

Biological and Pharmacological Activity of Higher Fungi: 20-Year Retrospective Analysis

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Abstract – The widespread occurrence of biological activities within the fungal kingdom is now widely accepted. Since ancient times the so called mushrooms meaning Basidiomycota have been used for medicinal purpose. All major human body functions were considered to benefit from fungi intake. These positive effects include prophylactic as well as curative actions. Historically, Oriental countries first recognized mushrooms as an important source of medicines. Recently, Occidental research starts to really consider this almost untapped source of therapeutic drugs. Indeed, discovering new major medicis is becoming a great challenge. The aim of the present review is to outline past and current major therapeutic interests and pharmacology of medicinal mushrooms, and their applications in human health care. Indeed, metabolites from Basidiomycota demonstrate verified pharmacological activity in major diseases such as chronic inflammation, oxidation associated pathologies, diabetes, infections (HIV, fungi, bacteria), immune system disorder and cancer.

Basidiomycota / biological activity / health care / pharmacology / therapeutics / metabolic and infectious diseases

Résumé – Le vaste potentiel d'activités biologiques au sein du règne fongique est maintenant validé par la communauté scientifique. Depuis plusieurs millénaires, les champignons sont en effet utilisés pour leurs propriétés médicinales. Les principales fonctions du corps humain sont susceptibles de bénéficier d'une consommation de champignons. Les effets positifs incluent des actions prophylactiques aussi bien que curatives. Historiquement les pays orientaux ont été les premiers à reconnaître les champignons comme une importante source de médicaments. La recherche occidentale commence seulement à étudier ce réservoir si peu exploité, de composés thérapeutiques. En effet, la découverte de nouveaux médicaments devient un challenge difficile. Le but de cette revue est de souligner les intérêts thérapeutiques principaux passés et présents des champignons médicinaux, ainsi que leurs applications en santé humaine. Les métabolites des Basidiomycota présentent des activités pharmacologiques vérifiées dans des

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pathologies majeures telles que l'inflammation chronique, les pathologies associées aux processus oxydatifs, le diabète, les infections (VIH, champignons et bactéries), les désordres immunologiques et le cancer.

Basidiomycota / activités biologiques / santé humaine / pharmacologie / thérapeutiques / maladies métaboliques et infectieuses

ABBREVIATIONS

AIDS: Acquired Immune Deficiency Syndrome
BAM: Biologically Active Metabolites
COX: Cyclooxygenase
GPx: Glutathione Peroxidase
HIV: Human Immunodeficiency Virus
IDDM: Insulin Dependent Diabetes Mellitus
IL(s): Interleukin(s)
IFN: Interferon
LZ-8: Ling Zhi 8
NF- κ B: Nuclear Factor κ B
NIDDM: Non Insulin Dependent Diabetes Mellitus
NK: Natural Killer
PSK: PSP Krestin
PSP: Polysaccharopeptides
ROS: Reactive Oxygen Species
SOD: Superoxide dismutase
TNF: Tumor Necrosis Factor

INTRODUCTION

Higher fungi have been used by mankind for millennia. Firstly they are used as part of regular diet for their nutritional value, completing population food intake. They contain minerals, vitamins and nutritive compounds such as proteins and polysaccharides and have low fat content (Breene, 1990; Chang, 1996; Manzi *et al.*, 1999; Mattila *et al.*, 2000). Secondly mushrooms fruiting bodies are also appreciated for delicacy. Indeed their palatability is exploited as taste and flavor enhancers when associated in food preparation and cooking (Misaki & Kakuta, 1995; Misaki & Kishida, 1995). Thirdly, higher fungi are used for medicinal purpose. Their pharmacological action and therapeutic interest in promoting human health are known for thousands of years (Batut, 1995; Fons *et al.*, 2005; Gunde-Cimerman, 1999; Obbs, 1996; Rapior *et al.*, 2000; Roumestan *et al.*, 2005).

Asian traditional medicine practices and nowadays modern medicine in Eastern countries as China, Japan, Korea and several Asian countries still use mushrooms for treatment of major diseases (Jikai, 2002; Konno, 1995; Ooi & Liu, 1999; Seo *et al.*, 2003). Ancient traditional uses are now clinically confirmed and constitute a strong base for intensive research and development of Basidiomycota biologically active metabolites (BAM) isolated or in combination (Kim & Kim, 1999; Reshetnikov *et al.*, 2000). According to literature, more than 270 medicinal fungi are reported in traditional Chinese medicine for their preventive and/or curative effects (Ding, 1987; Ying *et al.*, 1987). In Japan, the knowledge of biological activities from mushrooms is the same as in China. Four species are really very popular in medical care, i.e., Shiitake (*Lentinula edodes* (Berk.) Pegler),

Reishi or Mannentake (*Ganoderma lucidum* (Curtis) P. Karst.), Maitake (*Grifola frondosa* (Dicks.) Gray) and Enokitake (*Flammulina velutipes* (Curtis) Singer). They are sold in streets to consumers as a source of good health and lifetime prolongation. Some Japanese people can even run around for kilometers in order to pick up wild fungi as Reishi growing on very old plum trees and considered to be effective against cancer and degenerative diseases (Mayell, 2001; Ng, 1998).

