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Traditional Chinese medicine fungi as novel Anti-tumor agents: Insights into their mechanisms and cancer treatment potential

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Abstract
Traditional Chinese Medicine (TCM) is a complementary and integrative approach that has stood the test of time. It uses remedies from the animal, mineral, and plant kingdoms to treat various conditions. Among these, edible fungi are commonly employed for their tonic and immunomodulatory effects, and recent studies have focused on their potential in cancer treatment. Many fungi have shown anticancer effects by inducing apoptosis, inhibiting angiogenesis, decreasing mitochondrial membrane potential, and stimulating the immune system. *In vitro* studies have demonstrated reduced colony formation and migration abilities upon exposure to crude or solvent-extracted fungal compounds. *In vivo* studies using xenograft models confirmed these findings, and clinical trials on cancer patients undergoing chemotherapy suggest possible integration. Chemical analysis has revealed a correlation between the structure of fungal compounds and their anticancer activities, with the geographical origin of the fungi influencing their composition and therapeutic use. While current evidence is promising, researchers have yet to fully understand the molecular mechanisms behind these anticancer effects. This review presents an in-depth analysis of edible fungi as potential sources of novel anti-tumor compounds, based on both Western and Chinese databases.

Keywords: Edible fungi, anti-cancer properties, traditional Chinese medicine (TCM), immunomodulatory effects, ganoderma lucidum, bioactive compounds

Introduction
Traditional Chinese Medicine (TCM) is one of the complementary and alternative medical systems recognized by the World Health Organization. Originating in China over 4,000 years ago, it has gradually spread worldwide, integrating to varying degrees into Western healthcare systems. The TCM pharmacological compendium includes more than 11,000 remedies derived from the animal, mineral, and plant kingdoms. These remedies are typically prescribed as complex mixtures known as formulas for internal use but can also be applied topically as baths, ointments, or in combination with other techniques such as acupuncture.
As a complex medical system, TCM relies on a distinct set of principles and terminology that can sometimes be challenging to interpret. In recent years, efforts have been made to evaluate its safety and efficacy through evidence-based research, facilitating its integration into Western medicine. Nonetheless, certain remedies, such as red yeast rice and ginseng, have gained recognition in the West and are now key ingredients in dietary supplements. This growing interest in Chinese medicine has led to the identification of novel bioactive compounds with potential clinical applications. However, some traditional knowledge, as recorded in classical TCM texts, has been simplified during its adaptation to modern contexts.
Among natural bioactive products, medicinal mushrooms stand out due to their favorable safety profile and notable anti-cancer properties. Some exhibit direct cytotoxic effects, while others enhance immune surveillance by stimulating key immune cells such as natural killer (NK) cells, CD4+ T cells, and CD8+ T cells, thereby aiding in the recognition and elimination of malignant cells [1]. The following mechanisms are among the most commonly shared anti-cancer properties of medicinal fungi:

- Immune stimulation via cytokine release and natural killer (NK) cell involvement. The immune system serves as the primary defense against cancer. Through immunosurveillance, NK cells screen the environment for tumor-specific ligands such as CDMA1, E-cadherin, CA-125, PDL1, and carcinoembryonic antigen. Upon recognition, NK cells release lytic granules that induce cytotoxicity. A complex interplay of activating and inhibitory receptors regulates NK activity, balancing pro-death and pro-survival signals. Additionally, NK cells can mediate antibody-dependent cell cytotoxicity, a potent mechanism leading to cancer cell destruction, as confirmed by both *in vitro* and *in vivo* experiments [1].
- Apoptosis induction and regulation. Cancer cells often evade pro-apoptotic stimuli, leading to tumor progression and poor prognosis. Medicinal fungi appear to promote apoptotic signaling in tumor cells, thereby inhibiting cancer spread. For instance, fungal treatment has been associated with the upregulation of c-Kit, a proto-oncogene that, under specific conditions, can also function as an apoptosis stimulator [2]. Additionally, fungal extracts have been shown to modulate caspase-3, a key executioner of apoptosis. While caspase-3 is primarily recognized for its tumor-suppressive role, certain contexts reveal a dual function, contributing to both cell survival and cell death [3]. Apoptotic pathways are primarily classified as intrinsic (mitochondrial-mediated) and extrinsic (death receptor-mediated). Stress signals, including endoplasmic reticulum stress, can lead to mitochondrial membrane permeabilization, activating BAX/BAK and triggering cytochrome-C release. This, in turn, promotes apoptosome assembly and caspase activation, culminating in programmed cell death. In parallel, the extrinsic pathway is initiated by death receptors such as TNFR, TRAIL, and CD95, which activate caspase-8 and caspase-10, further propagating the apoptotic cascade [4]. Both pathways ultimately converge at caspase-3 and caspase-7 activation, reinforcing the role of medicinal fungi in promoting apoptosis through multiple molecular mechanisms.
- Angiogenesis inhibition. As highly energy-dependent entities, cancer cells promote the formation of new blood vessels to sustain their growth and proliferation. Vascular endothelial growth factor (VEGF) plays a central role in tumor-associated angiogenesis and is frequently upregulated in aggressive tumors with poor prognosis [5]. Inhibition of VEGF signaling disrupts vascular endothelial integrity, leading to blood flow impairment. This results in widespread apoptosis within tumor vasculature due to nutrient deprivation [6].
- Mitochondrial transmembrane depolarization. As the cell's energy factory, mitochondria play a crucial role in sustaining cell proliferation and survival, making them a potential target for cancer therapy. ATP production depends on maintaining the transmembrane proton gradient, and mitochondrial integrity is essential for cellular energy homeostasis. Permeabilization of the mitochondrial membrane, induced by pro-apoptotic factors such as Bax and Bak, leads to calcium ion overload and mitochondrial degradation [7]. Once cytochrome-C is released into the cytosol, it triggers the apoptotic cascade by activating the caspase family and promoting apoptosome formation, ultimately resulting in cell death.

