cryptogamie

mycologie

volume 36 n°1 2015

contents

Cryptogamie, Mycologie, 2015, 36 (1): 3-42

Polyporus umbellatus, an Edible-Medicinal Cultivated Mushroom with Multiple Developed Health-Care Products as Food, Medicine and Cosmetics: a review

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Abstract – *Polyporus umbellatus* is a medicinal mushroom belonging to the family *Polyporaceae* which forms characteristic underground sclerotia. These sclerotia have been used in Traditional Chinese Medicine for centuries and are used to treat edema and promote diuretic processes. Over the past few decades, researchers have found this taxon to contain many bioactive compounds shown to be responsible for antitumor, anticancer, antioxidant, free radical scavenging, immune system enhancement and antimicrobial activities. Due to its promising medicinal value, *P. umbellatus* is used as an ingredient in many medicinal products and food supplements. Thus demand for *P. umbellatus* has increased. To supply the high global demand, *P. umbellatus* is cultivated under natural or industrial conditions. In this review we discuss optimal conditions for the cultivation and culture of *P. umbellatus*. We also focus on the medicinal uses of *P. umbellatus*, the diversity of bioactive metabolites with various pharmacological properties and the medicinal products of great interest for health care or as alternative drugs.

Anticancer / Antimicrobial / Antioxidant / Antitumor / Bioactive molecules / Immunity / Medicinal mushroom / Polysaccharides / Steroid

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doi/10.7872/crym.v36.iss1.2015.3

INTRODUCTION

Mushrooms are defined as macrofungi with distinctive surface or subterranean fruiting bodies, large enough to be seen with the unaided eye. There are an estimated 140,000 species (Chang & Miles, 1992; Hawksworth, 2001; Wasser, 2002), but about 10% are thought to be named (Hawksworth, 2001; Lindequist *et al.*, 2005; Wasser & Didukh, 2005). The total number of edible and medicinal species is over 2300 Çağlarirmak, 2011; Ying *et al.*, 1987; Maass *et al.*, 2012). Mushrooms provide dietary protein, essential amino acids, carbohydrates, vitamins and minerals (Çağlarirmak, 2011; Cheung, 2008; Jong & Birmingham, 1990; Luangharn *et al.*, 2014; Smith *et al.*, 2002; Thatoi & Singdevsachan, 2014). Several thousands of years ago people in the Orient recognized that many edible and certain non-edible mushrooms have valuable health benefits (Cao *et al.*, 2012; Hobbs, 1995; Mortimer *et al.*, 2012; Smith *et al.*, 2002; Thawthong *et al.*, 2014; Alves *et al.*, 2012; Giavasis, 2014; Quang *et al.*, 2006).

Polyporus umbellatus (Pers.) Fr. is a medicinal mushroom in the family *Polyporaceae* of class Basidiomycetes (Choi *et al.*, 2003; Ying *et al.*, 1987; Zhou & Guo, 2009). It is a saprobe(Sekiya *et al.*, 2005; Sun & Yasukawa, 2008) which causes white rot of wood (Choi *et al.*, 2002; Lee *et al.*, 2007; Lee *et al.*, 2005; Ryvarden & Gilbertson, 1994; Zhao & Zhang, 1992). Scopoli (1772) initially named this fungus as *Boletus ramosissimus*. It was renamed as *Fungus ramosissimus* by Paulet (1793), *Boletus ramosus* by Vahl. (1797), and *Boletus umbellatus* by Persoon (1801, 821). Finally it was named *Polyporus umbellatus* by Fries, and this name has since been used (Partnership; Murrill, 1904; Robert *et al.*, 2005).

Polyporus umbellatus is commonly referred to as *Grifola umbellata* (Hall *et al.*, 2003; Roody, 2003; Xing *et al.*, 2012) and more infrequently *Dendropolyporus umbellatus* (Pouchus, 2012; Roody, 2003; Xing *et al.*, 2012). Its common names include Zhuling (猪苓) (Hog*Tuber*) in Chinese, Chorei-Maitake (wild boar dung Maitake) or Tsuchi-maitake (Earth Maitake) in Japanese, (Miyazaki & Oikawa, 1973; Stamets, 2000; Stamets, 2002) Eichhase in German, (Bachmeier *et al.*, 2011) Polypore en ombelle in French (Pouchus, 2012) and umbrella polypore in English (Fischer & Bessette, 1992; Lincoff, 2010; Lincoff & Nehring, 2011).

Polyporus umbellatus is widely distributed in the temperate regions of the Northern hemisphere in Asia, Europe and North America (Stamets, 2000; Zhao *et al.*, 2009c; Zhao *et al.*, 2009e; Zhou *et al.*, 2007; Kikuchi & Yamaji, 2010). In Asia, it has been recorded in China, (Ying *et al.*, 1987; Zhang *et al.*, 2010b; Zheng *et al.*, 2004; Zhou & Guo, 2009) India, (Núñez & Ryvarden, 1995; Núñez & Ryvarden, 2001) Japan, Korea and USSR (Kikuchi & Yamaji, 2010; Zhao & Zhang, 1992). In Europe it has been recorded in southern and central Europe, northern to most southern coastal areas of Fennoscandia, (Ryvarden & Gilbertson, 1994) Poland, (Zhao & Zhang, 1992) France, the UK (Courtecuisse, 1999) and Slovakia (Kunca, 2011). It has been found in north central and north-eastern parts of North America (Ryvarden & Gilbertson, 1994) and recorded from east Canada to Tennessee (Lincoff & Nehring, 2011). Gilbertson and Ryvarden reported this mushroom in Montana and Washington State (Stamets, 2000). The fungus has also been reported from Ithaca, (Murrill, 1904) Amherst, (Hitchcock, 1829) Ohio, Iowa, Idaho in USA (Lincoff & Nehring, 2011). *Polyporus umbellatus* prefers relatively warm regions in broad-leaved (Jong & Birmingham, 1990; Kikuchi & Yamaji, 2010; Kunca, 2011) and coniferous forest

(Stamets, 2000; Ying *et al.*, 1987). *Polyporus umbellatus* has been observed in deciduous forests, (Stamets, 2000) as sclerotium close to the stumps of hardwoods such as *Alnus, Carpinus, Castanea, Fagus* and *Quercus*. *Quercus* seems to be the favorite host of *P. umbellatus* and on a few occasions it has also been detected under *Picea* and *Pinus* trees (Núñez & Ryvarden, 1995; Overholts, 1914; Ryvarden & Gilbertson, 1994; Zhao & Zhang, 1992). The fungus has also been found around the roots of alder and Japanese oak (Ueno *et al.*, 1980). It prefers dead roots or buried wood, and birch, maples, willow and beech stumps (Stamets, 2000; Ying *et al.*, 1987). The fungal fruiting portion found on the ground is edible, whilst the underground part has medicinal properties (Jong & Birmingham, 1990; Ying *et al.*, 1987).The relative incidence of this fungus was higher in hilly terrains than in lowlands, while it was found only rarely in the uplands of Slovakia (Kunca, 2011). *Polyporus umbellatus* has been found in soil rich in lignicolous organic matter (Stamets, 2000) and mostly in acidic soils (Kunca, 2011). Through a diversity study carried out on *P. umbellatus* strains obtained from various parts of China, it was established that the fungus exhibits an uneven and high genetic diversity and an abundant environmental heterogeneity (Xing *et al.*, 2013a; Zhang *et al.*, 2012b). Molecular analysis based on rDNA data indicates significant inter and intra population variation. The nucleotide diversity was usually higher in the ITS sequences than in the 28S rDNA sequences (Xing *et al.*, 2013a).

Fossil records reveal that Polypores existed 300 million years ago, during the carboniferous age when the evolution of woody gymnosperms began (Zhao & Zhang, 1992). The genus *Polyporus* has been categorized into five groups and *P. umbellatus* belongs to a group which has branched stipes and/or sclerotia. Only *P. umbellatus* and *P. mylittae* form basidiocarps on sclerotia. Spore size, and the presence of a white to brownish pileus covered with fine scales distinguish *P. umbellatus* from *P. mylittae* (Zhao & Zhang, 1992). Macroscopically, *Grifola frondosa* (Maitake) appears to be a close relative of *P. umbellatus*, (Murrill, 1904) but biologically the two have different life cycles (Stamets, 2000).

REVIEW

The fungus

Mycelium

Polyporus umbellatus produces white, longitudinally linear mycelia on agar, in grain, and in sawdust media that soon become densely cottony, thick and peelable. When maturing on sterilized sawdust, concentric rings appear with an outer layer of yellowish, gelatinous exudate (Guo *et al.*, 2002; Stamets, 2000). It has a musty, sour, slightly bitter, and unpleasant odor (Stamets, 2000). *Polyporus umbellatus* mycelium requires a relatively long time to grow in artificial media (long lag phase) (Huang & Liu, 2007; Wang *et al.*, 2004). The relatively long time taken for the fusion of monokaryotic hyphae and slow growth of dikaryotic mycelium are the reasons for this (Xing & Guo, 2008). After this long lag phase, the conidia (asexual spores) are released by breaking up of the hyphae and a rapid growth of the mycelium can then be seen (Huang & Liu, 2007; Wang *et al.*, 2004). Xing and Guo revealed that the conidia of *P. umbellatus* could be produced from dikaryotic mycelia (Xing & Guo, 2008). Huang and Liu discovered an artificial medium which possesses the ability to shorten the lag phase in both the solid-state

and submerged culture of *P. umbellatus* (Huang & Liu, 2007). Zhang *et al.* reported the production of asexual spores and calcium oxalate crystals from the mycelium on potato dextrose agar (PDA) (Zhang *et al.*, 2010b). *Polyporus umbellatus* mycelia growing in PDA excrete intra and extracellular polysaccharides (Zhang *et al.*, 2010b). Correlation analysis indicate that intra and extracellular polysaccharide content had significant and positive relationship, but extracellular content was negatively correlated with daily mycelial growth rate (Zhang *et al.*, 2010b).

Sclerotia

Polyporus umbellatus forms an irregular tuber-like underground structure known as a sclerotium (Ying *et al.*, 1987; Choi *et al.*, 2002; Choi *et al.*, 2003). It is one of two *Polyporus* species which develops fruiting bodies on underground-buried sclerotia. Similar to other species, the sclerotia of *P. umbellatus* are connected with the rotten wood in the ground (Zhao & Zhang, 1992). The sclerotium of *P. umbellatus* is also formed adhering to the living roots of deciduous species belonging to genera *Quercus* and *Alnus* (Kikuchi & Yamaji, 2010).

The sclerotium of *P. umbellatus* is an irregular, bumpy, rugged and multi-branched tuber, woody in texture, the upper surface of which is dark brown to black and the inner part white (Choi *et al.*, 2002; Imazeki & Hongō, 1989; Kunca, 2011; Lee *et al.*, 2005; Ying *et al.*, 1987). The sclerotium of *P. umbellatus* is mild, sweet and bland in flavor and when dried is used as a crude drug for medicinal purposes in the Orient, i.e. China, Korea and Japan (Choi *et al.*, 2002; Jong & Birmingham, 1990; Kikuchi & Yamaji, 2010; Liu & Liu, 2009; Wu, 2005; Ying *et al.*, 1987). Sclerotia are formed underground; typically between 10 and 15 cm deep and are rarely found below a depth of 30 cm (Kikuchi & Yamaji, 2010). Sclerotia of *P. umbellatus* comprise hyphae and these hyphae are highly differentiated in structure. The hyphae are organized and form several distinctive layers inside the sclerotia (Guo & Xu, 1991). As in other higher fungi, the development of the sclerotium of *P. umbellatus* has three distinguishable stages (Choi *et al.*, 2002). During development, the colour in the sclerotium changes and a new primordium is formed. Large prismatic crystal structures and thick-walled cells in the centre of hyphae are formed in contrast with other fungal sclerotia (Choi *et al.*, 2002; Guo & Xu, 1992a). Sclerotia of *P. umbellatus* and the forest pathogenic fungus *Armillaria mellea* form a symbiotic relationship by means of mutual assimilation (Guo & Xu, 1992b) and growth of sclerotia depends on this relationship (Xing *et al.*, 2012). Previous studies have revealed that *A. mellea* appeared to be a nutritional factor which improves the growth of the sclerotium of *P. umbellatus* (Choi *et al.*, 2002; Guo *et al.*, 2002). *Armillaria mellea* increases mycelial growth and the production of metabolites such as ergone (Lee *et al.*, 2007). With promotion of mycelium growth of *P. umbellatus* by water extract of *A. mellea* rhizomorphs, it has been shown that *A. mellea* acts as a good carbon and nitrogen source upon which the growth of *P. umbellatus* depends (Guo *et al.*, 2011). When the rhizomorphs of *A. mellea* are introduced into the sclerotia of *P. umbellatus*, the sclerotium forms an enclosed cavity around them, in order to prevent excess colonization by *A. mellea*. Furthermore, the rhizomorphs inside the cavity are degraded and the resultant nutrients are absorbed by the sclerotium (Xing *et al.*, 2012).