Western countries were favoring more recently the biological properties of higher fungi notably used in allopathic medicine (Donatini, 2000; Erkel *et al.*, 1995; Thoen, 1982; Zsigmond, 1999). *Fomes fomentarius* (L.) J.J. Kickx, *Inonotus obliquus* (Ach. ex Pers.) Pilát and *Laricifomes officinalis* (Vill.) Kotl. & Pouzar are quite the only mushroom species having been therapeutically used by European people. Nevertheless, in the United States of America (USA), the market opens up to these new natural sources of potentially health promoting compounds. For instance, Reishi and Maitake become very popular as nutraceutical food (Chang, 1996; Chang & Buswell, 2003; Lakhanpal & Rana, 2005). It should be noticed that North America benefits of extensive natural resources probably still hiding a large Basidiomycota biodiversity.

Other western countries start now to better consider this perspective and researches are undergone in order to discover new pharmaceutical compounds for either disease prophylaxis or treatment or adjunct therapy (Badalyan *et al.*, 1996ab, 1997a/b, 2001; Francia *et al.*, 1999; Roussel *et al.*, 2002; Sullivan *et al.*, 2006; Zjawiony, 2004). In other words, medicine using fungal metabolites is now worldwide recognized (Alexandre *et al.*, 2004; McMorris *et al.*, 2001; Seiden *et al.*, 2006). Indeed Basidiomycota represent a larger untapped resource for new classes of pharmaceutical compounds that may change some of the general concepts of disease management (Chang, 1999; Kawagishi, 1995; Kiho *et al.*, 1994c; Wasser & Weis, 1999).

In this 20-year review, we outline major pharmacological and therapeutic interest from Basidiomycota mushrooms as source of bioactive natural products in promoting human health. After definition of current global interest of fungi (Basidiomycota) as potential therapeutic agent reservoir, major pharmacological action and their putative therapeutic applications will be presented in order to conclude about the potential interest of mushroom metabolites as future drug candidates.

MATERIALS

The mushroom species Latin names and authorities mentioned in this review come from Kerrigan (2005) and the Cabi Bioscience Database (<http://www.indexfungorum.org/BSM/bsm.asp>).

DISCUSSION

The use of mushrooms with potential therapeutic properties raises global interests from the scientific and clinical community based on two main reasons. First, mushrooms demonstrate their efficiency against numerous diseases and metabolic disturbances as serious as cancer or degenerative diseases. These therapeutic effects seem to lay on multiple and complex pharmacological actions

on different cellular and molecular targets. Mushroom compounds would act in combination to influence cell surface receptors, and to trigger various downstream signaling events leading to high pharmacological efficiency and specificity (Borchers *et al.*, 2004).

Secondly, fungal bioactive metabolites can be obtained from many origins either wild and cultivated fruiting bodies or from mycelial biomass and supernatant of submerged cultured using bioreactors (Bose, 1955; Cui & Chisti, 2003; Hara *et al.*, 1987; Harttig *et al.*, 1990; Hikino *et al.*, 1985; Sarkar *et al.*, 1993). Isolation and purification of natural or hemisynthetic active components (namely polyphenols, polysaccharides, protein-bound polysaccharides, sesquiterpenes, triterpenoids) require common analytical procedures (Abraham, 2001; Horesy & Kocourek, 1978; Karacsonyi & Kuniak, 1994; Liu, 1999; Mizuno *et al.*, 1996, 1998, 1999a/b; Ooi & Liu 1999; Shiharama *et al.*, 1962; Sugano *et al.*, 1982). Consequently, higher fungi present major advantages as putative valuable drug candidates for various pathologies as reported.

Anti-inflammatory effect

Since two decades, mushrooms have displayed *in vitro* as well as *in vivo* anti-inflammatory activities. Several *in vitro* mechanisms are involved as follows in:

– Inhibition of lipidic mediators of inflammation as cyclooxygenases i) by fatty acids and sterols of *G. frondosa* and *Agrocybe aegerita* (V. Brig.) Singer, and ii) by the ethanolic extract of *G. lucidum* (Hong *et al.*, 2004; Zhang *et al.*, 2002, 2003) and as 5-lipoxygenase by the acetone extract of *G. frondosa* (Hirota, 1997).

– Inhibition or diminution of cytokines level such as that of i) NF- κ B by panepoxydone identified from *Lentinus crinitus* (L.) Fr., ii) Interleukins (ILs), interferon (IFN- γ) and Tumor Necrosis Factor (TNF- α) by ethanolic extract of *Agaricus subrufescens* Peck [syn. *Agaricus brasiliensis* Wasser, M. Didukh, Amazonas & Stamets and *Agaricus blazei* Murrill; Kerrigan, 2005] as well as by polysaccharides and proteoglycans from *Phellinus linteus* (Berk. & M.A. Curtis) Teng (Erkel *et al.*, 1996; Kim *et al.*, 2003; Kuo *et al.*, 2002).