[Figure 1.1] provides an overview of the primary mechanisms through which medicinal fungi exert anti-cancer effects, including apoptosis induction and angiogenesis inhibition.

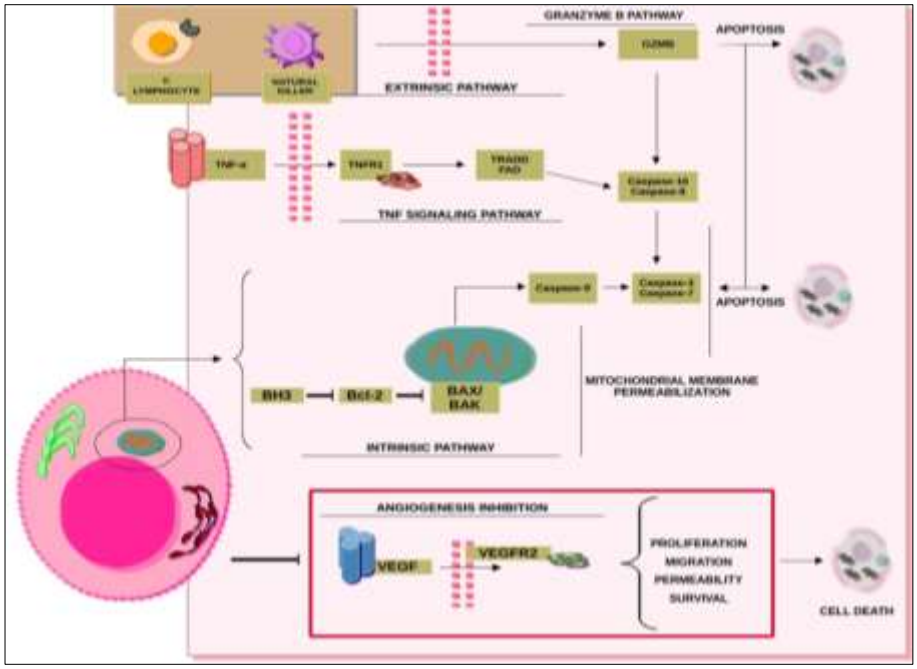

Fig 1: Mechanisms of anti-cancer activity mediated by medicinal fungi. The top section illustrates the activation of the extrinsic apoptotic pathway via natural killer (NK) cells and T-lymphocytes, which release granzyme B (GZMB) to trigger apoptosis. The TNF signaling pathway also induces apoptosis through TNF-α binding to TNFR1, leading to caspase activation. The intrinsic pathway involves mitochondrial membrane permeabilization, regulated by the BAX/BAK complex and Bcl-2 family proteins, ultimately resulting in cell death. The lower section highlights angiogenesis inhibition via VEGF downregulation, which impairs tumor proliferation, migration, and survival by restricting its vascular supply. Solid arrows indicate activation, while truncated lines represent inhibition or suppression.

Overall, more than 500 species of medicinal mushrooms are included in the TCM pharmacopoeia, with their availability varying by geographical region. The present study collected data from PubMed, Google Scholar, the China National Knowledge Infrastructure (CNKI), and Wanfang Data. Based on this literature, we explore key edible fungi with documented anticancer properties, summarizing their bioactive components, mechanisms of action, and potential therapeutic applications.

Anti-Cancer and Therapeutic Properties of Edible Fungi

竹黄 (*Shiraia bambusicola* Henn) is an anti-aging fungus traditionally prescribed to treat cough, stomach pain, leukorrhea, and rheumatism. Taxonomically classified as an ascomycete, it is a medically relevant fungus known for its rich content of photosensitizing pigments, including caryophyllin and hypocrellins A and B. Additional bioactive compounds identified in *Shiraia bambusicola* include 3,6,8-trihydroxy-1-methylketone, 3,8-dihydroxy-6-methoxy-1-methylketone, 2,3,6,8-tetrahydroxy-1-methylketone, 3,4,6,8-tetrahydroxy-1-methylketone, δ5,10-3β,17α,20β-pregnanetriol, macrosphelide A, (+)-griseofulvin, griseophenone A, and the potent anti-tumor compound 11,11′-dideoxyverticillin A [8].

11,11′-dideoxyverticillin A exhibits cytotoxic effects against NCI-H1975 (lung), HepG2 (liver), and MCF-7 (breast) cancer cell lines, while hypocrellin A (HCA) demonstrates significant anti-proliferative activity [9]. Upon activation, HCA induces the release of reactive oxygen species (ROS) and radicals, triggering lipid peroxidation and subsequent cell death [10]. Two major mechanisms have been proposed for this photosensitizing effect: (1) HCA may induce DNA damage through electron transfer from DNA bases to the HCA cation, and (2) it may generate singlet oxygen and superoxide anion radicals, amplifying cellular damage [11]. Additional anti-cancer mechanisms have also been suggested. Zhang *et al*. reported that *Shiraia* extract exerts pro-apoptotic effects in human gastric BGC823 cancer cells [12]. Meanwhile, Chen *et al*. demonstrated that 11,11′-dideoxyverticillin A inhibits angiogenesis in human umbilical vein endothelial cells by counteracting VEGF stimulation, reducing VEGF secretion, impairing cell motility, and hindering tube formation [13]. Beyond its anti-cancer properties, *Shiraia bambusicola* is rich in polysaccharides with immunomodulatory potential. Wang *et al*. found that its bioactive polysaccharides activate macrophages, thereby modulating immune responses [14]. Furthermore, evidence suggests that *Shiraia* polysaccharides may have anti-arthritic properties, highlighting their potential therapeutic application in inflammatory diseases [15].

