L-Tryptophan and its derivatives in edible mushrooms species

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Abstract

Mushrooms are able to accumulate both primary and secondary metabolites. Medicinal and antioxidant properties of mushrooms are an excellent combination of their nutrition value. Recent studies have demonstrated that edible mushroom species contain non–hallucinogenic indole compounds and their derivatives. The indole skeleton is the basis of the substances serving important functions in the human body, such as serotonin and melatonin. These compounds fulfill the role of neurotransmitters or their precursors, exhibit antioxidant, anticancer, anti–aging actions, regulate the diurnal cycle in humans and participate in blood coagulation. These compounds and their derivatives are also anti–inflammatory and analgesic therapeutics.

Key words: edible mushrooms, indole compounds, L–tryptophan, antidepressant agent, antioxidant activity

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Introduction

The main objects of interest in the field of indole compounds located in fruiting bodies of mushrooms were hallucinogenic substances, including alcaloides. Best known is the physiological action of hallucinogenic compounds such as: psilocybin, psilocin or common in Basidiomycota bufotenine. So far informations about non–hallucinogenic indole compounds found in Basidiomycota species relate mostly to L–tryptophan which is the biogenetic precursor of all indole compounds [1–3]. Research about nitrogenous compounds located in Macromycetes species, including non–proteinogenic amino acids, peptides and other substances, also heterocyclic, were presented by Liu [4]. Indole compounds of fruiting bodies of many species were not studied deeply. Knowledge of this metabolites seems to be important due to their biological activity in pharmaceutical and toxicological aspects. Besides, many compounds in the human body, for example tryptophan, serotonin or melatonin are based on the indole skeleton. Indole is the precursor for the group of indole compounds that are commonly seen in the tissues of living organisms: animals, plants and mushrooms. Indole is produced by lots of germs, for example by the *Enterobacteriaceae* family. This ability is used as one of the methods for the identification of this group of the germs. In very high dilution indole has got a smell of jasmine – it is one of the compounds of natural jasmine essential oil. It is used in perfumery to produce synthetic jasmine essential oil which is cheaper than the natural one. L–Tryptophan is the precursor of serotonin, melatonin, tryptamine and their metabolic pathway is presented in Fig. 1.

IAA – indole–3–acetic acid, 5–HTP – 5–hydroxytryptophan.

Performed HPLC analysis showed that all of the species of mushrooms that were studied contained non–hallucinogenic indole compounds. In the fruiting bodies of *Agaricus bisporus* melatonin, tryptamine, tryptophan, indole–3–acetic acid and kynurenic acid were quantitated (content from 0.11 to 6.21 mg/100 g d.w.). The analysis of indole compounds in the fruiting bodies of edible mushrooms e.g. *Lactarius deterrimus* with chromatography/densitometry method showed the presence of: L–tryptophan (0.24 mg/100 g d.w.) and their derivatives tryptamine (2.73), melatonin (0.19), indole–3–acetic acid (0.36) and indole (0.63) [5]. Content of serotonin quantitated in the fruiting bodies of *Agaricus bisporus* varied from 5.21 to 31.71 mg/100 g d.w. in the fruiting bodies of *Leccinum rufum*. Apart from serotonin there were melatonin, indole–3–acetonitrile, indole–3–acetic acid, tryptamine, 5–hydroxytryptophan (content from 0.08 to 1.05 mg/100 g D.W.) quantitated in the fruiting bodies of *Leccinum rufum*. Similar quantity of this compound was detected only in the fruiting bodies of *C. cibarius* (29.61 mg/100 g

