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## A review for cancer treatment with mushroom metabolites through targeting mitochondrial signaling pathway: *In vitro* and *in vivo* evaluations, clinical studies and future prospects for mycomedicine

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### ABSTRACT

Resistance to apoptosis stands as a roadblock to the successful pharmacological execution of anticancer drug effect. A comprehensive insight into apoptotic signaling pathways and an understanding of the mechanisms of apoptosis resistance are crucial to unveil new drug targets. At this juncture, researchers are heading towards natural sources in particular, mushroom as their potential drugs leads to being the reliable source of potent bioactive compounds. Given the continuous increase in cancer cases, the potent anticancer efficacy of mushrooms has inevitably become a fascinating object to researchers due to their higher safety margin and multi-target. This review aimed to collect and summarize all the available scientific data on mushrooms from their extracts to bioactive molecules in order to suggest their anticancer attributes via a mitochondrion-mediated intrinsic signaling mechanism. Compiled data revealed that bioactive components of mushrooms including polysaccharides, sterols and terpenoids as well as extracts prepared using 15 different solvents from 53 species could be effective in the supportive treatment of 20 various cancers. The underlying therapeutic mechanisms of the studied mushrooms are explored in this review through diverse and complementary investigations: *in vitro* assays, pre-clinical studies and clinical randomized controlled trials. The processes mainly involved were ROS production, mitochondrial membrane dysfunction, and action of caspase 3, caspase 9, XIAP, cIAP, p53, Bax, and Bcl-2. In summary, the study provides facts pertaining to the potential beneficial effect of mushroom extracts and their active compounds against various types of cancer and is shedding light on the underlying targeted signaling pathways.

**Abbreviations:** AIF, apoptosis-inducing factor; ANT2, adenine nucleotide translocator 2; Apaf, apoptotic protease activating factor; ATP, adenosine triphosphate; Bfl-1/A1, Bcl-2-related protein A1; BH, Bcl-2 homology domains; CAD, caspase activated DNAase; cFLIP, cellular FLICE-like inhibitory protein; cIAP, cellular inhibitor of apoptosis protein 1; CI-V, complex I-V; CyP-D, cyclophilin D; Cyt c, Cytochrome c; DLCS, delocalized lipophilic cations; Endo G, endonuclease G; ETC, mitochondrial electron transport chain; HP, hematologic parameters; IAP, inhibitors of apoptosis proteins; IMM, inner mitochondrial membrane; IMS, intermembrane space; Mcl-1, myeloid cell leukaemia 1; mPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; NADPH, nicotinamide adenine dinucleotide phosphate; OMM, outer mitochondrial membrane; OXPHOS, oxidative phosphorylation; PARP, poly(ADP-Ribose) polymerase; PS, phosphatidylserine; QOL, quality of life; ROS, reactive oxygen species; TM, transmembrane; VDAC, voltage-dependent anion channel; XAF1, XIAP-associated factor 1; XIAP, X-linked inhibitor of apoptosis protein;  $\Delta\Psi_m$ , mitochondrial membrane potential.

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## 1. Introduction

Over the past two-three decades the sector of medicine and health service prevention, nutrition programmes, early diagnosis, and screening programmes has benefited from many breakthroughs. Among medical improvements and innovations, cancer detection and treatments have saved many human lives; however cancer still represents a compelling social, emotional, economic and financial burden in families and on global societies [1,2]. A large number of cancer patients would choose conventional therapies such as surgery, chemotherapy, radiation therapy and the most recent immunotherapy depending on cancer classification to combat cancer where, mostly defeat step in above achievements [3–6]. World Health Organization predicted cancer as the most common disease and second major cause of death around the globe. The overall penetrance of this pathology has immensely increased; according to Cancer Statistics report from National Cancer Registry Programme India, the number of new cancer cases has projected to 1,392,179 by 2020 [7]. A study on the current and future cancer scenario of United State projected that most frequently detected cancer in 2040 will be breast (364,000 cases), followed by melanoma (219,000 cases), lung (208,000 cases), colorectal (147,000 cases); and prostate cancer (66,000 cases) [8]. Comprehensive data of world cancer cases for the past few decades also create a major health concern among human societies as 28.4 million cases of cancer are expected by 2040 [9]. The lack of availability of healthcare infrastructure in several countries immensely affects the treatment of vulnerable groups of patients diagnosed with cancer. Several barriers, namely, cost-effectiveness, education, income of the patients and location, are associated with various socio-economic and demographic challenges can be attributed as the primary reasons behind the implementation of cost-intensive cancer care in most of the countries of the planet as a result observable negative effect on countries economic growth [10]. As reports USA and China face the maximum economic hazards for cancer, 20.8% and 24.1% of the whole world burden, respectively though cancer related death is much higher in low and middle-economically growing countries [11]. To address these challenges, healthcare personnel must be thoroughly acquainted with the vulnerabilities associated with the treatment of patients diagnosed with this deadly and utterly complex health disease. The genomic instability, activation of proto-oncogene, apoptosis evasion, inactivation of tumor suppressor genes, angiogenesis and telomerase activity, are considered to be some of the major characteristics of cancer genesis [12]. Current anticancer therapy is primarily built on counteracting these hallmarks of cancer. Although more recent and conventional anticancer therapies are effective in a number of patients and result in an increase in survival rate, they also have major drawbacks such as compromised immunity [13,14]. Relentless efforts have been made in order to use safer and more effective alternative therapies that will target cancer cells more efficiently through the activation of the apoptotic pathway [15].

Several studies on ancestral knowledge regarding the nutritional and medicinal uses of natural resources have therefore been the basis of investigations in the scientific community [16]. Indeed, from the beginning of civilization onwards, mankind has always endorsed the dietary and medicinal values of natural resources that were available from various kingdoms [17]. During recent years natural products and their structural analogues being richly endowed with curative powers, have historically made a major contribution to biomedical and pharmaceutical research to develop novel therapeutics, specifically for cancer [18]. Natural products or compounds which have gained importance as a reliable tool for inventing novel drug leads include Ginkgetin [19], Oleandrin [20], Jaceosidin [21], Osthole [22] and the list continues. The extensive range of natural products is a wealth of bioactive compounds and the major source of novel drugs against several diseases among which cancer, which has drawn the attention of many researchers [23,24]. Mycomedicine, an exclusive kind of natural therapy including a wide variety of edible and inedible mushrooms as

well as fungi, along with their fungal-derived metabolites, has been broadly used in order to prevent, cure or decrease progression of various diseases [25,26]. Many studies have demonstrated that compounds extracted from mushrooms such as phenolic acids, flavonoids, polysaccharides and terpenoids, or even proteins work as anticancer agents by acting on a broad range of molecular mechanisms that are altered in cancer [27,28]. Moreover, it should be noted that consumption of edible and medicinal mushrooms is thought to be effective in lowering the risk of cancer [29–31]. Over the last 60 years, the rate of research that has been focusing on macrofungi has rapidly increased, but in several other fields of research, mushrooms are still being ignored as a potent source of beneficial products. Therefore characterization of a wide range of pharmacologically active compounds from mushrooms with high efficacy and low toxicity is required as well as in-depth analysis of single or multiple targets in order to act against cancer more accurately. So far, numerous studies have been conducted on the anticancer activity of mushroom extracts and bioactive compounds, but no one has yet attempted to summarize their results. Our review is the first comprehensive meta-analysis of all the eligible results related to the anticancer potential of bioactive isolated compounds of mushroom origin with an appropriate attention on the mitochondria-mediated signaling pathway. In the following sections we concisely introduce the role and identify targets of mitochondrial intrinsic apoptotic pathway. We then emphasize the molecular mechanisms of cancer genesis, traditional anticancer therapy and reported some significant breakthroughs in the discovery of the anticancer activity of various species of mushrooms followed by a brief discussion of current clinical trials using these mushrooms and their biologically active compounds. Overall, the data collected in this paper may prove a functional tool for scientists as we present a broad spectrum of bioactive components of mushroom species with anticancer efficacy and indicate their mode of action. This study also leads to the classification of mushrooms as nutraceuticals assisting the treatment of cancer diseases. A diet rich in certain mushrooms is scientifically proven to help cure specific types of cancer. It is hypothesized that the accumulated data will pave a path for researchers towards the development of these mushroom-derived compounds with anticancer activities into pharmacological drugs or can be exploited as novel anticancer agents in the future.

## 2. Search strategy/methods

A thorough search for the scientific literature on mushroom bioactive compounds against cancer was undertaken in electronic scientific databases, such as PubMed, Embase, Scopus and Web of Science databases. The search was performed using the keywords such as ‘mushroom’, ‘cancer’, ‘mitochondria’, ‘tumor’, ‘bioactive compound’ and ‘mushroom-mediated mitochondrial apoptotic pathway’. Studies from the last 10–12 years were taken into consideration. The criteria for the selection of specific studies were as follows: (a) mitochondrial-mediated anticancer mechanisms of mushroom compounds; (b) mushroom bioactive components that were tested *in vitro* (cell models) and *in vivo* (mice and rat models, case studies, randomized controlled trials) models (Fig. 1). Results obtained with only full versions of English-language articles were included. Articles that did not fulfil the above-mentioned requirements were excluded from the analysis. Due to a large number of variables, no systematic review was carried out. The research reviewed edible and non-edible species of mushrooms in terms of antitumor activity, considering different types of cancer and experimental models. For other related literature, cross-referencing searches were conducted.

## 3. Mushrooms: A new source of natural therapeutics

Nature has bestowed upon us with numerous natural resources in order to sustain a healthy life and among many resources, mushrooms are one such category. Mushroom, a fungi kingdom member belonging to the basidiomycetes and ascomycetes, feeds by being parasitic,

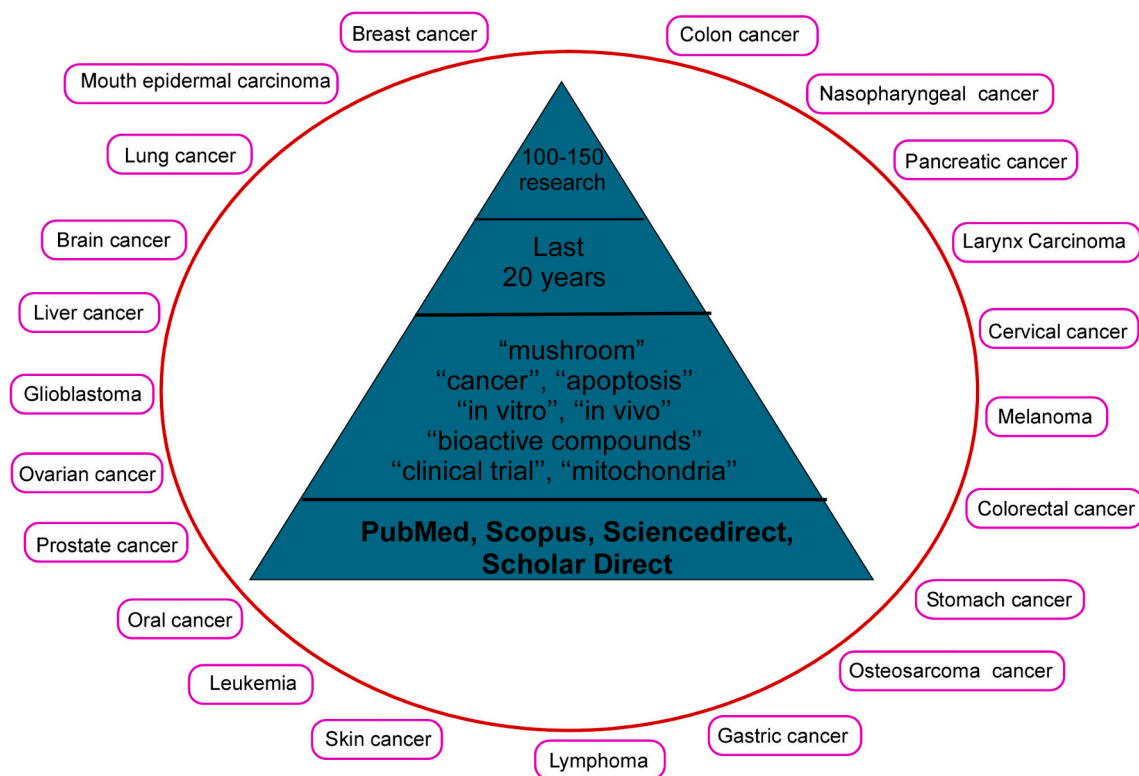


Fig. 1. A schematic diagram representing the criteria chosen for the selection of current study.