古尼虫草 (*Cordyceps gunnii*), commonly known as *Cordyceps hawkesii* Gray, *Cordyceps sinensis*, or sometimes *Cordyceps militaris*, is prescribed in Traditional Chinese Medicine for cough, hemoptysis, spermatorrhea, nocturnal emissions, debilitation, and fatigue. The anti-tumor activity of *Cordyceps gunnii* methanol extract was evaluated by Zhu *et al*. in MCF-7 (breast cancer) and HL-7702 (liver cancer) cell lines. Purification of the extract yielded three major components, FB1, FB2, and FB3. Among them, FB3, a steroid compound, demonstrated the highest efficacy, with an 84.54% inhibition rate, exhibiting significant anti-proliferative activity [16]. Cordycepin, one of the most studied bioactive compounds of *Cordyceps*, has been shown to possess strong anti-cancer properties. Yu *et al*. reported that treatment with 125 μg/mL of cordycepin reduced the viability of colon cancer cells *in vitro* [17]. Mechanistically, its pro-apoptotic effects are mediated via activation of the endogenous Bax-dependent mitochondrial apoptosis pathway [18]. *In vivo*, cordycepin inhibited the growth of human tongue cancer, while its co-administration with cisplatin suppressed metastasis by inhibiting the AKT pathway and activating AMPK [19]. Given that the AKT/PKB pathway promotes tumor cell proliferation via its downstream effector mTOR, targeting AKT and AMPK through cordycepin may impair oncogenic cell growth. Furthermore, Cui *et al*. demonstrated that cordycepin inhibits ovarian adenocarcinoma SKOV-3 cell expansion via Bax regulation, counteracting the CCL5-mediated Akt/NF-κB signaling pathway [20]. Cordycepin may also serve as an adjuvant to immunotherapy by enhancing immune cell sensitivity. Thepmalee *et al*. observed that ethanol extracts of *Cordyceps* increased NKG2D ligand expression in various cancer cell types, improving their susceptibility to immune cell-mediated death. The NKG2D immunoreceptor plays a key role in natural killer (NK) cell function, promoting cytotoxic activity. While responses may vary among cancer cell types, *Cordyceps* extracts' ability to support NK cell function presents a potential novel anti-cancer strategy [21]. Wu *et al*. investigated cordycepin impact on FGF-9-treated TM3 cells. FGF-9, a fibroblast growth factor involved in MAPK, PI3K/AKT, and PLC/PKC pathway regulation, is aberrantly active in several cancers, driving cell proliferation and survival [22]. In TM3 cells, FGF-9 stimulation led to enhanced proliferation, which was effectively counteracted by cordycepin, reducing cell viability and colony formation even in the presence of a proliferation promoter. Beyond its anti-cancer properties, *Cordyceps gunnii* exhibits additional pharmacological effects. It possesses mild hypotensive and anti-platelet aggregation properties, modulates Toll-like receptors (TLRs) to promote anti-inflammatory effects, and reduces ROS production. Clinically, it has also been used to alleviate hematuria and proteinuria, enhance energy levels, and improve endurance and stamina [23].

茯苓 (*Poria cocos* (Schw.) Wolf) is one of the most commonly used remedies in Traditional Chinese Medicine (TCM), frequently incorporated into prescriptions for various purposes. It is used to treat edema, dizziness, palpitations, gastric ailments, inappetence, restlessness, insomnia, and diarrhea. Historical records trace its use back to the classical formula Guizhi Fuling Wan, mentioned in the Synopsis of the Golden Chamber. Among its numerous applications, *Poria cocos* has been widely indicated in gynecological tumors [24]. In the past, it was also employed for conditions such as scrofula, throat ulcers, and toxin elimination [25]. Professor Lin Lizhu, a renowned TCM master, proposed that tumors are linked to impaired metabolism of body fluids, essence, and blood, which, over time, could lead to tumorigenesis. Based on this theory, he suggested that detoxifying remedies, such as *Poria cocos*, could provide therapeutic benefits [26]. While several case reports support its use in cancer therapy, more compelling evidence comes from *in vitro* investigations. Li *et al*. demonstrated that *Poria cocos* extract inhibited melanoma cell proliferation through the induction of c-kit-mediated apoptosis [27]. Similarly, raw *Poria cocos* extract induced cell cycle arrest in gastric and esophageal cancer cells,

leading to an accumulation of cells in the S phase and a consequent reduction in tumor invasiveness [28]. Wang *et al*. reported that in lung cancer cells treated with a combination of cisplatin and *Poria cocos*-derived astilbin, Bax expression and caspase-3 activation were upregulated, while Bcl-2 expression was downregulated, indicating enhanced apoptosis [29]. Another bioactive component, aiphanol, demonstrated anti-angiogenic properties by targeting VEGFR-2 and COX-2 [30]. Using a network pharmacology approach via the TCMSP database, Ma *et al*. identified COX-2, ESR1, and FOS as key targets in *Poria cocos*'s protective effects against breast cancer. These molecules are associated with poor prognosis and low survival rates in various cancers, suggesting that *Poria cocos* may exert tumor-suppressive effects through their modulation [31]. Supporting this in silico evaluation, experimental evidence demonstrated that *Poria cocos*-derived pachymic acid reduced COX-2 expression and induced cell cycle arrest in human ovarian carcinoma cell lines [32]. Further evidence of its anti-cancer potential was reported by Zheng *et al*., who found that *Poria cocos* inhibited gastric cancer cell growth, proliferation, invasion, migration, epithelial–mesenchymal transition, and promoted ferroptosis in both *in vitro* models and *in vivo* studies using C57BL/6 mice [33]. Beyond its anti-cancer properties, *Poria cocos* also exhibits neuroprotective effects. Zhang *et al*. reported that water-soluble polysaccharides from *Poria cocos* modulated the intestinal microbiota and increased serotonin, dopamine, norepinephrine, and GABA levels in a sleep-deprivation-induced anxiety rat model, ameliorating anxiety symptoms [34]. Given the high prevalence of anxiety among cancer patients, these neurological effects may offer additional therapeutic benefits. Finally, *Poria cocos* has shown promise in metabolic regulation. A meta-analysis and systematic review conducted by Di *et al*. highlighted its effectiveness in lowering fasting blood glucose levels, postprandial glucose levels, and glycated hemoglobin, suggesting potential applications in diabetes management [35].