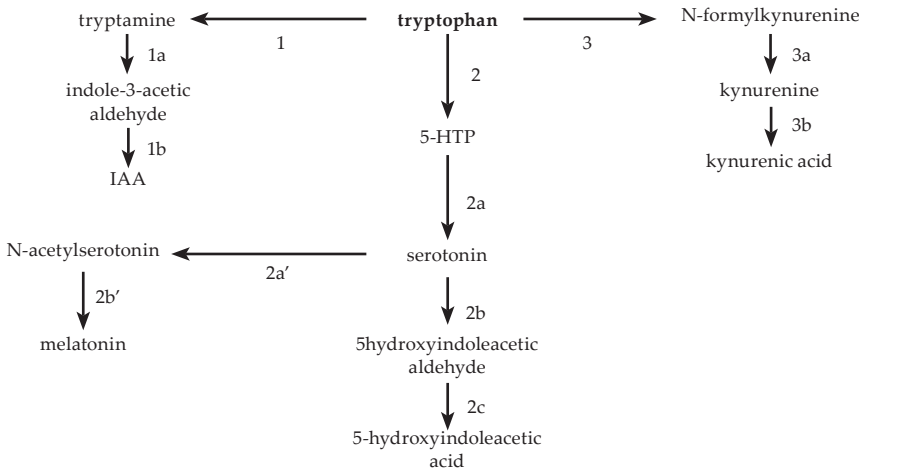

Fig 1. Metabolic pathway of tryptophan: 1. L–tryptophan decarboxylase, 1a. deaminase tryptamine, 1b. aldehyde dehydrogenase, 2. tryptophan hydroxylase, 2a. aromatic amino acid decarboxylase, 2b. monoaminoxidase, 2c. aldehyde dehydrogenase, 2a'. serotonin N–acetylase, 2b'. O–metyltransferase 5–hydroxyindole, 3. formylkynureninase, 3a. formamidase, 3b. kynurenine aminotransferase

d.w.). Other metabolite from this group which was detected in *Suillus luteus* was the final product of indole compounds metabolism in the human body – kynurenine sulfate in the content of 19.57 mg/100 g d.w. [6–14].

L–Tryptophan (Fig. 2) is an essential amino acid for humans, therefore it needs to be delivered to the body with food.

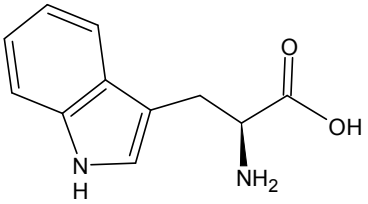

Fig. 2. L–Tryptophan

In the central nervous system of the human body tryptophan is modified to serotonin and melatonin. In the peripheral nervous system L–tryptophan undergoes three main transformations: decarboxylation which leads to tryptamine forming, hydroxylation to 5–hydroxytryptophan which is the precursor of serotonin and indole ring opening which leads to kynurenine forming. L–tryptophan tis also the precursor of niacin. Hypnotic and antidepressant activity (it crosses blood–brain barrier and is metabolized to serotonin) of this amino acid has been known for a long time [15,16]. Tryptophan is sometimes combined with other antidepressants in the depression therapy. It is also contained in some dietary supplements used in the treatment of depression, stress and sleep problems.

Each of species of mushrooms studied with HPLC and densitometric method contained L–tryptophan which is the precursor of indole–structure neurotransmitters and hormones in the human body. Contents of this metabolite varied from 0.16 to 25.60 mg/100 g d.w. L–tryptophan is an essential amino acid for human, which means it must be delivered with food. L–tryptophan is a substrate for synthesis of important for the body substances such as neurotransmitters (e.g. dopamine, melatonin, serotonin, adrenaline) or vitamins (niacin) [16]. The highest amount of L–tryptophan was quantitated in the extracts of the fruiting bodies of *Suillus. bovinus* without thermal processing – 25.90 mg/100 g d.w. The lowest amount of L–tryptophan was quantitated in the fruiting bodies of *Cantharellus cibarius.* Among the extracts treated with thermal–processing, the highest amount of L–tryptophan was quantitated in the fruiting bodies of *S. bovinus* – 17.71 mg/100 g d.w. Thermal–processed edible mushrooms, especially *S. bovinus* can be a source of L–tryptophan and an alternative to animal

products. In case of *Boletus edulis* (Fot.1), the amount of L–tryptophan was higher in thermal–processed material than in dried fruiting bodies.

