

Review

## *Amanita muscaria*: chemistry, biology, toxicology, and ethnomycology

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The fly agaric is a remarkable mushroom in many respects; these are its bearing, history, chemical components and the poisoning that it provokes when consumed. The 'pantherina' poisoning syndrome is characterized by central nervous system dysfunction. The main species responsible are *Amanita muscaria* and *A. pantherina* (*Amanitaceae*); however, some other species of the genus have been suspected for similar actions. Ibotenic acid and muscimol are the active components, and probably, some other substances detected in the latter species participate in the psychotropic effects. The use of the mushroom started in ancient times and is connected with mysticism. Current knowledge on the chemistry, toxicology, and biology relating to this mushroom is reviewed, together with distinctive features concerning this unique species.

### INTRODUCTION

The fly agaric, *Amanita muscaria*, and the panther, *A. pantherina*, are the species mainly involved in the 'pantherina-muscaria' poisoning syndrome. Poisoning cases are sometimes accidental and mainly those caused by *A. pantherina*, since this mushroom might be mistaken for some other species; but, in some cases, intentional consumption of *A. muscaria* occurs for recreational purposes. Prognosis of the poisoning is generally minor; although, very seldom lethal cases are mentioned. Central nervous system dysfunctions primarily characterize this poisoning. This review describes the unusual features associated with these species, medical, chemical, pharmacological, historical and phytogeographical and aims to synthesize current knowledge on these matter. The emphasis is, however, the chemical and biological properties of the substances found in the mushroom.

### THE SUSPICIOUS SPECIES

Detailed mycological data have already been published (Moser 1983, Bresinsky & Besl 1990, Takashi, Chihiro & Mitsuya 1999, Neville & Poumarat 2001). The main responsible species are *Amanita muscaria* (Fig. 1) and *A. pantherina*. The cap of *A. muscaria* can be

50 cm diam and bright red, orange, or even orange or yellow, apart from the white fleck. Many species of the *A. muscaria* complex bear so-called crassospores (Tulloss & Halling 1997). The species cannot be mistaken for any other perhaps except the edible *A. caesarea*. *A. pantherina* is also known as: 'panther cap', 'panther Amanita', 'panther agaric' (North America), 'pantherschwamm', 'krötenschwamm' (Germany), 'tignosa' (Italy), 'pantera', 'pixaca', 'hongo loco', 'hongo malo' (Spanish America) and 'amanite panthère' (French). The cap of *A. pantherina* is 5–10 cm diam and grey or grey-brown, grey yellow, paling when old, with small pure white flakes. This species, in some accidental poisoning cases, has been mistaken for the edible *A. rubescens* and *A. spissa*. These two species occur in many continents (Neville & Poumarat 2001) and grow in deciduous woods, especially beech and birch, and also coniferous ones (Hotson & Lewis 1934).

Some related species are suspected of poisoning or produce the active components detected in these fungi (Bresinsky & Besl 1990): *A. regalis* (Elonen, Tarssanen & Härkönen 1979) and *A. strobiliformis* (Takemoto, Yokobe & Nakajima 1964; syn. *A. solitaria* auct.). A few cases of poisoning by *A. gemmata* (Cornué 1961; syn. *A. junquillea*), *A. crenulata* (Buck 1965, Tulloss 1990), and *A. cothurnata* have also been reported, but their possible toxic potencies are disputed (Chilton & Ott 1976). Toxin content has been suggested to be related to the place of gathering, indicating chemical

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**Fig. 1.** *Amanita muscaria* (Italy: Piemonte, in woodland south of Torino, 1998). Photo: D. L. Hawksworth.

intraspecific variation (Benedict, Tyler & Brady 1966). Surprisingly, Chilton & Ott (1976) mentioned large amounts of chlorocrotylglycine and amino-2-hexadien-4,5-oic acid, both derivatives of glycine, in *A. smithiana*. Noting the functional identity ('toxicophore') of these latter substances, an enzyme inhibitor activity has to be suspected; nephrotoxic poisonings by this species have been reported (Leathem *et al.* 1997).

## THE POISONING SYNDROME

### *Characteristics of poisoning and symptomatology*

The poisoning syndrome due to *Amanita muscaria* and *A. pantherina* has been called 'mycoatropic', as the symptoms are similar to those induced by atropinic plants such as *Datura stramonium*, *Atropa belladonna*, and *Hyoscyamus niger*, but tropanic alkaloids are not present.

Chronosymptomatology is variable amongst subjects, depending on the rituals (Waser 1967, Festi 1985), and experimental and accidental poisonings. In rituals, the poisoned person (e.g. the shaman) is in search of a peculiar state of mind where autosuggestion is important. A 'delirium' is not completely created but the chemicals enhance the intellect (Levi-Strauss 1970).

Socio-cultural context and environment associated with the psychological and physiological state of the participant are pertinent (Rosenbohm 1995).

The 'pantherina-muscaria' syndrome is atropine-like and in the number and severity of poisoning cases fatality is rare. In most cases recovery is virtually complete after 24 h without noticeable after-effects (Bosman *et al.* 1965, Gerault & Girre 1977, Hatfield 1979, Lampe 1979, Bornet 1980, Gelfand & Harris 1982, Pegler & Watling 1982, Iancovitz 1983, Hanrahan & Gordon 1984, Benjamin 1992, Denoyer 1992). In contrast to *Cortinarius* (Michelot & Tebbett 1990), or *Gyromitra* poisoning syndromes (Michelot & Toth 1991), the fly agaric effects have a short latency like the *Coprinus* syndrome (Michelot 1992). In most cases as little as one cap, a cup of sautéed mushrooms, is a sufficient for psychotropic effects.

Symptoms start 30 min to 2 h after ingestion. A state of confusion, dizziness, and tiredness, visual and auditory aesthesia (hypersensitivity), space distortion, and unawareness of time; presents reinforced by the consumption of some psycho-sedative agents. Aggressive attitudes have not been reported. Dryness of the mouth and mydriasis (dilation of the pupils) have been mentioned. Hallucinations, vivid colour perception and a sense of time standing still, are disputed. A drowsiness period after 2 h follows, with vivid dreams. A deep sleep ends the poisoning, which lasts generally 8 h (Benjamin 1992, Davis & Williams 1999).

Subsequent gastrointestinal disorders with vomiting are inconstantly reported and are not characteristic of the syndrome (Festi & Bianchi 1992). No damage to organs has been reported although the active components may induce *in vivo* brain lesions. Regular consumption of the mushroom would probably be harmful, even though most human poisoning cases do not report any after-effects. Brain lesions in rodents treated with ibotenic acid and muscimol can occur (Lescaudron, Bitran & Stein 1992). According to Festi & Bianchi (1992), the biological effects are related to the period of collection, those collected in September induce more marked nausea and less narcotic and visionary experience than those collected in August. Mushroom intoxication in dogs has been reported; the chronosymptomatology is consistent with that in humans (Naudé & Berry 1997).

The symptomatology and chronology of poisoning events are summarized in Fig. 2.