云芝 (*Coriolus versicolor* (L. ex Fr.)), also known as Turkey Tail, is widely used in Traditional Chinese Medicine for treating jaundice, hypochondriac pain, inappetence, fatigue, and weakness. In the context of cancer therapy, numerous direct and indirect mechanisms have been attributed to *Coriolus versicolor*. Yang *et al*. reported that polysaccharide peptide (PSP), a key bioactive component isolated from *Coriolus versicolor*, promoted apoptosis in human leukemia HL-60 cells by reducing the Bcl-2/Bax ratio and increasing the expression and activity of caspase-3, caspase-8, and caspase-9 [36]. Similarly, Tang *et al*. demonstrated that PSP upregulated TNFR-1 expression in T lymphoblast Molt-4 cells, thereby enhancing TNFR-1-mediated apoptosis [37]. TNFR-1, through its interaction with TRADD domain proteins, facilitates the transduction of downstream apoptotic signals, ultimately leading to cell death. Beyond apoptosis, PSP has been shown to affect cell cycle progression. Chow *et al*. reported that PSP enhanced p21 gene transcription and reduced cyclin D1 expression, leading to cell cycle arrest at both the G1/S and G2/M transitions in breast cancer cells, effectively halting cell proliferation [38]. PSP also modulates early cell cycle transcription factors, such as AP-1 and EGR-1, while simultaneously downregulating the NF-κB signaling pathway, further contributing to its anti-tumor effects [39]. Similar to *Poria cocos*, *Coriolus versicolor* exhibits anti-angiogenic properties. Ho *et al*. observed that PSP inhibited VEGF expression in animal models, significantly reducing the formation of new blood vessels compared to control groups [40]. Additionally, PSP has been implicated in pyroptosis, a form of programmed cell death. It was found to increase pyroptotic event rates alongside elevated levels of procaspase-1, IL-18, and IL-1β. However, concerns have been raised that PSP-induced pyroptosis might have detrimental effects on patients, necessitating further research to clarify its clinical implications [41]. PSP also plays a role in immune modulation. It has been shown to enhance the TLR4/TIRAP/MAL/MyD88 signaling pathway response, leading to increased expression of these factors in macrophages, suggesting its potential as an immunotherapy adjuvant [42]. Additionally, PSP stimulates CD14+/CD16- monocytes, contributing to an improved anti-tumor immune response [43]. By modulating IL-6 signaling, PSP enhances natural killer cell activity. Through TLR modulation in T cells, it influences the p38 MAPK pathway, promoting T cell proliferation and pro-inflammatory cytokine release. Furthermore, PSP interacts with macrophages, augmenting phagocytosis and reactive oxygen species (ROS) production, while also mediating B lymphocyte activation, collectively exerting potent anti-proliferative effects [44].

灵芝 (*Ganoderma lucidum* (Leyss. ex Fr.) Karst.), commonly known as Reishi, is used in TCM to treat insomnia, restlessness, cough with phlegm, palpitations, and fatigue. In many Western countries, it is widely available as a nutritional supplement. A 2016 meta-analysis by Jin *et al*. revealed that combining *Ganoderma lucidum* with conventional chemotherapy or radiotherapy improved lung cancer treatment outcomes by 1.25 times compared to standard therapy alone [45]. Among its numerous bioactive compounds, several show promising anti-cancer properties. *Ganoderma* polysaccharides (GLPs), primarily homoglucans and glycans, exhibit notable bioactivity due to their structural conformation, though their biochemical composition may vary based on geographical origin, leading to different therapeutic outcomes. Fungal specimens rich in galactose have demonstrated anti-inflammatory effects, while those containing higher levels of glucose and mannose have been linked to anti-tumor activity. These sugars may interact with Toll-like receptors (TLRs), enhancing both the quality and quantity of immune responses [46]. Within polysaccharides, functional differences have also been observed: homopolysaccharides inhibit cancer cell growth via cyclin repression, whereas heteropolysaccharides enhance the antioxidant response. By simultaneously targeting cell proliferation and oxidative stress, *Ganoderma* may serve as a valuable adjunct in cancer therapy. Ganoderic acids (GAs), triterpenoids unique to *Ganoderma* species, have been shown to inhibit tumor proliferation, prevent metastasis, induce apoptosis, and regulate autophagy. Two key derivatives, GA-A and GA-B, have demonstrated potential as complementary treatments in gastric cancer. *In vitro* studies using HepG2 cells found that GA-A significantly reduced cancer cell migration and invasiveness ($p<0.01$). When co-administered with cisplatin, GA-A enhanced cancer cell death by inhibiting JAK signaling. Similarly, oxaliplatin exhibited increased tumor-suppressing effects in a xenograft model pre-treated with GA-A. Notably, GA-A also enhanced T-cell cytotoxic activity, highlighting its multi-target nature. GA-B, on the

