

# Toxicological and pharmacological profile of *Amanita muscaria* (L.) Lam. – a new rising opportunity for biomedicine

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## Abstract

*Amanita muscaria*, commonly known as fly agaric, is a basidiomycete. Its main psychoactive constituents are ibotenic acid and muscimol, both involved in ‘pantherina-muscaria’ poisoning syndrome. The rising pharmacological and toxicological interest based on lots of contradictive opinions concerning the use of *Amanita muscaria* extracts’ neuroprotective role against some neurodegenerative diseases such as Parkinson’s and Alzheimer’s, its potent role in the treatment of cerebral ischaemia and other socially significant health conditions gave the basis for this review. Facts about *Amanita muscaria*’s morphology, chemical content, toxicological and pharmacological characteristics and usage from ancient times to present-day’s opportunities in modern medicine are presented.

## Keywords

*Amanita muscaria*, muscimol, ibotenic acid

## Introduction

*Amanita* mushrooms belong to divis. Basidiomycota, class Agaricomycetes, ord. Agaricales, fam. Amanitaceae (Bas 1969; Persoon 1801). Species of the genus *Amanita* are distributed worldwide and are generally easy to recognize. Native to conifer and deciduous woodlands throughout the temperate and boreal regions of the Northern Hemisphere, including regions such as Hindu Kush, the Mediterranean, and also Central America (Tulloss 2005). There are around 1000 species of *Amanita* worldwide (Tulloss 2005). About 100 species of the genus are considered poisonous and about 50 are edible. Some recent molecular studies propose that before spreading across Asia, Europe, and North Ame-

rica, the genus had an ancestral origin in the Siberian-Beringian region in the Tertiary period (Geml et al. 2008).

The cap of *A. muscaria* may be orange or yellow (or rarely, with red and yellow alternating sectors) at first. Some populations in North America and Europe may have consistently yellow or white caps (Geml et al. 2008). According to Tulloss (2005) the cap is orange-red, 90–145 mm wide; the volva is distributed over the cap as white or yellow warts that are easily removed by rain; the gills are free to narrowly adnate, crowded to sub-crowded, and white or whitish; the short gills are truncate; the stipe is 60–210 × 8–22 mm and has a skirt-like annulus and notable bulb of a rather variable shape (up to 46 × 45 mm). Rings of volval material commonly encircle the top of the bulb and the base of the stipe. The spores measure (7.4)8.5



**Figure 1.** *A. muscaria* (L.) Lam. in Belasitsa Mountain, Bulgaria.

–11.5(13.1) × (5.6)6.5 – 8.5(9.8) μm and are broadly ellipsoid and inamyloid. Clamps are very common at bases of basidia (Fig. 1).

*A. muscaria* forms symbiotic ectomycorrhizal associations with a broad range of hosts from the families Betulaceae, Cistaceae, Cupressaceae, Pinaceae, Rosaceae and Salicaceae, though associates most frequently with tree members of genera *Betula*, *Pinus*, *Pice* and *Eucalyptus* (Dunk et al. 2011).

There is a vast amount of literature on the poisonous agents in *Amanita* species. Some produce alkaloids with hallucinogenic properties. *A. muscaria* as a widespread fungus containing ibotenic acid and muscimol (Takemoto et al. 1964, Eugster et al. 1965) has been used to catch flies for centuries due to the exclusive presence of glutamate-gated chloride channels in invertebrates where glutamate and ibotenic acid serve as excitatory and inhibitory neurotransmitters in insects (Stebelska 2013). Some simple preparation methods were soaking the fungus in milk or water or sprinkling milk directly on the cap, while others were more complex and included a combination of heat or mechanical processing and soaking (Rubel and Arora 2008). The release of ibotenic acid was time-dependent, with the extracted amount increasing over time (Lumpert and Kreft 2016).

Thousands of years before this usage began, the psychotropic effects of the mushroom were widely used by the inhabitants of Siberia, Kamchatka, and the Vikings. The ‘fairy’ mushrooms as well as *A. muscaria* appeared on rock paintings, dated back to 3500 BC, in a cave in present Algeria, depicting dancing figures, holding mushrooms in their hands (Wieczorek 2014). Similar findings from Central America suggest that hallucinogenic mushrooms were used in the Aztecs’ and the Mayas’ religious rituals (Feeney 2010).

