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The role of edible mushrooms in health: Evaluation of the evidence

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ABSTRACT

There have been relatively few direct intervention trials of mushroom consumption in humans, although those that have been completed to date indicate that mushrooms and their extracts are generally well-tolerated with few, if any, side-effects. Immunomodulating and anti-tumor effects of mushrooms and their extracts appear to hold potential health benefits. These benefits are primarily due to their polysaccharide content, either in the form of beta-glucans or polysaccharide-protein complexes, which appear to exert their anti-tumorigenic effects by enhancement of cellular immunity via effects on the balance of T helper cell populations and induction of certain interleukins and interferon (IFN)-γ. This review summarizes the current knowledge on edible mushrooms and their components on health outcomes, with a focus on the evaluation of the evidence from human trials. Where information is available from such trials, the active compounds are identified and their proposed mechanisms are discussed.

Contents

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1. Introduction

Alongside the mushrooms' long history as a food source is an equally long history of beliefs about their curative abilities in traditional medicine systems—both the folk medicine of the western world and traditional medicine of the orient. Although there are limited direct human intervention trials, there is a rapidly growing volume of *in vitro* and *in vivo* animal trials describing a range of possible health benefits including immunomodulatory, anti-tumor, anti-microbial effects and hypocholesterolemic effects.

Some of the more efficacious compounds in mushrooms are 1,6-branched 1,3-β-glucans which have been reported to inhibit tumor growth by stimulating the immune system via activation of macrophages, via balance of T helper cell populations and subsequent effects on natural killer (NK), cells and also via cytokine production (Hetland, Johnson, Lyberg, & Kvalheim, 2011). Other work has implicated polysaccharides with varying sugars such as beta- and alpha-glucans. (Borchers, Krishnamurthy, Keen, Meyers, & Gershwin, 2008). Such mushroom polysaccharides are beginning to be evaluated as adjuvant cancer therapy compounds alongside conventional cancer treatments (Standish et al., 2008).

The mechanisms by which these polysaccharides exert their immunomodulatory effects are not entirely clear, although structure–function relationships have been described between anti-tumor activities and structural characteristics of β-D-glucans, these mushroom polysaccharides generally do not exert cytotoxic effects on tumor cells, but have been shown to enhance host-mediated immunomodulatory responses (reviewed by Wong, Lai, & Cheung, 2011).

A recent systematic review has also provided evidence for immunomodulatory effects (increased NK cell activity, effects on IgG, IgM, neutrophil and leukocyte counts) in humans from oral ingestion of dietary polysaccharides (glucans) from some varieties of mushrooms (Ramberg, Nelson, & Sinnott, 2010), while inhibition of aromatase activity by mushroom extracts (Grube, Eng, Kao, Kwon, & Chen, 2001; Chen et al., 2006) and subsequent reduction of estrogen, is a potential adjuvant therapy for breast cancer patients with estrogen receptor positive tumors. While the effects and underlying mechanisms of mushroom polysaccharides in health outcomes have been more extensively evaluated, bioactive proteins from mushrooms (such as lectins, fungal immunomodulatory proteins (FIP), ribosome inactivating proteins (RIP), ribonucleases and other proteins have also been reported to possess similar anti-tumor, anti-viral and immunomodulatory activities (reviewed by Xu, Yan, Chen, & Zhang, 2011).

This review evaluates published human trials on mushroom consumption and health outcomes in order to identify the levels of evidence, and to identify areas where future human dietary intervention trials are warranted to substantiate the potential effects of mushroom consumption on human health outcomes. While the review focusses on human studies, animal and *in vitro* studies that provide lower levels of evidence are also discussed, particularly where they provide insights into cellular mechanisms.

2. Studies in humans

The properties and mechanisms of extracts and bioactive compounds from mushrooms that have been evaluated in a human population or human cell lines are outlined in Table 1. The human trials carried out to date have primarily been smaller observational studies, or studies without appropriate placebo or other matched controls, and therefore larger, double-blind, placebo controlled human studies are required before clear effects on human health outcomes can be substantiated. In general, the growing data suggest that the mushrooms and mushroom extracts tested are safe and generally well-tolerated. The most promising data appear to be those indicating an inverse relationship between mushroom consumption and breast cancer risk, although the data are based on food frequency/diet recalls, which can be affected by recall bias, and therefore, the effects need to be confirmed via intervention trials involving mushroom consumption.

Table 1 – Properties and mechanisms of bioactive compounds and mushroom extracts evaluated in a human population or human cell lines.

Effect/disease state	Bioactive or extract	Mushroom variety	Mechanism (*in vitro*/*in vivo*)	Reference
Anti-cancer (breast)	Ergosterol	Unspecified variety	Increase serum 25 (OH) vitamin D2 levels (*in vivo-humans*)	Furlanetto (2009)
	Aqueous extracts	*Agaricus bisporus*	Suppress aromatase activity and proliferation of MCF-7aro cells-hence suggesting a reduction in estrogen production (*breast cancer cell lines*)	Grube et al. (2001)
	Hydroxylated triterpenes	Multiple varieties	Downregulation of Akt/NF-kappaB signaling	Jiang et al. (2008)
	Polysaccharopeptides	*Ganerderma lucidum*	Apoptosis (*human cell lines*) Suppress oxidative stress stimulated phosphorylation of Erk1/2 resulting in downregulation of expression of c-fos and inhibition of transcription factors AP-1 and NF-kappaB	Wan et al. (2008), Thyagarajan et al. (2006)
Anti-cancer (colorectal)	Polysaccharide K (PSK) (in adjunct with immuno-chemotherapy)	*Coriolus versicolor* CM-10	Stimulate both innate and adaptive immune pathways in curatively resected colorectal cancer (*in vivo*)	Oba et al. (2007), Sakamoto et al. (2006)
	Unspecified bioactive/ extract	*Agaricus sylvaticus*	Benefits in hematological and immunological parameters & reduction in glycemic levels (*in vivo*)	Fortes et al. (2009)
	Lectin	*Agarius bisporus* (ABL)	Inhibit the proliferation of HT29 human colonic cells (*in vitro* -in human cells)	Yu et al. (1993)
	Unspecified bioactive/ extract	*Ganoderma lucidum*	Apoptosis (induced by increase in caspase-3 activity) & Anti-inflammatory function in HT-29 in human carcinoma cells (no toxicity in HT-29 cells in doses <10 mg/ml) (*in vivo*)	Hong et al. (2004)
	Aqueous extract	*Inonotus obliquus*	Apoptosis and inhibition of the growth of HT-29 colonic cancer cells via up-regulation of expression of pro-apoptotic proteins and down-regulation of anti-apoptotic proteins	Lee et al. (2009b)
Anti- cancer (cervical, ovarian, endometrial)	Unspecified extract	*Agaricus blazei* Murill Kyowa (AbMK)	Increase activity of natural killer cells Improve chemotherapy side effects (e.g. appetite, alopecia, emotional stability & general weakness) (*in vivo* undergoing chemotherapy)	Ahn et al. (2004)
	Lingzi Lentinan Clitocinet	*Ganoderma lucidium* *Lentinus edodes* *Leucopaxillus giganteus*	Anti-proliferative effects via induction of apoptosis	Chen et al. (2010), Liu et al. (2009), Ren et al. (2008)
Anti-cancer (gastric)	Polysaccharide K Lentinan (in adjunct with immuno-chemotherapy)	*Lentinus edodes*	Prolong survival; more effective in patients with lymph-node metastasis vs. non- node metastasis (*in vivo*)	Oba et al. (2009)
Anti-cancer (prostate)	Ethanol extract of whole mushroom	*Ganoderma lucidum*	Dose extract 6 mg per day improve the total International Prostate Symptom Score (IPSS) of men with lower urinary tract symptoms via strong 5-alphal-reductase inhibitory activity (*in vivo*)	Noguchi et al. (2008a, 2008b)
	Unspecified bioactive/ extract	*Ganoderma lucidum*	Inhibit proliferation and induce apoptosis in PC-3 human prostate cancer cells. Inhibition of prostate cancer-dependent angiogenesis is suggested to be due to modulation of MAPK and Akt signaling	Jiang et al. (2004b), Stanley et al. (2005)

(*continued on next page*)

Table 1 – (continued)

Effect/disease state	Bioactive or extract	Mushroom variety	Mechanism (*in vitro*/*in vivo*)	Reference
Anti-cancer (pancreatic – advanced solid malignancy)	Irofulven (cytotoxin)	*Omphalotus olearius*. Note: Not an edible mushroom	Daily dose of 10.64 mg/m2 as a 5 min i.v. infusion for 5 days every 4 weeks resulted in anti-tumor activity; and intermittent dosing schedules had positive pre-clinical anti-tumor effects (*in vivo*)	Eckhardt et al. (2000)
Immuno-modulation: (post-menopausal breast cancer)	Polysaccharide extract	*Grifola frondosa*	Immunologically stimulatory and inhibitory measurable effects in peripheral blood of patients free of disease after 1st treatment (*in vivo*)	Deng et al. (2009)
Immuno-modulation: (healthy volunteers)	Andosan™	*Agaricus blazei* Murill (AbM) (Himematsutake) 82% *Hericiums erinaceum* (Yamabushitake) 14.7% *Grifolia frondosa* 2.9%	Stimulation of whole blood *ex vivo* with 0.5–5.0% of extract containing AbM produced a dose-dependent increase in all cytokines studied from 2 to 399-fold (TNF-α). *In vivo* there was a significant reduction in levels of IL-1-β (97%), TNF-α (84%), IL-17 (50%) and IL-2 (46%). Discrepancy in results associated with antioxidant activity of AbM *in vivo* and limited absorption of its large beta-glucans across the intestinal mucosa to the reticuloendothelial system and blood.	Johnson et al. (2009)
Immuno-modulation (mild hypercholesterolemia)	Alpha-glucans	*Agaricus bisporus*	Consumption of fruit juice enriched with 5 g glucans/ day lowered lipopolysaccharide-induced TNFα production by 69%. No effects on IL-1β and IL-6 and decreased production of IL-12 and IL-10 was observed (*in vivo*). Contrarily alpha glucans has been observed to stimulate immune response in an *in vitro* mouse model.	Volman et al. (2010a)
Immuno-modulation (cancer)	Glucan	*Trametes versicolor*	Improved survival and immune function (*in vivo*)	Ramberg et al. (2010)
Immuno-modulation (variety of disease states)	Various mushroom bioactive(s)/extract(s)	Multiple variety	Effects on natural killer cells, macrophages, T cells and their cytokine production; and via the activation of Mitogen Activated Protein Kinase (MAPK) pathways	Kim et al. (2007)
Diabetes (type II)	AbM extract (in combination with metformain and gliclazide)	*Agaricus blazei* Murill (AbM)	Improve insulin resistance potentially by the mechanism that caused an increase in adiponectin concentration after taking the extract for 12 weeks (*in vivo*)	Hsu et al. (2007)
Cardiovascular disease (biomarkers)	Unspecified bioactive/ extract	*Pleurotus ostreatus* (Oyster Mushroom)	Significant reduction in systolic and diastolic blood pressure, blood glucose, total cholesterol and triglycerides (*in vivo*)	Khatun et al. (2007)
	Protein-bound polysaccharides (A-PBP and L-PBP)	*Agaricus blazei* *Lentinus edodes*	Weight-controlling and hypolipidemic effect via a mechanism involving absorption of cholesterol (*in vivo*)	Kweon et al. (2002)

Table 1 – (continued)

Effect/disease state	Bioactive or extract	Mushroom variety	Mechanism (*in vitro*/*in vivo*)	Reference
Brain health and cognition	Unspecified bioactive/extract	*Hericium erinaceus* (Yamabushitake)	Increase in scores on cognitive function scales in men and women diagnosed with mild cognitive impairment (*in vivo*)	Mori et al. (2009)
	Dilinoleoyl-phosphatidylethanolamine (DLPE)	*Hericium erinacium*	Protect against neuronal cell death caused by beta-amyloid peptide (A beta) toxicity, endoplasmic reticulum (ER) stress and oxidative stressImproves the Functional Independence Measure (FIM) score or retard disease progression in patients with dementia (*in vivo*)	Kawagishi and Zhuang (2008)
	Hericenones C to H; Erinacines A to I	*Hericium erinacium*	Induce synthesis of nerve growth factor (NGF) (*in vitro* and *in vivo*)	Kawagishi and Zhuang (2008)
Hepatitis B		*Agarius blazei* Murill (AbM)	Decrease levels aspartate aminotransferase and alanine aminotransferase, hence normalizing liver function of patients with Hepatitis B (*in vivo*).To be noted: results based on a sample of four patients thus larger and controlled studies are required to confirm the effects.	Hsu et al. (2008a)
	Ganopoly®	*Ganoderma lucidum*	Hypoglycemic activity, anti-viral and liver protective effects in chronic hepatitis B (*in vivo*). To be noted: authors indicated despite pharmacological activities, clinical proof is lacking.	Zhou et al. (2005)
Anti-viral (HIV)	1. Farnesyl hydroquinone, ganomycin I 2. Ganomycin B	*Ganoderma colossum*	Competitive inhibition of the HIV-1 protease enzyme by ganomycin B and docking with the HIV-1 protease crystal structure by both compounds	El Dine et al. (2009)
Anti-viral (poliomyelitis)	Polysaccharides	*Agarius brasiliensis* (previously *Agarius blazei ss* Heinem)	Anti-viral activity when added during poliovirus infection: potentially acting at the initial stage of viral replication	Faccin et al. (2007)
Asthma	Unspecified bioactive extract	Cordyceps (unspecified variety)	Inhibit proliferation and differentiation of Th2 cells and reduce the expression of cytokines by down-regulating the expression of GATA-3 mRNA and up-regulating the expression of Foxp3 mRNA in peripheral blood mononuclear cells. Alleviate chronic allergic inflammation by increasing the level of interleukin-10 (*in vivo*)	Sun et al. (2010)
Constipation	Fiber	*Auricularia* (ear mushrooms)	Fiber supplements using ear mushrooms improve constipation related symptoms without serious side effects (*in vivo*)	Kim et al. (2004)

Table 2 – Properties and mechanisms of bioactive compounds and mushroom extracts evaluated in animal models or animal cell lines.

Effect/disease state	Bioactive or extract	Mushroom variety	MECHANISM (*in vitro*/ *in vivo*)	Reference
Anti-cancer (bladder)	Maitake mushroom D fraction (in combination with interferon-alpha 2b)	*Grifola frondosa*	Reduce growth in T24 bladder cancer cells potentially by triggering double-stranded DNA-dependent protein kinase activation that may act on the cell cycle to cease cancer cell growth (*in vitro*)	Louie et al. (2010)
	Cordycepin (3′-deoxyadenosine)	*Cordyceps militaris*	Inhibit growth during cell-cycle progression of 5637 and T-24 bladder cancer cells largely due to G2/M-phase arrest (*in vitro*)	Lee et al. (2009c)
Anti-cancer (leukemia)	Agaritine	*Agaricus blazei* Murill	Inhibit proliferation of leukemic tumor cell lines (e.g. U937, MOLT4,HL60, K562)	Endo et al. (2010)
	Various unspecified bioactives/extracts	*Agaricus bisporus*; *Agaricus blazei*; *Hypsizigus marmoreus*; other unspecified varieties	Inhibit proliferation of HL-60 leukemia cells & other leukemia human cell lines via induction of apoptosis. Exhibit tumor-selective cytotoxicity with no significant cytotoxic effects on normal cell lines (*in vitro*)	Gao et al. (2007), Jin et al. (2007), Bae et al. (2009), Mizumoto et al. (2008), Hsu et al. (2008b), Calvino et al. (2010), Lau et al. (2004)
Anti-cancer (liver)	1. Triterpenoids 2. Hyper-branched beta-glucan Unspecified bioactive/extract(s)	*Ganoderma lucidum* *Pleurotus tuberregium* *Cordyceps sinensis* and *Inonotus obliquus*	Inhibit proliferation of HepG2 human hepatocellular carcinomas Exhibit tumor-selective cytotoxicity (*in vitro*)	Weng et al. (2007), Tao et al. (2006), Wu et al. (2007), Youn et al. (2008), Lin et al. (2003)
	3. Unspecified bioactive/ extract(s)	*Agaricus blazei* *Pleurotus pulmonarius*	Hepato-protective effects on both chemically-induced liver toxicity and hepato-carcinogenesis in rodents (*in vivo*)	Barbisan et al. (2002), Pinheiro et al. (2003), Wasonga et al. (2008)
Anti-cancer (lung)	Aqueous extract	*Hypsizigus marmoreus*	Intraperitoneal administration exhibit inhibitory activity against spontaneous tumor metastasis and decreases number of metastasised nodules in mice with Lewis lung carcinoma (*in vivo*)	Saitoh et al. (1997)
	Lucialdehydes A–C	*Ganoderma lucidum*	Cytotoxic against murine and human tumor cells (Lewis lung carcinoma, T-47D, Sarcoma 180, Meth-A tumor cell lines) (*in vivo*)	Gao et al. (2002)
	Unspecified bioactive/extract(s)	*Phellinus linteus*	Mediate cell-cycle arrest at a low concentration and apoptosis in response to a high dose in mouse and human lung cancer cell (*in vivo* and *in vitro*)	Guo et al. (2007)
Anti-cancer (lung and stomach)	Blazein	*Agaricus blazei* Murill (Himematsutake)	Induce cell death and morphological change indicative of apoptopic chromatin condensation in human lung cancer LU99 and stomach cancer KATOIII cells	Itoh et al. (2008)
Anti-cancer (lung and cervical)	Unspecified bioactive/extract(s)	*Pleurotus ferulae*	Exhibit cytotoxic effects on human lung and cancer cell lines (A549, SiHa and HeLa cells) (*in vitro*)	Choi et al. (2004)

Table 2 – Properties and mechanisms of bioactive compounds and mushroom extracts evaluated in animal models or animal cell lines.