Guo *et al.* classified another companion fungus (*Grifola* sp.) associated with sclerotia of wild *P. umbellatus,* which is related to sclerotial formation (Guo

et al., 2002). This companion fungus induces activation of *P. umbellatus* enzymes used in sclerotial formation and differentiation by supplying the nutrient supplements (Xing & Guo, 2004). Kikuchi and Yamaji discovered that not only *A. mellea*, but also five other *Armillaria* species may have a symbiotic relationship with *P. umbellatus* (Kikuchi & Yamaji, 2010). These *Armillaria* species are believed to have co-evolved with *P. umbellatus* and their population structure selected by nature under specific microenvironments (Zhang *et al.*, 2012b). Feng *et al.* also recorded *A. mellea* and *A. gallica* associated with sclerotia of *P. umbellatus* (Feng *et al.*, 2012). In addition, fungal species belonging to genera such as *Eurotium, Fusarium, Geomyces, Mucor* and *Penicillium* were identified residing with sclerotia of *P. umbellatus*, and these fungal communities varied with host location where observed in China (Xing *et al.*, 2012).

The sclerotia of *P. umbellatus* can survive in soils for a long time and have the ability to produce new sclerotia directly from the existing ones under appropriate conditions (Xiaoke & Shunxing, 2005). After months of dormancy the sclerotium become soft and swollen and on absorbing water produce fruiting bodies (Stamets, 2000). Unlike other sclerotium forming fungi, the sclerotia of *P. umbellatus* can be reproduced only from sclerotia and not hyphae (Wang *et al.*, 2004). The sclerotium of *P. umbellatus* is produced mainly in the provinces of Shanxi, Henan, Hebei, Sichuan, and Yunnan in China. In the process, the fruiting bodies collected in the spring and autumn are cleaned, dried, sliced, and used unprepared (Wu, 2005).

Fruiting bodies

The sclerotium of *P. umbellatus* swells with water and produces numerous multi-branched, circular mushrooms with umbellate caps (pilei) (Ying *et al.*, 1987; Stamets, 2000). It fruits annually (Zhao & Zhang, 1992). The pileus is fleshy and smooth when fresh, hard and brittle-wrinkled when dry (Núñez & Ryvarden, 1995; Overholts, 1914; Ryvarden & Gilbertson, 1994; Ying *et al.*, 1987). The fruiting body is one of the most fragile and delicate of mushrooms of species in the genus *Polyporus* (Stamets, 2000). The mushroom is centrally stipitate and the central part of the cap is concave or subfunnel-shaped (Murrill, 1904; Zhao & Zhang, 1992). Bouquets of mushrooms arise from a common stem base (Ryvarden & Gilbertson, 1994; Stamets, 2000). The multiple circular pilei arising from a common stem make this a very distinct species (Ryvarden, 2014). The stipe is thick at the base, thinner towards the pilei and richly branched (Núñez & Ryvarden, 1995). The fruit bodies are whitish at first, becoming brown with age, with an under side featuring circular to angular pores (Ryvarden & Gilbertson, 1994; Stamets, 2000). Pore surface on drying become brownish to brown; pores are suborbicular, angular, or irregulary lacerate (Zhao & Zhang, 1992). They are often waterlogged due to a high water carrying capacity (Stamets, 2000). The hyphal system of *P. umbellatus* is dimitic, non-septate and thin or slightly thick-walled and clamp connections can be observed on the hyaline generative hyphae (Dai *et al.*, 2014; Ryvarden & Gilbertson, 1994; Stamets, 2000; Zhao & Zhang, 1992). Few gloeoplerous hyphae are also present (Núñez & Ryvarden, 1995). A study carried out on the fruit body development of *P. umbellatus,* Guo *et al.* concluded that the fruit body possesses all three types of hyphae, known as trimitic hyphal system (Guo *et al.*, 1998). The fruit body bears clavate-shaped basidia, with 2-4-sterigmata, and basal clamps, in which basidiospores of cylindrical, hyaline, thin-walled, smooth and white in deposit are located (Overholts, 1914; Ryvarden & Gilbertson, 1994; Núñez & Ryvarden, 1995;

Stamets, 2000). Young fruiting bodies of *P. umbellatus* are edible (Ying *et al.*, 1987; Jong & Birmingham, 1990; Zhao & Zhang, 1992). The protein content is higher than the polysaccharide content in the fruiting body, therefore it has lower polysaccharide/protein ratio compared with *Ganoderma lucidum, Lentinula edodes, Macrocybe lobayensis, Schizophyllum commune, Trametes versicolor, Tremella fuciformis* and *Volvariella volvacea* (Liu *et al.*, 1997). The sporocarp production of *P. umbellatus* follows that of typical forest macrofungi. The sporocarp production of *P. umbellatus* increases significantly during some seasons and corresponds with weather patterns (Kunca, 2011).

Chemical composition

Fruiting bodies, sclerotium and mycelium of *P. umbellatus* contain important bioactive substances which are of different chemical composition and mode of action. Preliminary studies showed that the *P. umbellatus* contains 46.6% coarse fiber, 7.89% coarse protein, 6.64% ash and 0.5% of carbohydrate (Ying *et al.*, 1987). The sclerotium was investigated for its chemical content; Chen and Deng reported amino acids, water, crude proteins, fats, fiber and mineral compounds (Chen & Deng, 2003), while Lee *et al.* detected 78.2% polysaccharides, 16.8% proteins and 4% ash (Lee *et al.*, 2004). Others studies have demonstrated that the major chemical constituents of the *P. umbellatus* are polysaccharides and steroids (Zhao *et al.*, 2009f; Zhao *et al.*, 2009c; Zhao *et al.*, 2010a).

Guo *et al.* observed the pattern of changing nutrients contents through the development of cultured and wild sclerotia, and stated that with the increment of time, sugar and protein contents decrease (Guo *et al.*, 1992). In the first year of growth the amount of fat and in the consecutive year the polysaccharide content reach their maximum values. Although the amount of ergosterol is the highest in the subsequent year in cultured sclerotia, it is lowest in wild sclerotia (Guo *et al.*, 1992). The first chemical study on *P. umbellatus* recorded a fatty acid, 2-hydroxytetracosanoic acid [$CH_3(CH_2)_{21}CHOHCOOH$], isolated from the fruiting body of the *P. umbellatus* (Yosioka & Yamamoto, 1964). A water-soluble polysaccharide, a glucan which processed (1→3), (1→4), (1→6)-glycosidic linkages and branched at C-3 or C-6 positions of glucose residue, was isolated from the sclerotium of *P. umbellatus* (Miyazaki & Oikawa, 1973). Kato *et al.* obtained D-glucose and small quantities of D-galactose and D-mannose from an aqueous extract of the sclerotium (Kato *et al.*, 1978). The backbone of these polysaccharides comprised a β(1→3)linked D-glucose and the authors found similar β(1→4), β(1→6) linkages which previously recorded (Miyazaki & Oikawa, 1973). Gas chromatography and mass spectrometry analyses revealed that the polysaccharides of *P. umbellatus* consist of D-mannose, D-galactose, and D-glucose at the ratio 20:4:1 (Zhu, 1988). Ohno *et al.* determined the fungal (1→3)-β-D-glucan in several edible fungi, including *Grifola frondosa* and *P. umbellatus*, which possess two kinds of conformation in the solid state: helix (curdlan type) and native (laminaran type) (Ohno *et al.*, 1988; Ohno *et al.*, 1986). Their findings suggested that the (1→3)-β-D-glucan is the native form in the fruiting body (Jong & Birmingham, 1990). A patent has been obtained for the extraction method of β-glucan from the fruiting body of *P. umbellatus* (Lee & Park, 2001). Polysaccharides are major components existing in both plants and animals (Peng *et al.*, 2012) and glucans are one of the major polysaccharide constituents in the cell walls of fungi (Jong & Birmingham, 1990; Du *et al.*, 2014).

From the observation of spectral data, it was concluded that the water-soluble polysaccharides isolated from the mycelium and sclerotium were similar (Xu *et al.*, 2004; Tian *et al.*, 2005). Recently, Dai *et al.* investigated similar polysaccharides in an aqueous extract of the fruiting body with a molecular mass of 2.27×10^3kDa containing > 90% D-glucose as its monosaccharide constituent (Dai *et al.*, 2012). The polysaccharides consist of (1→6, 1→4)-linked-D-glucopyranosyl backbone, substituted at the O-3 position of (1→6)-linked-D-glucopyranosyl by (1→3)-linked-d-glucopyranosyl branches and approximately 2930 repeating units; each containing a side chain of no more than three residues in length (Dai *et al.*, 2012). Bi *et al.* isolated *P. umbellatus* polysaccharides using hot water extracts. According to Phenol-Sulfuric assay, two compounds were enclosed in this mixture, and they were placed as GUMP-1-1 and GUMP-1-2 while GUMP-1-1 was comprised of glucose, mannose and fructose, GUMP-1-2 also included uronic acid and protein (Bi *et al.*, 2013). Polysaccharide which aqueously extracted from fermented mycelium and fruiting body of *P. umbellatus* both consist of glucose and galactose (Sun & Zhou, 2014). The molecular weight of polysaccharide of mycelium was 857 kDa and molar ratio of glucose to galactose is 1.57:1, while from the fruiting body, the molecular weight was 679 kDa and molar ratio of glucose to galactose 5.42:1 (Sun & Zhou, 2014).

A method of extracting polysaccharides from the *P. umbellatus* mycelium by fermentation in a medium containing soya bean and additives was introduced by Xu and Zhou (Xu & Zhou, 2003). Similarly, a method of purifying *P. umbellatus* polysaccharides using a macroporous resin was discovered (Cui *et al.*, 2005). A method of extracting highly purified water soluble polysaccharides was introduced by Wang *et al.* (Wang *et al.*, 2006). Chen *et al.* introduced an ultrasonic extracting technique for polysaccharides of *P. umbellatus* (Chen *et al.*, 2008). The polysaccharide content that was extracted by this method was greatly improved compared with the boiling water method of extraction. Reduced extraction time, reduced ratio of material to liquid and lowered operating temperature are other advantages of this method.

Chen *et al.* discovered polyethylene glycol exhibiting effective stimulatory effects in mycelial biomass and exopolysaccharides production in submerged cultures of *P. umbellatus* (Chen *et al.*, 2010b). Wang *et al.* recommended optimum alcohol concentrations, pH values for polysaccharides extraction and fractional precipitation, (Wang *et al.*, 2010) while Li introduced a technique for extracting polysaccharides (Li, 2011). Zhang *et al.* obtained a higher polysaccharide yield from *P. umbellatus* using a microwave chemical extraction process (Zhang *et al.*, 2012a). Quantitative analysis of polysaccharides produced by fermentation of *P. umbellatus* mycelium was carried out using HPLC technique (Zhou *et al.*, 2001). A quantitative analysis of polysaccharides using phenol and sulfuric acid in *P. umbellatus* was introduced by Guangwen *et al.* (Guangwen *et al.*, 2007). This method is highly sensitive, simple, reproducible and accurate with stable data (Guangwen *et al.*, 2007). An optimum composition medium which included Soya bean, used for the production of maximum *P. umbellatus* mycelium, was introduced by Zhang and Yu (Zhang & Yu, 2008). Shen *et al.* found a chemical treatment to decolorize the precipitated water-soluble polysaccharides from *P. umbellatus* mycelium (Shen *et al.*, 2009). Du *et al.* patented a liquid suspension culture, which can produce a higher amount of polysaccharides and steroids from mycelium of *P. umbellatus* in a short fermentation period (Du *et al.*, 2011).