– Inhibition of inflammatory cell production (lymphocytes and macrophages) by *A. subrufescens* ethanolic extract (Kuo *et al.*, 2002) or apoptosis increasing by polysaccharides of *P. linteus* (Kim *et al.*, 2003).

Glucans of *Trametes gibbosa* (Pers.) Fr. antagonize *in vivo* the inflammation mediator complex induced by carrageenan (Czarnecki & Grzybek, 1995) notably in the rat while a *Cordyceps militaris* (L.) Link (Ascomycota) polysaccharide significantly suppresses the mouse ear oedema induced by croton oil (Yu *et al.*, 2004). *G. lucidum* (polyphenols, polysaccharides, terpenes) and *Pleurotus florida* Singer (methanolic extract) have shown anti-inflammatory potential on cell models as well as on animal models for both obvious acute and chronic inflammation (Jose *et al.*, 2004; Lakshmi *et al.*, 2003). At the same time, proteoglycans and polysaccharide isolated from *P. linteus* (Kim *et al.*, 2003) – a mushroom species empirically used for inflammation treatment for ages – were reported as bioactive on previous mentioned models as well as on arthritis model and on septic chock models. Several lanostane-type triterpene acids from *Piptoporus betulinus* (Bull.) P. Karst., suppress the 12-*O*-tetradecanoylphorbol-13-acetate induced oedema on mouse ears (Kamo *et al.*, 2003), a test which is also correlated with anticancer activity as previously described for *Wolfiporia extensa* (Peck) Ginns [syn. *Poria cocos* (Schwein.) F.A. Wolf] (Kaminaga *et al.*, 1996; Ukiya *et al.*, 2002).

Antioxidant activity

While relatively recent researches on anti-aging effects from natural products are of the highest importance for medical stakes (oncology, immunology...) and industrial BAM development (pharmacy, cosmetics), it opens prospects to scientists for the screening of antioxidizing natural agents among higher fungi.

Aerobic life form is associated with oxidation processes. These processes constitute the base of cellular respiration that allows energy production. Metabolic oxygen consumption is therefore necessary for survival of many types of living organisms. Paradoxically, this vital phenomenon is also the cause of cell and tissue damages leading to the inexorable aging process through production of free radicals and various reactive oxygen species (ROS). These very unstable compounds tend to stabilize by combining with structural and functional cell components therefore producing advanced end products that are deleterious to cells and tissues in the long term. These cellular and tissue impairments are now thought to be one of the major underlying mechanistic base of aging and development of pathologies such as diabetes, cardiovascular diseases, neurodegenerative diseases and cancer. Living organisms possess antioxidant internal defences that do not completely neutralize or repair oxidative injuries. One way to help the fight against these injuries is to increase antioxidant defences by intake of external antioxidant (Halliwell & Gutteridge, 1984; Simic, 1988).

Higher fungi are a natural source of potent bioactive antioxidant metabolites (Yang *et al.*, 2002). As for plant kingdom, phenolic metabolites with major antioxidant abilities start to be discovered in fungi kingdom. New kinds of molecular structures have been discovered that help understanding how higher fungi metabolites can fight against oxidative injuries. Various mechanisms are proposed i) direct antioxidant effects through sustaining of antioxidant levels for prevention of ROS production, ii) indirect antioxidant effects via host antioxidant enzyme defence system (SOD, GPx, catalase) induction and regulation, iii) direct reducing power of fungal metabolites, iv) radical scavenging effect via targeting of already produced ROS.

Indeed, phenolic compounds are heavily investigated for their potential high benefit on human health. *L. edodes* and *Volvariella volvacea* (Bull.) Singer extracts demonstrate antioxidant activities and free radical scavenging abilities (Cheung & Cheung, 2005). This pharmacological effect is correlated with phenolic compounds content in mushrooms as already known for grape fruits and wine (Landrault *et al.*, 2001). *L. edodes* is also inducer of SOD and GPx, two antioxidant enzymes (Cheung *et al.*, 2003). Farnesylphenol derivatives of grifolin, isolated from *Albatrellus sp.* possess antioxidative activities higher than α -tocopherol or *tert*-butylhydroxyanisole as well as antimicrobial, hypocholesterolemic and tyrosinase inhibitory activities (Nukata *et al.*, 2002). Complex polyphenols as azaphilones, cytochalasins and *p*-terphenyls purified from various inedible mushrooms (*Hypoxylon sp.*, *Telephora sp.* and *Paxillus sp.*) show free radical-scavenging activity against diphenyl-*p*-picrylhydrazyl (Quang *et al.*, 2006; Tsukamoto *et al.*, 2002).