other hand, increased the sensitivity of cancer cells to doxorubicin, paclitaxel, and vinblastine in *in vitro* settings. Clinical evidence supports these *in vitro* findings. In patients with colorectal cancer, 12 weeks of *Ganoderma* extract supplementation improved cachexia symptoms. Additionally, in individuals with gastrointestinal cancer, *Ganoderma* extract capsules, when combined with conventional therapy, enhanced immune response and overall quality of life. A 12-month study in patients with adenomas found that daily administration of *Ganoderma* culture medium extract (1.5 g/day) resulted in a reduction in both adenoma size and total count [47]. In prostate cancer cells, exposure to 2 mg/mL of *Ganoderma* extract for one to three days led to dose- and time-dependent reductions in cancer cell viability, migration, and invasiveness, alongside increased apoptosis [48]. Mechanistically, this effect was attributed to the inhibition of metalloproteinases, key enzymes involved in prostate cancer progression. Rahimnia *et al*. further reported that *Ganoderma* extract, when combined with docetaxel and flutamide, enhanced apoptosis, reduced migration, and increased tumor cell sensitivity to chemotherapy [49]. Similar effects were observed in ovarian cancer cells, where Dai *et al*. demonstrated that *Ganoderma* extract reduced tumor growth, downregulated VEGF, and upregulated Cx43. Given that VEGF promotes angiogenesis and Cx43 is associated with tumor suppression, these findings suggest that *Ganoderma* may exert anti-cancer effects by limiting vascularization while enhancing tumor-suppressive pathways [50].

鸟巢菌 (*Cyathus stercoreus* (Schw.) de Toni [*Nidularia stercorea* Schw.]) and *Cyathus striatus* (Huds. ex Pers.) Willd. [*Peziza striata* Huds.] are comparatively less studied in the context of anti-cancer therapy. However, preliminary research suggests they possess notable bioactive properties. *Cyathus stercoreus* has demonstrated antibacterial activity against *Staphylococcus aureus*, while *Cyathus* extracts have exhibited cytotoxic effects on breast and liver cancer cells, as observed by Chen *et al*. [51]. In a 2008 study, Kang *et al*. reported the radical-scavenging activity of cyathuscavins A, B, and C, compounds isolated from *Cyathus* cultures [52]. Notably, two other compounds, 15-O-acetylcyathatriol and 11-O-acetylcyathatriol, displayed even stronger anti-cancer effects, suppressing the proliferation of multiple cancer cell lines, including breast, gastric, cervical, colorectal, lung, prostate, and liver cancers. Additionally, cyathin-R was found to promote apoptosis via voltage-dependent anion channel 1 release [53]. Regarding *Cyathus striatus*, Sharvit *et al*. observed time- and dose-dependent inhibition of growth in HPAF-II and PL45 pancreatic cancer cells, accompanied by the activation of caspase-8, -3, and -9, indicating apoptosis induction. Differential expression analysis further highlighted the upregulation of apoptosis-related genes, with COX-2, JUN, and HMOX1 being the most significantly affected. *In vivo*, tumor growth inhibition was observed in animal models administered *Cyathus* extract [54]. Among the many bioactive components identified, striatal was noted as a potent pro-apoptotic agent. Fares *et al*. reported that a fraction containing striatal C exhibited stronger cancer cell growth inhibition than the complete mushroom extract in human pancreatic cancer cell lines. Similarly, cell cycle arrest and apoptosis induction were more pronounced in the fraction compared to the whole extract, suggesting that striatal C may be the key active component driving *Cyathus*' anti-cancer effects [55].

裂褶菌 (*Schizophyllum commune* Fr.), known as "树花" in TCM, is traditionally used to treat fatigue and debilitation. Animal studies have shown that tumor-bearing mice undergoing cyclophosphamide chemotherapy and treated with intracellular and extracellular mushroom polysaccharides at low, medium, and high doses for 10 days exhibited improved thymus and spleen function. The immune system of these mice was enhanced, resulting in a better response to chemotherapy [56]. The fruiting body of *Schizophyllum commune* contains polysaccharides rich in mannose, glucose, galactose, fucose, arabinose, xylose, rhamnose, glucosamine hydrochloride, and aminogalactose hydrochloride, all of which have been associated with notable anti-cancer activity. Zheng *et al*. reported glioma cell growth inhibition both *in vivo* and *in vitro*, as well as xenograft tumor growth inhibition and migration reduction, along with increased pro-apoptotic signals upon treatment with fungal polysaccharides. To date, no toxic effects have been observed in animal models, though further safety evaluations are necessary. The mechanism of action suggests that the polysaccharides reduce activation of the PI3K/AKT signaling pathway, which is crucial for tumor progression. Additionally, they help maintain intestinal architecture and limit pro-inflammatory mediator infiltration in the ileum. In terms of gut microbiome diversity, the treatment reduced the abundance of Verrucomicrobiota and Bacteroidetes, and the improvement of beneficial bacteria was correlated with the observed anti-cancer effects [57]. Further studies on *Schizophyllum commune* crude extract have shown mixed results. Menakongka *et al*. tested water and ethanol extracts on a human cholangiocarcinoma cell line. While the water extract had no effect on cancer cell proliferation, the ethanol extract significantly reduced cell proliferation at a dose of 200 µg/ml. Both extracts reduced cancer cell migration in wound healing assays, with the ethanol extract showing less effectiveness. Neither extract caused cytotoxicity [58]. Positive results were also reported in HeLa, MCF7, T47D, and WiDr cell lines. Ekowati *et al*. found that a chloroform extract of the fungus was effective in inhibiting growth in breast cancer cells, with cells showing increased sensitivity to the fungal bioactive components. The ethyl acetate extract also exhibited cytotoxicity, but with higher IC50 values compared to the chloroform extract. Both extracts showed a dose-dependent effect, with concentrated preparations yielding better results. The primary mechanism of cancer cell death was identified as apoptosis [59].

