Review

Human Poisoning from Poisonous Higher Fungi: Focus on Analytical Toxicology and Case Reports in Forensic Toxicology

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Abstract: Several families of higher fungi contain mycotoxins that cause serious or even fatal poisoning when consumed by humans. The aim of this review is to inventory, from an analytical point of view, poisoning cases linked with certain significantly toxic mycotoxins: orellanine, α- and β-amanitin, muscarine, ibotenic acid and muscimol, and gyromitrin. Clinicians are calling for the cases to be documented by toxicological analysis. This document is therefore a review of poisoning cases involving these mycotoxins reported in the literature and carries out an inventory of the analytical techniques available for their identification and quantification. It seems indeed that these poisonings are only rarely documented by toxicological analysis, due mainly to a lack of analytical methods in biological matrices. There are many reasons for this issue: the numerous varieties of mushroom involved, mycotoxins with different chemical structures, a lack of knowledge about distribution and metabolism. To sum up, we are faced with (i) obstacles to the documentation and interpretation of fatal (or non-fatal) poisoning cases and (ii) a real need for analytical methods of identifying and quantifying these mycotoxins (and their metabolites) in biological matrices.

Keywords: mushroom poisoning; mycotoxins; orellanine; analytical toxicology; amatoxins; forensic toxicology

1. Introduction

There is an extremely diverse range of fungi about which little is known. One million five hundred thousand species were known in 2002, 5.1 million in 2005, and the figure reached 13.5 million species in 2018. In reality, the exact number of fungal species on Earth is as yet unknown, since we are only aware of a tiny proportion of this diversity, of which only 100,000 species have been described [1]. Among these, there are about 5000 species of so-called higher fungi [2], those where the sporophore (the reproductive organ in fungi) is visible to the naked eye. Of these, a few dozen species of mushroom [1] contain mycotoxins, which, when ingested, could cause poisoning of varying degrees of severity and may even result in death. These poisonings can be classified according to 14 specific syndromes, some more serious than others: acromelalgic, cerebellar, coprinic, digestive (and resinoid), encephalopathy, gyromitrin, muscarinic, orellanus, pantherina, pavillus, phallidin, proximien, psilocybin (or narcotic), and rhabdomyolysis syndrome [3,4]. In 2019, White et al. proposed a new classification of mycotoxic syndromes based on the main clinical signs rather than toxins. The new classification is made up of
six groups (1. cytotoxic damage, 2. neurological damage, 3. muscular damage, 4. metabolic damage, 5. gastrointestinal irritation, and 6. other signs) divided into several subgroups [5]. Several case reports have shown that poisonings are mostly seasonal, between August and November, the period when mushrooms grow given the favorable climate [6]. In France, an average of 1300 poisoning cases per year was reported between 2010 and 2017 [6]. These poisonings are almost never documented by toxicological analysis, the cause of poisoning is mainly based on clinical signs and case history [7–9], since there are so few analytical methods for identifying the toxins described in the biological matrices [10,11]. There are many reasons: the numerous varieties of mushroom involved, mycotoxins with different chemical structures, a lack of knowledge about distribution and metabolism. The lack of analytical methods for identifying and quantifying these mycotoxins and their metabolites in the biological matrices is therefore an obstacle to knowledge and interpretation of cases of fatal and non-fatal poisoning. The main mycotoxins suspected in the most serious cases are as follows: orellanine, α- and β-amanitin, muscarine, muscimol, ibotenic acid, and gyromitrin. The aim of this work is to carry out a review of the literature, from an analytical point of view, of reported poisoning cases that involve these compounds, and to establish an inventory of the analytical techniques available for identifying and quantifying these mycotoxins.

2. Method

We performed a systematic review of the medical literature in order to identify manuscripts of interest. As the research was restricted to the forensic interest, our search strategies used a combination of standardized terms related to forensic situations (e.g., postmortem, intoxication, and poisoning) and key words that were implemented in NCBI PubMed (1900–present) and Google Scholar (1900–present). In order to reduce the number of results, the word “mushroom” was used as constant keyword. The used keywords were (number of identified articles): “orellanine” (50), “amanitins” (288), “ibotenic acid” (33), “muscimol” (44), “muscarine” (35), “gyromitrin” (27), “poisoning” (1906), and “intoxication” (266). Publications that were not found in the literature search but cited in retrieved publications were also considered. Overall, 256 cases reports were identified for orellanine, 800 for amanitins, 82 for ibotenic acid/muscimol/muscarine and at least 950 cases for gyromitrin. Focusing on the analytical concern, as we were interested in articles on identification and/or quantification of these mycotoxins in fungi or in human or animal biological matrices: additional key words were used in this way (e.g., chromatography, identification, quantification, etc.). All in all, 15 technical publications were selected for orellanine, 33 for the amanitins, 15 for ibotenic acid/muscimol/muscarine and at least 950 cases for gyromitrin. Focusing on the analytical concern, as we were interested in articles on identification and/or quantification of these mycotoxins in fungi or in human or animal biological matrices: additional key words were used in this way (e.g., chromatography, identification, quantification, etc.). All in all, 15 technical publications were selected for orellanine, 33 for the amanitins, 15 for ibotenic acid/muscimol/muscarine and at least 950 cases for gyromitrin. Every reported concentrations data have been converted to international system units.

3. Orellanine

3.1. Toxic Compounds

Orellanine \((C_{10}H_{8}N_{2}O_{6}, M = 252.2)\) was first identified in 1957 by Grzymala after a mass poisoning in Poland resulting in 19 deaths [12]. It was isolated in 1962 [13]. Orellanine is a bipyridine N-oxide \((2,2′\text{-bipyridine-3,3′,4,4′-tetrahydroxy-1,1′-dioxide})\) [14]. It is very polar \((\log P = -1.19)\) [15] and stable in the mushroom. However, it is photosensitive: once extracted, it is reduced by mono-hydroxylation to orellinine \((C_{10}H_{8}N_{2}O_{5}, M = 236.2)\), which has the same toxic properties as orellanine, then by bi-dehydroxylation to orelline (non-toxic) [16] (Figure 1). Orellanine is not thermosensitive: cooking the mushrooms does not reduce their toxicity [16]. To the best of our knowledge, no metabolism data regarding orellanine has been reported in any publication.

3.2. Toxic Mechanism and Toxicity in Humans and/or Animals

The toxicity of orellanine lies in its strong nephrotic properties leading to acute renal failure (group 1C in the White et al. classification [5]). Its toxic mechanism has not been precisely established yet. However, Richard and his team have shown that orellanine is responsible for the inhibition of
proteins in the cytoplasm and mitochondria of renal cells after tests on Madin–Darby canine renal cells [17]. Other hypotheses have been advanced such as the inhibition of DNA and RNA in the renal cells, glutathione depletion, or inhibition of mitochondrial adenosine triphosphate production [16,18].

There is high variability in clinical outcomes in the case of poisoning: the evolution can be spontaneously favorable or can deteriorate into chronic renal failure, requiring a kidney transplant [19]. There is no antidote for orellanine; treatment is symptomatic (hemodialysis, N-acetylcysteine, and steroids) [7,19,20]. Several studies in mice show that the oral median lethal dose (LD₅₀) is between 30 and 90 mg/kg [21,22]. However, humans have been shown to be far more sensitive than mice to this mycotoxin. In practice, the ingestion of 6 mushrooms can lead to acute renal failure requiring dialysis [23].

![Figure 1. Structure of orellanine and its decomposition products.](image)

### 3.3. Toxic Species

Orellanine is the main toxin found in mushrooms of the genus *Cortinarius* of the family Cortinariaceae. The most frequently reported in poisoning cases are *C. orellanus* [24,25] (Figure 2) and *C. speciosissimus* [7,19]. Some cases also mention *C. orellanosus* [23], *C. armillatus* [26], and *C. eartoxicus* [27]. The toxicity of *C. splendens* [28] is still in doubt. These species are mainly found in Europe and North America. Some cases of poisoning in Australia have also been reported [27,29].

![Figure 2. *Cortinarius orellanus* [30].](image)
3.4. Description of the Syndrome

Orellanine causes orellanus syndrome, which is characterized by a long latency period: between 2–4 and 14 days after ingestion [16]. To date, there is no scientific explanation for this exceptionally long latency period. The fact remains that this sometimes makes it difficult to link the ingestion with the clinical phase of poisoning. The first symptoms to appear are usually nausea, vomiting, diarrhea, stomach pains, extreme thirst, headaches, anuria, or polyuria depending on the case (cf. Table 5). These symptoms are followed by renal impairment necessitating transplantation. If left untreated, the patient may die of acute renal failure.

3.5. Human Poisoning Cases Reported

Many cases of orellanine poisoning have been reported in the literature since 1957. A number of them are listed nonexhaustively in Table 5. These cases include 27 reported deaths and 17 kidney transplants in people aged 14 and 60. Most poisonings are unintentional, sometimes by confusion with hallucinogenic mushrooms [29,31]. One case reports voluntary consumption of Cortinarius orellanus by a psychiatric patient [24]. Due to its long latency period, many patients consume mushrooms several times, sometimes a few days after the first meal [7,32,33]. The majority of patients have a serum creatinine over the physiological range at the arrival to the hospital. Those with a higher level underwent a renal transplantation.

3.6. Analytical Aspect

Research began in the late 1970s to develop a quick, sensitive, and reliable analytical method for identifying and quantifying orellanine in mushrooms as a first step, then in biological matrices such as blood, urine, or organs (cf. Table 2). Many methods are based on the thin layer chromatography, only one is based on the gas chromatography. Most recent methods consist of a liquid chromatography coupled with tandem mass spectrometry.
Table 1. Cases of orellanine poisoning.

| Ref. | Date of Intoxication | Country | N  | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms | Treatment | Notes | Toxin Quantification | Outcome | Mushroom Species |
|------|----------------------|---------|----|---------|-----------------------------------------------|----------|-----------|-------|----------------------|---------|-------------------|
| [12] | 1955–1957            | Poland  | 144| -       | -                                             | -        | -         | -     | 25 deaths            | Cortinarius orellanus |
| [34] | -                    | Finland | 9  | -       | -                                             | 6 hemodialysis | -      | -     | 4 renal transplantation | Cortinarius speciosissimus |
| [34] | NC                   | Sweden  | 2  | M/24    | NC/NC                                         | Nausea, vomiting, abdominal pain | Gastric aspiration, hemoperfusion, hemodialysis | -     | -                   | Renal function normal | Cortinarius speciosissimus |
|      |                      |         |    | F/47    | NC/NC                                         | Nausea, abdominal pain | -     | -     | -                   | Renal function normal | Cortinarius speciosissimus |
|      | M/31                 |         | H 36/D 10 | | | Plasma creatinine: 2945 µmol/L at D 10; Plasma urea: 48 mmol/L at D 10; Percutaneous renal biopsy at W 3 and W 7 after admission | -     | -     | -     | Renal function normal | Cortinarius speciosissimus |
| [19] | August 1979          | Scotland| 3  | M/30    | NC/NC                                         | Nausea, vomiting, anorexia, muscle and abdominal pain, night sweats, headache, bilateral loin pain, severe burning thirst, oliguria, anuria, acute renal failure | Hemodialysis | Consumption of the same mushroom on 2 consecutive days; Plasma creatinine: 1925 µmol/L at D 10; Plasma urea: 42 mmol/L at D 10; Percutaneous renal biopsy at W 2<sup>1/2</sup> and W 6 after admission | - | Renal transplantation at Mo 9 | Cortinarius speciosissimus |
|      |                      |         |    | F/25    | D 2/D 11                                      | -         | -         | -     | -                   | Renal function normal | Cortinarius speciosissimus |
| [35] | 1981                 | France  | 5  | -       | -                                             | -         | -         | -     | 3 positive development; 1 death of intracerebral hematoma; 1 chronic renal failure | Cortinarius splendens |
| [36] | September 1981       | Italy   | 2  | M/38    | D 2/NC                                        | Gastrointestinal disorder, acute renal failure | Plasma exchange, dialysis | Renal biopsy reveal tubulo-interstitial necrosis + interstitial oedema | - | Positive development | Cortinarius speciosissimus |
|      |                      |         |    | F/38    | | | | | Renal failure for 6 months | | Cortinarius speciosissimus |
Table 1. Cont.