Therefore it is not surprising that intrinsic antioxidant properties demonstrated *in vitro*, with *G. lucidum* or *P. linteus* can be transferred *in vivo* after mushroom consumption as food or "nutriceutic" food. Indeed antioxidant enzymes from subjects consuming mushrooms are specifically regulated (SOD, GPx, catalase). *Trametes versicolor* (L.) Lloyd appears as an inductor of enzyme systems involved in prevention of oxidative damages and more particularly of GPx (Cui &

Chisti, 2003). It is noteworthy to emphasize that mushrooms not only demonstrate direct antioxidant abilities but are also able to stimulate anti-radical host defence (Park *et al.*, 2001). The antioxidant and putative anti-aging effects of *G. lucidum* have reached pharmacological studies (Lin *et al.*, 1995; Lin & Zhang, 2004).

Among higher fungi, some species clearly demonstrate higher antioxidant properties when compared to others (Zhou *et al.*, 1989, 1991; Zhu *et al.*, 1999). Such mushroom species include in particular tree oyster mushroom, *Pleurotus ostreatus* (Jacq.) P. Kumm. This fungus seems to concentrate a complete “arsenal” against oxidative stresses. It includes basic antioxidant compounds (ascorbic acid / vitamin C, tocopherol / vitamin E, β -carotene), high content in phenolic compounds with extensive reducing and scavenging properties (Yang *et al.*, 2002). Other mushrooms with high antioxidant abilities include *A. aegerita* whose antioxidant effects and free radical scavenging abilities are correlated with its total phenolic content (Lo & Cheung, 2005). It should be also noticed that *A. subrufescens* show combined activities as antioxidant properties and COX inhibition acting on both free radical levels and inflammation, respectively (Borchers *et al.*, 2004).

As previously reported, it clearly appears that mushrooms are a sizeable source of antioxidant components already known or to be discovered. In addition on a dietary as well as on a medical point of view, higher fungi may provide potent beneficial effects on human health either directly as antioxidant or through prevention of alterations underlying major pathological states such as cancer, diabetes, neurodegenerative diseases, cardiovascular diseases and metabolic syndrome. Indeed antioxidant properties combined with antitumoral and immunomodulating effects lead to this “mushroom characteristic” health sustaining effect that they are recognized for (Lo & Cheung, 2005; Zhou *et al.*, 2005).

Activity on metabolic syndrome and related diseases: diabetes and hypertension

In the eighty's, international medical research advancement in cardiovascular area and insulin resistance led to recognize a concept named the metabolic syndrome by Reaven *et al.* (1988), previously known as syndrome X or insulin-resistance syndrome. The metabolic syndrome and associated pathologies, i.e., cardiovascular disease, type II diabetes and obesity have become much more life threatening for worldwide population than AIDS in terms of morbidity and mortality. It was and still is considered as the first pandemic not mediated by an external vector (Reaven *et al.*, 1988). The metabolic syndrome including subsequent pathologies is physiopathologically based on biochemical disturbances such as dyslipidemia, glucose intolerance, insulin resistance leading to progressive hyperglycemia, vascular and hematological perturbations (Leif & Mather, 2004). Interestingly, several subsets of mushrooms produce metabolites able to influence positively one or several of these disturbances.

As reported by literature, *Auricularia auricula-judae* (Fr.) Quél., *Cordyceps sinensis* (Berk.) Sacc. (Ascomycota), *G. lucidum*, *G. frondosa*, *Lyophyllum decastes* (Fr.) Singer, *P. ostreatus*, and *Tremella fuciformis* Berk. tend to reduce hyperlipidemia and typically hypercholesterolemia (Bobek *et al.*, 1991; Gunde-Cinerman & Plemenitas, 2001; Kamiya *et al.*, 1969; Kubo & Nanba, 1997; Ukawa *et al.*, 2001). Similarly, *C. sinensis*, *G. frondosa* and *L. edodes* regulate triglyceride levels in a positive way (Francia *et al.*, 1999; Yagishita *et al.*, 1977). All together these properties on blood stream lipid levels can limit atherosclerosis development in vasculature. Sediments on the arterial walls being stopped or even

lessened, arterial thrombosis and blood clots do not jeopardize subject health. *A. auricula-judae*, *Calyprella* sp., *G. lucidum*, *Kuehneromyces* sp., *Neolentinus adhaerens* (Alb. & Schwein.) Redhead & Ginns and *Panus* sp. demonstrate activity against platelet binding; this effect can contribute to decrease thrombosis and blood clot (Fan *et al.*, 1989; Lorenzen *et al.*, 1994, 1995).

Through all previous actions on lipids and platelets, vasculature internal diameter does not tend to be reduced therefore avoiding decreased blood flow and necrosis in tissue, hypertension and insulin resistance. Both latter physiological alterations need a closer assessment. First, regarding hypertension, *G. lucidum*, *G. frondosa*, *Tricholoma mongolicum* S. Imai and *Macrocybe gigantea* (Massee) Pegler & Lodge demonstrate abilities to decrease high blood pressure and related pathologies such as angina pectoris and atherosclerosis (Kabir *et al.*, 1988). According to the mushroom species, this effect is based on either a lectin type molecule or a peptide or a triterpenoid derivative (Lee *et al.*, 2004; Talpur *et al.*, 2002; Wang *et al.*, 1996c). Higher fungi are also considered as reducing the effects of risk factors reported for cardiovascular diseases (Francia, 1998; Kabir & Kimura, 1989; Rapior *et al.*, 2000).