The reason of that may be the degradation of indole compounds such as serotonin and 5–hydroxytryptophan (to tryptophan) which is suggested by their high level in *B. edulis* without thermal processing. In the fruiting bodies of *Armillaria mellea* which were analysed qualitatively with HPLC method and then quantitatively with chromatography/densitometry method presence of serotonin, tryptamine and L–tryptophan (contents varied from 2.21 to 4.47 mg/100 g d.w.) was alleged. Among all of the quantitated indole compounds in the fruiting bodies of *Armillaria mellea* the highest content was measured for L–tryptophan (4.47 mg/100 g d.w.) [8].

Fot.1. Boletus edulis – King bolete (fot. Magdalena Zając)

5–Hydroxytryptophan, a direct precursor of serotonin [17,18] when administered with food easily crosses blood–brain barrier in the central nervous system where is transformed to serotonin (serotonin does not cross blood–brain barrier). In some countries (Great Britain, United States of America, Canada) it is used as a diet supplement with antidepressant, appetite–reducing and hypnotic activity. For that purpose it is extracted from the seeds of African plant called *Griffonia simplicifolia*.[17]. Absorption of 5–hydroxytryptophan does not require the existence of transport molecule. It is not affected by the presence of other amino acids, therefore 5–hydroxytryptophan can be administered with meals without the impact of its effectiveness. Absorption of this compound after oral administration is good, ca. 70% of the dose reaches bloodstream. It is proved that therapeutic administration of 5–hydroxytryptophan can be effective in the treatment of such diseases as depression, fibromyalgia, chronic headaches and insomnia [17].

5–Hydroxytryptophan, direct precursor of serotonin and melatonin was present in non–processed as well as in thermal–processed fruiting bodies. However, the highest amounts of it were observed in the species of mushrooms that were not thermally processed. Maximal amounts of this metabolite were found in the extracts from non–processed fruiting bodies: *entinus. edodes* (24.83 mg/100 g d.w.), *Macrolepiota procera* (22.94 mg/100 g d.w.), *Suillus bovinus* (15.83 mg/100 g d.w.) and in the extracts from thermally–processed fruiting bodies of *Macrolepiota procera* (10.11 mg/100 g d.w.) [11]. 5–Methyltryptophan in non–processed species was quantitated only in *Leccinum scabrum* (Fot. 2), but its amount was highest of all studied species (8.32 mg/100 g d.w.).

The presence of this compound was confirmed in four species: *B. edulis, C. cibarius, Lactarius deliciosus* and *Pleurotus ostreatus* in the amounts similar to those quantitated in *L. scabrum* [6–14].

Serotonin – 5–hydroxytryptamine (Fig. 3) was isolated in 1937 from enterochromaffin–like cells located in the digestive tract. Its discoverer, Italian scientist was looking for the compound responsible for contraction of smooth muscles.

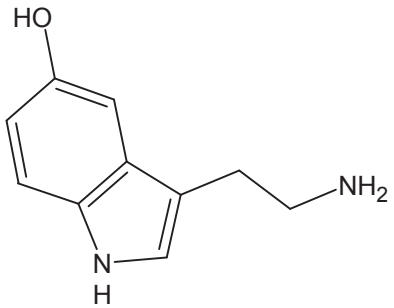

Fig. 3. Serotonin

At the time it was called "enteramine". In 1948 Maurice Rapport and Irvine Page isolated and

