, Grifola frondosa, and Flammulina velutipes [132].

Mushroom cell walls contain chitin and β-glucans. β -glucans are important in health and illness treatment [133]. These are cytotoxic to cancer cells and enhance the immune system by activating lymphocytes, NK cells, and macrophages, increasing cytokine production, reducing cancer cell growth, boosting

Table 1 Studies on the mechanism of action of mushrooms components.

Mushroom	Biological activity	Study	References
Genus *Pleurotus* .	Stimulate NK cell, macrophage, and T cell proliferation, maturation of lymphocytes, natural killer cells, and macrophages results in an increase in the weight and size of the spleen	In vitro	[133]
Lentinula edodes	Stimulate the release of cytotoxic and cytostatic IL-1, IL- 2, IL-6, IL-8, TNF-, and TNF, and prevent the proliferation of breast cancer cells and DNA synthesis.	In vitro	[175]

Trametes versicolor	Apoptosis, antiangiogenesis, antimetastasis, reversal of drug resistance, and immune modulation	In vitroClinical	[176]
Genus *Agaricus*	Induce apoptosis, inhibit angiogenesis, stimulate TNF-α production by BMM	In vitro	[177]
Genus Phellinus	anti-angiogenic effects by inhibiting the proliferation, migration, and assembly of human umbilical vein endothelial cells (HUVECs) into capillary-like structures	In vitro	[178]
Grifola frondosa	Macrophages are activated, and IL-1, IL-6, and IL-8 are released into the bloodstream.	In vitro	[179]
Genus *Ganoderma*	Cytotoxic to cancer cells, inhibits cancer cell growth, stimulates T cells, increases IL-1, IL-2, IL-6, TNF-, and IFN expression and secretion, inhibits cell motility and angiogenesis, inhibits proliferation and induces apoptosis, downregulate cyclins A and B and upregulate p21 and p27, arrest cell cycle	In vitro	[180]
Hericium erinaceus	Increase NK activity, activating macrophages, and inhibiting angiogenesis	In vitro	[181]
Fomes fomentarius	Inhibiting proliferation	In vitro	[182]
Schizophyllum commune	Immunomodulating effect	Clinical	[183]
Inonotus obliquus	Halting the cell cycle during the G0/G1 phase and killing B16- F10 cells and induced cell differentiation.	In vitro	[184]
Coprinus comatus	Inhibit cancer cell proliferation In vitro		[185]

4.1. Effects of mushrooms on cytokine production

Mushroom components modulate the immune system via a variety of molecular processes. Certain genes are upregulated, resulting in the generation of anti-inflammatory and anticancer cytokines. Numerous studies with mushroom compounds have demonstrated that a variety of genes and cytokines are affected in a variety of ways following in vitro and in vivo treatment. Cytokines are the immune system's messengers. They are either proteins or glycoproteins that immune cells produce to regulate the innate and adaptive immune systems. Following oral ingestion of mushroom chemicals, intestinal immune factors, such as dendritic cells and macrophages, are activated, releasing cytokines that induce local or systemic inflammation. Additionally, intestinal epithelial cells are induced to release IL-7, a key cytokine in cancer immunotherapy [134]. Incubation of promonocytic THP-1 cells with *Agaricus blazei* Murill extract induces the expression of a number of genes associated with anticancer chemokines, resulting in the secretion of a variety of cytokines, including the IL-23 subunit of the IL-12 family, IL-1, monocyte chemoattractant protein-1 (MCP-1), granulocyte colony stimulating factor (G-CSF), and tumor necrosis [10]. Additionally, Volman et al. demonstrated that *Agaricus bisporus* fruit bodies, caps, and stipes stimulate the generation of TNF-α by bone marrow-derived macrophages (BMM) [135]. *Ganoderma lucidum*, on the other hand, is a longevity-promoting tonic herb whose biological activities, particularly antitumor and immunomodulatory properties, include stimulating T cells and initiating an inflammatory response through the expression and production of chemokines such as IL-1, IL-2, IL-6, TNF- α, and interferon-gamma (IFN-) [136]. Grifolan from *Grifola frondosa* stimulates macrophage activity by raising the production of IL-1, IL-6, and IL8, hence activating and boosting the number of leukocytes [137]. Other mushroom constituents, such as polysaccharide peptide (PSP), polysaccharide (PSK), and lentinan, induce the release of a variety of cytokines in vitro, including IL-1, IL-2, IL-6, IL-8, TNF-α, and interferons. Additionally, Bittencourt et al. has shown that α-glucan from *Pseudallescheria boydii* stimulates in vitro TNF- α and IL-12 secretion. Increased IL-12 release shows that naive T cells have polarized into T helper (T) type 1 skewed responses, which are critical in fighting cancer cells [138]. *Sparassis crispa* extract induces splenocytes to release cytokines in mice via granulocyte macrophage colony stimulating factor (GMCSF) and Dectin-1, a -glucan receptor [139]. uncertain, although it is assumed to involve the activation of apoptosis and overexpression of apoptosis-inducing genes, as well as the arrest of cell division in vitro and in vivo [143]. Mushroom compounds injected into tumor masses induce cell apoptosis at various stages of the cell cycle, thereby inhibiting tumor cell proliferation. For example, lentinan and lectins derived from Shiitake are cytotoxic and cytostatic to MCF-7 breast cancer cells, respectively [144]. They also exert an anti-inflammatory effect by decreasing neoangiogenic and granulocyte-chemoattractant factor IL-8 levels and increasing cytotoxic T cell infiltration by reducing intratumor formation of reactive oxygen and nitrogen species and rebalancing the skewed T1/T2 balance in late cancers [145]. Phagocytes' propensity to infiltrate makes them critical for tumor elimination by phagocytosis and production of cytokines for direct or indirect anticancer activity, as well as antibody dependent cell mediated cytotoxicity (ADCC) [146]. Suppression of cell motility and vasculature in the tumor microenvironment are strong indicators of cancer metastasis and proliferation inhibition [147]. *Ganoderma lucidum* may reduce cell motility, proliferation, apoptosis, and angiogenesis in highly invasive human breast

