Chapter 6
Chemical and Bioactive Profiling of Wild Edible Mushrooms

Katarzyna Sułkowska-Ziaja, Katarzyna Kała, Jan Lazur, and Bożena Muszyńska

6.1 Introduction

6.1.1 Regulation of Secondary Metabolites Production in Fungi

Metabolism can be divided into two separate levels, basic metabolism and secondary metabolism. Basic metabolism is universal and applies to all species, because it is associated with substances that enable the implementation of basic life functions: carbohydrates, fats, proteins, nucleic acids-compounds that allow division, growth, breathing and reproduction, or necessary life processes. Secondary metabolism leads to the formation of compounds that may be useful for survival in adverse environmental conditions such as, for example, intense **UV radiation** or other (Brakhage and Schroeckh 2011). Mushrooms produce a number of secondary metabolites that play an important role in cellular processes such as transcription or cell-to-cell communication. Many of them have now been used as medicines; inter alia, **antibiotics** and immune suppressants. Examples are *Penicillum chrysogenum* used for the production of penicillin or immunosuppressive drugs, and lovastatin produced by *Tolypocladium inflatum* and *Aspergillus terreus*. Other examples are ergotamine synthesized by the genus *Claviceps* and gibberellins–plant growth hormones produced by *Fusarium fujikuroi* (Brakhage 2013).

Biotechnological methods, including mycelial cultures, are increasingly used in the studies of **secondary metabolites** of mushroom origin. They are a convenient alternative in acquiring biomass compared to sometimes hard-to-find material from the natural environment.

K. Sułkowska-Ziaja · K. Kała · J. Lazur · B. Muszyńska (✉)
Department of Pharmaceutical Botany, Faculty of Pharmacy, Jagiellonian University Medical College, Kraków, Poland

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The intensity with which they are produced, and consequently accumulated secondary metabolites in *in vitro* cultures, can be regulated, inter alia, with the substrate composition. The composition, which is optimal for the growth of the *in vitro* culture, does not always turn out to be suitable for the synthesis of secondary metabolites. For this reason, the optimization of the composition is usually performed separately in the event of the growth of culture and the synthesis of metabolites (Fox and Howlett 2008).

In numerous experiments, the accumulation of secondary metabolites may be affected by the concentration of sugars in the medium. Increased concentration of this group of compounds causes osmotic stress in the cells, which may result in increased production of metabolites (Brakhage 2013).

Another factor that affects the accumulation of metabolites is the total nitrogen content in the culture medium. This element in the medium is present in the form of $NO^{3-}$and NH^{4+} ions and the selection of their respective concentrations may have a positive effect on the number of secondary metabolites accumulated. Phosphorus is another important element important during the accumulation of metabolites. High concentration of phosphate ions favors an increase of **biomass**, but in many cases limits the accumulation of secondary metabolites. An effective method of increasing the production of secondary metabolites is the addition of precursors and elicitation.

Biosynthesis pathways of secondary metabolites are usually multi-step, and the individual steps run at different efficiencies. Increasing the synthesis of a given compound in *in-vitro* cultures can be achieved by the exogenous addition of precursors. According to this theory, all intermediate metabolite compounds found at the beginning of each pathway enables the biosynthesis of its products to be increased. The addition of a precursor to the culture medium often increases the biosynthesis of metabolites, using the feedback or shortening of the metabolic pathway. The given precursor must be a factor limiting the efficiency of the process, only then will it cause an increase in biosynthesis. An ideal precursor compound should be inexpensive and easily available to make its use cost-effective. Precursors that are often used to increase the synthesis of secondary metabolites are the amino acids from which tropane and indole alkaloids are synthesized. In the case of mycelial cultures, commonly used precursors of indole compounds are anthranilic acid and serine (Opoka et al. 2017).

The content of phenolic compounds, including phenolic acids, can be regulated by the addition of phenylalanine or tyrosinase.

The exact mechanism of elicitor's action has not yet been known. It is assumed that the activation of secondary metabolic pathways allows the body to survive under stressful conditions. Elicitors may, for example, be responsible for the induction of genes associated with synthetic pathways and the accumulation of secondary metabolites. Elicitors increase the production of secondary metabolites by using one or several mechanisms such as modulation of synthesis pathways, accumulation of compounds or limitation of their degradation rate (Palazón et al. 2003).

An example of an elicitor used in mycelial cultures is methyl jasmonate. It has been tested, among others, for the production of aflatoxin b-a carcinogenic

metabolite synthesized by some *Aspergillus* species. Concentration of methyl jasmonate had no significant effect on mycelial growth; however, it significantly influenced the increase in aflatoxin synthesis (Meimaroglou et al. 2009).

6.1.2 Main Groups of Bioactive Substances Which Are Occurring in Edible Mushroom

6.1.2.1 Carbohydrates

Trehalose is a disaccharide which is a reserve material in mushrooms and also has properties that protect cells against protein denaturation. In a subarachnoid hemorrhage model using RAW264.7 macrophages and vascular endothelial cells (HUVEC), it was shown that trehalose can inhibit the expression of **proinflammatory** proteins i.e., cyclooxygenase-2, inducible nitric oxide synthase iNOS, and inhibits IκB-α subunit degradation, the NF-κB nuclear transcription factor inhibitor (Echigo et al. 2012). *Agaricus bisporus* dried fruiting bodies contain about 1–3% of trehalose (Wannet et al. 1998).

6.1.2.2 Polysaccharides

Polysaccharides contained in the cell wall of mushrooms hypha, which include glucans, chitin and chitosans, are particularly valuable for the improvement of immunity and modulation of the defense response of the human body (Wu et al. 2004; Kozarski et al. 2014).

β-Glucans, due to their broad spectrum of activity in the immune system, are called biological response modifiers (Novak and Vetvicka 2009). The effect of β-glucans on pro-and anti-inflammatory cytokines has been demonstrated. One of the mechanisms of β-glucans action is binding to pattern recognition receptors (PRR) of immune cells as pathogen-associated molecular patterns (Muta 2006). Such receptors include dectin-1, complementary receptor 3 (CR3, CD11b/CD18), or TLRs (toll-like receptors). In this way, β-glucans activate cell proliferation and maturation of the immune system; stimulate the activation of macrophages and NK cells (Akramiene et al. 2007).

Anti-inflammatory effects are attributed to glucans obtained from *Inonotus obliquus* which *in vitro* demonstrated inhibitory activity of the NF-κB, COX-2 and iNOS signaling pathway in RAW 264.7 cells (Ma et al. 2013). One of the better-known, derived from *A. bisporus*, (1 → 6)-β-D-glucan with a linear structure, showed repressive action of pro-inflammatory genes in *in vitro* studies using the THP-1 cell line, and also inhibited inflammatory reaction induced by **lipopolysaccharide** (LPS), by repressing the expression of COX-2 and interleukin 1 (IL-1) proteins (Smiderle et al. 2013).

Edible mushrooms can be used in the treatment of cancer or as a support for conventional therapy, and even as agents that combat the side effects of cancer therapy (Patel and Goyal 2012; Zong et al. 2012). This has been confirmed in clinical studies in recent years (Kosanić et al. 2016; Meng et al. 2016).

Extracts and compounds isolated from mushrooms exhibit many mechanisms of **anticancer** activity, for example, inhibiting the kinase, and hence the cell cycle, or inhibiting angiogenesis. They are also inducers of reactive oxygen species, antimitotic agents, and topoisomerase inhibitors stimulating apoptosis of cancer-transformed cells (Patel and Goyal 2012; Kosanić et al. 2016). In the effective anticancer therapy, it is necessary to apply comprehensively acting factors, because cells that have undergone mutation have a unique ability to multiply and spread, creating metastases that cause high mortality (Zong et al. 2012).

The main and best-known compounds responsible for the anticancer effect are polysaccharides and their combinations with peptides (proteoglycans) or steroids (Ruthes et al. 2015; Kosanić et al. 2016; Meng et al. 2016; Singdevsachan et al. 2016). These compounds can be used in the treatment of cancer or viral diseases (e.g., AIDS), and used as prebiotics. Polysaccharides isolated from edible mushrooms activate the immune response in *in vitro* and *in vivo* studies, acting as biological stimulants. The most important anticancer polysaccharides are polysaccharide-protein complexes, fiber, (1 → 3) α-glucans and (1 → 3), (1 → 6)-β-glucans. In turn, heteropolysaccharides showing antiproliferative effect in relation to cancer cells have been shown to be substances that inhibit the development of cancers (carcinostatic), mainly after intraperitoneal or oral administration (Byerrum et al. 1957; Zong et al. 2012; Singdevsachan et al. 2016).