Steroids are one of the main components of *P. umbellatus.* Abe *et al.* reported that the fruiting body contains ergosta-4,6,8(14),22-tetraen-3-one (ergone) (Abe *et al.*, 1981). Later, the same compound was isolated from the

sclerotia of *P. umbellatus* (Lee *et al.*, 2005). Ergone is a fungal metabolite derived from ergosterol (Lee *et al.*, 2005; Lee *et al.*, 2007). Ergone isolated from *P. umbellatus* possesses a variety of pharmacological activities, both *in vivo* and *in vitro,* including cytotoxic, diuretic, and immunosuppressive effects (Sun *et al.*, 2013; Zhao *et al.*, 2011b). Lu *et al.* isolated four components, viz. ergosta-5,7,22-trien-3-ol (ergosterol), ergosta-7,22-dien-3-one, ergosta-7,22-dien-3-ol, and 5α,8α-epidioxyergosta-6,22-dien-3-ol, from the fruiting body of *P. umbellatus.* Three of these components (ergosta-7,22-dien-3-ol, ergosta-5,7,22-trien-3-ol, 5α,8α-epidioxyergosta-6,22-dien-3-ol) were shown to enhance of aggregation of platelets in rabbits induced by collagen and/or adenosine-5'-diphosphate *in vitro* (Lu *et al.*, 1985). The concentration at which the platelets are aggregated by these three active compounds is less than the effective concentration of cholesterol, which has a chemical structure very similar to ergosterol.

Ohsawa *et al.* identified seven polyporusterones from the fruiting bodies of *P. umbellatus* and named them as A, B, C, D, E, F and G (Ohsawa *et al.*, 1992). Four new compounds were isolated from the sclerotia, 9α-hydroxy-1,2,3,4,5,10,19-heptanorergosta-7,22-diene-6,9-lactone and ergosta-7,22-diene-3β,5α,6β-triol (Ohta *et al.*, 1996b) as well as 5α,8α-epidioxy-(24*S*)-24-methylcholest-6-en-3β-ol and 5α,8α-epidioxy-(24*R*)-24-methylcholesta-6,9(11),22-trien-3β-ol (Ohta *et al.*, 1996a). In addition, polyporusterones A and B previously recognized by Ohsawa *et al.* (Ohsawa *et al.*, 1992) were identified from the sclerotium by Ohta *et al.* (Ohta *et al.*, 1996a). Three alkaloids and two steroids were isolated from the sclerotia of *P. umbellatus*; the structures of these were ascertained as 9-β-D-ribofuranosyladenine (adenosine), 1-β-D-ribofuranosyluracil (uridine), 2,4-pyrimidinedione (uracil), ergosta-4,6,8(14),22-tetraen-3-one and ergosta-5,7,22-triene-3β-ol (ergosterol) on the basis of spectroscopic data and chemical correlations (Lee *et al.*, 2002). Two new polyporusterones named as polyprosteroneI and polyprosterone II were isolated from sclerotia of *P. umbellatus*. Their structures have been established based on spectral analysis (Zheng *et al.*, 2004). Two other polyperusterones named (20*S*,22*R*,24*R*)-16,22-epoxy-3β,14α,23β,25-tetrahydroxyergost-7-en-6-one and (23*R*,24*R*,25*R*)-23,26-epoxy-3β,14α,21α,22α-tetra-hydroxyergost-7-en-6-one were isolated from the sclerotia of *P. umbellatus* (Zhou *et al.*, 2007). Three polyporusterones were rediscovered in those experiments (Zhou *et al.*, 2007). Three new ecdysteroids (polyporoids A, B, C) with five known steroids, which were previously identified by Ohsawa *et al.* (Ohsawa *et al.*, 1992) and Ohta *et al.* (Ohta *et al.*, 1996b) were isolated from the ethyl acetate extract of the sclerotium. All these ecdysteroids exhibit anti-inflammatory activity against 12-O-tetradecanoylphorbol-13-acetate (TPA) induced inflammation in mice. The inhibitory effects of ecdysteroids are higher than indomethacin, a commercially available anti-inflammatory drug (Sun & Yasukawa, 2008). A new pentacylictriterpene named 1-β-hydroxylfriedelin was recently isolated from the *P. umbellatus* sclerotia and its structure has been elucidated (Zhao *et al.*, 2009c). Zhao *et al.* identified eight steroids in *P. umbellatus* using the HPLC coupled with mass spectroscopy detection (Zhao *et al.*, 2010c). Apart from (22*E*,24*R*)-ergosta-6-en-3?,5?,6?-triol steroid, all other steroids were identified (Lu *et al.*, 1985; Ohsawa *et al.*, 1992; Lee *et al.*, 2002; Sun & Yasukawa, 2008). Ergone can be used as a marker, in order to standardize production of *P. umbellatus* sclerotium. Since ergone combines florescence properties, it can be easily admitted for quantitative and qualitative analysis (Yuan *et al.*, 2003). Quantitative analysis of ergone levels in sclerotia have been carried out using a high performance liquid chromatography-ultraviolet detector (HPLC-UV) (Yuan *et al.*, 2003; Yuan *et al.*, 2004) and high performance liquid chromatography-fluorescence detector

(HPLC-FLD) and the results were verified using high performance liquid chromatography-atmospheric pressure chemical ionization-mass spectrometry (HPLC-APCI-MS/MS) (Zhao *et al.*, 2009f; Zhao *et al.*, 2009d). Ergone content depends on a number of factors, such as genetic variation, fungus origin, drying process and storage conditions (Zhao *et al.*, 2009f). The HPLC-APCI-MS method has been developed for qualitative analysis of known steroids in *P. umbellatus*, and can therefore be used for the quality control of *P. umbellatus*. This is necessary due to variations in the quality of *P. umbellatus* samples obtained from different localities (Zhao, 2009; Zhao *et al.*, 2010c). Zhao *et al.* subsequently developed a more accurate and precise method to determine ergone concentration from biological fluids using HPLC dual wavelength UV (Zhao *et al.*, 2010e). They developed a fast and sensitive HPLC–APCI-MS/MS method for the determination of ergosta- 4,6,8(14),22-tetraen-3-one (ergone) in rat plasma, the absolute recoveries of both ergone and ergosterol from the plasma being more than 95% (Zhao *et al.*, 2010b). The developed method has been successfully applied to pharmacokinetic study of the drug in rats. Zhao *et al.* introduced rapid resolution liquid chromatography with atmospheric pressure chemical ionization tandem multi-stage mass spectrometry (RRLC-APCI-MS^n) and HPLC-FLD for identification and quantification of ergonefrom rat plasma, urine and faeces (Zhao *et al.*, 2010d). These methods are suitable for analysis in preclinical and pharmacokinetic studies of ergone which is a major bioactive component of *P. umbellatus.*

Zhao *et al.* developed RRLC-APCI-MS^n and HPLC-APCI-MS/MS method for the identification and quantification of ergosterol and its metabolites in rat plasma, urine and faeces (Zhao *et al.*, 2011a). Chen *et al.* carried out a quantitative analysis of ergosterol recovered from blood plasma, urine and faeces caused by orally administering ergosterol obtained from *P. umbellatus* (Chen *et al.*, 2013). The cloud-point extraction technique was used for the first time in extracting ergosterol from blood plasma, urine and faeces, whereas HPLC-UV was used for quantitative measurement. The results indicated that the ergosterol level in faeces was higher than in plasma and urine (Chen *et al.*, 2013). It was shown that the above method is more suitable for pharmacokinetic analysis carried out using ergosterol.

Introduction for medicinal properties

Polyporus umbellatus is commonly used in traditional Chinese medicine (Huang & Liu, 2007; You *et al.*, 1994; Zhao *et al.*, 2009e). It was referred to in the well-known medical book *Shen Nung Pen Tsao Ching* between A.D. 25-220 about 1,600 years prior to the earliest foreign record (1801) (Zhao & Zhang, 1992). According to Li Shi-chen's Compendium of Materia Medica, *P. umbellatus* "opens up the texture and interspaces of the skin, and muscle, including the sweat pore, cures gonorrheal swelling, beriberi, leucorrhea, gestational urination, disturbances, foetus swelling and difficulty in urination" (Ying *et al.*, 1987; Jong & Birmingham, 1990).

Ying *et al.* recorded a number of Chinese traditional herbal formulas including lignicolous mushrooms as sclerotia of *P. umbellatus,* which can be used to treat conditions such as acute nephritis, systemic dropsy, thirst, difficulty in urination, edema, urination disturbance, sunstroke, watery diarrhea, jaundice, cirrhosis and ascites (Ying *et al.*, 1987). It has a diuretic effect on pathogenic dampness and is being used in traditional medicine combinations to treat oliguria,

edema, diarrhea, strangury with cloudy urine or leucorrhea (Wu, 2005; Liu & Liu, 2009). The sclerotium of *P. umbellatus* is also a Traditional Chinese Medicine used for edema and promoting diuresis (Xiaoke & Shunxing, 2005; Xing *et al.*, 2012). Ecdysteroids, which exist in the sclerotia, act as a defensive mechanism and exhibit various biological activities including *in vitro* cytotoxic, *in vivo* antitumor-promoter, and antioxidant activities (Sun & Yasukawa, 2008; Ueno *et al.*, 1980). Presently the wild sclerotium of *P. umbellatus* is the main source for medicinal uses (Xiaoke & Shunxing, 2005; Xing *et al.*, 2013b).

Antitumor activity

Tumors, also known as neoplasms, are swellings or abscesses formed by an abnormal proliferation of cells. Tumors can be benign, pre-malignant or malignant (De Silva *et al.*, 2012a). Ito *et al.* reported that water soluble glucan from sclerotia of *P. umbellatus* demonstrated a strong antitumor activity against subcutaneously implanted sarcoma 180, and also inhibited the growth of Shionogi carcinoma 42 and pulmonary tumor 7423 in mice (Ito, 1973). Chemical analysis confirmed this glucan-contains β-(1→3), β-(1→4), and β-(1→6) linked branches and signified coexistence of β-(1→3) and β-(1→6) branches as indispensable for the antitumor effect (Ito, 1973). Ito *et al.* investigated the influence of the sex of experimental animals on the antitumor activity of polysaccharide from sclerotia of *P. umbellatus* (Ito *et al.*, 1975). It was observed that the growth rate of male mice bearing Sarcoma 180, Ehrlich solid carcinoma, pulmonary tumor 7423 and MF-sarcoma was higher than female mice of the same kind. In addition, the regression rate of female mice treated with polysaccharides was high when compared to the male mice. Both males and females which experienced a regression of ascites tumor due to the administration of polysaccharides rejected the re-implanted Ehrlich ascites carcinoma, Sarcoma 180, NF-sarcoma and Shionogi carcinoma 42 (Ito *et al.*, 1975).