saprophytic or symbiotic species [32]. Mushrooms (namely also 'macrofungi') have a distinctive fruiting body, which can be either epigeous or hypogeous, large enough to be visible to the naked eye and to be easily hand-picked [33]. An updated estimate of fungal diversity showed about 2.2 to 3.8 million fungi species been predicted to exist in the world [34] among which 140,000 or perhaps as many as 220,000 species are expected to be mushrooms indicating only a fraction of all fungal species have been described so far (about 100,000) and an even smaller number explored for the production of pharmacologically relevant metabolites which will probably benefit to mankind [35]. About 2000 fungal species (31 genera) are found to be edible [36] and around 10% of 30 species are poisonous and a fairly minor number are considered deadly [37,38]. Recently, Li and his colleagues reviewed the world's edible mushroom species [39]. Mushrooms are scattered worldwide and have been regarded as an ingredient of gourmet cuisine across the globe [40]. Ethnomycology has been reported worldwide for ages and the consumption of macrofungi has indeed always been a part of traditional household uses as a complement to medicines [41,42]. The fruiting bodies of mushrooms also seemed to play vital roles in forest ecosystems as they possess distinctive abilities to break down wood, leaves, and other organic matter and recycle nutrients back into the system [43]. Wild and cultivated mushrooms have a unique texture, aroma, taste and flavor that make mushroom different from other food crops [44]. However, since ancient times mushrooms have been a food constituent in different diet cultures around the globe [45]. Mushrooms like button, oyster, and paddy straw mushrooms etc., are prime source of nutrients and flavory compounds, specifically with respect to their low calorie with high protein content, their contribution to essential amino acids [46] and their presence of important fibers, vitamins (B1, B2, B3, and C) and minerals [47]. The fresh basidiocarps also contain a proportionately larger amounts of carbohydrates (4–5%), low starch with notable amount of sodium, potassium and phosphorous with lower proportion of calcium and iron [40]. By virtue of having low fat, low starch and high fibre mushrooms have also come out to be an ideal nutriment for obese and diabetic people [48]. In addition to their food character, many

studies conducted in recent years, has found that the beneficial natural ingredients found in mushrooms are vital in curing several diseases and eliminating disease factors [49,50]. Mushrooms are acknowledged for their stimulating properties towards the immune system and are considered as one of the best diets for immunosuppressed people and vegetarians as high quality of proteins provided by edible mushrooms can be produced with higher biological efficiency than animal proteins [51]. A systematic review of observational studies reported that consumption of edible higher mushrooms was linked with a lower risk of diseases [29]. The medicinal value of mushrooms is due to the presence of their bioactive phenolic contents, carotenoids, flavonoids and high proportion of polyunsaturated fatty acids respective to total fatty acids content [52]. Medicinal mushrooms are currently regarded as functional therapeutic foods, as they are an excellent source of various nutraceuticals [53]. Hence, mushrooms can be included directly in the human diet or as health supplements to promote health and used as complementary and alternative medicines as their consumption helps cure several ailments [54]. Detailed studies on mushrooms reported that they are well-known for their bioactive compounds like lectins, polysaccharides ( $\beta$ -glucans), polysaccharide-peptides, polysaccharide-protein complexes, polyphenols, lanostanoids, other terpenoids, alkaloids, sterols, and phenolic structured compounds which encourage further research work on the prospective medicinal potential of the basidiocarps [55,56].

Although  $\beta$ -glucans (homopolysaccharides) with the main chain consisting of  $\beta$ -(1  $\rightarrow$  3) linkages with some  $\beta$ -(1  $\rightarrow$  6) branches as well as chitin, mannans, galactans, and xylans are believed to be the major bioactive polysaccharides of mushrooms, other types of mushroom polysaccharides (heteropolysaccharides) [57] as well as phenolic compounds also known as an excellent source of antioxidants [58] have numerous reported biological functions. The pharmaceutical potential of mushrooms has been elevating swiftly from the last decades, and it has been proposed that various mushrooms are like mini-pharmaceutical factories generating compounds with putative biological properties [59,60]. Presence of bioactive compounds in mushrooms are responsible for different biological and therapeutic activities as

depicted in Fig. 2 including anti-inflammatory [61], antimicrobial [62], antioxidant [63,64], antidiabetic [65], cardioprotective [66], hepatoprotective [67], antiviral [68] along with cancer prevention [69] potentials. Mushrooms also regulated the function of the immune system through its action on macrophages, T cells, dendritic cells (DC), natural killer (NK) cells, and hematopoietic stem cell activities which resulted in phagocytic activity [70]. Furthermore, numerous companies are developing capsules and tablets from mushroom combinations, and although expensive, these have health benefit as supportive cancer treatment [71].

#### 4. Role of mitochondria in cancer cells

Mitochondria, the energy-generating structures of the cell, produce ATP (adenosine triphosphate) are referred as “the powerhouse of the cell” involved in various processes such as cell differentiation, cell death signaling, and control of cell growth and division [72,73]. Mitochondria consist in several proteins that are essential for orderly cell function and proliferation; they hold a crucial part in the induction as well as the prevention of cell demise [74]. Mitochondrial biology has recently emerged and undergone a revolution through rapidly progressing biotechnologies, and the extent of knowledge highlighted the priority of mitochondrion-targeted therapies. Novel therapeutic leads are now

drawing attention to the mitochondrial pathway of apoptosis in such a way that developing original drugs that target the mitochondria is currently considered as the prime target in cancer chemotherapy [75,76].

#### 5. The mitochondrial control of apoptosis or intrinsic signaling pathway

The intrinsic pathway in which mitochondria are involved is not a receptor-mediated pathway but rather an intracellular pathway which can relay both activating and inhibitory signals. It is mostly activated by the absence of growth factor signals or in reaction to noxious stimuli from within the cell, like hypoxia, oxidative stress, DNA damage and other chemotherapeutic drug-related damage [77]. Mitochondria are a specialized organelle with an elaborate structure consisting of an outer mitochondrial membrane (OMM), an inner mitochondrial membrane (IMM), an intermembrane space (IMS) and a matrix (Fig. 3). The intermembrane space includes several proteins which are associated with cell death induction, such as apoptosis-inducing factors (AIF), Cytochrome c (Cyt c), Smac/DIABLO, Omi/HtrA2 and Endo G. All these components induce changes in the permeability of the mitochondrial inner membrane followed by the opening of membrane permeability transition (MPT) pores, thereby disrupting the mitochondrial

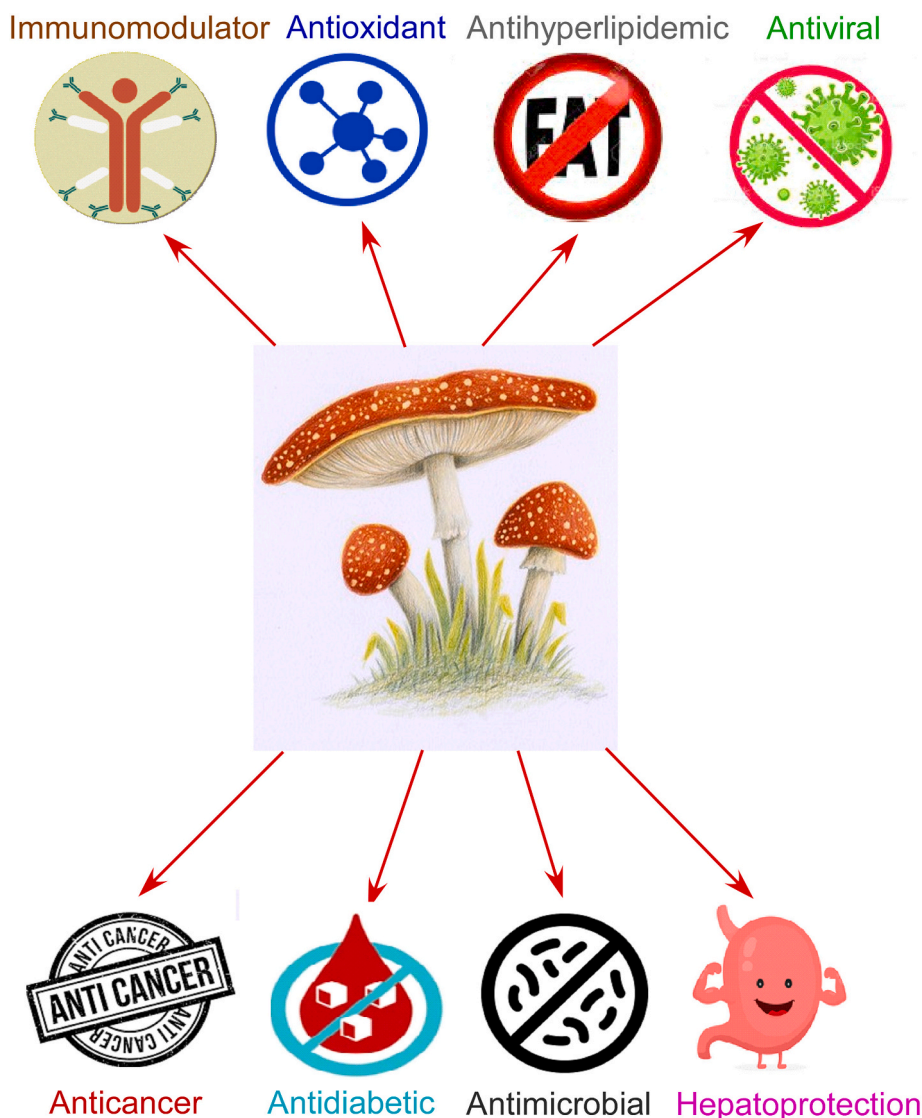


Fig. 2. Schematic diagram of various pharmacological activities exhibited by mushroom.

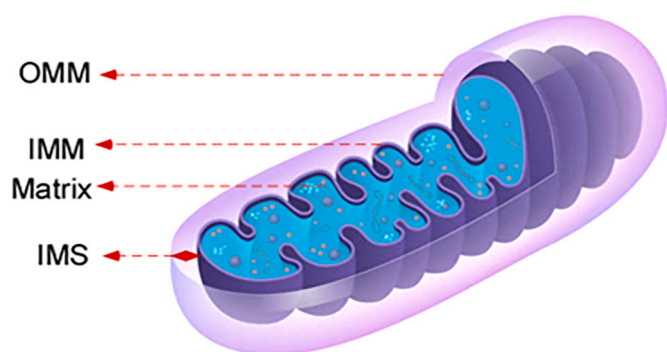


Fig. 3. The structure of a mitochondrion. OMM: Outer mitochondrial membrane, IMM: inner mitochondrial membrane, IMS: intermembrane space.

transmembrane potential and resulting in the release of pro-apoptotic proteins such as HtrA2/Omi, Cyt c and Smac/DIABLO into the cytosol from the intermembrane space. Cyt c release into the cytoplasm triggers the formation of the apoptosome (a complex consisting of dATP and Apaf-1) which activates procaspase 9 that in turn cleaves and activates the executioner caspases-3 and 7, which results in cell death [78]. The catalytic activity of Cyt c is further balanced by members of the IAP (inhibitor of apoptosis protein) family which are then controlled by

Smac/DIABLO and OMI/HtrA2 [79]. In later stages of apoptosis apart from the above-mentioned pro-apoptotic proteins other proteins such as CAD (caspase activated DNase), AIF (apoptosis inducing factor) and Endo G (endonucleases G) are also released from mitochondria. AIF and Endo G work independently from caspases whereas CAD is activated when ICAD inhibitor is cleaved by caspase 3. The AIF is responsible for DNA fragmentation while Endo G initiates the cleavage of nuclear chromatin into oligonucleosomal DNA fragments [80].

The intrinsic pathway is regulated by interplay between anti-apoptotic and pro-apoptotic members of the Bcl-2 protein family. Twenty proteins belong to the Bcl-2 family; they are segregated into three groups and harbour Bcl-2 domains of homology. Group 1 includes anti-apoptotic proteins and groups 2 and 3 consist of pro-apoptotic proteins one with only BH-3 protein. Anti-apoptotic proteins include Bcl-2, Bcl-w, Bcl-xL and BAG while pro-apoptotic members include Bax, Bok, Bak, Bim, Bik, Bid, Bad, Puma, Noxa and HRK [81]. The anti-apoptotic Bcl-2 family of proteins firmly control this pathway through the inhibition of the release of Cyt c [82–84]. Ratio of pro-apoptotic and anti-apoptotic Bcl-2 members mainly governs the permeability of the mitochondrial membrane [85]. The p53 gene commonly known as tumor suppressor gene encodes a nuclear protein with a vital role in the regulation of cell demise. Reports showed that p53 protein uses multiple pathways to induce cell death [86]. Studies established the fact that p53 transactivates various apoptotic factors, such as Puma, Noxa, p53-