The main psychoactive substances of the mushroom are muscimol, ibotenic acid and mukazon. When ingested the mushroom leads to a state resembling alcoholic intoxication (Meyer and Quenzer 2005) known as ‘pantherina-muscaria’ poisoning syndrome. The custom of peeling the cuticle before mushroom consumption aims to eliminate the highest content of psychoactive substances (Catalfomo and Eugster 1970). Cooking would eliminate the greater part of the active water-sol-

uble substances by heat. For instance, Mexican people ate the carpophore of *A. muscaria* without the cuticle and also discarded the cooking water. (Perez-Silva and Herrera-Suarez 1991) In Italy, after boiling and discarding the water, *A. muscaria* is preserved in brine prior to consumption. In North America, the mushroom is dried and then smoked after the red cuticle is peeled (Rubel and Arora 2008). Apart from intoxication in people who voluntarily ate the mushroom for a hallucinogenic experience, *A. muscaria* poisoning has been reported in children (Benjamin 1992) and in adults who ingested it by mistake. This is a case of misscollection because the white spots on the cap sometimes wash away during heavy rain and the mushrooms may resemble the edible *A. caesarea*. Death from this kind of mushroom is rare or rarely reported. If so, it is due to complications.

## Chemical compounds in *A. muscaria*

The chemical composition of the mushroom depends on the substrates, atmospheric conditions, age, and development stage. Mushrooms are rich in proteins, fats, carbohydrates, vitamins of group B (thiamine, riboflavin, pyridoxine, pantothenic acid, nicotinic acid, nicotinamide, folic acid and cobalamin), but also in ergosterol, biotin, phytochinone, and tocopherols.

According to FDA classification (2012) there are four main categories of mycotoxins:

- protoplasmic poisons (that result in generalized destruction of cells, followed by organ failure);
- neurotoxins (that cause neurological symptoms such as profuse sweating, coma, convulsions, hallucinations, excitement, depression, spastic colon);
- gastrointestinal irritants (that produce rapid, transient nausea, vomiting, abdominal cramping, and diarrhoea);
- disulfiram-like toxins (which are generally non-toxic and produce no symptoms unless alcohol is consumed within 72 h after ingestion);
- external intoxicants as heavy metals and radioactive contaminants (due to polluting environmental conditions where the mushrooms are harvested).

The pharmacology of *Amanita muscaria* is not entirely understood. Two primary compounds, ibotenic acid and muscimol, are known to be responsible for its psychoactive effects. Ibotenic acid, a neurotoxin, serves as a pro-drug to muscimol, with approximately 10–20% converting to muscimol after decarboxylation). Only 53 mg of muscimol are sufficient to produce psychoactive effects when ingested, while a dose of 93 mg produces a strong inebriation, including vomiting (Chilton and Ott 1975). In human volunteers, effects were measurable about 1 h after ingestion of 7.5 to 10 mg of muscimol, or 50 to 90 mg of ibotenic acid. These effects

continue for 3 to 4 h with some residual effects lasting as much as 10 to 24 h in some subjects. (Chilton and Ott 1975). Waser (1979) reported flushing, lassitude, and sleepness after ingestion of 20 mg of ibotenic acid and 5 mg of muscimol. The LD<sub>50</sub> of muscimol in rats ranges from 4.5 mg/kg administered intravenously to 45 mg/kg, oral gavage (p.o.) (Ott 1976). Experiments in dogs suggest that the effects of 20 mg/kg/day, p.o., are not cumulative (Waser 1979). Probably its psychoactivity is caused purely by the decarboxylation product of ibotenic acid, muscimol (Ott 1976).

