Fungal Diversity (2012) 55:1–35
DOI 10.1007/s13225-012-0151-3

ORIGINAL PAPER

Medicinal mushrooms in supportive cancer therapies: an approach to anti-cancer effects and putative mechanisms of action

Dilani D. De Silva · Sylvie Rapior · Françoise Fons · Ali H. Bahkali · Kevin D. Hyde

Received: 19 December 2011 / Accepted: 5 January 2012 / Published online: 27 January 2012

Abstract Medicinal mushrooms have been valued as natural sources of bioactive compounds since times immemorial and have been recognized as potential immunomodulating and anti-cancer agents. Their consumption has consistently been shown to have beneficial effects on human health. Cancer is a generic term for several types of diseases that can be chronic and are responsible for a large number of deaths worldwide. Although there has been considerable progress in modern cancer therapy research, difficulties in understanding the molecular behavior of various types of cancers and the numerous side effects experienced by patients from treatments means that this whole subject area is still problematic. Thus, biological immunotherapy using natural bioactive compounds as supportive treatments in conventional cancer therapies has become in vogue. Bioactive metabolites isolated from medicinal mushrooms have shown potential successes in cancer treatment as biological immunotherapeutic agents that stimulate the immune system against cancer cells. They also act as an effective source of anti-cancer agents, capable of interfering with cellular signal transduction pathways linked to cancer development and progression. In this review we compile available data on the characteristics of medicinal mushrooms that appear to be particularly effective as biological immunotherapeutic agents. Major consideration is given to biological constituents and the putative mechanisms of action by which bioactive compounds act on the human body. Consideration is also given to the benefits that have been claimed for the use of mushrooms in treating cancer and the future prospects of using medicinal mushrooms as potent supportive candidate bioagents for treatment of cancers is discussed.

Keywords Medicinal mushrooms · Cancer · Anti-cancer · Immunomodulation · Bioactive metabolites

D. D. De Silva · K. D. Hyde (✉)
Institute of Excellence in Fungal Research,
Mae Fah Luang University,
333 M.1 T. Tasud Muang District,
Chiang Rai 57100, Thailand
e-mail: kdhyde3@gmail.com

D. D. De Silva
e-mail: desilvadilani9@gmail.com

D. D. De Silva · K. D. Hyde
School of Science, Mae Fah Luang University,
333 M.1 T. Tasud Muang District,
Chiang Rai 57100, Thailand

D. D. De Silva
Department of Botany, Faculty of Science,
University of Peradeniya,
Peradeniya 20500, Sri Lanka

S. Rapior · F. Fons
Faculty of Pharmacy, University Montpellier 1, UMR 5175 CEFE,
BP 14491, 15, avenue Charles-Flahault,
34093, Montpellier Cedex 5, France

S. Rapior
e-mail: sylvie.rapior@univ-montp1.fr

A. H. Bahkali · K. D. Hyde
Botany and Microbiology Department, College of Science,
King Saud University,
Riyadh 11442, Saudi Arabia

Introduction

It is thought that the consumption of medicinal mushrooms can be beneficial to humans through their ability to cure various diseases (Ying et al. 1987; Hobbs 1995; Francia et al. 1999, 2007; Rapior et al. 2000; Didukh et al. 2003; Ferreira et al. 2010). Medicinal mushrooms have been used as natural products for centuries in traditional therapies for

the treatment of many diseases. There is renewed interest in using mushrooms in traditional medicines and in establishing their medicinal properties (Ying et al. 1987; Hobbs 1995; Chang and Mshigeni 2000; Samorini 2001; Lindequist et al. 2010). Species of medicinal mushrooms have a long history of use in disease treatment in folk medicines, especially in countries such as China, India, Japan and Korea (Hobbs 1995, 2000, 2004, 2005; Chang 1999; Mizuno 1999a, b; Reshetnikov et al. 2001; Ajith and Janardhanan 2007). The primary taxa traditionally used in these countries are *Cordyceps* spp., *Fomes fomentarius*, *Fomitopsis officinalis, Ganoderma lucidum*, *Grifola frondosa, Inonotus obliquus, Lentinula edodes* and *Piptoporus betulinus* (Table 1) (Hobbs 1995; Zhu et al. 1998a, b; Mizuno 1999a, b; Rapior et al. 2000; Mayell 2001; Pöder 2005).

The kingdom Fungi is regarded as one of the most diverse groups of organisms, second only to insects and generally recogonised as comprising of 1.5 million species classified in five different phyla; numerous species are thought to be still undiscovered (Hyde 2001). A recent estimate even suggested that there may be over 5 million species (Blackwell 2011). Mushrooms are generally considered to be the spore-bearing fruiting body of higher fungi (or macrofungi) and most belong to the Basidiomycota. These along with some Ascomycota are used in traditional medicine for treatment of diseases (Chang and Miles 1992; Wasser and Weis 1999b; Miles and Chang 1997; Moradali et al. 2007; Ferreira et al. 2010).

Chronic diseases have become a growing burden throughout the world (Strong et al. 2005; Beaglehole and Horton 2010; WHO 2011). Chronic diseases are conditions that persist for a year or more and result in lifelong disability (limit the activities associated with daily living), thus causing a decreased quality of life (WHO 2008; CDC 2011). They require ongoing medical attention. Several chronic diseases such as heart disease, stroke, various cancers, chronic respiratory diseases and diabetes, are by far the leading cause of mortality in the world (CDC 2011; Moullec et al. 2011; Ninot et al. 2011; WHO 2011). Some mushroom extracts have been shown to have promising effects on cardiovascular diseases, cancers, diabetes and many other diseases as well as having anti-viral, anti-bacterial, anti-parasitic, anti-inflammatory, nephroprotective, neuroprotective and hepatoprotective effects (Wasser and Weis 1999a; Poucheret et al. 2006; Chen and Seviour 2007; Francia et al. 2007; Guillamón et al. 2010; Wasser 2011).

Cancer is a broad term that encompasses a complex group of more than 100 different types of cancerous diseases that can develop in the body. Most of these can be consider as chronic diseases, which represent one of the main health problems of mankind in the 21st century and have become the leading cause of death around the world (Stewart et al. 2003; WHO 2004, 2011). The estimates reported by WHO indicate that 84 million people will die of cancer between 2005 and 2015 if the disease is untreated (CDC 2011; WHO 2011). In the United States, cancer is the second most common cause of death among children between the years of 1 and 14 (Jemal et al. 2009). Leukemia (particularly acute lymphocytic leukemia) is the most common cancer causing death in these children, followed by cancer of the brain and other parts of the nervous system (Jemal et al. 2009). As a chronic disease may cause death or have long lasting effects throughout the lifetime of an individual, finding a cure for cancer is a major challenge faced by the whole world in this century.

Today, conventional cancer therapies mainly consist of surgery, chemotherapy and radiation therapy, depending on the type of cancer and the stage of tumor development inside the body (Gibbs 2000; Chan et al. 2009; ACS 2011). The major problem arising from these treatments, especially radiotherapy and chemotherapy, are that they invariably result in damage or weakening of the patient's natural immunological defenses (which may already have been damaged by the cancer itself) and numerous side

Table 1 Traditionally used mushroom species

Scientific name	Common name	Chinese name	Japanese name
Cordyceps spp.	Caterpillar fungi	Summer-grass winter-worm (congcao)	Tochukaso
Fomes fomentarius	Tinder fungus	Mu ti ceng kong jun	Tsuriganetake
Fomitopsis officinalis (*Laricifomes officinalis*)	Wood conk or Agaricon	Ku bai ti	Tsugasarunokosikake
Ganoderma lucidum sensu lato	Ling zhi	Ling zhi or reishi	Saruno koshikake Mannentake
Grifola frondosa	Hen of the woods, Dancing mushroom	Hui Shu Hua	Maitake
Inonotus obliquus	Chaga, Cinderconk, Clinker fungus, Kabanoanatake	Bai Hua Rong	
Lentinula edodes	Shiitake, huagu, snake butter,	Xiang gu	Shiitake
Piptoporus betulinus	Birch polypore	Hua bo guan jun	Kanbatake

effects, causing serious damage and suffering to the patient (Devereux et al. 1997; Ratain and Relling 2001; Ehrke 2003; Maduro et al. 2003; Anon 2011).

Curing cancers has now focused on improving the patient's quality of life by modifying the host's biological response against the malignant invasion. As a supportive help to the treatments mentioned above, biological immunotherapy (sometimes called immunotherapy, biotherapy, or biological response modifier therapy) is now gaining more attention, since it considerably reduces the side effects and helps to overcome cancer growth (Leung et al. 2006; NCI 2006). This is a relatively new addition to the family of cancer treatments that includes conventional therapies mentioned above. Biological therapies use the body's immune system, either directly or indirectly, to fight cancer or to lessen the side effects that may be caused by some cancer treatments (Ehrke 2003; Auerbach 2006; NCI 2006; Kakimi et al. 2009).

There are many forms of biological immunotherapeutic agents, such as monoclonal anti-bodies, cancer vaccines, interferons, interleukins, colony-stimulating factors, gene therapy, and nonspecific immunomodulating agents (NCI 2006). Based on Asiatic ancestral knowledge, medicinal mushrooms are receiving more attention due to their immune-enhancing and stimulatory activities inside the human body (Kodama et al. 2005; Endo et al. 2010; Ferreira et al. 2010). Many mushroom-derived extracts are therefore recognized as immunomodulators or as biological response modifiers (BRMs) (Mizuno 1999a, b; Wasser and Weis 1999a, b; Wasser 2002; Leung et al. 2006; Zhang et al. 2007; Novak and Vetvicka 2009). In particular, medicinal mushrooms not only act as strong immunostimulators but also as a source of good anti-cancer agents, capable of interfering with particular cellular signal transduction pathways linked to cancer development and progression (Zaidman et al. 2005; Petrova et al. 2008; Kudugunti et al. 2010). Currently, more than 30 species of scientifically identified medicinal mushrooms have demonstrated anti-tumor activity in experimental studies (Wasser 2011).

In this review we discuss the biological nature of cancer and how medicinal mushrooms (also referred to as macromycetes) act as immunomodulatory agents. We identify the unique characteristics of medicinal mushrooms that qualify them for immunostimulation and anti-cancer effects and propose several fields of cancer therapy in which the use of mushrooms appears to be particularly effective. Major consideration is given to biological constituents and the hypothesized mechanisms of action by which bioactive compounds act on the human body. Finally, we explore the available nutraceutical and anti-cancer drugs with possible anti-cancer benefits and discuss the future prospectives of medicinal mushrooms as a potent supportive candidate for treatment of cancers. As a note of caution we must state that there are many medicinal mushroom products on the market that claim to have anti-cancer benefits, but in most cases these claims have not been verified. Therefore, the purpose of this review is to bring together the available scientific data relevant to the anti-cancer effects of consuming medicinal mushrooms and their products so that the reader can make a balanced judgment as to whether they might be effective. We do not claim at any stage of this review that consumption of medicinal mushrooms or their products can cure cancer.

Basic mechanisms of cancers

In general, cancer is an abnormal growth of cells that tend to proliferate in an uncontrolled way and, in some cases, to metastasize or spread (Borchers et al. 2004; Zaidman et al. 2005; Ruddon 2007; NCI 2011). Uncontrolled cell proliferation can be induced by many factors (biotic and abiotic), including chemical, physical, or biological agents (Anand et al. 2008; NCI 2011; WHO 2011).

The early stage of a cancer can be referred to as a neoplasm, an abnormal mass of tissue which results due to the autonomous (abnormal proliferation) growth of cells (Nowell 1986; Franks 1997; Ruddon 2007). The growth of neoplastic cells exceeds and is not coordinated with the normal tissues around it. Most neoplasms develope due to the clonal expansion of a single cell that has undergone neoplastic transformation. The transformation of a normal cell to a neoplastic cell can be caused by environmental chemicals, viruses, bacteria, hormones, and chronic inflammations that directly and irreversibly alter the cell genome (Franks 1997; Anand et al. 2008). This usually results in a lump or tumor. Neoplasms can be further classified into benign, potentially malignant (pre-cancer), or malignant (cancer) (Zaidman et al. 2005).

Cancer is a generic term for malignant neoplasms and three major developmental stages are often recognized (Feinberg et al. 2006). The first is initiation, in which a mutagen binds to the cell DNA and causes damage, which is insufficient to induce tumor production. The second stage is activation of a tumor promoter that causes the formation of small benign tumors (pre-cancer). Finally, in the third stage, progression, the normal genomic control over the cell cycle stops, resulting in uncontrolled cell proliferation (Nowell 1986; Borchers et al. 2004).

Neoplastic cells are characterized by the loss of some specialized functions and the acquisition of new biological properties (Fidler 1978; Franks 1997; Zaidman et al. 2005). They are usually less differentiated than normal cells and contain invading cells, which can multiply in the absence of growth-promoting factors required for proliferation of normal cells. Cancer cells are resistant to signals normally

causing programmed cell death (apoptosis). Cancer cells have limitless replicative potential, sustained angiogenesis (new blood vessel formation), and tissue invasion and metastasis (Fidler 1978). Neoplastic cells pass on their heritable biological characteristics to progeny cells (Abercrombie and Ambrose 1962; Nowell 1986; Anon 2010).

As noted above, cancer is a generic term for several types of diseases that may occur in different parts or organs of the human body (NCI 2011). Although there are many therapeutic techniques available in modern medicine to control or remove cancers, nearly all of them exert some kind of a side effect that affects the patient in long term (Kumar et al. 2005; ACS 2011).

Biologically active metabolites found in medicinal mushrooms may provide anti-cancer action with a minimum of side effects. Most of them activate natural immune responses of the host and therefore possibly can be used as supportive treatments for cancer prevention along with conventional therapies (Gao et al. 2004; Hyodo et al. 2005). Tables 2 and 3 provide information on some of the commonly used species of mushrooms with their reported bioactive metabolites claimed to be beneficial in cancer treatments.

Major bioactive compounds in medicinal mushrooms

Medicinal mushrooms have shown therapeutic action against the development of cancer cells, primarily because they contain a number of biologically active compounds (Bao et al. 2001a; Petrova et al. 2005; Moradali et al. 2007; Zhang et al. 2007; Lee and Hong 2011). This includes mainly high molecular weight compounds such as polysaccharides, proteins and lipids as well as a number of low molecular weight metabolites such as lectins, lactones, terpenoids, alkaloids, sterols and phenolic substances (Kidd 2000; Chan et al. 2009; Zhong and Xiao 2009). These substances have their origins as derivatives from many intermediates in the pathways involved in primary metabolism. Medicinal mushroom metabolites can therefore broadly be divided into two groups: (1) high molecular weight metabolites and (2) low molecular weight metabolites.

In the natural environment, fungi acquire nutrients from the surrounding substrata via the vegetative hyphae of the mycelium (Griffin 1994; Selosse 2000). This is used to acquire the energy required to maintain their primary metabolism (Isaac 1997). However, under adverse environmental conditions where nutrient depletion occurs, growth of the fungus slows down and parts of the mycelium switch to using various biochemical pathways (Isaac 1997). Primary metabolites that have accumulated in the fungus are converted to different products (known as secondary metabolites) which are not normally produced during the active growth and are not essential for normal vegetative proliferation (Mizuno et al. 1995b; Zjawiony 2004; Erkel and Anke 2008; Zhong and Xiao 2009).

Most of these fungal-derived constituents are important as bioactive metabolites that may be active against diseases such as cancer. Fungal bioactive metabolites provide their immunomodulating activity mainly through the activation of the natural immune system of the body of the host by interfering with several signal transduction pathways linked to cancer development (Zhang et al. 2007). It has been recognized that exceptional/abnormal gene expression is the fundamental cause of many diseases, including cancer (Jones and Baylin 2007; Ruddon 2007). Modulation of the intracellular signal transduction pathways and the activation of transcription factors regulating gene expression and many other cell mediated pathways have become novel therapeutic targets for such disorders (Clarke et al. 2001). Important pathways involved in cancer development are the nuclear factor-kappa B (NF-κB) pathway, mitogen activated protein kinase pathway (MAPK), AMP-activated kinase pathway, protein inhibitory pathways and many more others (Nakamura et al. 2003; Kumar et al. 2004; Zaidman et al. 2005; Tergaonkar 2006; Petrova et al. 2008; Wong et al. 2010a, b). Significantly, modulation of the nuclear factor-kappa B (NF-κB) pathway is crucial in cancer development as it induces the expression of genes coding for antigen receptors on immune cells, anti-apoptotic factors, cell adhesion molecules, pro-inflammatory cytokines or chemo attractants and angiogenesis factors for inflammatory cells (Kumar et al. 2004).

High molecular weight bioactive metabolites

In this review we refer to the high molecular weight compounds found in medicinal mushrooms that are mainly polysaccharides, polysaccharide-protein complexes/glycoconjugates (glycoproteins, glycopeptides, proteoglycans) and proteins which are produced through primary metabolism and essential for their continuous growth and biomass production (Isaac 1997; Wasser 2002; Moradali et al. 2007; Erkel and Anke 2008). These metabolites are integral constituents of the fungal fruiting body as well as the mycelium.

Polysaccharides (β-glucans)

Polysaccharides (carbohydrates), belonging to structurally diverse classes of macromolecules, are polymers that can be found abundantly in the cell walls of macrofungi. They are composed of various chemical compositions, including β-glucans (Mizuno et al. 1992, 1995a, b), hetero-β-glucans, glycans and heteroglycans (Gao et al. 1996), with immunomodulating and anti-tumor properties. Glucans are

Table 2 High molecular weight bioactive compounds of medicinal mushrooms which show anti-cancer effects

Mushroom species	Bioactive compounds (and common name)	References
Agaricus subrufescens (A. blazei Murrill A. brasiliensis)	Glucans β-(1→6)-D-polyglucose	Oshiman et al. 2002
Agrocybe cylindracea	α-(1→3)-D-glucan	Yoshida et al. 1996
Armillaria tabescens	α-(1→6)-D-glucan	Luo et al. 2008
Auricularia polytricha	(1→3)-linked-β-D glucopyranosyl (1→3, 6)-linked-β-D-glucopyranosyl	Song and Du 2010
Calvatia caelata (Lycoperdon utriforme)	Peptides	Lam et al. 2001
	Calcaelin (protein)	Ng et al. 2003
Cordyceps sinensis (Ophiocordyceps sinensis)	Polysaccharides	Sheng et al. 2011
	β-(1→3;1→4)-glucan	Zhang et al. 2008
Clitocybe nebularis	Ricin B-like lectin	Pohleven et al. 2009
Cryptoporus volvatus	β-(1→3)-glucan	Kitamura et al. 1994
Flammulina velutipes	FIP-fve immunomodulatory protein	Ko et al. 1995
Ganoderma lipsiense (G. applanatum)	Exo polysaccharides, glucans	Lee et al. 2007a
		Usui et al. 1983
Ganoderma lucidum sensu lato	Ganopoly	Paterson 2006
	β-(1→3;1→6)-glucan *Ganoderma* polysaccharides	Gao et al. 2003
	LZ- 8 Immunomodulatory protein	Lin et al. 2009
	GSG (*G. lucidum* spores glucan)	Guo et al. 2009
Ganoderma sinensis	FIP-gsi immunomodulatory protein	Li et al. 2010a
Ganoderma tsugae	FIP-gts immunomodulatory protein	Hsiao et al. 2008
Grifola frondosa	Maitake D-Fraction β-(1→3;1→6)-glucans with xylose and mannose	Matsui et al. 2001
Hericium erinaceus	Xylan, glucoxylan, β-glucans	Kim et al. 2011
		Lee and Hong 2010
Hypsizygus marmoreus	Hypsin proteins	Lam and Ng 2001
Inonotus obliquus	Endo-polysaccharide	Kim et al. 2006
	α-linked fucoglucomannan	Mizuno et al. 1999
Lentinula edodes	Lentinan β-(1→3;1→6)-glucan	Zhang et al. 2011
	Chain of (1→4), (1→3) glucanose residues with side chains of (1→4) glucanose	Yu et al. 2010
Lentinus polychrous	Polysaccharides	Thetsrimuang et al. 2011
Lentinus strigellus	Polysaccharides	Lin et al. 2004
Leucopaxillus giganteus	Galactomannoglucans	Mizuno et al. 1995a, b
Phellinus linteus	Proteoglycan (Protein-bound polysaccharides) mixed α/β-linkages and α-(1→6)-branched type (1→3)-glycans	Kim et al. 2003a
		Kim et al. 2003b
		Tsuji et al. 2010
Phellinus igniarius	Endo-polysaccharide	Yang et al. 2009
		Chen et al. 2011
Phellinus rimosus	Sporocarp extract	Ajith and Janaradhanan 2003
Pholiota adiposa (Hypodendrum adiposum)	Lectins	Zhang et al. 2009
Pleurotus ostreatus	β-glucans, Heteroglucans	Wasser and Weis 1999a, b
Pleurotus pulmonarius	Xyloglucan, proteoglucans	Zhuang et al. 1993
Pleurotus citrinopileatus	PCP-3A (Nonlectin glycoprotein) immunomodulatory protein	Chen et al. 2010a
Polyporus umbellatus (Dendropolyporus umbellatus)	Glucan	Yang et al. 2004
		Li et al. 2010c
Russula lepida	Lectins	Zhang et al. 2010

Table 2 (continued)

Mushroom species	Bioactive compounds (and common name)	References
Sparassis crispa	β- (1→3)-D-glucan	Ohno et al. 2003; Ohno et al. 2000
Schizophyllum commune	Schizophyllan (sizofiran or SPG)	Hobbs 2005
	(β-1→3;1→6-glucan)	Chan et al. 2009
Taiwanofungus camphorates (*Antrodia camphorata*)	Polysaccharides	Chen et al. 2010b
		Liu et al. 2004
Trametes versicolor	Polysaccharide peptide Protein bound β-(1→3;1→6)-glucan	Ooi and Liu 2000
	Polysaccharide-Kureha or polysaccharide-K, krestin	Price et al. 2010
	Immunomodulatory protein	Feng et al. 2011
Tremella fuciformis	β-(1→3)-D-glucans, heteroglycans with α-(1→3)-mannan backbone & xylose- and glucuronic acid side chains	Bin 2010
Tremella mesenterica	GXM (glucuronoxylomannan α-(1→3)-mannan)	Vinogradov et al. 2004
Tricholoma mongolicum	Lectins, sugar-binding proteins	Wang et al. 1996

polysaccharides composed of exclusively D-glucose sub units, while heteroglucans contain side chains of monosaccharides (i.e., glucose, galactose, mannose, xylose, arabinose, fucose, ribose or glucuronic acid) and may have different combinations of these (Zhang et al. 2007).

Glycans are polysaccharides containing units other than glucose in their structural backbone (Moradali et al. 2007). According to the basic sugar component in the main backbone, glycans are classified as galactans, fucans, xylans, and mannans. Heteroglycans contain side chains of different sugars such as arabinose, mannose, fucose, galactose, xylose and glucose as a main component or in different combinations (Wasser 2002; Moradali et al. 2007).

β-Glucans are one of the major constituents that make up the cell wall of fungi (Moradali et al. 2007; Novak et al. 2010). The basic β-D-glucans (i.e., linear polymers of D-glucose with other monosaccharides) are a repeating structure, with their D-glucose molecules joined together in linear chains by β-bonds (glycosidic bonds). These can extend from the carbon 1 of one saccharide ring to the carbon 3 of the next β-(1→3), from carbon 1 to carbon 4 β-(1→4), or from carbon 1 to carbon 6 β-(1→6). They differ from each other by their length and branching structures (Demleitner et al. 1992; Kidd 2000). In different aqueous solutions, β-glucans undergo conformational changes into triple helix, single helix or random coils. The immune functions of β-glucans are apparently dependent on their conformational complexity (Ohno 2005; Chen and Seviour 2007; Moradali et al. 2007; Chen et al. 2008a, b).