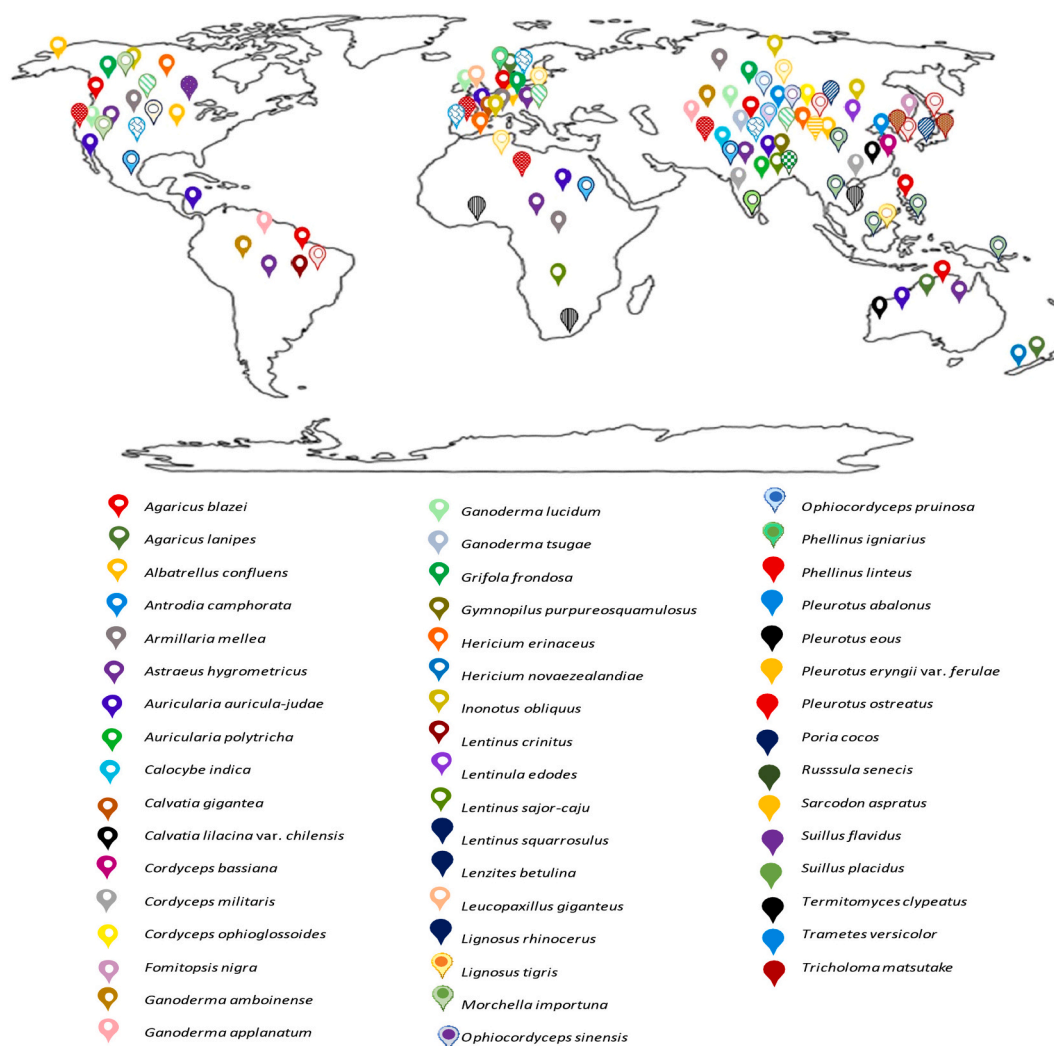


Fig. 4. An overview of places in world where specimens of mushrooms have been used for research in the field of cancer. The map has been generated automatically with help of [www.mapcustomizer.com](http://www.mapcustomizer.com) where different colours designate various mushrooms which were explored for its anticancer efficacy.

regulated-inducing protein 1 (p53AIP1) and Bax and it efficiently translocates to the mitochondrion where it interacts with anti-apoptotic proteins such as Bcl-2 and Bcl-xL. Additionally p53 can also trigger the generation of ROS. Therefore, inhibition of p53 will efficiently speed cell proliferation [87].

The new therapy in market i.e. ‘mycotherapy’ corresponds to the study of the research of extracts as well as bioactive compounds from mushrooms as therapeutics or health-stimulating factors [88]. Mycotherapy of cancer is comparatively a new and encouraging scientific field, which focuses on mushroom-derived anticancer agents [89]. In the past few years, the increasing number of studies disclosing that anticancer agents derived from mushrooms has become a matter of high significance, and has been taking into account the complexity and distribution of several cancer types in the worldwide population [90]. Fig. 4 shows several countries and continents where mushrooms have been explored as a potent chemopreventive agent. A huge diversity of compounds as well as complex fractions were extracted and/or purified from some edible as well as from medicinal mushrooms which have been reported to be of significant value in the management of cancer [91]. Mushrooms and their bioactive compounds also demonstrated promising results in various stages of clinical trials devoted to cancer treatment [92].

## 6. Targets of mitochondria for cancer remedial treatment

Mitochondria are at the crossroads of life and death-promoting paths. They are considered as choice targets in abnormal cells to abolish progression to malignancy. If mushrooms could target these enzymes, channels and proteins connected with mitochondria is expected to lead to the destruction of cancer cells (Fig. 5).

### 6.1. Targeting permeabilization of mitochondrial membrane

In healthy cells the IMM is impervious to ions, which allows the ETC to promptly maintain the proton gradient across this membrane. The electrochemical gradient across the IMM results in the mitochondrial membrane potential; maintaining the proton gradient is a firmly controlled mechanism and is indispensable for survival [93,94]. Interestingly in cancer cells, mitochondrial membrane potential was reported to be increased and this negative transmembrane potential allows the targeting with delocalized lipophilic cations (DLCs). High concentrations of DLCs are found to be toxic to the mitochondria [95], so if mushroom-derived compounds caused selective accumulation of DLCs within this organelle this would result in an increase in mitochondrial membrane potential, which would commit cancer cells to death.

## 6.2. Aiming at ion channels

Ion channels are associated with the exchange of fatty acids, ions, cholesterol, etc., and eventually control cell homeostasis. They are located either within the outer mitochondrial membrane or within the inner mitochondrial membrane [96] and they are considered as potent oncological targets [97].

### 6.2.1. Ion channels of the mitochondrial outer membrane

The presence of several channels in the outer membrane of mitochondria facilitates the entry of all the nutrients and exit of various apoptosis mediators. Among these translocases are involved in protein transport and voltage-dependent anion channel (VDAC) mediates transport of metabolites and regulates the release of Cyt c. All these channels play a role in the establishment of mitochondrial permeability transition pore (mPTP) which further induces the Cyt c release and commitment to apoptosis [98]. Among all the ion channels, VDACS (mitochondrial porins) play a key part in mitochondrial apoptosis as they connect with anti-apoptotic regulatory proteins (Bcl-2, Bcl-xL) [99] and further induce the release of pro-apoptotic proteins such as AIF, Cyt c, neutralizers of IAPs (SMAC/Diablo) into the cytosol [100]. Thus if mushroom-derived compounds could prevent the binding of anti-apoptotic regulatory proteins to VDAC this would increase the permeabilization of the mitochondrial outer membrane thereby allowing the pro-apoptotic proteins to cross it and accumulate into the cytoplasm where they would drive apoptosis.

### 6.2.2. Ion channels of the mitochondrial inner membrane

The mitochondrial permeability transition pore (mPTP), a high-conductance channel of IMM consists in a complex of many mitochondrial proteins and was reported to increase permeabilization of the mitochondrial inner membrane. mPTP components include VDAC, adenine nucleotide translocase (ANT) and cyclophilin D (CyP-D) [101,102]. Factors such as pH variation due to high  $Ca^{2+}$  concentration, ROS production and cooperation with proteins such as Bax trigger a conformational change which results in the opening of this pore thereby increasing the permeabilization of the IMM and generating an imbalance of the mitochondrial membrane potential. This results in swelling of the matrix followed by the rupture of the OMM and release of proteins from the intermembrane space [103,104]. Therefore mushroom extracts/bioactive compounds capable of disturbing mPTP would allow the specific targeting of the mitochondria and bypass apoptosis resistance upstream of the intrinsic mitochondrial pathway.

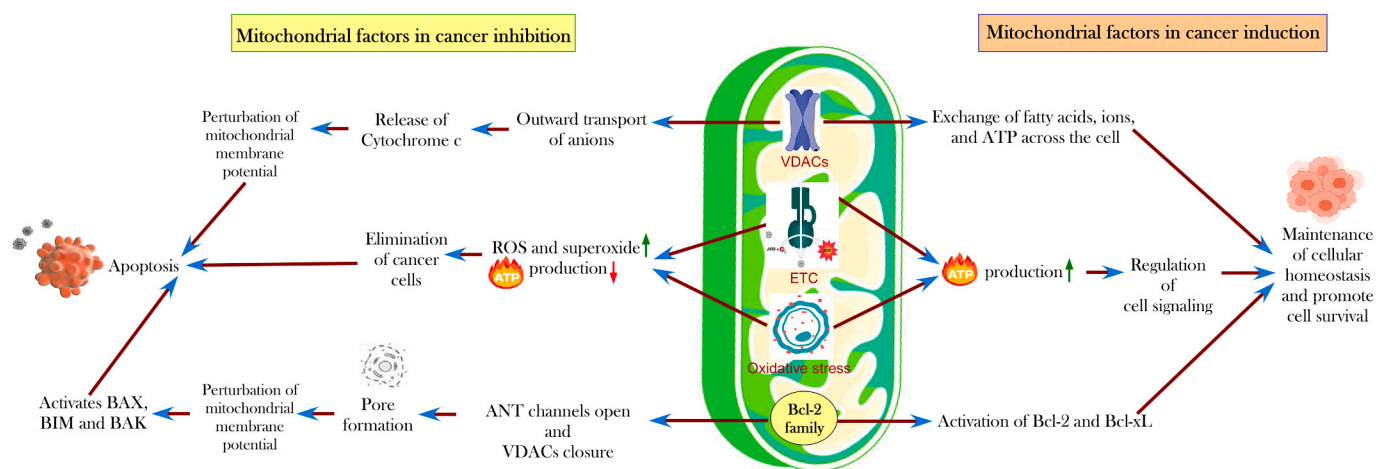


Fig. 5. Role of mitochondrion associated factors in cancer induction and inhibition.

### 6.3. Focusing on electron transport chain complexes

In mitochondria, electron transport chain (ETC) is a key player in energy production through oxidative phosphorylation. ETC consists in five complexes (CI, CII, CIII, CIV and CV) that are located within the mitochondrial inner membrane and are vital for energy production in the form of ATP [105]. Along with ATP production the ETC also produces ROS, and CI and CIII complexes which are the leading sites for superoxide generation, are involved in the regulation of cell signaling. The increase in the amount of ROS and superoxide generation lead to apoptosis [106]. Therefore inhibition of complexes I, II and III by mushroom-derived products would induce apoptosis by increasing the production of ROS and eventually eliminate cancer cells.

### 6.4. Directing oxidative stress

In humans oxidative phosphorylation (OXPHOS), the prime source of ATP production, also controls ROS generation in the mitochondria. Targeting OXPHOS will therefore result in elevated ROS formation as well as the reduction in ATP production which will ultimately trigger the chain of events of apoptosis and finally cell death [107]. Any pro-oxidant agent isolated from mushrooms which is capable of triggering oxidative stress by generating reactive oxygen species would be expected to commit cells to apoptosis.

### 6.5. Targeting Bcl-2 family

The Bcl-2 protein family were reported to play an integral part in shifting the balance between death and survival mostly by regulating the mitochondrial membrane potential [108]. In this context, pro-apoptotic proteins Bax and Bak have been observed to regulate the VDAC and ANT channels, thereby changing the mitochondrial functions such as the stimulation of the opening of ANT channels and closing of VDAC, which leads to pore formation, outer mitochondrial membrane dysfunction and swelling of the matrix that ultimately causes apoptosis [109,110]. Promoting pro-apoptotic proteins such as Bax and Bak over the pro-survival proteins such as Bcl-xL and Bcl-2 will result in a ratio driving cancer cells towards death and is an essential feature for any anticancer drug [111]. Therapeutic drugs derived from mushrooms could act either by suppressing the effect of pro-survival proteins or mimicking the anti-survival proteins to induce apoptotic cell death. The following section describes some of the *in-vitro* and *in-vivo* studies on the beneficial effects of mushroom-derived compounds/extracts by targeting all the above mentioned enzymes, channels and proteins connected with mitochondria to prevent cancer occurrence.

## 7. Mushroom bioactive molecules targeting mitochondria as a novel strategy to overcome cancer

More recently, macrofungi were investigated for potential bioactive metabolites and these fungi-derived bioactive molecules described as encouraging therapeutic agents [112–120]. A large body of literature elaborately covers the therapeutically active metabolites of edible or inedible macrofungi that are used for their medicinal properties, and thoroughly describes the mechanism of action of the active compounds and their anticancer efficacy. Those numerous lines of evidence highlighted the fact that most of the medicinal mushrooms produce their antitumor effects in cancer cells through the activation of the very common apoptotic signaling pathway i.e. mitochondria-mediated intrinsic signaling pathway. Table 1 has summarized 53 different mushrooms around the world that prevent the development of cancer by specifically targeting the mitochondria and inducing intrinsic apoptotic pathway in 20 various types of cancer in *in vitro* as well as in preclinical studies.

The medicinal mushrooms listed in Table 1 were placed in alphabetical order, they retain intriguing and various bioactive molecules,

included in extracts, polysaccharides and secondary metabolites. A diverse array of complex compounds derived from the secondary metabolism which is specific to each mushrooms include catechols, polyphenols, polysaccharides, quinones, sesquiterpenes and steroids (Table 1; Fig. 6).

### 7.1. Cell line studies

Mostly the macromolecules that were extracted from mushrooms trigger the intrinsic pathway by regulating the expression level of Bcl-2 family proteins, thereby shifting the balance between anti-apoptotic and pro-apoptotic proteins and resulting in cell death. The enclosed Table 1 presents different genera of mushrooms and their bioactive macromolecules that have successfully promoted apoptosis in various cancer cell lines with a specific focus on the mitochondria-mediated apoptotic pathway through the generation of oxidative stress, via the altering of their mitochondrial metabolism or by targeting mitochondrial complexes. Some of the most promising genera including *Agaricus*, *Cordyceps*, *Ganoderma*, *Grifola*, *Hericium*, *Lentinus*, *Lignosus*, *Ophiocordyceps*, *Phellinus*, *Pleurotus* and *Suillus* trigger apoptosis in tumor cells by shifting the balance between anti-apoptotic (such as Bcl-2, Bcl-xL) and pro-apoptotic (such as BAX, BAD, BIM, BAK, PUMA) protein levels. A list of mushrooms such as *Agaricus blazei* [121–126], *Agaricus lanipes* [127] *Antrodia camphorata* [128–134], *Armillaria mellea* [135–137], *Astraeus hygrometricus* [138–141], *Calvatia lilacina* var. *chilensis* [142], *Cordyceps militaris* [143–146], *Cordyceps ophioglossoides* [147], *Fomitopsis nigra* [148], *Ganoderma tsugae* [149], *Grifola frondosa* [150–154], *Gymnopilus purpureosquamulosus* [155], *Lentinus crinitus* [156], *Lentinula edodes* [157,158], *Lentinus squarrosulus* [159], *Lenzites betulina* [160], *Ophiocordyceps sinensis* [161–163], *Ophiocordyceps pruinosus* [164], *Phellinus linteus* [165–169], *Pleurotus abalonus* [170], *Pleurotus eous* [171], *Pleurotus eryngii* [172–174], *Russula senecis* [175], *Tricholoma matsutake* [176] produced remarkable effects in inhibiting the cancer cell progression by changing the ratio between Bax and Bcl-2 thereby building up maximum extra- and intra-cellular oxidative stress in cancer cells, which sequentially lead towards the activation of mitochondrial outer membrane permeabilization (MOMP), release of Cyt c and other proteins and induction of caspase-dependent cell death. Among the above-mentioned mushrooms *Agaricus blazei* [121–126], *Antrodia camphorata* [128–134], *Ganoderma lucidum* [167,177–182], *Grifola frondosa* [150–154], *Gymnopilus purpureosquamulosus* [155] were explored in detail.