and prostate cancer cells PSK (polysaccharide-Kureha; PSK), on the other hand, when injected directly into human stomach tumors prior to surgery, is rapidly absorbed by dendritic cells within and around the tumors, thereby enhancing patient survival and quality of life in patients with stomach cancer. Thus, PSK is cytotoxic to cancer cells directly [148]. According to Hsu et al., methanol extracts of *G. lucidum* and *G. tsugae* inhibit colorectal cancer cell growth within 72 h by downregulating cyclin A and B1 and upregulating p21 and p27, thereby arresting the cell cycle in G2/M and thus suppressing tumor growth, inducing cell death, and inhibiting cell proliferation in human colorectal cancer cells in vivo [149]. Volman et al. confirmed that mushroom extracts inhibit NF-kB transactivation in Caco-2 cells, with *A. blazei* Murill and *Coprinus comatus* exhibiting the greatest reduction in NF-kB transactivation, which can cause tumor cells to stop proliferating, die, or become susceptible to the action of antitumor agents [150]. Additionally, *L. edodes* fruit body water extracts suppress MCF-7 cell proliferation and DNA synthesis, demonstrating that this mushroom extract's cytostatic effect on cancer cell cycle is quite potent [142]. MCF7 cells treated with Huaier (*Trametes robiniophila*) extract undergo G0/G1 arrest, resulting in cell damage and apoptosis, and hot water extracts of *Coprinellus* sp., *Coprinellus comatus*, and *Flammulina velutipes* have also been shown to inhibit the proliferation of MCF7, MDA-MB-231, and BT-20 cells [151]. Another study demonstrated *Sanghuangprous vaninii* extract to have anticancer activity in human cervical cancer SiHa cells by blocking cell cycle and inducing cell apoptosis, involving the ER stress-mitochondrial pathway [152].

4.2. Effect of mushrooms on immune cells

After being detected by pathogen recognition receptors, mushroom chemicals injected directly into tumor cells or consumed orally trigger immune cells to induce cell mediated or direct cytotoxicity on tumor cells. Lentinan, for example, increases the generation of cytotoxic T cells and macrophages while also inducing nonspecific immunological responses [140]. *Pleurotus tuberregium* and *P. rhinoceros* extracts have antitumor effects by promoting lymphocyte and NK cell maturation and increasing macrophage proliferation, T helper cell proliferation, and CD4/CD8 ratio and population, which is accompanied by an increase in spleen weight and size, is attributed to increased numbers of monocytes and granulocytes among other immune cells [141]. Consumption of mushroom compounds thus initiates both innate and adaptive immunity by increasing immune surveillance against cancer through the involvement of monocytes, macrophages, NK cells, and B cells, CTLs secreting antitumor cytokines and activating immune organs, eliminating cancers, and strengthening the weakened immune system [142]. The effects of these mushroom compounds result in the removal of cancer cells, cell cycle arrest, and suppression of angiogenesis and metastasis. *4.3.*

Mushrooms prevent a number of malignancies, including hematological cancers in mice and leukemia in humans [142]. Their mode of action is apoptosis, and blocking angiogenesis. Mushroom compounds regulate the immune system in a variety of ways during cancer treatment [133].