Miyazaki *et al.* explained the structure of the antitumor glucans and proposed the probable structural units (Miyazaki *et al.*, 1978). Chemical analysis of the antitumor glucans of sclerotia of *P. umbellatus* revealed that polysaccharides bear the above mentioned linkages and it was further discovered that β-(1→3)and β-(1→6) linkages were consistent in the backbone of the structure of these glucans, while β-(1→4) and β-(1→6) linkages were found in the branches connected with the backbone (Miyazaki *et al.*, 1978). These glucans cause complete regression of subcutaneously implanted sarcoma 180 tumor cells in mice (Miyazaki *et al.*, 1978). Miyazaki *et al.* disclosed that the basic common unit of glucans of sclerotia from *P. umbellatus* is of primary importance and also that the chemical structure of the glucans influenced antitumor activity (Miyazaki *et al.*, 1979). This activity was influenced by the type of sugar linkage, length of the branch, branching frequency, molecular size and molecular conformation. The probable structural units of the four antitumor glucans using *P. umbellatus* were determined (Miyazaki *et al.*, 1979). Ueno *et al.* isolated an alkali-soluble β-D-glucan polysaccharide from sclerotia, similar to water soluble polysaccharides composed of a backbone of β-(1→3)-linked D-glucopyranosyl residues, and possessing of a single β-D-glucopyranosyl group joined through O-6 of every third D-glucopyranosyl residue of the backbone (Ueno *et al.*, 1980). In 1981, unknown authors from Japan obtained a patent for an antitumor glucan, which was isolated from the mycelium of *P. umbellatus*. This glucan was active against sarcoma 180 (Anonymous, 1981). Several alkali-soluble polysaccharides were isolated by Ueno *et al.* who confirmed occurrence of (1→3)-β-D-glucan and found that the O-6

substituent in the (1→3)-β-D-glucan was of major importance in antitumor activity against sarcoma 180. It was revealed that C-6 branched (1-3)-β-D-glucopyranosyl-(1-3)-β-D-glucopyranosyl is the common unit of antitumor active glucans and the branching frequency of the glucans is also significant for the antitumor activity process (Miyazaki, 1983). It was shown that *P. umbellatus* polysaccharides act against sarcoma 180 and Ehlich's carcinoma tumor, using the experiments carried out upon mice (Wang *et al.*, 1983). It was shown that these polysaccharides have the potential to suppress spontaneous metastasis in Lewis lung sarcoma, and act against uterine cancer U14 (Wang *et al.*, 1983).

Although Ito *et al.* signified that no activity was found in alkali soluble glucans against tumor cells, rather than water-soluble glucans (Ito, 1973), Ueno *et al.* showed that alkaline soluble polysaccharides are more effective than some water-soluble polysaccharides. The authors confirmed that alkaline soluble polysaccharides act against sarcoma 180 tumor cells more than water-soluble polysaccharides (Ueno *et al.*, 1982). Polysaccharides of *P. umbellatus* are known for their adoptogenic antitumor effect on mice bearing hepatoma H22 (Wei *et al.*, 1983b; Wei *et al.*, 1983a). The number of hepatoma H22cells in mice was reduced after treatment and the plasma corticosterone and liver glycogen content as well as enzyme activities were restored (Wei *et al.*, 1983b; Wei *et al.*, 1983a; Wu *et al.*, 1982). Polysaccharides with antitumor and immunomodulating activities have been obtained from the liquid culture medium of *P. umbellatus*. A branched D-glucotetraose was identified by Ogawa and Kaburagi as the repeating unit of the extracellular polysaccharide of *P. umbellatus* (Jong & Birmingham, 1990). Ito *et al.* gave a descriptive explanation of the mechanism of *P. umbellatus* polysaccharides against Sarcoma 180 tumor cells in mice. It was shown that these polysaccharides do not exhibit a direct cytocidal action against the tumors, while the activation of the C3, stimulation of the reticuloendothelial system and the inhibition of hepatic drug metabolizing enzymes cause a direct cytocidal action (Ito, 1986). *Polyporus umbellatus* combined with mitomycin C enhanced the life span of mice with an intrahepatic implantation of sarcoma 180 tumor cells by inhibiting the synthetic rates of DNA, RNA and protein in tumor cells (You *et al.*, 1994).

Cachexia, a common condition in many human cancer patients, particularly in gastrointestinal or lung cancer patients, is characterized by loss of weight, muscle atrophy, fatigue and weakness (Muscaritoli *et al.*, 2006). Cachexia results in eventual death of these patients. Toxohormone-L, a protein that inhibits food and water intake promoting anorexia was found in the patients with cachexia. *P. umbellatus* polysaccharides reduced cachexia caused by toxohormone-L protein in rats (Wu *et al.*, 1997). Xu *et al.* investigated cytotoxic activity of peripheral blood monocytes which is activated by polysaccharides of *P. umbellatus* and Interleukin 2 against tumor cells in culture. Cytotoxicity of killer cells co-stimulated by the polysaccharides and Interleukin 2 which are effective against both natural killer resistant and natural killer sensitive tumor cells (Xu *et al.*, 1998). *Polyporus umbellatus* polysaccharide enhances cytotoxic activity mediated by natural killer cells against target cells of YAC-1 cells and P-815 cells of mice (Nie *et al.*, 2000).

Chen *et al.* manufactured a tablet composed of components from *P. umbellatus, Poria cocos* and skin pulp of two *Bufo* species. They reported potential antitumor, immunostimulant and analgesic properties and the ability to remove toxic substances. This mixture has been used to produce pharmaceuticals and foods, which helps the human body against radiation and chemical (Chen *et al.*, 2007). The compound extract constituted *P. umbellatus* and two other

traditional Chinese medicines *Agrimonia pilosa* and Gambogia (dry resin secreted by *Garcinia hanburyi*) and inhibited human gastric carcinoma MGC-803 tumor cell growth *in vitro* and *in vivo* in a dose dependent manner. In an experiment carried out upon a sample of mice, it was shown that this compound induces programmed cell death in the above tumor cells and may be a promising novel anti-tumor drug in human gastric carcinoma (Zhao *et al.*, 2009a). According to an analysis done using different Chinese Traditional Antitumor Medicines, i.e., Ligustrazine Hydrochloride, Astragalus Mongholicus Bge, Matrine N-Oxide and Artesunate, *P. umbellatus* polysaccharides exhibit a down regulating effect upon immunosuppressors of colorectal tumor cells *in vitro* (Li *et al.*, 2011).

Other than polysaccharides, ergone extracted from the sclerotium of *P. umbellatus* shows an outstanding antitumor effect against human hepatocellular carcinoma HepG2 cells (Zhao *et al.*, 2011b). Cell proliferation is inhibited due to the effect of these tumor cells, upon the G2/M phase of the cell cycle and the induction of apoptosis generated from the caspase activation The above mentioned GUMP-1-1 and GUMP-1-2 polysaccharides (Bi *et al.*, 2013) significantly brought down tumor volumes in hepatoma H22 transplanted mice. These two polysaccharides maximum tumor inhibition rate and maximum life prolonged was recorded at a dose of 200mg/kg. Bi *et al.* also demonstrated that GUMP-1-1 and GUMP-1-2 *P. umbellatus* polysaccharides indicate a significant antitumor activity (Bi *et al.*, 2013).

Anticancer activity

The early stage of cancer is referred to as neoplasm, and exhibits uncontrolled cell proliferation resulting in an abnormal mass of cells (De Silva *et al.*, 2012a). Later these cells spread to surrounding tissues and even to distant sites. Cancers always show a malignant growth of cells (De Silva *et al.*, 2012a). *Polyporus umbellatus* is used as a medicine, especially in anticancer drugs (Wei *et al.*, 1983b; Zhao & Zhang, 1992). *Polyporus umbellatus* sclerotium have figured prominently in Chinese pharmacopeia, especially in the treatment of lung cancer (Ying *et al.*, 1987; Stamets, 2000). A polysaccharide extract (Khz) obtained fused mycelia of *P. umbellatus* and *Ganoderma lucidum*, inhibits the growth of A549 lung cancer cells (Kim *et al.*, 2012). Yang *et al.* pointed out experimentally and clinically that *P. umbellatus* inhibits the induction of bladder cancer (Yang, 1991). A clinical study evaluated the prophylactic effect of *P. umbellatus* on bladder cancer. It was shown that the stimulating immune responses of *P. umbellatus* and Bacillus Calmette Guerin on bladder recurrence was better than mitocycin C (Yang *et al.*, 1999). All seven polyperostones isolated from the fruiting body of *P. umbellatus* showed cytotoxic action on leukemia 1210 cell lines and inhibited cell proliferation (Ohsawa *et al.*, 1992). Histopathological studies showed that lymphocytes infiltrated and surrounded the cancer cells, and there was fibrosis in both normal and cancerous cells. These results indicate the potential use of *P. umbellatus* as an anticancer agent (You *et al.*, 1994). Polyperostone A and B show greater cytotoxicity in higher concentrations (Sekiya *et al.*, 2005). Methanol extracts of sclerotium of *P. umbellatus* exhibited a cytotoxic effect against human gastric cancer cells and ergone inhibited the growth of cancer cell lines in colon, cervix, liver and stomach. The cytotoxic effects were stronger against cancerous cells in liver and colon, than the cervix and stomach cancer cells (Lee *et al.*, 2005).

Ergone, (22*E*,24*R*)-ergosta-7,22-dien-3β-ol, 5α,8α-epidioxy-(22*E*,24*R*)-ergosta-6,22-dien-3β-ol, ergosta-6,22-dien-3β,5α,6β-triol, and polyporusterone B which were isolated from *P. umbellatus* show anticancer activity against HepG2,

Hep-2, and Hela cancer cells, while ergone exhibits selective cytotoxic activity against cancer cells (Zhao *et al.*, 2010a). Aqueous extracts of sclerotia of *P. umbellatus* are highly effective in inhibiting bladder carcinogenesis in rats, which is also associated with up regulation of glutathione S-transferase π and NAD(P)H quinoneoxidoreductase 1 in the bladder (Zhang *et al.*, 2011).

Immune system enhancement

Extracts of *P. umbellatus,* in a drug produced by "Institute of Chinese drugs, Academy of Chinese Traditional Medicine", enhance immunity (Ying *et al.*, 1987). It was reported that the polysaccharides of *P. umbellatus* show a significant protective effect against acute toxicity in mice livers and the treatment reestablished the activities of liver glucose-6-phospate and acid phosphatase (Lin & Wu, 1988). Polysaccharides of *P. umbellatus* produce significant hepatoprotective activity against hepatotoxicity caused by $CCl_4$and D-galactosamine in mice (Lin & Wu, 1988). Zhang *et al.* showed that in normal mice as well as in mice which had liver lesions upon using CCl_4; the number of macrophages and the amount of H_2O_2 released in peritoneal cavities were increased by polysaccharides from *P. umbellatus* (Zhang *et al.*, 1991). Polysaccharides from *P. umbellatus* can boost the cellular immunity of both normal mice and those with liver lesions (Zhang *et al.*, 1991). It was shown that *P. umbellatus* polysaccharides enhance the lymphocyte function of immunosuppressed mice, and upregulate the number of CD4+ T cells and IgG level as reported. The authors also concluded that *P. umbellatus* polysaccharide acts as an immune response upregulator (Nie *et al.*, 2000).

Yang *et al.* investigated the immunosuppressive effects of culture supernatant of sarcoma 180 cells in the presence or absence of *P. umbellatus* polysaccharide. The study was carried out using mice, where it was shown that *P. umbellatus* polysaccharides have the potential to offset the immunosuppressive effects taking place due to culture supernatant of sarcoma 180 cells, as well as downregulate the immunosuppressive substances which are synthesized and/or secreted by the culture supernatant of sarcoma 180 cells (Yang *et al.*, 2004). It was shown that the polysaccharides extracted separately from *P. umbellatus* mycelium and the sclerotium using aqueous extracts advanced the weight of immunological organs when administered orally to mice. It was shown that these two polysaccharides are similar and that no significant difference was observed in their ability to advance the weights of immunological organs (Tian *et al.*, 2005). Li *et al.* administrated orally to mice the polysaccharides extracted separately from *P. umbellatus* mycelium and sclerotium using an aqueous extract and followed this up with the celiac mononuclear macrophage test, erythrocyte rosette formation test, metatarsal swelling thickness test, lymphocyte transformation test, and EAC rosette test. It was established that the test group differed significantly ($P < 0.05$) from the control group, with *P. umbellatus* polysaccharides increasing the immunity of white mice (Li *et al.*, 2007).