Some glucans are linear or branched molecules that have a backbone composed of β- or α-linked glucose units (Fig. 1a,b), and some of these contain side chains that are attached at different positions (Wasser 2002; Moradali et al. 2007). The polysaccharide chain is mainly either β-(1→3) and β-(1→4), or mixed β-(1→3), β-(1→4) with β-(1→6) side chains (Kidd 2000). Hetero-β-D-glucans, which are linear polymers of glucose with other D-monosaccharides, can have anti-cancer activity, but α-D-glucans from mushrooms usually lack anti-cancer activity (Wasser 2002).

It has been suggested that a high degree of structural complexity is associated with more potent immunomodulatory and anti-cancer effects (Mizuno et al. 1996; Mizuno 1999a, b). The primary structure and bioactivity of a polysaccharide can vary according to its monosaccharide composition, configuration and position of glycosidic linkages, sequence of monosaccharides, as well as the nature, number and location of appended non-carbohydrate groups (Chen and Seviour 2007). Mushroom polysaccharides bound to proteins or peptides (polysaccharide-peptides) show higher potent anti-tumor activity than the corresponding free glucans (Sakagami and Aoki 1991; Cui and Chisti 2003).

Accordingly, mushroom polysaccharide-protein complexes can have different variations in their chemical structures such as glycoproteins (Kawagishi et al. 1989) and heteroglycanprotein complexes (Zhuang et al. 1993; Mizuno et al. 1996) glycopeptides and proteoglucans (Cui and Chisti 2003; Lee et al. 2010).

Hypothesized mechanism of action of β-glucans on cancer cells

Mushroom polysaccharides or β-glucans are thought to provide their anti-tumor action primarily through the activation of the immune response of the host organism (immunoenhancing activity/immune-modulation activity). In most cases mushroom polysaccharides do not directly affect tumor cells. Instead, they help the host to tolerate adverse biological

Table 3 Low-molecular-weight compounds from mushrooms that exert anti-cancer effects by interfering with cellular signal transduction pathways

Mushroom species	Bioactive compounds	Anti-cancer effects	References
Agaricus subrufescens (A. blazei Murrill, A. brasiliensis)	Agaritine [β-N-(γ-L(+)-glutamyl)-4-(hydroxymethyl) phenylhydrazine]	Induction of apoptosis in U937 leukemic cells via caspase-3/-9 activation through cytochrome c release from mitochondria.	Endo et al. 2010 Akiyama et al. 2011
	Ergosterol	Inhibition of neovascularization induced by Lewis lung carcinoma cells (tumor-induced neovascularization) Direct inhibition of angiogenesis induced by solid tumors.	Takaku et al. 2001
Agaricus bisporus	Caffeic acid phenethyl ester (CAPE)	Inhibition of NF-κB binding to DNA Suppression of aromatase activity	Grube et al. 2001
Albatrellus confluens	Grifolin	Inhibition of tumor cell growth by inducing apoptosis Induction of cell-cycle arrest in G1 phase via the ERK1/2 pathway	Ye et al. 2005, 2007
Antrodia cinnamomea	4-Acetylantroquinonol B	Inhibition of proliferation and growth of hepatocellular carcinoma cells (HCC). Arresting of cell cycle via cyclin-dependent kinases (CDKs) pathway (decreases of CDK2 and CDK4 and increase of the p27)	Lin and Chiang 2011
Armillaria mellea (Lepiota mellea)	Arnamial and related sesquiterpene aryl esters	Induction of apoptosis in different cancer cell lines	Misiek et al. 2009 Kim et al. 2010
Clitocybe alexandri	Clitocine [6-amino-5-nitro-4-(β-D-ribo-furanosylamino) pyrimidine]	Growth inhibitory activity against lung, colon and gastric human cancer cells.	Vaz et al. 2010
Cordyceps sinensis (*Ophiocordyceps sinensis)*	5α,8α-Epidioxy-22*E*-ergosta-6,22-dien-3β-ol	Cytotoxic effects on promyelocytic leukemia HL-60 cells	Li et al. 2004 Matsuda et al. 2009
	Ergosterol	Induction of apoptosis through activation of caspases-3/7.	Wu et al. 2007
Cordyceps militaris	Cordycepin (3′-deoxyadenosine)	Induction of apoptosis of human leukemia cells through a Reactive oxygen species (ROS)-mediated caspase pathway. Including mitochondrial dysfunction, activation of caspases, and cleavage of poly (ADP-ribose) polymerase protein.	Jeong et al. 2011
Cordyceps sinensis			
Trametes versicolor	Methanol extract (terpenoids & polyphenols)	In-vivo anti-melanoma activity through anti-proliferative, cytotoxic effects on tumor cells and promotion of macrophage activity	Harhaji et al. 2008
Ganoderma colossum (Polyporus colossus)	Lucidenic acids Colossolactones A-G	Inhibition of HepG2 cancer cell invasion by acting as inhibitor on the phorbol-12-myristate-13-acetate (PMA)-induced matrix metalloproteinase (MMP-9) expression.	Kleinwächter et al. 2001
Ganoderma lucidum sensu lato	Lucidenic acid B, triterpenoid compounds, ganoderic acids, lucidimol, ganodermanondiol, ganoderiol and ganodermanontriol	Induction of the apoptosis through a signaling cascade of death receptor-mediated and mitochondria-mediated, caspase pathways associated with inactivation of the Akt signal pathway.	Tang et al. 2006b Jang et al. 2010 Hsu et al. 2008
Ganoderma lucidum	Triterpenoid (ganoderic acid T)	Inhibition of tumor metastasis by the suppression of NF-κB activation likely abrogates the expression of matrix metalloproteinase MMP-2 and MMP-9.	Xu et al. 2010
	Ergosterol	Induction of apoptosis	Paterson 2006

Table 3 (continued)

Mushroom species	Bioactive compounds	Anti-cancer effects	References
Ganoderma sinensis	Ethanol extracts of both *G. lucidum* and *G. sinensis*	Activities on human breast cancer, hepatoma and myeloid leukemia. Anti- proliferation effect through apoptosis pathway and cell cycle arrest effect	Liu et al. 2009a
Grifola frondosa	Triacylglycerols (1-oleoyl-2-linoleoyl-3-palmitoylglycerol)	Inhibition of Cyclooxygenase activity	Zhang et al. 2002
Hericium erinaceus	Ethanol extracts containing terpenoids, sterols and phenols	Apoptosis, suppression of the cell proliferation via activation of mitochondria-mediated caspase-3 and -9	Kim et al. 2011 Mizuno 1999c
Inonotus obliquus	3β-hydroxy-lanosta-8,24-dien-21-al, inotodiol and lanosterol	In vivo anti-tumor effects on cancer cells.	Chung et al. 2010
		Inhibition proliferation of cancer cells through caspase-3 dependent apoptosis (Inotodiol)	Nomura et al. 2008
Lentinula edodes	Caffeic acid phenethyl ester (CAPE)	Inhibition of NF-κB binding to DNA Suppression of aromatase activity	Mattila et al. 2001
Lentinus crinitus	Panepoxydone	Interferes with the NF-κB mediated signal by inhibiting phosphorylation of IkB	Erkel et al. 1996
Lepista inversa	Clitocine [6-amino-5-nitro-4-(β-D-ribo-furanosylamino) pyrimidine]	Anti-tumor effects through the induction of apoptosis	Fortin et al. 2006 Bezivin et al. 2003
Leucopaxillus giganteus	Clitocine [6-amino-5-nitro-4-(β-D-ribo-furanosylamino) pyrimidine]	Induction of apoptosis by the activation of caspase-8, 9, and 3, release of cytochrome c from mitochondria, decrease of the Bcl-2 level, and increase of the Bax level.	Ren et al. 2008
Marasmius oreades	Sesquiterpenes	Anti-tumor effects through the blockage of NF-κB activation at the IκB kinase (IKK) activation pathway.	Petrova et al. 2007, 2009
	Mycelia culture extract	Inhibition of TNF-α-induced iNOS expression through both NF-κB and MAPK-dependent mechanisms	Ruimi et al. 2010
Omphalotus illudens	Irofulven (6-hydroxymethyl acylfulvene)	Inhibition of DNA synthesis, cell cycle arrest in S phase and induction of caspase-mediated apoptosis.	Alexandre et al. 2007
	Derivative of mushroom toxin illudin-S (sesquiterpene)	Induction of protein oxidation and mitochondrial dysfunction.	Herzig et al. 2003
Panus conchatus	Panepoxydone	Panepoxydone inhibits the TNF-α- or TPA-induced phosphorylation and degradation of IκB.	Umezawa 2006
	Cycloepoxydon	Cycloepoxydon a potent NF-κB inhibitory activity	Zaidman et al. 2005
Phellinus igniarius	Phelligridins (pyrano[4,3-c][2]benzopyran-1, 6-dione) derivatives	Cytotoxic activity against several human cancer cell lines	Wang et al. 2007 Mo et al. 2004
Phellinus linteus	Hispolon	Induction of apoptosis by ROS mediated caspase pathway leading to cytochrome c release & mitochondria dysfunction.	Chen et al. 2008a
	Caffeic acid phenethyl ester (CAPE)	Inhibition of DNA binding of NF-κB. Induction of the maturation of dendritic cells via NF-κB, ERK and p38 MAPK signal pathways	Nakamura et al. 2003
Pholiota spumosa	Putrescine-1,4-dicinnamide (phenylpropanoid derivative conjugated with polyamine putrescine)	Induction of apoptosis by ROS mediated caspase pathway leading to cytochrome c release and necrosis.	Russo et al. 2007

Table 3 (continued)

Mushroom species	Bioactive compounds	Anti-cancer effects	References
Polyporus umbellatus (Dendropolyporus umbellatus)	Cytotoxic steroids ergones (22E, 24R)-ergosta-7, 22-dien-3β-ol	Anti-cancer activity against HepG2 cells.	Zhao et al. 2010b
Poria cocos (Wolfiporia extensa)	Lanostane-type triterpene acids	Inhibitory effect on skin tumor promotion.	Akihisa et al. 2009
Taiwanofungus camphoratus (Antrodia camphorata)	Terpenoids(zhankuic acid A,C) maleic and succinic acid derivatives	Induction of apoptosis via suppression of the expression of apoptosis associated proteins	Chen et al. 2010b Yeh et al. 2009 Nakamura et al. 2004
Thelephora aurantiotincta	Thelephantin O, vialinin A, (p-terphenyl derivatives)	Anti-cancer activity against HepG2 and human colonic carcinoma cells.	Norikura et al. 2011

stresses and exert an enhanced immunity against development of cancer cells by supporting some or all of the major biological systems. These are recognized as Biological Response Modifiers (Parkinson 1995; Mizuno 1999b; Wasser and Weis 1999b; Kidd 2000; Zhang et al. 2007).

The human immune system has a remarkable ability to distinguish between the body's own cells, recognized as "self" and foreign cells, as "nonself", to mediate the immune responses. Mushroom β-glucans are a large group of macromolecules that are not naturally synthesized inside the human body, so these compounds are recognized as non-self molecules which activate the immunity (Brown and Gordon 2005).

Based on in vivo and in vitro studies on animals, it has been found that β-glucans rapidly enter the proximal small intestine (Fig. 2) and are captured by the macrophages after oral administration (Hong et al. 2004; Rice et al. 2005; Lehne et al. 2006; Chan et al. 2009). The β-glucans are then divided into smaller sized β-glucan fragments and are carried to the bone marrow and endothelial reticular system (Hong et al. 2004). These small fragments are then released by the macrophages and taken up by the circulating granulocytes, monocytes and dendritic cells (Hong et al. 2004; Rice et al. 2005). A natural immune response then is initiated with the support of β-glucans (Chan et al. 2009).

The human immune system consists of two major functional units, including the innate immune system and the adaptive or acquired immune system (McNeela and Mills 2001; Revillard 2002; Uthaisangsook et al. 2002). Innate immunity is present from the very beginning of an organism's life and is relatively non-specific, capable of responding to many but not all structurally related antigens (Uthaisangsook et al. 2002). The innate immune system does not confer long-lasting immunity against a pathogen (Brown and Gordon 2001; Munz et al. 2005).

Certain β-glucans from medicinal mushrooms appear to activate cell-mediated and humoral immunity via activation of different immune cells, leading to elimination of tumor cells or pathogens (Ladanyi et al. 1993; Kim et al. 1996; Kurashige et al. 1997; Brown et al. 2002). The activated macrophages (containing β-glucans) preferentially attack dead cells and intracellular pathogens (Munz et al. 2005). These macrophages also produce cytokines that prime natural killer (NK) cells and T lymphocytes, both of which are cytotoxic to tumor cells, via different mechanisms. Natural killer cells (NKs) secrete chemical substances that destroy tumor cells by bursting cell membranes. Neutrophils effectively destroy targeted cells by cell mediated phagocytosis (Prestwich et al. 2008).

The adaptive immune system allows for a stronger immune response as well as immunological memory, where each pathogen is "remembered" by a signature antigen (Revillard 2002; Munz et al. 2005). The adaptive immune

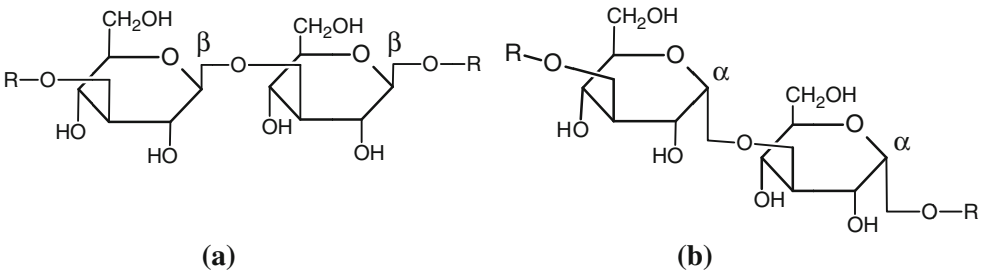


Fig. 1 Schematic representation of the molecular structure of β-(1→3)-D-glucans (**a**), and α-(1→3)-D-glucans (**b**)

response is antigen-specific and requires the recognition of specific "non-self" antigens in a process with combinational effect of T-cells (T lymphocytes) and B-cells (B lymphocytes). T-cells are mainly responsible for inducing cell-mediated immunity, whereas B cells produce antibodies that mediate humoral immunity (McNeela and Mills 2001; Revillard 2002). The adaptive immune response also involves dendritic cells, derived from monocytes, and these present antigens to T-cells for activation of immune responses (Munz et al. 2005). Cytotoxic T-cells secrete cytokines that stimulate cell mediate immunity to produce other tumoricidal chemical substances (Trinchieri 2003; Munz et al. 2005).

The hypothesized mechanism of action for fungal β-glucans against cancer cells in Fig. 3 is composed of a complex series of reactions inducing innate and adaptive immune systems (Chan et al. 2009). It should be noted, however, that all of these hypothesized mechanism of actions are based on animal data and there is very little evidence from human trials (Knudsen et al. 1993; Hong et al. 2004; Rice et al. 2005; Lehne et al. 2006; Vetvicka et al. 2007; Vos et al. 2007).

Membrane receptors involved in immune-modulation

Immune-modulation is a novel cancer treatment that involves indirect activation of the patient's natural immune defense system against pathogens (NCI 2006). Fungal β-glucans act as immunostimulants, involving both innate and adaptive immune responses. The reactor cells included in this process are monocytes, macrophages, dendritic cells, natural killer cells and neutrophils (Munz et al. 2005; Chen and Seviour 2007; Chan et al. 2009). β-Glucans also enhance phagocytosis and trigger a cascade of cytokine release, such as Tumor Necrosis Factor-alpha (TNF-α) and various types of interleukins (Leung et al. 2006; Chen and Seviour 2007).

The immune system of a multicellular organism is comprised of some special protein receptors called pattern recognition receptors, which detect strange compounds or nonself structures in the body (Leung et al. 2006; Chen and Seviour 2007). The microbe-specific molecules (nonself) that are recognized by a given pattern recognition receptors are called pathogen-associated molecular patterns. Thus, fungal β-glucans act as pathogen-associated molecular patterns on

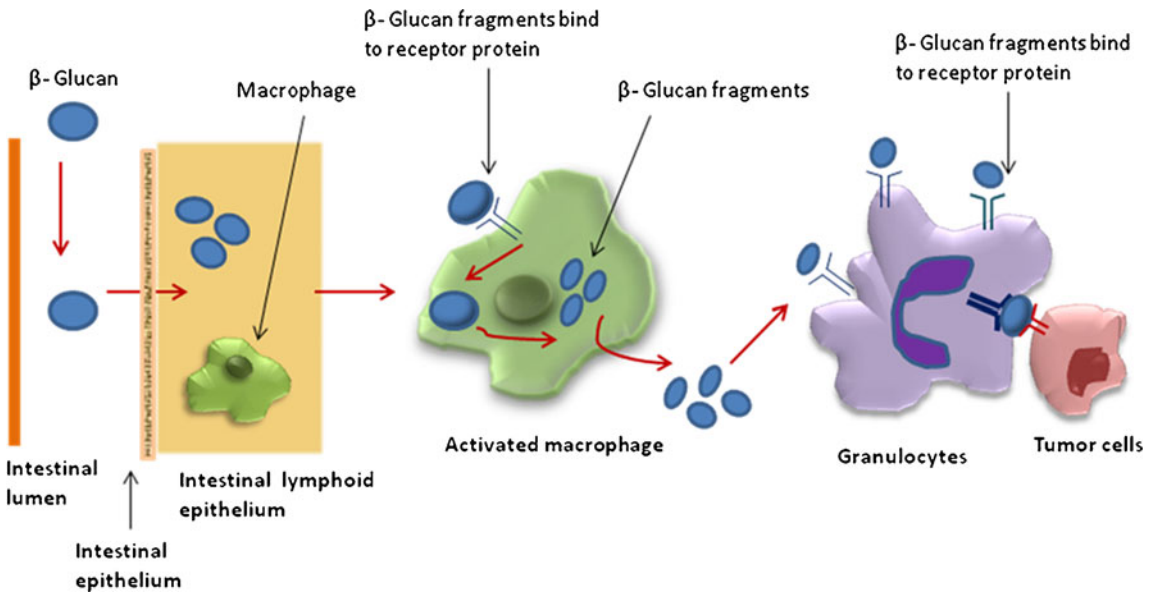


Fig. 2 β-glucan activation of macrophages (based on Chan et al. 2009 with modifications)

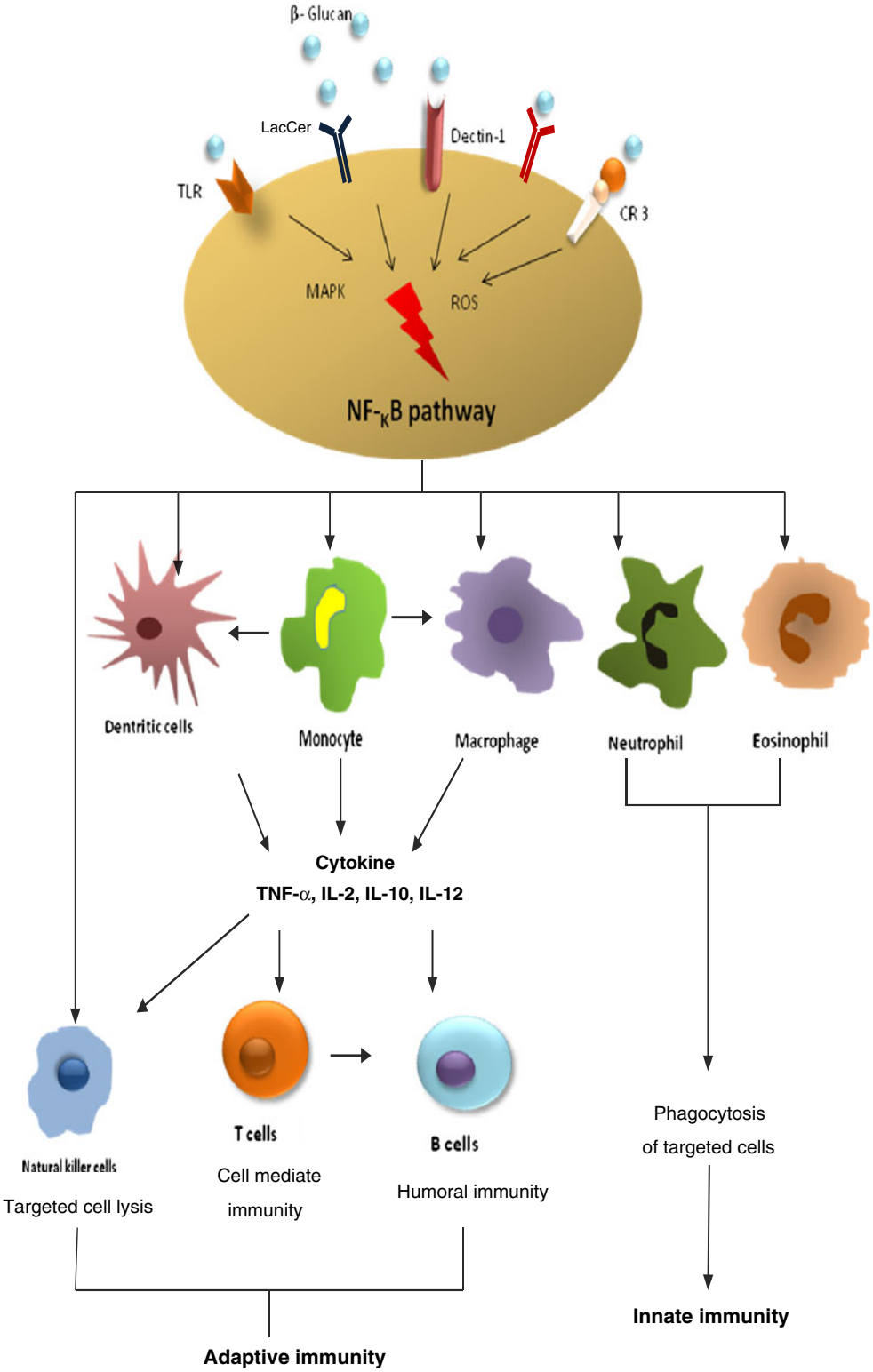


Fig. 3 Hypothesized immunostimulatory mechanism of action of β-glucans on immune cells (Chan et al. 2009)

these cell membrane receptors and trigger the immune function (Brown and Gordon 2005). In humans, a number of different receptors have been identified. These are dectin-1, complement receptor-3, scavenger receptors, lactosylceramide, and toll-like receptors (Gantner et al. 2003; Rogers et al. 2005; Brown 2006).

Evidence suggests that dectin-1 is a type II transmembrane protein receptor that binds β-(1→3) and β-(1→6)-

glucans and is most important in the activation of innate immune responses in macrophages (Herre et al. 2004; Willment et al. 2005). Binding of dectin-1 with β-glucans activates several signaling pathways to promote innate immune responses through activation of phagocytosis, reactive oxygen species production, and induction of inflammatory cytokines (Willment et al. 2001; Grunebach et al. 2002).

Toll-like receptors are a group of transmembrane protein receptors which respond to microbes, including fungi, bacteria, viruses and protozoa. This group of protein receptors may include about 11 members (Roeder et al. 2004). Toll-like receptor-2 induces the synthesis of various signaling pathways, including increasing levels of NF-κB and cytokine production, including TNF-α and interleukin (IL-12), which is mediated during many immune responses. Most recent studies have concluded that constituents from polysaccharopeptide krestin act as ligands for toll-like receptors-4, leading to induction of TNF-α and interleukin (IL-6) inflammatory cytokines (Price et al. 2010). Although their immune activities are still unclear, complement receptor-3; scavenger receptors and lactosylceramide receptors are also important in immune function (Thornton et al. 1996; Xia and Ross 1999).

Some evidence suggests that in a number of instances these receptors might act synergistically with each other to produce strong inflammatory responses by stimulating cytokines such as TNF-α, interleukins (IL-2 and IL-12) (Ariizumi et al. 2000; Takeda et al. 2003; Diniz et al. 2004).