头状秃马勃 (*Calvatia craniiformis* Schw. Fries) is less commonly prescribed by TCM practitioners compared to the previously mentioned fungi, but it is known to treat inflammation, promote muscle health, and alleviate pain and swelling. Its prominent bioactive component, calvatic acid, exhibits both antibacterial and anticancer properties. Gadoni *et al*. reported that calvatic acid, along with its analogues, inhibited GTP-induced microtubule protein polymerization. Since tubulin polymerization is essential for cancer development, calvatic acid could act as a cytotoxic agent targeting tumors [60]. *Calvatia gigantea* (大秃马勃), another edible mushroom from the *Calvatia* genus, also demonstrates anti-tumor properties. Extracts from this fungus effectively reduced cell viability in A549 lung cancer

cell lines, decreasing the expression of CCND1, CCND2, CDK4, and Akt. Western blot analysis further confirmed the upregulation of pro-apoptotic genes in the intervention group after 72 hours of incubation with the fungal extract. These alterations resulted in changes to the cell cycle, leading to arrested transitions and apoptosis activation via mitochondrial dysfunction [61]. Additionally, animal models transfected with murine hepatocellular carcinoma cells and treated with water or ethanol extracts of *Calvatia craniiformis* showed caspase-8 overexpression and significant tumor reduction. A dose-dependent effect was observed in both water- and ethanol-treated subjects. The authors speculated that the beneficial effects could be attributed to the β-D-glucan, a compound that can regulate oncoprotein gene expression by acting at the DNA polymerase level [62]. β-glucan also enhances immune system activity by boosting macrophage and granulocyte function. In line with this, Jameel and colleagues reported that an alcoholic gallic acid extract of *Calvatia* promoted tumor size reduction and slowed tumor progression in a dose-dependent manner [63].

桑黄 (*Phellinus igniarius* (L. ex Fr.) Quel.) [formerly *Fomes igniarius* (L.) Fr.; *Boletus igniarius* L.; *Polyporus igniarius* Fr.] is widely used in Traditional Chinese Medicine to treat various types of bleeding and diarrhea. While it is available as a phytotherapy supplement in Western countries, in China, it is commonly found in TCM formulations and is recognized for its anti-cancer properties. Yang *et al*. reported that an extract of *Phellinus* administered to murine sarcoma-bearing mice significantly reduced tumor burden and stimulated the immune system, resulting in extended lifespan of the animals [64]. The ethanolic extract from the fruiting body was shown to inhibit the proliferation of hepatocarcinoma SK-Hep-1 cells and exhibited synergistic effects with chemotherapy agents, such as oxaliplatin and 5-fluorouracil. The extract also hindered cell tube formation, suggesting its anti-angiogenic activity. Moreover, it reduced cancer cell migration and invasion *in vitro*, while MMP-2 expression decreased in a dose-dependent manner. The fungus also reduced VEGF expression, further confirming its anti-angiogenic effects. MMP-2 is crucial for cancer cell migration due to its collagen-degrading function, while VEGF plays a key role in metastasis initiation [65]. Thus, by reducing both MMP-2 and VEGF, *Phellinus* appears to counteract tumor expansion and inhibit growth. Shon and Nam observed that a water extract of *Phellinus* prevented mutagenesis induced by common mutagens like 4-nitro-o-phenylenediamine and sodium azide in *Salmonella* strains. The extract was reported to elevate quinone reductase activity, glutathione S-transferase activity, and glutathione levels, confirming its ability to stimulate natural anti-cancer mechanisms [66]. Li and colleagues purified *Phellinus* polysaccharides and reported growth inhibition in HepG2 and SW480 cell lines exposed to the extract, with compound IPSW-1 showing the highest inhibition rate [67]. Among the bioactive components, hispolon was found to promote apoptosis in human gastric cancer SGC-7901 cells in a dose- and time-dependent manner. This was accompanied by growth inhibition, pro-apoptotic caspase activation (particularly caspase-3), and upregulation of caspase-8 and caspase-9, suggesting mitochondrial-dependent apoptosis. MMP-2 reduction and cytochrome-C release further supported this mechanism. Additionally, ROS levels increased in treated cancer cells, with H_2O_2 accumulation. It was hypothesized that the GSH-dependent antioxidant system could not cope with the ROS accumulation induced by hispolon. Furthermore, hispolon enhanced the cytotoxicity of mitomycin, 5-fluorouracil, and doxorubicin [68]. Wang *et al*. confirmed that *Phellinus* ethanolic extract prompted cytoplasmic shrinkage, chromatin condensation, cell cycle arrest, loss of mitochondrial membrane potential, increased pro-apoptotic Bax expression, and decreased anti-apoptotic Bcl-2 expression, ultimately leading to apoptosis in gastric cancer SGC-7901 cells [69]. Gao and colleagues observed that tumor-bearing H22 mice injected with *Phellinus* polysaccharides showed tumor reduction compared to the saline control group. Interestingly, when administered with cyclophosphamide, the polysaccharide extract decreased the chemotherapeutic toxicity, suggesting potential use as a preventive measure against chemotherapy-related side effects. The spleen index of the animals increased, particularly in the group exposed to *Phellinus* from Gansu province. This effect was especially notable given that cyclophosphamide typically causes spleen alterations and immune system suppression. Mechanistically, elevated levels of IL-2, IL-12, and IFN-γ were observed upon treatment, indicating enhanced activation of natural killer cells and T-cells. These cytokines were also elevated in the combined polysaccharide-chemotherapy treatment, but no direct cytotoxicity was observed. This suggests that *Phellinus* polysaccharides primarily act by stimulating the immune system and possibly mitigating cyclophosphamide-induced immune depression [70].