Effect/disease state	Bioactive or extract	Mushroom variety	MECHANISM (*in vitro/ in vivo*)	Reference
Anti cancer (skin)	Unspecified bioactive/ extract(s)	*Lentinula edodes*	Reduce cell proliferation and induce apoptosis in CH72 mouse skin carcinoma cells (*in vivo*)	Gu and Belury (2005)
	Methanol extract	*Coriolus versicolour*	Reduce B-16 melanoma cell viability and the proliferation of tumor cells (arrest in the G-/G1 phase of the cell cycle) followed by apoptotic and secondary necrotic cell death (*in vitro*)	Harhaji et al. (2008)
	Proflamin	*Flammulina velutipes*	Increase median survival time of mice treated with B-16 and Ca-744 (*in vivo*)	Ikekawa et al. (1985)
	Acidic polysaccharide	*Phellinius linteus*	Inhibit melanoma cell metastasis in mice Directly inhibit cancer cell adhesion to and invasion through the extracellular matrix Increase macrophage NO production (*in vivo*)	Han et al. (2006)
DNA damage	Unspecified aqueous bioactive/ extract(s)	*Agaricus blazei* Murill	Reduce DNA damage in liver (induced by diethylnitrosamine (DEN) in adult male Wistar rats) (*in vivo*)	Barbisan et al. (2003)
	Heat-labile protein	*Agaricus bisporus*	Protect Raji cells (human lymphoma cell line) against H_2O_2O-induced oxidative damage to cellular DNA (*in vitro*)	Shi et al. (2002)
	1. Cold (20°) water extracts 2. Hot (100°) water extracts	*Agaricus bisporus* *Ganoderma lucidum*	Protective against H_2O_2O-induced oxidative damage to cellular DNA (*in vitro*)	Rocha et al. (2002)
	Unspecified bioactive/ extract(s)	*Inonotus obliquus*	Reduce DNA fragmentation	Park et al. (2004)
	Aqueous extract	*Agrocybe cylindracea* (strain B)	Protects DNA against OH-mediated strand breaks damage in HepG2 cells	Wang et al. (2004)
	Beta-glucan	*Agaricus brasiliensis*	In the dose range 20–80 μg/ml exhibited significant dose-dependent protective effect against damage induced by hydrogen peroxide and Trp-P-2	Angeli et al. (2006)
	Beta-glucan	*Agaricus blazei*	Protective against DNA damage caused by benzo[a]pyrene possibly mediated via binding to benzo[a]pyrene or the capture of free radicals produced during its activation	Angeli et al. (2009)
	3. Water-soluble polysaccharide; 4. Hot water extract	*Ganoderma lucidum*	Protective against hydroxyl radical-induced DNA strand breaks	Kim and Kim (1999)

(*continued on next page*)

Table 2 – Properties and mechanisms of bioactive compounds and mushroom extracts evaluated in animal models or animal cell lines.

Effect/disease state	Bioactive or extract	Mushroom variety	MECHANISM (*in vitro/ in vivo*)	Reference
	Aqueous extract	*Ganoderma lucidum*	Protection of radiation-induced plasmid pBR322 DNA strand breaks and inhibition of lipid peroxidation	Pillai et al. (2006)
	Protein extract Polysaccharide extract	*Ganoderma lucidum* (Selenium-enriched)	Strong protective effects against oxidative damage possibly associated with Se's role in increasing antioxidant activities of protein extracts Protection of DNA from hydroxyl radical oxidative damage	Zhao et al. (2004, 2008)
Anti-arthritic	Beta-(1,3/1,6)-D-glucan	*Pleurotus ostreatus*	Immuno-modulating effect on all cytokine plasma levels measured (*in vivo*)	Bauerova et al. (2009)
Bone health	Ethanol extracts	*Ganoderma lucidum*	Improve bone density in rats	Miyamoto et al. (2009)
	Vitamin D2 and/ or calcium	*Lentinula edodes* (UV irradiated)	May improve bone mineralization through a direct effect on the bone and by inducing the expression of calcium absorbing genes in the duodenum and kidney (*in vivo*)	Lee et al. (2009a)
	Aqueous extract	*Grifola frondosa*	Increase alkaline phosphatase activity of osteoblasts Increase mineralization hence acting as a bone-inducing agent	Saif et al. (2007)
	Pleurotus eryngii extracts (PEX)	*Pleurotus eryngii*	Alleviate the decrease in trabecular bone mineral density in ovariectomy-induced osteporosis in rats (*in vivo*)	Kim et al. (2006)
	Ethanol extract	*Pleurotus eryngii*	Protect against bone loss caused by estrogen deficiency	Shimizu et al. (2006)
Wound healing	Unspecified bioactive/ extract(s)	*Agaricus bisporus*	Dose-dependent inhibition of proliferation and lattice contraction in an *in vitro* model of wound healing (human ocular firoblasts in monolayers and in 3-D collagen lattices)	Batterbury et al. (2002)
	Includes beta-glucan	*Sparassis crispa* (SC)	Accelerate wound healing in diabetes mellitus via an increase in the migration of macrophages and fibroblasts, and beta-glucan from SC directly increasing the synthesis of type I collagen (*in vivo*)	Kwon et al. (2009)
	Polysaccharide fractions	*Ganoderma lucidum*	Active component with healing efficacy on acetic acid-induced ulcers in rats (*in vivo*)	Gao et al. (2004)

Table 2 – Properties and mechanisms of bioactive compounds and mushroom extracts evaluated in animal models or animal cell lines.

Effect/disease state	Bioactive or extract	Mushroom variety	MECHANISM (*in vitro*/ *in vivo*)	Reference
	Unspecified bioactive/ extract(s)	*Hericium erinaceus*	Reduce ulceration when used in pre-treatment in ethanol-induced gastric ulcers in rats (*in vivo*)	Mahmood et al. (2008)
Polysaccharide	*Lentinus edodes*	Increase activities of serum antioxidant enzymes and decrease levels of serum mucosal interleukin-2 (IL-2) and TNF-α in rats with oral ulceration (*in vivo*)	Yu et al. (2009b)	
Eye health	Unspecified bioactive/ extract(s)	*Pleurotus ostreatus*	*In vitro*: incubation of extract with selenite-challenged lenses result in a decrease in lens opacification by maintaining antioxidant components at near normal levels *In vivo*: extract prevents cataracts in 75% of rats	Isai et al. (2009)

However, *in vitro* and animal trials have reported an inhibition of aromatase activity and subsequent reduction of estrogen by mushroom extracts, which provide a physiologically-relevant mechanism for effects on estrogen receptor positive tumors. Preliminary new data showing protective effects of mushrooms on beta-amyloid peptide toxicity in the brain and mild cognitive impairment (both precursors to dementia) are promising and warrant further research on the ability of mushroom consumption to delay the onset of cognitive decline/Alzheimer's disease. In addition to the studies in human population groups and human cell lines provided in Table 1, the properties and mechanisms of bioactive compounds and mushroom extracts evaluated in animal models or animal cell lines are provided in Table 2.

2.1. *Anti-cancer studies*

Anti-tumor effects, primarily in human cell lines, have been reported from polysaccharides extracted from various mushrooms. The polysaccharides generally belong to the beta-glucan family of compounds and appear to exert their anti-tumorigenic effects via enhancement of cellular immunity. Anti-tumor effects of proteoglycan fractions from a variety of mushrooms, including *Agaricus bisporus*, involve the elevation of natural killer (NK) cell numbers and the stimulation of inducible nitric oxide (NO) synthase gene expression, which is then followed by NO production in macrophages via activation of the transcription factor, NF-kappaB. Activation of NK cells is likely via interferon-gamma and interleukin mediated pathways. While studies in human cell lines provide supporting evidence, well-designed human clinical trials are required before anti-cancer health outcomes in humans can be validated. In recent years, a number of human trials have been undertaken and these are outlined below.

2.1.1. *Breast cancer studies*

An epidemiological study of women with histologically confirmed breast cancer has identified that daily intake and the average consumption frequency of mushrooms were inversely associated with breast cancer risk, and a strong inverse association was found in post-menopausal women, but not in pre-menopausal women (Hong, Kim, Nam, Kong, & Kim, 2008), which is in contrast to another epidemiological study that has suggested a decreased risk of breast cancer from mushroom consumption by pre-menopausal women (Shin et al., 2010). In this latter study, greater mushroom intake was related to lower risk of breast cancers among premenopausal women for the highest vs. the lowest quartile intake. The association was stronger for premenopausal women with estrogen receptor (ER)+/progesterone receptor (PR) + tumors than those with ER−/PR− tumors, suggesting that this effect may be more robust among women with hormone receptor positive tumors. A possible mechanism for this effect may be via an inhibition of aromatase activity, described in both *in vitro* and animal trials (Grube et al., 2001; Chen et al., 2006), and more recently in a human trial of postmenopausal women diagnosed with breast cancer (Palomares et al., 2011) for *A. bisporus*. A subsequent reduction in estrogen, affecting estrogen receptor positive tumors was reported in animal trials. Recent evidence suggests that the anti-aromatase compound in *A. bisporus* is conjugated linoleic acid (CLA) (Kanaya et al., 2011).

However, an *in vitro* study using water-based extracts of *Coprinellus* sp., *Coprinus comatus*, *Flammulina velutipes*, significantly inhibited growth of both estrogen-receptor positive (ER+) and estrogen-receptor negative (ER−) breast cancer cells, induction of rapid apoptosis on both ER+ and ER− cells, and significantly inhibited MCF-7 tumor colony formation *in vitro*. These activities were dose-dependent, regardless of

the hormone receptor status of the cancer cells (Gu & Leonard, 2006).

Higher dietary intake of mushrooms decreased breast cancer risk in both pre- and post-menopausal women and an additional decreased risk of breast cancer was observed from a synergistic effect of mushrooms and green tea in a case–controlled study (Zhang, Huang, Xie, & Holman, 2009). Vitamin D2 could be one of the protective phytonutrients against breast cancer as mushrooms are rich in ergosterol, generating vitamin D2 when exposed to ultraviolet B (UVB) light and ergocalciferol being bioavailable and increasing serum 25(OH) vitamin D2 levels in humans (Furlanetto, 2009). While these human trials are promising, it should be noted that they were not direct intervention trials and mushroom consumption was assessed via quantitative food frequency questionnaires, which can be affected by recall bias.

Studies in animal models and human cell lines have provided insights into the possible mechanisms involved for the effects of mushrooms and their components on breast cancer, and several studies have shown that mushroom extracts are able to suppress the proliferation of breast cancer cell lines, without affecting the proliferation of normal (non-cancer) cell lines (Israilides et al., 2008; Jedinak & Sliva, 2008). An *in vitro* study using an aqueous extract of *A. bisporus* has identified suppression of aromatase activity and estrogen production as key mechanisms (Grube et al., 2001), which is supported by an animal model study that has reported that the major active compounds (in *A. bisporus*) are unsaturated fatty acids such as linoleic acid, linolenic acid, and CLA which have been shown to inhibit aromatase activity (Chen et al., 2006).Inhibition of proliferation of human breast cancer cell lines has also been suggested to be mediated via downregulation of Akt/NF-kappaB (transcription factor) signaling in several mushroom varieties (Jiang, Slivova, Harvey, Valachovicova, & Sliva, 2004a; Jiang, Slivova, & Sliva, 2006; Jin, Kim, & Choi, 2008), with a suggestion that the active components in mushrooms in these effects may be hydroxylated triterpenes (Jiang, Grieb, Thyagarajan, & Sliva, 2008). Suppression of the transcription factors NF-kappaB and AP-1 has also been demonstrated by *Ganerderma lucidum* (Thyagarajan, Jiang, Hopf, Adamec, & Sliva, 2006).

Polysaccharide K (Krestin, PSK), extracted from *Coriolus versicolor* strain CM-101, is a non-specific immunomodulatory polysaccharide which induces interleukin 2 (IL-2) and interferon (IFN)-γ, thereby stimulating lymphokine activated killer cells and enhancing natural killer cells (Sakamoto et al., 2006). Oral administration of PSK has been shown to significantly inhibit breast cancer growth in tumor-bearing neu transgenic mice (Lu et al., 2011), with the indication that PSK is a specific toll-like receptor 2 (TLR2) agonist and exerts its anti-tumor effects via stimulation of both innate and adaptive immune pathways. Mushroom polysaccharopeptides have also been implicated in apoptopic effects in human breast cancer cell lines (Wan, Sit, & Louie, 2008).

2.1.2. *Colorectal/colon cancer studies*

Two meta-analyses of randomised clinical trials have suggested that adjuvant immunochemotherapy with polysaccharide K from mushrooms can improve the survival of and disease-free survival of patients with curatively resected colorectal cancer (Oba et al., 2007; Sakamoto et al., 2006). The reduction of death rate by 29% and of recurrence by 28% by PSK immunochemotherapy over standard oral fluorinated pyrimidine based chemotherapy may have been due to restoration of immunity in patients who could have been immunosuppressed due to surgery and chemotherapy (Sakamoto et al., 2006). The mechanism of this effect is possibly via action of PSK on a toll-like receptor initiating a signaling cascade involving T helper 1 cells which induce IL-2 and IFN-γ and then activate natural killer cells. This sequence of signaling cascades has recently been described in the modulation of innate immunity of *Agaricus blazei* (Ab) (Hetland et al., 2011), although intake of 5% Ab over 4 weeks by male Wistar rats did not confirm chemopreventive activity on the initiation stage of rat colon carcinogenesis (Ziliotto, Barbisan, & Rodrigues, 2008; Ziliotto, Pinheiro, Barbisan, & Rodrigues, 2009).

A clinical study of healthy volunteers reported that *G. lucidum* did not affect their immune functions, but a subsequent open-labeled study (i.e. not double-blind or placebo controlled) evaluating water-soluble *G. lucidum* polysaccharides (Ganopoly®) in patients with advanced colorectal cancer reported that treatment with Ganopoly® tended to increase mitogenic reactivity to phytohemagglutinin. Larger double-blind trials are required to validate this effect and further studies are needed to determine the mechanism of action, efficacy, and safety of the water-soluble *G. lucidum* polysaccharides in cancer patients (Gao et al., 2005). A randomized, placebo-controlled, double-blind clinical trial in which patients with colorectal cancer were supplemented with *Agaricus sylvaticus* mushroom, orally, twice daily (30 mg/kg/day), for 6 months also suggested benefits in hematological and immunological parameters and reduced glycemic levels in patients with colorectal cancer (Fortes, Novaes, Recova, & Melo, 2009). These data suggest that mushrooms may have an immunostimulatory effect on immunocompromised patients, but not in a normal, healthy population.