Selected examples of important mushroom polysaccharides with anti-tumor activity

Mushroom-derived β-glucans have been used for centuries for health purposes. β-glucans have also been the subject of extensive research and are recognized as potential anti-cancer agents (Hobbs 1995; Kodama et al. 2002a, b; Zhang et al. 2005; Boonyanuphap and Hansawasdi 2010). β-Glucans derived from many different mushrooms, both cultivated and wild species, such as lentinan, schizophyllan, maitake D fraction, *Ganoderma* polysaccharides and Krestin have been approved in several countries as prescription drugs for the treatments of cancer (Mizuno 1999b; Girzal et al. 2011; Shang et al. 2011). Among the large pool of anti-tumor polysaccharides isolated from medicinal mushrooms (Table 2), several important examples are described below.

Lentinan

Lentinan is an anti-tumor polysaccharide produced by *Lentinula edodes*, which is commonly known as the Shiitake mushroom. This mushroom is widely consumed as a nutritional health food throughout the world, particularly in Asia, and is known to have very strong host-mediated anti-cancer activity via activation of the human immune system (Cheung 2008; Zhang et al. 2011). The chemical structure of lentinan is a β-(1→3)-D-glucan having two β-(1→6)-D-glucopyranoside branches for every five β-(1→3)-D-glucopyranoside linear linkages, with a moderate molecular weight of $5–15\times10^5$ Da (Zhang et al. 1999, 2001).

The molecular weight and a triple-helical conformation are known to be important factors for the immune-stimulating activity of lentinan (Bohn and BeMiller 1995). Triple-helical lentinan exhibits the strongest anti-cancer activity in mouse model experiments, with an inhibition ratio of 49.5%, which is close to that of a reference anti-cancer drug. Such bioactivity rapidly decreased when the polysaccharide changed to a single-flexible chain, thus showing the correlation between anti-cancer activity and the triple-helix structure of lentinan (Zhang et al. 2005; Surenjav et al. 2006).

The effective anti-cancer properties of lentinan were first reported by Chihara et al. (1969, 1970), using sarcoma 180 cancer cells transplanted into CD-1/ICD mice. Lentinan was shown to inhibit the growth of the cancer cells (Chihara et al. 1970). Lentinan has also satisfactorily been proven to potentiate human immunity (Wasser and Weis 1999a; Hobbs 2000). The immunostimulatory effects of lentinan involve the activation of numerous immune cells and modulating the release of cell signal messengers such as cytokines and chemical messengers such as nitric oxide, which increase the engulfing ability of immune cells (Ooi and Liu 1999; Hou and Chen 2008). The increase in cytokine production in immune cells has been demonstrated to be lentinan dose-dependent and inhibited the expression of caspase-3 in mice with liver cancer, reducing tumor growth (Shin et al. 2003; Lull et al. 2005; Fu et al. 2011).

The effect of chemically modified lentinan on the immune response indicates that sulfation can enhance the efficacy of lentinan to improve the human immune response to vaccines by enhancing the population of anti-body and white blood cells (Guo et al. 2008).

Open-label clinical studies indicate that lentinan can prolong life in patients with gastric, ovarian or colorectal cancer, as reviewed by several researchers (Borchers et al. 1999; Fujimoto et al. 2006).

Schizophyllan

Schizophyllan, sizofiran or SPG is another extensively studied mushroom-derived polysaccharide with immune modulating activity. This polysaccharide is obtained from the mushroom *Schizophyllum commune* and has been used in cancer treatment practices in several Asian countries (Furue 1987; Wasser 2002). Schizophyllan is a β-(1→3)-D-glucan,

having β-(1→6)-D-glucopyranoside side branches at every three repeating units, and it has received great interest because of its reversible coiled-helix transition. This generates a very stiff triple-helical structure in water, with a molecular weight of ~450,000 Da in neutral aqueous solutions (Yoneda et al. 1991). Although schizophyllan is similar to lentinan in composition and anti-tumor activity (Jong et al. 1991), the kinetics of gene expression of cytokines in schizophyllan have been shown to be different in several studies (Nemoto et al. 1993; Okazaki et al. 1995). Recently, new folate-conjugated schizophyllan showed specific affinity toward folate binding proteins and as a non-cytotoxic cancer-targeting antisense carrier that mediated effective antisense activity in cancer cells (Hasegawa et al. 2005). Schizophyllan displayed anti-tumor activity against several carcinomas and sarcoma cell lines (Wasser 2002; Hobbs 2005) and has been studied for its anti-cancer activity and used for the immunotherapy of stage II or III cervical cancers in combination with radiotherapy (Furue 1987; Sakagami et al. 1988; Shimizu et al. 1989). Clinical evaluation of schizophyllan as a surpportive agent on immunotherapy in treatment of head and neck cancer showed increased recovery rates in cancer patients when compared to a control group (Kimura et al. 1994).

Maitake D-fraction

This is a mixed β-D-glucan fraction prepared from the fruiting bodies of the mushroom *Grifola frondosa* (Maitake). This well known mushroom has been used as a food in Japan for hundreds of years, as people have believed in its medicinal properties (Mizuno 1999b; Mayell 2001). Maitake D-fraction contains mainly β-D-glucan material with β-(1→6) main chains and β-(1→4) branches, and the more common β-(1→3) main chains and β-(1→6) branches (Nanba 1997a; Matsui et al. 2001).

Experimental evidence has shown that maitake D-Fraction is a good apoptosis inducer and immune enhancer (Nanba 1997a, b; Konno 2001; Kodama et al. 2002a, b; Masuda et al. 2010). Most recent findings have confirmed the apoptotic effect of maitake D-fraction in breast cancer cells by upregulation of BAK-1 gene activation and further highlight the involvement of cytochrome C (Soares et al. 2011). Studies also suggest that the anti-tumor activity is also possibly related to the carcinoma angiogenesis induction (Matsui et al. 2001).

In 1998, the Food and Drug Administration (FDA) granted Maitake products, as an investigational new drug application (IND), to conduct a phase II pilot study using maitake D-fraction on patients with advanced breast and prostate cancers (Nanba 1995; Anon 1999; Konno 2001). Several in vivo and in vitro studies tested the chemosensitizing effect of the maitake fraction to improve the efficacy of chemotherapy and reduce possible side effects (Kodama et al. 2002b; Louie et al. 2010). Reduction of the immunosuppressive effect of chemotherapeutic drugs occurred as a result of an increase in the proliferation differentiation and activation of immune-competent cells and thus provided a potential clinical benefit for patients with cancer (Kodama et al. 2002b, 2005). Investigations showed the anti-tumor functions of D-Fraction in relation to its control of the balance between T lymphocyte subsets Th-1 and Th-2 and potentiated the activation of helper T-cells, resulting in enhanced cellular immunity and as a useful immunotherapeutic agent for cancer patients (Kodama et al. 2002b; Inoue et al. 2002).

Ganoderma polysaccharides

Mushrooms belonging to the genus *Ganoderma* are some of the oldest traditional medicines. In particular, *Ganoderma lucidum* (Reishi or Ling-Zhi) has been used extensively in traditional Chinese medicine as a tonic for promoting good health, perpetual youth, vitality, and longevity (Ying et al. 1987; Hobbs 1995; Chang and Mshigeni 2000).

This species has been intensively studied in recent years because of its intrinsic immunomodulating and anti-tumor properties (Liu et al. 2009a; Shang et al. 2011; Ye et al. 2011). It has become more important because the polysaccharides isolated from its fruiting bodies include some in which the main active ingredients contain (1→3) and/or β-(1→6)-D-glucans (Hung et al. 2008).

These polysaccharides have been reported to enhance the cytotoxic activity of natural killer cells and to increase TNF-α and interferon-γ release from macrophages and lymphocytes, respectively (Gao et al. 2004; Kuo et al. 2006). Recently, a crude extract of the polysaccharide from fruiting bodies has been reported to induce cytokines expression via a toll-like receptors-4 modulated protein kinase signaling pathway (Guo et al. 2009). Heteropolysaccharide–protein complexes with protein contents of 13.5 and 20.1% have also been isolated from the mycelium of *Ganoderma tsugae* and have been shown to have anti-tumor activities (Peng et al. 2005). It is generally believed that the compounds obtained from the mycelium are normally quite different from the metabolites of the same compound class derived from its sporocarps. As such, these results should be tested further.

The biological activities reported in preparations of *Ganoderma* mostly emphasize metabolites that include mainly polysaccharides and terpenoids. Research indicates that triterpenes from *G. lucidum* directly suppress growth and invasive behavior of cancer cells (Sliva 2003). On the other hand, the polysaccharides stimulate the immune system, resulting in the production of cytokines and activation of anti-cancer activities of immune cells, thus resulting

in a high synergistic effect (Gao et al. 2004; Anon 2006; Paterson 2006).

In recent years, much attention has been paid to the chemical components of *G. lucidum* spores and their versatile biological activities. It has been found that one such compound produces potential immunomodulatory effects and anti-tumor activities characteristic of a water-soluble polysaccharide, with proliferative response of splenocytes and induced anti-tumor activity against Lewis lung cancer in mice. It was an effective inducer of the MAPK pathway and spleen tyrosine kinase Syk-dependent TNF-α and interleukin-6 secretion in murine resident peritoneal macrophages (Guo et al. 2009). Moreover, the chemically modified α-D-glucan from spores of *G. lucidum* shows increasing stimulating effects of lymphocyte proliferation and antibody production when compared to unmodified glucans (Bao et al. 2001a, b).

In vitro and in vivo experimental evidence has demonstrated the chemopreventive effects of *G. lucidum* on cancer invasion and metastasis and it has been concluded that these effects occur through the modulation of kinase signaling and subsequent inhibition of activator protein-1 and NF-κB (Weng and Yen 2010). Most recent research found that the immunostimulatory activity of a proteoglycan fraction, (LZ-D-7), isolated from the fruiting body, activates the B-cells and could be an immunostimulatory drug to improve the immune response of tumor patients (Ye et al. 2011). Another study illustrated the induction of apoptosis by ethanol extracts of *G. lucidum* in human gastric carcinoma cells (Jang et al. 2010).

Polysaccharide—protein complexes (glycoproteins, glycopeptides, proteoglucans)

Medicinal mushrooms show an immunostimulatory activity not only because of bioactive polysaccharides but also in having varying combinations of polysaccharide-protein complexes or glycol-conjugates such as glycoproteins, glycopeptides and proteoglucans (Moradali et al. 2007). Polysaccharides can reach a higher level of complexity when they are covalently bound to other conjugate molecules such as polypeptides and proteins.

Glycoproteins are proteins that contain oligosaccharide chains (glucans) covalently attached to polypeptide side-chains. They are composed of a protein core that is surrounded by numerous glucan chains bound to protein moiety through O- or N-glycosidation (Wasser 2002; Moradali et al. 2007). *Agaricus subrufescens* (= *Agaricus blazei* Murrill *sensu* Heinemann) is a well-known mushroom having several biologically active metabolites, including polysaccharides and glycoproteins that are thought to be responsible for its immunostimulant and anti-tumor properties (Firenzuoli et al. 2008). A α-(1→4)-Glucan-β-(1→6)-glucan-protein complex isolated from *A. subrufescens* showed tumor growth-inhibitory effect through the host-mediated mechanisms, and several clinical trials have shown its pharmacological benefits on cancer treatment and immunostimulation (Gonzaga et al. 2009; Ishii et al. 2011).

Glycopeptides from *Trametes versicolor*

The best known commercial glycopeptide preparations of *Trametes versicolor* are polysaccharopeptide and polysaccharopeptide krestin. Both products are extracted from *T. versicolor* and have similar physiological activities but are structurally different. Polysaccharopeptide and polysaccharopeptide krestin are produced from CM-101 and Cov-1 strains of *T. versicolor,* respectively. Polysaccharopeptide and polysaccharopeptide krestin contain α-(1→4) and β-(1→3) glucosidic linkages in their polysaccharide chain, with D-glucose as the major monosaccharide present (Ng 1998). Arabinose and rhamnose are the other principal monosaccharides in the polysaccharopeptide, while polysaccharopeptide krestin contains fucose (Cui and Chisti 2003).

Polysaccharopeptide krestin seems to work during the multiple steps of cancer metastasis by inhibiting adhesion, invasion, motility, and metastatic growth of tumor cells in animal models. Adhesion and invasion are inhibited by suppression of cell matrix-degrading enzyme production by malignant cells (Katano et al. 1987; Kobayashi et al. 1995). Motility of malignant cells and subsequent attachment to blood vessels are inhibited by suppression of tumor-cell induced platelet aggregation and anti-angiogenic factors (Abe et al. 1990; Tanaka et al. 1991). Polysaccharopeptide krestin has also been shown to induce apoptosis (programmed cell death) in lymphoma, leukemia and pancreatic cells (Hattori et al. 2004; Jiménez-Medina et al. 2008). Transforming growth factor β1 (TGF-β1) and matrix metalloproteinases (MMPs) produced by tumor cells are regarded as important factors in tumor invasion. Evidence clearly shows that polysaccharopeptide krestin inhibited in vitro tumor invasiveness through suppression of MMPs and TGF-β1 and would seem to have possible use as an anti-metastatic drug, with more research planned in the future (Zhang et al. 2000).

Polysaccharopeptide krestin has been reported as a promising biological response modifier for clinical use of cancer patients in Japan (Kidd 2000), which remarkably prolongs survival and reduces the recurrence of tumors. The potential use of polysaccharopeptide krestin as an adjuvant for other conventional cancer therapies has been reported in many clinical studies (e.g., Torisu et al. 1990; Wan et al. 2008). A meta-analysis of randomized trials was conducted to evaluate the effectiveness of adjuvant immune-chemotherapy with polysaccharopeptide krestin for patients with gastric

cancer. It has been suggested that adjuvant immune-chemotherapy with polysaccharopeptide krestin improves the survival of patients after curative gastric cancer resection (Oba et al. 2007). The colon cancer patients who responded better to immunochemotherapy with polysaccharopeptide krestin support the presence of active diffuse nuclear accumulation type β-catenin (Yamashita et al. 2007). The effect of polysaccharopeptide krestin as an adjuvant treatment on non-small cell lung cancer patients after radical radiotherapy indicates satisfactory tumor shrinkage as compared to the non-administrated group (Hayakawa et al. 1993).

Proteoglycans from *Phellinus linteus*

Proteoglycans are proteins that consist of a core protein with one or more covalently attached glycosaminoglycan chain (s) that are heavily glycosylated (Moradali et al. 2007). It has been reported that the proteoglycans (protein-bound polysaccharides) from the fruiting bodies or mycelium of *Phellinus linteus* stimulate the hormonal and cell-mediated immune functions (Kim et al. 2003a, b, 2007) as well as suppressing tumor growth and metastasis. Lee et al. (2010) demonstrated anti-angiogenic activity in a methanolic extract of *P. linteus*, which revealed a novel inhibitor of angiogenesis, especially for tumor treatment and prevention. Studies suggest that *P. linteus* can act as an immune-potentiator and as a direct inhibitor of cancer cell adhesion (Han et al. 1999, 2006).

Most recently, the anti-cancer effect of an orally administered powder of freeze dried mycelia culture of *P. linteus* on mice bearing the Hep3B hepatoma cell line was investigated. Immune-modulatory and anti-tumor effects were established through increased secretion of interleukin-12, interferon gamma and TNF-α, which enhanced the activity of natural killer cells. These results also showed that an improved strain of *P. linteus* grown on germinated brown rice inhibited lung metastasis (Huang et al. 2011; Jeon et al. 2011). The important benefit of *P. linteus* fruiting body extracts (including proteoglucans and polysaccharides) compares favorably to conventional chemotherapeutics such as adriamycin, with its effective suppression of tumor growth and metastasis through the immune-potentiation of patients without any toxic effect (Zhu et al. 2008)

Bioactive mushroom proteins

Apart from the most extensively studied polysaccharide fraction, bioactive proteins constitute the second most abundant functional component in mushrooms (Ferreira et al. 2010; Wong et al. 2010a, b). Mushrooms produce a large number of proteins with significant biological activities, including lectins, ribosome inactivating proteins (RIPs), fungal immunomodulatory proteins (FIPs) and laccases (Wang et al. 1998; Wong et al. 2010a; Xu et al. 2011).

Lectins are proteins that can bind to cell surface carbohydrates, with an ability to produce cell agglutination and that show several anti-proliferative and anti-tumor activities against cancer cell lines (Zhang et al. 2009, 2010). Lectins are abundant in many species of mushrooms, including *Agaricus bisporus, Pleurotus ostreatus, Tricholoma mongolicum, Agaricus subrufescens* and *Grifola frondosa* (Wang et al. 1998). Recently discovered lectins from the mushroom *Russula lepida* and *Pholiota adiposa* showed anti-proliferative activity towards hepatoma HepG2 cells and breast cancer MCF-7 cells (Zhang et al. 2009). The protein involved belongs to the ricin B-like lectins and has been designated as *Clitocybe nebularis* lectin (CNL) and showed anti-proliferative effects elicited by binding to carbohydrate receptors on human leukemic T cells (Pohleven et al. 2009).

The ribosome inactivating proteins (RIPs) have an enzymatic activity that can suppress the ribosomes by eliminating parts of adenosine residues from rRNA. A new ribosome inactivating protein with anti-proliferative activity from the mushroom *Hypsizigus marmoreus* potently inhibited proliferation of HepG2 hepatoma, MCF-7 breast cancer cells and decreased the HIV-1 reverse transcriptase activity (Wong et al. 2008).

Fungal immunomodulatory proteins (FIPs) are a new class of bioactive proteins, with targeting ability of immune cells, isolated from mushrooms (Xu et al. 2011). Six fungal immunomodulatory proteins (FIPs), LZ-8, gts, gja, fve, vvo and gsi, have been isolated and purified, including three from Lingzhi mushrooms, LZ- 8 (*Ganoderma lucidum*) (Kino et al. 1989), FIP-gts (*Ganoderma tsugae*) (Hsiao et al. 2008) and (FIP-gsi) (*Ganoderma sinensis*) (Li et al. 2010a), two from edible mushrooms, FIP-fve (*Flammulina velutipes*) (Ko et al. 1995) and then FIP-vvo (*Volvariella volvacea*) (Maiti et al. 2008).

The fungal immunomodulatory protein, Ling Zhi-8 (LZ-8), which was isolated and purified from the mycelia of *G. lucidum* in 1989, has been regarded as one of the most important bioactive substances of *G. lucidum*. The native form of LZ-8 is a noncovalently bound homodimer with a molecular mass of 24 kDa. Each polypeptide consists of 110 amino acid residues with acetylated N terminals (Kino et al. 1989). Currently, several studies have been designed to develop an efficient preparation of new recombinant immunomodulatory proteins with higher activity (Lin et al. 2009, 2010). The immune modulatory effects of rLZ-8 (recombined Ling Zhi-8) on human monocyte-derived dendritic cells have demonstrated that binding of rLZ-8 to toll like receptor-4 could effectively induce the significant activation and maturation of human dendritic cells (Lin et al. 2009). Dendritic cells were activated via the NF-κB and MAPK

pathways and it has been proposed that rLZ-8-mediated signal transduction occurs in the regulation of interleukin-12, 10, p40 and expression (Kino et al. 1989; Lin et al. 2009). A new recombinant immunomodulatory protein, purified from *Ganoderma microsporum*, with anti-metastatic effect also has been found. It can inhibit epidermal growth factor mediated migration and invasion in A549 lung cancer cells (Lin et al. 2010).

For the first time (Lin et al. 2011) reported that LZ-8 acts as a promising adjuvant that enhances the efficacy of a DNA cancer vaccine by activating dendritic cells and promoting innate and adaptive immune responses through toll like receptor 4. This is the first study to apply LZ-8 to a DNA vaccine model for cancer therapy and determine the immunogenicity in vivo. These data provide a new insight for the application of LZ-8 for enhancing immunity in vaccine technology for preventing and treating various cancers.

A comparison between the functions of polysaccharides and protein LZ-8 from Reishi (*G. lucidum*) in regulating murine macrophages and T lymphocytes demonstrated that LZ-8 could activate murine macrophages and T lymphocytes but *Ganoderma* polysaccharides only activate the macrophages, suggesting their diverse roles in activating the innate and adaptive immunity (Yeh et al. 2010).

Li et al. (2010a) isolated Fungal Immunomodulatory Proteins (FIP-gsi) comprised of 111 amino acids from *Ganoderma sinensis*. Furthermore, FIP-gsi could enhance the production levels of cytokinine, including interleukin-2, 3 and 4 interferon gamma, TNF-α, and interleukin receptor-2 in mouse spleen cells. A novel immunomodulatory protein (TVC) from the medicinal mushroom *Trametes versicolor* markedly increases the proliferation of human peripheral blood lymphocytes and enhances the production of both nitric oxide and TNF-α by lipopolysaccharide-induced murine macrophages. The results indicate that TVC is an immunostimulant that can boost immune response (Feng et al. 2011; Li et al. 2011).

In several studies, a low-molecular weight protein fraction (MLP-fraction) from the fruiting body of the maitake mushroom *Grifola frondosa* that has potent anti-tumor activity was isolated (Kodama et al. 2010). It was found that the MLP-fraction enhanced the production of cytokines; interleukin-12 and interferon-gamma by splenocytes in tumor-bearing mice and clearly exhibited an inhibitory effect on tumor cell growth.

With advanced studies, many other potential immunomodulatory proteins have been reported from various species of mushrooms, including APP and PCP-3A, which were isolated from *Auricularia polytricha* and *Pleurotus citrinopileatus*, respectively (Sheu et al. 2004; Chen et al. 2010a). As more and more studies reveal new species of mushrooms, especially in the tropics (Dai 2010; Ge et al. 2010; Van de Putte et al. 2011; Zhao et al. 2010a, 2011) and further chemical analyses are carried out for bioactive compounds, we should expect many more novel and medicinal compounds to be discovered from mushrooms. Although there are increasing numbers of reports available for the identification of mushroom proteins, the mechanisms of actions (e.g. immunomodulation, anti-proliferation) are still poorly understood and further studies are warranted (Li et al. 2010c).

Low-molecular-weight bioactive metabolites (Fig. 4, Table 3)

Mushrooms produce a variety of complex low-molecular-weight compounds with diverse chemical compositions that we refer to in this review as phenolic compounds, polyketides, triterpenoids and steroids specific to each mushroom (Zaidman et al. 2005; Erkel and Anke 2008; Ferreira et al. 2010). The majority of these compounds are not involved in the central metabolic processes of the fungi (the generation of energy and the formation of the building blocks of proteins, nucleic acids, and cell membranes) and are known as secondary metabolites (Abraham 2001; Petrova et al. 2008).

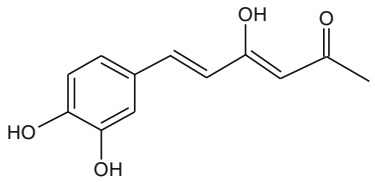
These substances are derived as intermediates in primary metabolism, but they can be classified according to five main metabolic sources. These are (1) amino acid-derived pathways, (2) the shikimic acid pathway, (3) the acetate–malonate pathway (4), the mevalonic acid pathway and (5) the polysaccharides and peptidopolysaccharides derived pathways. The acetate-malonate pathway and the mevalonic acid pathways are most often involved in secondary metabolism of basidiomycetes and they produce a greater variety of compounds (terpenoids, sesquiterpenoids, polyacetylenes) than the other pathways (Isaac 1997; Zaidman et al. 2005; Erkel and Anke 2008).

Many low molecular weight bioactive compounds isolated from medicinal mushrooms show direct beneficial effects on cancer development by modulating several cellular signal transduction pathways (nuclear factor-κB pathway [NF-κB], mitogen activated protein kinase pathway [MAPK]) and exerting inhibitory effects on processes such as cell differentiation, angiogenesis, carcinogenesis, and metastasis (Petrova et al. 2008; Zhong and Xiao 2009). A wide range of anti-tumor or immunostimulating bioactive metabolites with low molecular weights from mushrooms have been investigated (Table 3); several promising compounds have been chosen and their mechanism of action detailed below.