Pan *et al.* investigated the possibility of irradiation prevention and immunity regulation of *P. umbellatus* polysaccharides *in vitro* and *in vivo*. *Polyporus umbellatus* polysaccharides amplified cell proliferation rate and CD43+cell count of umbilical cord blood hematopoietic stem cells culture *in vitro*. Mice with transplanted umbilical cord blood hematopoietic stem cells and treated with *P. umbellatus* polysaccharides had the lowest death rate and shortest recorded recovery time. These polysaccharides amplify the hematopoietic stem cells, and these cells promote the immune and hematopoietic reconstruction of

transplanted mice (Pan *et al.*, 2008). Li *et al.* showed *P. umbellatus* polysaccharides induced phenotypic and functional changes in murine bone derived dendritic cells via toll-like receptor 4 (TLR-4). *Polyporus umbellatus* polysaccharides significantly stimulate the proliferation of mouse splenocytes and upregulated the expression of CD86 and CD11c in a dose dependent manner. The polysaccharide induces dendritic cell maturation and differentiation and then activates natural killer and Th1 cells to enhance immune responses. *Polyporus umbellatus* polysaccharides could also activate CD4+CD45RA+ T cells (Li *et al.*, 2010; Li & Xu, 2011a). A novel study also showed aqueously extracted polysaccharides from fermented mycelium of *P. umbellatus* increased the killing potency of natural killer cells of mouse spleen and promoted proliferation of mouse B and T cells (Sun & Zhou, 2014). Li and Xu studied the molecular mechanism of its immunostimulatory potency and immune responses of macrophages, using polysaccharides prepared from aqueous extract of *P. umbellatus*. The aqueous extract upregulated the activity of macrophages, while stimulating splenocyte proliferation and production of cytokines, as well as cytotoxic and inflammatory molecules. From experiments carried out using mice, it was concluded that the polysaccharides of *P. umbellatus* cause the increment of immune stimulating potency via TLR-4 activation of the signaling pathway (Li & Xu, 2011b).

Water-soluble polysaccharides extracted from the fruiting body of *P. umbellatus* have the potential to activate B cells, macrophages and dendritic cells. Depletion of branches of the polysaccharides causes a substantial reduction in the ability not only to activate B cells *in vitro,* but also to elicit specific IgM production *in vivo*. Virtually all healthy human subjects possess high-titer circulating antibodies that work against the ZPS backbone, suggesting that ZPS epitope is shared by environmental antigens capable of eliciting adaptive humoral responses in the population (Dai *et al.*, 2012). β-Glucans are major polysaccharide constituents of *P. umbellatus* (Miyazaki & Oikawa, 1973; Jong & Birmingham, 1990) and considered to be valuable biological response modifiers for their ability to enhance the activity of immune cells, aid in wound healing and prevent infections (Dai *et al.*, 2012). Polysaccharides extracted from *P. umbellatus* possess immunomodulatory activities (Peng *et al.*, 2012). Aqueously extracted polysaccharides, GUMP-1-1 and GUMP-1-2 could remarkably increase the spleen weight and splenocyte proliferation of hepatoma H22 tumor bearing mice, as a consequence improve the immune response (Bi *et al.*, 2013). These results indicate that the *P. umbellatus* immune activities are most probably due to its polysaccharides.

Diuretic effect

Sclerotia of *P. umbellatus* have been used from a long time in Traditional Chinese Medicines for urological disorders (Zjawiony, 2004; Sekiya *et al.*, 2005; Zhao *et al.*, 2009f). They are prominently used as herbal remedy with or without the combinations of other medications, in order to treat patients suffering from chronic kidney diseases (Zhao *et al.*, 2012b). In particular, an aqueous extract of dried sclerotia is traditionally used for diuresis (promoting urination) (Ying *et al.*, 1987; Jong & Birmingham, 1990; Yuan *et al.*, 2004; Wu, 2005; Zhao *et al.*, 2010e; Xing *et al.*, 2012).

The sclerotia of *P. umbellatus* is considered as an urination promoting component in traditional Chinese formulas such as Gorei-san (五苓散), Chorei-to (猪苓湯), Irei-to (胃苓湯) Bunsyou-to (分消湯), and Inchingorei-san (茵陳五苓散), (Yuan *et al.*, 2004; Zhao *et al.*, 2009f) which promote the diuretic

process and govern water metabolism. This signifies a relative diuretic effect causing reinforcement of water pathway functions capable of draining dampness, as is remarked in the ancient work *Shennong's Herbal Classics* (神農本草経). Furthermore, the sclerotium boosts the urination process and prevents dampness which in turn prevents further results in preventing edema, scanty urine, vaginal discharge, cloudy painful urinary dysfunction, jaundice and diarrhea (Wang *et al.*, 1964; Ying *et al.*, 1987; Yuan *et al.*, 2004; Xing *et al.*, 2012; Zhao *et al.*, 2012b). Clinical studies have confirmed that *P. umbellatus* is an effective diuretic medicine for the treatment of pyelonephritis, nephritis and urologic calculi without side effects (Jyothi, 2013).

Wang *et al.* demonstrated the diuretic effect of *P. umbellatus* by administrating decoction of sclerotium to un-anesthetized dogs, which increased urine output and excretion of sodium, potassium, and chloride ions (Wang *et al.*, 1964). Through experiments done with mice, it was concluded that the anti-aldosteronic effect of ergosta-4,6,8(14),22-tetraen-3-one (ergone) contained in *P. umbellatus* sclerotia promotes urination (Yuan *et al.*, 2004). Ergone isolated from many mushrooms has been shown to possess antialdosteronic diuretic properties (Lindequist *et al.*, 2005) and proven to prevent progression of renal injury and subsequent renal fibrosis (Zhao *et al.*, 2012a).

In oral dozes of *P. umbellatus* administered in Chinese Traditional Medicine treatments, (Wu, 2005) ergone is absorbed via the oral route (Yuan *et al.*, 2004). Although it was previously shown that ergone does not significantly affect urinary sodium and potassium excretion in normal rats (Yuan *et al.*, 2004), Zhao *et al.* demonstrated that ergone increased potassium, sodium and chloride excretion and the volume of urine excreted in normal rats (Zhao *et al.*, 2009e). In addition to ergone, the ergosterol and D-mannitol components included in *P. umbellatus* facilitate the diuretic process. Ergoneis the strongest diuretic drugs among these components (Zhao *et al.*, 2009e).

A patent has been issued for ergone as a diuretic drug (Zhao *et al.*, 2009b). Ergone contained in *P. umbellatus*, normalizes nitrogenous products and regulation of ions in unbalanced blood and urine of mice. Early administration of ergone prevents progression of renal injury and subsequent renal fibrosis in aristolochic acid nephropathy (Zhao *et al.*, 2011c). Although it is time dependent, with a sharp difference in metabolic profile, ergone present in *P. umbellatus* aids recovery from chronic renal failure in rats (Zhao *et al.*, 2012b). Kawashima *et al.* introduced a Choreito Japanese Traditional Medicine, which comprises sclerotia of *P. umbellatus*, as a successful treatment for renal disorders (Kawashima *et al.*, 2012).

Antioxidant and free radical scavenging activity

Free radical-induced oxidation is affective in the pathological processes which cause prolonged and degenerative diseases, such as cardiovascular disease, cancer, diabetes, neurodegenerative disease and ageing (Gan *et al.*, 2010). These free radicals damage cells causing DNA mutations, protein inactivation, lipid peroxidation, and cell apoptosis (Gan *et al.*, 2010). Mushrooms play a significant role in the search for efficacious, non-toxic substances, with free radical scavenging activity because the protein content of the polysaccharide extracts has a direct effect on free radical scavenging activity (Liu *et al.*, 1997). Due to the high protein content in the polysaccharide extract of fruiting body of *P. umbellatus,* it exhibits a strong superoxide and moderate hydroxyl radical scavenging activity when compared to *Coriolus versicolor, Ganoderma lucidum, Lentinula edodes,*

Schizophyllum commune, Tremella fuciformis, Trichloma lobeyense and *Volvariella volvacea* (Liu *et al.*, 1997). These studies signal that the anti-oxidant activity of *P. umbellatus* polysaccharides have the potential to treat oxidative stress related diseases.

Anti-oxidative activity plays an important role in atherogenesis, inflammation and ageing (Sekiya *et al.*, 2005). It was shown that *P. umbellatus* exhibits anti-oxidant and free radical scavenging activity in human red blood cells (RBC) *in vitro* and *in vivo* in mice (Sekiya *et al.*, 2005). 2,2-azo-bis(2-amidinopropane)dihydrochloride, free radical initiator induces hemolysis of RBC, while aqueous extracts of *P. umbellatus* inhibit this activity. Further they demonstrated that the two triterpenes, polyporusterones A and B present in a aqueous extract of *P. umbellatus,* exhibit inhibitory activities against free radical induced hemolysis of red blood cells *in vitro*. The antioxidative effect was dose-dependent and *P. umbellatus* strengthens the antioxidative effect of plasma *in vivo*. Results of *in vivo* tests indicated that *P. umbellatus* inhibited the free radical generation dose dependently. The free radical scavenging activities of a group of rats, treated *P. umbellatus* were significantly higher than the control group (Sekiya *et al.*, 2005).

Gan *et al.* evaluated the anti-oxidant activity and total phenolic contents of Chinese medicinal plants including *P. umbellatus*, which are used in treating rheumatic diseases. These evaluations were deduced using ferric-reducing antioxidant power and Trolox equivalent antioxidant capacity assays, and the values obtained for *P. umbellatus* were lower than other plants. They showed that, the phenolic compounds generate major increases in anti-oxidant capacity, while the polysaccharides of *P. umbellatus* showed anti-oxidant activity, although the phenolic content of *P. umbellatus* is lower (Gan *et al.*, 2010).

One of the antioxidant mechanisms of *P. umbellatus* was demonstrated using experiments on mice livers. Polysaccharides of *P. umbellatus* are able to suppress hepatic lipid peroxidation by increasing hepatic malondialdehyde: a major reactive aldehyde that is formed in the degradation of polyunsaturated lipids catalyzed by reactive oxygen species (Nielsen *et al.*, 1997). These polysaccharides also increased hepatic levels of glutathione which is an endogenous non-enzymatic antioxidant and major antioxidant such as superoxide dismutase, glutathione peroxidase, catalase in carbon tetrachloride treated mice together with the up regulation of their mRNA expression (Peng *et al.*, 2012). Free radical activity of the recently isolated GUMP-1-1 and GUMP-1-2 polysaccharides was investigated using a *P. umbellatus* aqueous extract (Bi *et al.*, 2013). During investigation, GUMP-1-2 exhibited a strong scavenging activity upon hydroxyl and superoxide free radicals, while in GUMP-1-1it was weak. The scavenging effect of GUMP-1-2 was dose dependent and exhibited significant increment on superoxide free radicals at a concentration of 0.8mg/ml. The high ironic acid content and average molecular weight of GUMP-1-2 are causes of this antioxidant activity (Bi *et al.*, 2013).

Hair growth

Polyporus umbellatus significantly increases regrowth of hair of mice (Inaoka *et al.*, 1994). 3,4-dihydroxybenzaldehyde extracted from sclerotium of *P. umbellatus* has a high potential to stimulate the regrowth of hair (Inaoka *et al.*, 1994). Ishida *et al.* identified hair regrowth promoting compounds as polyporusterones A, B which were previously isolated by Ohsawa *et al.* (Ohsawa *et al.*, 1992) and a new compound, acetosyringone (Ishida *et al.*, 1999b). Among

these, polyporusterone A is said to be more effective in mammals and the crystal structure has been analyzed further (Ishida *et al.*, 1999a).

Anti-viral activity

Combined administration of polysaccharides from *P. umbellatus* and *Salvia miltiorrhizae* increases normalization rate of alanine transaminase and negative conversion rate of HBeAg in patients with chronic hepatitis B (Xiong, 1993). Polysaccharides of *P. umbellatus* have the potential to cure chronic hepatitis B virus. These polysaccharides induce an effect upon the clearance of serum hepatitis B antigen and hepatitis B virus DNA and thereby present a possible cure for chronic hepatitis B (Liu *et al.*, 2001). Due to immune modulatory effects, polysaccharides of *P. umbellatus* have been widely used to treat hepatitis B or C together with antiviral drugs in the form of injections or tablets in China (Peng *et al.*, 2012). Hao *et al.* introduced a traditional Chinese medicine, which includes polysaccharides of *P. umbellatus*, plant and fungi ingredients and bears a higher curative rate and rapid action against AIDS. According to the authors, it is a non-toxic drug with no side effects (Hao *et al.*, 2011). Zhan patented a traditional Chinese medicine with extracts of *P. umbellatus* and related herbs, which inhibits the reproduction of the HIV and improves the CD4 immunocyte level (Zhan, 2012). Zhang *et al.* discovered a traditional Chinese medicine which improves the CD4+T lymphocyte level against the AIDS virus and exhibits good anti-inflammatory and abirritation effects (Zhang *et al.*, 2012c).