Several *in vitro* studies in HT-29 human colonic carcinoma cells with extracts from *G. lucidum* (Hong, Dunn, Shen, & Pence, 2004), *A. bisporus* lectin (ABL) (Yu, Fernig, Smith, Milton, & Rhodes, 1993) and other mushrooms have reported pro-apoptotic effects with no associated cytoxicity. It has been suggested that the pro-apoptotic effects in HT-29 cells is induced by an increase in the activity of caspase-3 (Hong et al., 2004). More recent studies have suggested the pro-apoptotic effects and inhibition of the growth of HT-29 colonic cancer cells is mediated through up-regulation of the expression of pro-apoptotic proteins and down-regulation of anti-apoptotic proteins (Lee, Hwang, & Yun, 2009b). The inhibition of proliferation has been shown to be reversible after removal of (*A. bisporus*) lectin (Yu et al., 1993) and the reversibility of the anti-proliferative effect was associated with the release of the lectin from cancer cells after internalization (Yu, Fernig, & Rhodes, 2000).

2.1.3. *Cervical, ovarian, endometrial cancer studies*

The effect of consumption of an extract from *A. blazei* Murill Kyowa (ABMK), on immunological status and quality of life

has been studied in cancer patients undergoing chemotherapy. One hundred cervical, ovarian, and endometrial cancer patients were treated either with carboplatin plus VP16 or with carboplatin plus taxol every 3 weeks for at least three cycles, with or without oral consumption of ABMK. The authors observed that natural killer cell activity was significantly higher in the ABMK-treated group compared to the non-treated placebo group ($n = 61$). However, no significant difference in lymphokine-activated killer and monocyte activities was observed. Chemotherapy-associated side effects such as appetite loss, alopecia, emotional instability, and general weakness were all reported to be improved by ABMK treatment (Ahn et al., 2004).Very little is known about the mechanisms involved in the effects of mushrooms or mushroom extracts in cervical, ovarian and endometrial cancers, with only a small number of reports suggesting anti-proliferative effects (Liu, Ning, Cao, & Huang, 2009; Chen et al., 2010) via an induction of apoptosis (Ren, Zhao, Yang, & Fu, 2008).

2.1.4. *Gastic cancer studies*

A meta-analysis of the effect of immunochemotherapy with lentinan compared to chemotherapy alone has been evaluated in patients with advanced gastric cancer across five randomised controlled trials. Lentinan significantly prolonged overall survival but was possibly more effective in patients with lymph-node metastasis than in non-node metastasis patients (Oba, Kobayashi, Matsui, Kodera, & Sakamoto, 2009).

Natural polysaccharides isolated from *Phellinus gilvus* (PG) have been shown to decrease cell proliferation and increase cell apoptosis in a dose-dependent manner *in vitro* in a model of human gastric adenocarcinoma and also to lead to a marked inhibition of tumor growth and a significant decrease in the incidence of peritoneal carcinomatosis (Bae, Jang, & Jin, 2006). Anti-proliferative (Chen, Zhao, Chen, & Li, 2008) and pro-apoptotic effects (Shomori, Yamamoto, Arifuku, Teramachi, & Ito, 2009) in human gastric cell lines also were reported for several mushroom extracts with both caspase-3 – dependent (Jin et al., 2006) (Shomori et al., 2009) and independent signaling cascades being implicated (Shomori et al., 2009).

2.1.5. *Prostate cancer studies*

Human trials to date have shown that mushrooms and their extracts to be ineffective in the treatment of clinical prostate cancer, although the treatments have been well-tolerated. Trials with *G. lucidum* (Noguchi et al., 2008a, 2008b) and with a polysaccharide/oligosaccharide complex obtained from a Shiitake mushroom extract (White, Hackman, Soares, Beckett, & Sun, 2002) showed no effect on prostate-specific antigen levels in patients with either lower urinary tract symptoms or patients with prostate cancer, respectively.

In other human trials, treatment with Senseiro (containing extracts from *A. blazei* Murill) and Rokkaku Reishi (containing the *G. lucidum* mushroom) for 6 months in patients with prostate cancer also failed to show a response in terms of serum prostate-specific antigen (Yoshimura et al., 2010), while a Phase II human trial of 74 early prostate cancer patients reported a mushroom mycelium extract to be ineffective in reducing by 50% or more the patient prostate specific antigen values (Sumiyoshi et al., 2010).

These human trial outcomes do not support *in vitro* mechanistic studies, where several mushrooms and their extracts have been reported to inhibit proliferation of human prostate cancer cell lines. An *A. blazei* extract (with a high ratio of beta-glucan) inhibited cell proliferation in both androgen-dependent and androgen-independent prostate cancer cell lines via an apoptotic pathway, with activities of caspase 3 and DNA fragmentation being enhanced the most in androgen-independent PC3 cells (Yu et al., 2009a). Beta-glucan from *Grifola frondosa* (Maitake) has a cytotoxic effect on human androgen-independent prostatic cancer PC-3 cells *in vitro*, leading to apoptosis (Fullerton et al., 2000), while a recent study has also suggested that a *Phellinus linteus* extract is able to sensitize advanced prostate cancer cells to apoptosis in athymic nude mice (Tsuji et al., 2010).

Inhibition of proliferation in a dose- and time-dependent manner and induction of apoptosis in PC-3 human prostate cancer cells by *G. lucidum* (Jiang et al., 2004b) has been determined to be caused by the inhibition of constitutively active AP-1 in prostate cancer cells, resulting in the down-regulation of secretion of vascular endothelial growth factor and transforming growth factor beta (TGF-beta1) from PC-3 cells, and *G. lucidum* inhibits prostate cancer-dependent angiogenesis by modulation of MAPK (mitogen activated protein kinase) and Akt signaling (Stanley, Harvey, Slivova, Jiang, & Sliva, 2005). The mechanisms by which mushrooms and their extracts affect prostate cancer cells appear to be multi-modal with gene network analysis of studies with *A. bisporus* identifying alterations in networks involved in apoptosis, growth and proliferation, lipid metabolism, the TCA cycle and immune responses (Adams, Phung, Wu, Ki, & Chen, 2008).

2.1.6. *Pancreatic cancer/solid malignancies*

Only one single trial on the effects of a mushroom-derived compound on pancreatic cancer in humans has been reported. A phase I trial and pharmacokinetic study of irofulven, a mushroom-derived cytotoxin has been carried out in 46 patients with advanced solid malignancies. While the highest dose used was not well tolerated (grade 4 neutropenia and renal toxicity), the authors recommended a lower dose of irofulven (10.64 mg/m^2) as a 5-min intravenous infusion daily for 5 days every 4 weeks. The preliminary anti-tumor activity documented in a patient with advanced pancreatic cancer and the positive pre-clinical anti-tumor effects observed on intermittent dosing schedules support a need for further trials on irofulven. It should be noted that the source of this compound (*Omphalotus olearius*) is not an edible mushroom (Eckhardt et al., 2000).

2.2. *Immune function*

Numerous studies have described the effects of mushrooms and mushroom extracts on immune function with implications for inhibiting tumor growth. Some of the more efficacious compounds reported are the 1,6-branched 1,3-β-glucans, thought to inhibit tumor growth by stimulating the immune system via effects on NK cells, macrophages and via T cells and their cytokine production. More recent work has implicated polysaccharides with varying sugars and some are

alpha- rather than beta-glucans. Furthermore, mushroom proteins, terpenes and furans have also been implicated in immune function. While considerable *in vitro* data exists, *in vivo* studies are few and the limited clinical studies that have been carried out have been with small numbers of patients and have often been poorly controlled.

A polysaccharide extract from *G. frondosa* (Maitake extract) has shown immunomodulatory effects in a phase I/II dose escalation trial in post-menopausal breast cancer patients ($n = 34$). No dose-limiting toxicity was encountered and there was a statistically significant association between Maitake and immunologic function. The dose–response curves for many endpoints were non-monotonic with intermediate doses having either immune enhancing or immune suppressing effects in peripheral blood compared with both high and low doses (Deng et al., 2009). Another clinical trial in breast cancer patients ($n = 82$) evaluating the immunomodulatory effects of Yunzhi–Danshen capsules (Yunzhi (*C. versicolor*); Danshen (*Salvia miltiorrhiza*)) showed significantly elevated B-lymphocytes in patients with breast cancer after taking Yunzhi–Danshen capsules, while plasma sIL-2R concentration was significantly decreased (Wong et al., 2005).

Discrepancies in results have been reported between *ex-vivo* and *in vivo* studies. After stimulation of whole blood from healthy volunteers *ex vivo* with 0.5–5.0% of a mushroom extract, mainly containing *A. blazei* Murill (AbM), a dose-dependent increase in all the cytokines studied was seen, ranging from two to 399-fold (TNFα). However, *in vivo*, in eight volunteers who completed the daily intake (60 ml) of the AbM extract for 12 days, a significant reduction was observed in levels of IL-1-β (97%), TNF-α (84%), IL-17 (50%) and IL-2 (46%). Another nine cytokines remained unaltered (Johnson et al., 2009). The discrepancy in cytokine release *ex vivo* and *in vivo* may partly be explained by the antioxidant activity of AbM *in vivo* and limited absorption of its large beta-glucans across the intestinal mucosa to the reticuloendothelial system and blood.

A double-blind randomized trial undertaken in mildly hypercholesterolemic subjects ($n = 56$) to examine the effects of alpha-glucans from *A. bisporus* reported that consumption of *A. bisporus* alpha-glucans lowered lipopolysaccharide-induced TNFα production by 69% compared to the control group, whereas no effect on IL-1β and IL-6 was observed. The authors suggested that *in vivo*, alpha-glucans had lost their efficacy to stimulate the immune response as observed in an *in vitro* mouse model (Volman, Mensink, van Griensven, & Plat, 2010a).

Reviews have been carried out on the immunobiology of mushrooms (Borchers et al., 2008), on the immunomodulatory activities of mushroom polysaccharides (Cheung, Wong, & Lai, 2011), and on the health effects of beta-glucans in mushrooms (Rop, Mlcek, & Jurikova, 2009; Rondanelli, Opizzi, & Monteferrario, 2009). A recent systematic review of immunomodulatory dietary polysaccharides concluded that glucan extracts from *Trametes versicolor* improved survival and immune function in human randomised controlled trials of cancer patients (Ramberg et al., 2010). Many of the potential therapeutic effects of mushrooms and mushroom components on a variety of diseases appear to be directly or indirectly mediated by enhancing natural immunity of the host via effects on natural killer (NK) cells, macrophages, via balance of T cells and their cytokine production, and via the activation of Mitogen Activated Protein Kinase (MAPK) pathways (Kim et al., 2007; Lin et al., 2009). A recent study has also suggested that branching of the beta-glucan chain is a requirement for immunostimulatory activity (Volman et al., 2010b).

2.3. *Diabetes*

A large number of animal studies, using both normal and diabetic animals, have demonstrated a hypoglycemic effect of mushrooms and mushroom components. This effect appears to be mediated via mushroom polysaccharides (possibly both alpha- and beta-glucans) via a direct interaction with insulin receptors on target tissues, although this mechanism remains to be confirmed.

A randomized, double-blinded, and placebo-controlled clinical trial ($n = 72$) showed that *A. blazei* Murill supplementation in combination with metformin and gliclazide improved insulin resistance in these subjects. An increase in adiponectin concentration after *A. blazei* Murill extract consumption for 12 weeks may be the mechanism that resulted in the reported effect (Hsu, Liao, Lin, Hwang, & Chou, 2007). Clinical investigation in diabetic patients ($n = 89$) has also shown that Oyster mushroom consumption significantly reduced systolic and diastolic blood pressure, lowered plasma glucose, total cholesterol and triglycerides significantly, with no significant change in body weight, and no deleterious effects on liver or kidney function (Khatun, Mahtab, Khanam, Sayeed, & Khan, 2007). These results in humans mirror the decreases in plasma glucose, cholesterol and triglyceride concentrations following *A. bisporus* consumption observed in rats (Jeong et al., 2010) and the reduction in blood pressure in Zucker fatty rats following oral administration of Maitake mushroom fractions (Talpur et al., 2002).

Aqueous extracts of various mushrooms have been shown to possess hypoglycemic activity and anti-hyperglycemic activity against diabetes-inducing compounds in obese and diabetic animal models. An aqueous extract of *G. lucidum* (0.03 and 0.3 g/kg) lowered the serum glucose level in obese/diabetic (+db/+db) mice after one week of treatment through the suppression of hepatic PEPCK gene expression (Seto et al., 2009). Aqueous extracts of *Pleurotus pulmonarius* also have been shown to possess hypoglycemic activity (Badole, Shah, Patel, Thakurdesai, & Bodhankar, 2006), as well as having synergistic anti-hyperglycemic effects with acarbose (Badole & Bodhankar, 2007) in alloxan-induced diabetic mice. A similar anti-hyperglycemic effect has been reported by *G. frondosa* (Cui, Han, Qu, & Lv, 2009) and *C. comatus* (Han & Liu, 2009) on an adrenaline-induced increase in blood glucose in mice, although in this study, the same result was not observed with *G. lucidum* and *G. frondosa*.

An alpha-glucan from *G. frondosa* was shown to affect a series of diabetes markers in KK-Ay mice, which may be related to an effect on insulin receptors by increasing insulin sensitivity and ameliorating insulin resistance of peripheral target tissues (Lei, Ma, & Wu, 2007). Beta-glucans and their enzymatically hydrolyzed oligosaccharides from *A. blazei* have anti-hyperglycemic, anti-hypertriglyceridemic, anti-hypercholesterolemic, and anti-arteriosclerotic activity indicating overall anti-diabetic activity in diabetic rats. However, the enzymatically hydrolyzed oligosaccharides have been shown

to have around twice the activity of beta-glucans with respect to anti-diabetogenic activity (Kim, Kim, Choi, & Lee, 2005). Semi-purified fractions of a submerged-culture broth of *A. blazei* Murill were also reported to reduce blood glucose levels in streptozotocin-induced diabetic rats (Oh et al., 2010).

Extracellular polysaccharides (EPS) from *Laetiporus sulphureus* var. miniatus have been shown to both stimulate insulin secretion (Hwang et al., 2008) and insulin sensitivity possibly via regulation of lipid metabolism (Cho et al., 2007) in diabetic mouse models. A polysaccharide isolated from *P. linteus* reportedly inhibited the development of autoimmune diabetes by regulating cytokine expression in non-obese diabetic mice (Kim et al., 2010). The hypoglycemic potential of EPS was also confirmed by histopathological examination that showed that EPS administration is able to restore impaired kidneys to almost normal architecture (Hye-Jin et al., 2007) as well as pancreatic islets of Langerhans (Yamac et al., 2008) in streptozotocin-induced rats.

The consistency between the effects of the mushroom extracts in diabetic animal models described above and preliminary data from human trials, which mirror decreases in plasma glucose, blood pressure, cholesterol and triglyceride concentrations, strengthens the level of evidence for anti-diabetogenic effects of the studied mushrooms and their extracts.

2.4. *Brain health/cognition*

Although very preliminary, data showing protective effects of mushrooms (*Hericium erinaceum*) on beta-amyloid peptide toxicity (Kawagishi & Zhuang, 2008) in the brain and mild cognitive impairment (both precursors to dementia) are promising. Preliminary human trials with *H. erinaceum* derivatives showed efficacy in patients with dementia in improving the Functional Independence Measure (FIM) score or retarding disease progression (Kawagishi & Zhuang, 2008), while a double-blind, parallel-group, placebo-controlled trial with oral administration of Yamabushitake (*Hericium erinaceus*) to 50 to 80-year-old Japanese men and women diagnosed with mild cognitive impairment reported significantly increased cognitive function scores compared to placebo during intake, but the scores decreased significantly following termination of the intake (Mori, Inatomi, Ouchi, Azumi, & Tuchida, 2009).

2.5. *Biomarkers for cardiovascular disease*

Oyster mushroom consumption by 89 diabetic patients significantly reduced systolic and diastolic blood pressure, total cholesterol and triglycerides, with no significant change in body weight and no deleterious effects on liver or kidney function (Khatun et al., 2007). Another study in 90 female volunteers demonstrated a weight-controlling and hypolipidemic effect of protein-bound polysaccharides from the mycelia of *A. blazei* and *Lentinus edodes*, via a mechanism involving absorption of cholesterol (Kweon, Kwon, Kwon, Ma, & Park, 2002). However, a double-blind, placebo-controlled, cross-over intervention study in adults ($n = 18$; ages 22–52 years) of a commercially available encapsulated Lingzhi preparation (equivalent to 13.2 g fresh mushroom/d) over 4 weeks failed to show any change in biomarkers for coronary heart disease risk (Wachtel-Galor, Tomlinson, & Benzie, 2004).