The importance of mushroom polysaccharides in modulating the function of the immune system and thus the potential inhibitory effect on cancers is of particular importance. One of the first clinically described activities of mushroom polysaccharides in the treatment of cancer comes from 1957 and was analyzed by Byerrum et al. (1957). The mechanism of this action on the immune system, confirmed in subsequent studies, involves the stimulation of immune system cells, including T lymphocytes and cytotoxic T lymphocytes (CTL), B lymphocytes, granulocytes (eosinophils and neutrophils), NK cells, or macrophages (Zhang et al. 2007; Roupas et al. 2012; Meng et al. 2016; Singdevsachan et al. 2016). This mechanism of action is particularly characteristic of β-1, 3-glucans. Numerous studies also suggest that β-glucans may enhance a specific cellular response by enhancing the secretion of IL-6, IL-8, IL-12 and IFN-ɣ from neutrophils, macrophages and NK cells (Meng et al. 2016; Singdevsachan et al. 2016). In addition, β-glucans found in fruiting bodies of edible mushrooms can be factors that stimulate new effectors cells that contribute to the formation of, inter alia, antibodies against cancer antigens, which is less popular than the classic cytotoxic effect triggered by chemotherapy (Singdevsachan et al. 2016).

For the anticancer effect, the ability to bind other molecules (proteins, steroids) is also an important issue, which results in an increased anticancer activity. Most of the polysaccharides used are glucans, which when combined with other protein molecules can be converted into glycoproteins, glycopeptides or proteoglycans.

The conformation of the polysaccharide chain is also key issue to the therapeutic effect. The most active polysaccharides are most often complexes with proteins with a molecular weight of 10,000 kDa. Human macrophages possess a polysaccharide receptor that is highly specific for glucose and mannose molecules, from which the anticancer effect of polysaccharides possessing these groups may result (Zhang et al. 2007; Patel and Goyal 2012; Roupas et al. 2012; Meng et al. 2016; Tian et al. 2016).

Among the edible species of mushrooms rich in polysaccharides with the structure described above, the anticancer effect is exhibited, inter alia, by species like *Cantharellus cibarius* (chanterelle), *Armillaria mellea* (honey fungus), *Flammulina velutipes* (golden needle mushroom), *Macrolepiota procera* (parasol mushroom), *Lentinula edodes*, *Tremella fuciformis* (snow fungus), *Hericium erinaceus* (lion's mane mushroom), *Agaricus bisporus* (portobello mushroom), *Agaricus blazei* (almond mushroom), *Agaricus campestris* (field mushroom), *Pleurotus ostreatus* (oyster mushroom), *Sparassis crispa* (cauliflower fungus), *Grifola frondosa* (Maitake Mushroom), *Boletus edulis* (penny bun), *Imleria badia* (bay bolete) and *Lactarius deliciosus* (saffron milk cap) (Zhang et al. 2007; Patel and Goyal 2012; Meng et al. 2016; Singdevsachan et al. 2016; Tian et al. 2016).

All over the world, modern medicine, and in particular Eastern one, uses *L. edodes* as an agent enhancing the body's strength, and the extract of this species as an anticancer substance. The **therapeutic effect** is mainly due to the polysaccharide –lentinan, which action reduces the size of the tumor by up to 90% (Zhang et al. 2007; Patel and Goyal 2012; Roupas et al. 2012; Kosanić et al. 2016; Meng et al. 2016; Tian et al. 2016).

Lentinan in terms of its chemical structure is β (1 → 3) glucan with β (1 → 6) branching with a molecular weight from 400 to 800 kDa (Fig. 6.1). This polysaccharide is most commonly used to treat solid tumors of the stomach, lungs, breasts, large intestine and malignant leukemia. It acts by activating the immune system and affects the restoration of the body" correct defense response. It induces a humoral immune response of the body, which consists in restoring the activity of helper T cells in host cells occupied by the cancer. Lentinan has no **cytotoxic** activity, practically showing no side effects. However, local irritation after injection, sporadic fever and vomiting are possible. The use of this substance has been shown to increase the average survival time of patients (Patel and Goyal 2012; Roupas et al. 2012; Meng et al. 2016; Singdevsachan et al. 2016; Muszyńska et al. 2017a, b, c).

Studies on the mechanism of lentinan action prove that it is dependent on the thymus and consists in enhancing the response of T helper precursors and macrophages, and thus some cytokines, produced by lymphocytes, after the diagnosis of cancer cells. The induction of interferon (IFN-ɣ) is also important for this activity. Lentinan is most often used in the treatment of gastric cancer as an aid during conventional treatment, including surgical tumor removal, chemotherapy or radiotherapy. This is a kind of synergistic effect, improving the general condition of the patient. Effective attempts have also been made to treat hepatocellular carcinoma, colorectal and pancreatic cancers while limiting side effects and thus improving the quality of life. Lentinan as an inhibitor of lymphocyte proliferation is also effective

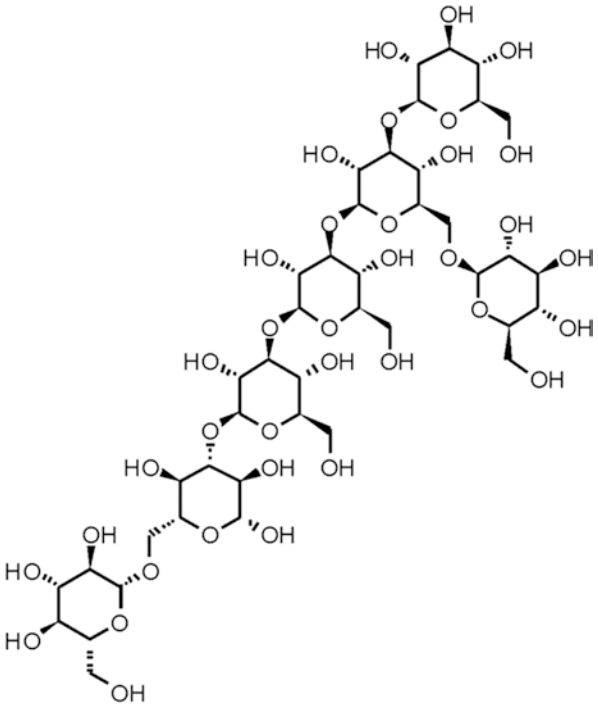


Fig. 6.1 Lentinan

in the treatment of leukemia. It has a selective **anti-proliferative** effect on the cancer-transformed skin cells (CH72), while not affecting healthy keratinocytes (C50). The use of lentinan as an adjuvant can improve the quality of life in patients with cancer because, like other fungal polysaccharides, it eliminates the side effects of chemo-and radiotherapy (Mantovani et al. 2008; Patel and Goyal 2012; Roupas et al. 2012; Zong et al. 2012; Lindequist et al. 2005; Meng et al. 2016; Singdevsachan et al. 2016; Muszyńska et al. 2017b).

Another example of polysaccharide responsible for anticancer activity is β-glucan isolated from *Sparassis crispa* fruiting bodies. Clinical trials were conducted in which patients suffering from tumors were administered orally powdered fruiting bodies of this species in an amount of 300 mg/day. Compared to the control group, a significant improvement was observed in many patients in the group supplemented with fruiting bodies (Roupas et al. 2012).

Lactarius deliciosus and *M. procera* are edible mushroom species exhibiting similar anticancer potential in *in vitro* studies. This activity was tested on human epithelial carcinoma cells (HeLa), human colorectal cancer (LS174) and human lung cancer (A549). The IC_{50} values ranged from 19.01 to 74.01 μg/mL for the *L. deliciosus* extract, and from 25.55 to 68.49 μg/mL for the *M. procera* extract, depending on the type of cell lines. The stronger anticancer effect against A549 and

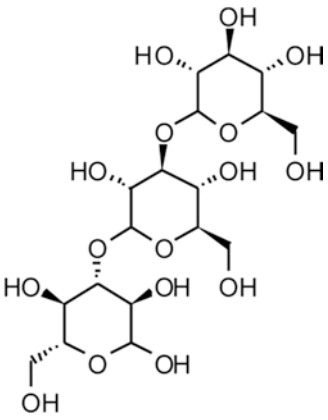
LS174 cell lines was demonstrated for *M. procera*, while *L. deliciosus* was more active against HeLa (Kosanić et al. 2016).