### *Treatment*

The appropriate treatment is mainly symptomatic. First, eliminate the toxic substances from the gastrointestinal tract out by vomiting (e.g. administration of ipecac syrup; Benjamin 1992), stomach washout, or the administration of activated charcoal and purging, preferably in an intensive care emergency unit (M. Denoyer, pers. comm.). The actions of the active principles, ibotenic acid and muscimol, have to be

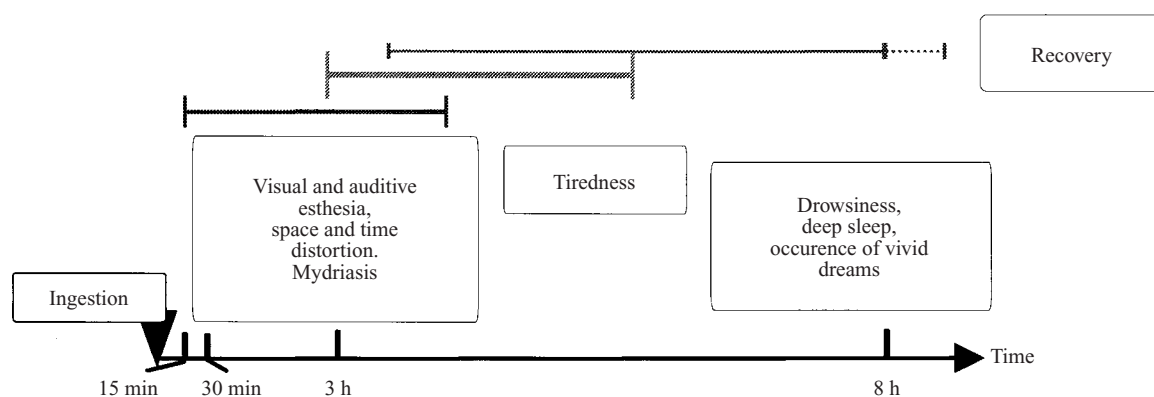


Fig. 2. Chronosymptomatology of the *Amanita muscaria* poisoning syndrome.

compared with that of atropine; consequently the use of the latter drug is strongly contraindicated. Physostigmine (eserine), a cholinesterase inhibitor, has been recommended as it counteracts the effects of poisoning by atropine and related antimuscarinic drugs. The intravenous dosage for adults and adolescents is 1–2 mg repeated when needed (Taylor 1992), the drug has also been used successfully in veterinary cases (Ridgway 1978). The administration of sedatives such as diazepam or clonazepam, by mouth or intravenously, in case of convulsions, as well as phenobarbitone has been suggested (Lambert & Larcan 1989, Garnier, Azoyan & Baud 1990, Benjamin 1992, Denoyer 1992). However, diazepam has been suspected as strengthening the action of muscimol (Hanrahan & Gordon 1984, Benjamin 1992). Contrary to some statements, cooking does not notably lower toxicity, demonstrating that the active components are not heat sensitive.

#### Legal status and enforcement

About 12 species of mushrooms are consumed for recreational purpose, but seldom *Amanita muscaria* (Samorini 1992). The Italian courts proscribe the use of psilocybin, psilocin and *A. muscaria* as well ('Stampa alternativa'). However, in Europe, interest in this type of drug is lower than in North America, where laws prohibit its use. The use of *A. muscaria*, even in Europe, is nevertheless growing. In some countries, possession of hallucinogenic mushrooms is not illegal, contrary to their purified substances and derivatives. In Europe, the current legislation mainly concerns *Psilocybe semilanceata*, and to a lesser extent *A. muscaria* (Festi 1985).

## CHEMICAL PRODUCTS

The fly agaric represented a challenge to chemists, biochemists, and biologists. The goals were: (1) the detection and mode of action of the substances involved in the psychotropic effect that might ultimately lead to the design of new drugs; (2) the isolation and chemical identification of the pigments responsible for

the characteristic hue of the cap; and (3) the discovery of miscellaneous unusual components. Amazingly, most substances produced are chemically and biogenetically interrelated, a common molecular architecture linking most of the structures (Eugster 1969).

#### The true toxins

Although the chemical constituents of this mushroom have been thoroughly investigated, a few details remain unclear; they concern the relationships between the physicochemical properties of the active components and the mode of consumption. For instance, Mexican people eat the carpophore of *Amanita muscaria* without the cuticle that has been peeled off, and also discard the cooking water (Pérez-Silva & Herrera-Suarez 1991). In Italy, after boiling and rejecting excess water, the mushroom is preserved in brine prior to consumption (Festi 1985). In North America, the red cuticle is peeled off, and the remainder dried, and then smoked (Ott 1978). These latter procedures would eliminate or destroy the greater part of the active water-soluble substances.

Muscimol and ibotenic acid are most likely to be the biologically active principles of the species of concern, but other active components are suspected. Different research groups performed almost simultaneous isolation and structure determination of the active components (Takemoto & Nakajima 1964c, Bowden & Drysdale 1965, Eugster, Müller & Good 1965, Good, Müller & Eugster 1965). The substances are isoxazole derivatives: ibotenic acid **1** (from 'iboten-gu-take', the Japanese name of *A. strobiliformis*, previously called 'pre-muscimol'; Good *et al.* 1965, Eugster & Takemoto 1967), its decarboxylation gives muscimol **2**; these compounds are only reported in *A. muscaria* and *A. pantherina* subspecies (Benedict *et al.* 1966).

Ibotenic acid (pantherin, agarin), i.e.  $\alpha$ -amino-3-hydroxy-5-isoxazoloacetic acid **1**, is colourless (crystals,  $C_5H_6N_2O_4$ , mol wt 158.11, mp 150–152 °C decomposition), readily soluble in cold water. Any attempt of dehydration leads to decarboxylation yielding quantitatively muscimol, thus suggesting that a meal

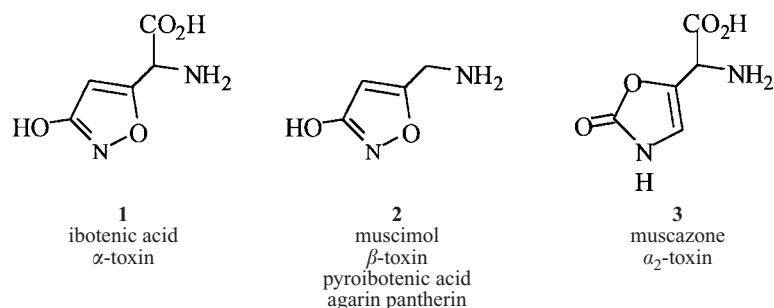


Fig. 3. Chemical structure of ibotenic acid, muscimol and muscazone.

of the cooked mushrooms, or even after gastric digestion, would only contain the latter substance, and be the agent responsible for the main symptoms. The red skin of the cap and the yellow tissue beneath contain the highest amounts of these substances, so explaining practices in removing it (Catalfomo & Eugster 1970a).

Muscimol, i.e. 5-(aminomethyl)-3-hydroxyisoxazole **2**, isolated from *A. muscaria*, is colourless (crystals, C<sub>4</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub>, mol wt 114.10, mp 175 ° decomposition) readily soluble in cold water (Bowden & Drysdale 1965). The structure of pantherine, isolated from *A. pantherina*, was found to be similar to that of ‘agarin’ (Konda, Takahashi & Onda 1985).

Muscazone, i.e. α-amino-2,3-dihydro-2-oxo-5-isoxazoleacetic acid **3**, is colourless (crystals, C<sub>5</sub>H<sub>6</sub>N<sub>2</sub>O<sub>4</sub>, mol wt 158.11, mp 190 °C decomposition) and was also detected and the structure confirmed by synthesis (Eugster *et al.* 1965, Fritz *et al.* 1965, Reiner & Eugster 1967). This lactame isomer of muscimol would result from photo-rearrangement of the latter structures (Göth *et al.* 1967), and is produced during isolation. Muscazone exhibits minor pharmacological activities in comparison with the previous substances. Interestingly, cycloserine (myxomycin, seromycin, D-4-amino-3-isoxazolidone) is an antimicrobial tuberculostatic agent that exhibits a similar carbon backbone as muscimol. It is known to induce effects on the central nervous system, but with a longer latency period: somnolence, confusion, and nervousness distinguish untoward effects (Mandell & Sande 1992) (Fig. 3).