2.6. *Anti-microbial properties*

Anti-microbial effects of a large number of mushroom varieties and mushroom components on both gram-positive and gram-negative bacteria have been confirmed via *in vitro* studies. A small number of animal studies have been undertaken and the data suggest that the anti-microbial effects *in vivo* may be mediated by effects on the immune system. Initial studies in humans suggested anti-microbial properties of extracts from *A. blazei* Murill and *G. lucidum*, although these studies did not have adequate controls in the experimental design, and therefore such effects have not yet been scientifically validated in humans.

A very small one-year open-label (not double-blind or placebo-controlled) pilot study reported that intake of *A. blazei* Murill (AbM) extract (1500 mg daily) over 12 months improved liver function in patients with hepatitis B, determined by a decrease in the mean level of aspartate aminotransferase and alanine aminotransferase decreased from 246.0 to 61.3 IU/L and 151.0 to 46.1 IU/L, respectively (Hsu, Hwang, Chiang, & Chou, 2008a). The initial observation seems to indicate a potential benefit of AbM extract in normalizing liver function of patients with hepatitis B, although clearly larger and controlled studies are required to confirm such effects.

Model studies have demonstrated anti-bacterial effects of *A. blazei* Murill (AbM) extract against systemic *Streptococcus pneumoniae 6B* infection in mice. The lack of an antibiotic effect on pneumococci *in vitro* and increased levels of cytokines MIP-2 and TNF in the serum of mice receiving AbM extract, indicated that its protective effect may be due to the involvement of the native immune system (Bernardshaw, Hetland, Ellertsen, Tryggestad, & Johnson, 2005a; Bernardshaw et al., 2005b). This group's subsequent study showed that an extract of *A. blazei* Murill can protect against lethal bacterial septicemia in a mouse model of fecal peritonitis. Mice (BALB/c) that were orally treated with AbM extract before bacterial challenge showed significantly lower levels of septicemia, as measured by the number of colony-forming units of bacteria in blood and by the survival rate of the animals (Bernardshaw, Hetland, Grinde, & Johnson, 2006).

Numerous *in vitro* studies have clearly demonstrated activities against gram-positive and gram-negative bacteria, yeasts and mycelial fungi, including dermatophytes and phytopathogens (Jagadish, Krishnan, Shenbhagaraman, & Kaviyarasan, 2009; Soboleva, Krasnopol'Skaia, Fedorova, & Katrukha, 2006; Hearst et al., 2009), including several foodborne pathogenic bacterial strains (Venturini, Rivera, Gonzalez, & Blanco, 2008). It has been suggested that such antimicrobial effects of mushroom extracts may be indirect, with a polysaccharide-rich fraction of *Agaricus brasiliensis* being shown to increase host resistance against some infectious agents through stimulation of the microbicidal activity of macrophages (Martins et al., 2008).

2.7. *Anti-viral properties*

Proteins, peptides and polysaccharopeptides from mushrooms have been reported to inhibit human immunodeficiency virus type 1 (HIV-1) reverse transcriptase and protease, the two enzymes of importance to the life cycle of

HIV. Inhibitory effects on hepatitis B and herpes simplex virus type 1 have also been reported. The anti-viral effects of mushrooms do not seem to be related to viral adsorption or virucidal effects (i.e. they do not kill the virus), however a number of studies have reported inhibitory effects at the initial stage of virus replication (Faccin et al., 2007).

Two phase I/II placebo-controlled trials in 98 HIV-positive patients were completed using lentinan, a beta-glucan isolated from *L. edodes* (Shiitake mushroom) (Gordon et al., 1998). The studies reported generally good tolerability of lentinan with observed side effects being mainly mild, particularly when infusion was carried out over a 30 min period. In the first study, where administration was over a 10 min period, there were nine side effects severe enough to be reported to the FDA (one case each of anaphylactoid reaction, back pain, leg pain, depression, rigor, fever, chills, granulocytopenia and elevated liver enzymes) with four patients discontinuing therapy because of side effects. In the second study, where infusion was over a 30 min period, there were no side effects reportable to the FDA but there were four drop-outs due to side effects or personal preference. Most side effects resolved promptly after the discontinuation of medication, and all of them were relieved within 24 h. The small number of patients in the study groups meant the data on possible increases in CD4 cell and neutrophil activity were inconclusive (Gordon et al., 1998).

Extracts of *G. frondosa* (Maitake) have shown activity against hepatitis B virus (Gu, Li, & Chao, 2006), herpes simplex virus type 1 (HSV-1) replication *in vitro* (Gu et al., 2007) and against the growth of influenza A/Aichi/2/68 virus (Obi et al., 2008). The effects of a mushroom-derived active hexose correlated compound (AHCC) on the immune response to influenza A virus (H1N1, PR8) infection were shown to be dose dependent with low-dose AHCC supplementation improving the response to influenza infection despite no effect on total NK cell cytotoxicity (Nogusa, Gerbino, & Ritz, 2009). Extracts from *P. linteus* also provided protection against variant H5N1 influenza viruses (Ichinohe et al., 2010).

Anti-viral activity of several mushroom extracts has been demonstated *in vitro* and *in vivo* in animal models. A polysaccharopeptide from the Turkey Tail mushroom *T.* (=Coriolus) *versicolor* was reported to inhibit HIV-1 reverse transcriptase and protease, the two enzymes of paramount importance to the life cycle of the HIV (Tzi, Wang, & Wan, 2006). Anti-HIV-1 protease activity was also reported for lanostane triterpenes from *Ganoderma colossum* (el Dine, el Halawany, Ma, & Hattori, 2008) and from *Ganoderma sinense* (Sato, Zhang, Ma, & Hattori, 2009), while nebrodeolysin from *Pleurotus nebrodensis* has been shown to possess anti-HIV-1 activity *in vitro* (Lv et al., 2009). Lectins from *A. bisporus*, *Phaseolus vulgaris*, *Momordica charantia*, *Ricinus communis* and its constituent chains have been shown to inhibit HIV-1 reverse transcriptase (Wang & Ng, 2001). A ubiquitin-like protein from *Pleurotus ostreatus* has also demonstrated inhibitory activity toward HIV-1 reverse transcriptase, which could be enhanced by succinylation (Wang & Ng, 2000). The evidence for an antiviral effect of several mushroom extracts via inhibition of HIV-1 reverse transcriptase and protease appears strong. A farnesyl hydroquinone, ganomycin I, isolated along with ganomycin B, from *G. colossum* has been reported to inhibit HIV-1 protease with IC_{50} values of 7.5 and 1.0 μg/ml, respectively (el Dine, el Halawany, Ma, & Hattori, 2009). Ganomycin B competitively inhibited the active site of the enzyme, with both compounds docking with the HIV-1 protease crystal structure.

2.8. *Asthma*

A *Cordyceps* extract has recently been evaluated in asthmatic children during remission stage (Sun et al., 2010). The *Cordyceps* extract inhibited the proliferation and differentiation of Th2 cells and reduced the expression of related cytokines by down-regulating the expression of GATA-3 mRNA and up-regulating the expression of Foxp3 mRNA in peripheral blood mononuclear cells. The extract was able to alleviate the chronic allergic inflammation by increasing the level of interleukin-10.

2.9. *Hepatitis*

Clinical effects and safety evaluation of *A. blazei* condensed liquid (Agaricus Mushroom Extract; ABCL) administered to human volunteers (10 male, 10 female) with chronic C-type hepatitis orally twice per day for 8 weeks reported no toxicological or other side effects (Inuzuka & Yoshida, 2002). A series of trials have evaluated *G. lucidum* on cancer, Type II diabetes, coronary heart disease, chronic hepatitis B, and neurasthenia. Treatment with Ganopoly® for 12 weeks showed hypoglycemic activity and produced some anti-viral and liver protective effects in patients with chronic hepatitis B infection. However, the same treatment regimen did not result in any objective response in late-stage cancer patients (Zhou, Gao, & Chan, 2005). Overall, the findings suggest that Ganopoly® may have some pharmacological activities, although clinical proof is lacking.

2.10. *Constipation*

Constipation is one of the most prevalent gastrointestinal complaints and high fiber intake is recommended as an initial therapy for constipation. Ear mushrooms (*Auricularia*) are known to have higher fiber contents (by ~50%) than other mushroom varieties. In patients with functional constipation, fiber supplements using ear mushrooms have been shown to significantly improve constipation related symptoms without serious side effects (Kim, Park, Choi, Lee, & Kim, 2004).

3. Medical conditions with lower levels of evidence

There are currently no published human clinical trials on mushrooms and the following medical conditions, and hence a summary of *in vitro* studies and *in vivo* animal trials is provided in Table 2 and briefly summarized below. Without confirmation of efficacy in humans, these studies provide a lower level of evidence.

3.1. *Bladder cancer*

The synergistic potentiation of interferon activity with Maitake mushroom on bladder cancer cells has recently been reported

(Louie, Rajamahanty, Won, Choudhury, & Konno, 2010). The combination of interferon-alpha2b (10,000 IU/ml) and Maitake mushroom D fraction (200 g/ml) reduced growth by ~75% in T24 bladder cancer cells. This effect may be due to triggering double-stranded DNA-dependent protein kinase activation that may act on the cell cycle to cease cancer cell growth.

Cordycepin (3′-deoxyadenosine), from *Cordyceps militaris*, has been shown to have anti-tumor effects in two different bladder cancer cell lines, 5637 and T-24 cells. Cordycepin treatment, at a dose of 200 μM (IC_{50}) during cell-cycle progression resulted in a significant and dose-dependent growth inhibition, which was largely due to G2/M-phase arrest (Lee, Kim, Choi, Kim, & Moon, 2009c).

3.2. Leukemia

A recent study demonstrated that agaritine purified from *A. blazei* Murrill exerts anti-tumor activity against leukemic cells *in vitro* (Endo et al., 2010). Agaritine inhibited the proliferation of leukemic cell lines U937, MOLT4, HL60 and K562, but showed no significant effect on normal lymphatic cells. The data also showed that this activity was distinct from that of beta-glucan, which indirectly suppresses proliferation of tumor cells. This conclusion of direct anti-tumor activity by agaritine against leukemic tumor cells *in vitro* contrasts to the carcinogenic activity previously ascribed to it in animal studies carried out around 20–30 years ago. Agaritine, a naturally occurring phenylhydrazine derivative present in *Agaricus* mushroom species, had been described as potentially carcinogenic in some studies, although the scientific validity of the experimental designs and rat models from which this conclusion was drawn have now been challenged. These newer studies, animal models, and human food safety studies with *Agaricus* mushrooms have been evaluated recently with the conclusion that agaritine from consumption of cultivated *A. bisporus* mushrooms poses no known toxicological risk to healthy humans (Roupas, Keogh, Noakes, Margetts, & Taylor, 2010).

Extracts from *A. bisporus* (Jagadish et al., 2009), *A. blazei* (Gao et al., 2007), *Hypsizigus marmoreus* (Mizumoto et al., 2008) and other mushrooms have been shown to inhibit cell proliferation of HL-60 leukemia cells and other leukemia human cell lines via the induction of apoptosis. Mechanisms by which apoptosis is induced include down-regulation of telomerase activity and up-regulation of mRNA expression of the caspase-3 gene (Gao et al., 2007), regulation of Bcl-2 and caspase-3 (Jin, Moon, Choi, Lee, & Kim, 2007), cleavage of poly (ADP-ribose) polymerase and pro-caspase 3 (Bae et al., 2009), mitochondrial membrane potential loss and caspase activation (Mizumoto et al., 2008), release of mitochondrial cytochrome c and subsequent activation of caspase-9 and caspase-3 (Hsu, Yu, & Yen, 2008b) and via the signal transduction kinases Akt and Erk (Calvino et al., 2010). These extracts appear to exert tumor-selective cytotoxicity, with studies reporting no significant cytotoxic effects on normal cell lines (Lau et al., 2004).

3.3. Liver cancer

Lucidenic acids (triterpenoids) isolated from *G. lucidum* (Weng, Chau, Chen, Chen, & Yen, 2007), hyperbranched beta-glucan, extracted from *Pleurotus tuberregium* (Tao, Zhang, & Cheung, 2006) and extracts from *Cordyceps sinensis* (Wu, Zhang, & Leung, 2007) and Chaga (*Inonotus obliquus*) mushrooms (Youn et al., 2008) have been shown to inhibit the proliferation of HepG2 human hepatocellular carcinomas. As reported above for human leukemia cell lines, such extracts appear to be have tumor-selective cytotoxicity, without significant effects on normal human liver cell lines (Lin, Li, Lee, & Kan, 2003). *In vivo* rodent studies have also reported hepato-protective effects on both chemically-induced liver toxicity and hepatocarcinogenesis by extracts from *A. blazei* (Barbisan et al., 2002; Pinheiro et al., 2003) and *P. pulmonarius* (Wasonga, Okoth, Mukuria, & Omwandho, 2008).

3.4. Lung cancer

An *in vivo* study in mice with Lewis lung carcinoma treated with an aqueous extract of *H. marmoreus* showed a significant increase in life span when given it by intraperitoneal administration, but not as much by oral administration. The extract inhibited spontaneous tumor metastasis in mice bearing the carcinoma and significantly decreased the number of metastasized nodules (Saitoh, Feng, Matsuzawa, & Ikekawa, 1997). *In vitro* studies have shown that three triterpene aldehydes, lucialdehydes A–C, from the fruiting bodies of *G. lucidum,* possess cytotoxicity against murine and human tumor cells (Lewis lung carcinoma (LLC), T-47D, Sarcoma 180, and Meth-A tumor cell lines) (Gao et al., 2002), while *P. linteus* has been shown to mediate cell-cycle arrest at a low concentration and apoptosis in response to a high dose in mouse and human lung cancer cells (Guo et al., 2007). Blazein, a steroid isolated from *A. blazei* Murrill (Himematsutake), has also been reported to induce cell death and morphological change indicative of apoptotic chromatin condensation in human lung cancer LU99 and stomach cancer KATO III cells (Itoh, Ito, & Hibasami, 2008), and an extract from *Pleurotus ferulae* has been reported to have cytotoxic effects on human lung cancer and cervical cancer cell lines (A549, SiHa and HeLa cells) (Choi, Cha, Kang, & Lee, 2004).

3.5. Skin cancer

L. edodes has been shown to reduce cell proliferation and induce apoptosis in CH72 mouse skin carcinoma cells via an induction of a transient G1 arrest with no effect in non-tumorigenic (C50) cells (Gu & Belury, 2005). Similarly, reduction of cell proliferation of B-16 melanoma cells by arrest in the G0/G1 phase of the cell cycle, followed by both apoptotic and secondary necrotic cell death has been demonstrated for a methanol extract of *C. versicolor* (Harhaji et al., 2008). In contrast, proflamin, isolated from *F. velutipes,* exhibited no cytotoxic effects against B-16 melanoma (B-16) and adenocarcinoma 755 (Ca-755) cultured cell lines *in vitro*, but increased the median survival time of mice treated with B-16 and Ca-755 by 86% and 84%, respectively, with no apparent adverse effects (Ikekawa et al., 1985).

An acidic polysaccharide from *P. linteus* has been shown to markedly inhibit melanoma cell metastasis in mice, and directly inhibit cancer cell adhesion to, and invasion through, the extracellular matrix, with an increase in macrophage

NO production but to have no direct effect on cancer cell growth. These results suggest that *P. linteus* has two anti-metastatic functions—it acts as an immunopotentiator and as a direct inhibitor of cancer cell adhesion (Han et al., 2006).