Extracts and bioactive substances obtained from these species efficiently activated cell death pathways in tumor cells which involve in particular the release of caspase-independent death effectors and caspase-activating molecules. Active pro-apoptotic protein caspase-8 either directly activates the extrinsic cell death cascade or is involved in the activation of the intrinsic pathway by some additional amplification which follows the release of Cyt c from mitochondria and endoplasmic reticulum that in turn triggers the formation of apoptogenic factors such as Apaf-1, AIF and induces the activity of pro-apoptotic proteins caspase 9 and caspase 3. The increased expression level of HtrA/Omi, endo G, Smac/DIABLO, AIF supported the mitochondria mediated caspase-independent cell death pathway. The various type of bioactive substances extracted from numerous macrofungi worked in a similar way to inhibit cancer cell proliferation. Polysaccharides extracted from *Auricularia auricula-judae* [167] and *Sarcodon aspratus* [183] targeted mitochondrial membrane potential which led to the release of Cyt c, thereby triggering apoptosis in different cancer cell lines. Some extracts of macrofungi such as hot water extract of *Hericium erinaceus* [184,185], aqueous extract of *Pleurotus ostreatus* [186,187] ethanol extract of *P. cocos* [188,189] and total ethanol extract of *P. ignarius* [190,191] followed a similar pathway to initiate apoptosis in cancer cells through the release of IMS proteins and Cyt c which drove tumor cells towards apoptosis by the mitochondrion-mediated intrinsic pathway. The active components such as grifolin, hispolon, iso-suillan, suillan, clitocine,



Table 1

Effect of mushroom extracts and bioactive compounds targeting mitochondrial intrinsic apoptotic pathway on different cancer types as *in vitro* and *in vivo* experiments.

Mushroom species	Extracts/Bioactive compounds	Experimental study		Concentration used		Target mechanism	Reference
		Cancer type	Model type	IC <sub>50</sub>	Working dose		
<i>Agaricus blazei</i> Murrill [= <i>Agaricus brasiliensis</i> Wasser, M. Didukh, Amazonas & Stamets; = <i>Agaricus subrufescens</i> Peck.]	<i>A. blazei</i> extract (ABE)	Gastric cancer	AGS cells	–	1.5 and 2 mg/mL	Bax $\uparrow$ , Bcl-2 $\downarrow$ , XIAP $\downarrow$ , cIAP-1 $\downarrow$ , activation of Cas-8/9/3 $\uparrow$ , cleavage of PARP	[121]
	Agarol	Lung cancer	A549 cells C57BL/6 mice	0.26 $\mu$ g/mL –	1 $\mu$ g/mL 10-100 mg/kg IP	p53 $\uparrow$ , ROS $\uparrow$ , $\Delta\Psi$ m $\downarrow$ , Bax $\uparrow$ , Bcl-2 $\downarrow$ , release of AIF from mitochondria to cytosol, Cas-3 activity $\uparrow$ , cleaved PARP	[122]
	50% hydroethanolic extract	Oral squamous cell carcinoma	CAL 27 cells	0.9 mg/mL	0.25-2 mg/mL	$\Delta\Psi$ m $\downarrow$ , release of AIF and Cyt-c from mitochondria to cytosol, Bax $\uparrow$ , Bad $\uparrow$ , Bcl-xL $\downarrow$ , XIAP $\downarrow$ , cIAP2 $\downarrow$ , Apaf $\uparrow$ , Endo G $\uparrow$ , Cas-9/3 activity $\uparrow$	[124]
	Hot water crude extracts of <i>A. brasiliensis</i> Murrill (ABM)			0.7 mg/mL	0.25-2 mg/mL	PARP cleavage ROS $\uparrow$ , $\Delta\Psi$ m $\downarrow$ , Bax $\uparrow$ , Bad $\uparrow$ , Bcl-2 $\downarrow$ , release of Cyt-c from mitochondria to cytosol, Cas-3/8/9 activation $\uparrow$ , PARP cleavage	
<i>Agaricus lanipes</i> (F.H. Møller & Jul. Schäffer) Hlavacek	<i>A. blazei</i> extract (ABE)	Leukemia	THP-1 cells	–	4 mg/mL	$\Delta\Psi$ m $\downarrow$ , Bcl-2 $\downarrow$ , Bax $\uparrow$ , Bcl-xL $\downarrow$ , Cas-9/3 activity $\uparrow$ , cleavage of PARP, AIF, HrtA2/Omi release from mitochondria to cytosol	[123,125]
	Blazeispirol A	Liver cancer	Hep3B cells	–	1-5 $\mu$ g/mL	Bax $\uparrow$ , Bcl-2 $\downarrow$ , Cas-3 activation $\uparrow$	[126]
	Methanolic extract	Lung cancer	A549 cells	250 $\mu$ g/mL	–	Bax $\uparrow$ , Bcl-2 $\downarrow$ , release of Cyt-c from mitochondria to cytosol, activation of Cas-3, 8 and 9 $\uparrow$	[127]
	Grifolin	Nasopharyngeal cancer	CNE1 cells U2OS cells	24 $\mu$ M –	30-50 $\mu$ M 50 $\mu$ M	$\Delta\Psi$ m $\downarrow$ , Cyt-c release from mitochondria to cytosol, Cas-9/3 activity $\uparrow$ , cleaved PARP,	[192]
<i>Albatrellus confuensis</i> (Albertini & Schweinitz) Kotlaba & Pouzar [= <i>Albatrellopsis confuensis</i> Teixeira]	Grifolin	Osteosarcoma	MG63 cells U2OS cells	– –	50 $\mu$ M 50 $\mu$ M	CIAP1 $\downarrow$ , XIAP $\downarrow$ , Survivin $\downarrow$ , $\Delta\Psi$ m $\downarrow$ , Cyt-c release from mitochondria to cytosol, Cas-9/3 $\uparrow$ , cleaved PARP,	[193]
	Neogrifolin	Osteosarcoma	MG63 cells SKOV-3 cells	– 41 $\mu$ g /mL	50 $\mu$ M 50-200 $\mu$ g/mL	Cyt-c release from mitochondria to cytosol, Cas-3/8/9 activation $\uparrow$ , Bad $\uparrow$ , Bim $\uparrow$ , Bak $\uparrow$ , Bcl-xL $\downarrow$	[194]
	Crude extraction of methanol and ethanol	Ovarian cancer	TOV-21G cells	37 $\mu$ g /mL	50-200 $\mu$ g/mL	Bax $\uparrow$ , Bcl-2 $\downarrow$ , Cyt-c release from mitochondria to cytosol, Cas-3 activation $\uparrow$ , cleaved PARP	[131]
	Fermented culture broth	Leukemia	HL-60 cells	–	25-150 $\mu$ g/mL	ROS $\uparrow$ , $\Delta\Psi$ m $\downarrow$ , Bax $\uparrow$ , Bak $\uparrow$ , PUMA $\uparrow$ , Bcl-2 $\downarrow$ , Bcl-xL $\downarrow$ , NADPH oxidase $\uparrow$ , cytosolic Cyt-c $\uparrow$ , mitochondrial cofilin $\uparrow$ , activation of caspase-2,3,8,9 $\uparrow$	[128]
<i>Antrodia camphorata</i> T.T. Chang & W.N. Chou [= <i>Taiwanofungus camphoratus</i> , <i>Antrodia cinnamomea</i> (M. Zang & C.H. Su) Sheng H. Wu, Z.H. Yu, Y.C. Dai & C.H. Su]	Methyl antcininate A (MAA)	Liver cancer	Huh7 cells	30.2 $\mu$ M	100 $\mu$ M	Bax $\uparrow$ , Bcl-2 $\downarrow$ , Bcl-xL $\downarrow$ , Survivin $\downarrow$ , Cytosolic Cyt-c $\uparrow$ , Cleavage of Cas-3 and PARP	[134]
	Antrocin	Breast cancer	MDA-MB-231 cells	0.6 $\mu$ M	1-10 $\mu$ M	Bax $\uparrow$ , Bcl-2 $\downarrow$ , Cleavage of PARP and Cas-3	[132]
	Methyl antcininate A (MAA)	Prostate cancer	PC-3 cells OEC-M1 cells	39.1 $\mu$ M 24.5 $\mu$ M	25-100 $\mu$ M 25 and 50 $\mu$ M	Bax $\uparrow$ , Bcl-2 $\downarrow$ , Bcl-xL $\downarrow$ , Cleavage of PARP, Cas-3 activity $\uparrow$	[133]
	Methyl antcininate A (MAA) Methyl antcininate B (MAB)	Oral cancer	OC-2 cells	37.4 $\mu$ M	25 and 50 $\mu$ M	ROS $\uparrow$ , $\Delta\Psi$ m $\downarrow$ , Bax $\uparrow$ , Bcl-2 $\downarrow$ , Bcl-xL $\downarrow$ , Cas-2,3,8,9 activity $\uparrow$ , Cleavage of PARP, Cytosolic fraction of Cyt-c $\uparrow$ , Cytosolic	[129]
Antcin B (AB)	Liver cancer	HepG2 cells	39.4 $\mu$ M	100 $\mu$ M		[130]	

(continued on next page)

Table 1 (continued)

Mushroom species	Extracts/Bioactive compounds	Experimental study		Concentration used		Target mechanism	Reference
		Cancer type	Model type	IC <sub>50</sub>	Working dose		
<i>Armillaria mellea</i> (Vahl) P. Kumm.	Armillarikin	Liver cancer	HepG2, HA22T and Huh 7 cells	–	6.25–50 µM	fraction of Bax↓, NADPH oxidase↑ ROS↑, ΔΨm↓, Cas-3,8,9 activity↑, cleavage of PARP	[137]
		Leukemia	K562 cells HL-60 cells U937 cells	12.2 µM 10.8 µM 12.2 µM	25 µM – –	ROS↑, ΔΨm↓, Cas-3,8,9 activation↑, cleavage of PARP	[136]
		Lung cancer	A549 cells	–	200 µg/mL	ΔΨm↓, release of Cyt-c from mitochondria to cytosol, Cas-3,9 activity↑	[135]
<i>Astraeus hygrometricus</i> (Persoon) Morgan	Polysaccharide from fruiting bodies of <i>A. mellea</i> (AMP)	Liver cancer	Hep3B cells HepG2 cells	58.8 µM 122 µM	40 µM 150 µM	ROS↑, ΔΨm↓, Bax↑, Bcl-2↓, Cas-9/3 activation↑	[138]
		Liver cancer	Hep3B cells	22.6 µM	10.3 and 20.6 µM	ROS↑, ΔΨm↓, Bax↑, tBID↑	[139]
		Liver cancer	HepG2 cells	65.92 µM	30.9 and 61.8 µM	Bcl-2↓, Cyt-c release from mitochondria to cytosol, Cas-9/3/8 activation↑	[140]
		Lung cancer	A549 cells	69.42 µM	30.9 and 61.8 µM	Same as liver cancer cells	[141]
<i>Auricularia auricula-judae</i> (Bulliard) Wettstein	Polysaccharides	Liver cancer	HepG2 and Bel-7404 cells	–	0.25-1 mg/mL	Bax↑, Bcl-2↓, Bcl-xL↓, cytosolic fraction of Cyt-c ↑, Apaf-1↑, XIAP↓, Cas-9/3 activity↑	[167]
<i>Auricularia polytricha</i> (Montagne) Saccardo	Crude polysaccharides	Lung cancer	A549 cells	28.07 µg/mL	25 and 50 µg/mL	Cytosolic fraction of Cyt-c↑, Cas-9/3 active↑, PARP cleavage	[217]
<i>Calocybe indica</i> Purkayastha & A. Chandra	Ethyl acetate extract (EAE)	Cervical carcinoma	HeLa cells	506 µg/mL	250-750 µg/mL	Bcl-2↓, p53↑, Cas-9/3 activation↑	[204]
			Caski cells	520 µg/mL	250-750 µg/mL		
<i>Calvatia gigantea</i> (Batsch) Lloyd	Methanolic extract	Lung cancer	A549 cells	500 µg/mL	–	Bcl-2↓, Bax↑, Cas-9/3 activation↑	[212]
<i>Calvatia lilacina</i> var. <i>chilensis</i> Spegazzini [= <i>Calvatia cyathiformis</i> (Bosc) Morgan]	Sub-fraction 7 of petroleum ether extract	Breast cancer	MDA-MB231 cells	–	50-200 µg/mL	ROS↑, Cyt-c release from mitochondria to cytosol, p53↑, Bax↑, Bcl-2↓, Cas-3 activity↑, Cleavage of PARP	[142]
<i>Cordyceps bassiana</i> Z.Z. Li, C. R. Li, B. Huang & M.Z. Fan	4-Isopropyl-2,6-bis(1-phenylethyl)phenol (KTH-13)	Brain cancer	C6 glioma cells HepG2 cells	64.9 µM 1.096 mg/mL	– –	Bax↑, Bcl-2↓, Cas-9/7/3 activation↑ ΔΨm↓, Bax↑, Cas-3/8 activation↑, cleavage of PARP	[169]
		Liver and Breast cancer	MCF-7 cells Male BALB/c nude mice	0.791 mg/mL	–		
			GBM8401 cells	–	1 g/kg per os		
	Aqueous extract	Glioblastoma	U-87MG cells	1.6 mg/mL 2.3 mg/mL	– –	Bax↑, Bcl-2↓, P53↑, Cas-8/3 activity↑	[145]
	Fermented mycelial of <i>C. militaris</i>						
<i>Cordyceps militaris</i> (L.) Link <i>Cordyceps ophioglossoides</i> (Ehrhart) Link [= <i>Tolyposcladium ophioglossoides</i> (Ehrhart) Quandt, Kepler & Spatafora]	Cordycepin	Liver cancer	HepG2 cells	37.9 µg/mL	10-20 µg/mL	ROS↑, ΔΨm↓, Bax↑, BAD↑, total BID↓, Bcl-2↓, Bcl-xL↓, Cas-3/8/9↑, cleavage of PARP, XIAP↓, cIAP-1↓	[143]
		Liver cancer	HepG2 cells	37.9 µg/mL	10-20 µg/mL	Bax↑, Bcl-2↓, activation of Cas-3/8/9↑, cleavage of PARP, XIAP↓, cIAP-1↓, cIAP-2↓	[146]
		Liver cancer	HepG2 cells	37.9 µg/mL	10-20 µg/mL	ΔΨm↓, Bax↑, release of AIF and Endo G from mitochondria to nucleus ROS↑, ΔΨm↓, Bax↑, Bcl-2↓, cytosolic Cyt-c↑, Survivin↓, activation of Cas-3,9↑, cleavage of PARP	[147]
<i>Fomitopsis nigra</i> (Berk.) Imaz. (= <i>Polyporus niger</i> Berk.)	Fomitoid-K	Oral squamous cancer	YD-10B cells	15 µM	–	ΔΨm↓, Bcl-xL↓, cytosolic Cyt-c release↑, cleaved Cas-3 and PARP	[148]
<i>Ganoderma amboinense</i> (Lam.) Pat.	Ganoderic acid X	Liver cancer	Huh-7 cells	39.6 µM	40 µM		[198]