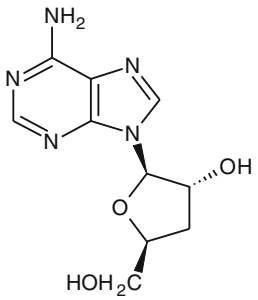
Cordycepin

Members of the genus *Cordyceps* are ascomycetous fungi commonly called caterpillar fungi and that grow as a result

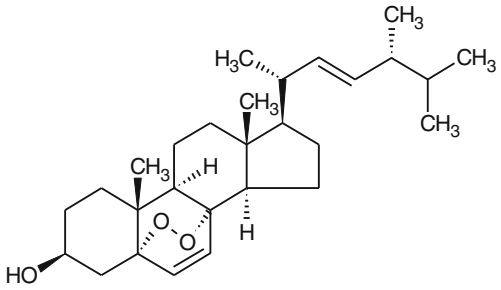
Fig. 4 Chemical structures of selected low-molecular-weight metabolites



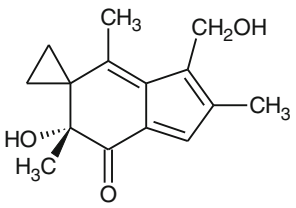
Hispolon



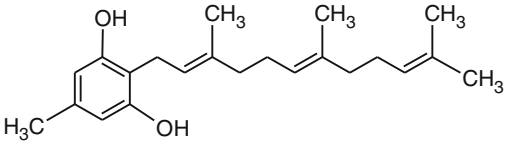
Cordycepin



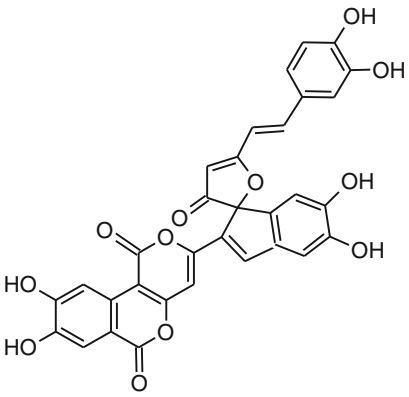
Ergosterol peroxide



Irofulven



Grifolin



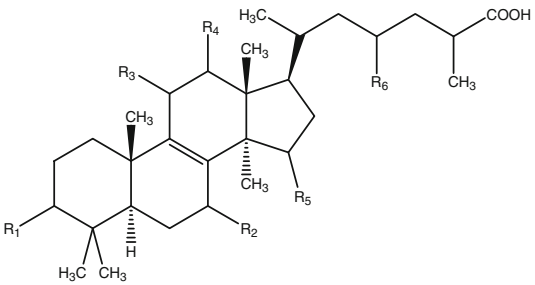
Phelligridin G

of a parasitic relationship between the fungus and the insect larva (Chen and Jin 1992). The fungus germinates in living organisms (in some cases the larvae), kills the insect, and then the *Cordyceps* fruiting body grows from the body of the insect (Chen and Jin 1992; Zhu et al. 1998a, b). Many species of *Cordyceps* have been identified for medicinal purposes and use in health supplements. These include *C. sinensis, C. militaris, C. pruinosa, C. subsessilis* and *C. ophioglossoides* (Hobbs 1995; Holliday and Cleaver 2008).

Cordycepin, or 3′-deoxyadenosine, is a derivative of the nucleoside adenosine, which was initially extracted from specimens in this genus but is now produced synthetically (Paterson 2008). Cordycepin was first isolated from a water extract of *C. sinensis*, and a major component of the butanol fraction of *C. militaris* was also identified as cordycepin by high performance liquid chromatography (Jeong et al. 2011).

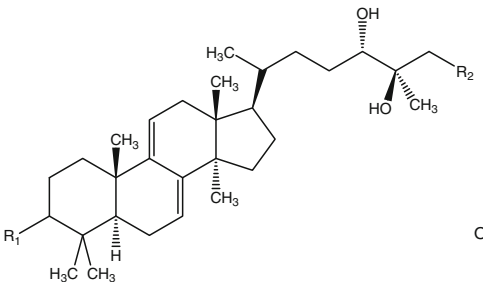
Cordycepin has two major effects on cells (Wong et al. 2010b). At a low dose cordycepin inhibits the uncontrolled growth and division of the cells and at high doses it stops cells from sticking together, which also inhibits growth. Both of these effects probably have the same underlying mechanism, which is that cordycepin interferes with protein metabolism. At low doses, cordycepin interferes with the production of mRNA and assembly of proteins. At higher doses cordycepin has a direct impact on the production of proteins. Wong et al. (2010b) demonstrated that at low doses cordycepin affects the poly (A) tails of specific mRNAs, and this correlates with a reduction in cell proliferation. At

Fig. 4 (continued)

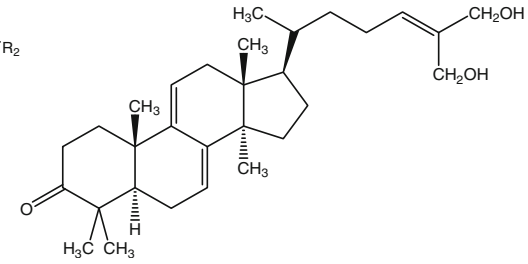


Ganoderic acids

A : R_1=R_3=R_6=O, R_2=R_5=β-OH, R_4=H
B : R_1=R_3=R_5=R_6 =O, R_2=β-OH, R_4=H
C : R_1=R_3=R_5=R_6=O, R_2=β-OH, R_4=H
D : R_1=R_3=R_5=R_6 =O, R_2= R_4 =β-OH
F : R_1=R_2=R_3=R_5=R_6 =O, R_4 =β-OH
G : R_1=R_2=R_4=β-OH, R_3 =R_5= R_6 =O
H : R_1=β-OH, R_2 =R_3= R_5 =R_6 =O, R_4= β-OAc
Z : R_1=β-OH, R_2 =R_3= R_4 =R_5 =R_6=H



Ganodermanontriol : R_1=O, R_2=OH
Ganodermanondiol : R_1=O, R_2=H
Lucidumol B : R_1=β-OH, R_2=H



Ganoderiol F

higher doses cordycepin also inhibits cell adhesion and virtually abolishes protein synthesis, probably through its effects on Akt and 4EBP phosphorylation. The most upstream target of cordycepin at higher doses appears to be AMP-activated kinase pathway, which it activates, leading to the observed reduction in the mammalian target of rapamycin signaling. Therefore, the two main effects of cordycepin appear to be the inhibition of polyadenylation at low doses and the activation of AMP-activated kinase pathway at higher doses (Wong et al. 2010b).

An experimentally developed strain of *Cordyceps sinensis* (Cs-4) has been used extensively in China, and products have been developed with approval of the Chinese Health Ministry (Zhu et al. 1998b). Several anamorphic mycelial strains, (e.g., *Paecilomyces hepiali* and *Hirsutella hepiali*) isolated from natural *C. sinensis* have been manufactured in large quantity by fermentation technology (Zhu et al. 1998a). This product has been clinically used against many diseases, including immune-stimulation and cancer prevention.

Cordycepin affects leukemia cells in humans by significantly inducing apoptosis through a mitochondria-mediated caspase-dependent pathway. Cordycepin is thought to induce apoptosis of human leukemia cells through a signaling cascade involving a reactive oxygen species-mediated caspase pathway (Khan et al. 2010; Jeong et al. 2011)

Cordycepin has also been used as adjuvant treatment in cancer prevention along with chemotherapy and radiotherapy and has shown many beneficial effects on patients, in some cases showing direct anti-tumor effects (Zhu et al. 1998a, b). Ten pure compounds isolated from the extracts of *Cordyceps militaris*, obtained through a solid-state cultivation process, showed potent anti-proliferation in PC-3 and colon 205 cells, while only one compound displayed such an effect in HepG2 cells. This study provides support for the use of *Cordyceps militaris* as an anti-inflammatory and anti-cancer agent (Lee and Hong 2011).

Ergosterol

The pro-vitamin D_2, ergosterol (ergosta-5,7,22-trien-3β-ol), is abundant in lichens and mushrooms such as *Agaricus subrufescens*, *Ganoderma lucidum*, *Lentinula edodes* (Takaku et al. 2001; Paterson 2006; Phillips et al. 2011) and *Cordyceps sinensis* and shows various types of bioactivity (Li et al. 2004; Wu et al. 2007). Ergosterol is mostly absent in the plant and animal kingdoms.

Ergosterol in mushrooms can be converted to vitamin D_2 by ultraviolet (UV) irradiation. Ergosterol undergoes photolysis when exposed to UV light at wavelengths of 280–320 nm, yielding a variety of photo irradiation products. The principal products are provitamin D_2, tachysterol, and lumisterol. Ergosterol peroxide (5α,8α-epidioxy-22*E*-ergosta-6,22-dien-3β-ol) is a steroidal derivative of ergosterol and shows various biological activities with strong immunomodulatory and anti-tumor activities (Krzyczkowski et al. 2009).

Inefficient programmed cell death (apoptosis) increases tumor development and resistance to cancer therapy. Thus, agents that induce apoptotic death of these cancer cells would be useful in controlling this malignancy. Evaluation of pro-apoptotic activity of ergosterol peroxide and (22*E*)-ergosta-7,22-dien-5α-hydroxy-3,6-dione on prostate cancer cells by Russo et al. (2010) indicated that these compounds can reduce the growth of prostate cancer cells, at least in part, by triggering an apoptotic process.

Ergosterol was isolated from *A. subrufescens* as an anti-angiogenic substance and indications are that the anti-tumor activity of ergosterol may be due to direct inhibition of angiogenesis induced by solid tumors (Takaku et al. 2001).

Grifolin

Grifolin is a natural biologically active metabolite isolated from the fruiting bodies of the mushroom *Albatrellus confluens* that has shown many pharmacological effects. Earlier research has shown that grifolin acts as an antibiotic (Hirata and Nahanishi 1950) and shows significant cholesterol lowering activity, anti-oxidative activity and antimicrobial activity (Sugiyama et al. 1992; Ding et al. 2001; Nukata et al. 2002).

Grifolin was identified as a potential antitumor agent that can inhibit tumor cell growth by inducing apoptosis in vitro for cancer cell lines. It was also shown that apoptosis of cells was induced by the activation of caspase-8,-9, and -3, release of cytochrome c from mitochondria, with a decrease of the Bcl-2 level and an increase of the Bax level (Ye et al. 2005; Song et al. 2007). Studies of molecular targets and the signaling mechanism underlying the anti-cancer effect found that grifolin significantly caused cell-cycle arrest in the G1-phase that is responsible for the inhibition of the ERK1/2 or the ERK5 pathway (Ye et al. 2007). Recent evidence suggests that upregulation of death-associated protein kinase 1 (DAPK1) via the p53–DAPK1 pathway is an important mechanism of grifolin that contributes to its ability to induce an apoptotic effect (Luo et al. 2011).

Polyphenolic compounds (styrylpyrone-class of phenols)

Medicinal mushrooms have been reported to produce a variety of polyphenolic pigments, known as styrylpyrone-class of phenols, derived from polyketide pathways, which show significant biological effects, including anti-cancer properties (Lee and Yun 2011). Styrylpyrone pigments are common constituents of *Phellinus* spp. and *Inonotus* spp. (*Hymenochaetaceae*). Hispidin was first isolated as a naturally occurring styrylpyrone from *Inonotus hispidus*, and a number of other hispidin-class metabolites have since been discovered (Gonindard et al. 1997). Recent studies have demonstrated that fruiting bodies of *Phellinus igniarius*, *P. linteus*, and *Inonotus obliqqus* contain unique styrylpyrone derivatives with many biological activities. Phelligridins A-J were isolated from the ethanolic extract of *Phellinus igniarius* together with inoscavin A and hispolon and showed anti-oxidative and cytotoxic effects (Wang et al. 2007; Lu et al. 2009; Huang et al. 2010).

Earlier studies showed that hispidin is more cytotoxic toward cancerous cells (pancreatic duct and keratinocyte) than normal cells (Gonindard et al. 1997). Hispolon from ethanol extracts of *Phellinus linteus* fruiting bodies induces apoptosis in human gastric cancer cells through a reactive oxygen species (ROS)-mediated mitochondrial pathway (Lu et al. 2009). This process is accompanied by the collapse of mitochondrial membrane potential, the release of cytochrome C and the activation of caspase-3 (Chen et al. 2006, 2008a). Hispolon has the ability to down regulate some proto-oncogenes (MDM2) important in tumorigenesis and a potential anti-tumor agent in breast and bladder cancers (Lu et al. 2009). Recently, hispolon has been identified as an anti-metastatic agent. It can inhibit the metastasis of SK-Hep1 cells by reduced expression of MMP-2, MMP-9, and uPA through the suppression of various signaling pathways and of the activity of PI3K/Akt and Ras homologue gene family (Huang et al. 2010).

Phelligridins are a hispidin-class of derivatives (pyrano [4,3-c][2]benzopyran-1,6-dione) from *Inonotus* and *Phellinus* spp. Phelligridins (C-F) from *P. igniarius* showed in vitro selective cytotoxicity against a human lung cancer cell line and a liver cancer cell line (Mo et al. 2004; Wang et al. 2007). Highly oxygenated metabolites, including Phelligridins D, E and G isolated from *Inonotus* and *Phellinus* spp. exhibited significant free radical scavenging activity (Lee et al. 2007b; Lee and Yun 2007). Phelligridin G was shown to be a powerful

anti-oxidant with activity against human ovarian and colon cancer cell lines (Wang et al. 2005). Co-culture of *Inonotus obliquus* with *Phellinus punctatusa* led to the development of a cost-effective strategy for up regulating biosynthesis of bioactive metabolites with potent anti-tumor and anti-proliferative effects on HeLa 229 cells. Changes in metabolic profiles with metabolites, including phelligridin C, phelligridin H, methyl inoscavin A, inoscavin C, methyl davallialactone, provide positive prospects in the future (Zheng et al. 2011).

Irofulven

Irofulven (6-hydroxymethylacylfulvene; MGI-114; MGI PHARMA, Inc., Bloomington, MN) is a novel semi-synthetic anti-cancer agent derived from the mushroom toxin illudin-S (McMorris et al. 1996). The latter sesquiterpenoid toxin produced by *Omphalotus illudens* was first identified as a very potent antibiotic (Lehmann et al. 2003). The highly toxic properties of illudin-S promoted the production of an analog with improved therapeutic potential, a semi-synthetic derivative known as irofulven (McMorris et al. 1996; McMorris 1999).

As an alkylating agent, irofulven has the ability to covalently bind to biological macromolecules, to inhibit DNA synthesis, and to induce apoptosis (Woynarowski et al. 1997; Kelner et al. 2008). In addition, it appears to interfere with redox homeostasis, leading to protein oxidation and mitochondrial dysfunction, which triggers a proapoptotic signal. Its cytotoxicity seems to be more specifically directed against malignant cells and the redox homeostasis that is maintained protects normal cells from the effects of irofulven (Liang et al. 2001; Leggas et al. 2002). In addition, an enhanced anti-tumor activity of irofulven was observed in combination with other anti-cancer agents (Poindessous et al. 2003; Kelner et al. 2008).

Currently, irofulven is one of the most extensively studied anti-tumor drugs to have undergone many clinical trials but it still requires further clarification. Irofulven produced different results in phase I and phase II trials of human cancer cell lines, including advanced melanoma (Pierson et al. 2002), advanced renal cell carcinoma (Alexandre et al. 2007) and pretreated ovarian carcinoma (Seiden et al. 2006). Studies showed that the cytotoxic activity of irofulven is greater when it is combined with other anti-angiogenic or chemotherapeutic drugs (Alexandre et al. 2004; Woo et al. 2005; Hilgers et al. 2006; Dings et al. 2008). Although irofulven has undergone many clinical trials, its chemotherapeutic behavior is not fully investigated, and irofulven has some limitations in usage in different cancer cell lines, a situation that requires further investigation.

Triterpenes of *Ganoderma sp.*

Ganoderma lucidum-derived polysaccharides prevent tumor metastasis indirectly via the activation of an immune response from the host organism, whereas triterpenes suppress invasive behavior of the cancer cells directly. Numerous triterpenoids, including more than one hundred pharmacologically-active metabolites, have been discovered, and these compounds have been proven to display wide-ranging biological activity (Cheng et al. 2010). These triterpenoids can be divided in to two groups depending on the ligand bound to 26th carbone position (C-26). One group has a C-26 carboxyl group and these are referred to as ganoderic acids, whereas the other group has a C-26 hydroxyl group and are known as *Ganoderma* alcohols (Liu et al. 2010). Triterpenoid components, including ganoderic acids, lucidimol-A, -B, ganodermanondiol, ganoderiol F and ganodermanontriol, have been demonstrated to exert cytotoxic effects on cancer cells (Chen and Chen 2003; Sliva 2003; Chang et al. 2006; Tang et al. 2006a; Weng and Yen 2010; Chin et al. 2011).

Triterpenes isolated from species of *Ganoderma* have anti-cancer properties (Cheng et al. 2010). Several cytotoxic triterpenoids have been reported as having inhibitory activities against human cervical cancer cells (Cheng et al. 2010; Xu et al. 2010). Triterpene-enriched extracts from *Ganoderma lucidum* inhibit the growth of hepatoma cells via suppressing protein kinase C, activating mitogen-activated protein kinases (Lin et al. 2003). Ganoderic acid T also induces apoptosis of metastatic lung tumor cells through an intrinsic pathway related to mitochondrial dysfunction (Tang et al. 2006b). Cytotoxicity of a ganoderic acid fraction called GA-Me has been tested on cultured human colon cancer cells (Chen et al. 2008b). The activation of the intrinsic mitochondria-dependent apoptotic pathway was identified and the data suggest that GA-Me may be a natural potential apoptosis inducing agent for human colon tumors (Zhou et al. 2011)

Novel drug discovery from medicinal mushrooms and clinical studies on patients

There has been growing interest in developing fungi and mushroom-derived products as drugs or dietary supplements and scientifically investigating the function of these products (Lindequist et al. 2005; Aly et al. 2010; Jakopovich 2011; Xu et al. 2011). Medicinal mushrooms with biologically active substances have been used in several human clinical trials and have shown promising results as supportive treatment when used along with conventional therapies (Zhuang and Wasser 2004; Wasser 2011). A trend toward integration of immune potentiating agents with cancer surgery, chemotherapy, and

radiation therapy is now considerably advanced in many Asian countries where mushroom preparations have been traditional anti-cancer medicines for centuries (Jiang and Silva 2010; Jakopovich 2011).

Many commercially developed mushroom polysaccharides such as Lentinan from *Lentinula edodes* (Chihara et al. 1969, 1970; Hobbs 2000), Schizophyllan (Sonifilan, Sizofiran, or SPG), from *Schizophyllum commune* (Hobbs 2005), polysaccharopeptide and polysaccharopeptide krestin, peptidoglucans from *Trametes versicolor* (Hobbs 2004), maitake D-fraction from *Grifola frondosa* (Zhuang and Wasser 2004; Boh and Berivic 2007) and a *Ganoderma* polysaccharide fraction from *G. lucidum* (Yuen and Gohel 2005; Zhou et al. 2005; Lin 2009; Mahajna et al. 2009; Wasser 2010) appear to mediate anti-tumor activity by activating the immune system and have proceeded through Phase I, II and III clinical trials, mainly in Japan and China, while such trials are also occurring in the United States and some European countries (Inoue et al. 1993; Nanba 1997b; Mizuno 1999b; Kidd 2000; Yamashita et al. 2007; Jakopovich 2011; Zhang et al. 2011).

Many experimental and clinical trials have been carried out that show promising cancer inhibitory and immunostimulatory activity in many other species of mushrooms, including *Cordyceps sinensis* (Holliday and Cleaver 2008), *Flammulina velutipes* (Maruyama and Ikekawa 2007), *Inonotus obliquus* (Mizuno et al. 1999; Park et al. 2005) and *Phellinus linteus* (Kim et al. 2007). Among low-molecular-weight mushroom compounds, only a few of the numerous newly discovered compounds have progressed to clinical evaluation. Irofulven is the most extensively studied compound in this group but needs future clinical confirmation before being recommended for use as an anti-cancer drug (Seiden et al. 2006; Alexandre et al. 2007).

What is the estimated use of medicinal mushrooms?

Cancer is one of the major chronic diseases responsible for human deaths worldwide (Anon 2010). Finding cures for this disease has been a challenge of great interest for scientists throughout this and the previous century. Even though it has proved difficult to find effective remedies for this complex disease, supportive treatment to improve the quality of life of cancer patients may significantly reduce suffering.

Development of anti-cancer drugs has become a fundamental trend among the large pharmaceutical companies; they spend billions of dollars on cancer research (Pollack 2009; Smith and Ryan 2009). Currently, the number of anti-cancer drugs being tested on humans is more than twice the number of experimental drugs for heart disease and stroke combined, as well as being nearly twice the total for AIDS and all other infectious diseases combined (Pollack 2009).

Exploration of natural sources for novel bioactive anti-tumor agents may provide leads or solutions for drug discovery and development (Lindequist et al. 2010; Liu et al. 2010; Xu et al. 2010; Aly et al. 2011). Many promising novel drugs have served as remarkable finds in the history of disease treatments (Aly et al. 2011). Some of the key drug products include antibiotics (penicillin, cephalosporins and fusidic acid), anti-fungal agents (griseofulvin, strobilurins and echinocandins) and anti-cholesterol agents (statins, Mevastatin and Lovastatin), and immunosuppressive drugs (cyclosporine). In addition, some pharmaceutical drug products such as the ergot alkaloids were developed from fungal bioactive compounds or their derivatives (Liu 2002; Li and Vederas 2009; Liu et al. 2009b; Smith and Ryan 2009; Aly et al. 2011). According to a 60-year review by Newman and Cragg (2007) of the study on natural sources of drug products, 47% of anti-cancer drugs were actually developed as a result of leads from natural products or directly derived from them. A 50-year retrospective analysis of drug discovery from fungi provides a comprehensive account of fungal secondary metabolites and their role as drug leads of enormous therapeutic potential (Aly et al. 2011).

Today, bioactive metabolites from medicinal mushrooms produce beneficial effects not only as pharmaceutical drugs but also as a novel class of supportive products with overall immune enhancement (Jiang and Silva 2010; Jakopovich 2011). These include dietary supplements, functional foods (nutraceuticals), nutriceuticals (a new class of compounds that have been extracted from either mushrooms or vegetative mycelia). A refined or partially refined extract that is consumed in the form of capsules or tablets as a dietary supplement, but not as a food, can have potential therapeutic applications as a mycopharmaceutical or as a designer food that produces beneficial effects with regular usage in a healthy diet (Chang and Buswell 2003; Chang 2006; Wasser and Akavia 2008; Wasser 2010). Examples of the available drug products and supplementary foods developed from medicinal mushrooms that claim to provide beneficial effects on immune stimulation and help in cancer prevention are shown in Table 4 and Plate 1.