假蜜环菌 (*Armillaria mellea* (Vahl) P. Kumm.), also known as honey mushroom, is commonly used in Traditional Chinese Medicine to treat pain, headache, insomnia, joint numbness, back and limb pain, hypertension, vascular headaches, dizziness, and epilepsy. A preliminary trial evaluating *Armillaria* polysaccharides in patients with lung cancer showed promising results. Patients in the intervention group, who received *Armillaria* polysaccharides alongside docetaxel therapy, exhibited elevated activities of SOD, GSH-Px, and GSH, along with reduced MDA levels. These findings suggested general anti-inflammatory effects of the polysaccharide mix in lung cancer patients [71]. *In vitro* studies by Chen *et al*. reported that a component of *Armillaria*, armillarikin, inhibited cell growth in hepatocellular carcinoma cells, altered cell morphology, caused loss of mitochondrial transmembrane potential, and stimulated caspase-mediated cell death. ROS-mediated cell death was also hypothesized and confirmed as part of the cytotoxic mechanism [72]. Further research demonstrated the benefits of armillarikin in human acute myeloid leukemia and chronic myeloid leukemia cell lines, where it inhibited cell growth, induced apoptosis, decreased mitochondrial potential, and activated caspases-8, -9, and -3 [73]. Yin *et al*. identified two potential cytotoxic candidates, sesquiterpenes isolated from the fungal culture broth of *Armillaria*, namely 10-dehydroxy-melleoliede B and 1-O-formyl-10-dehydroxy-melleoliede B. These compounds exhibited moderate cytotoxicity against breast, hepatocellular carcinoma, myeloid leukemia, colon, and lung cancer cell lines [74]. Another component, armillaridin, was studied by Chi and colleagues, who found that it reduced cell viability, promoted chromatin condensation, induced apoptotic body formation, hyperactivated caspase-3, decreased mitochondrial transmembrane potential, and caused

hypoploid cell formation in human squamous cell carcinoma and adenocarcinoma cell lines. Tumor growth was also inhibited in xenograft Balb/c nude mice. Furthermore, armillaridin was reported to act as a radiosensitizer *in vitro* [75]. Cytotoxicity in *Armillaria* has also been attributed to its melleolide fraction, which possesses antibiotic properties. Structure-activity relationship studies have shown that cytotoxicity is linked to the degree of hydroxylation of the sesquiterpene moiety, which is essential for its elevated cytotoxic ability [76]. Additionally, *Armillaria* polysaccharides have been shown to exhibit anti-cancer, anti-diabetic, and anti-oxidant activities in gastric, colon, and lung cancer cell lines [77]. Misiek *et al*. confirmed that elevated activity of caspase-3 and DNA fragmentation contributed to reduced cell viability in human intestinal cancer, breast adenocarcinoma, and leukemia cell lines [78].

安络小皮伞 (*Marasmiellus androsaceus* (L.:Fr.) Fr.), exhibits healing properties for joint pain, trauma, trigeminal neuralgia, and rheumatoid arthritis. Its anti-inflammatory activities have been extensively studied, with Zhao *et al*. demonstrating that it ameliorates chronic sciatic nerve compression hypersensitivity and thermal hypersensitivity in mice through the downregulation of inflammatory cytokines such as TNF-α and IL-1β [79]. However, its anti-cancer properties have been less explored. A study by Tianjin Nankai University found that *Marasmiellus* extract mitigated radiotherapy-induced intestinal toxicity. Radiotherapy is commonly associated with tissue injury, and depression is a frequent concern in cancer patients. Depressed individuals are believed to have an increased risk of radiation-related intestinal injury. Based on this, Chinese researchers assessed the ability of *Marasmiellus* to alleviate depression in animals, referencing prior studies confirming the fungus's ability to modulate mood swings. Depressed mice exhibited prolonged immobility, intestinal inflammation, and upregulated pro-inflammatory cytokines, along with reduced expression of Glut1, a factor essential for maintaining intestinal integrity. When Glut1 expression is downregulated, it can exacerbate pathology. Additionally, intestinal villi and goblet cells were reduced in these animals. For two weeks following irradiation, mice in the intervention group were given *Marasmiellus* mycelium suspension. These treated subjects exhibited fewer depression-related signs, longer colon length, reduced incidence of radiation enteritis, and improved intestinal epithelium integrity compared to the control group [80]. However, no positive effects were observed in non-depressed mice exposed to radiation and given the same intervention. Further analysis revealed differences in hippocampal miRNA expression between irradiated animals treated with the fungus and those untreated. The disruption observed in the miRNA pool was somewhat mitigated by the intervention, with modulation of miR-139–5p and miR-184–3p expression identified as the primary mechanism for depression amelioration. Therefore, by preventing hippocampal miRNA disruption, *Marasmiellus* may reduce depression and protect against radiotherapy-induced intestinal injury. In addition to its anti-inflammatory effects, *Marasmiellus* polysaccharides also exhibit anti-fatigue properties [81] and analgesic effects, possibly through increased serum 5-HT levels [82]. Similarly, a heteropolysaccharide extracted from *Marasmiellus palmivorus* (MFPS1) has shown promising anti-cancer activity. *In vitro*, MFPS1 exhibited cytotoxic effects when co-cultured with cancer cells and PBMC cells, though no cytotoxicity was observed in PBMC cells or directly on cancer cells. However, an increase in INF-γ and IL-12 was observed, suggesting enhanced immune surveillance and the activation of anti-cancer mechanisms. MFPS1 also stimulated IL-6 and TNF-α production, engaging CD4+ and CD8+ cells, leading to cancer cell death [83].