described 5–hydroxytryptamine. This compound was found after years of searching for the substance which action leaded to contraction and it was presumed that this effect is caused by platelets. It was named serotonin which comes from latin *serum* and greek *tonic*. In 1952 it has been proven that serotonin and enteramine is the same substance. Serotonin has got a wide spectrum of pharmacological activities and it acts as a neurotransmitter in the central nervous system and together with the melatonin as a regulator of the daily rhythm. Moreover, produced not only in the brain but mainly by enterochromaffin–like cells in duodenum it is involved in the contraction of smooth muscles, regulates gastrointestinal motility, affects blood pressure, takes part in blood clotting and acts as an antioxidant [17–20]. Serotonin, produced endogenously in the brain plays a very significant role in the regulation of sleep, anxiety, aggression, body temperature, mood, maturation process, regeneration and reduction of cell–aging process which leads to general improvement of the immunological system of the body. It is also one of the agents which regulate contraction and relaxation of blood vessels [22]. In patients with asthma it causes bronchi contraction. It is believed that serotonin takes part in the pathogenesis of migraine. Due to variety of serotonin activities it should not be a surprise that there are 7 types of serotonin receptors (5–HT) and several subtypes of each type. Many of drug classes act as agonists or antagonists of serotonin receptors or regulators of serotonin concentration. Drugs which act like that are mainly antidepressants, anxiolytics, antiemetics and antimigraine drugs. According to newest studies serotonin may be potentially used in the treatment of Alzheimer's disease [17–20]. It is used in the treatment of migraine and depression in doses from 100 to 600 mg. Actual presented studies show that there are species of edible mushrooms which contain more than 30 mg/100 g d.w. of this compound. In vitro studies showed that serotonin, melatonin and other indole derivatives (N–acetylserotonin, 6–methoxytryptamine) reduce lipid peroxidation in a dose–dependent mechanism [17–20].

The highest amount of serotonin was detected in the fruiting bodies of *Suillus luteus* (34.11 mg/100 g d.w.). Serotonin was quantitated also in the high amount in non–processed fruiting bodies of *C. cibarius* (29,61 mg/100g D.W.) though there was lack of it in thermal–processed material due to its thermolability. In case of *Armillaria mellea*, *Boletus badius*, *Boletus edulis*, *Lactarius deliciosus*, *Pleurotus ostreatus* (Fot. 3) presence of serotonin was confirmed also only for non–processed fruiting bodies. In non–processed *L. scabrum* amount of this metabolite was 13.09 mg/100 g d.w. which decreased to 2.07 mg in thermal–processed material of the same species.

On the other hand, serotonin was found in extracts of thermal–processed fruiting bodies of *L. edodes* i *S. bovinus* and was not detected in extracts from non–processed fruiting bodies of this mushrooms. If administered orally, serotonin does not cross to central nervous system through blood–brain barrier but can regulate gastrointestinal motility [17].

Kynurenine is an amino acid and metabolite of L–tryptophan used in the production of niacin. This compound is present in the blood and various human organs. 40% of this substance is synthesized by glial cells in central nervous system and remaining 60% derives from peripheral tissues and is accumulated in the plasma [21]

Fot. 2. Leccinum scabrum – the birch bolete (fot. Magdalena Zając)

As an antagonist of NMDA receptor, kynurenic acid is responsible for adaptation processes in the human body. This compound is present in every organ of mammals; its highest concentration is observed in hepatocytes and lowest is observed in the brain. It elicits dose–dependent hypotonia which

Fot. 3. Pleurotus ostreatus – the oyster mushroom (fot. Bożena Muszyńska)

is the mechanism of its neuroprotective activity in case of the hipoxia of the brain. Furthermore, kynurenic acid prevents the formation of gastric and duodenal ulcers [21]. In extracts from fruiting bodies of *C. cibarius*, *L. deliciosus* i *B. badius* high amounts of tryptophan degradation product: kynurenine sulfate (respectively 39.20; 4.81 i 3.53 mg/100 g d.w.) was detected [6–14]. In case of kynurenine sulfate and indole–3–acetic acid temperature causes their decomposition. Highest concentration of indole–3–acetonitrile was observed in extracts from thermal–processed fruiting bodies of *C. cibarius* (4.94 mg/100 g d.w.) and *B.edulis* (2.07 mg/100 g d.w.) [10,11]. Presented research of the presence of indole compounds in thermal–processed and non–processed mushrooms were performed for the first time.

Melatonin (Fig. 4). Other indole compounds which occurred most often in studied taxon are melatonin and tryptamine [23,24].