(continued on next page)

Table 1 (continued)

Mushroom species	Extracts/Bioactive compounds	Experimental study		Concentration used		Target mechanism	Reference
		Cancer type	Model type	IC <sub>50</sub>	Working dose		
<i>Ganoderma applanatum</i> (Pers.) Pat. [= <i>Ganoderma lipsiense</i> (Batsch) G.F. Atkinson]	Methanolic extract	Colon cancer	Caco-2	160 µg/mL	–	Bax↑, cl-2↓, Cas-3 activation↑	[205]
			Female swiss albino mice	–	200 mg/kg <i>per os</i>	Bax↑, Bcl-2↓, p53↑, Cas-3 activation↑	
<i>Ganoderma lucidum</i> (Curtis) P. Karst.	Reishimax (13.5% polysaccharide and 6% triterpenes)	Prostate cancer	PC-3 cells	0.25 mg/mL	0.25-1 mg/mL	Bcl-2↓, Bcl-xL↓, Bax↑	[178]
			Lung cancer	95-D cells	27.9 µg/mL	–	ΔΨm↓, cytosolic Cyt-c release↑, Bax↑, p53↑, Cas-3 activity↑
	Athymic mice	–		12.5 and 25 mg/kg CI			
	Alcohol extract	Breast cancer	MCF-7 cells	–	500 µg/mL	Bax↑, Cas-7 activation↑	[177]
	Ethanol extract (EGL)	Gastric cancer	AGS cells	–	0.5-2% EGL	Bcl-2↓, tBID↑, XIAP↑, Survivin↑, Cas-8/9/3 activation↑, PARP cleavage	[179]
	Polysaccharides	Liver cancer	HepG2 and Bel-7404 cells	–	0.25-1 mg/mL	Bax↑, Bcl-2↓, Bad↑, Smact↑, Apaf-1↑, Cas- 9/3 activation↑	[167]
			Breast cancer	MCF-7 cells	–	25-100 µg/mL	Bax↑, Bcl-2↓, Bcl-xL↓, Cas- 9/3 activity↑
	Total triterpenes (TT) Total triterpenes + DMBA (7,12-Dimethylbenz(a)anthracene)			Female Swiss albino mice	–	5, 10 and 20 mg applied topically	
	Water extract	Colorectal cancer	HCT116 cells	2.24 mg/mL	1.25-7.5 mg/mL	Bcl-2↓, Survivin↓, Pro Cas-3 and 9↓	[181]
			Male BALB/C nude mice	–	150, 300 mg/kg IP	Bcl-2↓, Cas-8 activity↑, Total PARP↓	
Ethanol extract	Leukemia, lymphoma and multiple myeloma	KBU, OCI-AML3 and MOLM13 cells	48.1 and 78.4 ppm	–	ROS↑, MMP↓, PARP1↑, Cas-3 activity↑	[182]	
<i>Ganoderma tsugae</i> Murrill	Ethanol extract	Leukemia	K562 cells	320 µg/mL	200-400 µg/mL	ROS↑, ΔΨm↓, Bax↑, tBid↑, Bcl-2↓, Cas-9/3/8 activity↑	[149]
<i>Grifola frondosa</i> (Dicks.) Gray	<i>G. frondosa</i> glycoprotein (GFG-3a)	Gastric cancer	SGC-7901 cells	78.32 µg/mL	50-200 µg/mL	Bax↑, Bad↑, p53↑, Bcl-2↓, Bcl-xL↓, Cas-8/3 activation↑	[150]
			Breast cancer	MCF-7 cells	335 µg/mL	50 and 200 µg/mL	ROS↑, ΔΨm↓, Bax↑, Bcl-2↓, Bcl-xL↓, Cas-3 activity↑, cleaved PARP
	MDA-MB-231 cells	412 µg/mL		50 and 200 µg/mL			
	D-fraction polysaccharide from <i>G. frondosa</i> (DFP)	Liver cancer	Male BALB/c mice	–	0.5 g/kg <i>per os</i>		
			SMMC-7721 cells	0.8 mg/mL	–	Bax↑, Bcl-2↓, Cytosolic Cyt-c↑, Cas- 9/3 activity↑, PARP cleavage	[152]
	Cold-water soluble polysaccharide of <i>G. frondosa</i> (cGFP)	Liver cancer	HepG2 cells	200 µg/mL	100-400 µg/mL	ΔΨm↓, Bax↑, Bcl-2↓, cytosolic Cyt-c↑, Cas- 9/3 activation↑	[153]
	Polysaccharides as (Fraction-A) (GFP-A)	Colon cancer	HT-29 cells	180 µg/mL	–	Bax↑, Bcl-2↓, Cas-9 activation↑, cytosolic Cyt-c↑	[154]
<i>Gymnopilus purpureosquamulosus</i> Hoil.	Ethanol extract	Leukemia, lymphoma and multiple myeloma	KBU cells	–	35 ppm	ΔΨm↓, ROS↑, Bax↑, XAF1↑, cytosolic fraction of Cyt-c↑, BIM↑, AIF↑, c-MYC↓, MCL1↓, XIAP1↓, Cas-9/3 activation↑, PARP1 cleavage	[155]
			J45.01	–	35 ppm		
			RPMI 8226 cells	–	35 ppm (parts per million)		
<i>Hericium erinaceus</i> (Bull.: Fr.) Pers.	Hot water extract (HWE)	Leukemia	U937 cells	–	500 µg/mL	ΔΨm↓, Bcl-2↓, BclxL↓, XIAP↓, cIAPs↓, Cytosolic Cyt-c↑, activation of Cas-3/8/9↑, Cleavage of PARP	[184]
			Gastric cancer	AGS cells	–	1-10 µM	Bax↑, Bcl-2↓, Bcl-xL↓, Cas-9/8/3 activation↑
	Microwaved 50% ethanol (MWE)						
Erinacine S							
<i>Hericium novae-zealandiae</i> (Colenso) Chr. A. Sm. & J. A. Cooper	Ethanol extract	Prostate cancer	DU145	0.33 mg/mL	–	Bax↑, Bcl-2↓, Cas-9/8/3 activation↑	[206]
			LNCaP	0.19 mg/mL	–		
			PC3	0.23 mg/mL	–		
	Ergosterol peroxide	Prostate cancer	DU145	21 µM	–		
			LNCaP	15 µM	–		
PC3	42 mg/mL	–					
<i>Inonotus obliquus</i> (Ach. ex Pers.) Pilát	Extract (diluted in McCoy's 5A medium)	Colorectal cancer	HCT-116 cells	10 mg/mL	–	Bax↑, Bad↑, Bcl-2↓, p53↑, Cas-3 activation↑	[199]

(continued on next page)

Table 1 (continued)

Mushroom species	Extracts/Bioactive compounds	Experimental study		Concentration used		Target mechanism	Reference
		Cancer type	Model type	IC <sub>50</sub>	Working dose		
	Polysaccharides	Lung cancer	LLC1, A549 cells C57BL/6 mice	0.3875 mg/mL –	0.2-1 mg/mL 50 mg/kg IP	AMPK↑, ΔΨm↓, ATP production↑, Bax↑, Bcl-2↓, Cas-3 activity↑, Cleaved PARP	[200]
<i>Lactarius chrysorrheus</i> Fr.	Hot water extract precipitate (HWEP)	Liver cancer	HepG2	296.42 μg/mL	31.25-1000 μg/mL	Bax↑, p53↑, Cas-3,8,9 activity↑, Bid↑, Bcl-2↓, Bcl-xL↓	[203]
		Pancreatic cancer	PANC-1	444.43 μg/mL	31.25-1000 μg/mL	p53↑, APAF1↑, Cas-3,9 activity↑, Bid↓, Bcl-2↓, Bcl-xL↓	
<i>Lentinus crinitus</i> (L.) Fr.	Panepoxydone	Breast cancer	MCF-7 cells	5 μM	2.5-10 μM	Bax↑, Bcl-2↓, Survivin↓, cleaved PARP	[156]
			MDA-MB-453 cells	4 μM	7.5-30 μM		
			MDA-MB 468 cells	6 μM	2-8 μM		
			MDA-MB 231 cells	15 μM	3-12 μM		
<i>Lentinula edodes</i> (Berk.) Pegler	Crude <i>L. edodes</i> polysaccharide fraction 1 (cLEP1)	Cervical carcinoma	HeLa cells	–	100-400 μg/mL	ΔΨm↓, Bax↑, Bcl-2↓, cytosolic Cyt-c↑, Cas-9/3 activation↑	[157]
	Aqueous Extract	Larynx Carcinoma	HEp-2 Cells	1 mg/mL	1-2 mg/mL	ΔΨm↓, ROS↑, Bax↑, Bcl-2↓, Bim↑, Cas-3/8 activity↑	[158]
<i>Lentinus sajor-caju</i> (Fr.) Fries [= <i>Pleurotus sajor-caju</i> (Fr.) Singer]	<i>Pleurotus sajor-caju</i> n-hexane extract (PSC-hex)	Colorectal cancer	HCT116 cells	0.05 mg/mL	0.025, 0.05 mg/mL	ROS↑, ΔΨm↓, Bax↑, Bcl-2↓, p53↑, Cas-3 activation↑	[201]
<i>Lentinus squarrosulus</i> Mont.	Peptide extract	Lung cancer	H460 cells	–	5-20 μg/mL	Bax↑, Bcl-2↓, Cas-3/8 activity↑, cleavage of PARP	[159]
<i>Lenzites betulina</i> (L.) Fr.	Ethanol extract of <i>L. betulina</i> (LBE)	Cervical carcinoma	HeLa cells	492.52 μg/mL	250 and 500 μg/mL	ROS↑, ΔΨm↓, Bax↑, Bcl-2↓, p53↑, Pro Cas-3,9↓, Total PARP↓	[160]
			Male swiss albino mice	–	10,25 and 50 mg/kg of LBE <i>per os</i>		
<i>Leucopaxillus giganteus</i> (Sibthorp) Singer	Clitocine	Cervical carcinoma	HeLa cells	15.2 μM	–	Bax↑, Bcl-2↓, Cytosolic Cyt-c↑, Cas-9/3 activity↑, PARP cleavage	[197]
<i>Lignosus rhinocerus</i> (Cooke) Ryvarden	Cold water extract (Fraction F5)	Breast cancer	MCF-7	3 μg/mL	–	Bax↑, Bcl-2↓, tBID↑, Cas-9/8 activation↑	[207]
<i>Lignosus tigris</i> Chon S. Tan	Cold water extract-High molecular weight proteins (CWE-HMWp)	Breast cancer	MCF-7 cells Female NCr nude mice	1.17 μg/mL 5 μg/g IP	–	Bax↑, Bcl-2↓, BID↑, Cas-3/7/8/9 activation↑	[215]
<i>Morchella importuna</i> M. Kuo, O'Donnell & T.J. Volk	<i>M. importuna</i> (MIPP) peptide	Cervical cancer	HeLa cells	–	50-200 μg/mL	Bax↑, Bcl-2↓, Cyt-c in cytosol↑, Cas-3/9 activation↑	[208]
<i>Ophiocordyceps sinensis</i> (Berk.) G.H. Sung, J.M. Sung, Hywel-Jones & Spatafora	Cordycepin	Pancreatic cancer	MIAPaCa-2 cells	106 μg/mL	100-400 μg/mL	ΔΨm↓, Bax↑, Bcl-2↓, activation of Cas-3,9 ↑, cleavage of PARP	[163]
			Capan-1 cells	108.1 μg/mL	100-400 μg/mL		
		Breast cancer	BALB/c nude mice	–	15 and 50 mg/kg IP	ROS↑, ΔΨm↓, Bax↑, Bcl-2↓, activation of Cas-3/8/9↑	[162]
			MCF-7 cells MDA-MB-231 cells	199 μM 136 μM	50 and 100 μM 50 and 100 μM		
Prostate cancer	Male BALB/c nude mice	–	30 mg/kg <i>per os</i>				
			PC-3 cells	–	5-25 μg/mL	ROS↑, ΔΨm↓, Bax↑, Bcl-2↓, Cas-3/9 activation↑, cleavage of PARP, XIAP↓, cIAP-1/2↓	[161]
<i>Ophiocordyceps pruinosus</i> (Petch) D. Johnson, G.H. Sung, Hywel-Jones & Spatafora	Butanol fraction of <i>C. pruinosus</i> (CPBF)	Cervical cancer	HeLa cells	–	10-200 μg/mL	ROS↑, ΔΨm↓, Bax↑, Bcl-2↓, BAD↑, cytosolic Cyt-c↑, Cas-9/3 activity↑, Translocation of AIF into nucleus	[164]
<i>Oudemansiella canarii</i> (Jungh.) Höhn	Ethanol extract	Leukemia, lymphoma and multiple myeloma	KBU, MOLM13, J45.01, U937, RPMI 8226, and MM.1R cells	51.3-66.0 ppm	–	ROS↑, MMP↓, PARP1↑, Cas-3 activity↑	[182]
<i>Phellinus igniarius</i> (L.) Quél.	Total ethanol extract of <i>P. igniarius</i> (TPI)	Gastric cancer	SGC-7901 cells	110.7 μg/mL	80-400 μg/mL	ΔΨm↓, Bax↑, Bcl-2↓, Cas-3/9 activity↑	[191]