Several syntheses of ibotenic acid and muscimol have been developed *via* different routes (Gagneux *et al.* 1965a, b, Sirakawa *et al.* 1966, Kishida *et al.* 1966, 1967, Fräter-Schröder, Good & Eugster 1969, Loev, Wilson & Goodman 1970, Nakamura 1971, McCarry & Savard 1981, Jäger & Frey 1982, Welch 1982, Oster & Harris 1983, Frey & Jäger 1985). Thio-derivatives and even more potent inhibitors of GABA uptake have been prepared (Lykkeberg & Krogsgaard-Larsen 1976, Krogsgaard-Larsen 1977). Gram-scale preparation has been performed by regiospecific 1,3-dipolar cycloaddition/elimination (Pevarello & Varasi 1992). Thio-muscimol derivatives have been prepared; they exhibit highly potent binding properties even able to displace GABA from its receptor (Melikian *et al.* 1992).

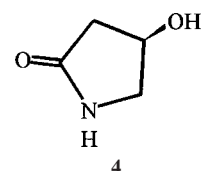


Fig. 4. Chemical structure of the hydroxypyrrolidone derivative.

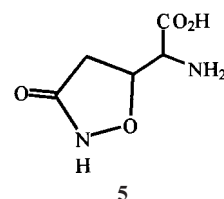


Fig. 5. Chemical structure of tricholomic acid.

#### Other active substances

(-)-R-4-hydroxy-pyrrolidone(2) **4**, whose structure is closely related to ibotenic acid and muscimol, was found in *Amanita muscaria* (Matsumoto *et al.* 1969a). This chemical frame is common in some micromycetes; they generally exhibit a potent biological activity against bacteria and other fungi (e.g. aureothrycin, equisetin). This additional compound, gives information on the biogenesis of ibotenic acid, muscimol, and muscazone. All probably originate from the same precursor, β-hydroxyglutamic acid; ring closures and decarboxylation then determine the structures of these products (Fig. 4).

Tricholomic acid **5**, a closely related dihydro derivative of ibotenic acid, has been identified in *Tricholoma muscarium* (Takemoto & Nakajima 1964b), and its structure was confirmed by synthesis (Iwasaki *et al.* 1965) (Fig. 5).

Stizolobic **6** and stizolobic acids **7**, known in *Stizolobium hasjoo* (Hattori & Komamine 1959, Senoh, Imamoto & Maeno 1964), have been found in *A. pantherina*, but not *A. muscaria*, low levels have been detected in *A. gemmata* (Chilton, Hsu & Zdybak 1974). Stizolobic acid, and to a lesser extent stizolobic acid, exhibit an excitatory action in an isolated rat spinal cord (Ishida & Shinozaki 1988). Biosynthetic studies show that both these amino acids originate from

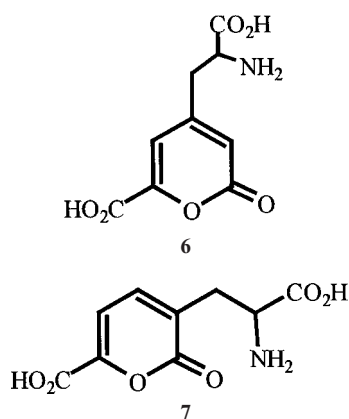


Fig. 6. Chemical structure of stizolobic and stizolobinic acids.

3,4-dihydroxyphenylalanine (DOPA) (Saito, Komamine & Senoh 1975, 1976, Saito, Komamine & Hatanaka 1978), and the enzymes implicated have been isolated and purified (Saito & Komamine 1978) (Fig. 6).

Muscarine has long been considered as the active principle in *A. muscaria* (Schmiedeberg & Koppe 1869, Kögl *et al.* 1957, Cox *et al.* 1958), due to a presumed action on the central nervous system. This was after discredited. Nevertheless, some publications still wrongly assert muscarine's involvement in the action, although several analyses have demonstrated that this agent, which occurs in minute amount in the *Amanita*'s of concern, is not responsible for the poisoning syndrome (Eugster & Müller 1959, Catalfomo & Eugster 1970b). The occurrence of only small amounts of muscarine **8**, i.e. tetrahydro-4-hydroxy-*N,N,N*-5-tetramethyl-2-furanmethanaminium, (0.0002–0.0003%, f.w.; chloride: stout prisms, mp 180–181 ° (Kögl *et al.* 1957, Cox *et al.* 1958), readily soluble in water) have been established in *A. muscaria* (Eugster & Schleusener 1969, Catalfomo & Eugster 1970a). They have to be considered minor components in comparison to some *Inocybe* spp. (to 0.43% in *I. substricta*) and *Clitocybe* spp. (to 0.15% in *C. dealbata*). The two *Amanita* species would not be able to induce any muscarinic syndrome without excessive consumption.

Equal quantities of the muscarine, showing the (+)-(2*S*,3*R*,5*S*) conformation, and (+)-(2*S*,3*S*,5*S*) *epi*-muscarine **9** have been detected in *A. pantherina* (Stadelmann, Müller & Eugster 1976a), as well as (–)-(2*S*,3*R*,5*R*) *allo*-muscarine **10** in *A. muscaria*. Although its occurrence was not demonstrated unambiguously, (+)-(2*S*,3*S*,5*R*) *epiallo*-muscarine **11** was not present in detectable amounts (Eugster & Schleusener 1969, Schleusener & Eugster 1970). Muscarine **8**, *epi*-muscarine **9** and *allo*-muscarine **10** have been detected in the mycelium of *A. muscaria* culture (Stadelmann, Müller & Eugster 1976b). Chemical syntheses of these compounds have been performed: *epiallo*-muscarine **11** (Corrodi, Hardegger & Kögl 1957), DL-muscarine and DL-*allo*-muscarine (Matsumoto, Ichihara & Ito 1969b) (Fig. 7).

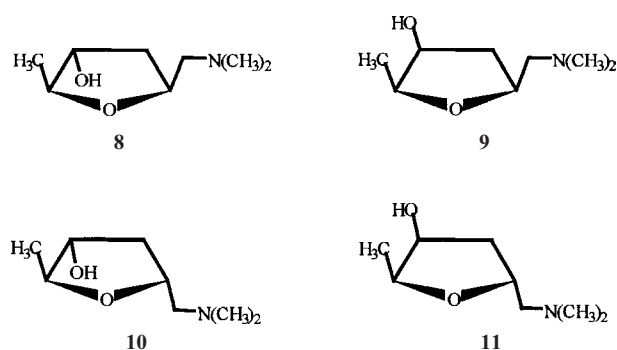


Fig. 7. Chemical structure of muscarines.

Two additional active components reported in *A. pantherina* are (2*R*),(1*R*)-2-amino-3-(1,2-dicarboxyethylthio) propanoic acid **12** and (2*R*),(1*S*)-2-amino-3-(1,2-dicarboxyethylthio) propanoic acid **13** (Fushiya *et al.* 1993). These are antagonists of *N*-methyl-D-aspartic acid (NMDA) receptors KI-II-A and KI-II-B respectively. Actions of these substances could be an alternative explanation of some additional effects observed during *Amanita* poisoning (Fig. 8).