Secondly, regarding insulin resistance, reduced peripheral effect of insulin is recorded in most cases of hypertension and associated cardiovascular diseases. In addition, insulin resistance is the major physiopathological disturbance in type II diabetes (named NIDDM = Non Insulin Dependent Diabetes Mellitus) and obesity, both diseases associated with severe cardiovascular complications (stroke, micro- and macro-angiopathy, hypertension) as reported by Lteif & Mather (2004). Considering these correlations, it is not surprising that a higher fungus active in hyperlipidemia and hypertension such as *G. frondosa* is active in NIDDM with a dual effect on both hyperglycemia and hyperinsulinemia suggesting action on peripheral insulin-resistance (Francia *et al.*, 1999; Gao *et al.*, 2004a; Kubo *et al.*, 1994). The other type of diabetes is type I diabetes (named IDDM = Insulin Dependent Diabetes Mellitus). This diabetes is different from NIDDM and comes from complete destruction of endocrine pancreas with hypo-insulinemia and severe hyperglycemia. Many higher fungi, i.e., *Agaricus bisporus* (J.E. Lange) Pilát, *A. aegerita*, *Agrocybe cylindracea* (DC.) Gillet, *C. sinensis*, *Tremella aurantia* Schwein. and *T. fuciformis* demonstrate hypoglycemic effect for IDDM mediated by polysaccharides that help controlling glycemia level (Gray & Flatt, 1998; Hwang *et al.*, 2005; Ishihira *et al.*, 2005; Kiho *et al.*, 1994 a/b, 1995, 1996, 1999; Zhang *et al.*, 2006).

All fungi effects aiming hyperlipidemia, platelet binding, hyperglycemia and hyperinsulinemia, are in fact not only improving biochemical disturbances but also prevent further long term non reversible alterations of structural and functional molecules that would have led to major metabolic pathologies. Through acting on fundamental risk factors, mushrooms influence positively the very upstream events that may lead to cardiovascular diseases, diabetes, obesity and also neurodegenerative diseases (Tsukamoto *et al.*, 2003) as well as to some cancer types. In that field, mushroom species, i.e., *Armillaria mellea* (Vahl.) P. Kumm., *A. auricula-judae*, *G. lucidum*, *G. frondosa*, *L. edodes* and *P. ostreatus* are already commercially developed (Wasser & Weis, 1999).

Antimicrobial activity

Antimicrobial activity including antibacterial, antifungal, antiparasitic and antiviral agents is the third widespread therapeutic effect reported for

mushrooms (Kettering *et al.*, 2005; Ngai & Ng, 2003; Nidiry, 2001; Obuchi *et al.*, 1990; Okamoto *et al.*, 1993; Smania *et al.*, 2003). Indeed it is thought that over 200 higher fungus species demonstrate antimicrobial properties (Anke & Sterner, 1991; Berg *et al.*, 1999; Gianetti *et al.*, 1996; Kettering *et al.*, 2005; Tringali & Piattelli, 1989; Tsuge *et al.*, 1999; Wang *et al.*, 1993; Yoon *et al.*, 1995).

As reported by authors (Wasser & Weis, 1999; Ying *et al.*, 1987), some species show combined biological properties such as *Agrocybe molesta* (Lasch) Singer (antibacterial/antifungal) and *F. velutipes* (antifungal/antiviral). Several common species, i.e., *Agaricus xanthodermus* Genev., *A. mellea*, *Clitocybe nebularis* (Batsch) Quél., *G. lucidum*, *G. frondosa*, *L. edodes*, *Omphalotus illudens* (Schwein.) Bresinsky & Besl., *P. betulinus*, *P. ostreatus* and *Rozites caperatus* (Pers.) P. Karst., generate a broad spectrum of antimicrobial activities including antibacterial, antiparasitic and antiviral effects (Beltran-Garcia *et al.*, 1997; Cherqui *et al.*, 1999; Donnelly *et al.*, 1985; Dornberger *et al.*, 1986; Min *et al.*, 1995; Piraino, 2006; Wasser & Weis, 1999; Ying *et al.*, 1987). *G. lucidum*, through a laccase, shows a potent inhibitory activity against HIV-1 reverse transcriptase (Wang & Ng, 2006).

Among antiviral bioactive mushroom metabolite, a polysaccharopeptide as PSK from *T. versicolor* displays anti-HIV effects. Interestingly, in addition of positive influence on immune system, it appears that direct inhibition of HIV-lymphocyte interaction could be observed, suggesting complex mechanisms (Zjawiony, 2004). Oppositely, another polysaccharopeptide as PSP would majorly act through immune system nonetheless, potential inhibition of HIV binding on CD4 immune receptors is possible. A well PSP could bind to HIV reverse transcriptase whose activity plays prominent role in HIV cellular pathogenicity (Cui & Chisti, 2003).