| Ref. | Date of Intoxication | Country | N | Sex/Age | Symptoms/Delay before Hospitalization | Symptoms | Treatment | Notes | Toxin Quantification | Outcome | Mushroom Species |
|------|----------------------|---------|---|---------|--------------------------------------|----------|-----------|-------|----------------------|---------|-------------------|
| [37] | NC                   | Germany | 2 |         |                                      |          |           |       | 2 renal failure       |         | Cortinarius speciosissimus |
|      |                      |         |   |         |                                      |          |           |       | Renal transplantation |         |                   |
| M/41 |                      |         |   | M/41    | D 1/D 8 Vomiting, severe burning thirst, polyuria, oliguria | Hemoperfusion, hemodialysis, peritoneal dialysis | 3 meals during 2 weeks; Serum creatinine: 1600 µmol/L at D 8 | -     |                     |         |                   |
|      |                      |         |   | M/44    | D 2/D 10 Nausea, vomiting, abdominal pain, oliguria, acute renal failure | Peritoneal dialysis, hemodialysis | Serum creatinine: 1500 µmol/L at D 10; Uremia: 37 mmol/L at D 10; Renal biopsy at Mo 2 reveal normal glomeruli and atrophic tubuli | -     | Renal transplantation at Mo 9–10 |         |                   |
|      | [32,33]              |         |   | F/47    | D 4/D 5 Nausea, vomiting, abdominal and muscular pain, intense burning thirst, polyuria, | Hemoperfusion, hemodialysis | Consumption of 15 fruit bodies; Serum creatinine: 402 µmol/L at D 5, 780 µmol/L at D 12 | -     | Renal function normal |         | Cortinarius speciosissimus |
|      | 1979–1993            | Sweden  | 22| M/24    | D 4/D 5 after 1st meal Nausea, abdominal and muscular pain, heavy thirst | Hemoperfusion, hemodialysis | Consumption of 4–6 fruit bodies on 2 occasions; Serum creatinine: 158 µmol/L at D 5, 380 µmol/L at D 12 | -     | Renal function normal |         |                   |
|      |                      |         |   | F/60    | H 12/NC Nausea, vomiting, hematuria, proteinuria, glycosuria, anuria | Hemoperfusion, hemodialysis | Consumption of 7 mushrooms; Serum creatinine: 154 µmol/L at D 7 | -     | Renal transplantation at Mo 6 |         |                   |
|      |                      |         |   | M/21    | D 3/NC Polyuria and then anuria | Hemoperfusion, hemodialysis | Consumption of 5 mushrooms | -     | Renal transplantation at Mo 30; Renal biopsy on transplantation kidney at Y 7 reveal atrophic tubuli |         |                   |
|      |                      |         |   | M/14    | D 4/D 10 Nausea, vomiting | Peritoneal dialysis | Serum creatinine: 1350 µmol/L at D 10; Uremia: 68 mmol/L at D 10 | Renal transplantation at Mo 8 | Cortinarius speciosissimus |         |                   |
| [38] | NC                   | Switzerland | 1 | M/14    | NC/D 5 Vomiting, anorexia, renal pain, leukocyturia, hematuria | hemodialysis | - | Renal transplantation at Mo 14 |         | Cortinarius speciosissimus |         |                   |
| Ref. | Date of Intoxication | Country       | N  | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms to Intoxication | Treatment | Notes to Intoxication | Toxin Quantification | Outcome | Mushroom Species |
|------|----------------------|---------------|----|---------|-----------------------------------------------|-------------------------|-----------|----------------------|----------------------|---------|------------------|
| 24   | November 1987        | France        | 1  | F/31    | D 8/D 10                                     | Nausea, vomiting, severe thirst, abdominal pain, renal failure | Hemodialysis, hemodialysis resin, plasmapheresis resin, furosemide, diltiazem, dopamine, vitamin C, amino acid | Psychiatric patient; Deliberate ingestion of 2 fruit bodies (≈ 20 g); Serum creatinine: 1100 µmol/L at D 10; Renal biopsy at D 13 and 180 reveal chronic interstitial nephritis | Detection by TLC; Plasma at D 10 = 6.12 mg/L; Renal biopsy at D 13 = 280 mg/L, at D 180 = 3000 mg/L | NC                  | Cortinarius orellanus |
| 25   | September 1987       | France        | 26 | M/between 21 and 28 | D 2–9/D 10–12 | Digestive disorders, asthenia, thirst, headache, chills, polyuria, lumbar pain, paresthesia, dysgeusia, skin rash, 12 acute tubulointerstitial nephritis with acute renal failure | 8 hemodialysis; 9 under corticosteroids | During a survival exercise; Serum creatinine: 172–2248 µmol/L | - | 1 renal transplantation at Mo 10; 1 chronic hemodialysis; 2 persisting renal failure; 22 renal function normal | Cortinarius orellanus |
| 39   | NC                   | Canada        | 1  | F/20    | H 8/D 5                                      | Nausea, vomiting, diarrhea, abdominal pain, proteinuria, pyuria, hematuria | Sodium polystyrene sulfonate | Confusion with hallucinogenic mushrooms; Serum creatinine: 356 µmol/L at D 5; Uremia: 10.1 mmol/L at D 5 | - | Renal function normal | NC |
| 40   | NC                   | Germany       | 1  | M/27    | D 9/D 14                                     | Nausea, anorexia, oliguria, leukocyturia, acute renal failure | Hemodialysis, peritoneal dialysis | Serum creatinine: 1450 µmol/L at D 14; Uremia: 59 mmol/L at D 14; Renal biopsy at D 14 reveal tubulointerstitial nephritis | - | Renal transplantation | Cortinarius orellanus |
| 41   | 1994–1995 Austria/ Northern Italy | 8  | M/74 | D 2/NC |                                             | Nausea, abdominal and loin pain, uremia | dialysis | - | TLC on fluids failed to detect orellanin | - | Cortinarius speciosissimus |
| Ref. | Date of Intoxication | Country | N  | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms                                                                 | Treatment                           | Notes                                                                 | Toxin Quantification | Outcome                                                                 | Mushroom Species   |
|------|----------------------|---------|----|---------|-----------------------------------------------|-------------------------------------------------------------------------|--------------------------------------|------------------------------------------------------------------------|---------------------|--------------------------------------------------------------------------------|-------------------|
| [41,42] | August 1995          | Austria | 1  | M/23    | NC/D 14                                       | Nausea, abdominal and loin pain, acute anuria                           | Hemodialysis                        | Consumption of 5 raw fruit bodies confused with hallucinogenic mushrooms; Renal biopsy at D 180 reveal acute interstitial nephritis | Orellanin not detected in the renal biopsy | Peritoneal dialysis; Waiting for renal transplantation 6 months later | Cortinarius speciosissimus |
| [41,43] | NC                   | Austria | 1  | M/28    | D 7/D 21                                      | Nausea, vomiting, lumbar pain, proteinuria, leukocyturia, erythocyturia, hyperphosphatemia, dehydration, anuria | Hemodialysis, probucol              | Consumption of 2 raw fruit bodies confused with hallucinogenic mushrooms; Serum creatinine: 2033 µmol/L at D 16; Uremia: 28.3 mmol/L at D 16 | Detection of orellanin in renal biopsy at W 5 by TLC = 35 mg/L | Hemodialysis 12 months later; Waiting for renal transplantation | Cortinarius speciosissimus |
| [44]    | NC                   | Austria | 4  | M/37    | NA/Nating                                   | Nausea, vomiting, dizziness, oliguria                                  | hemodialysis                         | Serum creatinine: 813 µmol/L at D 14; Uremia: 47 mmol/L at D 14       | -                   | Positive development                                                                |                    |
| [41,42] | F78                  | NC/Nating | 7 | D 7/D 11 | Nausea, vomiting, dizziness, malaise, arthralgia, severe metabolic acidosis, anuria | Hemodialysis, probucol, isradipine, urapidil, clonidine, hemodialysis, steroids |                     | Serum creatinine: 1768 µmol/L at D 11; Uremia: 80 mmol/L at D 11; Kidney biopsy reveal acute tubular necrosis, interstitial fibrosis | -                   | Chronic hemodialysis 10 months later                                                |                    |
| [44]    | F/56                 | D7/not admitted to the hospital | 1  | M/70    | NA/Nating                                   | Nausea, vomiting, anuria, malaise, arthralgia                           | hemodialysis                         | Underwent partial gastrectomy in 1949; Serum creatinine: 1768 µmol/L at D 9; Uremia: 48.3 mmol/L at D 9 | -                   | Chronic hemodialysis 10 months later                                                |                    |
| [31]    | NC                   | Spain   | 1  | M/32    | D 5/D 15                                     | Nausea, vomiting, anorexia, flanks and abdominal pain, acute renal failure, insomnia, anuria, dehydration, leukocytosis, glycosuria, proteinuria | Hemodialysis, rehydration            | Past of drug addict; Voluntary ingestion of 2 fruits bodies looking for hallucinogenic effects; Serum creatinine: 477 µmol/L at D 15; Uremia: 8.2 mmol/L at D 15; Renal biopsy at D 16 reveal acute tubulointerstitial nephritis | -                   | Positive development Cortinarius orellanus                                        |                    |
| Ref. | Date of Intoxication | Country | N | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms | Treatment | Notes | Toxin Quantification | Outcome | Mushroom Species |
|------|----------------------|---------|---|---------|-----------------------------------------------|----------|-----------|-------|---------------------|---------|-----------------|
| [45] | October 1994        | Italy   | 1 | M/53    | NC/H 18                                      | Oliguria | Activated charcoal, intravenous fluids, plasmapheresis, hemodialysis | Serum creatinine: 97.5 µmol/L at H 30; Percutaneous renal biopsy at D 8 reveal acute tubular necrosis with interstitial oedema | - | Renal allograft at Mo 17 | Cortinarius orellanus |
| [46] | August 1997         | Ireland | 2 | F/66    | D5/D10                                       | Vomiting, colicky diarrhea, abdominal pain, oliguria, hyponatremia, proteinuria | Hemodialysis, prednisolone, intravenous N-acetylcysteine | Past of left sided hydronephrosis; Serum creatinine: 1032 µmol/L at D 10; Uremia: 32.8 mmol/L at D 10 | - | Renal function normal | Cortinarius orellanus |
|      |                      |         |    |         |                                               |          |           |       |                     |         |                 |
| [29] | NC                   | Australia | 3 | M/26    | D 2/D 4                                     | Nausea, diarrhea, anuria | Hemodialysis, methylprednisolone, prednisolone | Serum creatinine: 376 µmol/L | - | NC |                 |
|      |                      |         |    |         |                                               |          |           |       |                     |         |                 |
|      |                      |         |    | M/17    | 1–2 weeks/2–3 week                           | Vomiting, epigastric, back and bilateral loin pain, acute renal failure, dehydration, oliguria | Intravenous fluids, intravenous frusemide, hemodialysis | Past of polysubstance abuse; Voluntary ingestion of 12 uncooked mushrooms looking for hallucinogenic effects; Serum creatinine: 1970 µmol/L; Uremia: 44.3 mmol/L; Renal biopsy reveals acute interstitial nephritis | - | Death of pulmonary oedema at Mo 5 | Cortinarius orellanus |
|      |                      |         |    |         |                                               |          |           |       |                     |         |                 |
| [27] | December 1985       | Australia, Tasmania | 2 | M/NC   | NC/D 7                                      | Kidney failure | Dialysis | Serum creatinine: 760 at D8; Uremia: 15.6 mmol/L at D 8 | - | Positive development; Patient failed to attend a scheduled outpatient appointment | Cortinarius cenoxydus |
|      |                      |         |    |         |                                               |           |          |       |                     |         |                 |

Table 1. Cont.
Table 1. Cont.

| Ref. | Date of Intoxication | Country              | N    | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms                  | Treatment                                                                 | Notes                                                                 | Toxic Quantification | Outcome                      | Mushroom Species            |
|------|----------------------|----------------------|------|---------|------------------------------------------------|---------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------|------------------------|------------------------------|-------------------------------|
| [7]  | NC Germany           | 2                    | M/30 | D 4/D 6 | Nausea, vomiting, back pain, proteinuria      | Intravenous N-acetylcysteine, selenium, hemodialysis | Consumption of remaining mushroom 3 days after the first; Serum creatinine: 459.7 µmol/L at D 6, 928 µmol/L at D 7; Uremia: 12.9 mmol/L at D 6, 21.1 mmol/L at D 7 | -                      | Renal function normal       | Cortinarius speciosissimus |
|      |                      |                      | F/29 | NC/D 6  | Nausea, back pain, proteinuria                | Intravenous N-acetylcysteine, selenium                         | Consumption of remaining mushroom 3 days after the first; Serum creatinine: 88.4 µmol/L at D 6; Uremia: 5.4 mmol/L at D 6 | -                      | Renal function normal       |                              |
| [23] | NC United States, Michigan | 1                   | F/53 | D 3/D 9 | Vomiting, diarrhea, oliguria                  | Intravenous sodium bicarbonate, sodium polystyrene sulfonate, hemodialysis | Consumption of 6 mushrooms; Serum creatinine: 1220 µmol/L at D 9; Uremia: 14.6 mmol/L at D 9; Renal biopsy at D 14 reveal acute tubular necrosis | -                      | Peritoneal dialysis 5 time a week | Cortinarius orellanus         |
| [20] | NC Norway            | 8                    | M-4F | D 2/D 7 | Gastrointestinal disorder, headache, myalgia, acute renal insufficiency, oliguria | 5 dialysis; 6 steroids + N-acetylcysteine                       | Serum creatinine: 150–1627 µmol/L                                      | -                      | 3 chronic hemodialysis; 5 partial recovery | Cortinarius orellanus         |
| [47] | NC Austria           | 2                    | F/62 | D 2/D 6 | Nausea, vomiting, epigastric pain acute renal failure, anemia | Prednisolone, intravenous N-acetylcysteine                  | Serum creatinine: 587 µmol/L at D 6; Uremia: 28.2 mmol/L at D 6; Renal biopsy at D 8 reveal acute interstitial nephritis | TLC on biopsy specimen failed to detect orellanin | Prednisolone for 103 D; Renal function normal | Cortinarius speciosissimus |
|      |                      |                      | M    | D 2/D 6 | Nausea                                        |                                                          | Serum creatinine: 890 µmol/L at D 6; Uremia: 36.8 mmol/L at D 6            | -                      |                              |                              |
| [46] | NC Wales             | 1                    | M/43 | D 4/D 14 | Nausea, vomiting, diarrhea, myalgia, fever, anuria, dehydration, hematuria, leukocyturia, acute kidney injury | Hemodialysis, methylprednisolone, prednisolone         | Blood creatinine: 2650 µmol/L at D 14; Uremia: 50 mmol/L at D 14; Kidney biopsy reveal severe interstitial nephritis at D 17 | -                      | Kidney transplantation at Mo 20 | Cortinarius speciosissimus |

N: number of patients; NC: not communicated; NA: not applicable; F: female; M: male; D: day; W: week; Mo: month; Y: year.
Table 2. Analytical methods for orellanine detection.

| Ref. | Matrix | Separation | Detection | Qualitative/Quantitative | LOD | LOQ | Linearity | Extraction Recovery | Additional Analytical Information |
|------|--------|------------|-----------|---------------------------|-----|-----|-----------|---------------------|----------------------------------|
| [14] | Mushrooms | TLC | UV | Qualitative | NA | NA | NA | NA | - |
| [49] | Mushrooms | TLC | UV (254 nm) | Qualitative | NA | NA | NA | NA | - |
| [50] | Mushrooms, mouse serum and kidney | HPLC | Electrochemistry (Working electrode: glassy carbon Ti-5A; Reference electrode: Ag/AgCl; Working potential: 900 mV) | Quantitative | 500 pg | NC | 50–500 ng on column | Alleged to 100% on overloaded mouse serum and directly injected, 25% for mouse kidney | Column: (200 mm × 4.6) 5 μm Nucleosil C18; Flow rate: 2 mL/min; Mobile phase: 0.05 citrate-phosphate buffer pH 4.5, 15.4% MeOH and PIC B6 1-hexane sulphonic acid 5 mM |
| [21] | Mushrooms | TLC | Spectrofluorometry ($\lambda_{\text{excitation}} = 396$ nm; $\lambda_{\text{emission}} = 447$ nm) | Quantitative | NC | NC | NC | NC | - |
| | | HPLC | MS | Qualitative | NA | NA | NA | NA | - |
| | - | NMR | Qualitative | NA | NA | NA | NA | - |
| [22] | Mushrooms | - | Polarography (Working electrode: dropping mercury; Reference electrode: saturated calomel) | Qualitative | NA | NA | NA | NA | - |
| [51] | Mushrooms | HPLC | UV (260, 290 nm) | Quantitative | 40–50 pg on column | NC | 5–500 ng on column | NC | Column: (150 mm × 4.6) 5 μM Rosil CN and (150 mm × 3.9) 5 μM µBondapak C18; Flow rate: 0.5 mL/min and 0.8 mL/min; Mobile phase: H$_3$PO$_4$ pH 1 and H$_3$PO$_4$ pH/ACN (94/6 v/v); 1-octane-sulphonic acid 2.5 Mm, RT: 4.43 min and 6.58 |
| [24] | Biological fluids and renal biopsy | TLC | Spectrofluorometry in 2D ($\lambda_{\text{excitation}} = 399$ nm; $\lambda_{\text{emission}} = 447$ nm) | Quantitative | 10 ng | NC | NC | NC | - |
| [28] | Mushrooms | TLC | Spectrofluorometry ($\lambda_{\text{excitation}} = 400$ nm; $\lambda_{\text{emission}} = 450$ nm) | Quantitative | 15 ng deposit | NC | NC | NC | - |
| | Electrophoresis | Spectrofluorometry ($\lambda_{\text{excitation}} = 400$ nm; $\lambda_{\text{emission}} = 450$ nm) | Quantitative | 25 ng deposit | NC | NC | NC | - |
| | - | ESR | Quantitative | 5000 ng | NC | NC | NC | - |
| [41] | Urine, blood and renal biopsy | TLC | UV (366 nm) | Semi quantitative | $\approx$ 10 ng | NC | NC | NC | - |
Table 2. Cont.

| Ref. | Matrix                      | Separation | Detection         | Qualitative/Quantitative | LOD   | LOQ    | Linearity | Extraction Recovery | Additional Analytical Information                                      |
|------|-----------------------------|------------|-------------------|--------------------------|-------|--------|-----------|---------------------|-----------------------------------------------------------------------|
| [52] | Mushrooms                   | TLC        | UV (365 nm)       | Semi quantitative        | 50 ng deposit | NC      | NC        | NC                  | -                                                                      |
|      | HPLC                        | Photodiode (288 nm) | Quantitative      | NC                        | NC    | NC     | NC        | NC                  | Preparative column: (115 mm × 13 mm) C18; Flow rate: 1 mL/min; Mobile phase: ACN/H2O (5/95 v/v) pH 1 1% TFA; RT: 6.5 min |
|      | HPLC                        | ESI-MS     | Quantitative      | NC                        | NC    | NC     | NC        | NC                  | Flow rate: 10 µL/min direct MS source                                      |
| [10] | Mushrooms and rat plasma    | HPLC       | ESI-MS/MS (triple Q) (253 to 191; 253 to 219; 253 to 163 m/z) | Quantitative             | 4.9 µg/L | NC      | 4.9–5000 µg/L | = 91% mushrooms | = 60% plasma                                                                  |
|      |                             |            | ESI-MS/MS (QTOF)  | Quantitative             | 4.9 µg/L | NC      | 4.9–5000 µg/L |                      |                                                                        |
| [53] | Rat gastric content         | HPLC       | (−) ESI-MS/MS (triple Q) (Scan range: 120–600 m/z) | Quantitative             | NC    | NC     | NC        | NC                  | Column: (50 mm × 2.1 mm) 2 µm Ascentis Express C18; Flow rate: 0.25 mL/min; Mobile phase: H2O 0.1 N HCOOH (A), ACN (B) |
| [54] | Rat gastric content         | GC         | MS with Supersonic Molecular Beam  | Qualitative               | NA    | NA     | NA        | NA                  | Column: (4 m × 2.5 mm ID), 0.1 µm VF-5HT; Flow rate: 8 mL/min; T injector: 200 °C; GC oven: 120–300 °C at 30 °C/min |
| [26] | Mushrooms                   | HPLC       | UV–visible (295 nm) | Quantitative             | 17,000 ng/g | NC      | 17,000–680,000 ng/g | 78.3%                   | Column: (150 mm × 4.6 mm) 3 µm PLRP-S C18; Flow rate: 0.3 mL/min; Mobile phase: 4 mM ammonium acetate (A), MeOH (B) |
|      |                             |            | ESI-MS/MS (triple Q) (253 to 163; 253 to 191; 253 to 219; 253 to 236 m/z) | Quantitative             | 30 ng/g | NC      | 6800–13,600 ng/g | 85.0%                 | Column: (250 mm × 4.1 mm) 10 µm Hamilton FRP-1; Flow rate: 0.4 mL/min; Mobile phase: H2O 1% HCOOH (A), ACN (B) |
| [55] | Mice kidney                 | HPLC       | UV–visible        | Quantitative             | 10 µg/g of tissue | NC      | 15–50 µg/g of tissue | NC                  | -                                                                      |
|      |                             | HPLC       | ESI-MS/MS (triple Q) (235 to 236 m/z) | Quantitative             | 20 ng/g | NC      | NC        | 91%                 |                                                                        |
| [56] | Standard solution           | PSI-HR-MS/MS (253.0468 to 219.0404 m/z) | Qualitative             | NA                        | NA    | NA     | NA        | NA                  | -                                                                      |

NA: not applicable; LOD: limit of detection; LOQ: limit of quantification; NC: not communicated.
Many poisoning cases in the biological matrices documented by research for orellanine have revealed the absence of orellanine in urine, plasma, and dialysis fluids between 2 and 25 days after the ingestion of mushrooms [41]. However, Rapior et al. using thin layer chromatography coupled with spectrofluorometry, reported a concentration of 6.12 mg/L in plasma 10 days after the ingestion of mushrooms [24]. Orellanine has also been quantified several times in renal biopsies with concentrations between 35 and 3000 mg/L up to 180 days after poisoning [24,41].

4. \(\alpha\)- and \(\beta\)-Amanitin

4.1. Toxic Compounds

Since the 1790s (Paulet’s research into the toxins of \textit{Amanita phalloides}, 1793–1808) [57], researchers have taken an interest in the compounds responsible for the toxicity of \textit{A. phalloides}. After the identification of other compounds contained in these mushrooms (e.g., phalloidin), Wieland et al. first isolated an amanitin in 1941 (which they later named \(\alpha\)-amanitin) then 8 other amatoxins were isolated and their structure described (\(\beta\)-amanitin, \(\gamma\)-amanitin, \(\epsilon\)-amanitin, amanin, amanullin, amaninamid, amanullinic acid, and proamanullin) [57]. The main toxins of certain mushrooms in this family are \(\alpha\)-amanitin and \(\beta\)-amanitin. \(\alpha\)-amanitin (C\(_{39}\)H\(_{54}\)N\(_{10}\)O\(_{14}\)S, M = 918.9) and \(\beta\)-amanitin (C\(_{39}\)H\(_{53}\)N\(_{9}\)O\(_{15}\)S, M = 919.9) are bicyclic octapeptides (Figure 3).