According to Stebelska (2013), psychedelic effects in adults occur after an oral intake of approx. 6 mg of muscimol or 30 to 60 mg ibotenic acid (one fruit body of *A. muscaria*, 50–70 g, may contain up to 70 mg of ibotenic acid). The symptoms such as dizziness, nausea, tiredness, a feeling of weightlessness, visual and auditory hypersensitivity, space distortion, unawareness of time, and coloured hallucinations start 20–30 min after ingestion and usually end within 2 to 8 h to full recovery in 24 h (Satora et al. 2005). There is no specific antidote or therapy. The treatment is mainly supportive and symptomatic. Only in the first 2 h activated charcoal may be given or urgent gastric lavage can be applied. Sedation is urgently needed. Atropine is not recommended but may be administered subcutaneously. Special attention must be given to medications for seizure control with precaution, because GABAergic anticonvulsants such as benzodiazepines or barbiturates may contribute to respiratory or central nervous system depression (Michelot and Melendez-Howell 2003; Benjamin 1992).

The main toxins in *A. muscaria* are muscarine, ibotenic acid, muscimol and muscazone (Eugster and Takemoto 1967). The mushroom is known as an effective bioaccumulator of vanadium (in an organometallic compound called amavadine) and other toxic metals (Berry et al. 1999). Stizolobic acid, stizolobinic acid and tricholomic acid are also present as derivatives of ibotenic acid. These three compounds are related to L-DOPA oxidation products, which are known to cause anticholinergic activity. These three amino acids can activate excitatory amino acid receptors, but there are probably not enough of these compounds to have an effect, at least in most *Amanita muscaria* poisonings (Chilton et al. 1974).

## Muscarine

In 1869, muscarine (Fig. 2) was isolated from European *A. muscaria* and was for decades believed to be the main active principle (Eugster 1979), from which the compound derives its name. Muscarine is a selective cholinergic agonist suspected to contribute to the overall activity of *A. muscaria*. Muscarine is both water soluble and thermostable (does not degrade with cooking). It is known to be responsible for reduced heart rate, lowering of blood pressure, vomiting, diarrhoea, bradycardia, bronchorrhoea, tearing, bronchospasm (asthmatic-like breathing), salivation, pupil contraction and blurred vision.

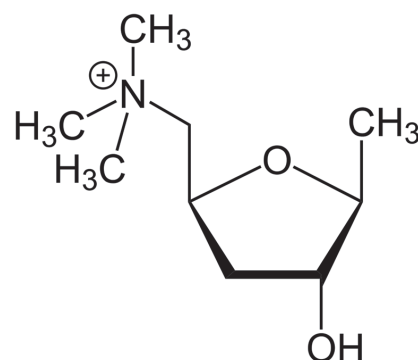


Figure 2. Structure of muscarine.

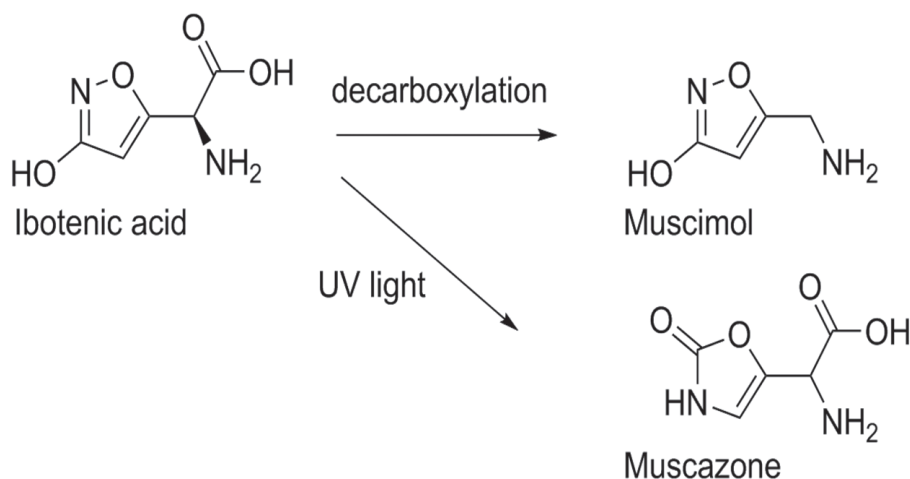
## Izoxazoles

Muscazone (Fig. 3) (2-Amino-2-(2-oxo-3H-1,3-oxazol-5-yl)acetic acid) is another compound that has been isolated from European specimens of the fly agaric (Fritz et al. 1965). It is a product of ibotenic acid breakdown by UV radiation. Muscazone has a minor pharmacological activity compared with the other agents (Catalfomo and Eugster 1970).