Many researchers have come to the conclusion that, to maximize a host-mediated response or to ‘awaken’ the immune system, a mixture of polysaccharides with some combination of mushroom extracts is best (Kurashige et al. 1997; Shamtsyan et al. 2004; Jakopovich 2011). These combinational effects appear to increase the number and activity of killer T and natural killer lymphocytes. Combining species of medicinal mushrooms sends the immune system multiple stimuli collectively, increasing intracellular reactions, awakening the body’s natural defenses (Ivanković et al. 2004; Zaidman et al. 2005; Borchers et al. 2008; Wasser 2010). One case study utilizing six medicinal mushrooms in breast cancer treatments resulted in complete

Table 4 Examples of marketed products of mushroom extracts with claimed immunostimulatory activity

Product name	Product function claim	Fungus/extract present	Web page
Dr Myko San – Health from Mushrooms	Reducing the risk of the occurrence of malignant diseases. Anti-tumor activity, without any toxic side effects.	Different mushroom species	www.mykosan.com Jakopovich 2011
Ganoderma Lucidum Spore	Anti-tumor and immuno-potentiating properties (enhancing the functioning of the immune system)	*Ganoderma lucidum* spore extract	www.herbhorizon.net Ganoderma_Spore.asp
Grifron Maitake Mushrooms	Overall health and immune support	*Grifola frondosa*	www.shokos.com MushroomWisdom.htm
I'm-Yunity®	Maintaining white blood cell levels and increasing immune proteins	COV-1® strain of *Coriolus versicolor*	www.imyunity.com
MC-S (Metabolic Cell Support)	Significantly enhances white blood cell (immune cell) proliferation while simultaneously suppressing cancer cell growth.	*Ganoderma Lucidum, Lentinus edodes* (mycelia) *Coriolus versicolor*	www.mc-s.com.au
MycoPhyto® Complex	Potential therapeutic value in the treatment of human breast cancer	Blend of mushroom mycelia from *Agaricus subrufescens*, *Cordyceps sinensis*, *Coriolus versicolor*, *Ganoderma lucidum*, *Grifola frondosa* and *Polyporus umbellatus*	Jiang and Silva 2010 www.econugenics.com
Red reishi	Overall immunity and suppression of tumors	*Ganoderma lucidum* fruit body and spores	www.reishiscience.com
Super Royal Agaricus Mushroom	Immune and kidney support	*Agaricus subrufescens*-fruting body extract *Grifola frondosa*-Maitake TD fraction	www.shokos.com/MushroomWisdom.htm

The co-authors of the present paper have not confirmed these claims

Plate 1 Examples of products marketed with claimed immune stimulatory and anti-cancer properties containing mushrooms or their extracts*. *1. Dr Myko San—Health from Mushrooms 2. Ganoderma Lucidum Spore 3.Grifron Maitake Mushrooms 4. I'm-Yunity® 5. MC-S (Metabolic Cell Support) 6. MycoPhyto® Complex 7. Red reishi 8. Super Royal Agaricus Mushroom*. * We have not confirmed the immune stimulatory and anti-cancer effects of these products

recovery (Shamtsyan et al. 2004). The formula inhibited the growth of highly metastatic human breast cancer cells and also suppressed metastatic potential of these cells without the side effects that are associated with cancer chemotherapy (Shamtsyan et al. 2004; Jiang and Silva 2010).

Among the large pool of chemical metabolites found in nature, discovery of biologically active metabolites from medicinal mushrooms give new insight to novel drug discovery that might be used against cancer. The high structural variability found in polysaccharide fractions and the unique reactive properties of low molecular weight secondary metabolites show potential ability for use in anti-cancer remedies. The high structural variability found in polysaccharides allows them to have a high capacity for carrying biological information (Chen and Seviour 2007). Immunostimulatory activity as a result of polysaccharides is believed to be mainly due to their high molecular weight and the high structural complexity associated with a branched triple helix structure (Bohn and BeMiller 1995). However, these characteristics make it difficult to synthesize polysaccharides in large scale production and certain physical properties restrict their pharmaceutical applicability (Wasser 2002; Ohno 2005; Zhang et al. 2007; Chen and Seviour 2007; Lehtovaara and Gu 2011).

Although the use of mushrooms in anti-cancer therapies has promise, there are few conclusive mechanistic studies of their constituents such as polysaccharides and evidence for

immunostimulatory action is still very hypothetical, especially where in vivo action is concerned. Another problem is that the macromolecular glucans and other therapeutic polymers from fungi may not exhibit favorable pharmacological and pharmacokinetic properties. In terms of analytics, it is also difficult to measure drug metabolism, which is one of the major prerequisites for approval of "ethical" pharmaceutical drugs. For this reason many of the mushroom derived anti-cancer preparations remain as Over-the-counter drugs (OTC drugs) or neutraceuticals. The recent papers by Chen and Seviour (2007), Chan et al. (2009) and Wasser (2011) have addressed the challenges (approval, analytical problems etc.) that are associated with the use of β-glucans in cancer treatments and should be considered as further references on how such topics can be addressed in a more scientific manner.

Furthermore, mycelial cultures of various mushroom species have also been shown to produce bioactive metabolites, usually different from those found in the fruiting bodies. Of particular note are the in vitro activities of terpenoids from cultures of basidiomycetes (Peng et al. 2005; Erkel and Anke 2008). The best known example for this is Pleuromutilin, which is derived from mycelial cultures of the genus *Clitopilus* (Hartley et al. 2009). Therefore, metabolites from cultures may not provide similar therapeutic benefits as those that have been claimed in traditional medicine. On the other hand, cultural extracts may produce other medicinal benefits. Since this is not the purpose of this review, readers should refer to other reviews (e.g., Abraham 2001; Shu et al. 2004; Zhong and Tang 2004; Lin and Liu 2006; Erkel and Anke 2008; Ferreira et al. 2010; Wasser 2011) for further information. However, it is important to realize that bioactive metabolites produced in the fruiting bodies may not be produced in mycelial cultures and vice versa.

At present, commercial mushroom products are developed either from mushrooms collected from field cultivation or submerged cultures of the same species. Adding precursors to the culture medium may facilitate or induce bioactive metabolite production from a mycelium (similar or different content of yield from those of fruiting bodies) through biotechnology and bioconversion methods.Culture conditions such as pH can affect the production of bioactive metabolites such as polysaccharides by *Agaricus subrufescens* in batch cultures (Shu et al. 2004). Zhong and Tang (2004) outlined several important metabolites produced by mushroom cultivation and advances in submerged culture of *Ganoderma lucidum*.

On the other hand, according to Heleno et al. (2011), fruiting bodies of edible species of *Boletus* can be used directly in the human diet as health foods, due to their primary metabolites such as proteins, carbohydrates, fatty acids, mainly linoleic acid, sugars, mainly mannitol and trehalose, and vitamins (tocopherols and ascorbic acid), as well as antioxidant secondary metabolites such as phenolic derivatives. In addition, the volatile organic compounds (VOC) identified from hydrodistillates and solvent extracts of the fruiting bodies of *Ganoderma lucidum* were investigated for cytotoxicity and antimicrobial activity by Campos Ziegenbein et al. (2006). Recently, Kinge and Mih (2011) demonstrated the cytotoxicity of three lanostane-type triterpenoids, isolated from fruiting bodies of *Ganoderma zonatum*, against five human tumour cell lines. It should also be noted that secondary metabolite (VOC) content can vary depending on whether mushrooms are fresh, dried or cooked (Rapior et al. 1997). This has an impact on the synergistic and/or additive effects of the consumption of fruiting bodies in the human diet as health foods.

Admittedly, most research has focused on mushroom secondary metabolites that directly affect intracellular transduction pathways, triggering specific signaling reactions that may lead to cancer inhibition. The metabolites such as caffeic acid phenethyl ester, cordycepin, panepoxydone and cycloepoxydon show specific cytotoxicity against tumor cells (Han et al. 2004; Zaidman et al. 2005; Erkel et al. 2007; Petrova et al. 2008, 2009; Yassin et al. 2008; Kudugunti et al. 2010). The discovery of the metabolic action of cordycepin indicated that the biochemical could be useful for treating a wide range of different cancers (Wong et al. 2010b).

The advancements in scientific research directed towards medicinal mushrooms and the activity of their biometabolites and their behavior at the cellular level make it possible to focus on new approaches (Wong et al. 2010b; Wasser 2011; Li et al. 2010b). Significantly, the knowledge of molecular biology, proteomics, genomics and pharmacology should be integrated to develop new approaches to apply these compounds to curing disease.

Conclusions and future prospective for novel drug discovery from medicinal mushrooms

Mushrooms have been treasured as remedies for disease and as natural health foods for thousands of years, and they are incredibly popular foods in numerous countries throughout the world (Lindequist et al. 2005; Ferreira et al. 2010). Cancers, on the other hand, are chronic human diseases which affect millions around in the world. Even though there has been remarkable progress in cancer treatment methods, this disease complex still causes serious and often fatal problems. The patient's desire for adequate support, reduction of the side effects of conventional medicines, strengthening of their immune system and enhancing quality of life are currently topics of concern among physicians. There is increasing evidence that medicinal mushrooms may provide an array of medicinally important compounds that have yet to be evaluated by Western medical scientists. Treatments based on medicinal mushrooms (mycotherapy/

biological immunotherapy) fulfill many of the requirements of supplementary cancer treatments and may serve as a direct remedy against cancer development.

The major bioactive metabolites found in medicinal mushrooms can be broadly categorized as high molecular weight metabolites and low molecular weight metabolites. High molecular weight metabolites such as polysaccharides, protein polysaccharides and fungal immunomodulatory proteins provide anti-cancer activity mainly thorough the activation of the immune system. Mushrooms may produce large numbers of low molecular weight compounds that not only activate the immune system but also control the cellular transduction pathways responsible for cancer development. Medicinal mushrooms are gifts from nature that contain biologically active metabolites which can be used as support remedies for cancer treatments. Additional studies of the activities and mechanisms of action of these metabolites are needed so to develop them as potent anti-cancer drugs. New methods and techniques integrated with biotechnology and other relevant disciplines are also required. In vivo experimentation with high-quality, long-term double-blinded, clinical studies with large trial populations will be needed to confirm the safety and effects of these mushroom-derived compounds on cancer patients.

More than 30 species of medicinal mushrooms are currently identified as sources for biologically active metabolites with potential anti-cancer properties. However, much of the evidence is based on traditional folklore (e.g., Traditional Chinese Medicine), results of in vitro assays, as well as conclusive in vivo data and even clinical traits (Jikai 2002). One must be aware, however, that in vitro assays will only give a hint as to the potential therapeutic value but are not normally considered as valid proof. They mark the very first steps in preclinical screening but are often used as advertising arguments for traditional medicines. Therefore, future investigations directed towards the structural suitability, mechanisms, and metabolism of these compounds is warranted to rationally improve them as potential drugs.

There are also many problems in the correct identification, taxonomy and nomenclature of medicinal mushrooms. For example, confusion exists with respect to the names *Agaricus blazei* and *Agaricus subrufescens* or many polypores (Kerrigan 2005; Dai 2010). There are, however, still countries and regions that have not been studied for their diversity of mushrooms. This is particularly true in tropical regions of the world (Hawksworth 2001; Hyde 2001; Aly et al. 2010; Boonyanuphap and Hansawasdi 2010). There is a need to explore tropical countries for the presence of mushrooms and to assay their bioactive metabolites that can be used as possible remedies for cancer treatments. A recent study determined that high levels of β-glucans are found in wild mushrooms in Thailand (Boonyanuphap and Hansawasdi 2010), while Hyde et al. (2010) reviewed the use of mushroom in cosmetics, including evidence for certain medical properties such as anti-aging. These studies indicate the need for investigations of wild mushrooms throughout poorly studied regions, since the species present have medicinal, biochemical and cultivatable potential. Studies are warranted to explore this un-tapped resource for the isolation and production of novel anti-cancer compounds of medicinal importance.

Acknowledgments This study was supported by a grant of the French-Thai cooperation PHC SIAM 2011 (project 25587RA). The authors are grateful to Professor Alain Fruchier (ENSCM, Montpellier, France) for his helpful comments and corrections relating to chemistry. The Global Research Network for Fungal Research and King Saud University are also thanked for support.

References

Abe Y, Miyake M, Horiuchi A, Kito K, Sagawa KS (1990) Induction of cytokines by polysaccharide K in the peripheral blood mononuclear cell culture. J Clin Exp Med (Tokyo) 152:617–618

Abercrombie M, Ambrose EJ (1962) The surface properties of cancer cells: a review. Cancer Res 22:525–548

Abraham WR (2001) Bioactive Sesquiterpenes produced by fungi: are they useful for humans as well? Curr Med Chem 8:583–606

ACS (2011) American Cancer Society. Treatments and side effects http://www.cancer.org

Ajith TA, Janaradhanan KK (2003) Cytotoxic and antitumor activities of a polypore macrofungus, *Phellinus rimosus* (Berk) Pilat. J Ethnopharmacol 84:157–162

Ajith TA, Janardhanan KK (2007) Indian medicinal mushrooms as a source of antioxidant and antitumor agents. J Clin Biochem Nutr 40:157–162

Akihisa T, Uchiyama E, Kikuchi T, Tokuda H, Suzuki T, Kimura Y (2009) Anti-tumor-promoting effects of 25-Methoxyporicoic acid A and other triterpene acids from *Poria cocos*. J Nat Prod 72:1786–1792

Akiyama H, Endo M, Matsui T, Katsuda I, Emi N, Kawamoto Y, Koike T, Beppu H (2011) Agaritine from *Agaricus blazei Murrill* induces apoptosis in the leukemic cell line U937. Biochim Biophys Acta 1810:519–525

Alexandre J, Raymond E, Kaci MO, Brain EC, Lokiec FO et al (2004) Phase I and pharmacokinetic study of Irofulven administered weekly or biweekly in advanced solid tumor patients. Clin Cancer Res 10:3377–3385

Alexandre J, Kahatt C, Cvitkovic FB, Faivre S, Shibata S et al (2007) A phase I and pharmacokinetic study of irofulven and capecitabine administered every 2 weeks in patients with advanced solid tumors. Invest New Drugs 25:453–462

Aly AH, Debbab A, Kjer J, Proksch P (2010) Fungal endophytes from higher plants: a prolific source of phytochemicals and other bioactive natural products. Fungal Divers 41:1–16

Aly AH, Debbab A, Proksch P (2011) Fifty years of drug discovery from fungi Review. Fungal Divers 50:3–19

Anand P, Kunnumakara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, Sung B, Aggarwal BB (2008) Cancer is a preventable disease that requires major lifestyle changes. Pharmaceut Res 25:2097–2116

Anon (2010) Council conclusions "Innovative approaches for chronic diseases in public health and healthcare systems". Council of the European Union 3053rd Employment, Social policy health and consumer affairs council meeting Brussels, 7

Anon (2011) Chemotherapy and cancer treatment, coping with side effects http://www.medicinenet.com/script/main/art.asp?articlekey=21716

Anon (1999) Maitake Products Inc. Maitake D-fraction technical support document. Paramus, New Jersey

Anon (2006) *Ganoderma lucidum* in cancer research. Leukemia Res 30:767–768

Ariizumi K, Shen GL, Shikano S, Xu S, Ritter R 3rd, Kumamoto T, Edelbaum D, Morita A, Bergstresser PR, Takashima A (2000) Identification of a novel, dendritic cell-associated molecule, dectin-1, by subtractive cDNA cloning. J Biol Chem 275:20157–20167

Auerbach L (2006) Complementary and alternative medicine in the treatment of prostate cancer. J Men's Health Gender Pract Med 3:397–403

Bao X, Duan J, Fang X, Fang J (2001a) Chemical modifications of the (1→3)-α-D-glucan from spores of *Ganoderma lucidum* and investigation of their physicochemical properties and immunological activity. Carbohyd Res 336:127–140

Bao XF, Liu CP, Fang JN, Li XY (2001b) Structural and immunological studies of a major polysaccharide from spores of *Ganoderma lucidum* (Fr.) Karst. Carbohyd Res 322:67–74

Beaglehole R, Horton R (2010) Chronic diseases: global action must match global evidence. Lancet 376:1619–1621

Bezivin C, Delcros JG, Fortin H, Amoros M, Boustie J (2003) Toxicity and antitumor activity of a crude extract from *Lepista inversa* (Scop.:Fr.) Pat. (Agaricomycetideae): a preliminary study. Int J Med Mushr 5:25–30

Bin C (2010) Optimization of extraction of *Tremella fuciformis* polysaccharides and its antioxidant and antitumour activities *in vitro*. Carbohyd Polym 81:420–424

Blackwell M (2011) The fungi: 1, 2, 3 … 5.1 million species? Am J Bot 98(3):426–438

Boh B, Berivic M (2007) *Grifola frondosa* (Diks.:Fr.) S.F. Gray (Maitake mushroom): medicinal properties, active compounds, and biotechnological cultivation. Int J Med Mushr 9:89–108

Bohn JA, BeMiller JN (1995) β-(1→3)-D-glucan as biological response modifiers: a review of structure–functional activity relationships. Carbohyd Polym 28:3–14

Boonyanuphap J, Hansawasdi C (2010) Spatial distribution of β-glucan containing wild mushroom communities in subtropical dry forest, Thailand. Fungal Divers 46:29–42

Borchers AT, Stern JS, Hackman RM, Keen CL, Gershwin ME (1999) Mushrooms, tumors, and immunity. Proc Soc Exp Biol Med 221:281–293

Borchers AT, Keen CL, Gershwin ME (2004) Mushrooms, tumors, and immunity: an update. Exp Biol Med (Maywood) 229:393–406

Borchers AT, Krishnamurthy A, Keen CL, Meyers FJ, Gershwin ME (2008) The immunobiology of mushrooms. Exp Biol Med (Maywood) 233:259–276

Brown GD (2006) Dectin-1: a signalling non-TLR pattern-recognition receptor. Nat Rev Immunol 6:33–43

Brown GD, Gordon S (2001) Immune recognition. A new receptor for β-glucans. Nature 413:36–37

Brown GD, Gordon S (2005) Immune recognition of fungal β-glucans. Cell Microbiol 7:471–479

Brown GD, Taylor PR, Reid DM, Willment JA, Williams DL, Martinez-Pomares L, Wong SY, Gordon S (2002) Dectin-1 is a major β-glucan receptor on macrophages. J Exp Med 196:407–412

Campos Ziegenbein F, Hanssen HP, König WA (2006) Secondary metabolites from *Ganoderma lucidum* and *Spongiporus leucomallellus*. Phytochemistry 67(2):202–211

CDC Centers for Disease control and prevention (2011) Chronic disease prevention and health promotion. Cancer addressing the cancer burden at a glance 2011 www.cdc.gov/nccdphp/publications/aag/dcpc.htm

Chan GCF, Chan WK, Yuen Sze DM (2009) The effects of β-glucan on human immune and cancer cells. J Hematol Oncol 2:1–11

Chang ST (1999) Global impact of edible and medicinal mushrooms on human welfare in the 21st century: nongreen revolution. Int J Med Mushr 1:1–8

Chang ST (2006) The need for scientific validation of culinary medicinal mushroom products. Int J Med Mushr 8:187–195

Chang ST, Buswell JA (2003) Medicinal mushrooms—a prominent source of nutriceuticals for the 21st century. Curr Trends Nutraceutical Res 1:257–280

Chang ST, Miles PG (1992) Mushroom biology: a new discipline. Mycologist 6:64–73

Chang ST, Mshigeni KE (2000) *Ganoderma lucidum*—Paramount among medicinal mushrooms. Discov Innov 12:97–101

Chang UM, Li CH, Lin LI, Huang CP, Kan LS, Lin SB (2006) Ganoderiol F, a *Ganoderma* triterpene, induces senescence in hepatoma HepG2 cells. Life Sci 79:1129–1139

Chen DH, Chen WKD (2003) Determination of ganoderic acids in triterpenoid constituents of *Ganoderma tsugae*. J Food Drug Anal 11:195–201

Chen SJ, Jin SY (1992) Summary of research of hosts of *Cordyceps sinensis* in china. Shizhen Guoyao Yanju 3:37–39

Chen J, Seviour R (2007) Medicinal importance of fungal β-(1#3), (1#6)-glucans. Mycol Res 111:635–652

Chen W, He FY, Li YQ (2006) The apoptosis effect of hispolon from *Phellinus linteus* (Berkeley & Curtis) Teng on human epidermoid κB cells. J Ethnopharmacol 105:280–285

Chen W, Zhao Z, Li L, Wu B, Chen SF, Zhou H, Wang Y, Li YQ (2008a) Hispolon induces apoptosis in human gastric cancer cells through a ROS-mediated mitochondrial pathway. Free Radic Biol Med 45:60–72

Chen NH, Liu JW, Zhong JJ (2008b) Ganoderic acid Me inhibits tumor invasion through down-regulating matrix metalloproteinases 2/9 gene expression. J Pharmacol Sci 108:212–216

Chen JN, Yu Ma C, Tsai PF, Wang YT, Wu JS (2010a) *In Vitro* antitumor and immunomodulatory effects of the protein PCP-3A from mushroom *Pleurotus citrinopileatus*. J Agric Food Chem 58:12117–12122

Chen YC, Ho HO, Su CH, Sheu MT (2010b) Anticancer effects of *Taiwanofungus camphoratus* extracts, isolated compounds and its combinational use. J Exp Clin Med 2(6):274–281

Chen L, Pan J, Li X, Zhou Y, Meng Q, Wang Q (2011) Endopolysaccharide of *Phellinus igniarius* exhibited anti-tumor effect through enhancement of cell mediated immunity. Int Immunopharmacol 11:255–259

Cheng CR, Yue QX, Wu ZY, Song XY, Tao SJ, Wu XH, Xu PP, Liu X, Guan SH, Guo DA (2010) Cytotoxic triterpenoids from *Ganoderma lucidum*. Phytochem 71:1579–1585

Cheung PC (2008) Mushrooms as functional food. Wiley, New York

Chihara G, Maeda Y, Hamuro J, Sasaki T, Fukuoka F (1969) Inhibition of mouse sarcoma 180 by polysaccharides from *Lentinus edodes* (Berk.) Sing. Nature 222:687–688

Chihara G, Hamuro J, Maeda Y, Arai Y, Fukuoka F (1970) Fractionation and purification of the polysaccharides with marked antitumour activity, especially lentinan, from *Lentinus edodes* (Berk.) Sing, an edible mushroom. Cancer Res 30:2776–2781

Chin SK, Law CL, Cheng PG (2011) Effect of drying on crude ganoderic acids and water soluble polysaccharides content in *Ganoderma lucidum*. Int J Pharm Pharm Sci 3:38–43

Chung MJ, Chung CK, Jeong Y, Ham SS (2010) Anti-cancer activity of subfractions containing pure compounds of Chaga mushroom (*Inonotus obliquus*) extract in human cancer cells and in Balbc/c mice bearing Sarcoma-180 cells. Nutr Res Pract 4(3):177–182

Clarke PA, Poele R, Wooster R, Workman P (2001) Gene expression microarray analysis in cancer biology, pharmacology, and drug development: progress and potential. Biochem Pharmacol 62:1311–1336

Cui J, Chisti Y (2003) Polysaccharopeptides of *Coriolus versicolor*: physiological activity, uses, and production. Biotechnol Adv 21:109–122

Dai YC (2010) *Hymenochaetaceae* (Basidiomycota) in China. Fungal Divers 45:131–343

Demleitner S, Kraus J, Franz G (1992) Synthesis and antitumour activity of derivatives of curdlan and lichenan branched at C-6. Carbohyd Res 226:239–246

Devereux S, Hatton MQF, Macbeth FR (1997) Immediate side effects of large fraction Radiotherapy. Clin Oncol 9:96–99

Didukh MY, Wasser SP, Nevo E (2003) Medicinal value of species of the family *Agaricaceae* Cohn (higher Basidiomycetes) current stage of knowledge and future perspectives. Int J Med Mushr 5:133–152

Ding ZH, Dong ZJ, Liu JK (2001) Albaconol, a novel prenylated resorcinol (=benzene-1,3-diol) from Basidiomycetes *Albatrellus confluens*. Helv Chim Acta 84:259–262

Dings RPM, Laar ESV, Webber J, Zhang Y, Griffin RJ et al (2008) Ovarian tumor growth regression using a combination of vascular targeting agents anginex or topomimetic 0118 and the chemotherapeutic irofulven. Cancer Lett 265:270–280

Diniz SN, Nomizo R, Cisalpino PS, Teixeira MM, Brown GD, Mantovani A, Gordon S, Reis LF, Dias AA (2004) PTX3 function as an opsonin for the dectin-1-dependent internalization of zymosan by macrophages. J Leukoc Biol 75:649–656

Ehrke MJ (2003) Immunomodulation in cancer therapeutics. Int Immunopharmacol 3:1105–1119

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. Biochim Biophys Acta 1800:669–673

Erkel G, Anke T (2008) Products from Basidiomycetes chapter 11. Biotechnology Set, 2nd edn. Wiley, New York, pp 490–526

Erkel G, Anke T, Sterner O (1996) Inhibition of NF-κB activation by panepoxydone. Biochem Biophys Res Commun 226:214–221