5. Application of mushroom loaded nano formulations for drug delivery to tumors

Nanotechnology is the process of designing, constructing, developing, and implementing materials and technologies on a nanometer (nm) scale, with 1 nm equal to one billionth of a meter [153–158]. Furthermore, nanobiotechnology is an intriguing convergence of nanotechnology and biotechnology that enables the realistic integration of nanoscale technology with the biology of molecules [153,159]. The application of nanobiotechnology to medicine is called nanomedicine, is concerned with overcoming challenges associated with various diseases at the nanoscale level where the vast majority biological molecules exist and function [160]. Today, there is a considerable emphasis on the application of nanomedicine to cancer [161,162]. Cancer nanomedicine is a new interdisciplinary research field spanning biology, chemistry, engineering, and medicine, intending to pioneer significant advancements in cancer detection, diagnosis, and therapy (Fig. 2) [163–165].

Nanotechnology has made a significant contribution to health sciences in treating various chronic diseases. Fabrication of nanoparticles (NPs) using green technology outperform those synthesized using physical and chemical approaches in multiple aspects. For example, green synthesis limits the use of costly chemicals, require less energy, and produce ecologically friendly product and byproducts [161]. Therefore, the environment-friendly production of NPs is considered the foundation for future nanomedicine.

5.1. Green synthesis of nanoparticles using mushroom and their anticancer effect

5.1.1. Silver nanoparticles

Silver nanoparticles (AgNPs) can induce cytotoxicity in tumor cells by altering their shape and decreasing their viability, as well as oxidative stress in different tumors [166]. Plant extracts have been extensively used in the fabrication of AgNPs as a natural reduction agent. Furthermore, mushrooms have a high potential for green synthesis of AgNPs due to their high secondary metabolite content [167]. Recently, microwave-assisted green synthesis of AgNPs using the crude extract of *B. edulis* (BE-NPs) and *C. versicolor* (CVAgNPs) mushrooms was reported by Kaplan et al. [168]. Anticancer activity of both the formulation against MCF-7, HT-29 and HUH-7 cell line demonstrated the significantly enhanced antiproliferative effect in a dose and timedepended manner [14]. In another study, Yahia et al. reported that AgNPs produced by *Pleurotus ostreatus* caused a significant decrease in cell viability of the MCF-7 cell line. Furthermore, treatment of MCF-7 cells with AgNPs demonstrated the dose-dependent inhibition of tumor progression [168]. In another study, Ismail et al. demonstrated that AgNPs fabricated by *Pleurotus ostreatus* extracts showed antitumor cytotoxicity against HepG2 and MCF-7 via caspase-dependent apoptosis, associated with the activation of p53 and the down-regulation of Bcl-2 [169]. Green synthesis of AgNPs using an aqueous extract of *Pleurotus djamor* var. *roseus* and its cytotoxicity against human prostate carcinoma (PC3) cells was investigated by Raman et al. Green synthesized AgNPs significantly prevented the proliferation of PC3 cells by inhibiting its progression, decreasing DNA synthesis, and

inducing apoptosis [170]. Govindappa et al. reported the fabrication of AgNPs using water extract of *Cladosporium perangustum* (Cp). Furthermore, it was demonstrated that CpAgNPs drastically reduced the viability of MCF-7 cancer cell line while increasing the activity of caspase-3, caspase-7, caspase-8, and caspase-9 by inducing mitochondrial-mediated apoptosis [171]. Antitumor potential of biosynthesized AgNPs from the extract of *Schizophyllum commune* (SC-AgNPs) and *Geopora sumneriana* in breast (MCF-7), lung (A549), colon (HT-29), and liver (HUH-7) cancer cell lines was studied by Goksen et al. [167]. SC-AgNPs and GS-AgNPs demonstrated significantly enhanced antiproliferative activities against tested cell lines in a dose-dependent manner [167]. Akhter et al. reported the green synthesis of endophytic fungus (*Botryosphaeria rhodina*) isolated from *Catharanthus roseus* . The developed AgNPs demonstrated significantly enhanced scavenger effect on free radical and apoptosis, including nuclear and DNA fragmentation against A549 cancer cell lines [172].