(continued on next page)

Table 1 (continued)

Mushroom species	Extracts/Bioactive compounds	Experimental study		Concentration used		Target mechanism	Reference
		Cancer type	Model type	IC <sub>50</sub>	Working dose		
			BALB/c nude mice	–	400 and 800 mg/kg	Bax/Bcl-2 ratio↑	
	Hispolon	Liver cancer	Hep3B cells	35.90 μM	22.5, 45, and 66.5 μM	Bax↑, Bcl-2↓, Bid↑, cytosolic Cyt-c release↑, Pro-Caspase 8↓, Cas- 9/3 activation↑, cleaved PARP	[190]
<i>Phellinus linteus</i> (Berk. & M.A. Curtis) Teng, Zhong Guo De Zhen Jun [= <i>Tropicoporus linteus</i> (Berk. & M.A. Curtis) L.W. Zhou & Y.C. Dai]	Hispolon	Gastric cancer	SGC-7901 cells	15.6 μg/mL	5-15 μg/mL	ROS↑, ΔΨm↓, Cyt-c in cytosol↑, Bax↑, Bak↑, Bcl-2↓, Bcl-xL↓, XIAP↓, Cas-9/3 activation↑, cleaved PARP	[166]
	Polysaccharides	Liver cancer	HepG2 and Bel-7404 cells	–	0.25-1 mg/mL	BAD↑, Bax↑, Bcl-2↓, Smac↑, Cas- 9/3 activation↑	[167]
	Hispolon	Mouth epidermal carcinoma	KB cells	4.62 μg/mL	2.5-10 μg/mL	ΔΨm↓, cytoplasmic Cyt-c↑, Cas- 3 activation↑	[165]
		Leukemia	NB4 cells	2.02 μg/mL	0.625-10 μg/mL	p53↑, Bax↑, Bcl-2↓, Bid↑, Cas- 9,3 activity↑, Pro Cas-8↓, cleaved PARP	[168]
		Colon cancer	HCT-116 cells	25 μM	5-25 μM	Bax↑, Bid↑, Bcl-2↓, Bcl-xL↓, c-FLIP↓, Cas- 3/9 activation ↑, cleavage of PARP	[169]
<i>Pleurotus abalonus</i> Y.H. Han, K.M. Chen & S. Cheng	Crude acidic polysaccharide fraction-3 (PAP-3)	Breast cancer	MCF-7 cells	193 μg/mL	200 μg/mL	ΔΨm↓, ROS↑, p53↑, Bax↑, Bcl-2↓, Cas- 3,9 activation↑, degradation of PARP	[170]
<i>Pleurotus eous</i> (Berk.) Sacc.	Crude polysaccharide	Breast cancer	MCF-7 cells	–	100- 500 μg	ROS↑, Bax↑, Bcl-2↓, Cas-9/3 activity↑	[171]
<i>Pleurotus eryngii</i> var. <i>ferulae</i> (Lanzi) Sacc.	<i>P. ferulae</i> ethanol extract components (PFEC)	Skin cancer	B16F10 cells C57BL/6 female mice	1.4 mg/mL	0.4-1.6 mg/mL 1 g/kg per os	ΔΨm↓, Bax↑, Bid↑, Bad↑, Bcl-2↓, Bcl-xL↓, Cas- 8/9/3 activation↑	[172]
	<i>P. ferulae</i> ergosterol peroxide (PFEP)	Gastrointestinal cancer	Eca-109 cells CT26 tumor in female BALB/c mice	23.17 μg/mL	10-40 μg/mL 20 or 40 mg/kg IP	ROS↑, ΔΨm↓, Bax↑, Bcl-2↓, Cas- 9/3 activation↑	[174]
	Ethanol extract of cultivated and wild <i>P. ferulae</i> (PFEE-C and PFEE-W)	Liver cancer	H22 and HepG2 cells	–	1.368-8.208 μg/mL of flavonoids (PFEE-C and PFEE-W)	ROS↑, ΔΨm↓, Bax↑, Bcl-2↓, activation of Cas-7,9,3↑, cleaved PARP	[173]
			Kunming male mice	–	2.74 or 5.48 mg/kg of flavonoids (PFEE-C)		
<i>Pleurotus ostreatus</i> (Jacq.) P. Kumm.	Hot water soluble (HWS) fraction from mycelium culture (polysaccharides)	Colon cancer	HT-29 cells	–	0.5% (w/v) HWS	Bax↑, cytoplasmic Cyt-c↑	[186]
	Aqueous extract	Colon cancer	COLO-205 cells	81.2 μg/mL	–	Bax↑, Bcl-2↓, Cas-9/3 activity↑	[187]
<i>Poria cocos</i> F.A. Wolf [= <i>Pachyma cocos</i> (Schwein.) Fr.]	Ethanol extract of <i>P. cocos</i> (EEPC)	Leukemia	U937 cells	–	90 μg/mL	Bax↑, tBid↑, Bcl-2↓, activation of Cas- 3/8/9↑, XIAP↓, cIAP-1↓, cIAP-2↓, release of Cyt-c into cytoplasm, cleavage of PARP	[188]
	Pachymic acid (PA)	Breast cancer	MDA-MB-231 cells	2.13 μg/mL	1-5 μg/mL	p53, Bax↑, Bcl-2↓, activation of Cas- 9/8/3↑, cleavage of PARP, cytosolic Cyt-c↑	[189]
	Ethanol extract		BALB/c female nude mice	–	700 mg/kg IP		
<i>Pulveroboletus ravenelii</i> (Berk & Curtis) Murrill	Pulveraven A	Breast cancer	MCF-7	71.74 μM	–	Bax↑, Bcl-2↓, Cas-9 cleaved↑	[210]
<i>Russula senecis</i> S. Imai	Ethanol extract	Liver cancer	Hep3B cells	367.21 μg/mL	100-400 μg/mL	ROS↑, ΔΨm↓, Bax↑, Bcl-2↓, Cas- 9 activation↑	[175]
<i>Sanghuangprouis vaninii</i> (Ljub.) L.W. Zhou & Y.C. Dai	Extract of <i>Sanghuangprouis vaninii</i> (ESV)	Cervical cancer	SiHa	71.8 ± 5.3 μg/mL	30,60 and 120 μg/mL	ROS↑, Bax↑, Bcl-2↓, Cas-9/3 activity↑	[214]
			Female BALB/c nude mice	–	50, 100 and 200 mg/kg	Bax↑, Bcl-2↓, Cas- 9/3 activity↑	
<i>Sarcodon aspratrus</i> (Berk.) S. Ito	Crude polysaccharide	Cervical carcinoma	HeLa cells	–	50-200 μg/mL	ΔΨm↓, Bax↑, Bcl-2↓, cytoplasmic Cyt-c↑, Cas-9/3 activity↑	[183]

(continued on next page)

Table 1 (continued)

Mushroom species	Extracts/Bioactive compounds	Experimental study		Concentration used		Target mechanism	Reference
		Cancer type	Model type	IC <sub>50</sub>	Working dose		
<i>Suillus flavus</i> (Withering) Singer [= <i>Suillus grevillei</i> (Klotzsch) Singer]	Iso-suillin	Erythroleukemia	K562 cells	0.87 µM	2.5-10 µM	ΔΨm↓, Bax↑, Bcl-2↓, Cytosolic Cyt-c↑, Cas- 9/8/3 activation↑	[195]
<i>Suillus placidus</i> (Bonord.) Singer	Suillin	Liver cancer	HepG2 cells	1.99 µM	2-6 µM	ΔΨm↓, Bad↑, Bid↑, cytoplasmic Cyt-c↑, Cas-9/8 activation↑	[196]
<i>Termitomyces clypeatus</i> R. Heim	Alkaline serine protease (AkP)	Liver cancer	HepG2 cells	75 nM	50 and 75 nM	Bax↑, Bcl-2↓, p53↑, Cas-3 activation↑	[209]
<i>Trametes versicolor</i> (L.) Lloyd	Ethanol extract	Breast cancer	MDA-MB-231 cells	514.0 µg/mL	–	Bcl-2↓, p53↑	[211]
			MCF-7 cells	271.7 µg/mL	–		
			T-47D cells	233.3 µg/mL	–		
<i>Tricholoma matsutake</i> (S. Ito & S. Imai) Singer	Aqueous extract	Liver cancer	HepG2 cells	5.3 mg/mL	2.5 and 5 mg/mL	ROS↑, ΔΨm↓, Bax↑, Bcl-2↓, BAD↑, activation of Cas-3/8/9 ↑, cleavage of PARP	[176]
			SMMC-7721 cells	3.4 mg/mL	2.5 and 5 mg/mL		
			BALB/c male nude mice	–	1 g/kg per os		

**Abbreviations:** AB antcin B, ABE *A. blazei* extract, ABM *A. brasiliensis* Murill, AkP Alkaline serine protease, AMP *A. mellea* polysaccharide, cGFP cold-water-soluble polysaccharide from *G. frondosa*, CI celiac injection, cLEP1 Crude *L. edodes* polysaccharide fraction 1, CPBF Butanol fraction of *C. pruinoso*, CWE-HMWp Cold water extract-High molecular weight proteins, DFP D-fraction polysaccharide, EAE Ethyl acetate extract, EEPc Ethanol extract of *P. cocos*, EGL Ethanol extract of *G. lucidum*, GFP *G. frondosa* crude polysaccharides, HWS Hot water soluble, IP Intraperitoneal administration, LBE *L. betulina* extract, MAA Methyl antcin A, MAB Methyl antcin B, MWE Microwaved ethanol, PAP *P. abalonus* Polysaccharides, per os oral administration, PFEC *P. ferulae* ethanol extract components, PFEE-C Ethanol extract of cultivated *P. ferulae*, PFEE-W Ethanol extract of wild *P. ferulae*, PFEP *P. ferulae* ergosterol peroxide, PSC-hex *P. sajor-caju* n-hexane extract, TPI Total ethanol extract of *P. ignarius*, TT Total triterpenes, Cas Caspase, Cyt-c Cytochrome c. Upregulate ↑, Downregulate ↓.

ganoderic acid X derived from *Albatrellus confluens* [192–194], *Phellinus linteus* [165–169], *Suillus flavus* [195], *Suillus placidus* [196], *Leucopaxillus giganteus* [197] and *Ganoderma amboinense* [198] were respectively able to successfully suppress the expression of caspase inhibitors such as X-linked IAP (XIAP, xIAP), cellular IAP (cIAP-1, cIAP2, cIAPs) that supports the activation of the caspase cascade in various tumor cell lines.