![Figure 3. Structure of amatoxins. R = NH\(_2\) for \(\alpha\)-amanitin, R = OH for \(\beta\)-amanitin.](image)

The amatoxins are not thermosensitive, which means they cannot be destroyed by either cooking or freezing the mushrooms [58]. Moreover, they are gastroresistant [58] and their metabolism is currently unknown.

4.2. Toxic Mechanism and Toxicity in Humans and/or Animals

In the new classification, the amatoxins are classified in the cytotoxic group (1A) [5] as they are responsible for inhibiting RNA polymerase II and the transcription of DNA into RNA by interfering with messenger RNA. This brings about inhibition of protein synthesis, which leads to cell necrosis. The first cells to be affected are those with a high rate of protein synthesis such as enterocytes, hepatocytes and proximal renal cells [59]. Studies in mice show that renal lesions only occur in poisoning with low levels of amatoxins. In poisoning cases with high levels, the subject die due to acute liver failure or hypoglycemia before the renal lesions appear [60,61]. Amatoxins are mainly eliminated in the bile, but there is an enterohepatic cycle, which prolongs the hepatoxic action [62].

Several studies show that the LD\(_{50}\) of \(\alpha\)-amanitin in humans is estimated to be 0.1 mg/kg per os [63]. Bearing in mind that a sporophore of \textit{Amanita phalloides} (20–25 g) can contain 5–8 mg of
amatoxins [64], the ingestion of one A. phalloides mushroom is theoretically a lethal dose for a 75 kg man. The same order of magnitude is found in mice in a study published by Wieland in 1959 [57] (LD_{50} = 0.1 mg/kg for \( \alpha \)-amanitin and 0.4 mg/kg for \( \beta \)-amanitin by intraperitoneal injection). Finally, it has been shown that the concentration of amatoxins in the mushroom increases during the first stages of the mushroom’s development, then decreases during the mature stage [65].

As with orellanine, no specific antidote exists for the amanitins. Treatment is symptomatic (dialysis, activated charcoal hemoperfusion, glucose/saline perfusion, etc.) [66,67]. Only kidney or liver transplantation (depending on the symptoms) can save a patient with multiple organ failure [67,68]. Some authors propose treatments such as thioctic acid (alpha lipoic acid) [69,70], penicillin G [71], or silibinin [72,73], which may be capable of limiting, if not inhibiting, the amatoxins’ penetration into the liver cells and/or interrupting the enterohepatic cycle of the toxins [74]. However, these treatments have not really been clinically proven and there is no evidence to support the use of penicillin G or of thioctic acid. They are therefore not considered as part of the protocol for treatment of amanitin poisoning.

In view of all the cases of amanitin poisoning reported in the literature, it seems clear that infants and small children are more sensitive to these mycotoxins than adults, probably because of their lower body mass: the same dose of toxins ingested will be more toxic and the percentage of fatalities will be higher in young subjects.

4.3. Toxic Species

The amatoxins are the compounds responsible for the toxicity of Amanita phalloides [57] (Figure 4) also known as “death cap” in English-speaking countries [58], and without doubt the most well-known poisonous mushroom in the world. Probably all members of section Phalloideae contain potentially lethal levels of amanitins. These mycotoxins are also found in other species such as A. verna [75] and A. virosa [62], A. bisporigera [76], and A. ocreata [77]. Other genera contain amatoxins including Galerina (G. marginata and G. autumnalis) and Lepiota (L. brunneoincarnata and L. helveola) within the main species of concern [78].

Amatoxin-containing mushroom species have been worldwide identified (Northern, Central, and Western Europe, North and South America, South-East Asia, and Northern and Southern Africa) [58].

It should be noted that Amanita phalloides contains two other groups of toxins: phallotoxins and virotoxins [58]. These two families of cyclic peptides are only toxic by parenteral administration as they are hardly (or not at all) absorbed by the gastrointestinal tract [58]. They are therefore not usually taken into consideration in Amanita phalloides poisoning.

4.4. Description of the Syndrome

The amatoxins are responsible for phalloidin syndrome, which, like orellanus syndrome, is characterized by a long latency period (between 6 and 24 h) after ingestion of the mushroom [58]. First occurring symptoms are gastrointestinal (nausea, vomiting, diarrhea, and stomach pains) over a period of about 24 h. The second stage is a period of remission, usually lasting 24–36 h. During this period, the serum activity levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) rise progressively, showing liver damage. The third stage is characterized by renal and hepatic impairment, which could result in hepatic encephalopathy, convulsions, coma and death (4–7 days after ingestion of mushrooms) [74]. Death by amatoxin poisoning is most often caused by liver, or kidney failure, or sometimes both (cf. Table 3).
Several studies show that the LD50 of α-amanitin in humans is estimated to be 0.1 mg/kg per os [63]. Bearing in mind that a sporophore of *Amanita phalloides* (20–25 g) can contain 5–8 mg of amatoxins [64], the ingestion of one *A. phalloides* mushroom is theoretically a lethal dose for a 75 kg man. The same order of magnitude is found in mice in a study published by Wieland in 1959 [57] (LD50 = 0.1 mg/kg for α-amanitin and 0.4 mg/kg for β-amanitin by intraperitoneal injection). Finally, it has been shown that the concentration of amatoxins in the mushroom increases during the first stages of the mushroom’s development, then decreases during the mature stage [65].

As with orellanine, no specific antidote exists for the amanitins. Treatment is symptomatic (dialysis, activated charcoal hemoperfusion, glucose/saline perfusion, etc.) [66,67]. Only kidney or liver transplantation (depending on the symptoms) can save a patient with multiple organ failure [67,68]. Some authors propose treatments such as thioctic acid (alpha lipoic acid) [69,70], penicillin G [71], or silibinin [72,73], which may be capable of limiting, if not inhibiting, the amatoxins’ penetration into the liver cells and/or interrupting the entero hepatic cycle of the toxins [74]. However, these treatments have not really been clinically proven and there is no evidence to support the use of penicillin G or of thioctic acid. They are therefore not considered as part of the protocol for treatment of amanitin poisoning.

In view of all the cases of amanitin poisoning reported in the literature, it seems clear that infants and small children are more sensitive to these mycotoxins than adults, probably because of their lower body mass: the same dose of toxins ingested will be more toxic and the percentage of fatalities will be higher in young subjects.

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Figure 4. *Amanita phalloides* [79].
Table 3. Cases of amatoxines poisoning.

| Ref. | Date of Intoxication | Country         | N  | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms                              | Treatment                                                            | Notes                                      | Toxin Quantification | Outcome                                                      | Mushroom Specie |
|------|----------------------|-----------------|----|---------|-----------------------------------------------|---------------------------------------|--------------------------------------------------------------------------------|------------------------------------------|---------------------|--------------------------------------------------------------|-----------------|
|      | 9 October 1944       | Great Britain   | 4  | F/26    |                                              | Vomiting, diarrhea, coma              | Gastric lavage, glucose, atropine, insulin                                    | Uremia: 25 mmol/L at D 3                  | -                   | Death at H 111 of gastric hemorrhages, kidney and liver failure | Amanita phalloides |
| [80] | 9 October 1944       |                 |    | F/38    |                                              | Vomiting, diarrhea, cyanosis          | Gastric lavage, atropine, magnesium sulfate, insulin, glucose, nikethamide, percortone | Uremia: 23.3 mmol/L at D 3                | -                   | Death at H 76 of gastric hemorrhages, kidney and liver failure |                |
|      | 25 September 1944    |                 |    | F/57    |                                              | Vomiting, diarrhea, abdominal pain, coma | Castor oil, intravenous plasma                                                      |                                          | -                   | Death at H 126 of kidney and liver failure                   |                |
|      | 18 August 1945       |                 |    | F/6     |                                              | Vomiting, diarrhea, cyanosis          | Gastric lavage, atropine                                                        |                                          | -                   | Death at H 60 of kidney and liver failure                    |                |
|      |                      |                 |    | F/≈ 25  |                                              | Jaundice, hallucinations             | NC                                                                               |                                          | -                   | Positive development                                          |                |
|      | [81] 1943            | Great Britain   | 3  | F/NC    |                                              | Vomiting, diarrhea, abdominal pain, severe muscular cramps, constipation, anorexia | NC                                                                               |                                          | -                   | Positive development                                          | Amanita phalloides |
|      |                      |                 |    | F/5     |                                              | Vomiting, diarrhea, delirium, coma    | NC                                                                               |                                          | -                   | Death at D 2 of liver degeneration                            |                |
| [82] | September 1961       | United States, Washington DC | 1 | M/8     |                                              | Vomiting, lethargy, inability to see, irrational response, cerebral oedema  | NC                                                                               | Visit to the hospital because of head trauma after a bike fall | Amatoxins identification in the liver by TLC | Death on the hospital D 4 | NC |
| Ref. | Date of Intoxication | Country | N | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms | Treatment | Notes | Toxin Quantification | Outcome | Mushroom Species |
|------|----------------------|---------|---|---------|-----------------------------------------------|----------|-----------|-------|---------------------|---------|-------------------|
| [83] | 13 November 1962     | United States, California | 2 | M/43 H 5/NC | Nausea, vomiting, diarrhea, oliguria, renal failure, dehydration, distension of the abdomen, hyperventilation, disorientation, hallucinations, coma, cyanosis, apnea | Peritoneal dialysis, intravenous plasma, antibiotics | Past of alcoholism; Serum creatinine: 1202 µmol/L at D 3; Uremia: 33 mmol/L at D 3; Septicemia complication | - | - | Death at D 12 of kidney and liver failure, central nervous system complication |
| [84] | United States, California | 5 | M/77 H 6/D 1 | Vomiting, slight lacrimation, acute renal failure, anuria, pruritus, dyspnea, confusion, hyponatremia, pulmonary edema | Atropine, peritoneal dialysis | Uremia: 10 mmol/L at D 4; Renal biopsy at D 43 reveal renal tubular necrosis | - | - | Positive development |
| [70] | Between 1968 and 1974 | United States, California | 28 | NC/Between 14 months and 87 years old | Nausea, vomiting, diarrhea, abdominal pain | Supportive care, 14 thioctic acid | Amatoxins identification in mushrooms by TLC | 8 deaths; 20 Positive development | A. phalloides, A. virosa, A. verna et G. autumnalis |
| [66] | Switzerland | 8 | 4 H–4 F/between 16 and 55 | Severe gastrointestinal disorders | Dialysis, hemoperfusion, penicillin, vitamin C | ALT peak at 1920 IU/L at D 3 for one patient | - | - | Positive development |

Table 3. Cont.
| Ref. | Date of Intoxication | Country | N | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms | Treatment | Notes | Toxin Quantification | Outcome | Mushroom Species |
|------|----------------------|---------|---|---------|---------------------------------------------|---------|-----------|-------|---------------------|---------|-------------------|
| [85] | Fall 1981            | United States, California | 10 | M/45 H 8/H 12 | Nausea, abdominal cramping, diarrhea, dehydration, oliguria, encephalopathy, respiratory arrest, seizures, hepatic coma | Rehydration, vitamin K, thioctic acid, diazepam, phenytoin | Consumption of 2 or 3 mushrooms; AST at D 6: 4220 U/L; ALT at D 6: 7272 U/L; Serum creatinine at D 11: 336 μmol/L. | - | Death at D 12 of kidney and liver failure, cerebral oedema | Mushroom Species |
|     |                      |         |   | M/80 D 1/H 48 | Nausea, vomiting, diarrhea, dehydration, confusion, hypotension, supraventricular tachycardia, oliguria, encephalopathy, coma | Rehydration, dextrose | Serum creatinine at D 2: 380 μmol/L; Uremia: 8.7 mmol/L; AST at D 4: 2410 U/L; ALT at D 4: 2500 U/L; Septicemia developed on D 7 | Amatoxins identification positive on the meal | Death at D 9 | NC |
|     |                      |         |   | M/39 H 12/D 4 | Vomiting, diarrhea, dehydration, hematemesis, cardiopulmonary arrest | Rehydration | AST at D 4: 4860 U/L; AST at D 5: 2820 U/L; ALT at D 5: 3220 U/L; Serum creatinine at D 5: 513 μmol/L. | - | Death at D 6 of multiorgan failure | Mushroom Species |
|     |                      |         |   | M/18 H 8–10/NC | Nausea, vomiting, abdominal cramps, diarrhea, dehydration, bradycardia, hypotension | Rehydration, dextrose, desamethasone, vitamin K, temporary transvenous pacemaker | Consumption of 10 mushrooms; AST at D 3: 5280 U/L; ALT at D 3: 5100 U/L. | - | Positive development | Amanita phalloides |
|     | 3 M–3 F/21–37        | H 8–12/NC |   | Nausea, vomiting, abdominal cramps, diarrhea | Supportive care, activated charcoal | | | | Positive development | Amanita species |
|     |                      |         |   | [86] November 1981 | Italy | 1 | F/21 H 10/NC | Nausea, vomiting, abdominal pain, diarrhea | Plasmapheresis, forced diuresis | 8 months of pregnancy | α-amanitin = 18.5 ng/mL in the serum by HPLC; No amatoxins in amniotic fluid | Positive development | Amanita phalloides |
|     | 28 February 1983     | United States, California | 1 | F/3 H 8/D 2 | Nausea, vomiting, abdominal pain, diarrhea, hypotension, oliguria, hematuria, encephalopathy grade III, coma | Rehydration, charcoal slurry, lactulose, dopamine and dobutamine hydrochloride, antibiotics, methylprednisolone, charcoal hemoperfusion | Consumption of 2 tablespoons of mushrooms; AST at D 2: 16,648 U/L; ALT at D 2: 9844 U/L; Left hepatic lobectomy on the transplant liver because of necrosis at D 9 | - | Orthotopic liver transplantation at D 5 + neurological deficits | Amanita ocreata |
Table 3. Cont.

| Ref. | Date of Intoxication | Country, State | N  | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms | Treatment | Notes | Toxic Quantiﬁcation | Outcome | Mushroom Species |
|------|----------------------|----------------|----|---------|-----------------------------------------------|---------|----------|-------|----------------------|---------|-------------------|
| [88] | 1982–1983            | United States, California | 21 | M–11 F/5–82 | H 6–29/D 1–12 | Nausea, vomiting, abdominal cramps, diarrhea | Supportive care, activated charcoal, 5 desamethasone | AST peak: 77–11674 U/L; ALT peak: 72–9233 U/L | Amatoxins identification positive in serum of 3 patients by RIA | 2 deaths; 19 Positive development | A. phalloides, A. ocreata, L. clypeolaria |
| [67] | NC                   | United States, California | 2 | F/19 | H 9/NC | Nausea, vomiting, diarrhea, abdominal pain, hepatic encephalopathy | Rehydration, gastric lavage, charcoal, dialysis | Consumption of 6 ounces of mushrooms; AST: 1608 U/L; ALT: 5600 U/L | - | Orthotopic liver transplantation | Amanita phalloides |
| [89] | 22 October 1988      | United States, Oregon | 5 | M–3 F/33–52 | H 7–11/<H 24 | Nausea, vomiting, diarrhea, abdominal cramps, dehydration, hypophosphatemia, 2 encephalopathy grade I and 2 encephalopathy grade II | Rehydration, silymarin, penicillin | Consumption of 60–100 mushrooms; 1 diabetic had undergone previous cholecystectomy and pelvic surgery; 1 pulmonary tuberculosis | - | Orthotopic liver transplantation | Amanita phalloides |
| [90] | 1984–1989            | France            | 45 | M–23 F/2–81 | H 6–24/NC | Gastrointestinal disorders; 43 hepatic injury; 6 functional renal failure | Supportive care, penicillin G, silibinin, 1 hemodialysis; 2 gastric lavage | AST peak: 380–17,000 U/L; ALT peak: 520–16,000 U/L | Amatoxins identification in biological matrix by HPLC-UV | 2 liver transplantation at D 5; 8 deaths; 35 positive development | Amanita phalloides |
| [91] | NC                   | United States, New York | 4 | F/90 | H 12/H 30 | Nausea, vomiting, diarrhea, weakness, hypotension, hepatic failure | Rehydration, penicillin, cimetidine, activated charcoal, vitamin K | Past of hypertension, permanent pacemaker; Serum creatine at D 2: 124 umol/L; Uremia at D2: 16.1 mmol/L; AST at D 7: 4099 U/L; ALT at D 7: 5394 U/L | Amatoxins identification positive in admission and post-mortem serum | Death at D 7 of hepatic failure | Amanita/Lepiota species |
|      |                      |                 |    | M/64 | H 12/H 30 | Nausea, vomiting, abdominal cramps | Rehydration, penicillin, cimetidine, activated charcoal, vitamin K | Serum creatine at D 2: 159 umol/L; Uremia at D2: 11.8 mmol/L; AST at D 5: 5620 U/L; ALT at D 5: 8620 U/L | - | Hepatitis |
|      |                      |                 |    | F/40 M/42 | H 3/H 18 | Nausea, vomiting, diarrhea | Rehydration, prochlorperazine, charcoal, penicillin, charcoal hemoperfusion, heparin | Consumption of 4–6 mushrooms | - | Positive development | Lepiota chlorophyllum |
Table 3. Cont.