3.6. DNA damage

In vitro studies have shown that a heat-labile protein from *A. bisporus* protects Raji cells (a human lymphoma cell line) against H_2O_2-induced oxidative damage to cellular DNA (Shi, Benzie, & Buswell, 2002). Similar protective effects against H_2O_2-induced oxidative damage to cellular DNA have been demonstrated with cold (20 °C) and hot (100 °C) water extracts of *A. bisporus* and *G. lucidum* fruit bodies, respectively. No protective effects were observed with mushroom derived preparations from *F. velutipes*, *Auricularia auricula*, *H. marmoreus*, *L. edodes*, *Pleurotus sajor-caju*, or *Volvariella volvacea* (Rocha, Barbisan, de Oliveira, & de Camargo, 2002). Similar reductions in DNA fragmentation (Comet assay), compared with H_2O_2 as a positive control, have been reported from Chaga mushroom (*I. obliquus*) (Park, Lee, Jeon, Jung, & Kang, 2004), while an aqueous extract from *Agrocybe cylindracea* strain B has also been shown to protect against DNA damage in HepG2 cells (Wang, Tsai, & Lin, 2004). Some edible mushrooms therefore represent a valuable source of biologically active compounds with potential for protecting cellular DNA from oxidative damage, while other mushroom varieties do not.

Beta-glucan from *A. brasiliensis* has been reported to be devoid of mutagenic activity and to provide a significant dose-dependent protective effect against DNA damage in the dose range 20–80 μg/ml (Angeli et al., 2006). Furthermore, a possible chemoprotective effect of beta-glucan extracted from *A. blazei* against DNA damage induced by benzo[a]pyrene, using the comet assay (genotoxicity) and micronucleus assay with cytokinesis block (mutagenicity) in a human hepatoma cell line (HepG2) has suggested that beta-glucan did not exert a genotoxic or mutagenic effect, but that it did protect against DNA damage via binding to benzo[a]pyrene or by the capture of free radicals produced during its activation (Angeli, Ribeiro, Bellini, & Mantovani, 2009).

It has been suggested that synthetic agaritine (i.e. not extracted from mushrooms) is quickly metabolized in mice and disappears in the plasma, whereas DNA damage after a single administration of synthetic agaritine lasts for a longer time (Kondo, Watanabe, Akiyama, & Maitani, 2008). The inference for DNA damage in this study was from a result of a separate *in vitro* test. While data with a particular marker of oxidative stress showed this effect, a similar experiment with a different marker of oxidative stress did not, thus the authors made these comments based on their results with one particular marker only. In contrast, recent research (Endo et al., 2010) has ascribed anti-tumor activity of agaritine (from mushrooms) against leukemic cells, and a recent review (Roupas et al., 2010) also concluded that agaritine from consumption of cultivated *A. bisporus* mushrooms poses no known toxicological risk to healthy humans. Another *in vivo* study demonstrated that crude extracts of *A. blazei* Murrill significantly reduced DNA damage in liver induced by diethylnitrosamine in adult male Wistar rats (Barbisan et al., 2003), while DNA strand breaking by the carbon-centered radical generated from 4-(hydroxymethyl) benzenediazonium salt from *A. bisporus* has been reported in the mouse (Hiramoto, Kaku, Kato, & Kikugawa, 1995).

Strong DNA protective effects from oxidative damage have been reported for protein extracts from selenium-enriched *G. lucidum* (Se-GLPr), and this effect increased with increasing Se content (Zhao et al., 2004). Polysaccharide extracts from Se-enriched *G. lucidum* have also been shown to protect DNA from hydroxyl radical oxidative damage in a dose dependent manner (Zhao et al., 2008). A water-soluble polysaccharide from *G. lucidum* was protective against hydroxyl radical-induced DNA strand breaks (Kim & Kim, 1999), and radioprotective properties of an aqueous extract of *G. lucidum* against radiation-induced plasmid pBR322 DNA strand breaks have been demonstrated that may be due to inhibition of lipid peroxidation (Pillai, Salvi, Maurya, Nair, & Janardhanan, 2006).

3.7. Rheumatoid arthritis

A polysaccharide–protein complex, isolated from *Phellinus rimosus* (Berk.), significantly increased lipid-peroxide levels in the plasma of adjuvant-induced arthritic rats. The antioxidant enzymes superoxide dismutase and glutathione peroxidase were elevated in adjuvant-induced rats, and reduced blood glutathione was decreased. Treatments with various concentrations of the polysaccharide–protein complex modulated the alterations produced in arthritic animals in a dose-dependent manner (Meera, Smina, Balan, Mathew, & Janardhanan, 2009). Anti-arthritic activity of a beta-(1,3/1,6)-D-glucan from *P. ostreatus* has been reported (Bauerova, Paulovicova, Mihalova, Svik, & Ponist, 2009; Rovensky, Stancikova, Svik, Bauerova, & Jurcovicova, 2011) in a rat model which involved an immunomodulating effect on cytokine plasma levels that changed markedly with arthritis progression.

3.8. Osteoporosis/bone mineral density

Ethanol extracts of *G. lucidum* have been evaluated against ovariectomized (Ovx)-induced deterioration of bone density in 11-week-old female Sprague Dawley (SD) rats (Miyamoto et al., 2009) with the treated rats showing improved bone density. *L. edodes* that are exposed to UV radiation contain enhanced vitamin D2 and have a much higher calcium content than non-irradiated mushrooms. A study in 4-week old mice fed low calcium and a vitamin D deficient diet showed significantly increased femur density and tibia thickness in mice fed calcium plus vitamin D2-enhanced mushrooms, and the expression of duodenal and renal calcium transport genes was significantly induced. The results indicated that in mice, vitamin D2 and/or calcium derived from irradiated *L. edodes* may improve bone mineralization directly and by inducing the expression of calcium-absorbing genes in the duodenum and kidney (Lee et al., 2009a). A recent randomized controlled trial has also demonstrated that the bioavailability of vitamin D2 from vitamin D2-enhanced mushrooms via UV-B irradiation improved vitamin D status in humans to a level similar to that of a vitamin D2 supplement (Urbain, Singler, Ihorst, Biesalski, & Bertz, 2011).

It has been suggested that the mechanisms for these effects is an increase in the alkaline phosphatase activity of

osteoblasts. The cultivation of human osteosarcoma cells HOS58 in the presence of an aqueous extract of *G. frondosa* resulted in a significant elevation of alkaline phosphatase activity of the cells in comparison to untreated cells. In another osteoblastic cell line (SaOS-2) cells incubated with *G. frondosa* for 21 days, showed a nearly 2-fold higher mineralization than cells cultured with a positive control, demonstrating the activity of *G. frondosa* extract as a bone-inducing agent (Saif, Lindequist, & Wende, 2007). *Pleurotus eryngii* extracts (PEX) have also been shown to increase alkaline phosphatase activity of osteoblasts and in the osteocalcin mRNA expression from primary osteoblasts. *In vivo* studies, using rats with ovariectomy-induced osteoporosis revealed that PEX alleviated a decrease in the trabecular bone mineral density (Kim et al., 2006). An ethanol extract of *P. eryngii* was also reported to help protect against bone loss caused by estrogen deficiency, without having a substantial effect on the uterus (Shimizu et al., 2006), and osteoclast forming suppressive compounds have been isolated from the mushroom *Agrocybe chaxingu* (Abel et al., 2007).

3.9. *Effects on wound healing*

Impaired wound healing in diabetes mellitus is a major clinical problem. Wound closure in streptozotocin-induced diabetic rats has been shown to be significantly accelerated by oral administration of *Sparassis crispa* (SC) a mushroom with a beta-glucan content of more than 40%, via a mechanism that may involve an increase in the migration of macrophages and fibroblasts, with beta-glucan from SC directly increasing the synthesis of type I collagen (Kwon, Qiu, Hashimoto, Yamamoto, & Kimura, 2009).

A dose-dependent inhibition of proliferation and lattice contraction without significant toxicity in an *in vitro* model of wound healing (human ocular fibroblasts in monolayers and in three-dimensional collagen lattices) by *A. bisporus* (0–100 μg/ml) has been shown (Batterbury, Tebbs, Rhodes, & Grierson, 2002), while *H. erinaceus* (Bull.: Fr.) Pers. (Aphyllophoromycetideae) (Mahmood et al., 2008), and polysaccharide fractions from both *G. lucidum* (Gao et al., 2004) and *L. edodes* (Yu, Yin, Qian, & Yan, 2009b) have demonstrated efficacy in treatment of ulceration in rats via mechanisms which involved raised activities of serum antioxidant enzymes and decreased levels of serum, mucosal interleukin-2 (IL-2) and TNF-α (Yu et al., 2009b).

3.10. *Eye health*

A recent study has evaluated the efficacy of *P. ostreatus* extract in preventing selenite-induced cataractogenesis. *In vitro*, simultaneous incubation of extract with selenite-challenged lenses caused a decrease in lens opacification by maintaining antioxidant components at near normal levels. *In vivo*, *P. ostreatus* prevented cataracts in 75% of rats (Isai et al., 2009).

4. Mushroom bioactive compounds and proposed mechanisms

Recent studies on mushrooms and their extracts (Tables 1 and 2), have identified roles involving host-mediated immunomodulatory responses, via stimulation of both innate and adaptive immune pathways, with implications for inhibition of tumor growth via anti-proliferative effects and induction of apoptosis in human cancer cells.

Polysaccharides from mushrooms, generally belonging to the beta-glucan family appear to inhibit tumor growth by stimulating the immune system. Some of the more efficacious compounds in mushrooms are 1,6-branched 1,3-β-glucans, which are recognized by pattern-recognition receptors on immune cells such as monocytes, granulocytes and dendritic cells. Beta-glucans in mushrooms are also known to exert immunomodulatory effects via activation of macrophages, balance of T helper cell (TH1 and TH2 in particular) populations and subsequent effects on natural killer (NK), cells and also via cytokine production (Hetland et al., 2011). In addition to beta-glucans, polysaccharides with other sugar moieties such as alpha-glucans have also been implicated (Borchers et al., 2008) while other studies with non-medicinal mushrooms containing 1,4-glucans have not shown similar effects suggesting that branching of the beta-glucans may provide specificity to the binding of these compounds to immune cells. While the majority of these mechanisms have been determined in in vitro or in vivo animal studies, some recent data have also provided evidence for such immunomodulatory effects (increased NK cell activity, effects on IgG, IgM, neutrophil and leukocyte counts) in humans from oral ingestion of dietary polysaccharides (glucans) from some varieties of mushrooms (Ramberg et al., 2010), which further strengthens this evidence.

Apoptosis and/or anti-proliferative effects on carcinomas and cell lines is a mechanism shared by several mushrooms and their extracts in studies of anti-cancer effects. The anti-tumor effects of proteoglycan fractions of mushrooms involve the elevation of natural killer (NK) cell numbers and the stimulation of inducible NO synthase gene expression, which is then followed by NO production in macrophages via activation of the transcription factor, NF-kappaB. Activation of NK cells is likely via interferon-gamma and interleukin mediated pathways. In addition to the apoptotic and anti-proliferative effects, the anti-inflammatory and anti-microbial/viral effects outlined may also contribute to the anti-carcinogenic effects of mushrooms and their extracts, although such direct links have not been established to date. As mentioned above, while the majority of such mechanisms have been determined in *in vitro* or *in vivo* animal studies, mushroom polysaccharides in particular are beginning to be evaluated as adjuvant cancer therapy compounds alongside conventional cancer treatments (Standish et al., 2008), particularly in breast cancer patients with estrogen receptor positive tumors where mushroom extracts have been shown to inhibit aromatase activity (Grube et al., 2001; Chen et al., 2006) and subsequent reduction of estrogen.

While the effects and underlying mechanisms of mushroom polysaccharides in health outcomes have been more extensively evaluated, bioactive proteins from mushrooms (such as lectins, fungal immunomodulatory proteins (FIP), ribosome inactivating proteins (RIP), ribonucleases and other proteins have also been reported to possess anti-tumor, anti-viral and immunomodulatory activities. Furthermore, ergosterol and agaritine, present in mushrooms of the *Agaricus* family, have been reported to inhibit proliferation

of leukemic cells without effects on normal lymphatic cells and that this activity was distinct from that of beta-glucan (Endo et al., 2010).

5. Conclusions

Although there have been relatively few direct intervention trials of mushroom consumption in humans, those that have been completed to date indicate that mushrooms and their extracts are generally well-tolerated with few, if any, side-effects. The most promising data appear to be those indicating an inverse relationship between mushroom consumption and breast cancer risk, although the data are generally based on food frequency questionnaires, which can be affected by recall bias, and therefore these effects need to be confirmed via direct intervention trials involving mushroom consumption. Although preliminary, new studies reporting protective effects of mushrooms on beta-amyloid peptide toxicity and mild cognitive impairment (both precursors to dementia) appear promising and warrant further research. Studies in humans have shown an increase in the antioxidant capacity in urine and no evidence of liver, renal or DNA toxicity, and no clinical problems with regard to blood test results, liver and renal function, glucose and lipid metabolism, or blood pressure. Mushroom components/extracts have been reported to have stronger health effects/benefits than whole mushrooms in the limited number of direct human trials to date.

Mushrooms and mushroom components have been reported to have a myriad of positive health benefits, mainly on the basis of *in vitro* and *in vivo* animal trials. However, the majority of these effects are indirect in that they are due to a stimulation or modulation of natural cellular immunity. Mushrooms and mushroom components exert many of their positive effects on health via a balance of T helper cells, the induction of interferon-gamma and certain interleukins or NO-mediated mechanisms. Many of these immunomodulating effects are due to the polysaccharide content of mushrooms, either from beta-glucans or from polysaccharide–protein complexes.

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REFERENCES

Abel, O., Suzuki, T., Ogawa, A., Akati, T., Masuda, K., Koyama, T., Yazawa, K., & Kawagishi, H. (2007). Osteoclast forming suppressive compounds from the mushroom *Agrocybe chaxingu*. *Yakugaku Zasshi-Journal of the Pharmaceutical Society of Japan, 127*, 64–66.

Adams, L. S., Phung, S., Wu, X. W., Ki, L., & Chen, S. A. (2008). White button mushroom (*Agaricus bisporus*) exhibits antiproliferative and proapoptotic properties and inhibits prostate tumor growth in athymic mice. *Nutrition and Cancer, 60*, 744–756.

Ahn, W. S., Kim, D. J., Chae, G. T., Lee, J. M., Bae, S. M., Sin, J. I., Kim, Y. W., Namkoong, S. E., & Lee, I. P. (2004). Natural killer cell activity and quality of life were improved by consumption of a mushroom extract, *Agaricus blazei* Murill Kyowa, in gynecological cancer patients undergoing chemotherapy. *International Journal of Gynecological Cancer, 14*, 589–594.

Angeli, J. P., Ribeiro, L. R., Bellini, M. F., & Mantovani, M. S. (2009). Beta-glucan extracted from the medicinal mushroom *Agaricus blazei* prevents the genotoxic effects of benzo[a]pyrene in the human hepatoma cell line HepG2. *Archives of Toxicology, 83*, 81–86.

Angeli, J. P., Ribeiro, L. R., Gonzaga, M. L., Soares Sde, A., Ricardo, M. P., Tsuboy, M. S., Stidl, R., Knasmueller, S., Linhares, R. E., & Mantovani, M. S. (2006). Protective effects of beta-glucan extracted from *Agaricus brasiliensis* against chemically induced DNA damage in human lymphocytes. *Cell Biology and Toxicology, 22*, 285–291.

Badole, S. L., & Bodhankar, S. L. (2007). Interaction study of aqueous extract of *Pleurotus pulmonarius* (Fr.) Quel-champ with acarbose in alloxan induced diabetic mice. *Journal of Applied Biomedicine, 5*, 157–166.

Badole, S. L., Shah, S. N., Patel, N. M., Thakurdesai, P. A., & Bodhankar, S. L. (2006). Hypoglycemic activity of aqueous extract of *Pleurotus pulmonarius* in alloxan-induced diabetic mice. *Pharmaceutical Biology, 44*, 421–425.

Bae, J. S., Jang, K. H., & Jin, H. K. (2006). Effects of natural polysaccharides on the growth and peritoneal carcinomatosis of human gastric adenocarcinoma in a nude mouse model. *Cancer Letters, 235*, 60–68.

Bae, J. S., Park, J. W., Park, S. H., Park, J. B., Rho, Y. H., Ryu, Y. B., Lee, K. S., Park, K. H., & Bae, Y. S. (2009). Apoptotic cell death of human leukaemia U937 cells by ubiquinone-9 purified from *Pleurotus eryngii*. *Natural Product Research, 23*, 1112–1119.