At the Centro de Investigaciones Biológicas in Madrid, two α-glucan polysaccharide fractions were isolated from *A. mellea* fruiting bodies. The main fraction consisted of linear chains of α-(1, 3)-and α-(1, 4)-glucan linked to the protein, while the other fraction contained α-(1, 3)-glucan. A fraction containing a combination of β-glucan and a peptide part was also obtained. This fraction showed an anticancer activity. During the examination of the chemical structure of peptide-glucan sugar part, the presence of glucose molecules connected by β-(1, 3) and β-(1, 6) bonds has been demonstrated (Muszyńska et al. 2011d).

High-β-glucan polysaccharide fractions derived from *A. blazei* species have been shown to be effective in treating prostate cancer, both dependent and independent of androgens. The induction of prostate cancer cell apoptosis was directly related to the activation of caspase-3 as a pro-apoptotic agent. The polysaccharide fraction obtained from this species is effective in the treatment of tumors in *in vivo* studies, with no cytotoxic effects. In addition, in therapy using 5-fluorouracil (5-FU), this species protected against leukopenia as a side effect of treatment with this substance. The properties of β-glucan obtained from this mushroom species have been improved by modifications involving the incorporation of sulfate groups that improve solubility (Mantovani et al. 2008; Patel and Goyal 2012; Roupas et al. 2012; Zong et al. 2012).

Also pleuran (β-1, 3-D-glucan), obtained from *P. ostreatus* species deserves an attention (Fig. 6.2). Its activity has been shown to slow down the formation of precancerous lesions of the 'Aberrant Crypt Foci' type (ACF) in the colon in rats of the Wistar strain. This action consisted in inhibiting the proliferation of cancer cells and inducing their apoptosis. In addition, a new polysaccharide (POPS-1), obtained from hot water extracts of this mushroom species showed significantly reduced toxicity in combination with commonly used 5-FU (Patel and Goyal 2012; Roupas et al. 2012; Meng et al. 2016).

Fig. 6.2 Pleuran



Diet rich in dried fruiting bodies of *P. ostreatus* reduced the toxicity in mice treated with cyclophosphamide and decreased pathological changes arising as a result of the appearance of dimethylhydrazine induced colon cancer in rats. The mechanism of action resulted from the strong antioxidant potential of these fruiting bodies. In turn, aqueous extracts obtained at high temperature from *H. erinaceus* fruiting bodies turned out to be rich in β-glucan, the administration of which contributed to the reduction of tumor mass in mice with induced colorectal cancer. The reduction in tumor mass was due to the induction of tumor necrosis factor and NK cell secretion, as well as macrophage activation and inhibition of angiogenesis (Patel and Goyal 2012; Roupas et al. 2012; Lindequist et al. 2005; Ruthes et al. 2015; Singdevsachan et al. 2016; Ment et al. 2016).

Grifola frondosa species is also a source of β-glucan, including the active fraction D, and MD fraction obtained by further purification. The MD fraction works by enhancing the activity inhibiting the spread of tumors, stimulating NK cells and reducing **nephrotoxicity** and **immunosuppression** induced by cisplatin treatment. MZF heteropolysaccharide with *in vivo* activity inhibiting tumor growth by stimulating cellular immunity was also isolated from this species. The use of whole powdered fruiting bodies with the addition of isolated MD fraction was used in patients with cancer diseases in the stages of tumor development II-IV. The use of such a combination resulted in an improvement in the general condition of patients, and even regression of the tumors themselves: 68.8% of patients diagnosed with breast cancer, 58.3% of patients with liver cancer and 62.5% of patients treated for lung cancer (Patel and Goyal 2012; Roupas et al. 2012; Zong et al. 2012; Cheung 2013; Lindequist et al. 2005).

Water insoluble polysaccharides such as, chemically sulfated polysaccharides (S-GAP-P) have also been classified as effective in the treatment of human gastric cancer (cancer cells SGC-7901). *Grifola frondosa* species proved to be effective not only in combination therapy alongside 5-FU, but also in S-GAP-P monotherapy, in which it induced the **apoptosis** of SGC-7901 cancer cells. The effect was dose-dependent. β-glucan from *G. frondosa* also showed a cytotoxic effect on human prostate cancer cells (PC-3). Induction of apoptosis has been confirmed in *in-vitro* studies of androgen-independent tumor (Patel and Goyal 2012; Roupas et al. 2012; Ruthes et al. 2015; Meng et al. 2016; Singdevsachan et al. 2016).

Interesting results were obtained in studies carried out using the species *F. velutipes* and *A. blazei*. The preventive effect on the incidence of cancer was observed especially in the group of farmers involved in the commercial cultivation of this edible mushroom–these species were a popular element of their daily diet. As a result of the consumption of mushrooms, the incidence of cancer was estimated at 40% lower compared to the general incidence in the population. To confirm the results obtained, tests were also carried out using mice. They were regularly fed the same species of mushrooms, and then cancer cells were introduced into the animal organisms. It was clearly observed that in the research group, in contrast to the control group, no cancer was developing, which confirms the strong preventive anticancer effect of polysaccharides from the species *F. velutipes* and *A. blazei* (Zhang et al. 2007).

6.1.2.3 Chitin

Mushroom cell walls contain a mixture of fibrous elements and matrix elements, rich in **chitin** (crosslinked N-acetylglucosamine polymer) and polysaccharides, such as β-D-glucans and mannans (Fig. 6.3). These elements of the cell wall are not digested in the human digestive tract, and thus constitute dietary fiber (Cheung 2013). Total fiber content varies on average from 2.7 to 4 g per 100 g of edible parts of fruiting bodies. However, the percentage content of chitin itself, for example, in *A. melenea* fruiting bodies calculated on the basis of glucosamine determinations in hydrolysates, calculated on the dry mass of the mushroom, is 6.4%. Physicochemical properties and molecular mass of chitosans isolated from mushrooms are identical to those isolated from chitin cuticle of crustaceans (Muszyńska et al. 2011b).

Chitosans reduce the concentration of LDL cholesterol (in the blood and liver) and serum triacylglycerides. In this way, they reduce the risk of cardiovascular diseases. They also affect the absorption of cholesterol from the gastrointestinal tract, causing a decrease in its total concentration in the blood and LDL fraction, without changing the concentration of HDL fraction (Rajewska and Bałasińska 2004; Cheung 2013; Muszyńska et al. 2013b). The mechanism of this phenomenon is not fully understood, but fiber found in mushrooms can be a good alternative to fiber from other foods. The hypocholesterolemic effect may be caused by a change in the absorption of nutrients from the gastrointestinal tract associated with the presence of fiber in the diet, effect on intestinal (or pancreatic) secretion, and indirectly on the metabolism of lipoproteins or bile acid. Considering the relatively high content of fiber and low fat content, edible mushrooms can become part of the diet, which is aimed at counteracting atherosclerosis (Fukushima et al. 2000; Siwulski et al. 2014).

Due to the presence of a large amount of dietary fiber in edible mushrooms, especially glucans (increasing the viscosity of the digestive content) and chitin, the excretion of bile acids and neutral steroids increases. In the acidic environment of the stomach, the amino groups present in the chitosan molecules assume a positive charge and combine with negatively charged bile acid residues. Low pH makes bile

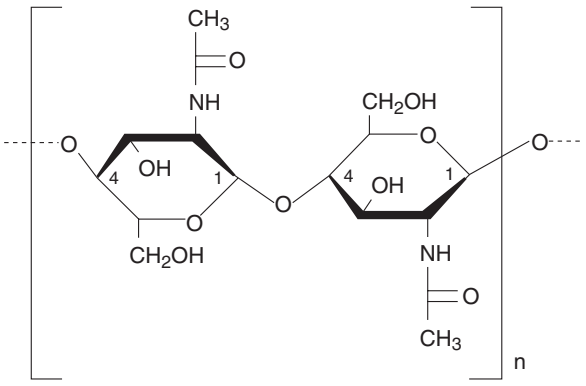


Fig. 6.3 Chitin

acid and chitosan complexes become insoluble and are excreted from the body. Chitin and its partially deacetylated form, i.e., chitosan, are widely used in the pharmaceutical industry. They are not only carriers for many drugs, but also are themselves components of slimming preparations. The slimming effect is related to the temporarily reduced absorption of lipids from various foods (Muszyńska 2012).