| Ref. | Date of Intoxication | Country       | N | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms                                                                 | Treatment                     | Notes                                                                 | Toxin Quantification | Outcome | Mushroom Species |
|------|----------------------|---------------|---|---------|-----------------------------------------------|---------------------------------------------------------------------------|---------------------------------|-----------------------------------------------------------------------|----------------------|----------|------------------|
| [68] | 1991–1992            | France        | 4 | F/27    | 10/NC                                         | Nausea, vomiting, abdominal pain, diarrhea, encephalopathy grade I, anemia, leukopenia | rehydration, silibinin, coxtazidime, hemodialysis                          | Consumption of 300 g of mushrooms; AST at D2: 2990 U/L; ALT at D2: 2730 U/L | -                    | Liver transplantation, chronic renal failure, myocardiopathy          | Lepiota helvella    |
|      |                      |               |   | M/35    | 12/NC                                         | Vomiting, diarrhea, abdominal pain, hepatitis                              | NC                              | Consumption of alcohol during the meal                                 | -                    | Positive development                                                 |                      |
|      |                      |               |   | F/33    | 12/NC                                         | Vomiting, diarrhea, abdominal pain, dehydration, hepatic cytolysis, disorientation, asterix | NC                              | AST at D2: 5800 U/L; ALT at D2: 2700 U/L                               | -                    | Liver transplantation at D 4                                        | Lepiota brunneolilacea |
|      |                      |               |   | F/8     | 12/NC                                         | Vomiting, diarrhea, abdominal pain, dehydration, encephalopathy grade III | rehydration, albumin                                                      | AST at D2: 1416 U/L; ALT at D2: 1560 U/L; ALT at D3: 5082 U/L            | -                    | Orthotopic liver transplantation at D 5                              |                      |
| [92] | 27 December 1996 to 5 January 1997 | Turkey        | 3 | M/9, 11, 14 | 12/H 30                                      | Nausea, vomiting, diarrhea, dehydration                                      | Gastric lavage, charcoal hemoperfusion, rehydration, lactulose, streptomycin, penicillin, forced diuresis, desamethasone, vitamins, hemodialysis | Consumptions of ≈ 80 g of mushrooms; AST peak: 276–1760 U/L; ALT peak: 388–3450 U/L | α-amanitin identification positive in serum by TLC | Positive development | Amanita phalloides |
| [93] | 27 December 1996 to 5 January 1997 | United States, California | 10 | M-1 F/12/68 | H 8–26/D 2–8                                      | Nausea, vomiting, diarrhea, abdominal cramps, weakness, rehydration, H2-blockers, activated charcoal, penicillin, N-acetylcysteine, vitamin K, hemodialysis | AST peak 594–6998 U/L; ALT peak: 930–7120 U/L                              | -                      | 2 deaths at D 7 and D 9 of multiorgan failure                         | Amanita phalloides |
| Ref. | Date of Intoxication | Country | N | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms | Treatment | Notes | Toxin Quantification | Outcome | Mushroom Species |
|------|----------------------|---------|---|---------|-----------------------------------------------|----------|-----------|-------|---------------------|---------|------------------|
|      | 1995                 | Australia | 2 | M/46    | NC/D 1                                        | Vomiting, diarrhea, hepatic and renal failure | rehydration, penicillin, N-acetylcysteine | Consumption of 8 mushrooms; ALT at D 3: >10,000 U/L; Serum creatinine at D 3: 535 µmol/L | - | Death at D 6 of hepatic failure waiting for a liver transplantation | Amanita phalloides |
| [94] | 1998                 |         | M/39 | H 18/H 36 | Nausea, vomiting, diarrhea, dehydration, rehydration, penicillin, N-acetylcysteine | Consumption of 3 mushrooms; ALT peak at D 3: 8199 U/L; Serum creatinine at D 2: 102 µmol/L | Positive development |
|      | 1988–1997            | Thailand | 5 | 3 M–2 F/7–45 | D 1–2/NC | Vomiting, diarrhea rehydration, activated charcoal, penicillin | 1 patient ALT peak: 2938 U/L | - | Positive development |
|      | F/36                 |         | H 12/NC | Nausea, vomiting, diarrhea, jaundice, acute liver failure, hepatic encephalopathy | Supportive care, vitamin K, neomycin, lactulose | Serum creatinine: 132.6 µmol/L; Uremia: 2.2 mmol/L; AST: 3400 U/L; ALT: 3930 U/L | - | Death at D 6 |
| [95] | NC                   | Thailand | 5 | M/8     | H 12/NC | Nausea, vomiting, diarrhea, jaundice, hepatic encephalopathy, convulsions, gastrointestinal bleeding, hypoglycemia | rehydration | Serum creatinine at D 4: 35.4 µmol/L; Uremia at D 4: 0.8 mmol/L; ALT at D 4: 1738 U/L | - | Death at D 5 | Amanita virosa |
|      | M/36                 |         | H 12/NC | Nausea, vomiting, diarrhea, acute liver failure, hepatic encephalopathy | | | | - | Death at D 4–6 |
|      | M/11                 |         | NC | | | | | | |
|      | F/6                  |         | | | | | | | |
| Ref. | Date of Intoxication | Country | N | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms | Treatment | Notes | Toxin Quantification | Outcome | Mushroom Species |
|------|----------------------|---------|---|---------|-----------------------------------------------|----------|-----------|-------|---------------------|---------|-------------------|
| [62] | United States, Ohio  | 4       |   | M/25    | NC/H11 Vomiting, abdominal cramps, diarrhea    | Charcoal hemoperfusion, fluid and electrolyte repletion, penicillin G, desamethasone | Consumption of 40–50 g of mushrooms | - | Positive development | Amanita virosa |
| [62] | NC                   |         |   | M/35    | H 10½/NC Nausea, vomiting, diarrhea, abdominal pain | Charcoal hemoperfusion, forced diuresis, hydration, vitamin K, decadron, penicillin G, vitamin C, cimetidine | Consumption of 40–50 g of mushrooms | - | Positive development | |
| [62] |  |         |   | M/47    | Nausea, vomiting, diarrhea, abdominal pain      | Charcoal hemoperfusion, rehydration, electrolyte repletion, penicillin G, desamethasone | AST peak: 154 U/L; ALT peak: 122 U/L | - | Positive development | |
| [96] | NC                   | Japan   | 1 | M/6     | H 6–10/H 36 Nausea, vomiting, diarrhea, abdominal pain, dehydration, hepatic insufficiency, mild proteinuria, glycosuria, hematuria | rehydration, plasma exchange, hemodialfiltration, activated charcoal | AST peak at H62: 18,450 U/L; ALT peak at H62: 13,554 U/L | Amatoxins identification negative in urine and blood at H80; Amatoxins identification positive in mushrooms by HPLC | Positive development | Possible Galerina fasciculata |
| [97] | NC                   | France  | 1 | F/22    | H 2/H 13 Nausea, vomiting, diarrhea, abdominal pain | rehydration, silymarin, activated charcoal, N-acetylcysteine, vitamins, antibiotics, fungizone | 2 months of pregnancy; AST peak at H53: 3200 U/L; ALT peak at H67: 4127 U/L | - | Positive development | Amanita phalloides |
| Ref. | Date of Intoxication | Country | N | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms | Treatment | Notes | Toxin Quantification | Outcome | Mushroom Species |
|------|----------------------|---------|---|---------|-----------------------------------------------|----------|-----------|-------|---------------------|----------|-------------------|
| [98] | NC Switzerland       | 1       | F/61 | H 12-16/H 36 | Nausea, vomiting, diarrhea, dehydration, hypoglycemia, | rehydration, vitamin K, penicillin G, silibinin, N-acetylcysteine | Dried and frozen mushrooms during 7-8 months; Serum creatinine at H 48: 270 μmol/L; AST at H 48: 1424 U/L; ALT at H 48: 2326 U/L | Amatoxins identification positive in urine at D 4: 37.3 μg/L | - | Death at D4 of liver and renal failure (patient declined the liver transplantation) | Amanita phalloides |
| [99] | NC Turkey            | 2       | M/44 | H 8/NC  | Nausea, diarrhea, abdominal pain, encephalopathy grade III, hepatitis | NC | Transplanted liver necrosis; AST at D 10 postoperative: 10,270 U/L; ALT at D 10 postoperative: 5670 U/L | - | - | Death at D 10 after an orthotopic liver transplantation | Amanita phalloides |
|      |                      |         | F/20 | NC/D 2 | Nausea, vomiting, diarrhea, confusion, lethargy, agitation, hepatic encephalopathy grade II, hepatitis | NC | - | - | - | Orthotopic liver transplantation | Amanita phalloides |
| [100] | NC Germany           | 1       | F/64 | NC | Hepatic encephalopathy grade III | NC | Obesity, hypertension, chronic heart failure | - | - | Hepatocyte transplantation | Amanita phalloides |
| [101] | NC Turkey            | 1       | M/11 | H 24/NC | Nausea, vomiting, abdominal cramps, diarrhea, metabolic acidosis, fever, jaundice, unconsciousness, hypotonia, hepatic encephalopathy grade III | Gastric lavage, activated charcoal, vitamin K, penicillin G, bicarbonate, ampicillin, lactulose, vitamin C, plasmapheresis | AST peak: 774 U/L; ALT peak: 200 U/L | - | - | Orthotopic liver transplantation | Amanita phalloides |
Table 3. Cont.

| Ref. | Date of Intoxication | Country | N | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms | Treatment | Notes | Toxin Quantification | Outcome | Mushroom Species |
|------|----------------------|---------|---|---------|-----------------------------------------------|----------|-----------|-------|---------------------|----------|-------------------|
| [102] | 1988–2002 Italy | 111 57 M–54 F/18–94 | H = 12/H 30–45 | Nausea, vomiting, diarrhea | rehydration, glucose, electrolyte repletion, vitamin K, activated charcoal, dexamethasone, penicillin G | AST peak: 4330 U/L; ALT peak: 5428 U/L | Amatoxins identification positive in urine in 62 patients | 2 deaths at D 11 and D 29 | Amatoxins-containing species |
| [103] | 2000–2004 Czech Republic | 34 17 M–17 F/1–73 | H 1–24/H 1–168 | Vomiting, diarrhea, abdominal cramps, weakness, hepatic failure, coagulopathy, encephalopathy, renal failure | Gastric lavage, activated charcoal, penicillin G, thioctic acid, hemoperfusion, hemodialysis, N-acetylcysteine, silymarin, forced diuresis | 5 intentional ingestion (suicide); 5 alcohol abuse | - | 3 deaths at D 5 of cardiac arrest, D 5 during liver transplantation and M 19 of renal damage; 14 persistent hepatic or renal damage | Amanita phalloides |

- M: Male, F: Female, NC: Not recorded
- H: Hours, D: Days
- NC: Not available
- AST: Aspartate aminotransferase, ALT: Alanine aminotransferase
- RIA: Radioimmunoassay
- Amatoxins: Amanita phalloides toxins

Positive development: Positive amatoxin identification in serum, urine and feces at H72 < 1.5 µg/L.
Table 3. Cont.

| Ref. | Date of Intoxication | Country | N | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms | Treatment | Notes | Toxin Quantification | Outcome | Mushroom Species |
|------|----------------------|---------|---|---------|-----------------------------------------------|----------|-----------|-------|---------------------|---------|------------------|
| [105] | January 2000 to October 2010 Germany | 79 | NC | Medial H 14.5/Medial H 29.4 | Nausea, vomiting, diarrhoea, abdominal pain, coagulopathy | Supportive care, silibinin, oral charcoal, plasmapheresis | - | - | AST medial peak: 3242 U/L; ALT medial peak: 3907 U/L | 4 deaths (3 liver transplantation); 3 liver transplantation alive; 3 positive development | Amanita phalloides |
| [106] | March 1992 to November 2009 Portugal | 10 | F/16-75 | H 7-12/<H 48 | Nausea, vomiting, diarrhoea, dehydration, acute liver failure, encephalopathy grade I | Supportive care, silibinin, penicillin G, N-acetylcyesteine, hemodialysis, hemodiafiltration | - | - | AST medial peak: 5295 U/L; ALT medial peak: 6919 U/L | 4 deaths (3 liver transplantation); 3 liver transplantation alive; 3 positive development | Amanita phalloides |
| [108,109] | January 1995 to December 2009 Switzerland | 32 | F/1, 4-74 | H 1, 25-6/NC | Nausea, vomiting, diarrhoea, dehydration, acute liver failure, encephalopathy grade I | Activated charcoal, silibinin, gastric lavage, forced diuresis, laxatives, penicillin G, N-acetylcyesteine | 2 intentional ingestions | - | Amatoxins identification positive in urines by ELISA; 1.6 < X < 118 µg/L | 5 deaths at D 3–9 of liver failure; 27 positive development | Amanita phalloides, Amanita virosa |

| Ref. | Date of Intoxication | Country | N | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms | Treatment | Notes | Toxin Quantification | Outcome | Mushroom Species |
|------|----------------------|---------|---|---------|-----------------------------------------------|----------|-----------|-------|---------------------|---------|------------------|
| [105] | NC Turkey | 1 | F/16 | H 7/D 3 | Nausea, vomiting, abdominal pain, diarrhoea, lethargy, liver failure | Supportive care, silibinin, oral charcoal, plasmapheresis | - | - | - | Liver transplantation at D 7 | Amanita phalloides |
| [106] | NC Tunisia | 4 | F/6 | H 7/NC | Vomiting, diarrhoea, abdominal pain, | - | - | - | Death at D 1 before arriving at emergencies of liver failure | - |
| [106] | NC Tunisia | 4 | F/12 | NC/H 12 | Vomiting, diarrhoea, abdominal pain, coma, brain oedema, hepatic cytolsis | NC | AST peak at D 3 > 10000 U/L; ALT peak at D 3 > 10,000 U/L | - | Brain death at D 3; Death at D 11 of multiorgan failure | Lepiota brunneoincarnata |
| [106] | NC Tunisia | 4 | M/3 | H 7/NC | Vomiting, diarrhoea, abdominal pain, hepatic cytolsis, acute renal failure, metabolic acidosis | AST peak at D 3 > 10,000 U/L; ALT peak at D 3 > 10,000 U/L | - | - | Death at D 4 of multiorgan failure | - | Lepiota brunneoincarnata |
| [72] | January 2000 to October 2010 Germany | 79 | NC | Medial H 14.5/Medial H 29.4 | Nausea, vomiting, diarrhoea, abdominal pain, coagulopathy | 9 activated charcoal, laxatives, silibinin, penicillin, 6 N-acetylcysteine | - | - | AST medial peak: 3242 U/L; ALT medial peak: 3907 U/L | 10 amatoxins identification positive in urine by ELISA; 15.3–125 µg/L (4 after H 48) | Amanita phalloides |
| [107] | NC Portugal | 4 | 4 M-6/F/16-75 | H 7-12/<H 48 | Nausea, vomiting, diarrhoea, dehydration, acute liver failure, encephalopathy grade I | Supportive care, silibinin, penicillin G, N-acetylcyesteine, hemodialysis, hemodiafiltration | - | - | AST medial peak: 5295 U/L; ALT medial peak: 6919 U/L | 4 deaths (3 liver transplantation); 3 liver transplantation alive; 3 positive development | Amanita phalloides |
| [107] | NC Portugal | 4 | 20 M–12/F/1, 4-74 | H 1, 25–6/NC | Nausea, vomiting, diarrhoea, dehydration, acute liver failure, encephalopathy grade I | Activated charcoal, silibinin, gastric lavage, forced diuresis, laxatives, penicillin G, N-acetylcyesteine | 2 intentional ingestions | - | Amatoxins identification positive in urines by ELISA; 1.6 < X < 118 µg/L | 5 deaths at D 3–9 of liver failure; 27 positive development | Amanita phalloides, Amanita virosa |
### Table 3. Cont.

| Ref. | Date of Intoxication | Country | N | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms | Treatment | Notes | Toxin Quantification | Outcome | Mushroom Species |
|------|----------------------|---------|---|---------|-----------------------------------------------|----------|-----------|-------|---------------------|---------|---------------------|
| [110] | November 2011 France | 3       | M/8 | NC/H9 | F/11 Vomiting, abdominal cramps | Nausea, vomiting, diarrhea, weakness, dehydration | Gastric lavage, activated charcoal, hemodialysis, rehydration, silibinin, \(N\)-acetylcysteine, penicillin G, multivitamin | Chemotherapy + surgery for a colon carcinoma 2 months before; Liver transplantation refused because of colon carcinoma; AST peak at H 90: 3570 U/L; ALT peak at H 90: 3280 U/L | - | Death at H 134 of cardiac arrest | *Amanita phalloides* |
| [77] | January 2002 to December 2012 Italy | 242 NC/Medial 53 | NC | Gastrointestinal disorders | Vomiting, diarrhea, abdominal cramps | Nausea, vomiting, diarrhea, weakness, dehydration | Gastric lavage, activated charcoal, hemodialysis, rehydration, silibinin, \(N\)-acetylcysteine | Chemotherapy + surgery for a colon carcinoma 2 months before; Liver transplantation refused because of colon carcinoma; AST peak at H 90: 3570 U/L; ALT peak at H 90: 3280 U/L | - | Death at H 134 of cardiac arrest | *Amanita phalloides* |
| [76] | NC United States, New York | 1 | M/65 | NC | Vomiting, diarrhea, abdominal pain | Nausea, vomiting, diarrhea, weakness, dehydration | Gastric lavage, activated charcoal, hemodialysis, rehydration, silibinin, \(N\)-acetylcysteine | Chemotherapy + surgery for a colon carcinoma 2 months before; Liver transplantation refused because of colon carcinoma; AST peak at H 90: 3570 U/L; ALT peak at H 90: 3280 U/L | - | Death at H 134 of cardiac arrest | *Amanita phalloides* |
Table 3. Cont.