Ibotenic acid and muscimol are structurally related. Muscimol, being structurally similar to GABA is a potent GABA<sub>A</sub> receptor agonist, while ibotenic acid is an agonist of NMDA glutamate receptors interactions causing the hallucinogenic effects observed during intoxication (Johnston, 2009).

Ibotenic acid, (*S*)-2-Amino-2-(3-hydroxyisoxazol-5-yl)acetic acid, is a colourless, crystalline substance soluble in water (Fig. 3). It is metabolized by decarboxylation in the stomach, liver, and brain (Nielsen et al. 1985) to equal amount of muscimol which pass the blood-brain barrier (Michelot and Melendez-Howell 2003). Both substances can be detected in urine within 1 h of exposure (Merovala et al. 2008). Ibotenic acid, unlike muscimol, is much more dangerous, causing ibotenate-induced seizures and lesions in specific brain regions, similar to Alzheimer's disease for which it is used in animal test models (Stebelska 2013). Stereotactic intrahippocampal administration of ibotenic acid (5 µg/µl) lesioned rats impairs cholinergic transmission, learning and memory performance (related to Alzheimer's disease) and thus chosen as a suitable model to understand drug efficacy in preventing Alzheimer's disease pathophysiology (Patocka et al. 2017).

Exposure to chronic stress in young male rats increases hippocampal glutaminergic receptor density or affinity, thus making *cornus ammonis* neurons more vulnerable to ibotenic acid (Conrad et al. 2007). In Alzheimer's disease (AD), where HPA (hypothalamic-pituitary-adrenal) activity is elevated, hippocampal NMDA receptor number does not generally decrease. The results on the presence of NMDA sites in the majority of AD cases indicate that receptor density is preserved except in cases where there is extremely severe cell loss. Rats exposed to the same paradigm of chronic restraint do not show increase in hippocampal NMDA or non-NMDA receptor binding (Geddes et al. 1986).



**Figure 3.** Chemical changes of ibotenic acid to muscazone and muscimol.

Muscimol (5-(Aminomethyl)-isoxazol-3-ol) was isolated from *A. muscaria* in the early 1960's (Takemoto et al. 1964; Eugster, Muller and Good 1965) as a colourless, crystalline substance, readily soluble in cold water (Fig. 3). It appears to be the essential principle of *Amanita muscaria* since it is present in very high concentration (0.03–0.1%) of fresh mushroom (DeFeudis 1980). Oral, systemic, or intracerebral administration of muscimol undoubtedly affects certain CNS functions and behaviour. Muscimol is a non-selective GABA<sub>A</sub> receptor agonist activating both pre- and postsynaptic receptors and partial agonist of GABA<sub>C</sub> receptors devoid of effects on the GABA-metabolizing enzyme, GABA<sub>A</sub> transaminase, and the GABA<sub>A</sub> uptake systems which also enters the brain after peripheral injection (Snodgrass 1978). It is reported to be a potent agonist at bicuculline-sensitive, strychnine-insensitive postsynaptic receptors of the mammalian central nervous system. For example, muscimol (3 mg/kg, i.p.) evokes serotonin rise and decreases catecholamine levels in the brain. The compound binds to GABA<sub>A</sub> receptors mainly in the areas of the forebrain, including the *caudate nucleus* and putamen, the thalamus and the hippocampal formation leading to the opening of the receptor associated with the chloride ion channel, which in turn leads to inhibition of neuronal activity, where these receptors are located (Stebelska 2013). Muscimol high-affinity binding in forebrain regions such as *caudate – putamen, thalamus, and hippocampus* was dependent on distinct population of GABA<sub>A</sub> receptors possibly containing subunit 6 and lacking subunit 1 as shown in knockout study in mice (Chandra et al. 2009).