Other active constituents detected in *A. muscaria* include choline, acetylcholine, betain, muscaridin, a quaternary trimethylammonium salt of 6-amino-2,3-dihydroxy-hexan, hercynin, (–)-*R*-hydroxy-4 pyrrolidone, uracile, hypoxanthin, xanthin, adenosin, a carbolic derivative, and β-D-*n*-butylglycopyranoside (Kögl, Salemink & Schuller 1960). Minor amounts of tropan alkaloids, atropine, hyoscyamine, scopolamine, and bufotenine have also been reported (Manikowski & Niezgodski 1962, Depovere & Moens 1984), although their occurrence is rejected by others (Brady & Tyler 1959, Subbaratnam & Cook 1963, Tyler & Gröger 1964, Eugster 1969). The occurrence of muscarine, muscaridine and choline was confirmed, when neither 1-hyoscyamine nor atropine were detected in Dutch specimens (Saleminck *et al.* 1963). The possible occurrence in *A. muscaria* of amatoxins and phallotoxins, the typical toxins of *A. phalloides*, were at first discounted (Catalfomo & Tyler 1961). However, highly sensitive detection methods, radio immunoassays, demonstrated traces of amatoxins (Faulstich & Cochet-Meilhac 1976), and phallotoxins are also suspected (Larcen 1979). Another possibly active compound, bufotenine (5-hydroxy-*N,N*-dimethyltryptamine), has been proposed (Waser 1967) but the occurrence of indolic hallucinogenic substances such as psilocybine frequently speculated, has not been confirmed.

### Pigments

The bright colour of *Amanita muscaria* has prompted investigations in several research groups; nowadays most of the structural features of the pigments have been elucidated (Musso 1982). Muscarufin **14** is the principal component; it is probably a putative derivative of a terphenylquinone (Kögl & Erxleben 1930); but

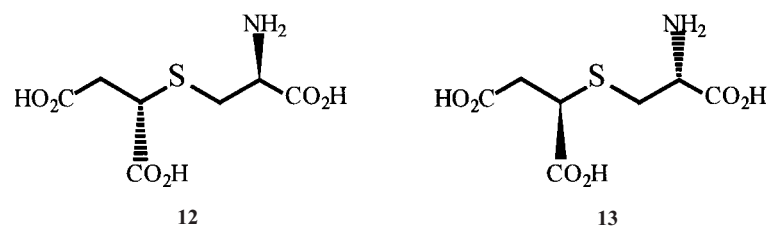


Fig. 8. Chemical structure of (2*R*),(1*R*)-2-amino-3-(1,2-dicarboxyethylthio) propanoic acid and (2*R*),(1*S*)-2-amino-3-(1,2-dicarboxyethylthio) propanoic acid.

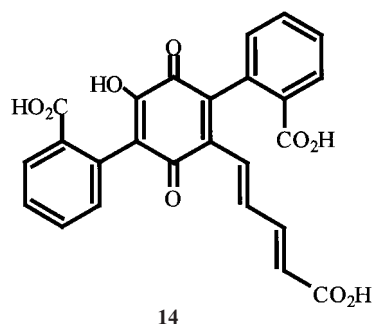


Fig. 9. Putative chemical structure of muscarufin.

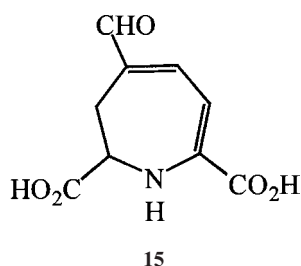


Fig. 10. Chemical structure of muscaflavin.

efforts by different groups to reproduce these evidently premature results failed (Musso 1979) (Fig. 9).

Musso also proposed a quite novel structure, muscaflavin **15**, for a yellow pigment, a result corroborated by a biosynthetic pathway that includes prior divergent oxidative cleavages of L-DOPA, further cyclization steps generating muscaflavin together with betalamic acid, stizolobic acid, and stizolobinic acid (Mabry 1967, Saito, Komamine & Senoh 1975, 1976, Saito, Komamine & Hatanaka 1978). The structure has been confirmed by synthesis (Barth, Kobayashi & Musso 1979, Burger *et al.* 1981). Muscaflavin has also been detected in red-fruited *Hygrocybe* species (von Ardenne *et al.* 1974, Steglich & Preuss 1975) (Fig. 10).

Different compounds, the muscaaurins I–VII **16**, have been proved to be the pigments responsible for the characteristic red-orange colour of the caps of several of other *Amanita* species such as *A. caesarea* (Döpp & Musso 1973). An elegant chromatographic procedure enables the separation of these pigments (Döpp & Musso 1974). Interestingly, ibotenic and stizolobic acids are essentially elements added to the whole structure of muscaaurins (Döpp *et al.* 1982, Depovere & Moens

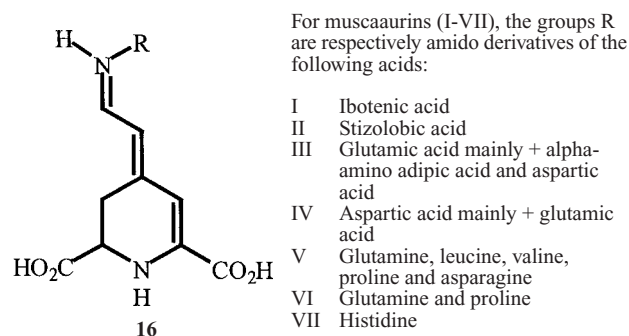


Fig. 11. Chemical structure of muscaaurins.

1984). The muscaaurins are betalaines and also originate from the transformation of DOPA (Fisher & Dreiding 1972). Muscapurpurin (purple) and muscarubin (red-brown), whose structures are closely related to the muscaaurins, have been isolated from *Amanita muscaria* (Döpp & Musso 1973, Musso 1979) (Fig. 11).

### Miscellaneous

Dioline 1,3 **17**, a-diester of glycerol and oleic acid; has been considered the putative fly attractant action of *Amanita muscaria* (Muto & Sugawara 1970) (Fig. 12).

Mushrooms are known for differential metal bioaccumulation. *A. muscaria* may concentrate vanadium to 200 ppm (30 times those reported in living organisms). Isolation, structure determination and synthesis of the pale blue vanadium complex, amavadin **18** (Kneifel & Bayer 1986), was confirmed by crystallography (Berry *et al.* 1999). Similarly, unusually high levels of selenium (to 17.8 ppm; Watkinson 1964) and heavy metals have been reported: cadmium 13.9, cobalt 2.6, chromium 1.7, lead 33.3, mercury 61.3, and nickel 7.5 ppm d.w. (Michelot *et al.* 1998, Siobud *et al.* 1999) (Fig. 13).

A lectin (APL) has been isolated from *A. pantherina* through Fast Protein Liquid Chromatography (FPLC), the molecular mass was estimated at 43 kDa and consists of two identical subunits (Zhuang *et al.* 1996). A  $\beta$ -(1 $\rightarrow$ 6) branched (1 $\rightarrow$ 3)-beta-D-glucan (AM-ASN) was isolated from *A. muscaria*. AM-ASN exhibited antitumour activity against Sarcoma 180 in mice (Kiho *et al.* 1992). Phallolysin, a typical haemolysin initially found in *A. phalloides* and able to agglutinate red blood cells has also been detected in *A. muscaria* (Seeger, Kraus & Wiedmann 1973).