Similarly, the polysaccharide lentinan from *L. edodes* demonstrates effects against influenza virus and polio virus as well as against some bacteria and parasites. These effects are mediated by immune system induction that even delays AIDS symptomatology appearance (Mattila *et al.*, 2000). This action would be linked to induction of increased level of interferon. *G. frondosa* also demonstrates anti-HIV properties. Its action is simultaneously general and topical. Indeed metabolites from this fungus are proposed to improve host defences against the virus, increasing T-helper immune cells. Additionally, specific fraction would be active on AIDS patient skin Kaposi's sarcoma (Mayell, 2001). Moreover, (+) and (-)-daurichomenic acids, one-step synthetic derivatives from grifolic acid show highly potent anti-HIV activity (Quang *et al.*, 2006).

As for anticancer properties, antimicrobial activity can be developed either directly against external aggressor or indirectly via immune system potentiation. It should also be noticed that molecular weight of active metabolites is not a discriminating criterion for structure-activity relationship, oppositely to anticancer activity. Finally, it should be mentioned that effects on immune system in pathologies such as AIDS might be of major importance since mushrooms metabolites are within the bioactive molecules that demonstrate positive influence on immune system.

Immunostimulating activity

Medical researches concerning immunopotentiators are of great importance with emergence of AIDS. Among higher fungi investigated for immunomodulating effects, several mushroom species demonstrate great

potential and some of them are already commercially developed. Basidiomycota containing immunomodulating metabolites include at least *G. lucidum*, *G. frondosa*, *L. edodes*, *T. versicolor*, *Tricholoma matsutake* (S. Ito & S. Imai) Singer (Matsutake) and *T. mongolicum* as reported by literature (Hoshi *et al.*, 2005; Wang *et al.*, 1996a/b; Wasser *et al.*, 2002; Zjawiony, 2004).

Lentinula edodes seems to be one of the most promising stimulator of immunofunctions. Scientists have notably undertaken studies on the Shiitake's strengthening on the human immune system (Suzuki *et al.*, 1977; Thérouane-Allard, 2002). This mushroom is already tested on HIV-positive patients in the USA and in Japan (Iizuka & Maeda, 1988, 1990; Sugano *et al.*, 1982). Lentinan from *L. edodes*, dramatically increases host immune defence, more specifically against external infections even against AIDS presenting symptoms appearance (Matilla *et al.*, 2000). The previous sesquiterpene metabolite is able to restore cellular immune response and humoral immune response blunted by cancer (Ooi & Liu, 1999).

Trametes versicolor with PSP and PSK activities influences immune system through increased production of i) interleukin-2 (IL-2), interleukin-6 (IL-6) and interferon (IFN) on the humoral side, ii) T-cells proliferation on the cellular side (Cui & Chisti, 2003; Ng, 1998). These pharmacological properties are accompanied by opposite effects to cyclophosphamide, clearly indicating a convincing immune system boosting action (Chu *et al.*, 2002).

Grifola frondosa also demonstrates immunomodulatory properties leading to a better global health status of patients with severe illness such as AIDS (Mayell, 2001). Its biologically active metabolites induce T-helper cells defence enhancement in HIV infected animals and patients. In addition *G. frondosa* stimulates activities of cytotoxic T-cells, Natural Killer cells (NK cells) and macrophages. Interleukin-1 (from macrophages), interleukin-2 (from T-cells) and lymphokines production is increased (Kodama *et al.*, 2002).

Ganoderma mushroom species are also potent immunomodulating fungi. Through their metabolites (glucans, LZ-8 and triterpenoids), they induce production of cytokines (ILs), Tumor Necrosis Factor (TNF) and IFN, and mobilize macrophages, NK cells, and lymphocytes B and T (Cao & Lin, 2006; Kino *et al.*, 1989; Lin, 2005; Lin & Zhang, 2004).

Whatever species of higher fungi with immunopharmacologic competences, immunomodulation is based on stimulation of host defence immune system, i) improved humoral immune response (interleukins, cytokines, TNF, IFN) and ii) improved cellular immune response (lymphocytes B and T, NK cells, macrophages).

These fundamental effects induce increased adaptability of human organism environmental stresses as well as enhancement of both specific and non-specific immunity and defence mechanisms. In addition to immune system enhancement, mushroom metabolites also sustain hormonal system allowing higher fungi to help the body fighting major diseases as viral infection or cancer. It should be noted that for cancer, T-cell components have to be intact. Moreover, immunopotential counterbalances immunosuppression frequently induced by chemotherapy and radiotherapy during conventional cancer treatment. Finally, in non-pathological conditions, immune system does not seem to be disturbed by fungi metabolites.

Obviously, immunomodulation represents a significant element of Basidiomycota pharmacological and therapeutic interest. Influence of mushroom metabolites on immune function, and over on hormonal system, appears to underlay some of the major beneficial effects of higher fungi (Cui & Chisti, 2003; Kodama *et al.*, 2002; Ooi & Liu, 1999; Wasser, 2002).