Erkel G, Wisser G, Anke T (2007) Influence of the fungal NF-κB inhibitor panepoxydone on inflammatory gene expression in MonoMac6 cells. Int Immunopharmacol 7(5):612–624

Feinberg AP, Ohlsson R, Henikoff S (2006) The epigenetic progenitor origin of human cancer. Nat Rev Genet 7:21–33

Feng L, HuaAn W, YongJie Z, Min A, XingZhong L (2011) Purification and characterization of a novel immunomodulatory protein from the medicinal mushroom *Trametes versicolor*. Sci China Life Sci 54:379–385

Ferreira ICFR, Vaz JA, Vasconcelos MH, Martins A (2010) Compounds from wild mushrooms with antitumor potential. Anticancer Agents Med Chem 10:424–436

Fidler IJ (1978) Tumor heterogeneity and the biology of cancer invasion and metastasis. Cancer Res 38:2651–2660

Firenzuoli F, Gori L, Lombardo G (2008) The medicinal mushroom *Agaricus blazei* Murrill: review of literature and pharmaco-toxicological problems. Evid Based Complement Alternat Med 5:3–15

Fortin H, Tomasi S, Delcros JG, Bansard JY, Boustie J (2006) *In vivo* antitumor activity of Clitocine, an exocyclic amino nucleoside isolated from *Lepista inversa*. Chem Med Chem 1:189–196

Francia C, Rapior S, Courtecuisse R, Siroux Y (1999) Current research findings on the effects of selected mushrooms on cardiovascular diseases. Int J Med Mushr 1:169–172

Francia C, Fons F, Poucheret P, Rapior S (2007) Activités biologiques des champignons: utilisations en médecine traditionnelle. Annales de la Société d'Horticulture et d'Histoire Naturelle de l'Hérault 147:77–88

Franks LM (1997) Prostatic cancer: future prospects for diagnosis and screening. Brit J Urol 79:107–108

Fu H, Guo WY, Yin H, Wang ZX, Li RD (2011) Inhibition of *Lentinus edodes* polysaccharides against liver tumour growth. Int J Phys Sci 6:116–120

Fujimoto K, Tomonaga M, Goto S (2006) A case of recurrent ovarian cancer successfully treated with adoptive immunotherapy and lentinan. Anticancer Res 26:4015–4018

Furue H (1987) Biological characteristics and clinical effect of sizolilan (SPG). Med Actual 23:335–346

Gantner BN, Simmons RM, Canavera SJ, Akira S, Underhill DM (2003) Collaborative induction of inflammatory responses by dectin-1 and toll-like receptor 2. J Exp Med 197:1107–1117

Gao QP, Seljelid R, Chen HQ, Jiang R (1996) Characterization of acidic heteroglycans from *Tremella fuciformis* Berk. with cytokine stimulating activity. Carbohyd Res 288:135–142

Gao Y, Zhou S, Jiang W, Huang M, Dai X (2003) Effects of ganopoly (a *Ganoderma lucidum* polysaccharide extract) on the immune functions in advanced-stage cancer patients. Immunol Invest 32:201–215

Gao Y, Chan E, Zhou S (2004) Immunomodulating activities of *Ganoderma*, a mushroom with medicinal properties. Food Rev Int 20:123–161

Ge ZW, Yang ZL, Vellinga EC (2010) The genus *Macrolepiota* (*Agaricaceae*, Basidiomycota) in China. Fungal Divers 45:81–98

Gibbs JB (2000) Mechanism-based target identification and drug discovery in cancer research. Science 287:1969–1973

Girzal VU, Neelagund S, Krishnappa M (2011) *Ganoderma lucidum:* a source for novel bioactive lectin. Protein Peptide Lett 18:1150–1157

Gonindard C, Bergonzi C, Denier C, Sergheraert C, Klaebe A, Chavant L, Hollande E (1997) Synthetic hispidin, a PKC inhibitor, is more cytotoxic toward cancer cells than normal cells *in vitro*. Cell Biol Toxicol 13:141–153

Gonzaga MLC, Bezerra DP, Alves APNN, Alencar NMN, Mesquita RO, Lima MW, Aguiar-Soares S, Pessoa C, Moraes MO, Costa-Lotufo LV (2009) *In vivo* growth-inhibition of Sarcoma 180 by an α-(1→4)-glucan-β-(1→6)-glucan-protein complex polysaccharide obtained from *Agaricus blazei* Murill. J Nat Med 63:32–40

Griffin DH (1994) Fungal physiology, 2nd edn. Wiley-Lis, Inc., New York

Grube BJ, Eng ET, Kao YC et al (2001) White button mushroom phytochemicals inhibit aromatase activity and breast cancer cell proliferation. J Nutr 131:3288–3293

Grunebach F, Weck MM, Reichert J, Brossart P (2002) Molecular and functional characterization of human dectin-1. Exp Hematol 30:1309–1315

Guillamón E, Lafuente AG, Lozano M, Arrigo MD, Rostagno MA, Villares A, Martínez JA (2010) Edible mushrooms: role in the prevention of cardiovascular diseases. Fitoterapia 81:715–723

Guo Z, Hu Y, Wang D, Ma X, Zhao X, Zhao B et al (2008) Sulfated modification can enhance the adjuvanticity of lentinan and improve the immune effect of ND vaccine. Vaccine 27:660–665

Guo L, Xie J, Ruan Y, Zhou L, Zhu H, Yun X, Jiang Y, Lü L, Chen K, Min Z, Wen Y, Gu J (2009) Characterization and immunostimulatory activity of a polysaccharide from the spores of *Ganoderma lucidum*. Int Immunopharmacol 9:1175–1182

Han SB, Lee CW, Jeon YJ, Hong ND, Yoo ID, Yang KH et al (1999) The inhibitory effect of polysaccharides isolated from *Phellinus linteus* on tumor growth and metastasis. Immunopharmacol 41:157–164

Han HC, Lindequist U, Hyun JW, Kim YH, An HS, Lee DH et al (2004) Apoptosis induction by acetoxyscirpendiol from *Paecilomyces tenuipes* in human leukaemia cell lines. Pharmazie 59:42–49

Han SB, Lee CW, Kang JS, Yoon YD, Lee KH, Lee K, Park SK, Kim HM (2006) Acidic polysaccharide from *Phellinus linteus* inhibits melanoma cell metastasis by blocking cell adhesion and invasion. Int Immunopharmacol 6:697–702

Harhaji LJ, Mijatovic S, Ivanic DM, Stojanovic I, Momcilovic M, Maksimovic V, Tufegdzic S, Marjanovic Z, Stojkovic MM, Vucinic Z, Grujicic ST (2008) Anti-tumor effect of *Coriolus versicolor* methanol extract against mouse B16 melanoma cells: *in vitro* and *in vivo* study. Food Chem Toxicol 46:1825–1833

Hartley AJ, Mattos-Shipley K, Collins CM, Kilaru S, Foster GD, Bailey AM (2009) Investigating pleuromutilin-producing *Clitopilus* species and related basidiomycetes. Microbiol Lett 297:24–30

Hasegawa T, Fujisawa T, Haraguchi S, Numata M, Karinaga R, Kimura T, Okumura S, Sakurai K, Shinkai S (2005) Schizophyllan–folate conjugate as a new non-cytotoxic and cancer-targeted antisense carrier. Bioorg Med Chem Lett 15:327–330

Hattori TS, Komatsu N, Shichijo S, Itoh K (2004) Protein-bound polysaccharide K induced apoptosis of the human Burkitt lymphoma cell line, Namalwa. Biomed Pharmacother 58:226–230

Hawksworth DL (2001) Mushrooms: the extent of the unexplored potential. Int J Med Mushr 3:333–337

Hayakawa K, Mitsuhashi N, Saito Y, Takahashi M, Katano S, Shiojima K, Furuta M, Nibe H (1993) Effect of Krestin (PSK) as adjuvant treatment on the prognosis after radical radiotherapy in patients with non small cell lung cancer. Anticancer Res 13:1815–1820

Heleno SA, Barros L, Sousa MJ, Martins A, Santos-Buelga C, Ferreira ICFR (2011) Targeted metabolites analysis in wild *Boletus* species. LWT - Food Sci Technol 44:1343–1348

Herre J, Gordon S, Brown GD (2004) Dectin-1 and its role in the recognition of β-glucans by macrophages. Mol Immunol 40:869–876

Herzig M, Trevino AV, Liang H, Salinas R, Waters S, MacDonald JR, Woynarowska B, Woynarowski J (2003) Apoptosis induction by the dual-action DNA- and protein-reactive antitumor drug irofulven is largely Bcl-2-independent. Biochem Pharmacol 65:503–513

Hilgers W, Faivre S, Chieze S, Alexandre J, Lokiec F et al (2006) A phase I and pharmacokinetic study of irofulven and cisplatin administered in a 30-min infusion every two weeks to patients with advanced solid tumors. Invest New Drugs 24:311–319

Hirata Y, Nahanishi K (1950) Grifolin, an antibiotic from a Basidiomycete. J Biol Chem 184:135–144

Hobbs C (1995) Medicinal mushrooms: an exploration of tradition, healing, and culture. Botanica Press, Santa Cruz, 251p

Hobbs C (2000) Medicinal value of *Lentinus edodes* (Berk.) Sing. (*Agaricomycetideae*). A literature review. Int J Med Mushr 2:287–302

Hobbs CR (2004) Medicinal value of Turkey Tail fungus *Trametes versicolor* (L.:Fr.) Pilát (*Aphyllophoromycetideae*). Int J Med Mushr 6:195–218

Hobbs CR (2005) The chemistry, nutritional value, immunopharmacology, and safety of the traditional food of medicinal split-gill fungus *Schizophyllum commune* Fr.:Fr. (*Aphyllophoromycetideae*). A literature review. Int J Med Mushr 7:127–140

Holliday H, Cleaver M (2008) Medicinal value of the caterpillar fungi species of the genus *Cordyceps* (Fr.) Link (Ascomycetes). Int J Med Mushr 10:209–218

Hong F, Yan J, Baran JT, Allendorf DJ, Hansen RD, Ostroff GR, Xing PX, Cheung NK, Ross GD (2004) Mechanism by which orally administered β-(1→3)-glucans enhance the tumoricidal activity of antitumor monoclonal antibodies in murine tumor models. J Immunol 173:797–806

Hou XJ, Chen W (2008) Optimization of extraction process of crude polysaccharides from wild edible BaChu mushroom by response surface methodology. Carbohyd Polym 72:67–74

Hsiao YM, Huang YL, Tang SC, Shieh GJ, Lai JY, Wang PH, Ying TH, Ko JL (2008) Effect of a fungal immunomodulatory protein from *Ganoderma tsugae* on cell cycle and interferon-gamma production through phosphatidylinositol 3-kinase signal pathway. Process Biochem 43:423–430

Hsu CL, Yu YS, Yen GC (2008) Lucidenic acid B induces apoptosis in human leukemia cells via a mitochondria-mediated pathway. J Agric Food Chem 56:3973–3980

Huang GJ, Yang CM, Chang YS, Amagaya S, Wang HC, Hou WC, Huang SS, Hu ML (2010) Hispolon suppresses SK-Hep1 human hepatoma cell metastasis by inhibiting matrix metalloproteinase-2/9 and urokinase-plasminogen activator through the PI3K/Akt and ERK signaling pathways. J Agric Food Chem 58(17):9468–9475

Huang HY, Chieh SY, Tso TK, Chien TY, Lin HT, Tsai YC (2011) Orally administered mycelial culture of *Phellinus linteus* exhibits antitumor effects in hepatoma cell-bearing mice. J Ethnopharmacol 133:460–466

Hung WT, Wang SH, Chen CH, Yang WB (2008) Structure determination of β-Glucans from *Ganoderma lucidum* with matrix-assisted laser desorption/ionization (MALDI) Mass Spectrometry. Molecules 13:1538–1550

Hyde KD (2001) Where are the missing fungi; Does Hong Kong have any answers. Mycol Res 105:1514–1518

Hyde KD, Bahkali AH, Moslem MA (2010) Fungi—an unusual source for cosmetics. Fungal Divers 43:1–9

Hyodo I, Amano N, Eguchi K, Narabayashi M, Imanishi J, Hirai M, Nakano T, Takashima S (2005) Nationwide survey on complementary and alternative medicine in cancer patients in Japan. J Clin Oncol 23:2645–2654

Inoue M, Tanaka Y, Sugita N, Yamasaki M, Yamanaka T, Minagawa J, Nakamuro K, Tani T, Okudaira Y, Karita T et al (1993) Improvement of long-term prognosis in patients with ovarian cancers by adjuvant sizofiran immunotherapy: a prospective randomized controlled study. Biotherapy 6:13–18

Inoue A, Kodama N, Nanba H (2002) Effect of Maitake (*Grifola frondosa*) D-fraction on the control of the T lymphocyte node Th-1/Th-2 proportion. Biol Pharm Bull 25:536–540

Isaac S (1997) Fungi naturally form many diverse biochemical products, some of which are now commercially important; how and why do they do this? Mycol Answers 11:182–183

Ishii PL, Prado CK, Mauro MO, Carreira CM, Mantovani MS, Ribeiro LR, Dichi JB, Oliveira RJ (2011) Evaluation of *Agaricus blazei in vivo* for antigenotoxic, anticarcinogenic, phagocytic and immunomodulatory activities. Regul Toxicol Pharmacol 59:412–422

Ivanković S, Hirsl N, Jakopovich I, Jurin M (2004) Influence of medicinal mushroom preparations on mouse tumors. Int J Med Mushr 6:107–116

Jakopovich I (2011) New dietary supplements from medicinal mushrooms: Dr Myko San—a registration report. Int J Med Mushr 13:307–313

Jang KJ, Han MH, Lee BH, Kim BW, Kim CH, Yoon HM, Choi YH (2010) Induction of apoptosis by ethanol extracts of *Ganoderma lucidum* in human gastric carcinoma cells. J Acupunct Meridian Stud 3:24–31

Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ (2009) Cancer statistics, 2009. Cancer J Clinicians 59:225–249

Jeon T, Hwang SG, Jung YH, Yang HS, Sung NY, Lee J, Park DK, Yoo YC (2011) Inhibitory effect of oral administration of sangwhang mushroom (*Phellinus linteus*) grown on germinated brown rice on experimental lung metastasis and tumor growth in mice. Food Sci Biotechnol 20:209–214

Jeong JW, Jin CY, Park C, Hong SH, Kim GY, Jeong YK, Lee JD, Yoo YH, Choi YH (2011) Induction of apoptosis by cordycepin via reactive oxygen species generation in human leukemia cells. Toxicol In Vitro 25:817–824

Jiang J, Silva D (2010) Novel medicinal mushroom blend suppresses growth and invasiveness of human breast cancer cells. Int J Oncology 37:1529–1536

Jikai L (2002) Biologically active substances from mushrooms in Yunnan, China. Heterocycles 57:157–167

Jiménez-Medina E, Berruguilla E, Romero I, Algarra I, Collado A, Garrido F, Garcia-Lora A (2008) The immunomodulator PSK induces *in vitro* cytotoxic activity in tumour cell lines via arrest of cell cycle and induction of apoptosis. Bio Med Central Cancer 8:78

Jones PA, Baylin SB (2007) The epigenomics of cancer. Cell 128:683–692

Jong SC, Birmingham JM, Pai SH (1991) Immunomodulatory substances of fungal origin. J Immun Immunopharmacol 11:115–122

Kakimi K, Nakajima J, Wada H (2009) Active specific immunotherapy and cell-transfer therapy for the treatment of non-small cell lung cancer. Lung Cancer 65:1–8

Katano M, Yamamoto Y, Torisu M (1987) A suppressive effect of PSK, protein-bound polysaccharide preparation, on tumor growth: a new effect of PSK on cell motility. Jpn J Cancer Chemother 14:2321–2326

Kawagishi H, Inagaki R, Kanao T, Mizuno T, Shimura K, Ito H, Hagiwara T, Hakamura T (1989) Fractionation and antitumor activity of the water-insoluble residue of *Agaricus blazei* fruiting bodies. Carbohyd Res 186:267–274

Kelner MJ, McMorris TC, Rojas RJ, Estes LA, Suthipinijtham P (2008) Synergy of irofulven in combination with other DNA damaging agents: synergistic interaction with altretamine, alkylating, and platinum-derived agents in the MV522 lung tumor model. Cancer Chemother Pharm 63:19–26

Kerrigan R (2005) *Agaricus subrufescens*, a cultivated edible and medicinal mushroom, and its synonyms. Mycologia 97:12–24

Khan MA, Tania M, Zhang DZ, Chen HC (2010) *Cordyceps* Mushroom: a potent anticancer nutraceutical. Open Nutraceuticals J 3:179–183

Kidd PM (2000) The use of mushroom Glucans and proteoglycans in cancer treatment. Altern Med Rev 5:4–27

Kim HM, Han SB, Oh GT, Kim YH, Hong DH, Hongt ND, Yoo ID (1996) Stimulation of humoral and cell mediated immunity by polysaccharide from mushroom *Phellinus linteus*. Int J Immunopharmacol 18:295–303

Kim GY, Park HS, Nam BH, Lee SJ, Lee JD (2003a) Purification and characterization of acidic proteo-heteroglycan from the fruiting body of *Phellinus linteus* (Berk & M.A. Curtis) Teng. Bioresource Technol 89:81–87

Kim GY, Park SK, Lee MK, Lee SH, Oh YH, Yoon S, Lee JD, Park YM (2003b) Proteoglycan isolated from *Phellinus linteus* activates murine B lymphocytes via protein kinase C and protein tyrosine kinase. Int Immunopharmacol 3:1281–1292

Kim YO, Park HW, Kim JH, Lee JY, Moon SH, Shin CS (2006) Anticancer effect and structural characterization of endo-polysaccharide from cultivated mycelia of *Inonotus obliquus*. Life Sci 79:72–80

Kim HG, Yoon DH, Lee WH, Han SK, Shrestha B, Kim CH, Lim MH, Chang W, Lim S, Choi S, Song WO, Sung JM, Hwang KC, Kim TW (2007) *Phellinus linteus* inhibits inflammatory mediators by suppressing redox-based NF-κB and MAPKs activation in lipopolysaccharide-induced RAW 264.7 macrophage. J Ethnopharmacol 114:307–315

Kim YS, Im J, Choi JN, Kang SS, Lee YJ, Lee CH, Yun CH, Son CG, Han SH (2010) Induction of ICAM-1 by *Armillariella mellea* is mediated through generation of reactive oxygen species and JNK activation. J Ethnopharmacol 128:198–205

Kim SP, Kang MY, Kim JH, Nam SH, Friedman M (2011) Composition and mechanism of antitumor effects of *Hericium erinaceus* mushroom extracts in tumor-bearing mice. J Agric Food Chem 59 (18):9861–9869

Kimura Y, Tojima H, Fukase S et al (1994) Clinical evaluation of sizofilan as assistant immunotherapy in treatment of head and neck cancer. Acta Otolaryngol 511:192–195

Kinge TR, Mih AM (2011) Secondary metabolites of oil palm isolates of *Ganoderma zonatum* Murill. from Cameroon and their cytotoxicity against five human tumour cell lines. Afr J Biotechnol 10 (42):8440–8447

Kino K, Yamashita A, Yamaoka K, Watanabe J, Tanaka S, Ko K et al (1989) Isolation and characterization of a new immunomodulatory protein, Ling Zhi-8 (LZ-8), from *Ganoderma lucidum*. J Biol Chem 264:472–478

Kitamura S, Hori T, Kurita K, Takeo K, Hara C, Itoh W et al (1994) Antitumor, branched β-(1→3)-D-glucan from a water extract fruiting bodies of *Cryptoporous volvatus*. Carbohyd Res 26:111–121

Kleinwächter P, Anh N, Kiet TT, Schlegel B, Dahse HM, Härtl A, Gräfe U (2001) Colossolactones, new triterpenoid metabolites from a Vietnamese mushroom *Ganoderma colossum*. J Nat Prod 64:236–239

Knudsen KE, Jensen BB, Hansen I (1993) Digestion of polysaccharides and other major components in the small and large intestine of pigs fed on diets consisting of oat fractions rich in β-D-glucan. Brit J Nutr 70:537–556

Ko JL, Hsu CI, Lin RH, Jai CL, Lin JY (1995) A new fungal immunomodulatory protein, FIP-fve isolated from the edible mushroom, *Flammulina velutipes* and its complete amino acid sequence. Eur J Biochem 228:244–249

Kobayashi H, Matsunaga K, Oguchi Y (1995) Antimetastatic effects of PSK (Krestin), a protein-bound polysaccharide obtained from basidiomycetes: an overview. Cancer Epidemiol Biomarkers Prev 4:275–281

Kodama N, Harada N, Nanba H (2002a) A polysaccharide, extract from *Grifola frondosa*, induces Th-1 dominant responses in carcinoma-bearing BALB/c mice. Jpn J Pharmacol 90:357–360

Kodama N, Komuta K, Nanba H (2002b) Can Maitake MD-fraction aid cancer patients? Altern Med Rev 7:236–239

Kodama N, Murata Y, Asakawa A, Inui A, Hayashi M, Sakai N, Nanba H (2005) Maitake D-Fraction enhances antitumor effects and reduces immunosuppression by mitomycin-C in tumor-bearing mice. Nutrition 21:624–629

Kodama N, Mizuno S, Nanba H, Saito N (2010) Potential antitumor activity of a low-molecular weight protein fraction from *Grifola frondosa* through enhancement of cytokine production. J Med Food 13:20–30

Konno S (2001) Maitake D-fraction: apoptosis inducer and immune enhancer. Altern Complementary Ther 17:102–107

Krzyczkowski W, Malinowska E, Suchocki P, Kleps J, Olejnik M, Herold F (2009) Isolation and quantitative determination of ergosterol peroxide in various edible mushroom species. Food Chem 113:351–355

Kudugunti SK, Vad NM, Whiteside AJ, Naik BU, Yusuf MA, Srivenugopal KS, Moridani MY (2010) Biochemical mechanism of caffeic acid phenylethyl ester (CAPE) selective toxicity towards melanoma cell lines. Chemico-Biol Interact 188:1–14

Kumar A, Takada Y, Boriek AM, Aggarwal BB (2004) Nuclear factor-κB: its role in health and disease. J Mol Med 82:434–448

Kumar RJ, Barqawi A, Crawford EA (2005) Adverse events associated with hormonal therapy for prostate cancer. Rev Urol 7:S37–S43

Kuo MC, Weng CY, Ha CL, Wu MJ (2006) *Ganoderma lucidum* mycelia enhance innate immunity by activating NF-κB. J Ethnopharmacol 103:217–222

Kurashige S, Akuzawa Y, Endo F (1997) Effects of *Lentinus edodes, Grifola frondosa* and *Pleurotus ostreatus* administration on cancer outbreak, and activities of macrophages and lymphocytes in mice treated with a carcinogen, N-butyl-N-butanolnitrosoamine. Immunopharmacol Immunotoxicol 19:175–183

Ladanyi A, Timar J, Lapis K (1993) Effect of lentinan on macrophage cytotoxicity against metastatic tumor cells. Cancer Immunol Immunother 36:123–126

Lam SK, Ng TB (2001) Hypsin, a novel thermostable ribosome inactivating protein with antifungal and antipoliferative activities from fruiting bodies of the edible mushroom *Hypsizigus marmoreus*. Biochem Biophys Res Commun 285:1071–1075

Lam YW, Ng TB, Wang HX (2001) Antipoliferative and antimitogenic activities in a peptide from puffball mushroom *Calvatia caelata*. Biochem Biophys Res Commun 289:744–749

Lee JS, Hong EK (2010) *Hericium erinaceus* enhances doxorubicin-induced apoptosis in human hepatocellular carcinoma cells. Cancer Lett 297:144–154

Lee JS, Hong EK (2011) Immunostimulating activity of the polysaccharides isolated from *Cordyceps militaris*. Int Immunopharmacol 11:1226–1233

Lee IK, Yun BS (2007) Highly oxygenated and unsaturated metabolites providing a diversity of hispidin class antioxidants in the medicinal mushrooms *Inonotus* and *Phellinus*. Bioorgan Med Chem 15:3309–3314