| Ref. | Date of Intoxication | Country | N | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms | Treatment Notes | Toxin Quantification | Outcome | Mushroom Species |
|------|----------------------|---------|---|---------|-----------------------------------------------|----------|----------------|---------------------|---------|------------------|
| [75] | August 2014          | Sweden  | 6 | NC      |                                               | Nausea, vomiting, diarrhea, weakness, fatigue, confusion, neurological reaction depression, liver encephalopathy grade III, renal failure | Consumption of the same mushroom on 2 occasions; AST peak: 4714 U/L; ALT peak: 5824 U/L; Serum creatinine peak: 180,000 µmol/L; Uremia: 13.3 mmol/L | Death at hospitalization D 5 of hepatorenal failure | | Amanita verna |
|      | August 2014          | Sweden  | 6 | NC      |                                               | Nausea, vomiting, diarrhea, weakness, fatigue, abdominal pain | Consumption of the same mushroom on 2 occasions; AST peak: 3600 U/L; ALT peak: 6025 U/L; Serum creatinine peak: 250,000 µmol/L; Uremia: 1.9 mmol/L | Death at hospitalization D 5 of hepatorenal failure | | |
| [113] | August 2014          | Turkey  | 1 | M/61    |                                               | Nausea, vomiting, diarrhea, abdominal pain, fatigue, dehydration | Voluntary ingestion of 2 caps in order to test the toxicity = 21.3 mg amatoxins AST peak at H 72: 1777 U/L; ALT peak at H 72: 2496 U/L | positive development | Amanita phalloides | α-amanitin in urine at D 4: 2.7 µg/L; β-amanitin in urine on D 4: 1.25 µg/L | |
| [114] | August 2014          | Turkey  | 1 | M/61    |                                               | Nausea, vomiting, diarrhea, abdominal pain, fatigue, dehydration | Voluntary ingestion of 2 caps in order to test the toxicity = 21.3 mg amatoxins AST peak at H 72: 1777 U/L; ALT peak at H 72: 2496 U/L | | Amanita phalloides | α-amanitin in urine at D 4: 2.7 µg/L; β-amanitin in urine on D 4: 1.25 µg/L | |

Notes:
- NC: Not Cited
| Ref.     | Date of Intoxication | Country   | N | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms                                                                 | Treatment                                                   | Notes                                                                 | Toxin Quantification | Outcome | Mushroom Species                      |
|----------|----------------------|-----------|---|---------|-----------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------|----------------------------------------------------------------------|-----------------------|----------|---------------------------------------|
| [115]    | October 18, 2013     | Turkey    | 1 | M/39    | NC/H 12                                       | Nausea, vomiting, diarrhea, abdominal pain, dehydration, jaundice        | Gastric lavage, activated charcoal, rehydration, N-acetylcysteine, antihistamine, vitamins, corticosteroid | Consumption of 5 mushrooms = 19.93 mg amatoxins; ALT peak at H 90: 5124 U/L | -                     | positive development | Lepiota brunneoincarnata |
| [73]     | 1999–2015            | Slovenia  | 32| NC      | NC                                            | 29 silibinin, rehydration                                               | 8 PSS1; 8 PSS2; 3 PSS3; Serum creatinine PSS3 group: 185.6 ± 40.7 µmol/L | -                                                                      | -                     | 1 death; 1 liver transplantation; 30 positive development | Amanita phalloides    |
|          | April 2013           | Hong Kong |   |          |                                               | Vomiting, diarrhea                                                      | N-acetylcysteine, silibinin, penicillin G, activated charcoal          | Serum creatinine at H 30: 229 µmol/L; ALT peak at H 48: 4856 U/L | Amatoxins identification positive in urine | positive development | Amanita farinosa        |
|          | March 2015           | Hong Kong |   |          |                                               | Vomiting, diarrhea, fever                                               | N-acetylcysteine, silibinin, penicillin G, vitamin K, activated charcoal | ALT peak at H 72: 5132 U/L                                      | Amatoxins identification positive in urine | Liver transplantation at D 5 | Amanita farinosa        |
| [116]    | March 2015           | South Africa | 7 | F/43    | H 12/D 5                                       | Vomiting, diarrhea, jaundice, confusion, hepatic encephalopathy         | Supportive care                                                      | -                                                                      | -                     | Death at D 6                        | NC                   |
|          |                      | Hong Kong |   | M/44    | H 12/                                          | Vomiting, diarrhea                                                      | N-acetylcysteine, activated charcoal                                   | -                                                                      | Amatoxins identification negative in urine | positive development | NC                   |
|          |                      | China     |   | M/74    | H 9/D 1                                        | Vomiting, diarrhea                                                      | N-acetylcysteine, silibinin, penicillin G, activated charcoal          | -                                                                      | Amatoxins identification positive in urine | positive development | NC                   |
|          |                      | China     |   | F/40    | H 8/D 4                                        | Vomiting, diarrhea, dehydration                                        | N-acetylcysteine, silibinin, penicillin G, activated charcoal          | -                                                                      | -                     | positive development               | NC                   |
### Table 3. Cont.

| Ref. | Date of Intoxication | Country          | N  | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms                                                                 | Treatment                                      | Notes                                    | Toxin Quantification | Outcome | Mushroom Species |
|------|----------------------|------------------|----|---------|-----------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------|-------------------|-------------------|---------|------------------|
| [117] | July 2007 to August 2016 | Czech Republic    | 23 | M–11 F/7–78 | H 2–48/H 8–60 | Nausea, vomiting, diarrhea, abdominal pain, 5 hepatic encephalopathy grade I and II, 3 hepatic encephalopathy grade III and IV | Activated charcoal, rehydration, N-acetylcysteine, silibinin, hemoperfusion, plasmapheresis | AST: 0.5–95 U/L | -                 | 2 deaths (1 at Mo 2 after liver transplantation); 5 liver transplantation; 16 positive development | Amanita phalloides |
| [118] | 28 November 2013     | China            | 13 | 13 M/19–56 | H 9–21/NC | Nausea, vomiting, diarrhea, abdominal pain, fatigue, weakness, anorexia, palpitation, chest tightness, eye pain, blurred vision, leg cramps, oliguria, tachycardia | Rehydration, antiemetics, silibinin, Shenshuaining, hemodialysis | Consumption of ≈ 10–120 g of mushrooms; AST peak: 2600 U/L; ALT peak: 3581 U/L | -                 | positive development | Galerina sulciceps |

N: number of patients; NC: not communicated; F: female; M: male; H: hour; D: day; Mo: month; AST: aspartate aminotransferase; ALT: alanine aminotransferase.
4.5. Human Poisoning Cases Reported

Given the large number of mushroom species containing amanitins throughout the world, a great number of amatoxin poisoning cases have been reported in the literature since the beginning of the last century (Table 3). Of these recorded poisonings, 72 deaths and 33 liver transplants are listed. Five of the deaths occurred up to several months after liver transplantation. This suggests persistent toxicity capable of damaging the graft. One case is unusual, the patient ate 2 caps of *Amanita phalloides* only in order to test the toxicity [114].

The result is fatal in 10–30% of cases [58], with the percentage tending to decrease mainly due to liver transplantation.

4.6. Analytical Aspect

Research began in the mid-1970s to develop a sensitive and reliable analytical method for identifying and quantifying α- and β-amanitin through radioimmunological techniques, thin layer chromatography or liquid chromatography-UV detection. Technological developments over the years have enabled researchers to reach better and better sensitivity levels using high-resolution mass detectors (cf. Table 7).
Table 4. Analytical methods for amatoxins detection.

| Ref. | Matrix                                    | Separation       | Detection       | Qualitative/Quantitative | LOD     | LOQ   | Linearity | Extraction Recovery | Additional Analytical Information |
|------|-------------------------------------------|------------------|-----------------|--------------------------|---------|-------|-----------|--------------------|----------------------------------|
| [119]| Rabbit serum                              | RIA              | Qualitative     | α: 50 pg                 | NA      | NA    |           | NA                 |                                   |
| [70] | Pure substances                           | TLC              | Qualitative     | α: 50 µg                | NA      | NA    |           | NA                 |                                   |
| [120]| Mushrooms                                 | HPTLC            | Spectrophotometry| Quantitative            | 50 ng deposit | NC | NC      | NC      | -                  |                                  |
| [121]| Serum, urine, duodenal fluid, gastric     | RIA              | Quantitative    | 3 µg/L                  | NC      | 3.3–100 µg/L | NC    | -                  |                                  |
|      | juice, mushrooms                          |                  |                 |                          |         |       |           |                    |                                  |
| [122]| Serum, urine, stomach washings           | HPLC             | Quantitative    | 10 µg/L                 | NC      | 20–500 µg/L | 110%  | -                  |                                  |
| [123]| Serum, urine, mushrooms                   | HPLC             | Quantitative    | 10 ng                   | NC      | 0.5–20 mg/L | α: 81.1–98.1% | β: 80.6–97.3% |                                  |
|      |                                           |                  |                 |                          |         |       |           |                    |                                  |
| [124]| Plasma, urine                             | RIA              | Quantitative    | 0.1 µg/L plasma          | NC      | 0.1–20 µg/L | 101.3% | plasma; 1–100 µg/L | 110% urine                      |
|      |                                           |                  |                 | 1 µg/L plasma; 1–100 µg/L|         |       |           |                    |                                  |
| [125]| Serum, urine                              | HPLC             | Quantitative    | α: 40 pg on column       | NC      | 1–1000 µg/L | α: 53–65% | β: 36%            |                                  |
|      | (Amperometry (Reference electrode: Ag/AgCl; Working potential: 600 mV))|          |                 | β: 80 pg on column       |         |       |           |                    |                                  |
| [126]| Plasma                                    | HPLC             | Quantitative    | 9.74 µg/L               | 10 µg/L | 10–100 µg/L | 67.3–105.56% | -                  |                                  |
|      | (Amperometry/EC (Reference electrode: Ag/AgCl; Working potential: 350 mV))|          |                 |                          |         |       |           |                    |                                  |
| [127]| Plasma                                    | HPLC             | Quantitative    | 2 µg/L                  | NC      | 3–200 µg/L | 80–82.5% | -                  |                                  |

Columns: (250 mm x 4.6 mm) 5 µm Ultrasphere ODS C18; Flow rate: 1 mL/min; Mobile phase: 0.02 M ammonium acetate/ACN (88/12; v/v) pH 5; RT α: 12.1 min, β: 7.4 min

Column: (125 mm x 4.0 mm) 5 µm Lachrosoorb RP-18; Flow rate: 1 mL/min; Mobile phase: ACN (A), 0.01 M acetic acid-ammonium acetate buffer pH 5 (B); RT α: 14.9 min, β: 9.1 min

Column: (250 mm x 4.6 mm) 5 µm Spherisorb ODS2 - (250 mm x 4.6 mm) 5 µm Hypersil WP300 Butyl; Flow rate: 1 mL/min; Mobile phase: 0.02 M ammonium acetate/ACN (92:8; v/v) 0.5 mM EDTA pH 5; RT α: 16.5 min, β: 12.0 min

Column: (150 mm x 4.6 mm) 5 µm PLRP-S 100 Å; Flow rate: 0.5 mL/min; Mobile phase: 0.05 M phosphate buffer—ACN (91/9; v/v) pH 9.5
Table 4. Cont.

| Ref. | Matrix          | Separation | Detection      | Qualitative/Quantitative | LOD                  | LOQ                  | Linearity | Extraction Recovery | Additional Analytical Information |
|------|-----------------|------------|----------------|--------------------------|-----------------------|----------------------|-----------|--------------------|-----------------------------------|
| [128,129] | Mushrooms      | HPLC       | UV (214, 295 nm) | Quantitative             | 10 µg/L = 0.5 ng/g mushrooms | NC                   | NC        | NC                 | Column: (250 mm × 4.6 mm) 5 µm Ultrasphere ODS; Flow rate: 1 mL/min; Mobile phase: 0.02 M aqueous ammonium acetate/ACN (90/10; v/v) A (76/24; v/v) B |
| [63] | Urine, mushrooms | Electrophoresis | DAD: 190–350 nm | Quantitative             | 1000 µg/L             | NC                   | 1–1000 mg/L | NC                 | Capillary length: 36 cm (50 µm); T separation: 25°C; Buffer: 100 mM phosphate (pH 2.4) |
| [130] | Urine          | HPLC       | Coulometry (Full scale range 50 µA until 12.5 min, 20 µA up to 20 min) | Quantitative for α-amanitin | 2 µg/L | 10 µg/L | 10–200 µg/L | 77–80.4% | Column: (250 mm × 4.6 mm) Supercel LC 18; Flow rate: 1 mL/min; Mobile phase: 0.005 M bisodic phosphate aqueous solution pH 7.2 and ACN (90/10; v/v); Electrode: graphite |
| [131] | Plasma, urine   | HPLC       | ESI-UV-MS (UV: 302 nm) (SIM mode (+): α-919, 920, 921 m/z; β-920, 921 m/z) | Quantitative for α-amanitin | 2.5 µg/L | 5.0 µg/L | 5–75 µg/L | α-: 49.1–62.5%, β-: 52.1–57.5% | Column: (100 mm × 2.1 mm) 3 µm HP ODS Hypersil RP-18; Flow rate: gradient; Mobile phase: MeOH:0.01 M ammonium acetate pH 5 (10/90; v/v); Electrode: graphite |
| [132] | Serum, urine    | ELISA      | -              | Quantitative for β-amanitin | 0.08 µg/L | 0.08–2 µg/L | NC        | -                  | Column: (250 mm × 2.0 mm) 5 µm 80 Å TSK-Gel Amide 80; Flow rate: 0.2 mL/min; Mobile phase: 2 mM ammonium formate + 5mM HCOOH (A), ACN (B), MeOH (C); RF: α-: ≈ 7.18 min, β-: ≈ 8.94 min |
| [133] | Mushrooms       | HPLC       | HILIC-ESI-MS/MS (ion trap) (scan range: 600–930 m/z) | Quantitative | 20 ng/g | α-: 26.8 ng/g | 20–500 µg/L | 63–75% | Column: (250 mm × 2.0 mm) 5 µm Synergi RP-Polar; Flow rate: 0.5 mL/min; Mobile phase: 0.01 M ammonium acetate in H2O 0.1% HCOOH (A), 0.01 M ammonium acetate in MeOH 0.1% HCOOH (B); RT: α-: 4.5 min |
| [134] | Serum, liver    | HPLC       | ESI-MS/MS/MS (ion trap) (α-941 to 746 (CE 40%)) m/z; Full-scan of product ions of m/z 746 (CE 25%) | Quantitative for α-amanitin | 0.26 ng/g (serum) 0.5 ng/g (liver) | NC | 1–50 µg/L | 95% (serum) 98% (liver) | Column: (100 mm × 4.6 mm) Synergi RP-Polar; Flow rate: 0.5 mL/min; Mobile phase: 0.01 M ammonium acetate in H2O 0.1% HCOOH (A), 0.01 M ammonium acetate in MeOH 0.1% HCOOH (B); RT: α-: 4.5 min |
| [135] | Urine           | Electrophoresis | DAD (214 nm) | Quantitative | 2.5 µg/L | 5 µg/L | 5–100 µg/L | NC        | Capillary length: 48 cm (75 µm); T separation: 25°C |
Table 4. Cont.