Other bioactive compounds such as fomitoid-K, armillarikin, astrakurkurone, astrakurkulol isolated from *Fomitopsis nigra* [148], *Armillaria mellea* [135–137], *Astraeus hygrometricus* [138–141], respectively, few extracts such as peptide extract of *Lentinus squarrosulus* [159], Sub-fraction 7 of petroleum ether extract of *Calvatia lilacina* var. *chilensis* [142] along with some mushroom fractions such as butanol fraction of *Ophiocordyceps pruinoso* [164] and polysaccharide fraction 1 (cLEP1) extracted from *Lentinula edodes* [157,158] promoted apoptosis through the release of apoptotic proteins as well as inducing ROS in tumor cells. Reactive oxygen species also contribute to mitochondrial damage, degrade DNA, lipids and carbohydrates also regulate lipid peroxidation and protein oxidation that further commits unhealthy cells to mitochondria-mediated cell death. *Ophiocordyceps sinensis* [161–163], *Cordyceps militaris* [143–146], *Inonotus obliquus* [199,200], *Ganoderma tsugae* [149], *Pleurotus eryngii* var. *ferulae* [172–174], *Pleurotus abalonus* [170], *Pleurotus eous* [171], *Lenzites betulina* [160], *Lentinus sajor-caju* [201], *Russula senecis* [175] and *Tricholoma matsutake* [176] were described as a source of efficient triggers of ROS generation in cancer cells and induced ROS-dependent apoptosis.

Most of the mushroom-derived bioactive substances that triggered apoptosis through the regulation of Bcl-2 family proteins also have a tendency to activate the tumor suppressor p53 protein which will further promote apoptosis through mitochondria in cancer cells [202]. Most of the following mushrooms *Lactarius chrysorrheus* [203], *Agaricus blazei* [121–126], *Calocybe indica* [204], *Calvatia lilacina* var. *chilensis* [142], *Cordyceps militaris* [143–146], *Ganoderma applanatum* [205], *Grifola frondosa* [150–154], *Hericium novae-zealandiae* [206], *Inonotus obliquus* [199,200], *Lentinus sajor-caju* [201], *Lenzites betulina* [160], *Pleurotus abalonus* [170] and *Poria cocos* [188,189] have components that promoted the transcription-dependent cell death pathway by activating the expression of pro-apoptotic proteins, such as Bax, PUMA and BID which also play an important role in mitochondria-mediated intrinsic cell death pathway. Cold water extract from *Lignosus*

*rhinoceros* [207], peptide from *Morchella importuna* [208], alkaline serine protease eluted from *Termitomyces clypeatus* [209], hispolon derived from *Phellinus linteus* [165–169], Pulveraven A purified from *Pulveroboletus ravenelii* [210] and ethanol fraction from *Trametes versicolor* [211] triggered cell death through a direct interaction with anti-apoptotic proteins Bcl-2 and/or Bcl-XL, which antagonized their effects and resulted in the release of Bax and Bid. Apart from direct interaction between Bax and Bcl-2, *Lignosus rhinoceros* [207], *Morchella importuna* [208] and *Pulveroboletus ravenelii* [210] further execute cell death via activation of initiator caspase 9 in respective cell lines.

The macromolecules and different extracts belonging to the genera *Ganoderma* [149,178,179,198], *Pleurotus* [170–172] as well as the following mushroom species as *Agaricus blazei* [125], *Albatrellus confluens* [193,194], *Anrotdia camphorata* [130,132], *Astraeus hygrometricus* [138–141], *Auricularia auricula-judae* [167], *Calvatia gigantea* [212], *Fomitopsis nigra* [148], *Grifola frondosa* [150,152,154], *Gymnopilus purpureosquamulosus* [155], *Hericium erinaceus* [185], *Inonotus obliquus* [200], *Lentinus squarrosulus* [159], *Phellinus igniarius* [191], *Phellinus linteus* [169], *Poria cocos* [189] and *Suillus placidus* [196] successfully inhibited the pro-survival proteins of PI3K-Akt pathway along with the mitochondrial intrinsic pathway which further regulate the proliferation of tumor cells. Phosphatidylinositol 3-kinase (PI3K) and Akt (protein kinase B) belong to one of the major regulator components of cellular processes that include mammalian cell proliferation, survival, cell growth, tumor invasion, glucose metabolism and angiogenesis. Activated Akt was established as a major survival factor in cancer cells. Moreover it is the central component of the PI3K-Akt signaling pathway that phosphorylates a number of upstream (Phosphatidylinositol 3-kinase, Phosphatase and tensin homolog) and downstream (mTOR, p53, NF-κβ) proteins that are involved in the modulation of apoptosis. The bioactive products extracted from mushrooms also reduced the expression levels of PI3K, PIP3, Akt, mTOR and promoted the over expression of p53 which resulted in intrinsic apoptosis in many cancer cell lines.

## 7.2. Preclinical studies

Evidence indicated that fractions of mushrooms have a potential use in the treatment of varied types of cancer both *in vitro* and *in vivo*. MOMP (mitochondrial outer membrane potential) is a process that is essentially

intrinsic to the outer membrane and controlled by members of the Bcl-2 family of proteins to promote or prevent the formation of large, protein permeable pores [213]. Aqueous extracts of *C. militaris* and *T. matsutake* have been demonstrated to regulate the mitochondrial outer membrane permeabilization by a release of BH3-only proteins like Bax, Bad from their inhibitory complexes. This promoted their conformational changes and further activated the initiator caspase of the mitochondrial pathway which resulted in the cleavage of cellular substrates leading to apoptotic cell death in liver and breast cancer cells [143,176]. Both the aqueous extracts at a similar dose of 1 g/kg significantly reduced tumor growth in BALB/c nude mice that were xenografted with MCF-7 breast cancer cells [143,176]. Similarly extract of *Sanghuangprou vaninii* also induced apoptosis in SiHa cervical cancer cells as well as a dose-dependent antitumor effect in xenografted BALB/c mice [214]. Studies reported that upon exposure to the ethanol extract of cultivated and wild *P. ferulae* as well as their ergosterol peroxide mitochondrial ROS (mtROS) production directly stimulated the dissipation of the  $\Delta\Psi_m$ , activated the upregulation of Bax and downregulated the anti-apoptotic marker Bcl-2. The change in the ratio of Bax/Bcl-2 further triggered the caspase cascade to culminate in cell death in hepatocellular carcinoma, melanoma and gastrointestinal cancer respectively [173,174,195]. Similar observations were also noted in gastric cancer cells as well in BALB/c nude mice by the total ethanol extract of *P. igniarius* [191]. The ethanol extracts of *P. ferulae* has also demonstrated potential antitumor activity in kunming mice xenografted with H22 mouse liver cell line [173] as well as in C57BL/6 female mice bearing B16F10 melanoma tumors [172].

MOMP effectively represents a point-of-no-return, it is highly regulated, largely by members of the Bcl-2 protein family. BAX or BAK activation requires direct interaction with a member of the BH3-only protein family. Cold water extract-high molecular weight proteins (CWE-HMWp) from *L. tigris* caused conformational changes of Bax and Bid, leading to their oligomerisation within the mitochondrial outer membrane further resulting in the activation of effector caspases, including caspase 3, 6 and 7 in breast cancer cells which in turn triggered cell death and slowed down MCF-7 tumor growth in female NCr nude mice [215]. Cordycepin isolated from *O. sinensis* have demonstrated potential anticancer activity against various cancer cell lines as well as in *in vivo* model through intrinsic pathway [163]. Similar reports were also noted in *G. lucidum* where both the triterpenes as well as water extract demonstrated remarkable anticancer efficacy towards HCT116 colorectal xenografts [181] along with an anticarcinogenic effect in DMBA-induced skin papilloma and mammary carcinoma [180].

Photo-activated reactive oxygen species (ROS) may trigger mitochondrial permeability transition pore (mPTP) induction within individual mitochondria in intact cell systems [216]. Polysaccharide reported from *G. frondosa* and *I. obliquus* disrupted the outer mitochondrial membrane potential causing transition pores through which release of cytochrome *c* into the cytoplasm is mediated which in turn incited the formation of a multiprotein complex called the apoptosome. Apoptosome supports the activation of caspase-9 through enforced multimerization, which in turn cleaves and activates the effector caspase-3 resulting in the subsequent degradation of cellular death substrates like PARP to induce cellular death in breast [151] and lung cancer cells [196] respectively. Both the polysaccharides exhibited potent antitumor effect in MCF-7 xenografted BALB/c mice with an oral *Grifola frondosa* polysaccharide dose of 0.5 g/kg [151] as well as in C57BL/6 mice grafted with LLC1 lung carcinoma cells and *i.p* injected with 50 mg/kg *Inonotus obliquus* polysaccharide [200]. Crude polysaccharides from *A. polytricha* also induced apoptosis in A549 lung adenocarcinoma cells via the release of Cyt *c* and activation of downstream caspases. The intraperitoneal injection of this crude polysaccharide at 1 mg/kg or 3 mg/kg in BALB/c-nu nude mice resulted in a significant delay in the growth of A549 xenografts [217].

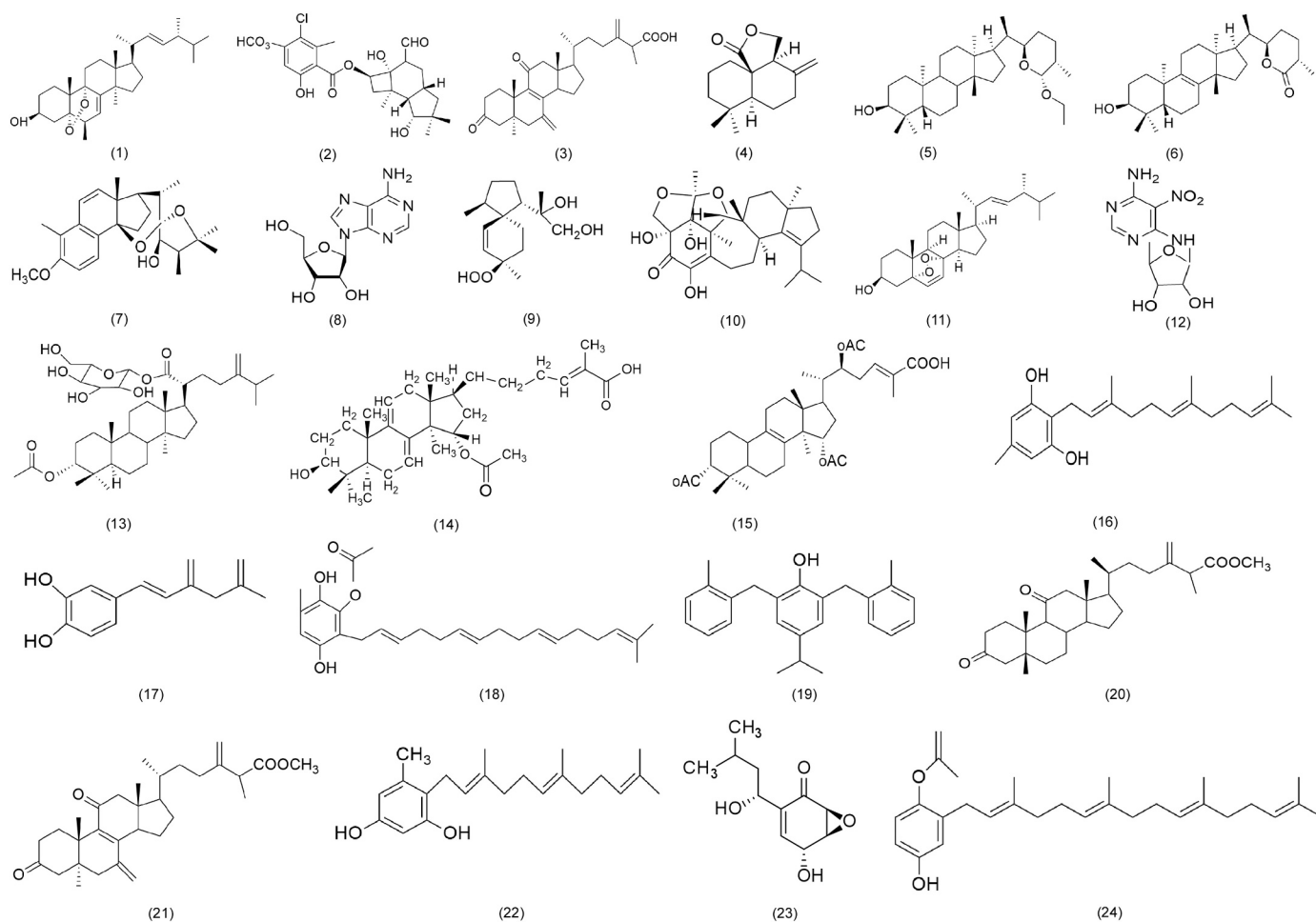
Death signals originating from cellular stress activate an intrinsic apoptotic pathway that is mediated largely by the mitochondria. Sterols

like Agarol and Ganoderic acid T both exerted anticancer effects *in vitro* and *in vivo* in lung adenocarcinoma models. The *in vitro* assays showed that p53 participated directly in the intrinsic apoptosis pathway by activating the ROS production and interacting with the multi-domain members of the Bcl-2 family which in turn ruptured mitochondrial outer membrane and released apoptogenic proteins like Cyt *c* and AIF (apoptosis inducing factor). Cytochrome *c* in conjunction with apoptosis protease activating factor (APAF-1) and pro-caspase 9 formed an 'apoptosome'. This complex then promoted the activation of caspase 9, which in turn activated effector caspases like caspase 3 that collectively orchestrated the execution of apoptosis [122,218]. When Agarol was administered to A549 xenografted C57BL/6 mice a significant reduction in tumor volume was reported [122]. Similarly the methanolic extract of *G. applanatum* [205] and ethanolic extract of *L. betulina* [160] as well as *P. cocos* [188] also showed potent anticancer activity against colon, cervical and breast cancer respectively via direct participation of p53 in the intrinsic apoptosis pathway. The oral suspension of methanolic and ethanolic extract in Swiss albino mice successfully inhibited tumor through the same apoptotic pathway as shown *in vitro* [160,205] while the ethanolic extract of *P. cocos* was injected intraperitoneally to BALB/c female nude mice at 70 mg/kg for evaluation of tumor growth inhibition [188].