Lee IK, Yun BS (2011) Styrylpyrone-class compounds from medicinal fungi *Phellinus* and *Inonotus* spp., and their medicinal Importance. J Antibiot 64:349–359

Lee WY, Park Y, Ahn JK, Ka KH, Park SY (2007a) Factors influencing the production of endopolysaccharide and exopolysaccharide from *Ganoderma applanatum*. Enzyme Microb Tech 40:249–254

Lee IK, Kim YS, Jang YW, Jung JY, Yun BS (2007b) New antioxidant polyphenols from the medicinal mushroom *Inonotus obliquus*. Bioorg Med Chem Lett 17(24):6678–6681

Lee YS, Kim YH, Shin EK, Kim DH, Lim SS, Lee JY, Kim JK (2010) Anti-angiogenic activity of methanol extract of *Phellinus linteus* and its fractions. J Ethnopharmacol 131:56–62

Leggas M, Stewart CF, Woo MH, Fouladi M, Cheshre PJ, Peterson JK, Friedman HS, Billups C, Houghton PJ (2002) Relation between Irofulven (MGI-114) systemic exposure and tumor response in human solid tumor xenografts. Clin Cancer Res 8:3000–3007

Lehmann VK, Huang A, Calero IS, Wilson GR, Rinehart KL (2003) Illudin S, the sole antiviral compound in mature fruiting bodies of *Omphalotus illudens*. J Nat Prod 66:1257–1258

Lehne G, Haneberg B, Gaustad P, Johansen PW, Preus H, Abrahamsen TG (2006) Oral administration of a new soluble branched β-(1→3)-D-glucan is well tolerated and can lead to increased salivary concentrations of immunoglobulin A in healthy volunteers. Clin Exp Immunol 143:65–69

Lehtovaara BC, Gu FX (2011) Pharmacological, structural, and drug delivery properties and applications of β-(1→3)-glucans. J Agric Food Chem 59:6813–6828

Leung MYK, Liu C, Koon JCM, Fung KP (2006) Polysaccharide biological response modifiers. Immunol Lett 105:101–111

Li JWH, Vederas JC (2009) Drug discovery and natural products: end of an era or an endless frontier. Science 325:161–165

Li SP, Li P, Lai CM, Gong YX, Kan KKW, Dong TTX, Tsim KWK, Wang YT (2004) Simultaneous determination of ergosterol, nucleosides and their bases from natural and cultured *Cordyceps* by pressurized liquid extraction and high-performance liquid chromatography. J Chromatogr 1036:239–243

Li Q, Wang X, Chen Y, Lin J, Zhou X (2010a) Cytokines expression induced by *Ganoderma sinensis* fungal immunomodulatory proteins (FIP-gsi) in mouse spleen cells. Appl Biochem Biotechnol 162:1403–1413

Li YQ, Zhang BC, Wang XQ, Yan HD, Chen G, Zhang XW (2010b) Proteomic analysis of apoptosis induction in human lung cancer cells by recombinant MVL. Amino Acids 41(4):923–932. doi:10.1007/s00726-010-0791-0

Li X, Xu W, Chen J (2010c) Polysaccharide purified from *Polyporus umbellatus* (Per) Fr induces the activation and maturation of murine bone-derived dendritic cells via toll-like receptor 4. Cell Immunol 265(1):50–56. doi:10.1016/j.cellimm.2010.07.002

Li F, Wen H, Zhang Y, An M, Liu XZ (2011) Purification and characterization of a novel immunomodulatory protein from the medicinal mushroom *Trametes versicolor*. Sci China Life Sci 54:379–385

Liang H, Herzig M, Salinas R (2001) Pro-oxidative distortion of the cellular redox-homeostasis in irofulven-induced apoptosis. Clin Cancer Res 7:3723

Lin Z-B (2009) Lingzhi. From mystery to science. Peking University Medical Press, Beijing, 162 p

Lin YW, Chiang BH (2011) 4-Acetylantroquinonol B Isolated from *Antrodia cinnamomea* arrests proliferation of human hepatocellular carcinoma HepG2 cell by affecting p53, p21 and p27 Levels. J Agric Food Chem 59:8625–8631

Lin JT, Liu WH (2006) *o*-Orsellinaldehyde from the submerged culture of the edible mushroom *Grifola frondosa* exhibits selective cytotoxic effect against Hep 3B cells through apoptosis. J Agric Food Chem 54:7564–7569

Lin SB, Li CH, Lee SS, Kan LS (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 Sci 72:2381–2390

Lin Y, Lai P, Huang Y, Xie H (2004) Immune-competent polysaccharides from the submerged cultured mycelium of culinary-medicinal mushroom *Lentinus srigellus* Berk. & Curt. (*Agaricomycetideae*). Int J Med Mushr 6:49–55

Lin YL, Liang YC, Tseng YS, Huang HY, Chou SY, Hseu RS et al (2009) An immunomodulatory protein, Ling Zhi-8, induced activation and maturation of human monocyte-derived dendritic cells by the NF-κB and MAPK pathways. J Leukoc Biol 86:877–889

Lin CH, Sheu GT, Lin YW, Yeh CS, Huang YH, Lai YC et al (2010) A new immunomodulatory protein from *Ganoderma microsporum* inhibits epidermal growth factor mediated migration and invasion in A549 lung cancer cells. Process Biochem 45:1537–1542

Lin CC, Yu YL, Shih CC, Liu KJ, Ou KL, Hong LZ et al (2011) A novel adjuvant Ling Zhi-8 enhances the efficacy of DNA cancer vaccine by activating dendritic cells. Cancer Immunol Immun 60:1019–1027

Lindequist U, Niedermeyer THJ, Jülich WD (2005) The pharmacological potential of mushrooms. Evid Based Complement Alternat Med 2:285–299

Lindequist U, Rausch R, Füssel A, Hanssen HP (2010) Higher fungi in traditional and modern medicine. Med Monatsschr Pharm 33:40–48

Liu J (2002) Biologically active substances from mushrooms in Yunnan, China. Heterocycles 57:157–167

Liu JJ, Huang TS, Hsu ML, Chen CC, Lin WS, Lu FJ, Chang WH (2004) Antitumor effects of the partially purified polysaccharides from *Antrodia camphorata* and the mechanism of its action. Toxicol Appl Pharmacol 201:186–193

Liu YW, Gao JL, Guan J, Qian ZM, Feng K, Li SP (2009a) Evaluation of antiproliferative activities and action mechanisms of extracts from two species of *Ganoderma* on tumor cell lines. J Agric Food Chem 57:3087–3093

Liu K, Ding X, Deng B, Chen W (2009b) Isolation and characterization of endophytic taxol-producing fungi from *Taxus chinensis*. J Ind Microbiol Biotechnol 36:1171–1177

Liu J, Shimizu K, Kondo R (2010) The effects of ganoderma alcohols isolated from *Ganoderma lucidum* on the androgen receptor binding and the growth of LNCaP cells. Fitoterapia 81:1067–1072

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 Int 105:1011–1015

Lu TL, Huang GJ, Lu TJ, Wu JB, Wu CH, Yang TC, Iizuka A, Chen YF (2009) Hispolon from *Phellinus linteus* has antiproliferative effects via MDM2-recruited ERK1/2 activity in breast and bladder cancer cells. Food Chem Toxicol 47:2013–2021

Lull C, Wichers HJ, Savelkoul HFJ (2005) Antiinflammatory and immunomodulating properties of fungal metabolites. Mediat Inflamm 2:63–80

Luo X, Xu X, Yu M, Yang Z, Zheng L (2008) Characterisation and immunostimulatory activity of an α-(1→6)-D-glucan from the cultured *Armillaria tabescens* mycelia. Food Chem 111:357–363

Luo XJ, Li LL, Deng QP, Yu XF, Yang LF, Luo FJ, Xiao LB, Chen XY, Ye M, Liu JK, Cao Y (2011) Grifolin, a potent antitumour natural product upregulates death-associated protein kinase 1 DAPK1 via p53 in nasopharyngeal carcinoma cells. Eur J Cancer 47(2):316–325

Maduro JH, Pras E, Willemse PHB, de Vries EGE (2003) Acute and long-term toxicity following radiotherapy alone or in combination with chemotherapy for locally advanced cervical cancer. Cancer Treat Rev 29:471–488

Mahajna J, Dotan N, Zaidman B-Z, Petrova RD, Wasser SP (2009) Pharmacological values of medicinal mushrooms for prostate cancer therapy: the case of *Ganoderma lucidum*. Nutrit Cancer 61:16–26

Maiti S, Bhutia SK, Mallick SK, Kumar A, Khadgi N, Maiti TK (2008) Antiproliferative and immunostimulatory protein fraction from edible mushrooms. Environ Toxicol Pharmacol 26:187–191

Maruyama H, Ikekawa T (2007) Immunomodulation and antitumor activity of a mushroom product, proflamin, isolated from *Flammulina velutipes* (W.Curt.:Fr.) Singer (*Agaricomycetideae*). Int J Med Mushr 9:109–122

Masuda Y, Ito K, Konishi M, Nanba H (2010) A polysaccharide extracted from *Grifola frondosa* enhances the anti-tumor activity of bone marrow-derived dendritic cell-based immunotherapy against murine colon cancer. Cancer Immunol Immun 59:1531–1541

Matsuda H, Akaki J, Nakamura S, Okazaki Y, Kojima H, Tamesada M, Yoshikawa M (2009) Apoptosis-inducing effects of sterols from the dried powder of cultured mycelium of *Cordyceps sinensis*. Chem Pharm Bull (Tokyo) 57:411–414

Matsui K, Kodama N, Nanba H (2001) Effects of Maitake (*Grifola frondosa*) D-fraction on the carcinoma angiogenesis. Cancer Lett 172:193–198

Mattila P, Konko K, Eurola M et al (2001) Contents of vitamins, mineral elements and some phenolic compounds in cultivated mushrooms. J Agric Food Chem 49:2343–2348

Mayell M (2001) Maitake extracts and their therapeutic potential. Altern Med Rev 6:48–60

McMorris TC (1999) Discovery and development of sesquiterpenoid derived hydroxymethylacylfulvene: a new anticancer drug. Bioorg Med Chem 7:881–886

McMorris TC, Kelner MJ, Wang W, Yu J, Estes LA, Taetle R (1996) (Hydroxymethyl) acylfulvene: an illudin derivative with superior antitumor properties. J Nat Prod 59:896–899

McNeela EA, Mills KHG (2001) Manipulating the immune system: humoral versus cell-mediated immunity. Adv Drug Deliv Rev 51:43–54

Miles PG, Chang ST (1997) Mushroom biology: concise basics and current developments. World Scientific Press, pp 161–175

Misiek M, Williams J, Schmich K, Hüttel W, Merfort I, Salomon CE, Aldrich CC, Hoffmeister D (2009) Structure and cytotoxicity of arnamial and related fungal Sesquiterpene Aryl Esters. J Nat Prod 72:1888–1891

Mizuno T (1999a) Medicinal effects and utilization of *Cordyceps* (Fr.) Link (Ascomycetes) and *Isaria* Fr. (Mitosporic fungi) Chinese caterpillar fungi, "Tochukaso". Int J Med Mushr 1:251–262

Mizuno T (1999b) The extraction and development of antitumor-active polysaccharides from medicinal mushrooms in Japan. Int J Med Mushr 1:9–29

Mizuno T (1999c) Bioactive substances in *Hericium erinaceus* (Bull., Fr.) Pers. (Yambushitake) and its medicinal utilization. Int J Med Mushr 2:105–119

Mizuno T, Wasa T, Ito H, Suzuki C, Ukai N (1992) Antitumor-active polysaccharides isolated from the fruiting body of *Hericium erinaceum*, an edible and medicinal mushroom called yamabushitake or houtou. Biosci Biotechnol Biochem 56:347–348

Mizuno T, Kinoshita T, Zhuang C, Ito H, Mayuzumi Y (1995a) Antitumor-active heteroglycans from Niohshimeji mushroom, *Tricholoma giganteum*. Biosci Biotechnol Biochem 59:568–571

Mizuno T, Saito H, Nishitoba T, Kawagishi H (1995b) Antitumor active substances from mushrooms. Food Rev Int 11:23–61

Mizuno T, Yeohlui P, Kinoshita T, Zhuang C, Ito H, Mayuzumi Y (1996) Antitumor activity and chemical modification of polysaccharides from Niohshimeji mushroom, *Tricholoma giganteum*. Biosci Biotechnol Biochem 60:30–33

Mizuno T, Zhuang AK, Okamoto H, Kiho T, Ukai S, Leclerc S, Meijer L (1999) Antitumor and hypoglycemic activities of polysaccharides from the sclerotia and mycelia of *Inonotus obliquus* (Pers.:Fr.) Pil. (*Aphyllophoromycetideae*). Int J Med Mushr 1:301–316

Mo S, Wang S, Zhou G, Yang Y, Li Y, Chen X, Shi J (2004) Phelligridins C-F: cytotoxic pyrano[4,3-c][2]benzopyran-1,6-dione and furo[3,2-c]pyran-4-one derivatives from the fungus *Phellinus igniarius*. J Nat Prod 67:823–828

Moradali MF, Mostafavi H, Ghods S, Hedjaroude GA (2007) Immunomodulating and anticancer agents in the realm of macromycetes fungi (macrofungi). Int Immunopharmacol 7:701–724

Moullec G, Maïano C, Morin JS, Monthuy-Blanc J, Rosello L, Ninot G (2011) A very short visual analog form of the center for epidemiologic studies depression scale (CES-D) for the idiographic measurement of depression. J Affect Disord 128:220–234

Munz C, Steinman RM, Fujii S (2005) Dendritic cell maturation by innate lymphocytes: coordinated stimulation of innate and adaptive immunity. J Exp Med 202:203–207

Nakamura T, Akiyama Y, Matsugo S et al (2003) Purification of caffeic acid as an anti-oxidant from submerged culture mycelia of *Phellinus linteus* (Berk. et Curt.) Teng (*Aphyllophoromycetideae*). Int J Med Mushr 5:163–167

Nakamura N, Hirakawa A, Gao JJ, Kakuda H, Shiro M, Komatsu Y, Sheu CC et al (2004) Five new maleic and succinic acid derivatives from the mycelium of *Antrodia camphorata* and their cytotoxic effects on LLC tumor cell line. J Nat Prod 67:46–48

Nanba H (1995) Results of non-controlled clinical study for various cancer patients using Maitake D-fraction. Explore 6:19–21

Nanba H (1997a) Effect of Maitake D-fraction on cancer prevention. Ann N Y Acad Sci 833:204–207

Nanba H (1997b) Maitake D-fraction: healing and preventive potential for cancer. J Orthomol Med 12:43–49

NCI (2006) National cancer institute. Biological therapies for cancer. Questions and answers. http://www.cancer.gov/cancertopics/factsheet/Therapy/biological

NCI (2011) National cancer institute. Cancer topics http://www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer

Nemoto J, Ohno N, Saito K, Adachi Y, Yasomae T (1993) Expression of interleukin-1 family mRNAs by a highly branched β-(1→3)-D-glucan, OL-2. Biol Pharm Bull 16:1046–1050

Newman DJ, Cragg GM (2007) Natural products as sources of new drugs over the last 25 years. J Nat Prod 70:461–477

Ng TB (1998) A review of research on the protein-bound polysaccharide (polysaccharopeptide, PSP) from the mushroom *Coriolus versicolor* (Basidiomycetes: *Polyporaceae*). Gen Pharmacol 30:1–4

Ng TB, Lam YW, Wang H (2003) Calcaelin, a new protein with translation-inhibiting, antiproliferative and antimitogenic activities from the mosaic puffball mushroom *Calvatia caelata*. Planta Med 69:212–217

Ninot G, Moullec G, Picot MC, Jaussent A, Desplan M, Brun JF, Mercier J, Hayot M, Prefaut C (2011) Outcomes of a one month hospital self-management program in moderate to severe COPD patients: a randomized controlled trial. Resp Med 105:377–385

Nomura M, Takahashi T, Uesugi A, Tanaka R, Kobayashi S (2008) Inotodiol, a lanostane triterpenoid, from *Inonotus obliquus* inhibits cell proliferation through caspase-3-dependent apoptosis. Anticancer Res 28:2691–2696

Norikura T, Fujiwara K, Narita T, Yamaguchi S, Morinaga Y, Iwai K, Matsue H (2011) Anticancer activities of Thelephantin O and Vialinin A isolated from *Thelephora aurantiotincta*. J Agric Food Chem 59:6974–6979

Novak M, Vetvicka V (2009) Glucans as biological response modifiers. Endocr Metab Immune Disord-Drug Targets 9:67–75

Novak M, Rapkova R, Copikova J, Sarka E (2010) beta-glucan composition and structure: an evolution of views. Proceedings of the 6th international conference on polysaccharides-Glycoscience, 17–21

Nowell PC (1986) Mechanisms of tumor progression. Cancer Res 46:2203–2207

Nukata M, Hashimoto T, Yamamoto I, Iwasaki N, Tanaka M, Asakawa Y (2002) Neogrifolin derivatives possessing antioxidative activity from the mushroom *Albatrellus ovinus*. Phytochemistry 59:731–737

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 Immunol Immunother 56:905–911

Ohno N (2005) Structural diversity and physiological functions of β-glucans. Int J Med Mushr 7:167–174

Ohno N, Miura NN, Nakajima M, Yadomae T (2000) Anti-tumor 1,3-β-glucan from cultured fruit body of *Sparassis crispa*. Biol Pharm Bull 23:866–872

Ohno N, Nameda S, Harada T et al (2003) Immunomodulating activity of a S-glucan preparation, SCG, extracted from a culinary-medicinal mushroom, Sparassis crispa Wulf.: Fr. (Aphyllophoromycetidae), and application to cancer patients. Int J Med Mushr 5:359–368

Okazaki M, Adachi Y, Ohno N, Yadomae T (1995) Structure-activity relationship of β-(1→3)-D-glucans in the induction of cytokine production from macrophages *in vitro*. Biol Pharm Bull 18:1320–1327

Ooi VE, Liu F (1999) A review of pharmacology activities of mushroom polysaccharides. Int J Med Mushr 1:195–206

Ooi VE, Liu F (2000) Immunomodulation and anti-cancer activity of polysaccharide–protein complexes. Curr Med Chem 7:715

Oshiman K, Fujimiya Y, Ebina T, Suzuki I, Noji M (2002) Orally administered b-1,6-D-polyglucose extracted from *Agaricus blazei* results in tumor regression in tumor-bearing mice. Planta Med 68:610–614

Park YM, Won JH, Kim YH, Choi JW, Park HJ, Lee KT (2005) *In vivo* and *in vitro* anti-inflammatory and anti-nociceptive effects of the methanol extract of *Inonotus obliquus*. J Ethnopharmacol 101:120–128

Parkinson DR (1995) Present status of biological response modifiers in cancer. Am J Med 99:54–56

Paterson RRM (2006) *Ganoderma* - A therapeutic fungal biofactory (Review). Phytochemistry 67:1985–2001

Paterson RRM (2008) *Cordyceps* - A traditional Chinese medicine and another fungal therapeutic biofactory? Phytochemistry 69:1469–1495

Peng Y, Zhang L, Zeng F, Kennedy JF (2005) Structure and antitumor activities of the water-soluble polysaccharides from *Ganoderma tsugae* mycelium. Carbohyd Polym 59:385–392

Petrova RD, Wasser SP, Mahajna J, Denchev CM, Nevo E (2005) Potential role of medicinal mushrooms in breast cancer treatment: current knowledge and future perspectives. Int J Med Mushr 7:141–155

Petrova RD, Mahajna J, Reznick AZ, Wasser SP, Denchev CM, Nevo E (2007) Fungal substances as modulators of NF-kappaB activation pathway. Mol Biol Rep 34(3):145–154

Petrova RD, Reznick AZ, Wasser SP, Denchev CM, Nevo E, Mahajna J (2008) Fungal metabolites modulating NF-κB activity: an approach to cancer therapy and chemoprevention. Oncol Rep 19:299–308

Petrova R, Mahajna J, Wasser SP, Ruimi N, Denchev CM, Sussan S, Nevo E, Reznick AZ (2009) *Marasmius oreades* substances block NF-κB activity through interference with IKK activation pathway. Mol Biol Rep 36:737–744

Phillips KM, Ruggio DM, Horst RL, Minor B, Simon RR, Feeney MJ, Byrdwell WC, Haytowitz DB (2011) Vitamin D and sterol composition of 10 types of mushrooms from retail suppliers in the United States. J Agric Food Chem 59:7841–7853

Pierson AS, Gibbs P, Richards J, Russ P, Eckhardt SG, Gonzalez R (2002) A phase II study of Irofulven (MGI 114) in patients with stage IV melanoma. Invest New Drugs 20:357–362

Pöder R (2005) The Ice man's fungi: facts and mysteries. Int J Med Mushr 7:357–359

Pohleven J, Obermajer N, Sabotič J, Anžlovar S, Sepčić K, Kos J, Kralj B, Štrukelj B, Brzin J (2009) Purification, characterization and cloning of a ricin B-like lectin from mushroom *Clitocybe nebularis* with antiproliferative activity against human leukemic T cells. Biochim Biophys Acta 1790:173–181

Poindessous V, Koeppel F, Raymond E, Cvitkovic E, Waters SJ, Larsen AK (2003) Enhanced antitumor activity of irofulven in combination with 5-fluorouracil and cisplatin in human colon and ovarian carcinoma cells. Int J Oncol 23:1347–1355

Pollack A (2009) Drug firms see fortune in treating cancer. Int Herald Tribune, pp 15–16

Poucheret P, Fons F, Rapior S (2006) Biological and pharmacological activity of higher fungi: 20-year retrospective analysis. Cryptogam Mycol 27:311–333

Prestwich RJ, Errington F, Hatfield P, Merrick AE, Ilett EJ, Selby PJ, Melcher AA (2008) The immune system—is it relevant to cancer development, progression and treatment? Clin Oncol 20:101–112

Price LA, Wenner CA, Sloper DT, Slaton JW, Novack JP (2010) Role for toll-like receptor 4 in TNF-alpha secretion by murine macrophages in response to polysaccharide Krestin, a *Trametes versicolor* mushroom extract. Fitoterapia 81:914–919

Rapior S, Fruchier A, Bessiere JM (1997) Volatile aroma constituents of *Agaricus* and *Boletes*. In: Pandalai SG (ed) Recent Research Developments in Phytochemistry, vol 1. Publ. Research Signpost, Trivandrum, pp 567–584

Rapior S, Courtecuisse R, Francia C, Siroux Y (2000) Activités biologiques des champignons: recherches actuelles sur les facteurs de risque des maladies cardio-vasculaires. Annales de la Société d'Horticulture et d'Histoire Naturelle de l'Hérault 140:26–31

Ratain MJ, Relling MV (2001) Gazing into a crystal ball—cancer therapy in the post-genomic era. Nat Med 7:283–285

Ren G, Zhao YP, Yang L, Fu CX (2008) Anti-proliferative effect of clitocine from the mushroom *Leucopaxillus giganteus* on human cervical cancer HeLa cells by inducing apoptosis. Cancer Lett 262:190–200

Reshetnikov SV, Wasser SP, Tan KK (2001) Higher Basidiomycota as a source of antitumor and immunostimulating polysaccharides. Int J Med Mushr 3:361–394

Revillard JP (2002) Innate immunity. Eur J Dermatol 12:224–227

Rice PJ, Adams EL, Ozment-Skelton T, Gonzalez AJ, Goldman MP, Lockhart BE, Barker LA, Breuel KF, Deponti WK, Kalbfleisch JH (2005) Oral delivery and gastrointestinal absorption of soluble glucans stimulate increased resistance to infectious challenge. J Pharmocol Exp Ther 314:1079–1086

Roeder A, Kirschning CJ, Rupec RA, Schaller M, Weindl G, Korting HC (2004) Toll-like receptors as key mediators in innate antifungal immunity. Med Mycol 42:485–498