The effectiveness of chitosan has been proven through research focusing on two groups of volunteers who were on a low-calorie diet. Patients taking chitosan regularly reduced weight significantly faster within a month. In the research group, the weight loss was 7 kg, while in the control group this loss was only 3 kg (Rajewska and Bałasińska 2004). In addition to beneficial effects on fat metabolism and weight loss effect, studies have also shown an improvement in sugar metabolism. The consumption of *A. bisporus* species in this case resulted in a 24.7% reduction in blood glucose levels in rats that had deliberately induced type II diabetes. The desired effect was also obtained in rats with hypercholesterolemia, who after eating the mushroom, in addition to the decrease in total cholesterol, LDL and triglycerides also achieved an increase in the level of HDL fraction beneficial for the proper functioning of the organism (Jeong et al. 2010).

6.1.2.4 Lectins

Lectins are a kind of glycoproteins, necessary for the proper growth of mushroom fruiting bodies. They are also a protective factor for the mushrooms against the toxins from the environment, for example pesticides, as well as bacteria and even viruses (Varrot et al. 2013; Singh et al. 2015). Lectins found in edible mushrooms turned out to be the subject of research, due to the anticancer effect associated with the immunomodulatory potential, realized by stimulating the maturation of immune cells. A mixture of lectins (lectin A and lectin B) isolated from *A. bisporus* species (ABL) has **antiproliferative** activity on epithelial tumor cells, without inducing a direct cytotoxic effect. *In-vitro* studies using HT-29-human colon cancer cells have shown that lectins isolated from *A. bisporus* have the ability to induce apoptosis in these cells, bypassing the **cytotoxic** effect. This effect may be associated with an increase in **caspase-3** activity (Wang et al. 1998;Carrizo et al. 2005; Roupas et al. 2012; Singh et al. 2015). For AAL lectin obtained from the *Agrocybe aegerita* species, a precise relationship was established between the elements of the structure and the induced anticancer effect on both mouse and human cells. This is important because it may be the first step to design specific molecules that will later be used in therapy. AAL acts by inducing apoptosis in cancer cells. To achieve this activity, the dimeric organization of the lectin molecule is necessary. The presence of glucose and galactose in the carbohydrate functional group is also necessary (Ng 2004; Li et al. 2008; Singh et al. 2015).

In addition, lectins from edible mushroom species such as *G. frondosa, F. velutipes, Tricholoma mongilicum, Volvariella volvacea*, *Pleurotus citrinopileatus* and *P. ostreatus* have been found to possess immunomodulatory potential as well as anticancer, anti-proliferative and cytotoxic properties.

It was possible to isolate **heterodimeric** lectin from *V. volvacea* species, which has the potential to inhibit the growth and development of cancer cells. Importantly, this lectin lengthens the survival time of sarcoma 180 tumor-bearing mice. Elongation of the survival period is dose dependent. In contrast, the *G. frondosa* species has been tested for its cytotoxic effect on HeLa tumor cells. Lectin specific for N-acetylgalactosamine was responsible for this effect (Li et al. 2008; Singh et al. 2015). In turn, *P. citrinopileatus* is a species rich in homodimeric lectin that inhibits the growth of the murine sarcoma 180 cancer as early as 20 days in case of intra peritoneal, daily administration at a dose of 5 mg/kg body weight. The anticancer effect is similar to that exhibited by *P. ostreatus* (Li et al. 2008; Patel and Goyal 2012).

Lectin isolated from *P. ostreatus* species showed anticancer activity against mouse H-22 hepatoma and sarcoma S-180 tumors, reducing the number of cancer cells (Ng 2004; Li et al. 2008; Singh et al. 2015). This lectin works by inhibiting the growth of both these tumors by 75% and 88%, respectively. To achieve this effect, a dose of 1.5 mg lectin/kg body weight by intra peritoneal injection for 20 days was required. This treatment caused a decrease in the weight of mice in comparison to the control group, but the survival time significantly increased (Ng 2004).

Lectins derived from *T. mongolicum* species (TML1 and TML2) inhibit the development of sarcoma 180. They are compounds with a molecular weight of approximately 36–38 kDa. Both TML1 and TML2 inhibit the growth of these cells, with TML2 being more effective. The activity of both these lectins is based additionally on the stimulation of macrophages for the production of nitrite ions (NO^{2-}). In addition, they show anticancer activity by stimulating the immune system *in vivo*, while the **anti-proliferative** effect is only observed *in vitro* (Wang et al. 1996; Wang et al. 1998; Ng 2004; Singh et al. 2015).

Mushroom lectins have also been tested as compounds with therapeutic potential in the prevention and treatment of diabetes, inter alia, due to the induction of β-cell division of pancreatic islets. The study aimed to determine the rate of β cell regeneration in mice and to understand the mechanisms of their proliferation. The analysis was carried out on the basis of glucose concentration measurements and the degree of insulin secretion after the administration of fungal lectins. Comparing the results, the effect of lectins from *A. bisporus* on reducing the blood glucose level, increasing its tolerance and increase in β-cell mass of pancreatic is proved (Wang et al. 2012). Analyzing also the composition and properties of fatty acids obtained from *C. cibarius* species, it has been shown that as PPAR-γ agonists, they inhibit the development of insulin resistance and are therefore effective antidiabetic agents (Hong et al. 2012). *Armillaria mellea* fruiting bodies have demonstrated the presence of a therapeutically important peptide-prosomatostatin, which has anticancer activity especially in the treatment of pancreatic cancer (Muszyńska et al. 2013b).

The fruiting bodies and mycelia of *Antrodia camphorata* in traditional Eastern medicine are in turn used as an anticancer agent due to the presence of ubiquinone derivative. Importantly, this compound has selective activity, affecting only cancer-affected cells, omitting healthy cells (Hu et al. 2016).

6.1.2.5 Amino Acids and Proteins

Anti-inflammatory properties of mushrooms are associated with the free amino acids contained in them (both endogenous and exogenous ones) that can affect the metabolism of prostaglandins. The anti-inflammatory properties of *P. ostreatus* are partly explained by the content of amino acids such as leucine, isoleucine, tyrosine and phenylalanine (Jedinak et al. 2011).

Ergothioneine is an important amino acid exogenous to humans, i.e., must be supplied with food. A good source of this compound is fruiting bodies of edible mushrooms (Fig. 6.4). This amino acid assimilated from the diet is particularly important for cells, tissues and organs sensitive to oxidative stress, such as erythrocytes, the lens of the eye, semen or skin (Chen et al. 2012). *In vivo* studies in the mouse HR-1 model (hairless) that ergothioneine isolated from *C. comatus* significantly reduced the amount of DNA damage and inhibited inflammation caused by UV-B radiation (Asahi et al. 2016). Additionally, ergothioneine–a strong **antioxidant** isolated from *A. bisporus*, has a beneficial effect during cancer therapy due to its strong anti-mutagenic properties as well as chemo-and radio protective activity (Chen et al. 2012; Muszyńska et al. 2017b).

Arginine present in *A. bisporus* species is another substance used in the supplementation of cancer patients. It not only improves the condition of the body and has a beneficial effect on the immune system, but also prolongs the life expectancy of cancer patients. This effect is due to delayed growth of tumor and the appearance of metastases (Novaes et al. 2013).

Also noteworthy are the young, closed, edible fruiting bodies of *Coprinus comatus*. Studies have shown that they can also be effective in the treatment of estrogen-independent breast cancer. In addition, their inhibitory effect on the development of prostate cancer cells (LNCaP cells) has been demonstrated. In turn, an immunomodulatory protein (FIP-fve), which has anticancer activity involving an activation of T lymphocytes, was isolated from *F. velutipes* species. This effect was tested against the mouse model of hepatoma. The aqueous extract turned out to be rich in another anticancer substance–flammulin. The presence of stable hemagglutinin, which is responsible for inhibiting the proliferation of tumor cells in the case of leukemia (L1210 cells), was also an important issue. Aqueous extracts from both *C. comatus* and *F. velutipes* have been shown to be effective in the treatment of estrogen-dependent and estrogen-independent breast cancer *in vitro*. The observed anticancer effect (caused by the induction of apoptosis of altered cells) was dependent on the dose of both extracts.