Melatonin (N–acetyl–5–methoxytryptamine) is produced mainly in pineal gland by pinealocytes, retina and in the digestive tract. L–tryptophan is the precursor in this synthesis and it is transformed to 5–hydroxytryptophan and next to 6–hydroxytryptamine. Serotonin is modified to melatonin in two–steps process. Production of melatonin is inhibited by the light. In the darkness production and excretion of melatonin are increased. Cells of the pineal gland uptake 5–hydroxytryptamine from blood and metabolize it to melatonin and its derivatives. Excretion of melatonin increases in case of darkness and decreases due to exposition to the light. This substance is involved in the regulation of sleep, mood and reproduction – it coordinates the functioning of the biological body clock which controls daily rhythms; it also enhances cellular self–renewal processes and acts as anti–aging and anticancer agent. Biological effects occur due to activation of melatonin receptors. Melatonin is available as a medicinal product used as an adjuvant in the therapy of sleep problems connected to the time zone change or shift working [25,26]. Melatonin is also a strong antioxidant and delays aging processes by free radicals neutralization, e.g. radical hydroxyl (•OH). As a result it may reduce damage of some types of Parkinson's disease. Then there are research which show that it is effective in the treatment of Alzheimer's disease. In the neurodegenerative diseases melatonin plays nueroprotective role [23,26]. Studies had shown that melatonin has also got immunomodulatory and anti–inflammatory activities. Unfortunately, the level of melatonin after thirty five and mainly after forty year of age sharply

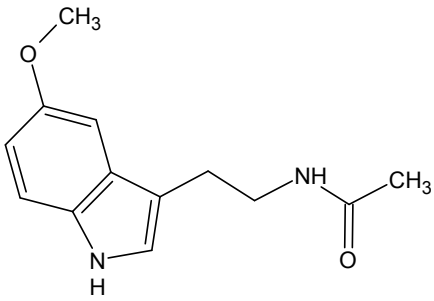

Fig. 4. Melatonin

decreases which leads to faster aging and increased risk of cancer. Serotonin, melatonin and their derivatives are also used as anti–inflammatory and analgesic drugs [24]. Melatonin was less often quantitated in studied species of mushrooms. It was present in small amounts in extracts from fruiting bodies of *B. edulis*, *C. cibarius*, *L. deliciosus*, *Lentinus edodes* i *M. procera* (from 0.07 to 1.29 mg/100 g d.w.) [6–14]. Highest content of this metabolite was contained in the *C. cibarius* (4.40 mg/100 g d.w.) [9].

Tryptamine – 3–2–aminoethyl–indole (Fig.5) is an biogenic amine occurring in living organisms and synthesized from tryptophan.

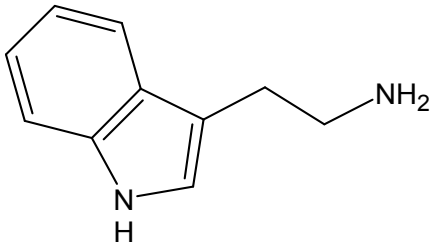

Fig. 5. Tryptamine

Its presence was also detected in the human brain and it is believed that tryptamine plays the role of neuromodulator or neurotransmitter and that there are tryptamine receptors existing. This compound is the basal structure for the group of substances called tryptamines. There are many biologically active substances located in this group. Best known of tryptamines are serotonin and melatonin. Some of tryptamines found its use in the medicine (e.g. sumatriptan and its derivatives) [27–31]. Tryptamine is the only one of studied metabolites that may interact with drugs e.g. with monoamine oxidase inhibitors (MAO–I) which may lead to fatal intoxication [16].

Tryptamine in trace amounts is located in the brain of mammals and plays there a role of neuromodulator [21–31]. Its presence was quantitated in thermally–processed as well as in non–processed mushrooms and the content varied from 0.01 to 3.15 mg/100 g d.w. in non–processed material which was similar to the content in processed material: 0.36 – 3.15 mg/100 g d.w. 5–Methyltryptamine was detected in three species of mushrooms*: Suillus bovinus*, *Macrolepiota procera* i *Auricularia polytricha* (respectively 6.51; 2.54; 0.19 mg/100 g d.w.) but its content decreased after thermal–processing (respectively 0.12; 0.93; 0.06 mg/100 g d.w.) [14].