### Central nervous system activity

Like LSD, muscimol and ibotenic acid induce a generalized increase of serotonin but only muscimol keeps the serotonin concentration increased in midbrain and hypothalamus after pre-treatment with p-chlorophenylalanine (a serotonin synthesis inhibitor). Muscimol and LSD

cause a decrease of the catecholamines, as on the contrary ibotenic acid increases the catecholamine concentration (Konig-Bersin et al. 1970).

A low dose of muscimol injected at doses of 0.5–1 mg/kg i.p. affects the EEG of cats and rabbits (De Carolis et al. 1969). These observations further support a localization of action of muscimol in the brain rather than in the peripheral nervous system.

Recently it has been suggested that GABA is involved in morphine analgesia. The injection of 0.15 to 0.2 mg/kg of muscimol i.v., lowered ED<sub>50</sub> dose of morphine in mice and rats. Muscimol given alone, at doses up to 2.0 mg/kg (i.v.) failed to cause analgesia in mice or rats. However, when injected intravenously 10 min before morphine at a dose of 0.15 mg for morphine analgesia in mice from 4.1 mg/kg (s.c.) to 1.6 mg/ ED<sub>50</sub> is highly significant (Biggio et al. 1977).

Reversible inactivation of brain areas is an useful method for inferring brain-behaviour relationships. Infusion of GABA or of the GABA receptor agonist muscimol is considered one interesting reversible inactivation method because it may not affect fibres of passage and may therefore be compared to axon-sparing types of lesions (Majchrzak et al. 2000). Concluding that reversible inactivation techniques significantly contribute to the knowledge of “where and when” neuronal events for learning and memory take place in the brain.

In concern to affecting memory, intra-hippocampal infusion of muscimol increased the percent of neurons active in *cornu ammonius* (CA3) significantly, improving rats' learning and memory abilities in both normal and AD-type rats suggesting that intensification of GABAergic processes may be an useful pharmacotherapeutic strategy in early memory decline in AD (Pilipenko et al. 2015). Infusions of muscimol into the dorsal hippocampus in male rats produce impairments in fear learning (at a dose of 0.5 mg of muscimol per hemisphere) (Corcoran and Maren 2001) and working memory (at a dose of 0.03–0.06 µg of muscimol) (Mao and Robinson 1998).

These findings suggest that because muscimol is a potent GABA<sub>A</sub> agonist, it is likely that hippocampal infusions of muscimol modulate learning through increased neural inhibition of the hippocampus.

The activation of the GABA<sub>A</sub> receptor by muscimol modulates the hypothalamic–pituitary–gonadal (HPG) axis increasing kisspeptin expression through stimulating KiSS-1 mRNA expression, in the hypothalamic neurons. Kisspeptin is a neuropeptide closely linked to the reproductive function of multiple species. Surprisingly, the natural GABA compound had no effect on KiSS-1 gene expression, in contrast to muscimol (Kanasaki et al. 2017).

Muscimol was also used as a prototype substance for the design of THIP (Gaboxazole, 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol hydrochloride,) an izoxazole investigated as insomnia and seizure medication but withdrawn from phase 3 clinical trials, due to efficacy and side effects problems (Johnston et al. 2009). The GABA receptors agonist used in a double-blind study administered orally (5–10 mg per day) to ten patients with Huntington's disease did not result in improvement of motor or cognitive functions but significantly ameliorated chorea in the most severely hyperkinetic patient, and it was associated with the appearance of dystonic features, electroencephalographic changes, and behavioural alterations in five patients. Moreover, adverse effects as increased irritability, agitation and lethargy, lack of attention, loss of appetite, and insomnia occurred in five patients and appeared to be dose related in each instance (Shoulson et al. 1978). However, the constant failure to prove muscimol's potential effect as an anticonvulsant only indicates that the GABA disturbances connected with motor deficits does not alone account for the clinical features of the ongoing disorders.