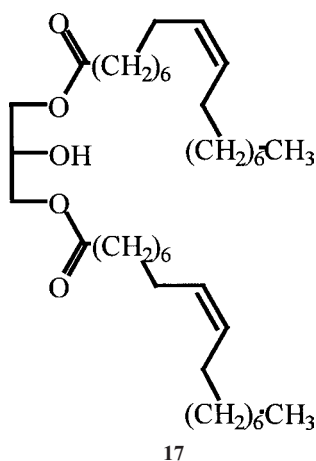


Fig. 12. Chemical structure of dioleine-1,3, diester of glycerol.

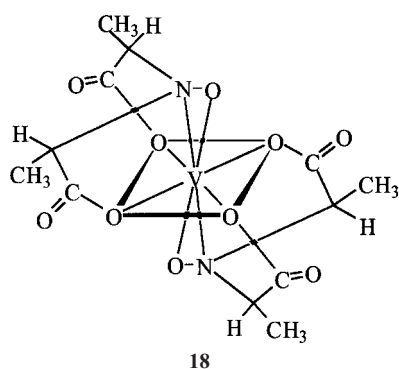


Fig. 13. Chemical structure of amavadin.

### Toxin detection, content, and occurrence

Several techniques provided information on the active components in fungi; they are useful for both forensic science and chemotaxonomy (Dorizzi *et al.* 1992).

Due to efforts to obtain pure muscarine, the estimation of the total muscarinic activity and potency of mushrooms was formerly performed by bioassays on rats (salivation and lacrymation; Malone *et al.* 1961, 1962). Detection and quantitative analysis of muscarine in *Inocybe* species has been undertaken by paper chromatography (eluent: *n*-butanol/methanol/water 10/3/2 v/v, staining Thies & Reuther's 1954 reagent; Brown *et al.* 1962). The isomer ratios were detected in the same genus by gas chromatography of the norbases (Catalfomo & Eugster 1970b). Muscarine has been identified in the red caps of Mexican fly agarics by cellulose column chromatography and identification as muscarinetetrachloroaurate (Eugster & Müller 1959).

Isoxazole derivatives have been explored in various *Amanita* species by two-dimensional paper chromatography (eluent: 1, *n*-butanol/acetic acid/water 1/1/1; 2, butanol/pyridine/water 1/1/1 v/v, staining: ninhydrin; Benedict, Tyler & Brady 1966). Ibotenic acid and muscimol were detected in *A. muscaria* and *A. pantherina*, and in intergrades of *A. pantherina* and *A. gemmata*, but not in *A. strobiliformis* by this method. Some

probable isoxazole derivatives were detected in *A. solitaria*. Subsequently, Benedict *et al.* (1966) suggested that the latter substances are chemotaxonomical markers for the differentiation of species and even subspecies. High performance thin layer chromatography (HPTLC) on silica gel allows the detection of muscarine (eluent: *n*-butanol/ethanol 95%/acetic acid/water 80/20/10/30, chromogenic reagent: modified Dragendorff) and muscimol (eluent 2-butanol/ethanol 95% acetic acid/water 75/25/5/25, a chromogenic reagent often used for amino acids). HPTLC permits an evaluation of muscimol equivalents since the experimental procedure, extraction with formic acid, facilitates the decarboxilation of ibotenic acid. The levels of muscimol detected in the samples were of 0.19% d.w. (*A. muscaria*), and 0.3% d.w. (*A. pantherina*). Stijve (1981) made clear the amounts of muscarine were very low (0.009% for *A. muscaria* and lower than 0.0005% for *A. pantherina*). On the other hand, some *Inocybe* and *Clitocybe* species, responsible for the typical muscarine syndrome contain this substance in the range of 0.1–0.3% d.w.

A very sensitive analysis of muscimol and ibotenic acid can detect down to 30 ng of the compound. This technique makes use of an automated amino acid analyser equipped with a microbore column. The highest content of toxins is reported to be in the yellow flesh beneath the cuticle, ibotenic acid: 548 nmol g<sup>-1</sup> f.w. and muscimol: 366 nmol g<sup>-1</sup> f.w. (Gore & Jordan 1982).

HPLC has been developed for *A. muscaria* content analysis (Lund 1979). Ibotenic acid was assayed on two columns connected in series: (1) Ibotenic acid, LiChrosorb-NH<sub>2</sub> 10 μ column (Merck, Darmstadt, Germany) and a Nucleosil 5CN (Macherey Nagel, Düren Germany) with 0.05 M sodium acetate buffer pH 4 as eluent; (2) muscimol on LiChrosorb-NH<sub>2</sub> 10 μ column, 0.05 M with sodium acetate buffer pH 4/methanol 1/9 v/v as eluent. The amount of ibotenic acid was estimated at 100 ppm f.w. and that of muscimol <3 ppm. Mushrooms extracts treated with acetic acid had muscimol at 40 ppm, demonstrating that ibotenic acid is the major component in the fungus, while muscimol is the real psychotropic substance resulting from decarboxilation occurring during the preparation of the meal and the gastric digestion. Therefore, the two substances must be considered as a functional entity, so-called 'pilzotropine'. An ion-interaction HPLC method permitted the simultaneous detection of muscimol and ibotenic acid. The stationary phase was a reverse C<sub>18</sub> matrix, and the mobile phase aqueous octylammonium *o*-phosphate 5 mm. The amounts of both compounds were higher in caps than in stems; the mean values for ibotenic acid and muscimol respectively were (f.w.): 990 mg kg<sup>-1</sup> (caps), 230 mg kg<sup>-1</sup> (stems), and 380 mg kg<sup>-1</sup> (caps), and 80 mg kg<sup>-1</sup> (stems). These substances were not detected in *A. mappa* (Gennaro *et al.* 1997). A fresh average size fruit body of *A. muscaria* (60–70 g) contains up to 70 mg of

ibotenic acid (Catalfomo & Eugster 1970a, Ott, Preston & Chilton 1975). Reverse phase HPLC (column: Shim-Pack P-NH<sub>2</sub>/S 2054 allows the detection of ibotenic acid (limit: 18 ppm) and muscimol (limit: 10 ppm) (Komiyama *et al.* 1985).

Muscimol as its trimethylsilyl (Repke, Leslie & Kish 1978) or trifluoroacetyl derivatives (Michelot, Brouard & Labia 1993) has been detected by gas chromatography coupled with mass spectrometry (GC-MS).

## MODE OF ACTION OF THE TOXINS

### *The 'insecticidal' effect*

A large number of publications traditionally refer to the insecticidal properties of *Amanita muscaria*. Early investigations simultaneously described such an unusual property for ibotenic acid, 'agarin', with qualitative experiments (*Amanita* Factor B; Takemoto & Nakajima 1964a, Takemoto, Nakajima & Sakuma 1964, Takemoto, Yokobe & Nakajima 1964, Bowden, Drysdale & Mogeys 1965). Moreover a tripeptide, 'pantherine', with such a biological ability has been found in the fungus (Onda, Fukushima & Akagawa 1964). However, quantitative experiments of Catalfomo & Eugster (1970a), who named the substance 'prämuscimol', showed that diptera were weakly sensitive to any toxic action by contact or ingestion. These results were confirmed by Matile (2000). A putative use of *A. muscaria* components for house fly (*Musca domestica*) control has been discussed with regard to the increasing importance of resistance (Petzsch 1960). Such a reputed characteristic must be rationalized because of the names of the mushroom in different countries and arising comes from oral tradition, tales, paintings, and folklore.

### *In vivo action of ibotenic related toxins*

Besides experimental data on animals, there are a few veterinary reports of accidental cat poisonings, with early symptoms 15–30 min after ingestion (Ridgway 1978). A state of excitement, which lasts up to 4 h, quickly follows a brief period of drowsiness. The animal then passes into a deep sleep, and recovery is usually within 24 h.