Anti-bacterial activity

Polyporus umbellatus is used in China as an antibacterial drug (College, 1982). *Polyporus umbellatus* exhibits strong inhibitory activity *in vitro* against urogenital *Chlamydia trachomatis* (Li *et al.*, 2000), the most common bacterial sexually transmitted disease (Black, 1997). Extract of fermentation broth of *P. umbellatus* shows antibiosis against *Bacillus subtilis, Candida tropicalis, Escherichia coli, Fusarium graminearum, Saccharomyces cerevisae,* and *Staphylococcus aureus* (Sun & Zhou, 2014; Wang *et al.*, 2009). This bacteriostasis substance is similar to non-water-soluble type II antibiotics and sensitive to acid alkali and unstable to heat. This poorly stable antibiotic-like substance and ester-peptide antibiotic shows similar absorption pattern in UV spectrum (Wang *et al.*, 2009).

Anti-protozoal activity

Polyporus umbellatus showed inhibitory activity against protozoan parasite *Plasmodium falciparum*, one of the main causative agents of malaria in humans (Lovy *et al.*, 2000).

Cultivation

Cultivation for sclerotium production

Due to the perceived medicinal value of *P. umbellatus,* the commercial need for sclerotia has greatly increased in recent years. The result is that the wild source of *P. umbellatus* will soon be exhausted (Guo *et al.*, 2002). The decrease in wild sclerotial production and the increase in demand have stimulated interest in the search for substitutes for the natural source of sclerotium (Liu & Guo, 2009). However, to face the high demands of the global market, it is necessary

to cultivate strains of *P. umbellatus* under artificial or semi artificial growth conditions (Huang & Liu, 2007; Zhou *et al.*, 2007).

Sclerotia of *P. umbellatus* were successfully cultured in China co-inoculated with *A. mellea* (plantation, 1978). This technique is not useful for large scale production due to slow growth and the difficulty of obtaining sufficient seed sclerotia from nature for artificial cultivation (Guo *et al.*, 2002). Guo and Li reported that the hyphae isolated from basidiospores of *P. umbellatus* successfully formed white or brown sclerotia in solid and liquid medium (Guo & Li, 1982). Wang *et al.* also obtained sclerotia in liquid medium (Wang *et al.*, 1982). However, the methods were limited to laboratory conditions and unable to meet the requirements for mass production (Guo *et al.*, 2002). Guo and Xu developed a technique for cultivating sclerotia of *P. umbellatus* (Guo & Xu, 1993). Guo *et al.* produced sclerotium in an artificial media using a dual culture method (Guo *et al.*, 2002). They demonstrated that *P. umbellatus* could not form sclerotia without *A. mellea.* Xing and Guo artificially developed the sclerotium of *P. umbellatus* in a wheat bran medium and showed that the artificially developed and wild sclerotia are morphologically very similar (Xiaoke & Shunxing, 2005). The studies concluded that *P. umbellatus* favours aerobic conditions and therefore the burying depth of inoculum plays a significant role in its cultivation (Choi *et al.*, 2003). Sclerotia cultivated using root inoculation develop more quickly than those cultivated when buried. Root inoculation has been found more appropriate for the development of the sclerotia of *P. umbellatus* due to many beneficial factors such as the simplicity of the inoculation process, reduced cultivation period and facility of harvest (Choi *et al.*, 2003). Yang cultivated *P. umbellatus* in a sawdust-based medium. It is a method which has both a brief productive cycle and a high survival rate, and could be tried at the industrial level (Yang, 2003).

Liu patented a method for cultivating *P. umbellatus* using basswood dibbling and an implanting method or rot plant embedding method. These methods enable the sclerotium to develop and immediately form fruiting bodies without the support of any other companion fungus. The strong resistance, impurity repulsing ability, lack of seasonal limitation and cheapness are significant benefits of this method (Liu, 2004). Guo *et al.* patented three growth media where sclerotial formation equivalent to that of wild sclerotia obtained from the mycelia of *P. umbellatus* are produced; they proposed these as industrially useful methods with high sclerotia formation ability (Guo *et al.*, 2007).

It was found that *P. umbellatus* sclerotium could be proliferated with high efficiency in a short period of time, through symbiotic culturing with *A. mellea* (Kikuchi, 2007). The method of cultivating *P. umbellatus* with *A. mellea* in the natural environment under applicable environmental conditions improves the quality and yield of artificially cultured *P. umbellatus* (He *et al.*, 2007). A low cost method which can rapidly produce the sclerotia of *P. umbellatus* - using corn grits and wood chips and/or blocks of media inside polythene bags - was developed (Jin *et al.*, 2010). Zhang introduced a simple, low cost method of growing *P. umbellatus* in humic acid media with prepared natural organic substances (Zhang, 2011). Lee *et al.* introduced a method for the cultivation of *P. umbellatus* using agricultural and industrial by-products but without pesticides and heavy metals and avoiding the use of soil (Lee *et al.*, 2011). A method of inter-planting *Glastrodia elata* with *P. umbellatus,* after culturing *A. mellea* with *Glastrodia elata*, was reported (Sun *et al.*, 2011). Xue introduced an artificial cultivation method by imitating the growing mechanism of the wild sclerotia. This method generated a higher production rate in a short period of time and produced better-purified sclerotia

(Xue, 2012). A large-scale cultivation method aimed at producing higher yields, using a tank type pit inside forests was described by Zhang (Zhang, 2012b).

The carbon source (the type of medium used in producing *P. umbellatus* sclerotia artificially) is significant in the induction of sclerotium formation (Cheng *et al.*, 2006). It was shown that for the formation of sclerotia an appropriate medium is malt extract agar modified with GPC (Glucose, Peptone, Corn steep liquor), and 18-25° optimum temperature (Cheng *et al.*, 2006). It was confirmed that fructose and peptone were the best carbon and nitrogen sources for sclerotium formation (Liu & Guo, 2009). The carbon source affects the formation of sclerotia, while the nitrogen source influences morphological transformation. Vitamins and minerals are not essentially needed for the sclerotial formation (Liu & Guo, 2009). Xing *et al.* highlighted that the carbon source and an initial high pH are essential factors for sclerotial formation at low temperature in sawdust media (Xing *et al.*, 2013b). They concluded that mycelia subjected to environmental stress by exposure to low temperatures and enhanced reactive oxygen species can induce higher sclerotial formation and polysaccharide content than in nutritional agar medium (Xing *et al.*, 2013b). Presently cultivation of *P. umbellatus* is being carried out in China, through artificial infection of *Armillaria* (Kikuchi, 2007; Kikuchi & Yamaji, 2010; Xing *et al.*, 2012; Zhou *et al.*, 2012; Xing *et al.*, 2013b).

Cultivation for mycelium production

Suitable carbon and nitrogen sources for mycelial growth and extracellular polysaccharides production are glucose and yeast extract (Gu *et al.*, 2001). Of six carbohydrates, fructose, glucose, sucrose and starch significantly promoted mycelial growth and starch was most effective for the production of mycelium (Lee *et al.*, 2007). A submerged culture media was optimized by Lee *et al.* for production of ergone using mycelium of *P. umbellatus,* wherein the mycelium and ergone production were significantly increased by co-culturing *P. umbellatus* with *A. mellea* (Lee *et al.*, 2007). Cui *et al.* discovered a method to increase the yield of mycelium of *P. umbellatus* in a short time, by pre-fermenting the growing media with *A. mellea*. This is a low cost method which produces high amounts of polysaccharides and minimizes heavy metal contents (Cui *et al.*, 2007). Guo *et al.* patented a low cost medium which contains wheat bran and glucose that boosts higher mycelium yield and polysaccharide content (Guo *et al.*, 2008). Huang and Liu investigated the optimum conditions required for the growth of *P. umbellatus* mycelium, and for production of exopolysaccharides. They observed that glucose and yeast extracts are the best carbon and nitrogen sources, and pH5 and 6 are optimum (Huang & Liu, 2008). Xing *et al.* investigated the environmental factors, using optimum mycelium growth of *P. umbellatus* at pH8 in dark conditions and temperature of 25°C and a maximum polysaccharide content was produced at pH8 –10 at 5°C (Xing *et al.*, 2012).

Although yeast and peptone were found to be the best nitrogen sources for *P. umbellatus*, the costs are prohibitive. Therefore their use for fermentation on an industrial scale is not viable (Chen *et al.*, 2010a). Chen *et al.* used a submerged culture fermentation method, using whey as a cheap alternative nitrogen source which facilitated higher mycelium growth and high exopolysaccharide production. The maximum biomass and exopolysaccharides production obtained was from 3% glucose and 50% whey broth (Chen *et al.*, 2010a). Table 1 lists some of the methods used for cultivation and production of polysaccharides from *P. umbellatus*.

Table 1. Methods used for cultivation of sclerotia and production of polysaccharide derivatives from *P. umbellatus*. Abrreviations: asl = above sea level, eps =exopolysaccharide, mat=mean annual temperature

Type of the method		*Materials*	*Host used for experiment*	*Yield*	*Time taken*	*Mode*	*References*
	1	Both mycelia (*P. umbellatus* and *A. mellea*) plugs were cultured in Sawdust wheat bran medium in flask grit medium in flower pots	 *Quercus variabilis*	Sclerotia	 30 days 90-120 days	Laboratory	(Guo *et al.*, 2002; Xiaoke & Shunxing, 2005)
	2	Sclerotia attached lateral root of host and *A. tabescens*, or *A. mellea*pre-inoculated wood logs	*Castanea crenata* *Quercus mongolica*	Sclerotia weight increased 7-40 times	10 months	Outdoor	(Choi *et al.*, 2003)
	3	Sclerotia with *A. mellea* or *Armillaria* sp. pre-inoculated wood logs	None	Sclerotia weight not increased significantly	12 months	Outdoor	(Choi *et al.*, 2003)
	4	*A. mellea* inoculated sticks with *P. umbellatus* sclerotia slices as seeds + tree leaves in a dug pit (70 cm × 30 cm) in forest. Cellar covered by soil	Broad leaved wood stick (unknown sp.) Diameter 8-12 cm, length 60 cm	Sclerotia yield unknown	Unknown	Scrub forest 1000-1800 m, asl, mat.11-12°C, soil pH 5-6.5	(He *et al.*, 2007)
With support of *Armillaria* sp.	5	1st stage: Corn flour, sucrose or glucose, beef extract, water and agar 2nd stage: 1st stage culture + *A. mellea* corn grits, wood chip and/or wood block 3rd stage: Sub cultured 2nd stage in polypropylene bagwith2nd stage culture medium	Broad leaved wood (unknown sp.)	Sclerotia yield unknown	 30-45 days	 20-25°C	(Jin *et al.*, 2010)
	6	Culturing of *A mellea*, in *G. elata* seeds, sowing *P. umbellatus* and those seeds layer by layer	*G. elata*	Sclerotia yield unknown	Unknown	Outdoor	(Sun *et al.*, 2011)
	7	Sand, wood chips with *A. mellea* pre-inoculated wood and *P. umbellatus* in boxes + liquid fertilizer	Unknown wood sp.	Yield unknown	Unknown	Indoor (under controlled temperature and humidity)	(Fan, 2014)
	8	Materials (bagasse or corncob media + wheat bran, corn powder, lime, and/or sugar, water) pre fermented with *A. mellea* and inoculated *P. umbellatus* in plastic bags	Unknown	eps yield unknown	5-7 months	Indoor18-32°C	(Cui *et al.*, 2007)