Antitumoral activity

Antitumoral activity is the most significant therapeutic interest associated with mushrooms. It concerns over 50 higher fungi especially selected with high efficiency on various tumors and cancer process types (Cochran, 1978; Kidd, 2000; Tomasi *et al.*, 2004).

Inonotus obliquus was used in popular Russian medicine from the 16th to the 17th century (Roy, 1977). *Bjerkandera fumosa* (Pers.) P. Karst., *C. sinensis*, *F. fomentarius*, *Ganoderma applanatum* (Pers.) Pat., *Hericum erinaceus* (Bull.) Pers., *Polyporus umbellatus* (Pers.) Fr. and *T. versicolor* are currently used in traditional medicine in Chinese hospitals (Mizuno, 1995a/b, 1996; Wu *et al.*, in press; Ying *et al.*, 1987). *G. lucidum* and *L. edodes* are already commercially developed in Japan and China (Wasser & Weis, 1999).

At the present time, research findings on the antitumoral metabolites are of the highest importance. The authors demonstrated Basidiomycota metabolites to be potential source of antitumoral agents particularly polysaccharides and more specifically polysaccharides from fungal cell walls (Ebina *et al.*, 2004; Fuji *et al.* 1978; Kerrigan, 2005; Lu, 1995; Mizuno *et al.*, 1995; Yoshioka *et al.*, 1985). These polysaccharides are often β -glucans with various branching types (Furukawa *et al.*, 2006). General rules coming for observation is that (i) higher molecular weight metabolites demonstrate superior pharmacological activity than lower molecular weight metabolites and, (ii) β -(1-3) linkages in the main molecular axe are needed combined with β -(1-6) branching for anti-neoplasm activity (Mizuno *et al.*, 1996, 1999a/b; Tao *et al.*, 2006).

In addition, active molecule structures vary greatly. They can have linear or branched patterns; they can be made of variable sugar units leading to different types of glucans as fucans (fucose), galactans (galactose), xylans (xylose) and mannans (mannose). They also can present side chains of non saccharide type such as peptides to form polysaccharopeptides (PSP) or PSK (PSP Krestin) previously mentioned. Multiple combinations of these various components can be found. This flexibility of branching when compared to nucleic acid or proteins explains the vast chemical variability and therefore the numerous kinds of compounds discovered or to be discovered (Sharon & Lis, 1993). Another reason for great changes comes from the fact that "different strain of one Basidiomycota species can produce different polysaccharides with different properties" as mentioned by Wasser (2002). All these elements suggest that molecular diversity in higher fungi may lead to constitution of a potential large chemical collection. In addition, it should be noticed that this structural particularity of native molecules from mushrooms suggests larger possibility of chemical engineered modification. This structural biodiversity allows molecular structures and physicochemical properties adjustment to specific targeted pharmacological and/or kinetical profile for improved pharmaceutical potential (Mizuno *et al.*, 1996).

Among mushrooms with antitumor activity, *T. versicolor* demonstrates promising features. Depending on strains, different peptide-bound polysaccharides as PSP and PSK are produced by Cov-1 strain (China) and CM-101 strain (Japan), respectively (Sakagami & Takeda, 1993). Both proteoglycans containing the same polysaccharide part and differing from their protein component (Ng, 1998; Wasser, 2002) are of great interest as adjunct of cancer chemotherapy and radiotherapy. They improve regular therapeutic efficacy and tolerance (reduction of side effects), slow down tumor growth and tend to prevent metastasis (Cui & Chisti, 2003; Ng, 1998). On a general point of view, global patient health status is significantly improved in gastric, intestinal and lung cancer.

Precise molecular mechanism of action of PSP and PSK is still not elucidated. Nonetheless these compounds would act through host immune system enhancement (Ng, 1998) more than via direct cytotoxic effects.

The glucan derivative lentinan from *L. edodes* demonstrates simultaneously antitumor intrinsic activity and prophylactic ability (Mattila *et al.*, 2000). This compound is currently approved for gastric cancer. The single inconvenient comes from poor oral route absorption requiring injection route (Mayell, 2001). Nonetheless this molecule is of interest as adjunct therapy in cancer to induce carcinostatic effects.

Grifola frondosa and *Albatrellus sp.* derived compounds (D and MD fractions, grifolin) have anti-neoplasm activity in gastrointestinal, lung, liver and breast cancers. An important feature comes from *per os* good absorption of these molecules (Kodama *et al.*, 2002; Konno *et al.*, 2002; Mayell, 2001; Ye *et al.*, 2005).

Omphalotus illudens produces anticancer drugs as illudin S. This sesquiterpenoid toxin was first identified as a very potent antibiotic directed against *Staphylococcus aureus* (Lehmann *et al.*, 2003). Because of its high toxicity, illudin S was given up and hemisynthetic derivatives were produced as irofulven (McMorris *et al.*, 1996, 2001). The latter compound demonstrates probant anticancer properties against solid tumors working as a DNA-alkylating agent. In addition, its cytotoxicity seems to be more specifically addressed against malignant cells having less tropism for normal cells, therefore potentially increasing efficacy and tolerance with tight therapeutic protocol (Leggas *et al.*, 2002; Yeo *et al.*, in press).