| Ref. | Matrix | Separation | Detection | Qualitative/Quantitative | LOD | LOQ | Linearity | Extraction Recovery | Additional Analytical Information |
|------|--------|------------|-----------|--------------------------|-----|-----|-----------|----------------------|-----------------------------------|
| [136] | Plasma | HPLC | ESI-MS/MS (ion trap) (SIM mode: α: 919–921 m/z; β: 920–922 m/z) | Quantitative | 0.5 µg/L | NC | 10–500 µg/L | 77–79% | Column: (150 mm × 2.0 mm) Capcell Pak C18 UG120; Flow rate: 0.2 mL/min; Mobile phase: H₂O 0.1% HCOOH (A), ACN 0.1% HCOOH (B); RT: α: 19.0 min, β: 20.1 min |
| [137] | Mushrooms | HPLC | ESI-TOF-MS (Full-scan: 100–1000 m/z) | Quantitative | 30 ng/g | NC | 100–1000 ng/g | 53.1–69.6% | Column: (150 mm × 2.0 mm) 3 µm TSK-gel Amide-80; Flow rate: 1 mL/min; Mobile phase: ACN (A), 15% MeOH in 10 mM ammonium acetate (B) |
| [11] | Serum, urine | UPLC | ESI-MS/MS (triple Q) (α: 919.6 to 919.6 (20 eV); β: 920.6 to 920.6 (20 eV) m/z) | Quantitative | 0.5–1.5 µg/L | NC | 2–420 µg/L | 91.3–110% | Column: (100 mm × 2.1 mm) 1.7 µm ACQUITY BEH Shield RP18; Flow rate: 0.4 mL/min; Mobile phase: H₂O 0.1% HCOOH (A), MeOH (B); RT: α: 2.23 min, β: 2.49 min |
| [138] | Urine | MALDI | ESI-TOF-MS-MS | Quantitative | 0.5 µg/L | NC | 10–500 µg/L | - | - |
| [139] | Urine, liver | UPLC | ESI-MS/MS (triple Q) (α: 919.48 to 259.13 (44 eV); β: 920.48 to 259.13 (42 eV) m/z) | Quantitative | 0.20 µg/L (urine) | 0.46–0.57 µg/L (urine) | 10–200 µg/L (et ng/g) | 90.4–105.0% (urine) | Column: (100 mm × 2.1 mm) 1.8 µm ACQUITY HSS T3; Flow rate: 0.5 mL/min; Mobile phase: 0.02 M ammonium acetate pH 5 (A), ACN (B); RT: α: 5.73 min, β: 5.27 min |
| [140] | Urine | UPLC | (-) ESI-HR/MS/MS (orbitrap) (SIM mode: α: 917.3458 m/z; β: 918.3298 m/z) | Quantitative for α-amanitin | 1 µg/L | 1 µg/L | 1–100 µg/L | 64–102% | Column: (150 mm × 2.1 mm) 2.6 µm TF Accucore PhenylHexyl; Mobile phase: 10 mM ammonium acetate in H₂O 0.01% HCOOH pH 5 (A), ACN 0.1% HCOOH (B), 2-propanol/ACN (1:1; v/v) (C); RT: α: 8.23 min, β: 7.61 min |
| [141] | Urine | UPLC | HR/MS/MS (orbitrap) (SIM mode: α: 919.3614 m/z; β: 920.3455 m/z) | Quantitative | α: 0.25 µg/L; β: 0.5 µg/L; α: 0.5 µg/L; β: 0.75 µg/L | 1–100 µg/L | 88.4–93.4% | Column: (100 mm × 2.1 mm) 2.6 µm Accucore C18; Flow rate: 0.4 mL/min; Mobile phase: 10 mM ammonium acetate buffer 0.1% HCOOH (A), ACN 0.1% HCOOH (B); RT: α: 1.9 min, β: 1.7 min |
Table 4. Cont.

| Ref. | Matrix                  | Separation | Detection          | Qualitative/Quantitative | LOD  | LOQ    | Linearity  | Extraction Recovery | Additional Analytical Information                                                                 |
|------|-------------------------|------------|--------------------|--------------------------|------|--------|------------|---------------------|---------------------------------------------------------------------------------------------------|
| [142] | Mushrooms               | HPLC       | DAD (303 nm)       | Quantitative             | 2 ng/g | NC     | NC         | NC                  | Column: (150 mm × 4.6 mm) 5 µm C18; Flow rate: 1 mL/min; Mobile phase: 0.05 M ammonium acetate pH 5.5 with HCOOH/ACN (90:10; v/v) |
| [143] | Urine                   | UPLC       | ESI-TOF/MS (Full-scan 50–1000 m/z) | Quantitative             | 1 µg/L | NC     | 1–1000 µg/L | 86–98%              | Column: (100 mm × 2.1 mm) 2.2 µm Acclaim RS 120, C18; Flow rate: 0.2 mL/min; Mobile phase: H₂O/ACN (99:1; v/v) 2 mM ammonium formate, 0.1% HCOOH (A), ACN/H₂O (99:1; v/v) 2 mM ammonium formate, 0.1% HCOOH (B); RT: α: 6.05 min, β: 6.08 min |
| [144] | Rat liver and kidney    | HPLC       | DAD-EC (UV: 305 nm) | Quantitative for α-amanitin | 110 ng/g (liver) 160 ng/g (kidney) 10 ng/g (liver) 40 ng/g (kidney) | UV: 110 ng/g (liver) 160 ng/g (kidney) UV: 330 ng/g (liver) 500 ng/g (kidney) 40 ng/g (kidney) | UV: 50–1000 µg/L (liver) UV: 210–10000 µg/L (kidney) UV: 110–10000 µg/L (kidney) UV: 99.4% (liver) 100% (kidney) EC: 98.8% (liver) 99.7% (kidney) | UV: 99.4% (liver) 100% (kidney) EC: 98.8% (liver) 99.7% (kidney) | Column: (250 mm × 4.6 mm) 5 µm Spherisorb RP-18 ODS2; Flow rate: 1 mL/min; Mobile phase: 20% MeOH in 50 mM citric acid, 0.46 mM octanessulfonic acid pH 5.5 with 10 M NaOH |
| [145] | Serum, urine             | UPLC       | ESI-MS/MS (triple Q) (α: 919.5 to 259.1 (42 eV)/919.5 to 86.0 (68 eV) m/z; β: 920.5 to 259.1 (42 eV)/920.5 to 86.0 (71 eV) m/z) | Quantitative             | 0.5–1 ng/g | 1–2.5 ng/g | 1–100 µg/L | 80.7–88.6%          | Column: (100 mm × 2.1) 1.6 µm; Flow rate: 0.2 mL/min; Mobile phase: 0.2% HCOOH in H₂O (A), 0.2% HCOOH in MeOH (B); RT α: 4.72 min, β: 4.96 min |
| [146] | Food with mushrooms     | HPLC       | (-) ESI-MS/MS (triple Q) (α: 917.4 to 205.1/917.4 to 257.1 m/z; β: 918.4 to 257.1 m/z) | Quantitative             | 5 ng/g | 10 ng/g | 10–2000 ng/g | 77.6–90.4%          | Column: (150 mm × 3.0 mm) 2.5 µm XBridge™ BEH C18; Flow rate: 0.3 mL/min; Mobile phase: MeOH (A), 0.03% ammonia solution in H₂O pH 10.5 (B) |
| Ref. | Matrix          | Separation | Detection                          | Qualitative/Quantitative | LOD       | LOQ       | Linearity | Extraction Recovery | Additional Analytical Information |
|------|----------------|------------|------------------------------------|--------------------------|-----------|-----------|-----------|---------------------|-----------------------------------|
| [147] | Rat plasma     | HPLC       | (+) ESI-MS/MS (triple Q)           | Quantitative for α-amanitin | 3.0 µg/L  | 8.5 µg/L  | 10–1500 µg/L | 85–115%             | Column: (100 mm × 2.1 mm) 5 µm Hypersil GOLD C18; Flow rate: 0.2 mL/min; Mobile phase: 0.02 mol/L ammonium acetate, 0.1% HCOOH (A), ACN (B); RT: 4.86 min |
| [148] | Rat plasma and urine | HPLC | PDA-MS/MS/MS (IT-TOF)              | Qualitative              | NC        | NA        | NA        | NA                  | Column: (100 mm × 2.1 mm) 3 µm Inertil ODS-3; Flow rate: 0.2 mL/min; Mobile Phase: 20 mM ammonium acetate, 0.1% HCOOH (A), ACN (B); RT α: 11.05 min, β: 10.20 min |
| [149] | Urine          | HPLC       | ESI-MS/MS (triple Q)               | Quantitative with 15N10 α-amanitin | α: 0.458 µg/L | β: 0.930 µg/L | NC         | α: 1–200 µg/L, β: 2.5–200 µg/L, γ: 71.1% | Column: (50 mm × 2.1 mm) 1.7 µm Acquity BEH HILIC; Flow rate: gradient; Mobile phase: 10 mM ammonium formate in ACN (25/75); v/v 1% HCOOH (A), 10 mM ammonium formate in ACN (10/90); v/v 0.2% HCOOH (B) |
| [56]  | Standard solution | -         | PSI-HR-MS/MS (α: 919.3610 to 86.0606 m/z; β: 920.3405 to 86.0606 m/z) | Qualitative           | NA        | NA        | NA        | NA                  | -                                 |
| [150] | Mushrooms      | -          | LFIA                               | Qualitative             | α: 10 µg/L | β: 2000 µg/L | γ: 10 µg/L | NA                  | -                                 |

NA: not applicable; LOD: limit of detection; LOQ: limit of quantification; NC: not communicated; RT: retention time; DAD: diode array detection; EC: electrochemical.
Testing for amanitins in various biological samples in a known case of amatoxin poisoning has revealed the elimination kinetics of these compounds. It is possible to find amanitins in blood (plasma or serum) up to 36–48 h after ingestion [61,90,151] in concentrations varying from 10 to 200 µg/L [91] and in urine up to 96 h after ingestion [89,151]. The urine concentrations range from 1 to 7100 µg/L, with a peak between 24 and 72 h [90,140,151].

Jaeger et al. have shown that it is also possible to find high concentrations of α- and β-amanitin in gastroduodenal fluid and feces (between 208 and 4950 µg/L in gastroduodenal fluid and between 23 and 14,900 µg/L in feces) [90].

The amanitins have hepatic and renal tropism. As a consequence, it should be of interest to assay them in these matrices. Jaeger et al. reported concentrations of 10–3298 µg/L found in the liver and kidney samples (from autopsy or biopsy) of poisoned subjects [90].

There is an immunological technique for assaying alpha and gamma amanitins (but not beta amanitin) in urine available as a kit (BÜHLMANN ELISA kit). Its limit of detection is 0.22 µg/L with a limit of quantification of 1.5 µg/L [152].

5. Muscarine

5.1. Toxic Compounds

The first attempt to isolate muscarine, which was considered the main active substance in Amanita muscaria [153], dates back to the early 1810s with Braconnot and Schrader. At that time several researchers had tried in vain to isolate this psychoactive compound. It was not until 1869 that Schmiedeberg and Koppe believed they had isolated the substance and called it muscarine. The substance they isolated proved to be a mixture of muscarine and choline. Pure muscarine was actually isolated for the first time by King in 1922 [154]. The structure of muscarine was proposed in 1957 by Kögl et al. [155]: C₉H₂₀NO₅⁺, M = 174.3 (Figure 5). Muscarine (tetrahydro-4-hydroxy-N,N,N-5-tetramethyl-2-furanmethanaminium) is a water-soluble thermostable alkaloid [154]. To the best of our knowledge, no studies or metabolism data have been published about this mycotoxin.

![Figure 5. Structure of muscarine.](image-url)

5.2. Toxic Mechanism and Toxicity in Humans and/or Animals

Muscarine is an agonist for the neurotransmitter acetylcholine; it activates muscarinic acetylcholine receptors and thereby activates the parasympathetic nervous system [155]. Due to its positively charged quaternary amine group, muscarine does not cross the blood–brain barrier and therefore does not reach the central nervous system. This mechanism of action puts it in group 2B of the White et al. classification [5] (neurotoxic molecules that do not reach the central nervous system). Unlike many mycotoxins, there is an antidote to muscarine: atropine. Administered intravenously, atropine counters the toxic cardiac effects of muscarine [156]. Muscarine poisoning must be proven (for example by identifying the mushroom species ingested) before administering atropine, since atropine can exacerbate some symptoms if administered in error (see ibotenic acid and muscimol, below).

The toxic effects of muscarine vary according to the amount ingested. Muscarine poisoning is rarely fatal; patients with pre-existing cardiac disorders will be more sensitive. The symptomatology
usually resolves after a few hours. In cases where the patient is severely dehydrated, compensation for fluid and electrolyte loss should be considered [2].

Toxicity studies show the i.v. LD$_{50}$ of muscarine in mice is 0.23 mg/kg [157,158]. No numerical data for humans have been published.

No mechanism or preferential route of elimination of muscarine from the organism has been described in the literature.

5.3. Toxic Species

Muscarine is actively present in several mushroom families: around 40 *Inocybes* of the family Inocybaceae (*I. erubescens, I. subdestricta, I. fastigiata, I. geophilla*, etc.), around 15 *Clytocybes* (Figure 6) of the family Tricholomataceae (*C. cerussata, C. dealbata, C. rivulosa, C. phylophilla*, etc.) [156]. It is also found in the genus *Amanita* (*A. muscaria* and *A. pantherina*) but in minute quantities [159], which makes its toxic action insignificant compared with these mushrooms’ other active compounds. *Amanita muscaria* takes its name from muscarine since, as explained above, muscarine was isolated from this species. However, the fly agaric only contains 0.0002–0.0003% of muscarine [153,159,160]. By comparison, *I. subdestricta* contains 0.43% and *C. dealbata* 0.15% [153].

![Figure 6. Clitocybe rivulosa (copyright ©Andgelo Mombert) [161].](image)

Due to the great diversity of mushrooms containing muscarine, the toxin has been identified on every continent.

5.4. Description of the Syndrome

The syndrome associated with muscarine is called muscarinic syndrome. It has a short latency period (<6 h) as the first symptoms appear between 15 min and 2 h after ingestion [156]. The main clinical signs of muscarine poisoning are gastrointestinal distress (nausea, vomiting, diarrhea, and stomach pains), extreme sweating, bronchial, salivary and ocular hypersecretion, and blurred vision. Observed bradycardia, hypotension, and miosis are the direct consequences of acetylcholine receptors activation. In the most severe cases muscarine can cause myoclonus, convulsions, and loss of consciousness that may lead to coma and the death of the patient (cf. Table 5).
Table 5. Cases of ibotenic acid, muscimol, and muscarine poisoning.

| Ref. | Date of Intoxication | Country     | N | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms                                                                 | Treatment                                                                 | Notes                                                                 | Toxin Quantification | Outcome                                      | Mushroom Specie       |
|------|----------------------|-------------|---|---------|------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------|----------------------|---------------------------------------------|----------------------|
|      | 20 July 1964         | United States, Massachusetts | 1 | M/58    | H 2/H 4                                      | Nausea, vomiting, diarrhea, salivation, blurred vision, disorientation, disorders of the state of consciousness | Gastric lavage, glucose, atropine                                         | Obesity, concomitant consumption of alcohol                         | -                   | Positive development                        | Amanita crenulata     |
| [163] | NC South Africa 4    | 4           |   | M/62    | H 0.5/H 1.5                                  | Dizziness, tiredness, clouding vision, vomiting, miosis, nausea, miosis  | Atropine, diuresis, gastric lavage, rehydration, antibiotic, sedative, analgesic |                                                                      | -                   | Positive development with mental deficit for 6 weeks | Amanita pantherina    |

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**Symptoms**: Dizziness, tiredness, clouding vision, vomiting, miosis, salivation, twitching, agitation, visual hallucinations.

**Treatment**:
- Atropine, diuresis, gastric lavage, rehydration, antibiotic, sedative, analgesic
- Gastric lavage, atropine, rehydration, antibiotic, sedative, analgesic
- Gastric lavage, atropine, rehydration, sedative, analgesic
- Gastric lavage, atropine, rehydration, analeptics, antibiotic, tracheostomy, sedative, analgesic

**Notes**:
- Consumption of 2 tablespoonful
- Obesity, concomitant consumption of alcohol
- Positive development

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**Mushroom Specie**:
- Amanita pantherina
- Amanita crenulata
| Ref. | Date of Intoxication | Country       | N  | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms                                      | Treatment                                      | Notes                                                                                     | Toxin Quantification | Outcome                  | Mushroom Species          |
|------|----------------------|---------------|----|---------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------|-----------------------|--------------------------|----------------------------|
| [164] | 17 December 1980     | Zimbabwe      | 2  | M/10    | [165] 17 December 1980 Zimbabwe 2 M/10 NC     | Nausea, vomiting, dizziness, disorders of the state of consciousness, twitching, mydriasis | Glucose                                      | Consumption of a handful of mushrooms                                                      | -                     | Positive development     | Amanita pantherina         |
| [166] | 27 September 1981    | United States, New York | 1  | M/58    | [166] 27 September 1981 United States, New York 1 M/58 H 1.5 | Nausea, vomiting, diarrhea, sudation, confusion, agitation, disorientation, visual hallucinations | Rehydration, gastric lavage, activated charcoal | Consumption of cooked mushrooms                                                         | -                     | Positive development     | Amanita muscaria           |
| [167] | NC United States, Missouri | 5  | 4 M, 1F/NC |     | [167] NC United States, Missouri 5 4 M, 1F/NC | Vomiting, diarrhea, abdominal cramps, salivation, diaphoresis, tiredness, weakness, mydriasis, blurred vision, bradycardia | Atropine                                      | -                                                                                         | -                     | Positive development     | Amanita muscaria suspected |
| [168] | 1979–1989; Between 6 April 6 and 23 May United States, Washington | 11 | 8 M, 3 F/11 months to 20 YO | NC | [168] 1979–1989; Between 6 April 6 and 23 May United States, Washington 11 8 M, 3 F/11 months to 20 YO | Vomiting, incoherent babbling, confusion, irritability, hysteria, hallucinations, myodonic jerking, lethargy, ataxia, bradycardia, mydriasis | Syrup of Ipecac, gastric lavage, charcoal, anticonvulsants, atropine | 1 voluntary consumption seeking hallucinogenic experience; 1 autistic male | -                     | Positive development     | Amanita pantherina, Amanita muscaria |
Table 5. Cont.