Considering the diagnosis, biochemical changes develop 30 min after peritoneal injection of aqueous extracts of *Amanita muscaria*, *A. pantherina* and *A. rubrovolvata* into male rats. These are decreases of acetylcholine esterase activity, liver glycogen, blood urea nitrogen, together with increase of blood glucose level; serum transaminase activities were not affected. The values returned to normal within 6 h (Yamahura *et al.* 1983). The latter data demonstrate that the poisoning is not serious and that vital organs like liver and kidneys are not affected. Vegetative functions are hardly influenced by the toxins. A bioassay was designed to monitor the efficiency of extraction and purification procedures, the prolongation of sleeping time

in mice after administration of a short-acting narcotic (Müller & Eugster 1965). Further studies show that a muscimol active dose given orally is 7.5–10 mg, and the LD<sub>50</sub> (i.p.) is 2.5 mg kg<sup>-1</sup> for mice and 3.5 mg kg<sup>-1</sup> for rats (von Theobald *et al.* 1968). After intraperitoneal injection and oral administration of muscimol (4–8 mg kg<sup>-1</sup>) and ibotenic acid (16 mg kg<sup>-1</sup>), the diameter of mouse pupils is broadened. Both drugs induce a marked anorexogenic action on mice (2–3 mg kg<sup>-1</sup> oral) with sedation, hypnosis, muscle twitching and catalepsy (Waser 1967, Matsui & Kamioka 1979). The drug produces electroencephalogram (EEG) alterations that are different from those provoked by hallucinogenic substances such as LSD or mescaline (Worms, Depoortere & Lloyd 1979). The EEG patterns resemble those induced by anticholinergic drugs such as atropine and Ditran (Scotti de Carolis, Lipparini & Longo 1969). The effects are slightly affected by physostigmine (eserine) (Johnston 1971, Saji & Reiss 1987). Bilateral injections of ibotenic acid into the nucleus basalis of rats cause fewer problems than kainic acid (Pepeu & Casamenti 1991).

Most probably, after ingestion, the low pH gastric fluid hydrolyses ibotenic acid into muscimol; afterwards, the active component proceeds to the brain or is eliminated *via* the systemic circulation. The remnant of the active component in the urine accounts for the tradition of drinking the urine of the shaman or of deers who consumes the mushrooms in some Siberian tribes in order to get a 'second-hand' stimulus (Wasson & Wasson 1957). Both ibotenic acid and muscimol are found in human urine 1 h after consumptions; this observation was confirmed experimentally on mice (Ott, Preston & Chilton 1975).

Thus, *a priori*, an acidic decarboxylation step in the gastrointestinal tract would produce muscimol that afterwards enters the central nervous system *via* the systemic circulation (Brehm, Hjets & Krogsgaard-Larsen 1972). Ibotenic acid has been shown to be the key component of *A. muscaria* and *A. pantherina* (Lund 1979). No direct toxic action on typical target systems implicated in mushroom poisonings (i.e. liver, kidneys, essential metabolism) has been reported (Michelot & Tebbett 1990, Michelot & Toth 1991, Michelot 1992). Nevertheless, repetitive injections of ibotenic acid induce a transient change in GABA receptor sensitivity (Taira, Uusi-Oukari & Korpi 1993) and might produce lesions in the basal forebrain as it destroys a small percentage of cholinergic cells (Harrington & Wenk 1992); the consequence *in vivo* would be a significant and prolonged learning and memory deficit (Connor, Langlais & Thal 1991). In the case of young mammals, muscimol also disturbs the development of the hypothalamic noradrenaline system (Taira & Smith 1993).

### *Biochemical mode of action of ibotenic related toxins*

Ibotenic acid, and particularly muscimol, have to be regarded as the substances responsible for the



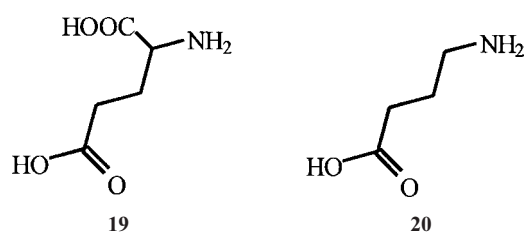


Fig. 14. Chemical structure of glutamic acid and GABA.

psychotropic action of *Amanita muscaria*. The effects of both substances are similar but not identical to the effect of the fungus *in toto*. Ibotenic acid and muscimol are members of a distinctive class of alkaloids, the excitatory amino acids. This group includes kainic acid, domoic acid, tricholomic acid, quisqualic acid, yunaine, and petalonine; all naturally occurring amino acids (Takemoto 1978, McGeer & McGeer 1981, 1983).

Ibotenic acid and muscimol are respectively conformationally restricted derivatives of glutamic acid 19 and gamma-aminobutyric acid (GABA) 20. Consequently, they act like neurotransmitters involved in the control of neuronal activity in the mammalian central nervous system, operating on spinal neurones (Curtis, Lodge & McLennan 1979). Ibotenic acid is known to act on glutamic acid receptors, and muscimol acts on GABA receptors in the snail *Helix aspersa* (Walker, Woodruff & Kerkut 1971). The same effect is observed in cats; ibotenic acid and excitant action, muscimol and depressant action (Johnston *et al.* 1968). Nevertheless, unlike glutamic acid and GABA, ibotenic acid and muscimol cross the blood–brain barrier (Olpe & Koella 1978), most probably by active transport, counterfeiting endogenous neurotransmitters and causing brain disorders (Fig. 14).

Glutamic acid is a major excitatory neurotransmitter in mammalian central nervous systems and its receptors are implicated in neurological disorders such as epilepsy and Huntington's disease. Inhibitory glutamate receptors (IGluRs) constitute a class of ion channel proteins equivalent to glycine and GABA receptors. Ibotenic acid acts on IgluRs (Cleland 1996). Considering the minimum energy of the mono-anion, ibotenic acid displays a rigid structural analogue of L-glutamate. Hence it presents the suitable shape of glutamate agonists confirmed by molecular orbital theory (Borthwick & Steward 1976). The central inhibitor receptor necessitates an effector displaying two highly charged sites of opposite signs separated by approximately 6 Å (Kier & Truitt 1970); this conformation was confirmed by X-ray analysis (Brehm, Hjeds & Krosggaard-Larsen 1972). AMPA, a synthetic analogue of ibotenic acid, displays the same typical moiety and was found to be more effective and specific glutamate agonist than the parent compound (Watkins, Krosggaard-Larsen & Honoré 1990). Intraperitoneal injections of muscimol and ibotenic acid produce an increase of serotonin and dopamine in the brain of mice and rats (König-Bersin *et al.* 1970, Gundlach & Beart 1980).

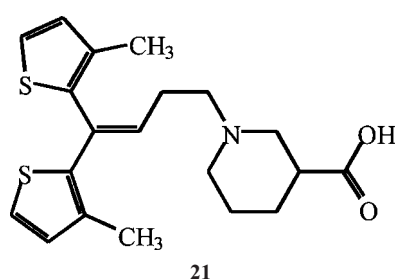


Fig. 15. Chemical structure of tiagabine.

These variations might result from reduced turnover of neurotransmitters, therefore elevations could contribute to psychotonic actions and even accentuate some of them (e.g. anorexia, central pupil dilatation).

There is evidence that damaged function of GABA-mediated inhibitory synapses is implied in experimental and clinical seizure disorders. Decreased concentration, and then activity of GABA, may have a role in human epilepsy. Muscimol is a potent conformational analogue and biologically active bioisostere (Krosggaard *et al.* 2000) (Fig. 15).