槐栓菌 (*Auricularia auricula* (L.:Fr.) Underw.), commonly known as Judas' ear, is used in Traditional Chinese Medicine to treat hemorrhoidal bleeding, vaginal discharge, gynecological disturbances, and to strengthen the body. Numerous clinical trials support its therapeutic benefits. For example, in patients with liver cancer who underwent laparoscopic hepatectomy, co-administration of *Auricularia* granules with lenvatinib monotherapy resulted in a lower recurrence rate of metastasis (8.51% vs. 25.53%), which was statistically significant. Furthermore, levels of C-reactive protein, IL-1, IL-6, and TNF-α were reduced, indicating improved immune response and reduced inflammation and metastasis incidence [78]. In another randomized controlled trial involving 80 liver cancer patients, fungal granules were shown to increase miR-429 expression and decrease TRAF6, enhancing tumor sensitivity to transarterial chemoembolization (TACE). The total effective rate in the intervention group (fungal extract + TACE) was 95%, compared to 80% in the control group, which received sorafenib tosylate capsules combined with TACE [79]. A study conducted between 2020 and 2022 at Chengdu Sixth People's Hospital assessed the effects of *Auricularia* in non-small cell lung carcinoma patients. The intervention group received gemcitabine and cisplatin combined with fungal capsules, while the control group received the same regimen without the fungi. The results showed a higher remission rate in the fungal group. Additionally, Th1 and Th1/Th2 ratios were elevated in the intervention group, while Th2 was higher in the control. Tumor markers, including cancer antigen-125, carcinoembryonic antigen, and cytokeratin fragment-21, were downregulated in the intervention group, suggesting a potential therapeutic effect in non-small cell lung carcinoma [80]. In a trial involving 60 patients with advanced triple-negative breast cancer, the intervention group received fungal granules in addition to fluorouracil, epirubicin, and cyclophosphamide. The objective response rate and disease control rate were higher in the intervention group, and VEGF levels were significantly reduced, indicating potential anti-cancer and anti-angiogenic activity of the fungus [81]. *In vitro* studies on human gastric cancer cell lines (HGC-27, MGC-803) treated with *Auricularia* supernatant showed reduced cell viability, colony formation, and migration in a dose- and time-dependent manner. Apoptosis rates were 62.13% and 54.50% for each cell subtype, with upregulation of apoptotic signals, further confirming the anti-cancer activity of the fungal extract [82]. Similarly, in hepatocellular carcinoma cell lines, the *Auricularia* intervention decreased cell viability, induced DNA damage, and increased apoptosis through the PARP and caspase pathways. Anti-oxidant activity was also reduced, as indicated by lower SOD activation. Pro-apoptotic factors, including caspase-3, Bak, Bid, and Bik, were upregulated, while Bcl-xl and Akt, which inhibit caspase activity through cytochrome-C induction, were downregulated, further confirming the pro-apoptotic effects [83]. Lectins, bioactive compounds in *Auricularia*, exhibit anti-tumor and anti-microbial activities.

Liu *et al*. evaluated the properties of *Auricularia* lectins using lung cancer cell lines and found reduced cell growth in a dose- and time-dependent manner. RNA sequencing revealed 350 differentially expressed genes between treated and untreated cells, with KEGG and GO analyses highlighting enriched pathways such as Toll-like receptor signaling, NF-κB signaling, the PD-1 pathway in cancer, and the MAPK signaling pathway. Key factors, including JUN, TLR4, and MYD88, were elevated in untreated cancer cells but downregulated in treated specimens. *In vivo* experiments in mice showed that *Auricularia* treatment regulated pulmonary flora, leading to changes in bacterial abundance and diversity, suggesting a reduced ability for pathogenic bacteria to colonize the lungs [84]. Finally, Shahar *et al*. reported that *Auricularia* ethyl acetate extract inhibits TrkB activity. The Trk family, involved in the PI3K, RAS/MAPK, and ERK signaling pathways, is frequently dysregulated in cancers. Trk inhibitors such as *Auricularia* are therefore proposed as a natural source of novel anti-cancer drugs [85].

Conclusion

Edible fungi from the TCM compendium manifest anti-apoptotic, anti-angiogenesis, and immunomodulatory activity *in vitro* and *in vivo*. Randomized trials have also confirmed the validity of their integration in various conditions. Given the richness of bioactive components, edible mushrooms hold significant potential in cancer therapy. However, there is still much to explore, particularly in identifying novel active principles and understanding their precise mechanisms of action. Future research should focus on in-depth clinical trials to confirm these initial findings and establish standardized dosing regimens. Additionally, exploring synergistic effects with other conventional or alternative therapies could open new avenues for integrative cancer treatment. As the field progresses, the potential for edible fungi to serve as complementary agents in cancer management becomes increasingly promising.

Abbreviations

Ganoderic acid (GA), Ganoderma polysaccharides (GLPs), Hypocrellin A (HCA), Natural Killer (NK) cells, Polysaccharide peptide (PSP), Reactive oxygen species (ROS), Transarterial chemoembolization (TACE), Traditional Chinese Medicine (TCM), Toll-like receptor (TLR), Tumor necrosis factor receptor (TNFR), Vascular endothelial growth factor (VEGF).

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Dal Pozzo Lisa and Scarsella Secondo: Contributed to the study conception, writing, and revision of the manuscript.
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