Barbisan, L. F., Miyamoto, M., Scolastici, C., Salvadori, D. M., Ribeiro, L. R., Eira, A. F., & de Camargo, J. L. (2002). Influence of aqueous extract of *Agaricus blazei* on rat liver toxicity induced by different doses of diethylnitrosamine. *Journal of Ethnopharmacology, 83*, 25–32.

Barbisan, L. F., Scolastici, C., Miyamoto, M., Salvadori, D. M., Ribeiro, L. R., da Eira, A. F., & de Camargo, J. L. (2003). Effects of crude extracts of *Agaricus blazei* on DNA damage and on rat liver carcinogenesis induced by diethylnitrosamine. *Genetics and Molecular Research, 2*, 295–308.

Batterbury, M., Tebbs, C. A., Rhodes, J. M., & Grierson, I. (2002). *Agaricus bisporus* (edible mushroom lectin) inhibits ocular fibroblast proliferation and collagen lattice contraction. *Experimental Eye Research, 74*, 361–370.

Bauerova, K., Paulovicova, E., Mihalova, D., Svik, K., & Ponist, S. (2009). Study of new ways of supplementary and combinatory therapy of rheumatoid arthritis with immunomodulators. Glucomannan and Imunoglukan in adjuvant arthritis. *Toxicological and Industrial Health, 25*, 329–335.

Bernardshaw, S., Hetland, G., Ellertsen, L. K., Tryggestad, A. M., & Johnson, E. (2005a). An extract of the medicinal mushroom *Agaricus blazei* Murill differentially stimulates production of pro-inflammatory cytokines in human monocytes and human vein endothelial cells in vitro. *Inflammation, 29*, 147–153.

Bernardshaw, S., Hetland, G., Grinde, B., & Johnson, E. (2006). An extract of the mushroom *Agaricus blazei* Murill protects against lethal septicemia in a mouse model of fecal peritonitis. *Shock, 25*, 420–425.

Bernardshaw, S., Johnson, E., & Hetland, G. (2005b). An extract of the mushroom *Agaricus blazei* murill administered orally protects against systemic *Streptococcus pneumoniae* infection in mice. *Scandinavian Journal of Immunology, 62*, 393–398.

Borchers, A. T., Krishnamurthy, A., Keen, C. L., Meyers, F. J., & Gershwin, M. E. (2008). The immunobiology of mushrooms. *Experimental Biology and Medicine (Maywood), 233*, 259–276.

Calvino, E., Manjon, J. L., Sancho, P., Tejedor, M. C., Herraez, A., & Diez, J. C. (2010). *Ganoderma lucidum* induced apoptosis in NB4

human leukemia cells: Involvement of Akt and Erk. *Journal of Ethnopharmacology, 128*, 71–78.
Chen, S., Oh, S. R., Phung, S., Hur, G., Ye, I. J., Kwok, S. L., Shrode, G. E., Belury, M., Adams, L. S., & Williams, D. (2006). Anti-aromatase activity of phytochemicals in White Button Mushrooms (*Agaricus bisporus*). *Cancer Research, 66*, 12026–12034.
Chen, X., Wang, W., Li, S., Xue, J., Fan, L., Sheng, Z., & Chen, Y. (2010). Optimization of ultrasound-assisted extraction of Lingzhi polysaccharides using response surface methodology and its inhibitory effect on cervical cancer cells. *Carbohydrate Polymers, 80*, 944–948.
Chen, W., Zhao, Z., Chen, S.-F., & Li, Y.-Q. (2008). Optimization for the production of exopolysaccharide from *Fomes fomentarius* in submerged culture and its antitumor effect in vitro. *Bioresource Technology, 99*, 3187–3194.
Cheung, P. C. K., Wong, K. H., & Lai, C. K. M. (2011). Immunomodulatory activities of mushroom sclerotial polysaccharides. *Food Hydrocolloids, 25*, 150–158.
Cho, E. J., Hwang, H. J., Kim, S. W., Oh, J. Y., Baek, Y. M., Choi, J. W., Bae, S. H., & Yun, J. W. (2007). Hypoglycemic effects of exopolysaccharides produced by mycelial cultures of two different mushrooms *Tremella fuciformis* and *Phellinus baumii* in ob/ob mice. *Applied Microbiology and Biotechnology, 75*, 1257–1265.
Choi, D. B., Cha, W. S., Kang, S. H., & Lee, B. R. (2004). Effect of *Pleurotus ferulae* extracts on viability of human lung cancer and cervical cancer cell lines. *Biotechnology and Bioprocess Engineering, 9*, 356–361.
Cui, B., Han, L., Qu, J., & Lv, Y. (2009). Hypoglycemic activity of *Grifola frondosa* rich in vanadium. *Biological Trace Element Research, 131*, 186–191.
Deng, G., Lin, H., Seidman, A., Fornier, M., D'Andrea, G., Wesa, K., Yeung, S., Cunningham-Rundles, S., Vickers, A. J., & Cassileth, B. (2009). A phase I/II trial of a polysaccharide extract from *Grifola frondosa* (Maitake mushroom) in breast cancer patients: Immunological effects. *Journal of Cancer Research and Clinical Oncology, 135*, 1215–1221.
Eckhardt, S. G., Baker, S. D., Britten, C. D., Hidalgo, M., Siu, L., Hammond, L. A., Villalona-Calero, M. A., Felton, S., Drengler, R., Kuhn, J. G., Clark, G. M., Smith, S. L., Macdonald, J. R., Smith, C., Moczygemba, J., Weitman, S., von Hoff, D. D., & Rowinsky, E. K. (2000). Phase I and pharmacokinetic study of irofulven, a novel mushroom-derived cytotoxin, administered for five consecutive days every four weeks in patients with advanced solid malignancies. *Journal of Clinical Oncology, 18*, 4086–4097.
el Dine, R. S., el Halawany, A. M., Ma, C. M., & Hattori, M. (2008). Anti-HIV-1 protease activity of lanostane triterpenes from the vietnamese mushroom *Ganoderma colossum*. *Journal of Natural Products, 71*, 1022–1026.
el Dine, R. S., el Halawany, A. M., Ma, C. M., & Hattori, M. (2009). Inhibition of the dimerization and active site of HIV-1 protease by secondary metabolites from the Vietnamese mushroom *Ganoderma colossum*. *Journal of Natural Products, 72*, 2019–2023.
Endo, M., Beppu, H., Akiyama, H., Wakamatsu, K., Ito, S., Kawamoto, Y., Shimpo, K., Sumiya, T., Koike, T., & Matsui, T. (2010). Agaritine purified from *Agaricus blazei* Murrill exerts anti-tumor activity against leukemic cells. *Biochimica et Biophysica Acta, 1800*, 669–673.
Faccin, L. C., Benati, F., Rincao, V. P., Mantovani, M. S., Soares, S. A., Gonzaga, M. L., Nozawa, C., & Carvalho Linhares, R. E. (2007). Antiviral activity of aqueous and ethanol extracts and of an isolated polysaccharide from *Agaricus brasiliensis* against poliovirus type 1. *Letters in Applied Microbiology, 45*, 24–28.
Fortes, R. C., Novaes, M., Recova, V. L., & Melo, A. L. (2009). Immunological, hematological, and glycemia effects of dietary supplementation with *Agaricus sylvaticus* on patients' colorectal cancer. *Experimental Biology and Medicine, 234*, 53–62.
Fullerton, S. A., Samadi, A. A., Tortorelis, D. G., Choudhury, M. S., Mallouh, C., Tazaki, H., & Konno, S. (2000). Induction of apoptosis in human prostatic cancer cells with beta-glucan (Maitake mushroom polysaccharide). *Molecular Urology, 4*, 7–13.
Furlanetto, T. W. (2009). Vitamin D2 could be one of the protective phytochemicals. *International Journal of Cancer, 125*, 1994.
Gao, J.-J., Min, B.-S., Ahn, E.-M., Nakamura, N., Lee, H.-K., & Hattori, M. (2002). New triterpene aldehydes, lucialdehydes A–C, from *Ganoderma lucidum* and their cytotoxicity against murine and human tumor cells. *Chemical and Pharmaceutical Bulletin, 50*, 837–840.
Gao, L., Sun, Y., Chen, C., Xi, Y., Wang, J., & Wang, Z. (2007). Primary mechanism of apoptosis induction in a leukemia cell line by fraction FA-2-b-? prepared from the mushroom *Agaricus blazei* Murill. *Brazilian Journal of Medical and Biological Research, 40*, 1545–1555.
Gao, Y., Tang, W., Dai, X., Gao, H., Chen, G., Ye, J., Chan, E., Huang, M., & Zhou, S. (2005). Immune responses to water-soluble Ling Zhi mushroom *Ganoderma lucidum* (W.Curt.:Fr.) P. Karst. Polysaccharides in patients with advanced colorectal cancer. *International Journal of Medicinal Mushrooms, 7*, 525–537.
Gao, Y., Tang, W., Gao, H., Chan, E., Lan, J., & Zhou, S. (2004). *Ganoderma lucidum* polysaccharide fractions accelerate healing of acetic acid-induced ulcers in rats. *Journal of Medicinal Food, 7*, 417–421.
Gordon, M., Bihari, B., Goosby, E., Gorter, R., Greco, M., Guralnik, M., Mimura, T., Rudinicki, V., Wong, R., & Kaneko, Y. (1998). A placebo-controlled trial of the immune modulator, lentinan, in HIV-positive patients: A phase I/II trial. *Journal of Medicine, 29*, 305–330.
Grube, B. J., Eng, E. T., Kao, Y. C., Kwon, A., & Chen, S. (2001). White button mushroom phytochemicals inhibit aromatase activity and breast cancer cell proliferation. *Journal of Nutrition, 131*, 3288–3293.
Gu, Y.-H., & Belury, M. A. (2005). Selective induction of apoptosis in murine skin carcinoma cells (CH72) by an ethanol extract of *Lentinula edodes*. *Cancer Letters, 220*, 21–28.
Gu, Y. H., & Leonard, J. (2006). In vitro effects on proliferation, apoptosis and colony inhibition in ER-dependent and ER-independent human breast cancer cells by selected mushroom species. *Oncology Reports, 15*, 417–423.
Gu, C. Q., Li, J., & Chao, F. H. (2006). Inhibition of hepatitis B virus by D-fraction from *Grifola frondosa*: Synergistic effect of combination with interferon-alpha in HepG2 2.2.15. *Antiviral Research, 72*, 162–165.
Gu, C. Q., Li, J. W., Chao, F., Jin, M., Wang, X. W., & Shen, Z. Q. (2007). Isolation, identification and function of a novel anti-HSV-1 protein from *Grifola frondosa*. *Antiviral Research, 75*, 250–257.
Guo, J. J., Zhu, T. B., Collins, L., Xiao, Z. X. J., Kim, S. H., & Chen, C. Y. (2007). Modulation of lung cancer growth arrest and apoptosis by *Phellinus linteus*. *Molecular Carcinogenesis, 46*, 144–154.
Han, S.-B., Lee, C. W., Kang, J. S., Yoon, Y. D., Lee, K. H., Lee, K., Park, S.-K., & Kim, H. M. (2006). Acidic polysaccharide from *Phellinus linteus* inhibits melanoma cell metastasis by blocking cell adhesion and invasion. *International Immunopharmacology, 6*, 697–702.
Han, C., & Liu, T. (2009). A comparison of hypoglycemic activity of three species of basidiomycetes rich in vanadium. *Biological Trace Element Research, 127*, 177–182.
Harhaji, L., Mijatovic, S., Maksimov-Ivanic, D., Stojanovic, I., Momcilovic, M., Maksimovic, V., Tufegdzic, S., Marjanovic, Z., Mostarica-Stojkovic, M., Vucinic, Z., & Stosic-Grujicic, S. (2008). Anti-tumor effect of *Coriolus versicolor* methanol extract against mouse B16 melanoma cells: In vitro and in vivo study. *Food and Chemical Toxicology, 46*, 1825–1833.

Hearst, R., Nelson, D., McCollum, G., Millar, B. C., Maeda, Y., Goldsmith, C. E., Rooney, P. J., Loughrey, A., Rao, J. R., & Moore, J. E. (2009). An examination of antibacterial and antifungal properties of constituents of Shiitake (*Lentinula edodes*) and oyster (*Pleurotus ostreatus*) mushrooms. *Complementary Therapies in Clinical Practice, 15*, 5–7.

Hetland, G., Johnson, E., Lyberg, T., & Kvalheim, G. (2011). The mushroom *Agaricus blazei* Murill elicits medicinal effects on tumor, infection, allergy, and inflammation through its modulation of innate immunity and amelioration of Th1/Th2 imbalance and inflammation. *Advances in Pharmacological Sciences*, Article 157015. http://dx.doi.org/10.1155/2011/157015.

Hiramoto, K., Kaku, M., Kato, T., & Kikugawa, K. (1995). DNA strand breaking by the carbon-centered radical generated from 4-(hydroxymethyl) benzenediazonium salt, a carcinogen in mushroom *Agaricus bisporus*. *Chemico-Biological Interactions, 94*, 21–36.

Hong, K. J., Dunn, D. M., Shen, C. L., & Pence, B. C. (2004). Effects of *Ganoderma lucidum* on apoptotic and anti-inflammatory function in HT-29 human colonic carcinoma cells. *Phytotherapy Research, 18*, 768–770.

Hong, S. A., Kim, K., Nam, S. J., Kong, G., & Kim, M. K. (2008). A case–control study on the dietary intake of mushrooms and breast cancer risk among Korean women. *International Journal of Cancer, 122*, 919–923.

Hsu, C. H., Hwang, H. J., Chiang, Y. H., & Chou, P. (2008a). The mushroom *Agaricus blazei* Murill extract normalizes liver function in patients with chronic hepatitis B. *Journal of Alternative and Complementary Medicine, 14*, 299–301.

Hsu, C.-H., Liao, Y.-L., Lin, S.-C., Hwang, K.-C., & Chou, P. (2007). The mushroom *Agaricus blazei* Murill in combination with metformin and gliclazide improves insulin resistance in type 2 diabetes: A randomized, double-blinded, and placebo-controlled clinical trial. *Journal of Alternative and Complementary Medicine, 13*, 97–102.

Hsu, C. L., Yu, Y. S., & Yen, G. C. (2008b). Lucidenic acid B induces apoptosis in human leukemia cells via a mitochondria-mediated pathway. *Journal of Agricultural and Food Chemistry, 56*, 3973–3980.

Hwang, H. S., Lee, S. H., Baek, Y. M., Kim, S. W., Jeong, Y. K., & Yun, J. W. (2008). Production of extracellular polysaccharides by submerged mycelial culture of *Laetiporus sulphureus* var. miniatus and their insulinotropic properties. *Applied Microbiology and Biotechnology, 78*, 419–429.

Hye-Jin, H., Baek, Y. M., Kim, S. W., Kumar, G. S., Cho, E. J., Oh, J. Y., & Yun, J. W. (2007). Differential expression of kidney proteins in Streptozotocin-induced diabetic rats in response to hypoglycemic fungal polysaccharides. *Journal of Microbiology and Biotechnology, 17*, 2005–2017.

Ichinohe, T., Ainai, A., Nakamura, T., Akiyama, Y., Maeyama, J., Odagiri, T., Tashiro, M., Takahashi, H., Sawa, H., Tamura, S., Chiba, J., Kurata, T., Sata, T., & Hasegawa, H. (2010). Induction of cross-protective immunity against influenza A virus H5N1 by an intranasal vaccine with extracts of mushroom mycelia. *Journal of Medical Virology, 82*, 128–137.

Ikekawa, T., Maruyama, H., Miyano, T., Okura, A., Sawasaki, Y., Naito, K., Kawamura, K., & Shiratori, K. (1985). Proflamin, a new antitumor agent: Preparation, physicochemical properties and antitumor activity. *Japanese Journal of Cancer Research, 76*, 142–148.

Inuzuka, H., & Yoshida, T. (2002). Clinical utility of ABCL (Agaricus Mushroom Extract) treatment for C-type hepatitis. *Japanese Pharmacology and Therapeutics, 30*, 103–107.