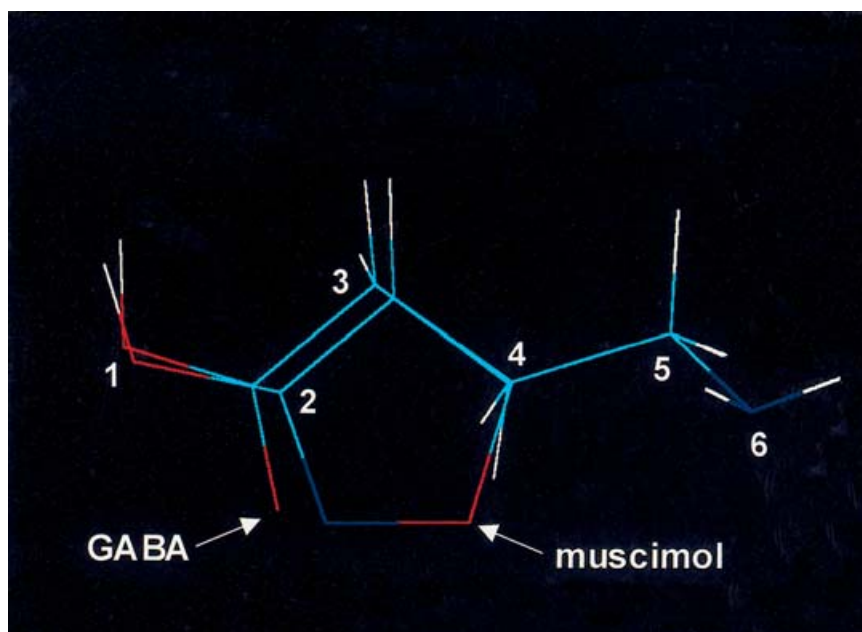
This toxin tightly binds with the gamma-aminobutyrate receptor (de Feudis 1980). Moreover, it is also an inhibitor of neuronal and glial GABA uptake and a substrate for the GABA-metabolizing enzyme: GABA transaminase. Subsequently, some research teams tried to improve the potency of drugs. Lipophilicity is of considerable interest for the prediction of the transport, adsorption and distribution properties of molecules, and so is an important factor in drug design. More lipophilic bioisosteres of muscimol and GABA have been synthesized, such as Tiagabine 21. This drug was marketed as a therapeutic agent for the treatment of epilepsy, Gabatril<sup>®</sup> (Krosggaard-Larsen 1977, Krosggaard-Larsen *et al.* 1994, Krosggaard-Larsen, Frölund & Frydenvang 2000) (Figs 16, 17).

The above biological and pharmacological activities account for the psychotropic effects of *A. muscaria*.

## ETHNOMYCOLOGY

### *Distinctive features of Amanita muscaria*

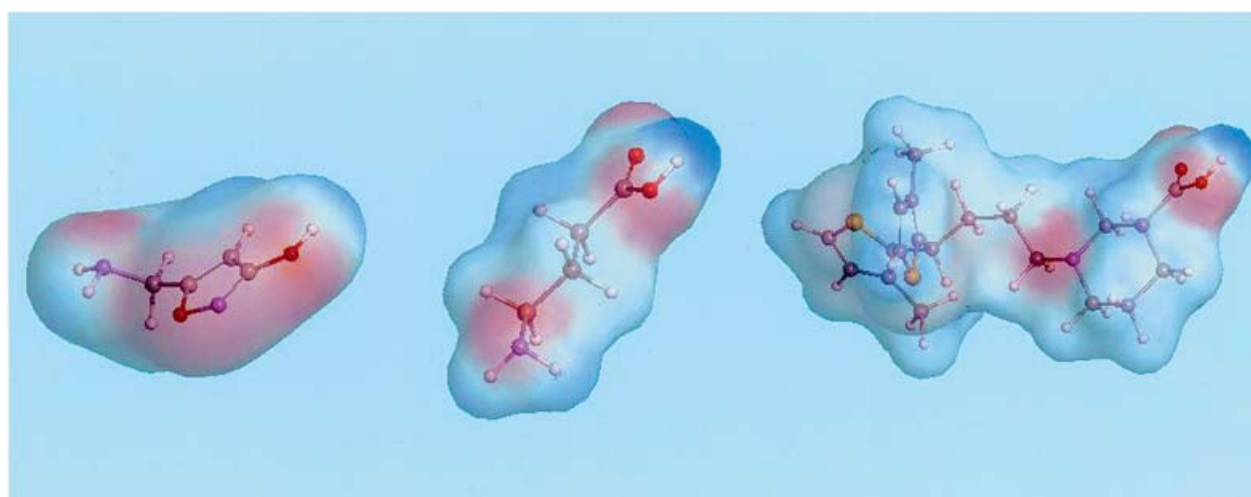
Among all mushrooms species, the fly agaric has long been a source of interest and attractiveness; it embodies the concept of the 'mushroom' and is probably the most illustrated one. Despite an evil reputation, this mushroom, unique in its striking appearance, is the most widely used pictogram for wild mushrooms. Its uses include illustrations of tales for children, and strip cartoons. Christmas tree decorations, pastries, and even tattoos (Davis & Williams 1999) as well as the artefacts (Taylor-Hawksworth 2001) are responsible for this renown. Because of its vivid colour, white spots, sturdy habit and its psychoactive properties, the fly agaric still exerts great fascination. Shamans, sorcerers, and witches made use of it, all classes of officiating 'priests' in different ethnic groups which are



**Fig. 16.** Chemical conformations ‘3D sticks’ of superimposed molecules of GABA and muscimol. The two structures exhibit a tight-fitting alignment of similar atoms (backbone oxygen 1→nitrogen 6). The conformational flexibility of GABA and the stereochemistry of the bioisostere analogue – muscimol – allow similar affinities for the GABA transporters.

geographically and culturally distant. The ‘priests’ try to escape the human condition and use the mushroom in ‘religious’ rituals. Beside the chroniclers of the 18th and 19th century in northern Europe and Asia (Heim 1964), Wasson (1959) forcefully argued that this mushroom represents the ‘soma’ of some ancient Aryan tribes. This concept designates a ‘plant’ that produces a juice when squeezed, that is thereafter filtered and handled as a divine inebriating agent. He stated that several parts of the Rig Veda conveyed that ancient peoples extensively consumed the mushroom for its

psychoactive properties. Besides various symbols that might correspond to *A. muscaria* and originate from northern and southern Asian traditions, some may also be discerned in Buddhist myths. They appear to be echoed in Germanic tradition, possibly in some characteristics related to the god Odin (Hajicek-Dobberstein 1995). A few publications argue that Christianity originates from a cult of *A. muscaria*, Jesus was supposedly being invested with the energy of the mushroom (Allegro 1970, 1971), but other religious and secular biblical scholars discredit this (King 1970). Nowadays,



**Fig. 17.** Molecular modelling of muscimol, GABA and tiagabine displaying solvation surfaces. Minimization was achieved by the software Hyperchem 4<sup>®</sup> software (Hypercube) with force field ‘MM2’ and molecular dynamics at the lowest energy. Visualization of 3D structures was completed by the software Weblabviewer<sup>®</sup> (MSI). Blue and red colours represent negative and positive charges, while white represents zones with high lipophilicity. Muscimol possesses a similar backbone to GABA with corresponding charge scattering. Although tiagabine contains a pyrrolidine ring (vs a linear chain for GABA), the models emphasize similar conformations and distributions of electrostatic charges (at the right side). The existence of two thiophenyl rings (at the left side) yields the proper lipophilicity that helps tiagabine to cross the blood–brain barrier.

reliable sources report that Ostyak and Vogul tribes in western Siberia, and Kamchadal, Koryak, Chukchi tribes in eastern Siberia, still use *A. muscaria* for shamanistic rites. However, in contrast to hallucinogenic mushrooms, mainly species of *Psilocybe* used in Meso-american culture (Heim & Wasson 1958, Guzman *et al.* 2000), the fly agaric is not a true object of religious and ritual veneration (Nyberg 1992).