Table 1. Methods used for cultivation of sclerotia and production of polysaccharide derivatives from *P. umbellatus*. Abrreviations: asl = above sea level, eps =exopolysaccharide, mat=mean annual temperature *(continued)*

Type of the method		*Materials*	*Host used for experiment*	*Yield*	*Time taken*	*Mode*	*References*
	9	Starch, fructose, peptone, formic acid, KH_2PO_4, $MgSO_4$, $FeSO_4$, yeast extract, media 25°C, pH 4.5(liquid medium)	None	Dry mycelium yield 3.5 g/l, Ergone 86.9 µg/g of dry mycelium	15 days	Laboratory 25°C	(Lee *et al.*, 2007)
Without support of *Armillaria* sp.	1	Sclerotia initially formed on PDA and after growing on sawdust bran medium	None	Sclerotia max weight 30 g	25 days on PDA, about 70-90 days on sawdust	Indoor	(Yang, 2003)
	2	Cultured on PDA and then cultivated on sawdust, bran, rice sweets, and chaff medium	None	Fruiting body			(Liu, 2004)
	3	Cultured on PDA Next in a liquid media Then in three solid media as follows. 1. glycerol, peptone, corn steep liquor, agar, water 2. mannitol, peptone, corn steep liquor, agar, and water 3. sawdust (or wheat stalk, corn stalk, or corn cob), soybean cake powder, glycerol, corn steep liquor, and water	None	Sclerotia yield unknown	30-50 days 12-20 days 25-50 days 25-50 days 30-120 days		(Guo *et al.*, 2007)
	4	Fructose 50.0 g/l, peptone 4.0 g/l, K_2HPO_4 1 g/l, KH_2PO_4 0.46 g/l, $MgSO_4$ 0.5 g/l, vitamin $B_1$0.05 mg/l, agar 10 g/l, deionized water		5.40 g of sclerotial weight/100 g substrate	30-40 days	Laboratory	(Liu & Guo, 2009)
	5	Sawdust, cottonseed hull, brewers grain etc. medium cultured in a box, a paper bag or a bottle on the ground		Yield unknown	Unknown	Indoor	(Lee *et al.*, 2011)
	6	Glucose 3.5%, peptone 3.0%, yeast extract 0.2%, KH_2PO_4 0.3%, $MgSO_4$0.15%, and vitamin B_1 0.001%) + *P. umbellatus* broth concentrate 5-10% (pH 5.5) (liquid medium)		eps production 310 mg/ml	36 hours	Laboratory 25°C	(Zhou *et al.*, 2001)

Table 1. Methods used for cultivation of sclerotia and production of polysaccharide derivatives from *P. umbellatus*. Abrreviations: asl = above sea level, eps =exopolysaccharide, mat=mean annual temperature *(continued)*

Type of the method		*Materials*	*Host used for experiment*	*Yield*	*Time taken*	*Mode*	*References*
	7	Wheat bran, glucose, KH_2PO_4, $MgSO_4$ (liquid medium)		Myceliumeps yield unknown	18-30 days	Laboratory	(Guo *et al.*, 2008)
	8	Main media (glucose 2.5%, peptone 0.5%, yeast extract 0.5%, KH_2PO_4 0.1%, $MgSO_4$: $7H_2O$ 0.1%, and vitamin B_1 0.005%) + *P. umbellatus* broth concentrate7 (pH 5.5) (liquid medium)		Mycelia production 12.7 g/l	11 days	Laboratory (rotary shaker at 25°C, 100 rpm)	(Huang & Liu, 2007)
	9	glucose 3%, skim milk 0.2%, KH_2PO_4 0.1%, $MgSO_4$: $7H_2O$ 0.1%, and vitamin B_1 0.005% (pH 5)(liquid medium)		eps production 0.571 g/l	14 days	Laboratory (rotary shaker 100 rpm, at 25°)	(Huang & Liu, 2008)
	10	glucose 3%, whey broth 50%, KH_2PO_4 0.1%, $MgSO_4$: $7H_2O$ 0.1%and vitamin B_1 0.005% (liquid medium)		eps production 0.632 g/l	14 days	Laboratory (rotary shaker at 25°C, 100 rpm)	(Chen *et al.*, 2010a)
Unknown (with or without *Armillaria*sp.)	1	*P. umbellatus* (sclerotia as seeds) + humic acid media 5-7 parts + primary soil 3-4 parts by weight in dredging cellar (1.3-1.6 m × 1-1.3 m × 1-1.3m)		Sclerotia yield unknown		Dredging cellar built in slope land (15-35°C)	(Zhang, 2011)
	2	Tank type pit in forest Size of pit 30 cm × 80 cm × 3 m		Sclerotia can be harvested more than one time		Dwarf shrub forest land 1,000-1,500 m asl	(Zhang, 2012b)

Products

Due to the above mentioned medicinal effects, the edible mushroom *P. umbellatus* is used as a non-toxic and low cost bioactive ingredient for manufactured pharmaceutical products, and food supplements, having no side effects as well as in cosmetics and beverages

Medicinal products and dietary supplements

Tian *et al.* manufactured an injection composed of antitumor polysaccharides of *P. umbellatus*. Less than 3000 patients were used for clinical testing of this product and no significant side effects were recorded (Tian *et al.*, 1980). Kim and Lee produced a medicine incorporating *P. umbellatus* which inhibits immune-modulation and tumor growth. This medicine promotes the T-cells activity, increases production of interferon-γ and interleukin-6 and inhibits angiogenesis and tumor growth (Kim & Lee, 2006). An antitumor drug with *P. umbellatus* and other herbs which has synergistic effects and can be made into oral formulations and injections was produced (Wei, 2007). Li and Wang manufactured a probiotic with *P. umbellatus* polysaccharides, which improved immunity in tumor bearing mice and nutritional conditions of cancer patients (Li & Wang, 2009). Tien-Hsien liquid (THL), which is used as an anti-cancer dietary supplement is a herbal mixture of *P. umbellatus* extracts and 13 other Chinese herbs. The antitumor and cytotoxic properties of *P. umbellatus* cause induction of apoptosis of human cancer cells (Sun *et al.*, 2005). MycoPhyto Complex (Plate 1) is an anticancer dietary supplement, which includes a blend of mycelia of *P. umbellatus* and five other mushroom species. It has potential therapeutic value in the treatment of invasive human breast cancer (Jiang & Sliva, 2010). Using *P. umbellatus,* a pill with anti-tumor and anti-aging effects was introduced by Chen *et al.* (Chen *et al.*, 2012). Zhang manufactured a tablet with 30-80% *P. umbellatus* polysaccharides which minimizes adverse effects and maintains fast absorption. This tablet is able to adjust immunity function and can be used as adjuvant medicine in bladder cancer mice (Zhang, 2012a).

Cho *et al.* developed a red ginseng extraction product including *P. umbellatus*, which effectively improves sexual enhancement with powerful ejaculation (Cho *et al.*, 2004). Kuok *et al.* manufactured a herbal product which includes *P. umbellatus* as an ingredient preventing and treatments of prostate disorders including prostatitis, benign prostate hyperplasia, prostatic carcinoma, tumor, elevated blood levels of prostate specific antigen and irritative voiding symptoms such as nocturia and excessive frequency and urgency of urination (Kuok & Ly, 2004). A medicinal composition which contained *P. umbellatus* is used for treating gynecological inflammation such as pelvic inflammation, chronic pelvic inflammatory disease, ovarian cystitis, colpitis, cervicitis and adnexitis. Apart from relieving inflammation it can be used to stop bleeding, and release smooth muscle spasms in the uterus (Wang & Hou, 2007).

A food supplement which includes *P. umbellatus* and some other components was produced by Takeda, and was used as a treatment for high cholesterol, diabetes, hypertension, and liver problems (Takeda, 2005). The product of Cho *et al.* has been effective also in preventing arteriosclerosis, hypertension and diabetes (Cho *et al.*, 2004). Similarly, Chai *et al.* manufactured a health care product, which can improve hypoglycemic, hypolipidemic and immunity (Chai *et al.*, 2012).

A herbal extract including *P. umbellatus* which can repress the level of acetaldehyde in blood was produced; this product represses the level of acetaldehyde in alcoholic digestion and heals hangover (Kim *et al.*, 2010).

A herbal drink, with *P. umbellatus* was introduced by Hong which alleviated alcohol hangover and recovered the liver function (Hong, 2010). Li introduced a beverage, which can relieve alcoholism and nourish the liver (Li, 2012).

Wang and Wang obtained a patent for Chinese medicine compositions which include *P. umbellatus*, and these productions show therapeutic effect upon digestive system disorders and nausea, vomiting, dizziness, and hypotension (Wang & Wang, 2010).

Qu produced a pill, which includes *P. umbellatus* polysaccharides, for treatments of Hepatitis B (Qu, 2005). A sulfate compound, containing *P. umbellatus* and with an anti-hepatitis B virus activity, was synthesized (Liu *et al.*, 2006). A Chinese medicine composition, which includes *P. umbellatus* has been used for treatments of hepatitis and fatty liver (Zhang, 2007). A medicinal composition with *P. umbellatus* can be effective in promoting blood circulation and diuresis, relieving pain, killing *Escherichia coli* and *Candida albicans* (Wang & Hou, 2007). Miao *et al.* produced an immune protection agent against fowl infectious bursal disease virus, using *P. umbellatus* (Miao *et al.*, 2010).

Market research and development is taking place on *P. umbellatus* capsules, injections, lyophilized powder agent and many preparations. Zhang *et al.* registered a Chinese patent for manufacturing powder and polysaccharides using the *P. umbellatus* mycelium as pharmacological products, i.e., granules, capsules and oral liquids (Zhang *et al.*, 2005). The capsule disintegration is slow and thereby the biological use is said to be low; Injection is in frozen-dry powder form and production costs are high and therefore the medicine is not cost effective. Tablets with high speed disintegration and dispersion are more convenient and have high biological use (Zhang *et al.*, 2012a). Patent certifications have been issued to many Chinese and Korean medicinal compositions which contain *P. umbellatus* as a major component. These medicinal compositions are used to treat many human diseases. Accordingly, *P. umbellatus* is used in Chinese medicinal compositions for treatments of condyloma (Qin, 2013), Obesity (Fang *et al.*, 2012; Ran, 2013; Wang, 2013a; Wang, 2013b), abdominal distention caused in the early stages of Traumatic injury, relieving constipation and swelling of limbs (Xia *et al.*, 2013), common cold in young children (Zhang *et al.*, 2013a), the treatments and prevention of facial paralysis (Liu, 2013), throat pain and oral ulcers (Sun, 2013b), diabetes mellitus (Ding & Dai, 2013; Lee *et al.*, 2013; Sun, 2013a; Sun, 2014), glomerulonephritis (Guo, 2012), chronic nephritis (Li, 2013a), pyelonephritis (Yan *et al.*, 2013), the treatments and prevention of liver related diseases such as fatty liver (Sun, 2013c; Zhou, 2013), chronic hepatitis and cirrhosis (Fu *et al.*, 2013; Hu & Lu, 2013; Xu, 2013; Zhao *et al.*, 2013), the treatments of chronic renal failure (Wang, 2013c), nephropathy (Guo, 2013), diarrhea (Ma, 2013b; Li *et al.*, 2013), leg ulcers (Qiu & Teng, 2013), infantile bronchial asthma causing due to cold fluid- retention and fever (He & Xie, 2013), inflammation and immune dysfunction caused by multi resistant bacteria infections (Kim, 2012; Zhang *et al.*, 2013b), urinary stone (Li, 2013c), damp-heat type gallstone (Ma, 2013a), chronic enteritis (Zou, 2013), acute mastitis causing due to alcoholism (Yuan, 2013), acute mastitis due to milk stasis (Xing, 2013), chronic renal insufficiency (Xin, 2013), hepatitis B (Li, 2013b), nodular prurigo (Zeng, 2013), cystitis (He, 2013; Yuan *et al.*, 2012), macular hemorrhage of high myopia (Guan, 2013), hydroperitoneum (Shao & Wu, 2013), eczema (Zhan & Zhan, 2013), senile retinopathy and macular degeneration (Hu *et al.*, 2013), dysmenorrhea and uterine bleeding (Wang, 2014), benign prostatic hyperplasia and urinary disorders such as urinary urgency, difficulty urinating, incontinence, urinary retention, hematuria (Zeng, 2014) Dietary supplements which contain *P. umbellatus* and their beneficial effects are shown in Table 2 and Plate 1.