Potential of inhibitory mechanisms may be important to neuronal protection from the effects of ischaemia. The GABA<sub>A</sub> agonist effects of muscimol showed protective role in a dose-dependent manner in both rat and rabbit microsphere embolism model of ischaemia (Lyden and Hedges 1992). In a model of forebrain ischaemia, muscimol given 7 days before the onset, protected the cortex, hippocampus, substantia nigra, striatum and thalamus (Sternau et al. 1989), suggesting that the damaging effects from forebrain ischemia may be a result of excessive excitability or loss of inhibitory influence.

## Anticarcinogenic effects

Sonnenberg (1988) found that gastric cancer occurred more frequently in patients who had ischaemic heart disease or cerebrovascular disease, and concluded that gastric cancer and diseases related to hypertension share a common etiologic factor. Prolonged administration of the GABA<sub>A</sub> receptor-agonist muscimol (i.p. injections of 0.5 mg/kg body weight) attenuated the enhancement of *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG)-induced gastric carcinogenesis in spontaneously hypertensive rats (SHR) on the 52<sup>th</sup> week, resulting in a significant reduction in the incidence of gastric cancer (Tatsuta et

al. 1992) was again connected with GABA agonists activity over the control of anterior pituitary hormones; the sympathetic and parasympathetic nervous system. Using muscimol as a GABA<sub>A</sub> receptors agonist proved its protective role in treatment of oral squamous cell carcinoma (Jing Ma et al. 2016).

## Other bioactive compounds

### Antioxidants

Last but not least *A. muscaria*, like the other mushrooms from the genus, contain a vast amount of biologically active compounds with proven antioxidant activity: proteins and peptides (glutathione and ergothioneine), phenolic compounds (flavonoids, lignans, oxidized polyphenols, phenolic acids, stilbenes and tannins), vitamins and derivatives (ascorbic acid, ergosterol, tocopherols, carotenoids), and minerals (zinc and selenium). Their antioxidant properties and ability to scavenge free radicals have been further demonstrated in studies using rodent models with hepatic injury, induced by either streptozotocin (STZ), carbon tetrachloride (CCl<sub>4</sub>), or D-galactosamine (D-GalN). For example, the activation of GABA<sub>A</sub> receptor inhibits stem cell proliferation but protects differentiated cells from injures (Wang et al. 2017). Muscimol treatment decreases the formation of pseudo bile ductiles and the enlargement of hepatocytic canaliculi in GalN-treated rats revealing that a complex GABA signalling system exists in the rat liver. Its activation protects the liver against toxic injury (Wang et al. 2017).

### Pigments

The colouring of *A. muscaria* is due to a complicated mixture of pigments. Muscarufin and muscaflavin are terphenylquinone derivatives which give the yellow colouring. The betalain group composed of numerous betalamic acid condensates (muscapurpurin and muscaaurins) with different amino acids, ibotenic or stizolobic acid are responsible for the typical red-orange colour of the caps of *A. muscaria* (Michelot & Melendez-Howell, 2003). By repeated chromatography the pigment mixture has been fractionated into at least ten components, i. e. the orange muscaaurins, the yellow muscaflavin, the red-violet muscapurpurin and the red muscarubrin (Stintzing et al. 2007).

### Polysaccharides

Among polysaccharides, glucans are the most abundant and widely distributed carbohydrates in the fungal cell wall. A fucomannogalactan (Ruthes et al. 2013) and a (1→3),(1→6)-linked β-D-glucan (Kiho et al. 1994) were isolated from *A. muscaria* fruiting bodies and their biological activities were further studied against pain and inflammation as well as antitumor activity. All of these activities are a subject of further studies.

## Conclusion

The findings suggest that *A. muscaria* offers a great versatility of beneficial effects in cell protection and especially in neuroprotection, cardio protection, hepatoprotection, inflammation process, oxidative stress, and may even contribute to development of new drugs. The adverse effects

also call for supervised and cautious designed studies with pre-cautious administration of its active compounds especially muscimol. Still, mycotherapy turns to be a very promising territory for future investigations, but a lot of experiments, would be needed to validate the usefulness of *A. muscaria* and its compounds, either alone or in combination with existing therapies.

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