Isai, M., Elanchezhian, R., Sakthivel, M., Chinnakkaruppan, A., Rajamohan, M., Jesudasan, C. N., Thomas, P. A., & Geraldine, P. (2009). Anticataractogenic effect of an extract of the oyster mushroom, *Pleurotus ostreatus*, in an experimental animal model. *Current Eye Research, 34*, 264–273.

Israilides, C., Kletsas, D., Arapoglou, D., Philippoussis, A., Pratsinis, H., Ebringerova, A., Hribalova, V., & Harding, S. E. (2008). In vitro cytostatic and immunomodulatory properties of the medicinal mushroom *Lentinula edodes*. *Phytomedicine, 15*, 512–519.

Itoh, H., Ito, H., & Hibasami, H. (2008). Blazein of a new steroid isolated from *Agaricus blazei* Murrill (himematsutake) induces cell death and morphological change indicative of apoptotic chromatin condensation in human lung cancer LU99 and stomach cancer KATO III cells. *Oncology Reports, 20*, 1359–1361.

Jagadish, L. K., Krishnan, V. V., Shenbhagaraman, R., & Kaviyarasan, V. (2009). Comparative study on the antioxidant, anticancer and antimicrobial property of *Agaricus bisporus* (J. E. Lange) imbach before and after boiling. *African Journal of Biotechnology, 8*, 654–661.

Jedinak, A., & Sliva, D. (2008). *Pleurotus ostreatus* inhibits proliferation of human breast and colon cancer cells through p53-dependent as well as p53-independent pathway. *International Journal of Oncology, 33*, 1307–1313.

Jeong, S., Jeong, Y., Yang, B., Islam, R., Koyyalamudi, S. R., Pang, G., Cho, K., & Song, C. (2010). White button mushroom (*Agaricus bisporus*) lowers blood glucose and cholesterol levels in diabetic and hypercholesterolemic rats. *Nutrition Research, 30*, 49–56.

Jiang, J. H., Grieb, B., Thyagarajan, A., & Sliva, D. (2008). Ganoderic acids suppress growth and invasive behavior of breast cancer cells by modulating Ap-1 and Nf-Kappa B signaling. *International Journal of Molecular Medicine, 21*, 577–584.

Jiang, J., Slivova, V., Harvey, K., Valachovicova, T., & Sliva, D. (2004a). *Ganoderma lucidum* suppresses growth of breast cancer cells through the inhibition of Akt/NF-kappaB signaling. *Nutrition and Cancer, 49*, 209–216.

Jiang, J., Slivova, V., & Sliva, D. (2006). *Ganoderma lucidum* inhibits proliferation of human breast cancer cells by down-regulation of estrogen receptor and NF-kappaB signaling. *International Journal of Oncology, 29*, 695–703.

Jiang, J., Slivova, V., Valachovicova, T., Harvey, K., & Sliva, D. (2004b). *Ganoderma lucidum* inhibits proliferation and induces apoptosis in human prostate cancer cells PC-3. *International Journal of Oncology, 24*, 1093–1099.

Jin, C. Y., Choi, Y. H., Moon, D. O., Park, C., Park, Y. M., Jeong, S. C., Heo, M. S., Lee, T. H., Lee, J. D., & Kim, G. Y. (2006). Induction of G2/M arrest and apoptosis in human gastric epithelial AGS cells by aqueous extract of *Agaricus blazei*. *Oncology Reports, 16*, 1349–1355.

Jin, C. Y., Kim, G. Y., & Choi, Y. H. (2008). Induction of apoptosis by aqueous extract of *Cordyceps militaris* through activation of caspases and inactivation of Akt in human breast cancer MDA-MB-231 Cells. *Journal of Microbiology and Biotechnology, 18*, 1997–2003.

Jin, C. Y., Moon, D. O., Choi, Y. H., Lee, J. D., & Kim, G. Y. (2007). Bcl-2 and caspase-3 are major regulators in *Agaricus blazei*-induced human leukemic U937 cell apoptosis through dephoshorylation of Akt. *Biological and Pharmaceutical Bulletin, 30*, 1432–1437.

Johnson, E., Forland, D. T., Saetre, L., Bernardshaw, S. V., Lyberg, T., & Hetland, G. (2009). Effect of an extract based on the medicinal mushroom *Agaricus blazei* murill on release of cytokines, chemokines and leukocyte growth factors in human blood ex vivo and in vivo. *Scandinavian Journal of Immunology, 69*, 242–250.

Kanaya, N., Kubo, M., Liu, Z., Chu, P., Wang, C., & Chen, Y.-C. Y. S. (2011). Protective effects of white button mushroom (*Agaricus bisporus*) against hepatic steatosis in ovariectomized mice as a model of postmenopausal women. *PLoS ONE, 6*, e26654.

Kawagishi, H., & Zhuang, C. (2008). Compounds for dementia from *Hericium erinaceum*. *Drugs of the Future, 33*, 149–155.

Khatun, K., Mahtab, H., Khanam, P. A., Sayeed, M. A., & Khan, K. A. (2007). Oyster mushroom reduced blood glucose and cholesterol in diabetic subjects. *Mymensingh Medical Journal, 16*, 94–99.

Kim, H. M., Kang, J. S., Kim, J. Y., Park, S. K., Kim, H. S., Lee, Y. J., Yun, J., Hong, J. T., Kim, Y., & Han, S. B. (2010). Evaluation of antidiabetic activity of polysaccharide isolated from *Phellinus linteus* in non-obese diabetic mouse. *International Immunopharmacology, 10*, 72–78.

Kim, K. C., & Kim, I. G. (1999). *Ganoderma lucidum* extract protects DNA from strand breakage caused by hydroxyl radical and UV irradiation. *International Journal of Molecular Medicine, 4*, 273–277.

Kim, Y. W., Kim, K. H., Choi, H. J., & Lee, D. S. (2005). Anti-diabetic activity of beta-glucans and their enzymatically hydrolyzed oligosaccharides from *Agaricus blazei*. *Biotechnology Letters, 27*, 483–487.

Kim, S. W., Kim, H. G., Lee, B. E., Hwang, H. H., Baek, D. H., & Ko, S. Y. (2006). Effects of mushroom, *Pleurotus eryngii*, extracts on bone metabolism. *Clinical Nutrition, 25*, 166–170.

Kim, T. I., Park, S. J., Choi, C. H., Lee, S. K., & Kim, W. H. (2004). Effect of ear mushroom (Auricularia) on functional constipation. *Korean Journal of Gastroenterology, 44*, 34–41.

Kim, H. G., Yoon, D. H., Lee, W. H., Han, S. K., Shrestha, B., Kim, C. H., Lim, M. H., Chang, W., Lim, S., Choi, S., Song, W. O., Sung, J. M., Hwang, K. C., & Kim, T. W. (2007). *Phellinus linteus* inhibits inflammatory mediators by suppressing redox-based NF-κB and MAPKs activation in lipopolysaccharide-induced RAW 264.7 macrophage. *Journal of Ethnopharmacology, 114*, 307–315.

Kondo, K., Watanabe, A., Akiyama, H., & Maitani, T. (2008). The metabolisms of agaritine, a mushroom hydrazine in mice. *Food and Chemical Toxicology, 46*, 854–862.

Kweon, M.-H., Kwon, S.-T., Kwon, S.-H., Ma, M.-S., & Park, Y. I. (2002). Lowering effects in plasma cholesterol and body weight by mycelial extracts of two mushrooms: *Agaricus blazai* and *Lentinus edodes*. *Korean Journal of Microbiology and Biotechnology, 30*, 402–409.

Kwon, A. H., Qiu, Z., Hashimoto, M., Yamamoto, K., & Kimura, T. (2009). Effects of medicinal mushroom (*Sparassis crispa*) on wound healing in streptozotocin-induced diabetic rats. *American Journal of Surgery, 197*, 503–509.

Lau, C. B. S., Ho, C. Y., Kim, C. F., Leung, K. N., Fung, K. P., Tse, T. F., Chan, H. H. L., & Chow, M. S. S. (2004). Cytotoxic activities of *Coriolus versicolor* (Yunzhi) extract on human leukemia and lymphoma cells by induction of apoptosis. *Life Sciences, 75*, 797–808.

Lee, G., Byun, H., Yoon, K., Lee, J., Choi, K., & Jeung, E. (2009a). Dietary calcium and vitamin D2 supplementation with enhanced *Lentinula edodes* improves osteoporosis-like symptoms and induces duodenal and renal active calcium transport gene expression in mice. *European Journal of Nutrition, 48*, 75–83.

Lee, S. H., Hwang, H. S., & Yun, J. W. (2009b). Antitumor activity of water extract of a mushroom, *Inonotus obliquus*, against HT-29 human colon cancer cells. *Phytotherapy Research, 23*, 1784–1789.

Lee, S. J., Kim, S. K., Choi, W. S., Kim, W. J., & Moon, S. K. (2009c). Cordycepin causes p21WAF1-mediated G2/M cell-cycle arrest by regulating c-Jun N-terminal kinase activation in human bladder cancer cells. *Archives of Biochemistry and Biophysics, 490*, 103–109.

Lei, H., Ma, X., & Wu, W. T. (2007). Anti-diabetic effect of an alpha-glucan from fruit body of Maitake (*Grifola frondosa*) on Kk-Ay mice. *Journal of Pharmacy and Pharmacology, 59*, 575–582.

Lin, S.-B., Li, C.-H., Lee, S.-S., & Kan, L.-S. (2003). Triterpene-enriched extracts from *Ganoderma lucidum* inhibit growth of hepatoma cells via suppressing protein kinase C, activating mitogen-activated protein kinases and G2-phase cell cycle arrest. *Life Sciences, 72*, 2381–2390.

Lin, Y. L., Liang, Y. C., Tseng, Y. S., Huang, H. Y., Chou, S. Y., Hseu, R. S., Huang, C. T., & Chiang, B. L. (2009). An immunomodulatory protein, Ling Zhi-8, induced activation and maturation of human monocyte-derived dendritic cells by the NF-kappaB and MAPK pathways. *Journal of Leukocyte Biology, 86*, 877–889.

Liu, J., Ning, A., Cao, J., & Huang, M. (2009). Preliminary study on the anti-tumor effect of protein extracts of *Lentinus edodes* C91–3 fermentation broth in mice with cervical cancer U14. *Zhongguo Weishengtaxixue Zazhi/Chinese Journal of Microecology, 21*, 622–623.

Louie, B., Rajamahanty, S., Won, J., Choudhury, M., & Konno, S. (2010). Synergistic potentiation of interferon activity with maitake mushroom D-fraction on bladder cancer cells. *BJU International, 105*, 1011–1015.

Lu, H., Yang, Y., Gad, E., Wenner, C. A., Chang, A., Larson, E. R., Dang, Y., Martzen, M., Standish, L. J., & Disis, M. L. (2011). Polysaccharide krestin is a novel TLR2 agonist that mediates inhibition of tumor growth via stimulation of CD8 T cells and NK cells. *Clinical Cancer Research, 17*, 67–76.

Lv, H., Kong, Y., Yao, Q., Zhang, B., Leng, F. W., Bian, H. J., Balzarini, J., van Damme, E., & Bao, J. K. (2009). Nebrodeolysin, a novel hemolytic protein from mushroom *Pleurotus nebrodensis* with apoptosis-inducing and anti-HIV-1 effects. *Phytomedicine, 16*, 198–205.

Mahmood, A., Suzita, N., Vikineswary, S., Noorlidah, A., Wong, K., & Hapipah Mohd, A. (2008). Effect of culinary-medicinal lion's mane mushroom, *Hericium erinaceus* (Bull.: Fr.) Pers. (Aphyllophoromycetideae), on ethanol-induced gastric ulcers in rats. *International Journal of Medicinal Mushrooms, 10*, 325–330.

Martins, P. R., Gameiro, M. C., Castoldi, L., Romagnoli, G. G., Lopez, F. C., Pinto, A. V., Loyola, W., & Kaneno, R. (2008). Polysaccharide-rich fraction of *Agaricus brasiliensis* enhances the Candidacidal activity of murine marophages. *Memorias Do Instituto Oswaldo Cruz, 103*, 244–250.

Meera, C. R., Smina, T. P., Balan, N., Mathew, J., & Janardhanan, K. K. (2009). Antiarthritic activity of a polysaccharide-protein complex isolated from *Phellinus rimosus* (Berk.) Pilat (Aphyllophoromycetideae) in Freund's complete adjuvant-induced arthritic rats. *International Journal of Medicinal Mushrooms, 11*, 21–28.

Miyamoto, I., Liu, J., Shimizu, K., Sato, M., Kukita, A., Kukita, T., & Kondo, R. (2009). Regulation of osteoclastogenesis by ganoderic acid DM isolated from *Ganoderma lucidum*. *European Journal of Pharmacology, 602*, 1–7.

Mizumoto, H., Ohnogi, H., Mizutani, S., Enoki, T., Asada, K., Sugimoto, Y., & Kato, I. (2008). Mechanism of apoptosis induced by polyterpene from Buna-shimeji (*Hypsizigus marmoreus*) in HL-60 cells. *Nippon Shokuhin Kagaku Kogaku Kaishi = Journal of the Japanese Society for Food Science and Technology,, 55*, 612–618.

Mori, K., Inatomi, S., Ouchi, K., Azumi, Y., & Tuchida, T. (2009). Improving effects of the mushroom Yamabushitake (*Hericium erinaceus*) on mild cognitive impairment: A double-blind placebo-controlled clinical trial. *Phytotherapy Research, 23*, 367–372.

Noguchi, M., Kakuma, T., Tomiyasu, K., Kurita, Y., Kukihara, H., Konishi, F., Kumamoto, S., Shimizu, K., Kondo, R., & Matsuoka, K. (2008a). Effect of an extract of *Ganoderma lucidum* in men with lower urinary tract symptoms: A double-blind, placebo-controlled randomized and dose-ranging study. *Asian Journal of Andrology, 10*, 651–658.

Noguchi, M., Kakuma, T., Tomiyasu, K., Yamada, A., Itoh, K., Konishi, F., Kumamoto, S., Shimizu, K., Kondo, R., & Matsuoka, K. (2008b). Randomized clinical trial of an ethanol extract of *Ganoderma lucidum* in men with lower urinary tract symptoms. *Asian Journal of Andrology, 10*, 777–785.

Nogusa, S., Gerbino, J., & Ritz, B. W. (2009). Low-dose supplementation with active hexose correlated compound improves the immune response to acute influenza infection in C57BL/6 mice. *Nutrition Research, 29*, 139–143.

Oba, K., Kobayashi, M., Matsui, T., Kodera, Y., & Sakamoto, J. (2009). Individual patient based meta-analysis of lentinan for unresectable/recurrent gastric cancer. *Anticancer Research, 29*, 2739–2745.

Oba, K., Teramukai, S., Kobayashi, M., Matsui, T., Kodera, Y., & Sakamoto, J. (2007). Efficacy of adjuvant immunochemotherapy with polysaccharide K for patients with curative resections of gastric cancer. *Cancer Immunology Immunotherapy, 56*, 905–911.

Obi, N., Hayashi, K., Miyahara, T., Shimada, Y., Terasawa, K., Watanabe, M., Takeyama, M., Obi, R., & Ochiai, H. (2008). Inhibitory effect of TNF-alpha produced by macrophages stimulated with *Grifola frondosa* extract (ME) on the growth of influenza a/Aichi/2/68 virus in MDCK cells. *American Journal of Chinese Medicine, 36*, 1171–1183.

Oh, T. W., Kim, Y. A., Jang, W. J., Byeon, J. I., Ryu, C. H., Kim, J. O., & Ha, Y. L. (2010). Semipurified fractions from the submerged-culture broth of *Agaricus blazei* Murill reduce blood glucose levels in streptozotocin-induced diabetic rats. *Journal of Agricultural and Food Chemistry, 58*, 4113–4119.

Palomares, M.R., Rodriguez, J., Phung, S., Stanczyk, F.Z., Lacey, S.F., Synold, T.W., Denison, S., Frankel, P.H., & Chen, S. (2011). A dose-finding clinical trail of mushroom powder in postmenopausal breast cancer survivors for secondary breast cancer prevention. *Journal of Clinical Oncology, 29*(15) (Suppl.), abstract p.1582.

Park, Y. K., Lee, H. B., Jeon, E. J., Jung, H. S., & Kang, M. H. (2004). Chaga mushroom extract inhibits oxidative DNA damage in human lymphocytes as assessed by Comet assay. *BioFactors, 21*, 109–112.