| Ref. | Date of Intoxication | Country | N | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms | Treatment | Notes | Toxin Quantification | Outcome | Mushroom Species |
|------|-----------------------|---------|---|---------|-----------------------------------------------|----------|-----------|-------|----------------------|---------|-------------------|
| [169] | NC Poland            | 5       | F/18 | H 0.33/H 5 | Auditory and visual hallucinations, tiredness, gastric pain, loss of consciousness | Activated charcoal, antidiarrheal, potassium chloride | Voluntary consumption seeking hallucinogenic experience, concomitant consumption of alcohol | - | Positive development | Amanita muscaria |
| [170] | NC Australia        | 1       | F/53 | H1/H3 | Headache, chest and abdominal pain, vomiting, diarrhea, sweating, confusion, hypotension, bradycardia, metabolic and respiratory acidosis | Intubation, rehydration, atropine, adrenaline, noradrenaline, metaraminol, glucagon, activated charcoal, dialysis | Consumption of 2 mushrooms | | Death at H10 | Rubinoboletus sensu lato pro tempe |
| [171] | NC Poland           | 2       | F/47 | H2/NC | Nausea, abdominal pain, vomiting, diarrhea, agitation, vertigo, paresthesia of left arm, mystical experiences, speech disorder | NC | Confusion with Macrolepiota procera; Consumption of 5 mushrooms | - | Positive development | Amanita pantherina |
| [171] | NC Poland           | 2       | F/27 | H2/H3 | Nausea, abdominal pain, vomiting, diarrhea, dizziness, anxiety, humming in head | Activated charcoal, laxatives, infusions, electrolytes supplementation | | | | |
| [9]    | NC Slovenia          | 1       | M/48 | H1.5/H4 | Nausea, vomiting, somnolence, disturbance of consciousness, myoclonus, hyperthermia, tachycardia, confusion, visual and auditory hallucinations and paranoia at H18 | Activated charcoal, midazolam, olanzapine | Confusion with Amanita caesarea | - | paranoid psychosis with auditory and visual hallucinations for 5 days | Amanita muscaria |
Table 5. Cont.

| Ref. | Date of Intoxication | Country | N  | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms                                      | Treatment                                      | Notes                                                        | Toxin Quantification  | Outcome                                      | Mushroom Species |
|------|----------------------|---------|----|---------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-------------------------------------------------------------|----------------------|---------------------------------------------|------------------|
| [172]| 5 October 2005       | France  | 2  | M/67    | H 2/H 15                                      | Vomiting, abdominal pain, diarrhea, sudation, miosis | Rehydration, activated charcoal, laxative, atropine | Medical history of arterial hypertension, dyslipidemia, renal colic | -                    | Positive development                        | *Inocybe patouillardii* |
|      |                      |         |    | F/67    | H 2/H 15                                      | Vomiting, abdominal pain, diarrhea, sudation, miosis, disturbance of consciousness, cardiac arrest, hypothermia, tachycardia | Intubation, adrenaline, atropine, antibiotic, anticonvulsant | Medical history of diabetes, arterial hypertension, dyslipidemia, hypothyroidism, restrictive respiratory failure secondary to obesity | -                    | Death of postanoxic encephalopathy at J 7   |                   |
| [173]| November 2006 to January 2008 | Israel | 14 | 8–60   | H 0.25–2/NC                                   | Nausea, vomiting, abdominal pain, diarrhea, diaphoresis, salivation, lacrimation, tachycardia, blurred vision, miosis | Rehydration, antiemetic, atropine | Confusion with *Suillus granulatus* and *Tricholoma terreum*; Consumption of cooked mushrooms | -                    | Positive development                        | *Inocybe fastigiata, I. geophylla, I. patouillardii* |
| [174]| Autumn 2006          | Turkey  | 1  | M/11    | H 2/NC                                        | Vomiting, abdominal pain, diarrhea, salivation | NC                                      | Confusion with *Russula* sp.; Consumption of cooked mushrooms | -                    | Death at D 4                                 | *Inocybe rimosa*   |
|      |                      |         |    |         |                                               |                                               | Nausea, vomiting, abdominal pain, sweating, motor and sensory deficit in the lower limbs, bradycardia, miosis, hypothermia, dehydration, functional renal failure, occlusive thrombosis | Atropine, surgery for the occlusive thrombosis | Medical history of bi-femoral bypass surgery in 1989 | -                    | Positive development                        | NC                |
| [175]| 2010                | France  | 23 | M/59    | H 1/NC                                        | Vomiting, diarrhea, sweating, bradycardia, cardiovascular collapse, miosis, hypothermia, dehydration, functional renal failure | Atropine                                      | Medical history of lower limb arteriopathy obliterans | -                    | Positive development                        |                  |
|      |                      |         |    | F/76    | H 0.5/NC                                      | Vomiting, diarrhea, sweating, bradycardia, cardiovascular collapse, miosis, hypothermia, dehydration, functional renal failure | Atropine                                      | Medical history of lower limb arteriopathy obliterans | -                    | Positive development                        |                  |
Table 5. Cont.

| Ref. | Date of Intoxication | Country          | N   | Sex/Age | Offset of Symptoms/Delay before Hospitalization | Symptoms | Treatment                                      | Notes | Toxin Quantification | Outcome       | Mushroom Species |
|------|----------------------|-------------------|-----|---------|-----------------------------------------------|----------|------------------------------------------------|-------|---------------------|---------------|------------------|
| [155] | NC Czech Republic    | 1 M/55            | NC  | NC/NC   | NC/N  | NC                                           | -      | In urine: muscarine: 0.045 mg/L               |       | Death               | Amanita muscaria |
|       |                      |                   |     |         |       | Vomiting, hallucinations                      | Gastric lavage, activated charcoal, intubation |       | In urine: IBO at H 4: 47.7 mg/L; MUS at H 4: 9.9 mg/L |               |                  |
|       |                      |                   | F/28| H 1.5/NC|       | dizziness                                     | Gastric lavage, activated charcoal             | Confusion with Amanita rubescens               |       | In urine: IBO at H 8: 32.2 mg/L; MUS at H 8: 6.0 mg/L | Positive development | Amanita pantherina |
|       |                      |                   | M/66| NC/NC   |       | Diarrhea, agitation, incoherence               | NC                                             | -                                              |       | In urine: IBO at H 6: 55.2 mg/L; MUS at H 6: 7.4 mg/L |               |                  |
|       |                      |                   | M/62| NC/H 6  |       | Nausea, vomiting, hallucinations               | Activated charcoal, laxative, diuresis         | -                                              |       | In urine: IBO at H 3: 37.3 mg/L; MUS at H 3: 7.6 mg/L |               |                  |
| [177] | NC Japan             | 1 M/59            | NC  | NC/NC   | NC    | NC                                           | -                                              | In serum: IBO: 95.9 µg/L; MUS: 105 µg/L       | Positive development | Amanita ibotengitake |
| [178] | Springtime Poland    | 1 M/21            | NC  | NC/NC   | Unconscious, seizure, mydriasis, salivation, hyperthermia | Intubation, gastric lavage, rehydration       | Voluntary consumption seeking hallucinogenic experience; Stop his treatment for depression; Consumption of marijuana | -                                              | Positive development | Amanita muscaria |

N: number of patients; NC: Not communicated; F: female; M: male; H: hour; D: day; IBO: ibotenic acid; MUS: muscimol.
5.5. Human Poisoning Cases Reported

Case reports about muscarine poisoning are relatively rare. Table 5 shows published cases of muscarine poisoning. A fatal outcome was observed in three cases: an 11-year-old child [174], a 67-year-old woman presenting comorbidities (diabetes, arterial hypertension, and respiratory insufficiency) [172], and a 53-year-old woman with no particular medical history [170]. The other cases present a positive outcome.

5.6. Analytical Aspect

Since muscarine was isolated in 1922 [154], few analytical techniques have been published for identifying and quantifying the compound in different matrices. The first published techniques used thin layer chromatography or gas chromatography with mass detection for qualitative and/or quantitative analysis of muscarine in mushrooms. The technological advances of the early 21st century have enabled considerably greater sensitivity with liquid chromatography techniques coupled to tandem mass spectrometry. With these techniques it is now possible to quantify muscarine in biological matrices such as urine (Table 6).

To the best of our knowledge, no research on muscarine in blood or any other biological matrix has been published. Only one publication mentions a numerical value for muscarine in urine: 0.045 mg/L of muscarine was found in the urine of a 55-year-old suspected of having ingested A. muscaria [155].
Table 6. Analytical methods for muscarine detection.

| Ref.   | Matrix     | Separation | Detection                  | Qualitative/Quantitative | LOD    | LOQ    | Linearity | Extraction Recovery | Additional Analytical Information                                                                 |
|--------|------------|------------|-----------------------------|--------------------------|--------|--------|-----------|---------------------|--------------------------------------------------------------------------------------------------|
| [179]  | Mushrooms  | TLC        | Reactant of Thies and Reuther | Quantitative             | 6 µg   | NC     | NC        | NC                  | -                                                                                                 |
|        | Mushrooms  | TLC        | SIMS-MS                     | Quantitative             | 10 µg deposit | NA     | NA     | NA        | NA                  | Column: (250 mm × 4.6 mm) 10 µm Lichrosorb RP-8; Mobile phase: H₂O 1% glacial acetic acid (A), ACN (B) |
| [180]  | Mushrooms  | HPLC       | UV (254 nm)                 | Qualitative              | NC     | NA     | NA        | NA                  | -                                                                                                 |
|        | Mushrooms  | HPLC       | MS/MS (triple Q)            | Qualitative              | NC     | NA     | NA        | NA                  | -                                                                                                 |
| [133]  | Mushrooms  | UPLC-HILIC | ESI-MS/MS (ion trap)        | Quantitative             | 5 ng/g | 5.1 ng/g | 5–50 µg/L | 84–94%                                                         | Column: (250 mm × 2.0 mm) 5 µm Lichrosorb RP-8; Mobile phase: 2 mM ammonium formate + 5 mM HCOOH (A), ACN (B), MeOH (C); RT: × 9.5 min |
| [158]  | Urine      | HPLC       | ESI-MS (Full-scan mode)     | Qualitative              | 3 µg/L | NC     | NC        | 90%                                                            | Column: (150 mm × 2.0 mm) 5 µm Gemini C18; Flow rate: 0.2 mL/min; Mobile phase: 8 mmol/L heptafluorobutyreric acid in H₂O; RT: 14.2 min |
| [155]  | Urine      | HPLC       | ESI-MS                      | Quantitative             | 0.09 µg/L | 0.3 µg/L | 0.3–2000 µg/L | 95–96%                                                         | Column: (150 mm × 2.0 mm) 5 µm Gemini C18; Flow rate: 0.2 mL/min; Mobile phase: 8 mmol/L heptafluorobutyreric acid in H₂O (A), ACN (B); RT: 10.0 min |
| [181]  | Mushrooms  | HPLC       | ESI-MS/MS (triple Q)        | Quantitative             | NC     | NC     | NC        | NC                  | Column: (150 mm × 2.0 mm) 5 µm Gemini C18; Flow rate: 0.15 mL/min; Mobile phase: H₂O (A), ACN (B), RT: 1.8 min |
| [182]  | Urine      | Electrophoresis | ESI-MS/MS (triple Q) (SIM and MRM mode) | Quantitative         | 0.73 µg/L | NC     | 0.1–10.00 mg/L | 92.6–95.4%                                                  | Capillary length: 100 cm (50 µm); Sheath liquid: H₂O/MeOH/CH₃COOH (20):79.65:0.35 v/v/v; Flow rate: 0.4 mL/min |
| [143]  | Urine      | UPLC       | ESI-TOF/MS                  | Quantitative             | 0.09 µg/L | NC     | 0.1–100 µg/L | 97%                                                            | Column: (100 mm × 2.1 mm) 2.2 µm Acclaim RS 120, C18; Flow rate: 0.2 mL/min; Mobile phase: H₂O/ACN (99:1); Mixture: 2 mM ammonium formate, 0.1% HCOOH (A), ACN/H₂O (99:1); Mixture: 2 mM ammonium formate, 0.1% HCOOH (B); RT: 2.05 min |
| [56]   |           |            | PSI-HR-MS/MS (ac: 174.1486 to 174.1486 m/z) | Quantitative             | NA     | NA     | NA        | NA                  | -                                                                                                 |

NA: not applicable; LOD: limit of detection; LOQ: limit of quantification; NC: not communicated; RT: retention time.
6. Ibotenic Acid, Muscimol

6.1. Toxic Compounds

Ibotenic acid or α-amino-3-hydroxy-5-isoxazoleacetic acid (C₅H₆N₂O₄, M = 158.1) is an alkaloid, which is degraded by decarboxylation into muscimol (3-hydroxy-5-aminomethylisoxazole, C₄H₆N₂O₂, M = 114.1; Figures 7 and 8). These compounds, isolated and described in the 1960s by a Japanese team, are thermostable [153] but the dehydration of ibotenic acid leads to the formation of muscimol by decarboxylation [183]. It would therefore be logical to consider the toxicity of cooked A. muscaria and A. pantherina mushrooms to be mainly attributable to muscimol. These two mycotoxins are the major factors in poisoning, but other toxins have also been identified in the mushrooms, including muscarine, in very low quantities, and muscazone, a structural isomer of ibotenic acid with less potent psychoactive properties than muscimol or ibotenic acid [153,183].

![Structure of ibotenic acid.](image1)

![Structure of muscimol.](image2)

DeFeudis [160] states that muscimol is metabolized quickly after ingestion, and that consequently, its toxicity is shared with its psychoactive metabolites. However, no concrete metabolic study has been published about muscimol or ibotenic acid.

6.2. Toxic Mechanism and Toxicity in Humans and/or Animals

Ibotenic acid and muscimol are isoxazoles derived from glutamic acid and γ-aminobutyric acid (GABA) respectively [183]. Ibotenic acid and muscimol can cross the blood–brain barrier and thus act on the central nervous system [184], which puts them in group 2C of the White et al. classification [5] (neurotoxic molecules that reach the central nervous system). Ibotenic acid is a glutamate neurotransmitter agonist, a powerful neuronal excitant. It acts on the glutamic acid receptors associated with memory and learning. Muscimol is a γ-aminobutyric acid (GABA) agonist. It acts on the GABA receptors with a depressant effect and therefore causes related toxic effects such as visual distortions/hallucinations, loss of balance, slight muscle contractions, and altered sensory perceptions [153,183]. These two alkaloids are preferentially eliminated in urine [153,183]. Ibotenic acid and muscimol can be detected in urine one hour after mushroom ingestion [153].

Fatal poisoning by ibotenic acid and muscimol is very rare [153]. There is no antidote; the only treatment is symptomatic. Hospitalization for neurological surveillance is recommended [156]. In some cases it is necessary to sedate the patient to manage excessive agitation [9,162]. Atropine is to be avoided as it has a similar action to ibotenic acid and muscimol.

Ibotenic acid and muscimol are lethal in very high doses. The LD₅₀ in rats is 129 mg/kg for ibotenic acid and 45 mg/kg for muscimol [158,185,186]. Stebelska [185] refers to a study of the toxicity of isoxazoles on mammals: the oral LD₅₀ for muscimol is 10 mg/kg in rabbits and the oral LD₅₀ for ibotenic acid is 38 mg/kg in mice. As with muscarine, no data for humans have yet been published.
A sporophore of *Amanita muscaria* can contain between 292 and 6570 µg/g of ibotenic acid and between 73 and 2440 µg/g of muscimol [187]. Given the average weight of 60 g and the minimal dose to produce psychotropic effects of 30–60 mg of ibotenic acid and around 6–10 mg of muscimol, a single mushroom is enough to experience hallucinogenic effects [185]. Some studies have shown that the intensity of the effects varies according to which part of the mushroom is consumed. Indeed, the cap of the mushroom has a higher concentration of psychoactive substances than the stem [188,189].

### 6.3. Toxic Species

Ibotenic acid and muscimol are mainly found in *Amanita muscaria* (Figure 9) and *Amanita pantherina* mushrooms, which belong to the genus *Amanita* of the family Amanitaceae. Virtually all mushrooms in genus *Amanita* contain high levels of muscimol and ibotenic acid. *A. muscaria* is undoubtedly the most iconic mushroom in the world, represented in illustrations, cartoons, etc., due to its bright colors and white spotted cap. These mushrooms have been identified in the United States, sub-Saharan Africa (South Africa, Zimbabwe) Japan, and Europe (cf. Table 5).

![Amanita muscaria](Figure 9. *Amanita muscaria* [190]).

The possession, purchase, and sale of ibotenic acid and muscimol are not regulated in France. However, the possession, purchase, and sale of *Amanita muscaria* are illegal in the Netherlands [191], the state of Louisiana in the USA, the UK [192], and Romania [192]. In Thailand hallucinogenic mushrooms are classified as class V narcotics and are therefore illegal [193]. In Japan these two mushroom species are sold openly as dried mushrooms or dried mushroom “powder” on the internet and in “smoke shops” [186].

### 6.4. Description of the Syndrome

The syndrome produced by consuming mushrooms containing ibotenic acid and muscimol is called pantherina syndrome (or myco-atropine syndrome) [156]. The syndrome is characterized by a short latency period (30 min to 3 h) [156]. The first perceptible effects after ingestion are mainly nausea, vomiting, and diarrhea, followed by characteristic symptoms of central nervous system dysfunction (confusion, dizziness, myoclonus, visual and auditory hypersensitivity, and distortion of time and space) accompanied by mydriasis, fatigue, and drowsiness (cf. Table 5). The phenomenon of
hallucinations has been discussed. After 2 h the subject presents altered states of consciousness lasting approximately 8 h [153].

Pantherina syndrome is sometimes confused with drunkenness.

6.5. Human Poisoning Cases Reported

The consumption of *Amanita muscaria* is connected with mysticism since the mushroom’s psychotropic properties have been known and prized for several thousand years. *A. muscaria* was traditionally used in religious, spiritual, or shamanic rituals by some tribes in Northern Europe and Northern Asia (Siberian shamans of tribes such as the Ostyak, Vogul, Kamchadal, Koryak, and Chukchi) [153]. The “Rig Veda”, the ancient Hindu text considered one of the world’s great religious works (composition estimated between 1500 and 900 BC) [194], advocates “Soma”. The term Soma has several meanings in Hindu mythology: a ritual drink, the plant (or the mushroom), and the god. Several hypotheses argue that Soma was extracted from *Amanita muscaria* [195,196]. In his book “*Amanita muscaria; Herb of Immortality*” Teeter considers the fly agaric to be at the centre of all religions and beliefs [197]. Theories about *A. muscaria* as soma have been very thoroughly debunked [198].