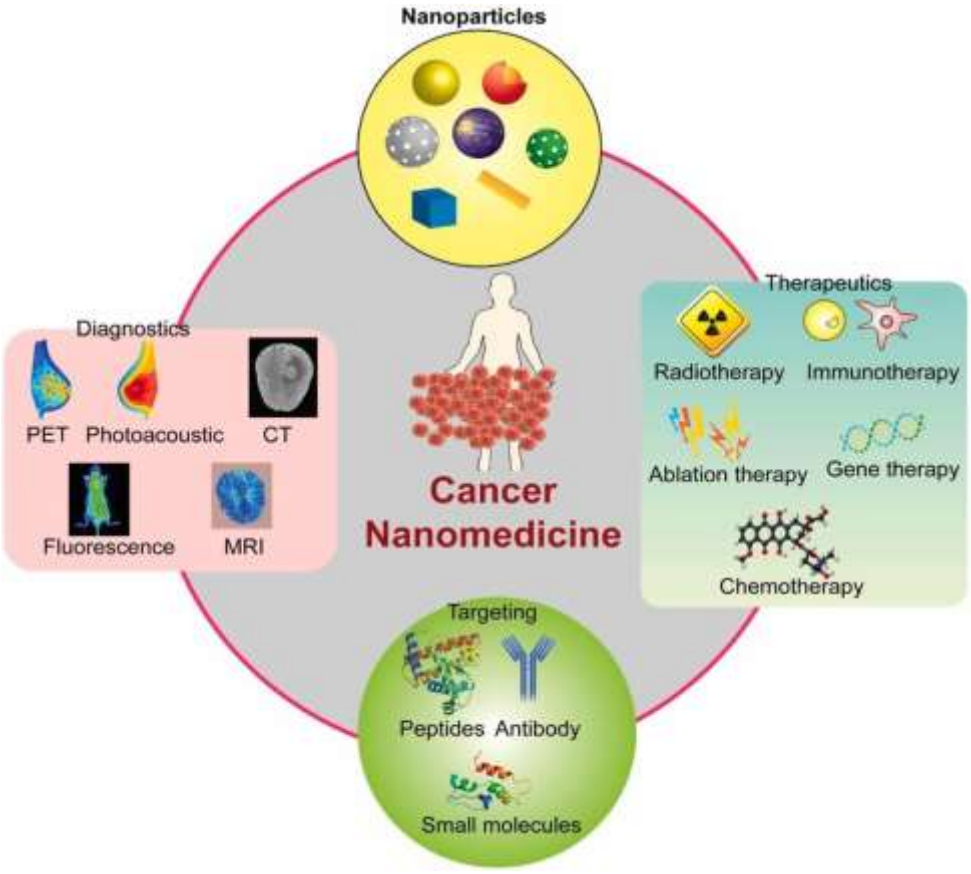

Fig. 2. Nanotechnology and its application drug delivery to tumors.

5.1.2. Gold nanoparticles

From ancient times, colloidal gold (Au) has been explored for its potential use in medicine [155,156,173]. Nevertheless, the production and evaluation of diverse AuNPs have only recently piqued the curiosity of scientists. The possibility to manipulate the surface functionality of AuNPs with different targeting ligand and functional moiety greatly expand their potential for biomedical application, particularly in cancer treatment. Because of their small size, unique physicochemical properties, ease of surface modification, excellent biocompatibility, and other advantages, biosynthesized colloidal gold nanoparticles are appealing in many biomedical applications, including cancer theranostic. Several studies have reported the green synthesis of AuNPs and their potential application in health care.

Furthermore, it has also been reported that the proliferation of cancer cells can possibly be inhibited in a time and dose-dependent manner after being treated with biosynthesized AuNPs. Recently, the anticancer potential of AuNPs obtained by green synthesis using the *Fusarium solani* was reported by Clarance et al. The developed AuNPs demonstrated significantly enhanced cytotoxicity against HeLa and MCF-7 cancer cell lines in dose-dependent manners [174]. Similarly, biofabricated AuNPs (using the aqueous extract of the endophytic *Cladosporium sp*. isolated from *Commiphora wightii*) demonstrated significantly enhanced apoptotic activity against breast cancer cell line MCF-7. Furthermore, in-vivo, anticancer activity of biofabricated AuNPs showed significantly reduced cancer growth in the tumor-bearing mice model and potentially improved the life span of the tumor-bearing animal [15].

6. Conclusion and future perspective

Mushroom is a treasure trove of numerous bioactive phytoconstituents of which very less are reported and many more are yet to identify. Among many *Ganoderma lucidum* is a promising mushroom species against cancer which is mostly recommended by Asian physicians. Many clinical trials have been conducted to ascertain the efficacy of the same, however, sufficient justification of using the same as first line treatment for cancer is yet to be established for which further improvement in methodological quality and clinical research is warranted as suggested by some published systematic review. There are several mushroom products containing extract or their bioactive phytoconstituents especially in the form of food supplements which are available in the market that claims to possess potent anti-cancer activity; however, no mushroom products are currently found to be marketed as anticancer drugs. In United States, food supplements do not need pre- approval from Food and Drug Administration for marketing until and unless claimed as drugs for specific diseases or ailments. So, there is a high chance of false claim of such supplements without a systematic scientific validation. There should be in-depth evaluation of these mushroom products belonging to different geographical regions and there is urgent need for technological advancement for further purification of the bioactive phytoconstituents before claiming mushroom and their products as having anti-cancer activity in human beings.

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