In presented studies other indole derivatives occurring in fruiting bodies of mushrooms are plant's auxins. Indole–3–acetic acid is plant hormone (phytohormone) from the auxin group. This compound regulates growth and cells division. It is considered to be one of the most important of natural auxins. The other compound from the same group is indolile–3–acetonitrile which is indole–3–acetic acid derivative. Presence of indole–3–acetic acid was confirmed only in case of two species: *Lactarius deliciosus* i *Pleurotus ostreatus* (2.04 and 0.21 mg/100 g d.w.). Highest concentration of indoleacetonitrile was observed in extracts from thermal–processed fruiting bodies of *Cantharellus cibarius* (4.94 mg/100 g d.w.) and *B. edulis* (2.07 mg/100 g d.w.) [14] Presented research of the presence of indole compounds in thermal–processed and non–processed mushrooms were performed for the first time [14].

The biggest variety of indole compounds was quantitated in extracts from non–processed fruiting bodies of *C. cibarius*. There were investigated whether either extracts from *C. cibarius* fruiting bodies or *in vitro* cultures derived from it contain similar indole compounds: serotonin, melatonin, L–tryptophan, 5–hydroxytryptophan, 5–methylotryptophan, indole, indole–3–acetonitryle and kynurenine sulphate (in fruiting bodies the contents ranged from 0.02 to 17.61 mg/100 g d.w.) [12]. Additionally, fruiting bodies also accumulate tryptamine. Substances which were present in the highest quantity in the examined material were serotonin, L–tryptophan and 5–hydroxytryptophan. The lowest amount of indole compounds (L–tryptophan and tryptamine only) was detected in thermal–processed fruiting bodies of *Armillaria Mellea* [14].

Conclusions

In conclusion, it is important to say that edible mushrooms are valuable source of physiologically active non–hallucinogenic indole compounds. However, preparation of dishes from mushrooms affects the concentration of the studied metabolites. Growth of the temperature causes partial loss of their amount but even after thermal–processing they are still great source of indole compounds, especially of precursors of indole derivatives with antidepressant and antioxidant activities such as L–tryptophan, 5–hydroxytryptophan, tryptamine, serotonin and melatonin. It is important that serotonin does not cross blood–brain barrier but other compounds such as L–tryptophan and 5–hydroxytryptophan have got

that ability and they are modified to serotonin in the brain which is the reason of their antidepressant activity. Besides, eating meals containing mushrooms is safe and beneficial due to their health–improving compounds which protect the organism from civilisation diseases. Analysis of studied species of mushrooms shows, that even after thermal–processing of fruiting bodies of *Cantharellus cibarius*, *Boletus badius*, *Lactarius deliciosus*, *Macrolepiota procera*, *Pleurotus ostreatus* and *Suillus bovinus* they are the richest source of bioactive indole compounds.

Resumo

Fungoj kapablas akumuli ĉiujn metabolaĵojn ĉu primarajn aŭ sinsekvajn. Kuracaj kaj antioksidantaj proprecoj de fungoj estas bona kombinaĵo kiel valora enhavo de nutraĵo. La lastaj studoj demonstras, ke manĝeblaj specoj de fungoj enhavas nehalucinogenajn indolajn kemiajn kombinaĵojn kaj iliajn sinsekvajn kombinaĵojn. Sur la kemia strukturo de indolaj kemiaj kombinaĵoj baziĝas substancoj, kiuj estas bezonataj por la homa korpo kiel serotonino kaj melatonino. Tiuj ĉi kemiaj kombinaĵoj plenumas rolon de neŭrotransmisiloj aŭ iliaj prekursoroj, antioksidantiloj, antikanceraj agantoj, antimaljunigiloj, regulantoj de diurna ciklo de homoj kaj partoprenas en reguligo de koagulado de sango. Tiuj ĉi kemiaĵoj kaj ĝiaj postsekvaĵoj havas kontraŭinflaman kaj kontraŭdoloran efikon.

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