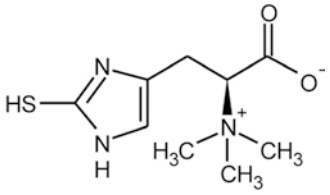


Fig. 6.4 Ergothioneine

6.1.2.6 Fatty Acids

Fatty acids contained in mushrooms may support anti-inflammatory processes in the human body, due to the high content of unsaturated fatty acids (Ayaz et al. 2011; Öztürk et al. 2011). Polyunsaturated fatty acids (PUFA) are precursors of eicosanoids, signaling molecules necessary for proper regulation of cellular processes in muscles, blood vessels, nerve cells and in the immune system. Eicosanoids provide a balance between inflammatory and anti-inflammatory processes (Dennis and Norris 2015).

The polyunsaturated fatty acids (PUFAs) include the n-3, n-6 and n-9 acids. Maintaining proper proportions of fatty acids of the n-3 to n-6 series in the diet is crucial for preventing the development of cardiovascular diseases and cancers. α-Linolenic acid (ALA) is an essential ingredient in normal nutrition, a precursor to the long-chain PUFAs of then-3 series. It also has anti-inflammatory effects (Gdula-Argasińska et al. 2015).

Comparative studies on the composition of more than a dozen species of mushrooms showed the highest share of the following fatty acids: linoleic (C18:2 n-6), oleic (C18:1 n-9) and palmitic (C16:0) (Ayaz et al. 2011).

In experiments conducted by Grzywacz et al. (2016) on murine macrophages RAW 264.7 activated with LPS, anti-inflammatory effects of extracts from *I. badia* biomass have been demonstrated. It involved an inhibition of COX-2 expression, prostaglandin E2 synthase (cPGES), p50 and p65 NF-κB subunits, which can be explained by high content of unsaturated fatty acids. Biomass from *I. badia* was characterized by a 5% content of ALA, which did not appear in fruiting bodies (Grzywacz et al. 2016).

In the *C. cibarius* extracts, the presence of fatty acids with agonist activity toward peroxisome proliferator-activated receptors (**PPAR-γ**) has been demonstrated. PPAR receptors play a special role in the metabolism of lipids and carbohydrates, in the differentiation of adipocytes and in the regulation of inflammatory processes. Extracts of *C. cibarius* species therefore have a therapeutic effect in the case of inflammatory diseases and some cancers (Hong et al. 2012).

6.1.2.7 Phenolic Compounds

A particularly important group of secondary metabolites found in mushroom fruiting bodies with proven antioxidant and anti-inflammatory properties *in vitro* and *in vivo* are **phenolic compounds** (Czapski 2005; Elmastas et al. 2007; Ferreira et al. 2009). Species as *C. cibarius, A. bisporus, B. edulis, Calocybe gambosa*, *Hygrophorus marzuolus* and *L deliciosus* contain the high content (about 15 mg/g DM) of one of the most active antioxidants in mushrooms, i.e., caffeic acid (Reis et al. 2012; Muszyńska et al. 2013a).

Caffeic acid also demonstrates anti-inflammatory activity. In *in vitro* studies using human HUVEC vascular cells and TNF-α induced U937 monocytes, the potential role of caffeic acid in the treatment of inflammatory changes in

cardiovascular disease has been demonstrated. Significant reduction of monocyte adhesion to HUVEC cells was observed in cultures supplemented with caffeic acid. In addition, caffeic acid inhibited MPC-1 expression in monocytes (chemoattractant of protein 1), IL-8 and translocation of NF-κB in the nucleus (Moon et al. 2009).

Anti-inflammatory properties associated with the activity of phenolic compounds derived from edible mushrooms: *A. bisporus, B. edulis, C. cibarius, H. marzuolus, L. deliciosus* and *P. ostreatus*, were tested *in vitro* using LPS activated RPS 264.7 macrophages. The results of the experiments showed the inhibitory effect of extracts on the expression of inflammatory markers such as IL-1β and IL-6 and the production of NO. The species of *A. bisporus, C. cibarius* and *L. deliciosus* showed the highest anti-inflammatory efficacy in the tested model (Palacios et al. 2011). In another experiment, the anti-inflammatory properties of the extract from *Elaphomyces granulatus* were confirmed. Inhibition of COX-2 activity in RAW 264.7 macrophages was observed and the antioxidant activity of the extracts was found. The effect obtained was probably related to the content of phenolic compounds, including syringic acid isolated from *E. granulates* (Stanikunaite et al. 2009).

6.1.2.8 Indole Compounds

Indole compounds have a particularly strong effect on the immune and nervous systems of animals. The *C. cibarius* species contain a large amount of serotonin −17.61 mg/100 g DM. and kynurenine sulfate −3.62 mg/100 g DM as well as lower amounts of melatonin, L-tryptophan, 5-hydroxytryptophan, 5-methyltryptophan, indole, indole-3-acetonitrile. Studies have shown that the content of indole compounds in biomass from *in vitro* cultures (mycelium) can be much higher than in fruiting bodies (Muszyńska et al. 2016a).

The content of non-hemolynogenic indole compounds and their release into artificial digestive juices was tested in the *A. bisporus* species. The following indole compounds have been identified and identified in the fruiting bodies: L-tryptophan, 5-hydroxy-L-tryptophan, melatonin, serotonin, tryptamine and 5-methyltryptamine, which indicates that this popular edible species is their good food source (Muszyńska et al. 2016b).

In the human body, L-tryptophan, one of the amino acids, can be transformed into other indole derivatives with high biological activity, for example serotonin, melatonin and niacin (vitamin B3) (Fukuwatari and Shibata 2013).

Melatonin, a compound with a broad spectrum of action in the body, is also an effective scavenger of free radicals, protecting cells from damage and the development of inflammatory reactions. Melatonin has been shown to regulate cytokine production by preventing translocation of NF-κB into the cell nucleus. Moreover, it can affect the reduction of damage associated with acute inflammation. It is related to the inhibition of adhesion molecules generation by leukocytes, thus affecting their migration process (Reiter et al. 2000). The positive effect of melatonin on the course of inflammatory neurodegenerative diseases, such as dementia, Alzheimer's

and Parkinson's disease, or multiple sclerosis has also been demonstrated (Esposito and Cuzzocrea 2010). Scientific experiments indicate that serotonin (5-hydroxytryptamine) reduced allergic pneumonia in the C57BL/6 mouse model by 70–90%. In addition, a decrease in expression induced by transglutaminase 2 allergens was observed as well as a decrease in serotonylation of proteins in the pulmonary endothelium and a decrease in the migration of leukocytes and eosinophils. The addition of serotonin to cell cultures resulted in a reduction in the serotonylation of TNF-α induced protein. This indicates the important role of serotonin in the leukocyte migration process, which may be important in the treatment of allergic diseases (Abdala-Valencia et al. 2012).

Analysis of selected species of mushrooms indicates that even thermally processed (boiled) fruiting bodies of *C. cibarius, I. badia, L. deliciosus, M. procera, P. ostreatus* and *S. bovinus* are a valuable reservoir of compounds with **antidepressant** activity (Turner et al. 2006; Muszyńska et al. 2011c). The highest content of serotonin was demonstrated among the analyzed indole compounds in *C. cibarius* fruiting bodies. The species containing significant amounts of this neurotransmitter are also: *Leccinum scabrum*, *A. mellea, I. badia, B. edulis, L. deliciosus* and *P. ostreatus*.

Serotonin, a substance with multidirectional pharmacological activity that plays, inter alia, the role of the neurotransmitter in the central nervous system together with melatonin is regulated by the daily cycle (Fig. 6.5). Serotonin, generated endogenously in the brain, plays a very important role in regulating sleep, anxiety, aggression, body temperature, mood, the course of maturation, regeneration and inhibition of the aging process of cells, thus contributing to the general strengthening of the body's immune system. It is also one of the factors regulating the contraction and relaxation of blood vessels (Turner et al. 2006; Muszyńska et al. 2011c).

Serotonin, after ingestion, does not penetrate the blood-brain barrier into the central nervous system, but it can regulate the functioning of the gastrointestinal (intestinal) tract (Birdsall 1998). In patients with asthma, this substance causes bronchospasm. It is involved in the pathogenesis of migraine and vascular headaches.