Two attitudes coexist in world cultures towards mushrooms consumption: mycophilic and mycophobic. They are present traditionally among the word cultures. Some groups (e.g. German, Celtic, British) have a dislike for mushrooms, while others (e.g. Slavic, Lithuanian, French, Italian, Spanish, and other Mediterranean ones) are, to a certain extent, fond of them (Levi-Strauss 1970, Festi 1985). The mycophobic attitude possibly corresponds to remnants of a primitive worship/fear of mushrooms connected with 'folk wisdom'. This feeling is conveyed in language and etymology, possibly starting from Neolithic and Palaeolithic times. Unconsciously, some people make a clear-cut distinction between 'safe' mushrooms and suspicious mushrooms for instance mushrooms *vs* toadstools in English, and setas, hongos *vs* hongos venenosos in Spanish. The different attitudes are documented by Lowy (1974) who travelled widely in Latin America and various steps in the mycophobia/mycophily scale (Heim & Wasson 1958). Moreover, educated people are careful about mushrooms, when those of less developed cultures tend to consume them more readily.

### ***The name of the mushroom***

The designation of the species as 'fly agaric', 'bug agaric', is surprisingly equivalent all over the world: 'amanite tue-mouche' (French), 'Fliegenpilz' (German), 'muchomor' (Russian), 'moscario' (Italian), 'hongo mosquero', 'hongo matamoscas' (Spanish). The name of *Amanita strobiliformis* in Japanese is 'haetorimodashi', fly-killer). At the beginning of the last century, Atkinson (1901) mentioned the practice concerning a preparation of the mushroom to kill flies. The presumed insecticidal effect against flies should, however, be discounted since experiments show that a percentage of flies exposed to the juice of the mushroom did not die, but were rather subjected to transient behaviour disorder (i.e. became intoxicated). However, a few experiments do show that some species of *Amanita* inhibit the growth of *Drosophila melanogaster* larvae fed with powdered fruit bodies (Besl, Krump & Schefcsik 1987).

The 'fly' name may be explained in another way, since it bears the same semantic sound in several languages. Going back to ancient times in many countries, 'fly' has been identified with madness or supernatural possession. In the Middle Ages, it was believed that flies or other insects could penetrate the head of a person and cause mental illness. This is evidenced in Hyeronimus

Bosch's painting 1510 'Paradise and Hell': on the left panel, one can see very well high above in the sky the rebellious angels, who flew from heaven as a crowd of hideous insects. The Prado Museum in Madrid exhibits another painting by the same artist 'The garden of earthly delight' 1504. *A. muscaria* can be distinguished on the left-hand panel of the work (Heim 1968). In Europe, some other terms naming the mushroom are reminiscent of madness, for example 'Narrenschwamm' (German), 'oriol fol' (Catalan), 'mjioulo folo' (Toulouse dialect), 'coucourlo foulo' (langue d'oc), and 'ovolo matto' (northern Italian) (Festi 1985). Conversely, the fly-possession link could be rather beneficial to shamans. The Bible is no exception; 'Evil One', Belzebut, means 'Lord of the flies' and is synonymous with a false God adored by drunkards. It is likely that *A. muscaria* was named 'mushroom of the flies' because it is able to induce divine or evil states of possession similar to those that flies were supposed to produce in human brains. In Mexico, a Quiche idiom that describes hazardous, frightful potentialities is 'itzel cocox', meaning the diabolical mushroom (Lowy 1974). The original meaning was evidently forgotten or misinterpreted over time, giving way to the so-called insecticidal activity.

With respect to rituals and beliefs, the habitat of the fly agaric is pertinent. The tree has long been considered the 'Tree of Life', identified with the 'Weed of Immortality', and later the 'Tree of Knowledge' and with the 'Forbidden Fruit' in the Genesis (Levi-Strauss 1970, Festi & Bianchi 1992). Thus, it appears to be at the origins of religious practices (Wasson 1959). Its roots were said to 'swallow the pool of water of life' and nourish the 'sacred mushroom', 'his mind is the mind of a woman who offers her milk to anybody that comes towards her' (Wasson & Wasson 1957, Festi 1985). *A. muscaria* is often mycorrhizally associated with *Betula*, and also *Abies*, *Cistus*, *Picea*, *Pinus*, and *Quercus* species (Pegler 1983, Castro 1998, Contu 2000, Curreli 2000).

The appearance of the mushroom is unique, colourful, red and covered by whitish patches. It would be possible to consider this aposematic as it is seen in ladybirds, dendrobate frogs, etc. The conspicuous markings make it easily recognizable and warn would-be predators that it contains toxins.

### ***Paintings, frescos, and archaeological data***

Historical documents, such as wall paintings, wood-carvings, and sculptures suggest that the psychotropic properties of some mushrooms have been known from ancient times and that consumption was for religious, social and therapeutic purposes, and occurred in all continents (Heim 1964, Festi 1985). Representations of *Amanita* mushrooms, most probably *A. muscaria*, have been reported in polychromatic rock paintings in the Sahara (Samorini 1992); such works date from the Palaeolithic 9000–7000 BC (Heim 1964, Festi 1985).

The American surgeon general Puharich (1959) was particularly interested in extrasensory perception after World War II and searched for psychotropic substances able to induce latent abilities among 'sensitive' subjects. He investigated the mycology, biology, physiology, ethnology, etymology, and comparative linguistics of *A. muscaria* and its psychotropic properties. Further, he attempted to prove there were cults in ancient Egypt equivalent to those of the Indo-European transmigrations, and present today in eastern Siberia. Puharich also noted the comparison with cults in Central America related to hallucinogenic mushrooms. His conclusions confirm those of Samorini (1992) relating to other parts of north Africa. Among the various pieces of evidence he produced is an unambiguous distinction between a mushroom, a sunshade, and a lotus flower on seals illustrating a ritual ceremony in the pre-Snefrou period (before 2200 BC).

## CONCLUSION

*Amanita muscaria* occupies a unique position amongst all mushrooms. Its emblematic aspect merges with the psychotropic effects and the chemical load. As far as toxic effects are concerned, consumption of *A. muscaria* and *A. pantherina* does not induce any critical organ damage. Thus, in the case of such a poisoning, the victims are not considered endangered, but intensive care is recommended. Nevertheless, severe neuron and even brain lesions could be anticipated in cases of recurrent consumption.

*A. muscaria* has contributed to the progress of chemistry and pharmacology. Noteworthy, is that in most European countries, the possession, sale and consumption of the species are not yet subject to legislation such as in place for the more widely recognized hallucinogenic species (i.e. *Psilocybe*, *Panaeolus* and other species containing psilocybin-related toxins). *A. muscaria* is not yet the object of any drug-traffic, an aspect reflected in the lack of awareness amongst possible consumers or applicants for recreational purposes. Considering the effects so far reported, *A. muscaria* has a low psychotropic action, but still a toxic one.

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