Rogers NC, Slack EC, Edwards AD, Nolte MA, Schulz O, Schweighoffer E, Williams DL, Gordon S, Tybulewicz VL, Brown GD, Reis e Sousa C (2005) Syk-dependent cytokine induction by Dectin-1 reveals a novel pattern recognition pathway for C type lectins. Immunity 22:507–517

Ruddon RW (2007) Cancer biology, 4th edn. Oxford University Press, USA

Ruimi N, Petrova RD, Agbaria R, Sussan S, Wasser SP, Reznick AZ, Mahajna J (2010) Inhibition of TNFα-induced iNOS expression in HSV-tk transduced 9L glioblastoma cell lines by Marasmius oreades substances through NF-κB- and MAPK-dependent mechanisms. Mol Biol Rep 37(8):3801–3812

Russo A, Piovano M, Clericuzio M, Lombardo L, Tabasso S, Chamy MC, Vidari G, Cardile V, Vita-Finzi P, Garbarino JA (2007) Putrescine-1,4-dicinnamide from *Pholiota spumosa* (Basidiomycetes) inhibits cell growth of human prostate cancer cells. Phytomedicine 14:185–191

Russo A, Cardile V, Piovano M, Caggia S, Espinoza CL, Garbarino JA (2010) Pro-apoptotic activity of ergosterol peroxide and (22*E*)-ergosta-7,22-dien-5α-hydroxy-3,6-dione in human prostate cancer cells. Chem Biol Int 184:352–358

Sakagami H, Aoki T (1991) Induction of immunopotentiation activity by a protein bound polysaccharide, PSK. Anticancer Res 11:993–1000

Sakagami Y, Mizoguchi Y, Shin T, Seki S, Kobayashi K, Morisawa S, Yamamoto S (1988) Effects of an anti-tumor polysaccharide, Schizophyllan, on interferon-γ and interleukin-2 production by peripheral blood mononuclear cells. Biochem Biophys Res Commun 155:650–655

Samorini G (2001) New data on the ethnomycology of psychoactive mushrooms. Int J Med Mushr 3:257–278

Seiden MV, Gordon AN, Bodurka DC, Matulonis UA, Penson RT, Reed E, Alberts DS, Weems G (2006) A phase II study of irofulven in women with recurrent and heavily pretreated ovarian cancer. Gynecol Oncol 101:55–61

Selosse MA (2000) La symbiose. Structures et fonctions, rôle écologique et évolutif. Vuibert edn, Paris, France 154 p

Shamtsyan M, Konusova V, Maksimova Y, Goloshchev A, Panchenko A, Simbirtsev A, Petrishchev N, Denisova N (2004) Immunomodulating and anti-tumor action of extracts of several mushrooms. J Biotechnol 113:77–83

Shang D, Li Y, Wang C et al (2011) A novel polysaccharide from Se-enriched *Ganoderma lucidum* induces apoptosis of human breast cancer cells. Oncol Rep 25:267–272

Sheng L, Chen J, Li J, Zhang W (2011) An exopolysaccharide from cultivated *Cordyceps sinensis* and its effects on cytokine expressions of immunocytes. Appl Biochem Biotech 163:669–678

Sheu F, Chien PJ, Chien AL, Chen YF, Chin KL (2004) Isolation and characterization of an immunomodulatory protein (APP) from the Jew's Ear mushroom *Auricularia polytricha*. Food Chem 87:593–600

Shimizu Y, Chen JT, Hirai Y, Nakayama K, Hamada T, Fujimoto I, Hasumi K (1989) Augmentation of immune responses of pelvic lymph node lymphocytes in cervical cancer patients by sizofiran. Nihon Sanka Fujinka Gakkai Zasshi 41:2013–2014

Shin KH, Lim SS, Lee S, Lee YS, Jung SH, Cho SY (2003) Anti-tumour and immuno-stimulating activities of the fruiting bodies of *Paecilomyces japonica*, a new type of *Cordyceps* spp. Phytother Res 17:830–833

Shu CH, Lin KJ, Wen BJ (2004) Effects of culture pH on the production of bioactive polysaccharides by *Agaricus blazei* in batch cultures. J Chem Technol Biotechnol 79:998–1002

Sliva D (2003) *Ganoderma lucidum* (Reishi) in cancer treatment. Integr Cancer Ther 2:358–364

Smith D, Ryan MJ (2009) Fungal sources for new drug discovery. In Access Science, ©McGraw-Hill Companies http://www.accessscience.com

Soares R, Meireles M, Rocha A, Pirraco A, Obiol D, Alonso E, Joos G, Balogh G (2011) Maitake (D Fraction) mushroom extract induces apoptosis in breast cancer cells by BAK-1 gene activation source. J Med Food 14:563–572

Song G, Du Q (2010) Isolation of a polysaccharide with anticancer activity from *Auricularia polytricha* using high-speed countercurrent chromatography with an aqueous two-phase system. J Chromatogr A 1217:5930–5934

Song J, Rui-Ping P, Jing-Nan S, Gang H, Jin W, Jia-Guo Z (2007) Grifolin induces apoptosis via inhibition of PI3K/AKT signalling pathway in human osteosarcoma cells. Apoptosis 12(7):1317–1326

Stewart BW, Kleihues P et al (2003) World cancer report. WHO International Agency for Research on Cancer (IARC) Press, Lyon

Strong K, Mathers C, Leeder S, Beaglehole R (2005) Preventing chronic diseases: how many lives can we save? Lancet 366:1578–1582

Sugiyama K, Kawagishi H, Tanaka A, Saeki S, Yoshida S, Sakamoto H, Ishiguro Y (1992) Isolation of plasma cholesterol-lowering components from ningyotake (*Polyporus confluens*) mushroom. J Nutr Sci Vitaminol 38:335–342

Surenjav U, Zhang L, Xu X, Zhang X, Zeng F (2006) Effects of molecular structure on antitumor activities of β-(1→3)-D-glucans from different *Lentinus edodes*. Carbohyd Polym 63:97–104

Takaku T, Kimura Y, Okuda H (2001) Isolation of an antitumor compound from *Agaricus blazei* Murill and its mechanism of action. Biochem Mol Action Nutr 131:1409–1413

Takeda K, Kaisho T, Akira S (2003) Toll-like receptors. Ann Rev Immunol 21:335–376

Tanaka K, Wakasugi J, Seki F, Koizumi Y, Tsuchiya S (1991) Effect of PSK on cell growth, chemotaxis and platelet aggregating activity of colon 26 cell line. Proceedings of the 50th Annual Japanese Cancer Association Meeting, 263

Tang W, Gu T, Zhong JJ (2006a) Separation of targeted ganoderic acids from *Ganoderma lucidum* by reversed phase liquid chromatography with ultraviolet and mass spectrometry detections. Biochem Eng J 32:205–210

Tang W, Liu JW, Zhao WM, Wei DZ, Zhong JJ (2006b) Ganoderic acid T from *Ganoderma lucidum* mycelia induces mitochondria mediated apoptosis in lung cancer cells. Life Sci 80:205–211

Tergaonkar V (2006) Signaling networks in focus NF-κB pathway: a good signaling paradigm and therapeutic target. Int J Biochem Cell B 38:1647–1653

Thetsrimuang C, Khammuang S, Chiablaem K, Srisomsap C, Sarnthima R (2011) Antioxidant properties and cytotoxicity of crude polysaccharides from *Lentinus polychrous* Lév. Food Chem 128:634–639

Thornton BP, Vetvicka V, Pitman M, Goldman RC, Ross GD (1996) Analysis of the sugar specificity and molecular location of the β-glucan-binding lectin site of complement receptor type 3 (CD11b/CD18). J Immunol 156:1235–1246

Torisu M, Hayashi Y, Ishimitsu T, Fujimura T, Iwasaki K et al (1990) Significant prolongation of disease –free period gained by oral polysaccharide K (PSK) administration after curative surgical operation of colorectal cancer. Cancer Immunol Immunother 31:261–268

Trinchieri G (2003) Interleukin-12 and the regulation of innate resistance and adaptive immunity. Nat Rev Immunol 3:133–146

Tsuji T, Du W, Nishioka T, Chen L, Yamamoto D, Chen CY (2010) *Phellinus linteus* extract sensitizes advanced prostate cancer cells to apoptosis in athymic nude mice. PLoS One 5(3):e9885

Umezawa K (2006) Inhibition of tumor growth by NF-KB inhibitors. Cancer Sci 97:990–995

Usui T, Iwasaki Y, Mizuno T, Tanaka M, Shinkai K, Arakawa M (1983) Isolation and characterization of anti-tumor active β-D-glucans from the fruit bodies of *Ganoderma applanatum*. Carbohyd Res 115:273–280

Uthaisangsook S, Day NK, Bahna SL, Good RA, Haraguchi S (2002) Innate immunity and its role against infections. Ann Allerg Asthma Immunol 88:253–264

Van de Putte K, Nuytinck J, Stubbe D, Le HT, Verbeken A (2011) *Lactarius volemus sensu lato* (Russulales) from northern Thailand: morphological and phylogenetic species concepts explored. Fungal Divers 45:99–130

Vaz JA, Heleno SA, Martins A, Almeida GM, Vasconcelos MH, Ferreira ICFR (2010) Wild mushrooms *Clitocybe alexandri* and *Lepista inversa*: *in vitro* antioxidant activity and growth inhibition of human tumour cell lines. Food Chem Toxicol 48:2881–2884

Vetvicka V, Dvorak B, Vetvickova J, Richter J, Krizan J, Sima P, Yvin JC (2007) Orally administered marine β-(1→3)-D-glucan Phycarine stimulates both humoral and cellular immunity. Int J Biol Macromol 40:291–298

Vinogradov E, Petersen BO, Duusb JO, Wasserc S (2004) The structure of the glucuronoxylomannan produced by culinary medicinal

yellow brain mushroom (*Tremella mesenterica* Ritz.:Fr., Heterobasidiomycetes) grown as one cell biomass in submerged culture. Carbohyd Res 339:1483–1489

Vos A, M'Rabet L, Stahl B, Boehm G, Garssen J (2007) Immune-modulatory effects and potential working mechanisms of orally applied nondigestible carbohydrates. Crit Rev Immunol 27:97–140

Wan JM, Sit WH, Louie JC (2008) Polysaccharopeptide enhances the anticancer activity of doxorubicin and etoposide on human breast cancer cells ZR-75-30. Int J Oncol 32:689–699

Wang HX, Liu WK, Ng TB, Ooi VEC, Chang ST (1996) The immunomodulatory and antitumor activities of lectins from the mushroom *Tricholoma mongolicum*. Immunopharmacology 31:205–211

Wang H, Ng TB, Ooi VE (1998) Lectins from mushrooms. Mycol Res 102:897–906

Wang Y, Mo SY, Wang SJ, Li S, Yang YC, Shi JG (2005) A unique highly oxygenated Pyrano[4,3-*c*][2]benzopyran-1,6-dione derivative with antioxidant and cytotoxic activities from the fungus *Phellinus igniarius*. Org Lett 7(9):1675–1678

Wang Y, Shang XY, Wang SJ, Mo SY, Li S, Yang YC, Ye F, Shi JG, Lan H (2007) Structures, biogenesis, and biological activities of Pyrano[4,3-*c*]isochromen-4-one derivatives from the fungus *Phellinus igniarius*. J Nat Prod 70:296–299

Wasser SP (2002) Medicinal mushrooms as a source of antitumor and immunomodulating polysaccharides. Appl Microbiol Biot 60:258–274

Wasser SP (2010) Shiitake. In: Encyclopedia of dietary supplements, 2nd edn. Informa Healthcare, New York, pp 719–726

Wasser SP (2011) Current findings, future trends, and unsolved problems in studies of medicinal mushrooms. Appl Microbiol Biotechnol 89:1323–1332

Wasser SP, Akavia E (2008) Regulatory issues of mushrooms as functional foods and dietary supplements: safety and efficacy. In: Cheung PCK (ed) Mushrooms as functional foods. Wiley, New York, pp 199–221

Wasser SP, Weis AL (1999a) Therapeutic effects of substances occurring in higher basidiomycetes mushrooms: a modern perspective. Crit Rev Immunol 19:65–96

Wasser SP, Weis AL (1999b) Medicinal properties of substances occurring in higher Basidiomycetes mushrooms: current perspectives. Int J Med Mushr 1:31–62

Weng CJ, Yen GC (2010) The *in vitro* and *in vivo* experimental evidences disclose the chemopreventive effects of *Ganoderma lucidum* on cancer invasion and metastasis. Clin Exp Metastasis 27:361–369

WHO (2004) World Health Organization. The world health report 2004: changing history. Geneva

WHO (2008) 2008–2013 Action plan for the global strategy for the prevention and control of non-communicable diseases. Prevent and control cardiovascular diseases, cancers, chronic respiratory diseases, diabetes

WHO (2011) World Health Organization. www.who.int/mediacentre/events/annual/world_cancer_day

Willment JA, Gordon S, Brown GD (2001) Characterization of the human β-glucan receptor and its alternatively spliced isoforms. J Biol Chem 276:43818–43823

Willment JA, Marshall AS, Reid DM, Williams DL, Wong SY, Gordon S, Brown GD (2005) The human β-glucan receptor is widely expressed and functionally equivalent to murine Dectin-1 on primary cells. Eur J Immunol 35:1539–1547

Wong JH, Wang HX, Ng TB (2008) Marmorin, a new ribosome inactivating protein with antiproliferative and HIV-1 reverse transcriptase inhibitory activities from the mushroom *Hypsizigus marmoreus*. Appl Microbiol Biotechnol 81:669–674

Wong YY, Moon A, Duffin R, Barateig AB, Meijer HA, Clemens MJ, de Moor CH (2010a) Cordycepin inhibits protein synthesis and cell adhesion through effects on signal transduction. J Biol Chem 285:2610–2621

Wong JH, Ng TB, Cheung RCF, Ye XJ, Wang HX, Lam SK et al (2010b) Proteins with antifungal properties and other medicinal applications from plants and mushrooms. Appl Microbiol Biotechnol 87:1221–1235

Woo MH, Peterson JK, Billups C, Liang H, Bjornsti MA, Houghton PJ (2005) Enhanced antitumor activity of irofulven in combination with irinotecan in pediatric solid tumor xenograft models. Cancer Chemother Pharmacol 55:411–419

Woynarowski J, Napier C, Koester S (1997) Effects on DNA integrity and apoptosis induction by a novel antitumor sesquiterpene drug, 6-hydroxymethylacylfulvene (HMAF). Biochem Pharmacol l54:1181–1193

Wu JY, Zhang QX, Leung PH (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

Xia Y, Ross GD (1999) Generation of recombinant fragments of CD11b expressing the functional β-glucan-binding lectin site of CR3 (CD11b/CD18). J Immunol 162:7285–7293

Xu K, Liang X, Gao F, Zhong J, Liu J (2010) Antimetastatic effect of ganoderic acid T *in vitro* through inhibition of cancer cell invasion. Process Biochem 45:1261–1267

Xu X, Yan H, Chen J, Zhang X (2011) Bioactive proteins from mushrooms. Biotechnol Adv 29:667–674

Yamashita K, Ougolkov AV, Nakazato H, Ito K, Ohashi Y, Kitakata H, Yasumoto K et al (2007) Adjuvant immunochemotherapy with protein-bound polysaccharide K for colon cancer in relation to oncogenic β-catenin activation. Dis Colon Rectum 50:1169–1181

Yang L, Wang R, Liu J, Tong H, Deng Y, Li Q (2004) The effect of *Polyporus umbellatus* polysaccharide on the immunosuppression property of culture supernatant of S180 cells. Chinese J Cell Mol Immunol 20:234–237

Yang Y, Ye L, Zhang JS, Liu YF, Tang QL (2009) Structural analysis of a bioactive polysaccharide, PISPI, from the medicinal mushroom *Phellinus igniarius*. Biosci Biotechnol Bichem 73:134–139

Yassin M, Wasser SP, Mahajna J (2008) Substances from the medicinal mushroom *Daedalea gibbosa* inhibit kinase activity of native and T315I mutated Bcr-Abl. Int J Oncol 32:1197–1204

Ye M, Liu JK, Lu ZX, Zhao Y, Liu SF, Li LL, Tan M, Weng XX, Li W, Cao Y (2005) Grifolin, a potential antitumor natural product from the mushroom *Albatrellus confluens*, inhibits tumor cell growth by inducing apoptosis in vitro. FEBS Lett 579(16):3437–3443

Ye M, Luo X, Li L, Shi Y, Tan M, Weng X, Li W, Liu J, Cao Y (2007) Grifolin, a potential antitumor natural product from the mushroom *Albatrellus confluens*, induces cell-cycle arrest in G1 phase via the ERK1/2 pathway. Cancer Lett 258(2):199–207

Ye LB, Zheng X, Zhang J, Tang Q, Yang Y, Wang X, Li J, Liu YF, Pan YJ (2011) Biochemical characterization of a proteoglycan complex from an edible mushroom *Ganoderma lucidum* fruiting bodies and its immunoregulatory activity. Food Res Int 44:367–372

Yeh CT, Rao YK, Yao CJ, Yeh CF, Li CH, Chuang SE, Luong JH et al (2009) Cytotoxic triterpenes from *Antrodia camphorata* and their mode of action in HT-29 human colon cancer cells. Cancer Lett 285:73–79

Yeh CH, Chen HC, Yang JJ, Chuang WI, Sheu F (2010) Polysaccharides PS-G and protein LZ-8 from Reishi (*Ganoderma lucidum*) exhibit diverse functions in regulating murine macrophages and T lymphocytes. J Agric Food Chem 58:8535–8544

Ying J, Mao X, Ma Q, Zong Y, Wen H (1987) Icons of medicinal fungi from China (translated, Yuehan X). Science Press, Beijing

Yoneda K, Ueta E, Yamamoto T, Osaki T (1991) Immunoregulatory effects of Sizofiran (SPG) on lymphocytes and polymorphonuclear leukocytes. Clin Exp Immunol 86:229–235

Yoshida I, Kiho T, Usui S, Sakushima M, Ukai S (1996) Polysaccharides in fungi. XXXVII. Immunomodulating activities of carboxymethylated

derivatives of linear (1→3)-α-D-glucans extracted from the fruiting bodies of *Agrocybe cylindracea* and *Amanita muscaria*. Biol Pharm Bull 19:114–121

Yu Z, Ming G, Kaiping W, Zhixiang C, Liquan D, Jingyu L, Fang Z (2010) Structure, chain conformation and antitumor activity of a novel polysaccharide from *Lentinus edodes*. Fitoterapia 81:1163–1170

Yuen JWM, Gohel MDI (2005) Anti-cancer effects of *Ganoderma lucidum*: a review of scientific evidence. Nutrit Cancer 53:11–17

Zaidman BZ, Yassin M, Mahajna J, Wasser SP (2005) Medicinal mushroom modulators of molecular targets as cancer therapeutics. Appl Microbiol Biotechnol 67:453–468

Zhang P, Zhang L, Cheng S (1999) Chemical structure and molecular weight of (1→3)-α-D-glucan from *Lentinus edodes*. Biosci Biotechnol Biochem 63:1197–1202

Zhang H, Morisaki T, Matsunaga H, Sato N, Uchiyama A, Hashizume K et al (2000) Protein-bound polysaccharide PSK inhibits tumor invasiveness by down-regulation of TGF-β1 and MMPs. Clin Exp Metastasis 18:343–352

Zhang L, Zhang X, Zhou Q, Zhang P, Zhang M, Li X (2001) Triple helix of β-glucan from *Lentinus edodes* in 0.5 M NaCl aqueous solution characterized by light scattering. Polym J 33:317–321

Zhang Y, Mills GL, Nair MG (2002) Cyclooxygenase inhibitory and antioxidant compounds from the mycelia of the edible mushroom *Grifola frondosa*. J Agric Food Chem 50:7581–7585

Zhang L, Li X, Xu X, Zeng F (2005) Correlation between antitumor activity, molecular weight, and conformation of lentinan. Carbohyd Res 340:1515–1521

Zhang M, Cui SW, Cheung PCK, Wang Q (2007) Anti-tumor polysaccharides from mushrooms: a review on their isolation, structural characteristics and antitumor activity. Trends Food Sci Technol 18:4–19

Zhang W, Li J, Qiu S, Chen J, Zheng Y (2008) Effects of the exopolysaccharide fraction (EPSF) from a cultivated *Cordyceps sinensis* on immunocytes of H22 tumor bearing mice. Fitoterapia 79:168–173

Zhang GQ, Sun J, Wang HX, Ng TB (2009) A novel lectin with antiproliferative activity from the medicinal mushroom *Pholiota adiposa*. Acta Biochim Pol 56:415–421

Zhang G, Sun J, Wang H, Ng TB (2010) First isolation and characterization of a novel lectin with potent antitumor activity from a *Russula* mushroom. Phytomedicine 17:775–781

Zhang Y, Li S, Wang X, Zhang L, Cheung PCK (2011) Advances in lentinan: isolation, structure, chain conformation and bioactivities. Food Hydrocolloid 25:196–206

Zhao RI, Desjardin DE, Soytong K, Perry BA, Hyde KD (2010a) A monograph of *Micropsalliota* in Northern Thailand based on morphological and molecular data. Fungal Divers 45:33–79

Zhao YY, Chao X, Zhang Y, Lin RC, Sun WJ (2010b) Cytotoxic steroids from *Polyporus umbellatus*. Planta Medica 76 (15):1755–1758

Zhao RL, Karunarathna SC, Raspé O, Parra LA, Guinberteau J, Moinard M, De Kesel A, Barroso G, Desjardin D, Courtecuisse R, Hyde KD, Guelly AK, Callac P (2011) Major clades in tropical *Agaricus*. Fungal Divers 51(1):279–296. doi:10.1007/s13225-011-0136-7

Zheng W, Zhao Y, Zheng X, Liu Y, Pan S, Dai Y, Liu F (2011) Production of antioxidant and antitumor metabolites by submerged cultures of *Inonotus obliquus* cocultured with *Phellinus punctatus*. Appl Microbiol Biotechnol 89(1):157–167

Zhong JJ, Tang YJ (2004) Submerged cultivation of medicinal mushrooms for production of valuable bioactive metabolites. Adv Biochem Eng Biotechnol 87:25–59

Zhong JJ, Xiao JH (2009) Secondary metabolites from higher fungi: discovery, bioactivity, and bioproduction. Adv Biochem Eng Biotechnol 113:79–150

Zhou X, Lin JY, Zhao J, Sun X, Tang K (2005) *Ganodermataceae*: natural products and their related pharmacological functions. Am J Chin Med 35:559–574

Zhou L, Shi P, Chen NH, Zhong JJ (2011) Ganoderic acid Me induces apoptosis through mitochondria dysfunctions in human colon carcinoma cells. Process Biochem 46:219–225

Zhu JS, Halpern GM, Jones K (1998a) The scientific rediscovery of an ancient Chinese herbal medicine: *Cordyceps sinensis* part 1. J Altern Complement Med 4:289–303

Zhu JS, Halpern GM, Jones K (1998b) The scientific rediscovery of a precious ancient Chinese herbal regimen: *Cordyceps sinensis* part II. J Altern Complement Med 4:429–457

Zhu T, Kim SH, Chen CY (2008) A medicinal mushroom: *Phellinus linteus*. Curr Med Chem 15:1330–1335

Zhuang C, Wasser SP (2004) Medicinal value of culinary-medicinal Maitake mushroom *Grifola frondosa* (Dicks.:Fr.) S.F.Gray (*Aphyllophoromycetideae*). Int J Med Mushr 6:287–313

Zhuang C, Mizuno T, Shimada A, Ito H, Suzuki C, Mayuzumi Y, Okamoto H, Ma Y, Li J (1993) Antitumor protein-containing polysaccharides from a Chinese mushroom Fengweigu or Houbitake, *Pleurotus sajor-caju* (Fr.) Sing. Biosci Biotechnol Biochem 57:901–906

Zjawiony JK (2004) Biologically active compounds from Aphyllophorales (Polypore) Fungi. J Nat Prod 67:300–310