The wide range of activities regulated by serotonin is explained by the existence of 7 types of serotonin receptors (5-HT), and several subtypes within them. Many classes of drugs work via serotonin receptors, being agonists or antagonists of these or by affecting the release of **serotonin**. These drugs include, above all, antidepressants, anxiolytics, antiemetics and antimigraine (Birdsall 1998).

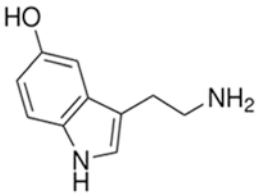


Fig. 6.5 Serotonin

Information on the occurrence of indole compounds in *Basidiomycota* species also applies to L-tryptophan, which is a biogenetic precursor to all **indole compounds** (e.g., dopamine, melatonin, serotonin, and adrenaline) and vitamins (e.g., niacin) (Birdsall 1998; Turner et al. 2006; Muszyńska et al. 2011b). The determined L-tryptophan content ranged from 0.16 to 25.90/100 g DM (in extracts from *S. bovinus* fruiting bodies) (Muszyńska and Sułkowska-Ziaja 2012).

L-tryptophan is an amino acid that is exogenous to the human body and must therefore be supplied with food. Among the extracts from heat-treated fruiting bodies, the extract of the fruiting bodies of the *Suillus bovinus* contained the largest amount of L-tryptophan-17.71 mg/100 g DM (Muszyńska and Sułkowska-Ziaja 2012).

Processed edible mushrooms, especially *S. bovinus*, can be its source, which is why they are an alternative to animal foods. In the case of *B. edulis*, the amount of L-tryptophan was higher in the processed material than in the dried fruiting bodies. 5-Hydroxytryptophan (5-HTP), a direct precursor of serotonin and melatonin, was present in both thermally unprocessed and processed fruiting bodies. However, the highest amounts of this compound in the discussed species were found in uncooked mushrooms. The maximum amounts of this metabolite were found in fruiting bodies extracts of: *L. edodes* 24.83 mg/100 g DM, *M. procera* (22.94 mg/100 g DM), *S. bovinus* (15.83 mg/100 g DM). According to the latest research, 5-HTP is a potential drug in the treatment of Alzheimer's disease (Birdsall 1998; Muszyńska et al. 2011a, b; Muszyńska and Sułkowska-Ziaja 2012; Muszyńska et al. 2013c).

5-Methyltryptophan was only marked in *L. scabrum* fruiting bodies. This compound was also detected in cooked fruiting bodies of four species: *B. edulis, C. cibarius, L. deliciosus* and *P. ostreatus*, in amounts comparable to those found in *L. scabrum* (Muszyńska et al. 2011a, b; Muszyńska and Sułkowska-Ziaja 2012; Muszyńska et al. 2013c). The indole compound determined in the studied species was also melatonin. It was found in small amounts in extracts from the fruiting bodies of *B. edulis, C. cibarius, L. deliciosus, L. edodes* and *M. procera* (from 0.07 to 1.29 mg/100 g DM) (Muszyńska et al. 2011a, b; Muszyńska and Sułkowska-Ziaja 2012; Muszyńska et al. 2013c).

6.1.2.9 Enzymes

Lactase present in *Agrocybe cylindracea* species is an important enzyme with anticancer activity. Lactases also occur, inter alia, in the species of *H. erinaceus, A. blazei, L. edodes, P. ostreatus, C. cibarius*, or *Pleurotus eryngii*. However, their anticancer activity was not analyzed. Lactase is used to purify contaminated water as a biosensor or fabric dye. It is a lignin-degrading enzyme, participates in mushrooms morphogenesis, and further catalyzes oxidation reactions of organic compounds, including phenolic compounds (Zhang et al. 2010).

The studies carried out have shown that the lactase present in *A. calvacea* has anti-proliferative activity against MCF-7 breast cancer cells (IC_{50} = 6.5 μM) and HepG2 liver cancer cells (IC_{50} = 5.6 μM). The activity of lactase isolated from this

species of mushrooms was the highest while maintaining the pH in the range of 3–4, while at the pH of about 9, its activity completely disappeared. In addition, raising the temperature to 50 °C had a positive effect on the enzyme activity; however, a further temperature increase adversely affected enzyme degradation (Elmastas et al. 2007; Endo et al. 2010).

The activity against MCF-7 and HepG2 tumor cells was also demonstrated for the lactase isolated from the edible species of *Clitocybe maxima*. The IC_{50} for these cancer cells was 3.0 μM and 12.3 μM, respectively (Zhang et al. 2010).

Another example of an enzyme with anticancer activity is tyrosinase extracted from *A. bisporus*, characterized by a high degree of similarity to that found in the human body. This mushroom species is a very good and cheap source of tyrosinase (Labus et al. 2011; Zaidi et al. 2014; Kampmann et al. 2015). Studies carried out on the enzyme isolated from *A. bisporus* have shown that it has a protective effect on human lymphoma cell lines, preventing them from the negative effects of damaging factors such as perhydrol (Shi et al. 2002). In addition, the genoprotective activity of this species, resulting from the presence of tyrosinase was investigated. The putative DNA-protective effect was associated with the pathway of tyrosine up to L-DOPY, followed by conversion of this metabolite to dopaquinone (Shi et al. 2002; Jani et al. 2016).

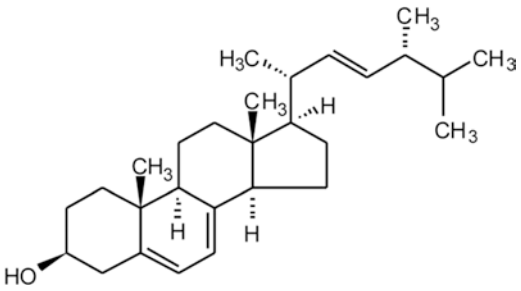
6.1.2.10 Terpenoids

The compounds from the terpenoid group with anti-inflammatory, anti-proliferative and anticancer potential were also isolated from the *Poria cocos* of the *Polyporaceae* family. The anti-inflammatory activity of extracts from this mushroom has been confirmed in an *in vitro* model using RAW 264.7 macrophages. A decrease in the generation of pro-inflammatory mediators was observed by inactivating the NF-κB signaling pathway (Jeong et al. 2014). In turn, the anticancer activity of mushroom terpenoids was tested on the U937 line. The concentration and time-dependent effects of anti-proliferative and pro apoptotic effects of the extracts studied were related to the release of cytochrome C to the cytosol, caspase-3,-8 and-9 activation, PARP degradation and loss of mitochondrial membrane potential. The obtained results indicate the potential of the *P. cocos* species in the treatment of leukemia (Choi 2015). A series of triterpenes with a similar inhibitory effect on the NF-κB signaling pathway were isolated from another species, *Inonotus obliquus* (Jiang et al. 2008). In turn, the *A. camphorata* extracts showed NO, TNF-α and IL-12 reducing properties (Rao et al. 2007).

6.1.2.11 Tocopherols and Steroids

Tocopherols, the most active of which is α-tocopherol, have anti-inflammatory, anticancer activity and also prevent peroxidation of cell membranes phospholipids (Jiang 2014).

Fig. 6.6 Ergosterol



In many species of mushrooms, the presence of ergosterol (a precursor to vitamin D) (Fig. 6.6), ergocalciferol and other sterols (including ergosta-7,22-dienol, ergosta-5,7-dienol, ergosta-7-enol, cerevisterol, β-sitosterol, ergosterol peroxide, β-sitosterol, or 7-dehydrostigmasterol) has been detected. Among others, the fruiting bodies of *A. bisporus* are a rich source of ergosterol (about 61.5 mg/100 g).and ergocalciferol (Muszyńska et al. 2017a). A good source of vitamin D is also *C. cibarius*, in which the content of ergocalciferol even after a few years of storage of dried specimens is in the range of 0.12–6.3 μg/g DM (Phillips et al. 2011; Jiang 2014).

In addition, it turned out that subjecting the mushrooms to irradiation with UV-B and UV-C radiation allows them to increase the content of **vitamin D_2** (Strange et al. 2015; Drori et al. 2016). It is indicated that even more than half of the world's population suffers from a deficiency of this vitamin (Stepień et al. 2013). One of the mechanisms of the anti-inflammatory action of ergosterol and its derivatives is the inhibition of NF-κB translocation into the cell nucleus and thus the prevention of the expression of proinflammatory genes (Phillips et al. 2011).