Clitocybe nebularis also shows anticancer properties. It produces clitocypin, a cystein protease inhibitor potentially of interest in cancer treatment since cystein proteinases are involved in cancer development (as well as in rheumatoid arthritis) (Brzin *et al.*, 2000).

Ganoderma lucidum is another major mushroom with anti-neoplasm properties (Thyagarajan *et al.*, 2006; Yuen & Gohel, 2005). Metabolites demonstrating this potential include polysaccharides of β -D-glucan type, proteins such as LZ-8, and triterpenoids. They reduce mitogenicity, angiogenesis and tumorigenic cells. More specifically tripterenoids are thought to bear the direct cytotoxic effects against tumor cells (El-Mekkawy *et al.*, 1998; Gao *et al.*, 2004b; Shim *et al.*, 2004).

Pholiota spumosa (Fr.) Singer produces a polyamine (putrescine-1,4-dicinnamide) that inhibits the growth of an androgen independent human prostate cancer cells. High level of polyamines found in tumor cells and synthetic analogs of spermine or spermidine have shown good results against cancer cells such as prostate cancer. This *Pholiota* putrescine derivative could be a promising molecule for the treatment of prostate cancer (Russo *et al.*, in press).

General mechanisms can be drawn from observations of mushrooms anticarcinogenic properties as follows: i) prophylactic effect, preventing oncogenesis from normal cells, ii) inhibition of tumor cells proliferation, iii) direct cytotoxicity on cancer cells, iv) prevention of metastasis phenomenon, v) potentialisation of conventional chemotherapy effects with decreased toxicity and side effects, vi) no induction of harmful effects in realization of the pre-cited actions, and very good innocuousness of mushrooms metabolites with proper doses. These effects are mediated via direct or indirect mechanisms including antioxidant defence activation and most of all host immune system potentiation. Indeed it should be noticed that most antitumor polysaccharides derived from higher fungi origin also possess immunomodulating properties (Ikekawa *et al.*, 1968, 1969, 1985; Ikekawa 1995 a/b; Wasser, 2002; Zaidman *et al.*, 2005).

CONCLUSION

Since three millennia, traditional uses of medicinal mushrooms have been orally, then via handwritten, passed on to therapists and scientists in Asian countries as China and Japan. The market opened up recently in the USA and Europe to higher fungi providing good health. Hundreds of papers discuss Basidiomycota therapeutic indications mainly antitumoral, antidiabetic, antimicrobial, immunostimulating, anti-inflammatory and antioxidant effects as well as in cardiovascular disease (Hobbs, 1996; Komatsu *et al.*, 1963, 1973; McDonald *et al.*, 1997; Shimizu *et al.*, 1985; Suzuki *et al.*, 1984). In addition, the broad spectrum of biological activities from mushrooms suggests further screening and research in that promising field of health care substances.

Moreover, considering consumer's preference for natural components, the potential for biotechnological production of BAM from higher fungi could represent an advantageous alternative to native sources. As thousands of Basidiomycota species are still unknown, wild and cultured higher fungi represent a major source of novel metabolites. The latter defined as BAM bear hopes for five main reasons.

(i) They represent a therapeutic revival. Brand new compounds directly and/or indirectly active on major diseases begin to be discovered and are to be discovered that may substitute less active and/or more toxic compounds: novel antibiotic components will help to face growing bacteria resistances while novel mushroom metabolites may target complex endogenous metabolic diseases such as metabolic syndrome (diabetes and cardiovascular diseases) based on common metabolic impairments.

(ii) They bring adjuvant therapy to conventional treatment synergizing and potentiating classical treatments as chemotherapy. This helps decreasing doses therefore toxicity of the main treatment and also reduces resistance occurrence. In addition, the BAM may also bring comfort to patient under heavy treatment with important adverse effects, promoting better subject compliance.

(iii) They not only cure but have also important prophylactic properties. Basidiomycota metabolites may bring a paradigm shift in our medical way to maintain health in patients, not only focusing on treating the problem (curing or stopping pathology) when it occurs but also by preventing its occurrence.

(iv) Basidiomycota biodiversity in addition to variable growth conditions generates extreme molecular diversity of the major types of compounds as notably polysaccharides and polysaccharopeptides. The great structural diversity supported by high molecular flexibility associated with polysaccharide branching possibilities leads to a larger number of compounds than originally thought. Moreover this flexibility leads to great opportunities of molecular modifications and adjustments via engineering to optimize pharmacological and kinetic properties for a given therapeutic goal.

(v) Finally, BAM from Basidiomycota will be indubitably used as pharmacological tools to investigate and better understand human physiology and physiopathology as well as mechanism of drug action.

Mushroom metabolites defining new generations of pharmacologically active compounds, should definitely help fill some of the weaknesses of current therapeutic arsenal and develop it against present and future therapeutic challenges.

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