### 7.3. Clinical studies

Medicinal mushrooms have been successfully used with limited side-effects [219]. Currently, various trials are being conducted in order to evaluate the advantage of using commercial preparations consisting of medicinal mushroom extracts in cancer treatment. It is estimated that more than 600 clinical trials using medicinal mushrooms have been performed worldwide [220,221]. A comprehensive cell culture, animal model and clinical trial, investigation has been undertaken in order to demonstrate the anticancer effects of mushrooms. Table 2 is illustrating the wealth of bioactive compounds extracted from these mushrooms which are been evaluated in clinical trials and few of them are currently being used in the clinics as they are acknowledged to be more target-specific with negligible side effects. Primarily the use of mycomedicine was through oral intake. Numerous clinical trials involving mycomedicines as anticancer agents provided some major advantages as supportive therapies. Mycomedicines combined with chemotherapy were able to reduce the adverse side effects in cancer patients, helped improve the quality of life (QOL), and increased the survival rate of cancer patients. Moreover, it helped improve the immunological functions as evidenced by better hematologic parameters (HP), increased antitumor activity, and improved immune balance and immunomodulation [222].

Grifolan, a polysaccharide that was extracted from *Grifola frondosa* [223], *Trametes versicolor*, a mushroom-derived protein bound polysaccharide (PSK, Krestin), and PSP polysaccharide peptide have completed their phase I clinical trial against breast with encouraging results [224,225]. Clinically-approved semisynthetic anticancer drug illudin-S, purified from *Omphalotus illudens* as well as *Omphalotus nidiformis* were effective in prostate, ovarian and renal cell carcinoma through the control of DNA replication [226,227]. A polysaccharide lentinan isolated from *Lentinula edodes* was used in combination with LEM and immunotherapy to treat lung, gastric, colorectal and gynecology cancer and a better tumor response was reported with lentinan along with a significant improvement in quality of life [228]. Recently, Chinese Pharmacopoeia was updated with six medicinally-relevant fungi among which *Ganoderma lucidum* has been extensively explored by researchers. It has also been approved for evaluation in clinical trials, mainly as an anticancer agent [229]. *Coriolus versicolor* which is another relevant mushroom has been explored extensively in the field of anticancer drug development. Consumption of *C. versicolor* derived compounds, polysaccharopeptide (PSP) significantly improved the QOL by reducing potential risk of mortality in breast, gastric and colorectal



**Fig. 6.** Chemical structures of the low-molecular-weight (LMW) compounds with anticancer potential found in mushrooms. Agarol (1), Armillarikin (2), Antcin B (3), Antrocin (4), Astrakurkurool (5), Astrakurkurone (6), Blazeispirol A (7), Cordycepin (8), Cordycepol C (9), Erinacine S (10), Ergosterol peroxide (11), Clitocine (12), Fomitoside-K (13), Ganoderic acid X (14), Ganoderic acid T (15), Grifolin (16), Hispolon (17), Iso-suillin (18), KTH-13 (19), Methylanticinate A (20), Methylanticinate B (21), Neogrifolin (22), Panepoxydone (23), Suillin (24).

cancer patients when compared with conventional cancer treatment [230].

More metabolites and different extracts of various mushrooms such as *A. bisporus*, *A. blazei*, *A. sylvaticus*, *A. cinnamomea*, *O. nidiformis*, *P. cornucopiae* and *S. commune* are still under clinical investigation, among which all species of *Agaricus* and *Antrodia cinnamomea* were the most explored by researchers at the clinical level [231,232]. When extracts of *Agaricus blazei*, *Agaricus sylvaticus* and *Antrodia cinnamomea* were used as nutritional supplements in patients who underwent chemotherapy the severity of multiple myeloma, breast cancer, colorectal cancer was reduced [233–238]. The oyster extract of *Pleurotus cornucopiae* and schizophyllan (SPG) isolated from *Schizophyllum commune* potentially reduced the size of tumors in cervical, gastric cancer patients with stage II or III burden [239–241]. The ongoing clinical trials are expected to corroborate the previous clinical evidence on antitumor potential of mycomedicine-derived compounds and are hoped to facilitate their development as anticancer agents. *Grifola frondosa* and *Agaricus bisporus* also showed promising results in phase I trial against lung neoplasms and prostate carcinoma respectively [242]. The secondary metabolites of *Agaricus blazei* and *Omphalotus illudens* completed the phase II clinical trial run as against multiple myeloma, thyroid, gastric, epithelial ovarian carcinoma [242]. Various mushroom-derived secondary metabolites and extracts are currently under investigation in the clinical setting in the hope for their approval as potential anticancer drugs either as a single therapy or in combination with conventional compounds.

## 8. Conclusion

Targeting the mitochondria by cutting off the required energy to fuel the proliferation of cancer cells, is an attractive and original strategy. The comprehensive study in this review has distinctly demonstrated that metabolic processes that are specifically deregulated within a tumor is a clear indication of the cancer cell population dependency on mitochondrial respiration in contrast to glycolysis. Thus, targeting mitochondria and its associated components through a new set of potential anticancer compounds is expected to be an asset in precision medicine. Mushrooms are a treasure trove for a variety of bioactive compounds among which very few are reported and many more are yet to identify. The review states that mushroom extracts and bioactive compounds have shown a potential anticancer effect against 20 different types of cancers. The majority of extracts and bioactive compounds showed cytotoxicity against liver and breast cancer followed by cervical and lung cancer models. The experimental evidence provided in the review allows us to predict the underlying molecular mechanism of various mushroom-derived compounds through the mitochondrial pathway. Mitochondria are not only the site where antiapoptotic and proapoptotic proteins interact and determine cell fates, but also the origin of signals that initiate the activation of caspases through various mechanisms.

A large number of mushrooms demonstrated promising effects as anticancer therapeutics in *in vitro* systems which give confidence to the scientist for further investigation in *in vivo* models. Most *in vivo* studies



were performed in mice models using various xenografted cancer cell lines. Among all the listed mushrooms a wealth of bioactive compounds was mainly extracted from *Antrodia camphorata* followed by *Agaricus blazei* and *Ganoderma lucidum*. *Ganoderma*, *Lentinus* and *Pleurotus* are at present the most investigated genera for potential drug leads against cancer. The literature reported that the majority of clinical studies were carried out with *Lentinula edodes*, *Coriolus versicolor* and *Ganoderma lucidum* followed by *Agaricus bisporus* and *Grifola frondosa*. Although many clinical trials have been conducted to ascertain the efficacy of mushroom-derived bioactive components, further improvement in methodological quality and clinical research is warranted as suggested by some published systematic reviews before they can be recommended as first-line treatment.

In summary our study is the first comprehensive review of all available research related to the anticancer properties of mushroom extracts, as well as their bioactive compounds with anticancer

mechanisms linked to the mitochondria-mediated intrinsic signaling pathway. This review aimed to become a compendium of comprehensive knowledge for researchers, physicians, and companies as it would significantly contribute to address shortcomings in knowledge regarding medicinal mushrooms and benefit the research community. This improved knowledge in targeted signaling pathways will help researchers design preclinical and clinical studies in order to investigate the anticancer efficacy of mushroom extracts and their bioactive compounds in various cancers. The quoted results may also contribute to the classification of mushrooms as nutraceuticals or to the creation of dietary supplements to cancer therapy.

### 8.1. Outlook for the future

This review accurately offers molecular insight into the action of mushroom-derived compounds and it was designed to help the scientific

**Table 2**  
Selected clinical studies of mushrooms with anticancer activity.

Origin	Bioactive molecules	Identifier	Investigator	First Submitted	Last Updated	Cancer type	Study Phase/ Type	Status	Source
<i>Agaricus bisporus</i>	Extract, Lectin, Polysaccharides	NCT00709020	S. Chen	2008	2015	Breast cancer	Phase I n = 16	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
		NCT00779168	W. Twardowski	2008	2019	Prostate cancer	Phase I, n = 32	Active	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
		NCT04519879	C.S. Lau	2020	2022	Prostate cancer	Phase II n = 132	Active	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
<i>Agaricus blazei</i> Murrill	Extract, Agaricus polysaccharides	NCT00970021	J.M. Tangen	2009	2014	Multiple myeloma	Phase II n = 40	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
		NM	R. C. Fortes	2008	2008	Breast cancer, Colorectal cancer	Randomized clinical trial, n = 56	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
<i>Agaricus sylvaticus</i>	Extract	NM	R. C. Fortes	2008	2008	Breast cancer, Colorectal cancer	Randomized clinical trial, n = 56	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
<i>Antrodia cinnamomea</i>	Aqueous extract	NCT01287286	Ming-Yen Tsai	2016	2016	Metastatic adenocarcinoma	Randomized clinical study n = 37	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
<i>Coriolus versicolor</i>	Extract	NCT00647075	P. Gascon	2008	2010	Breast cancer	Phase IV n = 60	Unknown	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
	Extract	NCT00680667	C. Torkelson	2008	2017	Breast cancer	Phase I n = 11	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
		NCT02568787	J.E. Lewis	2015	2017	Breast cancer	Phase I n = 23	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
<i>Grifola frondosa</i> (Dicks.) Gray	Extract, Polysaccharides	NCT02603016	S. Jiao	2015	2017	Lung and Breast neoplasms	Phase I n = 480	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
		NM	X. Jin	2012	2012	Various types cancer	Randomized, clinical trial n = 373	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
<i>Ganoderma lucidum</i>	Spore vs mycelium	NM	X. Jin	2012	2012	Various types cancer	Randomized, clinical trial n = 373	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
<i>Lentinula edodes</i>	Genistein Combined Polysaccharide (GCP), Arabinoxyl	NCT00269555,	R. Hackmanand	NM	NM	Prostate cancer, Hepatocellular carcinoma and hepatitis B and C infection	Open pilot study n = 10	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
		NCT01018381	M.H. Bang						
<i>Omphalotus illudens</i>	A semisynthetic derivative of illudin S	NCT00124527, NCT00062257, NCT00019552	E. Inc., W. Yeo, G.A. Sarosy	NM	NM	Thyroid cancer, Metastatic gastric cancer, Persistent epithelial ovarian cancer	Phase 2 n = NM	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
<i>Omphalotus nidiformis</i>	Illudin S (Irofulven)	NM	C. Munoz	2022	2022	Prostate cancer	Phase II n = NM	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
<i>Pleurotus cornucopiae</i>	Oyster extract	NM	D. Krishnamoorthy	2016	2016	Various types cancer	Double-blind, placebo controlled study n = 20	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
<i>Schizophyllum commune</i>	Schizophyllan (SPG)	NM	H.U. Nakao	1985	1985	Gastric cancer	Phase I n = 154	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
<i>Trametes versicolor</i>	Krestin, PSK, PSP	NCT00680667	C. Torkelson	NM	NM	Breast cancer	Phase 1 n = NM	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
Soy Powder+	Extract	NCT00269555	R. Hackman	2005	2010	Prostate cancer	NM	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
<i>Grifola frondosa</i> (Dicks.) Gray							n = 62		<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
Rice bran+	Extract	NCT01018381	M.H. Bang	2009	2009	Liver cancer	NM n = 130	Completed	<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>
<i>Grifola frondosa</i> (Dicks.) Gray									<a href="https://clinicaltrials.gov">ClinicalTrials.gov</a>

n participants; NM Not mentioned.

community with crafting potential anticancer drug leads from the wide array of mushroom genera, but this review also highlighted some major drawbacks of these studies, which if resolved could be very beneficial in the future. A large part of studies on the effect of macrofungi in cancer has only dealt with the identification of non-specific cytotoxic effects in cancer cells, barely focusing on the modulation of the selective oncogenic signaling pathways which might be relevant targets in cancer treatment. Only a limited amount of compounds among the plentiful resources that were isolated has been fully characterized. Structure-activity relationships should be thoroughly investigated in order to promote the antitumor effects of these potential leads and would also shed light on their interplay with diverse nodes of signaling pathways. In various aforementioned studies, the anticancer activity of mushroom extracts has been determined rather than the effects of one active component. Most of the analyses did not mention the IC<sub>50</sub> values of the bioactive components used in these *in vitro* cancer models, which is paramount in early studies to define the potency of a given compound and thus its value as a potential anticancer therapy, either as a single drug or in combination. In spite of the favourable outcome of the exposure to these mushroom-derived molecules of these *in vitro* and *in vivo* studies, methodical preclinical studies are a prerequisite for their further use in the clinical setting as well as promoting the therapeutic benefit assessment of mushrooms. Finally attention should also be drawn to the potential safety issues related to this type of mycomedicine and the need for thorough toxicological data collection before any compound borrowed from the biodiversity is considered as a suitable alternative to conventional cancer therapies. Current knowledge should be expanded in order to fully characterize the physicochemical properties of mushroom-extracted bioactive compounds that can target intracellular organelles such as mitochondria in the hope that mushrooms will finally be carried from bench to bedside to treat cancer.

#### Authors' contribution

KA and JS-G conceived and designed the review article. SN and RS performed the literature search and wrote the manuscript. SR, SA, JS-G and KA analysed the data. JS-G, KA, SR and SA reviewed and edited the article. SN and RS revised the manuscript.

#### Declaration of Competing Interest

The authors declare that they have no conflict of interest.

#### Data availability

Data will be made available on request.

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