The ergosterol present in the fruiting bodies of edible mushrooms, for example *I. badia* and *A. bisporus*, has anti-inflammatory and anticancer activity (Barros et al. 2008a). Anti-inflammatory properties in the mouse model were also showed for an extract of *L. edodes* enriched with ergosterol. The studies showed that in C57B1/6 mice with mitogen-induced (concanavalin A) liver inflammation, supplementation with Shiitake extract, enriched with vitamin D, caused a significant reduction in liver damage. The histopathological image of tissues was improved as well as the plasma level of transaminases and INF-γ decreased. In addition, the anti-inflammatory effect of vitamin D and mushroom extract was synergistic (Drori et al. 2016). In another experiment, it was observed that supplementation with powdered *A. bisporus* fruiting bodies enriched with vitamin D2, contributed to a significant reduction in the level of hsCRP protein after four weeks, which is a marker of inflammation in humans (Stepień et al. 2013).

The anticancer effect is also demonstrated by ergosterol (5, 7, 22-ergostatrien-3β-ol), present not only in *A. bisporus*, but also in other species from the Agaricales taxon. It occurs in most species of mushrooms from the Basidiomycota group. Ergosterol accounts for 83–89% of the total content of mushroom sterols. It inhibits the process of angiogenesis, which is associated with solid tumors, prevents tumor growth and prevents the migration and proliferation of cancer-affected cells.

This effect was determined by *in vitro* culturing of cancer cell lines as well as in *in-vivo* studies on rats (Yuan et al. 2008; Shao et al. 2010; Roupas et al. 2012; Novaes et al. 2013).

The content of ergosterol in species of cultivated mushrooms such as *A. bisporus, L. edodes*, or *P. ostreatus* is between 3.7–5.1 mg/g DM, while for wild growing species of *Cantharellus tubaeformis*, *C. cibarius* and *B. edulis*, these amounts are slightly lower, in the range of 1.4–4.0 mg/g DM. The protective effect of ergosterol on lymphocyte levels in patients undergoing chemotherapy has also been confirmed. This therapy is safe and well tolerated by patients. In addition, ergocalciferol (vitamin D2) present in edible mushrooms, resulting from ergosterol as a result of exposure to UV rays with a wavelength of 280–320 nm, is one of the preventive factors in cancer therapy (Shao et al. 2010; Roupas et al. 2012; Novaes et al. 2013).

In order to determine the antioxidant activity of mushroom extracts, lipids of rat liver microsomes were used in *in-vitro* tests, which were peroxidized according to the Fe^{2+}/ascorbate method. *A. mellea* and *Pleurotus cornucopiae* showed significant inhibition of **lipid peroxidation** (22.8% and 19.5%, respectively) at a concentration of 100 mg/mL, compared to the control group. Experiments have shown that the compound responsible for antioxidant activity is ergosterol peroxide (Krzyczkowski et al. 2009; Kampmann et al. 2015). As the concentration increased, this compound showed an increasing tendency to inhibit lipid peroxidation. The antioxidant activity of ergosterol peroxide was also compared with the effect of other antioxidants. It was confirmed that ergosterol peroxide showed a stronger effect than α-tocopherol and thiourea (by 19.2% and 21.5%, respectively) (Elmastas et al. 2007; Krzyczkowski et al. 2009).

Vitamin D_2, especially its hydroxylated form, is one of the potential anticancer drugs used in the treatment of, inter alia, melanoma. This effect is due to the inhibition of keratinocyte differentiation in *in vivo* studies and thus inducing protection against photodamage after topical administration. In the study of melanoma, ergosterol and dihydroergosterol also inhibited DNA synthesis due to the local metabolism of ergosterol, expressing cytochrome P-450scc by melanoma cells. Similarly, 17α-and 24-dihydroxyergosterol inhibited the proliferation of human epidermal keratinocytes cell lines. These results consistently confirm the antiproliferative effect and thus the anticancer effect of ergosterol metabolites on cells not only animal but also human (Słomiński et al. 2015).

Scientific research also indicates the existence of a connection between the appropriate level of vitamin D_2, also this of mushroom origin, and a reduced risk of prostate, ovarian, breast and large intestine cancer (Shao et al. 2010). Some species of mushrooms are a rich source of ergocalciferol, apart from *A. bisporus*, these include for example *G. frondosa, Morchella* spp., and *L. edodes* (Phillips et al. 2011).

Ergosterol derivative compounds, including ergosterol peroxide, also have antioxidant and anticancer activity, in this case based on cytotoxic activity against cancer cell lines and inhibition of their growth. It was possible to isolate ergosterol peroxide, or other sterols of this kind of action, inter alia, from the species of *Paecilomyces tenuipes* and *Cordyceps sinensis*. The *P. tenuipes* species also exhibited anticancer activity in *in vivo* studies (Lindequist et al. 2005; Hong et al. 2007).

In addition, ergosterol peroxide was first isolated from *H. erinaceus* species, which exhibits anticancer activity. The discussed substance was also obtained from other species of edible mushrooms considered to be medicinal, including *V. volvacea, I. badia, B. edulis, Suillus bovinus*, *Morchella esculenta*and *A. mellea* (Krzyczkowski et al. 2009).

Ergosterol peroxide isolated from the edible *Sarcodon aspratus* species has been shown to inhibit the growth of promyelocytic leukemia (HL60) cells. This effect was noticed for a dose above 10 μM of ergosterol peroxide (Takei et al. 2005).

Hypsizigus marmoreus species is also a source of ergosterol and ergosterol peroxide. It turned out that thanks to compounds from the group of sterols, fruiting bodies of this species can inhibit the TPA-induced (13-acetate-12-O-tetradecanoylphorbol) not only inflammatory ear swelling, but also tumor growth in mice during the two-stage carcinogenesis induced by TPA and DMBA (7 12-dimethylbenz[α]anthracene) (Yaoita et al. 2002).

Agaricus blazei species, in addition to anti-leukemia, also showed anticancer activity against KATO III stomach cancer cells and LU99 lung cancer cells. This activity was possible due to the presence of a steroid–blazein. The activity of six other steroids isolated in the form of acetone extracts from *A. blazei* species, which showed anticancer activity, was also examined. Based on the obtained research results, it was found that these compounds have anti-mutagenic potential (Lindequist et al. 2005; Endo et al. 2010; Patel and Goyal 2012; Roupas et al. 2012).

The bioactive steroid ergosta-4, 6, 8 (14), 22-tetra-3-one with antiproliferative and cytotoxic activity against **HepG2** cells was isolated from the edible species of *Russula cyanoxantha*. Under the influence of this compound, HepG2 cells undergo apoptosis as a result of inhibition of **cell cycle** (G2/M phase), chromatin condensation and cell nucleus fragmentation (Endo et al. 2010; Patel and Goyal 2012; Roupas et al. 2012).

6.1.2.12 Vitamins

The composition of five species of fungi from Uganda, *Termitomyces microcarpus, Termitomyces tyleranus, Termitomyces clypeatus, Polyporus tenuculi*s and *Volvariella speciosa* was investigated. The dried mushrooms contained folic acid, niacin, vitamin C and thiamine and small amounts of riboflavin, β-carotene (Fig. 6.7)

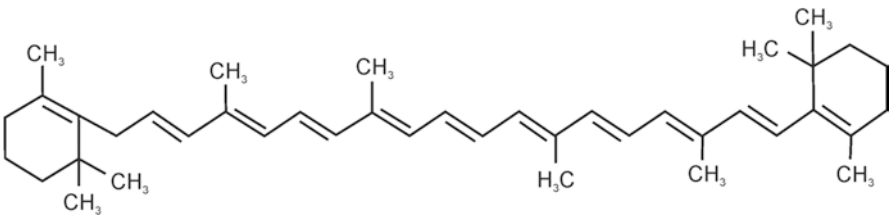


Fig. 6.7 β-carotene

and α-tocopherol. In these species, however, pantothenic acid, biotin and vitamin B_{12} have not been detected. The examined mushrooms contained a large amount of folic acid, the shortage of which is a frequent problem in the diet (Nakalembe et al. 2015).

The fruiting bodies of, inter alia, *A. bisporus* and *C. cibarius* are rich in B vitamins group, including thiamine, riboflavin, biotin and pyridoxine. These species are also a good source of tocopherols, carotenoids, and vitamin C (Barros et al. 2008b; Muszyńska et al. 2016a; Muszyńska et al. 2017a).