Pillai, T. G., Salvi, V. P., Maurya, D. K., Nair, C. K. K., & Janardhanan, K. K. (2006). Prevention of radiation-induced damages by aqueous extract of *Ganoderma lucidum* occurring in southern parts of India. *Current Science, 91*, 341–344.

Pinheiro, F., Faria, R. R., de Camargo, J. L., Spinardi-Barbisan, A. L., da Eira, A. F., & Barbisan, L. F. (2003). Chemoprevention of preneoplastic liver foci development by dietary mushroom *Agaricus blazei* Murrill in the rat. *Food and Chemical Toxicology, 41*, 1543–1550.

Ramberg, J. E., Nelson, E. D., & Sinnott, R. A. (2010). Immunomodulatory dietary polysaccharides: A systematic review of the literature. *Nutrition Journal, 9*(54) (on-line journal).

Ren, G., Zhao, Y.-P., Yang, L., & Fu, C.-X. (2008). Anti-proliferative effect of clitocine from the mushroom *Leucopaxillus giganteus* on human cervical cancer HeLa cells by inducing apoptosis. *Cancer Letters, 262*, 190–200.

Rocha, N. S., Barbisan, L. F., de Oliveira, M. L. C., & de Camargo, J. L. V. (2002). Mushroom-derived preparations in the prevention of H_2O_2-induced oxidative damage to cellular DNA. *Teratogenesis Carcinogenesis and Mutagenesis, 22*, 103–111.

Rondanelli, M., Opizzi, A., & Monteferrario, F. (2009). The biological activity of beta-glucans. *Minerva Medica, 100*, 237–245.

Rop, O., Mlcek, J., & Jurikova, T. (2009). Beta-glucans in higher fungi and their health effects. *Nutrition Reviews, 67*, 624–631.

Roupas, P., Keogh, J., Noakes, M., Margetts, C., & Taylor, P. (2010). Mushrooms and agaritine: A mini-review. *Journal of Functional Foods, 2*, 91–98.

Rovensky, J., Stancikova, M., Svik, K., Bauerova, K., & Jurcovicova, J. (2011). The effects of beta-glucan isolated from *Pleurotus ostreatus* on methotrexate treatment in rats with adjuvant arthritis. *Rheumatology International, 31*, 507–511.

Saif, A., Lindequist, U., & Wende, K. (2007). Stimulating effects of *Grifola frondosa* (Maitake) on human osteoblastic cell cultures. *Journal of Natural Medicines, 61*, 231–238.

Saitoh, H., Feng, W., Matsuzawa, T., & Ikekawa, T. (1997). Antitumor activity of *Hypsizigus marmoreus*. II. Preventive effect against lung metastasis of Lewis lung carcinoma. *Yakugaku Zasshi, 117*, 1006–1010.

Sakamoto, J., Morita, S., Oba, K., Matsui, T., Kobayashi, M., Nakazato, H., & Ohashi, Y. (2006). Efficacy of adjuvant immunochemotherapy with polysaccharide K for patients with curatively resected colorectal cancer: A meta-analysis of centrally randomized controlled clinical trials. *Cancer Immunology Immunotherapy, 55*, 404–411.

Sato, N., Zhang, Q., Ma, C. M., & Hattori, M. (2009). Anti-human immunodeficiency virus-1 protease activity of new lanostane-type triterpenoids from *Ganoderma sinense*. *Chemical and Pharmaceitical Bulletin (Tokyo), 57*, 1076–1080.

Seto, S. W., Lam, T. Y., Tam, H. L., Au, A. L., Chan, S. W., Wu, J. H., Yu, P. H., Leung, G. P., Ngai, S. M., Yeung, J. H., Leung, P. S., Lee, S. M., & Kwan, Y. W. (2009). Novel hypoglycemic effects of *Ganoderma lucidum* water-extract in obese/diabetic (+db/+db) mice. *Phytomedicine, 16*, 426–436.

Shi, Y.-L., Benzie, I. F. F., & Buswell, J. A. (2002). Role of tyrosinase in the genoprotective effect of the edible mushroom, *Agaricus bisporus*. *Life Sciences, 70*, 1595–1608.

Shimizu, K., Yamanaka, M., Gyokusen, M., Kaneko, S., Tsutsui, M., Sato, J., Sato, I., Sato, M., & Kondo, R. (2006). Estrogen-like activity and prevention effect of bone loss in calcium deficient ovariectomized rats by the extract of *Pleurotus eryngii*. *Phytotherapy Research, 20*, 659–664.

Shin, A., Kim, J., Lim, S. Y., Kim, G., Sung, M. K., Lee, E. S., & Ro, J. (2010). Dietary mushroom intake and the risk of breast cancer based on hormone receptor status. *Nutrition and Cancer, 62*, 476–483.

Shomori, K., Yamamoto, M., Arifuku, I., Teramachi, K., & Ito, H. (2009). Antitumor effects of a water-soluble extract from Maitake (*Grifola frondosa*) on human gastric cancer cell lines. *Oncology Reports, 22*, 615–620.

Soboleva, A. I. U., Krasnopol'Skaia, L. M., Fedorova, G. B., & Katrukha, G. S. (2006). Antibiotic properties of the strains of the basidiomycete *Lentinus edodes* (Berk.) sing. *Antibiotiki Khimioterapiya, 51*, 3–8.

Standish, L. J., Wenner, C. A., Sweet, E. S., Bridge, C., Nelson, A., Martzen, M., Novack, J., & Torkelson, C. (2008). *Trametes versicolor* mushroom immune therapy in breast cancer. *Journal of the Society for Integrative Oncology, 6*, 122–128.

Stanley, G., Harvey, K., Slivova, V., Jiang, J., & Sliva, D. (2005). *Ganoderma lucidum* suppresses angiogenesis through the inhibition of secretion of VEGF and TGF-beta1 from prostate cancer cells. *Biochemical and Biophysical Research Communications, 330*, 46–52.

Sumiyoshi, Y., Hashine, K., Kakehi, Y., Yoshimura, K., Satou, T., Kuruma, H., Namiki, S., & Shinohara, N. (2010). Dietary administration of mushroom mycelium extracts in patients with early stage prostate cancers managed expectantly: A phase II study. *Japanese Journal of Clinical Oncology, 40*, 967–972.

Sun, W., Yu, J., Shi, Y. M., Zhang, H., Wang, Y., & Wu, B. B. (2010). Effects of Cordyceps extract on cytokines and transcription factors in peripheral blood mononuclear cells of asthmatic children during remission stage. *Zhong Xi Yi Jie He Xue Bao, 8*, 341–346.

Talpur, N., Echard, B., Dadgar, A., Aggarwal, S., Zhuang, C., Bagchi, D., & Preuss, H. G. (2002). Effects of Maitake mushroom fractions on blood pressure of Zucker fatty rats. *Research Communications in Molecular Pathology and Pharmacology, 112*, 68–82.

Tao, Y. Z., Zhang, L., & Cheung, P. C. K. (2006). Physicochemical properties and antitumor activities of water-soluble native and sulfated hyperbranched mushroom polysaccharides. *Carbohydrate Research, 341*, 2261–2269.

Thyagarajan, A., Jiang, J., Hopf, A., Adamec, J., & Sliva, D. (2006). Inhibition of oxidative stress-induced invasiveness of cancer cells by *Ganoderma lucidum* is mediated through the suppression of interleukin-8 secretion. *International Journal of Molecular Medicine, 18*, 657–664.

Tsuji, T., Du, W., Nishioka, T., Chen, L., Yamamoto, D., & Chen, C. Y. (2010). *Phellinus linteus* extract sensitizes advanced prostate cancer cells to apoptosis in athymic nude mice. *PLoS ONE,* 5, e9885.

Tzi, B. N., Wang, H., & Wan, D. C. C. (2006). Polysaccharopeptide from the Turkey Tail fungus *Trametes versicolor* (L.:Fr.) pilat inhibits human immunodeficiency virus type 1 reverse transciptase and protease. *International Journal of Medicinal Mushrooms,* 8, 39–43.

Urbain, P., Singler, F., Ihorst, G., Biesalski, H-K., & Bertz, H. (2011). Bioavailability of vitamin D2 from UV-B-irradiated button mushrooms in healthy adults deficient in serum 25-hydroxyvitamin D: A randomized controlled trial. *European Journal of Clinical Nutrition*, 1–7.

Venturini, M. E., Rivera, C. S., Gonzalez, C., & Blanco, D. (2008). Antimicrobial activity of extracts of edible wild and cultivated mushrooms against foodborne bacterial strains. *Journal of Food Protection, 71*, 1701–1706.

Volman, J. J., Helsper, J. P., Wei, S., Baars, J. J., van Griensven, L. J., Sonnenberg, A. S., Mensink, R. P., & Plat, J. (2010b). Effects of mushroom-derived beta-glucan-rich polysaccharide extracts on nitric oxide production by bone marrow-derived macrophages and nuclear factor-kappaB transactivation in Caco-2 reporter cells: Can effects be explained by structure? *Molecular Nutrition and Food Research,* 54, 268–276.

Volman, J. J., Mensink, R. P., van Griensven, L. J., & Plat, J. (2010a). Effects of alpha-glucans from *Agaricus bisporus* on ex vivo cytokine production by LPS and PHA-stimulated PBMCs; a placebo-controlled study in slightly hypercholesterolemic subjects. *European Journal of Clinical Nutrition, 64*, 720–726.

Wachtel-Galor, S., Tomlinson, B., & Benzie, I. F. F. (2004). *Ganoderma lucidum* ('Lingzhi'), a Chinese medicinal mushroom: Biomarker responses in a controlled human supplementation study. *British Journal of Nutrition, 91*, 263–269.

Wan, J. M.-F., Sit, W.-H., & Louie, J. C.-Y. (2008). Polysaccharopeptide enhances the anticancer activity of doxorubicin and etoposide on human breast cancer cells ZR-75-30. *International Journal of Oncology, 32*, 689–699.

Wang, H. X., & Ng, T. B. (2000). Isolation of a novel ubiquitin-like protein from *Pleurotus ostreatus* mushroom with anti-human immunodeficiency virus, translation-inhibitory, and ribonuclease activities. *Biochemical and Biophysical Research Communications, 276*, 587–593.

Wang, H. X., & Ng, T. B. (2001). Examination of lectins, polysaccharopeptide, polysaccharide, alkaloid, coumarin and trypsin inhibitors for inhibitory activity against human immunodeficiency virus reverse transcriptase and glycohydrolases. *Planta Medica, 67*, 669–672.

Wang, L. H., Tsai, S. J., & Lin, S. Y. (2004). Aqueous extract from Taiwanese *Agrocybe cylindracea* strain B protects DNA against center. OH-mediated strand breaks. *Journal of Food and Drug Analysis, 12*, 277–285.

Wasonga, C. G., Okoth, S. A., Mukuria, J. C., & Omwandho, C. O. (2008). Mushroom polysaccharide extracts delay progression of carcinogenesis in mice. *Journal of Experimental Therapeutics and Oncology, 7*, 147–152.

Weng, C.-J., Chau, C.-F., Chen, K.-D., Chen, D.-H., & Yen, G.-C. (2007). The anti-invasive effect of lucidenic acids isolated from a new *Ganoderma lucidum* strain. *Molecular Nutrition and Food Research,* 51, 1472–1477.

White, R. W. D., Hackman, R. M., Soares, S. E., Beckett, L. A., & Sun, B. X. (2002). Effects of a mushroom mycelium extract on the treatment of prostate cancer. *Urology, 60*, 640–644.

Wong, C. K., Bao, Y. X., Wong, E. L. Y., Leung, P. C., Fung, K. P., & Lam, C. W. K. (2005). Immunomodulatory activities of Yunzhi and Danshen in post-treatment breast cancer patients. *American Journal of Chinese Medicine, 33*, 381–395.

Wong, K., Lai, C. K. M., & Cheung, P. C. K. (2011). Immunomodulatory activities of mushroom sclerotial polysaccharides. *Food Hydrocolloids, 25*, 150–158.

Wu, H. Y., Zhang, Q. X., & Leung, P. H. (2007). Inhibitory effects of ethyl acetate extract of *Cordyceps sinensis* mycelium on various cancer cells in culture and B16 melanoma in C57bl/6 mice. *Phytomedicine, 14*, 43–49.

Xu, X. F., Yan, H. D., Chen, J., & Zhang, X. W. (2011). Bioactive proteins from mushrooms. *Biotechnology Advances, 29*, 667–674.

Yamac, M., Kanbak, G., Zeytinoglu, M., Bayramoglu, G., Senturk, H., & Uyanoglu, M. (2008). Hypoglycemic effect of *Lentinus strigosus* (Schwein.) Fr. Crude exopolysaccharide in streptozotocin-induced diabetic rats. *Journal of Medicinal Food, 11*, 513–517.

Yoshimura, K., Kamoto, T., Ogawa, O., Matsui, S., Tsuchiya, N., Tada, H., Murata, K., Habuchi, T., & Fukushima, M. (2010). Medical mushrooms used for biochemical failure after radical treatment for prostate cancer: An open-label study. *International Journal of Urology, 17*, 548–554.

Youn, M. A., Kim, J. K., Park, S. Y., Kim, Y., Kim, S. J., Lee, J. S., Chai, K. Y., Kim, H. J., Cui, M. X., So, H. S., Kim, K. Y., & Park, R. (2008). Chaga mushroom (*Inonotus obliquus*) induces G(0)/G(1) arrest and apoptosis in human hepatoma HepG2 cells. *World Journal of Gastroenterology, 14*, 511–517.

Yu, L. G., Fernig, D. G., & Rhodes, J. M. (2000). Intracellular trafficking and release of intact edible mushroom lectin from HT29 human colon cancer cells. *European Journal of Biochemistry, 267*, 2122–2126.

Yu, L., Fernig, D. G., Smith, J. A., Milton, J. D., & Rhodes, J. M. (1993). Reversible inhibition of proliferation of epithelial cell lines by *Agaricus bisporus* (edible mushroom) lectin. *Cancer Research, 53*, 4627–4632.

Yu, C. H., Kan, S. F., Shu, C. H., Lu, T. J., Sun-Hwang, L., & Wang, P. S. (2009a). Inhibitory mechanisms of *Agaricus blazei* Murill on the growth of prostate cancer in vitro and in vivo. *Journal of Nutritional Biochemistry, 20*, 753–764.

Yu, Z. H., Yin, L. H., Qian, Y., & Yan, L. (2009b). Effect of *Lentinus edodes* polysaccharide on oxidative stress, immunity activity and oral ulceration of rats stimulated by phenol. *Carbohydrate Polymers, 75*, 115–118.

Zhang, M., Huang, J., Xie, X., & Holman, C. D. J. (2009). Dietary intakes of mushrooms and green tea combine to reduce the risk of breast cancer in Chinese women. *International Journal of Cancer, 124*, 1404–1408.

Zhao, L., Zhao, G. H., Du, M., Zhao, Z. D., Xiao, L. X., & Hu, X. S. (2008). Effect of selenium on increasing free radical scavenging activities of polysaccharide extracts from a Se-enriched mushroom species of the genus Ganoderma. *European Food Research and Technology, 226*, 499–505.

Zhao, L., Zhao, G., Hui, B., Mao, Z., Tong, J., & Hu, X. (2004). Effect of selenium on increasing the antioxidant activity of protein extracts from a selenium-enriched mushroom species of the Ganoderma genus. *Journal of Food Science, 69*, C184–C188.

Zhou, S., Gao, Y., & Chan, E. (2005). Clinical trials for medicinal mushrooms: Experience with *Ganoderma lucidum* (W.Curt.:Fr.) Lloyd (Lingzhi Mushroom). *International Journal of Medicinal Mushrooms, 7*, 111–117.

Ziliotto, L., Barbisan, L. F., & Rodrigues, M. A. M. (2008). Lack of chemoprevention of dietary *Agaricus blazei* against rat colonic aberrant crypt foci. *Human and Experimental Toxicology, 27*, 505–511.

Ziliotto, L., Pinheiro, F., Barbisan, L. F., & Rodrigues, M. A. M. (2009). Screening for in vitro and in vivo antitumor activities of the mushroom *Agaricus blazei*. *Nutrition and Cancer, 61*, 245–250.