Table 2. Dietary supplements with *P. umbellatus* alone or in mixtures. The co-authors of the present paper have not confirmed these claims

Name	*Category*	*Tablet/Capsule*	*Doze*	*Ingredients*	*Function*	*Certified by*	*Web page*
Complexe Hepato Bio	Dietary supplement	1000 mg Capsules	1 to 2 capsules per day	*P. umbellatus* mycelium 20%	Enhance liver function	Certified according to EU Reg. 834/07	http://www.nature-et-forme.com/complexe-hepato-bio/p466#info_tabs_1
Mushroom 6 Immune Support Complex		Capsules	1 to 2 capsules 1-3 times daily	*Cordyceps sinensis, Ganoderma lucidum, Lentinula edodes, Poria cocos, P. umbellatus, Trametes versicolor,*	Relief of inflammatory conditions, supporting immune function, supporting white blood cell production and providing antioxidant protection		http://www.bioceuticals.com.au/product/preview/Mushroom-6/print
Mycophyto® Complex	Dietary supplement	Powder/ Capsules	4g-8g or 6 capsules/ 1-3 times daily	*Agaricus subrufescens, Coriolus, Ganoderma, Cordyceps sinensis, P. umbellatus,* Maitake	Strength immune system		http://www.choosecra.com/store/supplements/myco-phyto.html
Polyporus-MRL	Dietary supplement	500 mg Tablet		*P. umbellatus* mycelium and primordia	Supports the immune system	100% Organic in the USA by Quality Assurance International and EU Council Regulation (EEC) No. 2092/91	http://www.mycologyresearch.com/products.asp?product=Polyporus
P. umbellatus, 180 capsules		300 mg Capsules	Up to 3capsules per day	*P. umbellatus* fruitbody	antitumor effects, diuretic effects, antioxidant and free-radical scavenging activity, immune system enhancement, hair growth, antiviral effects	Good manufacturing practices quality assured	http://www.shopssl.de/epages/es105220.sf/en_GB/?ObjectPath=/Shops/es105220_Prime-Visions/Products/PU180
P. umbellatus Extract		500 mg Capsules		*P. umbellatus* sclerotium	Enhances the body's immune response to an antigen		http://www.activehealth.co.uk/Polyporus-Umbellatus-Extract__p-70.aspx
Polyporus Fungal Body	Dietary supplement	1000 mg Capsules		*P. umbellatus* mycelium *Poria cocos* mycelium	Unknown		http://dsld.nlm.nih.gov/dsld/Ingredient.jsp?db=adsld%2C&item=POLYPORUS+FUNGAL+BODY
P. umbellatus – HdT	Food supplement	450 mg Capsules	1-2 capsule per day		Suitable for diabetics and people who suffer from celiac disease		http://www.hifasdaterra.com/index.php/extracto-ecologico-polyporus-hdt/
Zhu Ling (*P. umbellatus*) Hot-water extract		425 mg Capsules		*P. umbellatus* sclerotium	Diuretic, anticancer activity		http://www.mushroomnutrition.com/polyporus/polyporus-mn-60-cab.html

Fig. 1. Examples of *Polyporus umbellatus* – containing products. **1.** ComplexeHepato Bio; **2.** Mushroom 6 Immune Support Complex; **3.** Myco-Phyto Complex; **4.** Polyporus-MRL; **5.** *Polyporus umbellatus*-HdT; **6.** *Polyporus umbellatus* Extract; **7.** Zhu Ling (*Polyporus umbellatus*) Hot water extract.

Cosmetics

Polyporus umbellatus is used for production of cosmetics. Tsuji *et al.* produced topical and bath preparations composed of *P. umbellatus* that prevent skin aging (Tsuji *et al.*, 1995), A product including *P. umbellatus* extracts inhibits testosterone 5α-reductase activity and antimicrobial activity against propionibacterium acnes, which can be used for acne prevention and treatment (Rang *et al.*, 2009), A herbal product of *P. umbellatus* with antioxidant, cell-activating, collagen synthesis-promoting effects for skin ageing prevention was produced (Yoon *et al.*, 2012), β(1→6) branched β(1→3) glucan as an active ingredient of *P. umbellatus* can deter skin aging, impart skin whitening effect and cure skin damage effectively (Du *et al.*, 2014; Hyde *et al.*, 2010). The β-glucan was also found promising as an active ingredient in anti-wrinkle activity, wound healing, antioxidant activity and moisturizing effect (Du *et al.*, 2014; Hyde *et al.*, 2010). Therefore *P. umbellatus* has a cosmetics producing potential.

Food and beverages

Due to the promising and enduring effects of *P. umbellatus* as a medicinal mushroom, it is used in the manufacture of various foods and beverages. Wine produced with extracts of *P. umbellatus* as an ingredient, is a healthy drink, which includes amino acids and vitamins (Zhou *et al.*, 2008). A wine (Baek *et al.*, 2012a) and a rice extracts (Baek *et al.*, 2012b) which contained, mycelial extract of *P. umbellatus* bare anti-diabetic and anti-obesity effects. Yoon manufactured a sauce containing *P. umbellatus* (Yoon, 2012). Han produced an

instant tea powder consisting of edible mushrooms including *P. umbellatus*, claiming the potential to prevent respiratory tract infections (Han, 2013). A product of tea granules containing *P. umbellatus* is capable of nourishing blood and prevent anemia (Liu, 2014). Hot water preparations containing *P. umbellatus* are health improving beverages (Lee *et al.*, 2012).

Other *polyporus umbellatus*-containing products

Polyporus umbellatus is used in the production of fertilizers: Wu produced a fertilizer for the cultivation of *Daucus carota* using *P. umbellatus* (Wu, 2010) while Xu developed a fertilizer for the cultivation of *Arctium lappa* using *P. umbellatus* as a component (Xu, 2010).

Many suppliers who have been selling extract of *P. umbellatus* advertise online. Most of them are Chinese suppliers (Alibaba.com). Experiments proved that the polysaccharides content of these extracts vary between 10% and 40%. Fruiting body and sclerotium of *P. umbellatus* were used as source and extraction was done using solvents such as hot water and ethanol resulting in a final greyish brown powdery product. Supplying capability varies from 200kg to 200 tons per month. Under proper storage conditions these powders have a long shelf life, up to 2 to 3 years (Alibaba.com).

CONCLUSION AND PERSPECTIVES

Mushrooms have long been valued by the mankind as a medicinal resource (De Silva *et al.*, 2012a; De Silva *et al.*, 2012b; De Silva *et al.*, 2013; Poucheret *et al.*, 2006; Wasser, 2002). Mushrooms or their extracts are used globally in the form of dietary supplements (Jiang & Sliva, 2010). Indeed, fungi form a major and largely untapped source of powerful new pharmaceutical products (Lo & Wasser, 2011; Poucheret *et al.*, 2006; Wasser, 2002) *Polyporus umbellatus* contains biologically active substances in cultured mycelium, cultured broth, fruit body and sclerotium. *P. umbellatus* has the potential to promote diuretic action, and as a medicinal treatment for many chronic and serious diseases. For example, *P. umbellatus* has the potential to treat cancers, which are the second largest cause of death in people (Daba & Ezeronye, 2003), HIV, *Chlamydia trachomatis* – the most common sexually transmitted diseases in the United States (Black, 1997) and Diabetes mellitus – causing 2.2 % of deaths in the world (De Silva *et al.*, 2012b; Lo & Wasser, 2011). In addition, *P. umbellatus* has shown anti-obesity (Baek *et al.*, 2012b) and anti-skin ageing (Tsuji *et al.*, 1995) properties without any side effects. Therefore with potential medicinal value *P. umbellatus* has great value in the global market (Huang & Liu, 2007).

Polyporus umbellatus can be used to produce exopolysaccharides and ergone. Exopolysaccharides produced from mushrooms have been shown to have special medical effects in clinical trials. In addition, polysaccharides can also be used in industrial applications such as emulsifying and foam stabilizing agents, food coatings and thickening agents (Chen *et al.*, 2010b).

Polyporus umbellatus is one of the most valuable medicinal mushrooms and widely used in east Asian countries such as China, Japan, Korea and Taiwan (Huang & Liu, 2007; Yin *et al.*, 2012). Nowadays the demand on *P. umbellatus* has increased drastically due to its promising effects (Zhou *et al.*, 2007). Taking Korea

as an example, the demand for *P. umbellatus* has increased year on year since they began to use it as an herbal medicine and as a result they now import it from China (Choi *et al.*, 2002). Wild sources of *P. umbellatus* are seriously depleted due to a lack of effective protection (Xing *et al.*, 2013b; Huang & Liu, 2007; Xiaoke & Shunxing, 2005) and over-exploitation due to demand on the global market (Yin *et al.*, 2012). It is therefore considered as an endangered medicinal fungus in China (Zhang *et al.*, 2012b).

In practice, it would take a long time to cultivate *P. umbellatus* in both solid and submerged cultivations (Chen *et al.*, 2010b). The fungus has a long lag phase and mycelial growth of *P. umbellatus* is much slower than that of other mushroom species (Huang & Liu, 2007). Artificial cultivation of *P. umbellatus* is time consuming and labour intensive (Huang & Liu, 2007). Cultivation of *P. umbellatus* via infection with *A. mellea* has been practiced over the past 30 years; this technique is restricted by a low proliferation rate, unstable yield and lack of natural sclerotia to serve as seeds (Xu *et al.*, 1998).

It is an unsolved problem that the sclerotium is not produced directly from the hyphae, which effectively impedes the production scale and the production efficiency of *P. umbellatus* (Xiaoke & Shunxing, 2005). It is necessary to develop efficient artificial cultivating methods for developing the sclerotia and fruiting bodies within shorter time periods to meet demand in the global market. Asexual propagation is signified as the main pathway followed in order to produce cultivated products of *P. umbellatus* (Zhang *et al.*, 2010a).

On the other hand *P. umbellatus* can be used sustainably by reducing overexploitation and preventing the depletion of natural habitats. *Polyporus umbellatus* grows successfully in forest ecosystems, while forest management practices such as tree cutting (specially host trees) interrupts the growth of the former (Kunca, 2011). *Polyporus umbellatus* is able to produce new sclerotia under appropriate conditions. Due to this it is possible to enhance the natural production by conserving natural habitat. It is also possible to make people aware that during the harvesting of sclerotia retaining some as seeds will allow the microhabitat to be reconstructed. Depletion of natural habitats undoubtedly checks the presence of this mushroom (Yin *et al.*, 2012).

Polyporus umbellatus is an edible medicinal mushroom of great interest for healthy people or patients mainly used by food, pharmaceutical and cosmetic industries. Many products are indeed developed from *P. umbellatus* mycelium, sclerotium and exopolysaccharides such as natural health foods and traditional medicine as well as food supplements used to prevent, support or cure several diseases.

Acknowledgements. We would like to thank Humidtropics, a CGIAR Research Program that aims to develop new opportunities for improved livelihoods in a sustainable environment, for partially funding this work. Kevin D. Hyde thanks the Chinese Academy of Sciences, project number 2013T2S0030, for the award of Visiting Professorship for Senior International Scientists at Kunming Institute of Botany. INRA (Project AGASIA of the regional program Bio-Asie), the project Value added products from Basidiomycetes: Putting Thailand's biodiversity to use (BRN049/2553), the National Research Council of Thailand (NRCT), projects – Taxonomy, Phylogeny and cultivation of *Lentinus* species in northern Thailand (NRCT/55201020007), Mae Fah Luang University project – Taxonomy, Phylogeny and cultivation of *Lentinus* species in northern Thailand (MFU/54 1 01 02 00 48), and Thailand Research Fund grant – Taxonomy, Phylogeny and biochemistry of Thai Basidiomycetes (BRG 5580009) are also thanked for supporting this study.

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