6.1.3 Other Compounds of Biological Activity

6.1.3.1 Statins

In 1971, while searching for new antibiotics produced by mushrooms, Akira Endo working for the pharmaceutical company Sankyo Co. discovered a class of compounds that reduced plasma cholesterol levels. Two years later, the research group isolated the compound responsible for the hypolipemic effect–mevastatin from *Penicillium citrinium*. Mevastatin served as the basis for further synthetic compounds from the statins group commonly used today (Wang et al. 1998; Carrizo et al. 2005; Li et al. 2008; Varrot et al. 2013; Singh et al. 2015).

Statins are inhibitors of 3-methyl-glutaryl coenzyme A reductase, the basic enzyme of endogenous cholesterol biosynthesis. They block the pathway of mevalonic acid, which causes lowering of cholesterol in the body. The **hypolipidemic** properties are used to treat: hypercholesterolemia, strokes and cardiovascular diseases. Other effects of statins proven *in vitro* and *in-vivo* include **cytotoxic** and **cytostatic** activity against various tumor cell lines. They result from such mechanisms of these compounds action as proapoptotic, anti-metastatic and anti-angiogenic activity. Natural statins include, inter alia, lovastatin, which in large quantities is observed in *P. ostreatus*, especially in its lamellar hymenophore. The addition of this species to the diet effectively reduces the accumulation of cholesterol in the blood and liver, reduces the production of VLDL and LDL for increasing HDL levels, attacks reduce the absorption of cholesterol and the activity of 3-hydroxy-3-methylglutaryl-coenzymeA reductase (HMG-CoA) in the liver. Another statin (eritadermin) having the above-mentioned properties is found in the Asian species *L. edodes* (Wang et al. 1998; Carrizo et al. 2005; Li et al. 2008; Varrot et al. 2013; Singh et al. 2015).

6.1.3.2 Theanine

The results of controlled trials in which edible mushrooms showed a synergistic, beneficial effect on reducing the incidence of cancer along with the consumption of green tea are also interesting. Theanine found in green tea also becomes a substance

considered in cancer therapy. A popular species that becomes the source of theanine as a result of fermentation is *I. badia*.

Theanine shows a similar effect to synthetic anticancer substances such as irinotecan, doxorubicin or cisplatin, hence its effectiveness during therapy is assumed (Patel and Goyal 2012; Roupas et al. 2012).

Armillaria mellea fruiting bodies showed the presence of therapeutically important peptide-prosomatostatin, which has anticancer activity especially in the treatment of pancreatic cancer (Muszyńska et al. 2013b). The fruiting bodies and mycelia of *Antrodia camphorata* in traditional Eastern medicine are in turn used as an anticancer agent due to the presence of ubiquinone derivative. Importantly, this compound has selective activity, affecting only cancer cells, omitting the healthy cells (Hu et al. 2016).

6.1.3.3 Agaritine

Agaritine present in hot-obtained aqueous extracts was isolated from *A. blazei*. Agaritine was active against human lymphoma cells (U937), inducing their apoptosis *in vitro*. This activity also involved other leukemia cell lines, including HL60, MOLT4 and K562. The effect of this substance involved the damage to tumor cells DNA, through their fragmentation and to release cytochrome c from them. This mushroom species is used as an adjuvant during chemotherapy (Endo et al. 2010).

Currently, the consumption of mushrooms from Agaricales taxon containing agaritine is not only completely safe, but also beneficial for human health. *Agaricus bisporus* species has also been shown to be effective in inhibiting leukemia; among others HL60 cells by induction of their apoptosis (Lindequist et al. 2005; Endo et al. 2010; Roupas et al. 2012).

6.1.3.4 Bioelements

The bioelements with antioxidant and anti-inflammatory properties, accumulated by mushrooms, include, inter alia, zinc, copper, iron and selenium (Kalač 2010; Reczyński et al. 2013). The microelement with significant anti-inflammatory effects found in mushrooms is zinc. Its content in fruiting bodies of various species of edible mushrooms is in the range of 150–200 mg/kg DM (Reczyński et al. 2013; Muszyńska et al. 2015). The studies have also demonstrated good ability to accumulate zinc (II) ions by biomass from *in vitro* cultures from substrates enriched with this element (Reczyński et al. 2013; Muszyńska et al. 2015).

The mechanism of anti-inflammatory action of zinc is based on the induction of transcription of zinc-dependent transcription factors such as MTF-1 or A20 and inhibition of NF-κB activation, which is reflected in a decrease in the production of proinflammatory cytokines (Prasad 2014; Grzywacz et al. 2015). In turn, disorders of zinc homeostasis or its chronic deficiency contribute to the weakening of immunity, increase the production of pro-inflammatory cytokines and may affect the passage of inflammation into a chronic state (Cousins et al. 2006; Prasad 2014).

The studies conducted with the use of RAW 264.7 macrophages demonstrated the anti-inflammatory and anti-oxidative effect of *I. badia* biomass extracts obtained from substrates enriched with zinc (II) compounds. Cells incubated with extracts and activated with LPS showed a significant decrease in the **expression** of COX-2, cPGES, NF-κB p50 and NF-κB p65 proteins as well as the increase in GSTM1 expression, compared to the inflammatory cells induced by LPS (Ahmad et al. 2013). Zinc is a compound with antidepressant activity. The role of this element in the treatment of depression consists in modulating the sensitivity of NMDA-type glutamate receptors necessary for the proper action of antidepressants (Muszyńska et al. 2011a, c; Muszyńska and Sułkowska-Ziaja 2012; Muszyńska et al. 2013c).

Natural sources of zinc are fruiting bodies of edible mushrooms in which the content of this ingredient is from 25–200 mg/kg of dry matter. According to research, the best source of zinc is the fruiting bodies of *Lycoperdon perlatum*, in which its content is in the range of 150–200 mg/kg of dry matter. A good source of this bioelement is also the fruiting bodies of: *A. campestris, B. edulis, M. procera, I. badia* or *L. scabrum* (Kalač 2010; Reczyński et al. 2013).

Edible mushrooms are one of the best food sources of selenium (Falandysz 2008; Dogan et al. 2016). The content of selenium in fruiting bodies varies from about 0.5 to 20 mg/kg DM. Some species contain much more of it, for example selenium content in the fruiting bodies of *Albatrellus prescaprae* was 400 mg/kg DM, while in *A. sporporus* fruiting bodies this value reached the level of 0.150 mg/kg DM (Falandysz 2008; Maseko et al. 2014; Dogan et al. 2016). The element is essential for the proper functioning of the immune system.

Selenium with proteins forms seleno proteins, involved in the proper differentiation and proliferation and activation of cells of the immune system, thus affecting the innate and adaptive immune response. The immunoregulatory function of selenium is also manifested by effects on key leukocyte functions, such as adhesion and migration, **phagocytosis**, as well as cytokine secretion, which may be important in autoimmune diseases and chronic inflammation. Selenoproteins also play an important role in the cells in antioxidative processes. Selenium is an important factor in the fight against free radicals, which results, inter alia, from its presence in the structure of superoxide dismutase (**SOD**) or **glutathione peroxidase** (Huang et al. 2012; Maseko et al. 2014).

Magnesium is an element that guarantees proper physiological activity of the neuromuscular system. In edible mushroom species, the content of this element is in the range of 25–125 mg/kg DM, and the best is *Boletus edulis*, in which magnesium content reaches 75–125 mg/kg DM (Muszyńska et al. 2011a, c; Muszyńska and Sułkowska-Ziaja 2012; Muszyńska et al. 2013c).

Copper, like zinc, is a cofactor of many enzymes, including these of protective activity under oxidative stress. These enzymes include superoxide dismutase and ceruloplasmin-the main serum oxidase, which plays an important role in the transport of copper and iron homeostasis. An important role of copper in the regulation of inflammatory processes has been demonstrated (Moon et al. 2009). The high content of this element was demonstrated in such mushrooms species as *Lycoperdon perlatum* and *M. procera* (Kalač 2010).

6.1.4 Summary

It should be borne in mind that edible mushrooms contain a wealth of pharmacologically active compounds which properties we are only beginning to discover. Reports from recent years indicate that edible mushrooms extract show beneficial health and therapeutic effects, especially in relation to civilization diseases, such as those with cancer, inflammation, neurodegenerative or immune background. Certainly, some edible mushrooms can already be described as "superfood" and recommended as a valuable component of the daily diet.

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