*A. muscaria* or *A. pantherina* poisonings can happen accidentally, through confusion with an edible mushroom species or ignorance of the fungi kingdom. However, a large proportion of these poisonings are from voluntary recreational consumption from those seeking psychotropic effects. Table 5 lists some examples. Only one case of death of a 55-year-old man attributed to an *Amanita muscaria* poisoning was reported [155]. Unfortunately, in this case, only muscarine in urine was quantified, neither ibotenic acid nor muscimol.

6.6. Analytical Aspect

Analytical techniques have been developed since the early 1980s with the aim of identifying and quantifying the principal mycotoxins responsible for pantherina syndrome. Liquid chromatography is the most widely used technique. It was not until the late 2000s that researchers considered the detection of isoxazoles in biological matrices (urine and serum; Table 7).

Some poisoning cases have been documented where patients’ biological samples were investigated for ibotenic acid and muscimol. Stříbrný et al. [176] reported varying concentrations of ibotenic acid between 32 and 55 mg/L, and of muscimol between 6 and 10 mg/L in urine (3–8 h after ingestion). Hasegawa et al. [177] reported concentrations of 96 µg/L of ibotenic acid and 101 µg/L of muscimol in the serum of a subject poisoned by *A. ibotengutake* (without specifying the period between ingestion and sampling).
Table 7. Analytical methods for ibotenic acid and muscimol detection.

| Ref. | Matrix   | Separation | Detection          | Qualitative/Quantitative | LOD      | LOQ      | Linearity | Extraction Recovery | Additional Analytical Information                                                                 |
|------|----------|------------|--------------------|--------------------------|----------|----------|-----------|--------------------|--------------------------------------------------------------------------------------------------|
| [199]| Mushrooms| GC         | MS                 | Quantitative             | NC       | NC       | NC        | NC                 |                                                    |
|      |          |            |                    |                          |          |          |           |        | Columns: (0.75 m × 2.8 mm) OV-101 and (1.2 m × 2.8 mm) SE-30; Helium flow rate: 20 mL/min; T transfer line: 175 °C |
| [200]| Mushrooms| HPLC       | UV (440, 570 nm)   | Quantitative             | 30 ng    | NC       | NC        | NC                 | Column: (350 mm × 2.7 mm); RT IBO: 11 min, MUS: 83 min                                           |
|      |          |            |                    |                          |          |          |           |        |                                                              |
| [188]| Mushrooms| HPLC       | UV (210 nm)        | Quantitative             | 1 ppm    | NC       | <98%      | NC                 | Column: (25 mm × 4.0 mm) IRICA RP-18T; Flow rate: 0.6 mL/min; Mobile phase: H2O/ACN/MeOH (65:20:15; v/v/v) with 2.1 mM sodium dodecyl sulfate + 4 mM H3PO4, isocratic mode |
| [201]| Mushrooms| HPLC       | UV (230, 254 nm)   | Quantitative             | 18 µg/L IBO 0 µg/L MUS | 50–1000 µg/L IBO 100–3000 µg/L MUS | NC |                                                    |
|      |          |            |                    |                          |          |          |           |        | Column: (250 mm × 4.6 mm) 5 µm Spherisorb S5 ODS-2; Flow rate: 0.1 mL/min; Mobile phase: 5 mM octylammonium α-phosphate |
| [202]| Mushrooms| HPLC       | PDA                | Quantitative just of IBO| NC       | NC       | NC        | NC                 | Preparative column IBO: (115 mm × 13 mm) C18; Flow rate IBO: 0.5 mL/min; RT IBO: 8.2 min; Column MUS: (150 mm × 4.6) Zorbax SB-Aq; Flow rate MUS: 1.0 mL/min; RT MUS: 12.8 min; Mobile phase: H2O/ACN/MeOH (65:20:15; v/v/v) with 2.1 mM sodium dodecyl sulfate + 4 mM H3PO4, isocratic mode |
|      |          |            |                    |                          |          |          |           |        |                                                    |
|      |          |            |                    |                          |          |          |           |        | Column: (100 mm × 2.1 mm) 5µm X Terra™ MS C18; Flow rate: 0.5 mL/min; Mobile phase: H2O/MeOH (19:1; v/v) to ACN/H2O/MeOH (18:1:1; v/v/v) |
| [203]| Mushrooms| HPLC       | ESI-MS/MS (triple Q) | Quantitative             | NC       | NC       | NC        | NC                 | Column: (150 mm × 2.1 mm) 5µm Uptisphere ODB C18; Flow rate: 0.2 mL/min; Mobile phase: 2 mM ammonium formiate buffer pH 3 (A), ACN (B) |
|      |          |            | IBO: 159 to 113;1,159 to 42.3 m/z; MUS: 115.1 to 98.1; 115.1 to 67.2; 115.1 to 39.4 m/z |                          |          |          |           |        |                                                    |
| [189]| Mushrooms| GC         | MS (SIM: IBO: 257 m/z, MUS: 243 m/z) | Quantitative IBO/MUS | 10–400 ppm IBO 25–2000 ppm MUS | NC |                                                    |
|      |          |            |                    |                          |          |          |           |        | Column: (30 m × 0.25 mm) 0.25 µm DB-5 ms; Helium flow rate: 53 mL/min; T injector: 250 °C; Toven: 100 °C |
|      |          |            |                    |                          |          |          |           |        |                                                    |
Table 7. Cont.

| Ref. | Matrix | Separation | Detection | Qualitative/Quantitative | LOD | LOQ | Linearity | Extraction Recovery | Additional Analytical Information |
|------|--------|------------|-----------|---------------------------|-----|-----|-----------|---------------------|----------------------------------|
| [204] | Mushrooms | HPLC | UV (256 nm) | Quantitative | 7.8 ppm IBO, 1.4 ppm MUS | 25.9 ppm IBO, 4.6 ppm MUS | 40–2500 ppm IBO, 25–2500 ppm MUS | 95.4–101.1% | Column: (150 mm × 2.1 mm) 3.5 µm Symmetry C18; Flow rate: 0.2 mL/min; Mobile phase: 10 mM ammonium acetate (A), ACN (B); RT IBO: 25.92 min, MUS: 24.65 min. |
| [158] | Urine | HPLC | (Full-scan mode) | Quantitative | 50 µg/L IBO, 40 µg/L MUS | NC | NC | 15% IBO, 22% MUS | Column: (150 mm × 2.0 mm) 5 µm Gemini C18; Flow rate: 0.2 mL/min; Mobile phase: 8 mmol/L heptafluorobutyric acid in H₂O; RT: IBO 2.6 min, MUS 4.6 min. |
| [176] | Urine | GC | (Full Scan) | Quantitative | 1 mg/L | NC | 1–15 mg/L | 74% IBO, 80% MUS | Column: (15 m × 0.25 mm) 0.25 µm HP-5MS; Helium flow rate: 1.5 mL/min; T injector: 220 °C; T transfer line: 250 °C |
| [186] | Mushrooms | LC-HILIC | ESI-MS/MS (triple Q) | Quantitative | <10 µg/g | NC | 10–500 µg/g | 84.6–107% | Column: (150 mm × 2.0 mm) 3 µm TSK-GEL Amide-80; Flow rate: 0.5 mL/min; Mobile phase: H₂O: 0.5% HCOOH (A), ACN 0.5% HCOOH (B). |
| [177] | Serum | LC-HILIC | ESI-MS/MS (triple Q) | Quantitative | 1 µg/L IBO, 2.5 µg/L MUS | NC | 10–1000 µg/L | 87.9–103% | Column: (150 mm × 2.0 mm) 3 µm TSK-GEL Amide-80; Flow rate: 0.5 mL/min; Mobile phase: H₂O: 0.5% HCOOH (A), ACN 0.5% HCOOH (B). |
| [187] | Mushrooms | Electrophoresis | PDA (214 nm) | Quantitative | 1.5 µg/g IBO, 1.8 µg/g MUS | 4.6 µg/g IBO, 5.4 µg/g MUS | 2.5–7000 mg/L | 87–95% | Capillary length: 57 cm (75 µm); Running buffer: 25 mM sodium phosphate pH 3 (5.95; v/v%) |
| [182] | Urine | Electrophoresis | ESI-MS/MS (triple Q) | Quantitative | 0.15 µg/L IBO, 0.05 µg/L MUS | NC | 10–1000 µg/L | 92.6–95.4% | Capillary length: 100 cm (50 µm); Flow rate: 0.4 mL/min; Sheath liquid: H₂O:MeOH:CH₃COOH (20:79.65:0.35, v/v/v%) |
| [205] | Urine | NMR | - | Quantitative | 30 mg/L IBO, 3 mg/L MUS | NC | 2–417 mg/L IBO, 3–278 mg/L MUS | NC | - |
| [56] | Standard solution | - | - | Qualitative | NA | NA | NA | NA | - |

NA: not applicable; LOD: limit of detection; LOQ: limit of quantification; NC: not communicated; RT: retention time; IBO: ibotenic acid; MUS: muscimol.
7. Gyromitrin

7.1. Toxic Compounds

In 1885, Boehm and Külz isolated an oily substance from the false morel, which they believed to be the substance responsible for the mushroom’s toxicity. More advanced studies have shown that it is actually a mixture of non-toxic organic acids. Gyromitrin was finally isolated, synthesized and definitively identified in 1968 by List and Luft as acetaldehyde N-methyl-N-formylhydrazine or gyromitrin (C₄H₈N₂O, M = 100.1) [206–208]. The hydrolytic cleavage of gyromitrin (Figure 10) leads to the formation of N-methyl-N-formylhydrazine and then methylhydrazine (or monomethylhydrazine, MMH) [209,210], which is used in astronautics as a rocket propellant [209]. Gyromitrin belongs to the hydrazine family and is volatile, thermosensitive, and very soluble in water [207]. This mycotoxin can be partially eliminated by drying or boiling the mushroom. Pyysalo [211] has shown that these measures can reduce the quantity of gyromitrin originally contained in the mushroom by up to 99–100%.

\[
\begin{align*}
\text{Gyromitrin} & \rightarrow \text{N-Methyl-N-formylhydrazine} \\
& \rightarrow \text{N-Methylhydrazine}
\end{align*}
\]

Figure 10. Structure of gyromitrin and its metabolites [209].

7.2. Toxic Mechanism and Toxicity in Humans and/or Animals

Gyromitrin is classed as a GABA-inhibiting mycotoxin, group 4A in the White et al. classification [5]. Its mechanism of toxic action is connected with the production of MMH. MMH interacts with pyridoxine dependent coenzymes, resulting in inhibition of glutamic acid decarboxylase and thus reduced GABA production, causing the neurological symptoms to occur. MMH can also cause methemoglobinemia [207,212]. In addition, MMH produces radical species that lead secondarily to hepatic cytolysis [207].

N-methyl-N-formylhydrazine and methylhydrazine are known to be hepatotoxic through the mechanism of producing radical species, but they are also known to be carcinogenic in animals [209,213].

Several studies have been conducted on animals to determine the lethal dose of 50% for gyromitrin and MMH. Patocka et al. [209] reported an oral LD₅₀ for gyromitrin of 344 mg/kg in mice, 320 mg/kg in rats, 50–70 mg/kg in rabbits, and a resistance of over 400 mg/kg in chickens. In humans, the oral LD₅₀ is estimated at 20–50 mg/kg in adults and 10–30 mg/kg in children [207]. Studies of the lethal dose of monomethylhydrazine have also been published, reporting a dose of 4.8–8 mg/kg in adults and 1.6–4.8 mg/kg in children [212]. Pyysalo et al. reported a concentration of 50 mg of gyromitrin/kg in fresh mushrooms (Finnish species).

There is considerable variation in individual responses to gyromitrin poisoning: ranging from simple stomach upset to the death of the patient (cf. Table 8). The outcome is fatal in approximately 10% of cases [207].

Treatment of gyromitrin poisoning is symptomatic. It may include administration of vitamin B₆ (pyridoxine) to stop seizures and/or anticonvulsants such as clonazepam [207,212].
### Table 8. Cases of gyromitrine poisoning.

| Ref. | Date of intoxication | Country | N   | Sex/Age | Offset of symptoms/Delay before hospitalization | Symptoms | Treatment | Notes | Toxin Quantification | Outcome | Mushroom specie |
|------|----------------------|---------|-----|---------|-----------------------------------------------|----------|-----------|-------|----------------------|----------|------------------|
| [214] | 11 May 1935 | United States, Michigan | 7   | F/69    | NC/D 1 | Vomiting, severe chest and leg pain, fever, tachycardia, convulsions, coma | Morphine, atropine, stomach wash, caffeine, sodium benzoate | Consumption of dried mushrooms after having been parboiled | - | - | Death at D 5 | Gyromitra esculenta |
| [215] | Between 1782 and 1965 | Eastern Europe | Minimum of 654 | - | - | Gastrointestinal disorders | NC | - | - | - | At least 114 death | Gyromitra esculenta |
|       | 9 June 1962 | France | 1   | F/8     | D 3/NC | Vomiting, agitation, delirium, bilateral mydriasis, coma, muscular hypertonia, arterial hypertension | NC | Consumption on 2 occasions | - | - | Death of liver failure | |
|       | April 1964 | France | 3   | F/4     | H 12/NC | Vomiting, subictus, delirium, agitation, coma, oliguria, fever, respiratory collapse, liver failure | Tracheotomy, artificial ventilation | Consumption several times over 3 weeks | - | - | Death of liver failure at H 102 | Gyromitra esculenta |
|       |         |         | F/NC | -     | - | Vomiting, liver failure | NC | - | - | - | Positive development | |
|       | Between 1817 and 1965 | NC | 282 | NC/NC | NC/NC | Vomiting | NC | - | - | 21 death | |
| [206] | NC | Italy | 1   | F/53    | D 1/D 1 | Vomiting, diarrhea, jaundice, hypotension, anuria, severe enlargement of the liver, right hemiplegia, coma | Plasma infusion, corticosteroids | Autopsy: liver necrosis, brain edema, TLC on intestine extract | - | - | Death at D 3 | Gyromitra esculenta |
| [212] | Springtime | Canada | 2   | F/49    | H 2/D 1 | Nausea, vomiting, abdominal pain, hot and cold chills, fatigue, anorexia, jaundice | Rehydration, analgesic, antiemetic, Vitamin B6, antacid, antihistamine | AST on D 5: 431 U/L; ALT on D 5: 472 U/L | - | - | Positive development | Gyromitra esculenta |
|       |         |         | M/56 | NC/D 1 | - | Nausea, vomiting, abdominal pain, jaundice, headache | - | AST on D 4: 116 U/L | - | - | |

N: number of patients; NC: not communicated; F: female; M: male; H: hour; D: day; AST: aspartate aminotransferase; ALT: alanine aminotransferase.
7.3. Toxic Species

Gyromitrin is the main toxin in mushrooms of the genus *Gyromitra* of the family Discinaceae. The most common mushroom is *Gyromitra esculenta* (Figure 11), which is often confused with morel, hence its nickname: false morel [207] shares a subgroup with *G. fastigiate* [207] and *G. ambigua* [217]. There is no evidence that *G. gigas* contains gyromitrin. It would appear that a large proportion of the genus *Gyromitra* contains gyromitrin [209].

![Figure 11. Gyromitra esculenta [218].](image)

It should be noted that *G. esculenta* contains other toxins beside gyromitrin: pentanal \(N\)-methyl-\(N\)-formylhydrazone, 3-methylbutanal \(N\)-methyl-\(N\)-formylhydrazone, and hexanal \(N\)-methyl-\(N\)-formylhydrazone [210]. All these compounds lead to the formation of methylhydrazine by hydrolysis [209,210]. In addition, there is a small amount of \(N\)-methyl-\(N\)-formylhydrazine in the mushroom, formed by hydrolytic cleavage [209].

This fungi genus is found mainly in the northern hemisphere (Canada, United States, and Eastern Europe). Long considered edible, *G. esculenta* has been the cause of many deaths.

7.4. Description of the Syndrome

The syndrome resulting from gyromitrin poisoning is called gyromitra syndrome [156]. It is characterized by a long latency period (between 5 and 12 h) after consuming the mushrooms [207]. Like the majority of mushroom poisonings, the first perceptible symptoms are nausea, vomiting, stomach pains, and sometimes bloody diarrhea, resulting in dehydration and headaches. MMH being hepatotoxic, there is often jaundice, indicating liver damage. In severe cases of poisoning there are altered states of consciousness, lack of motor coordination, seizures, and coma, which may lead to the death of the patient (c.f. Table 8).

In most cases the symptoms disappear 2–6 h after ingesting the mushrooms [212].

7.5. Human Poisoning Cases Reported

The first cases of gyromitrin poisoning were reported in 1782, then towards the end of the 1800s [215,216]. Franke et al. [215] reported a large number of poisonings in Eastern Europe between 1782 and 1965. However, there are fewer cases of poisoning reported than for the other mycotoxins due
to this toxin’s thermosensitivity (Table 8). Due to the long latency period, some patient ate mushrooms several times. Some of these patients died of liver failure [216].

7.6. Analytical Aspect

Very few quantitative analytical techniques regarding gyromitrin have been reported in the literature (Table 9). The majority report a quantification of MMH in mushrooms using gas chromatography. Only three publications have covered biological matrices in mice or humans. It should be noted that some authors measure methylhydrazine rather than gyromitrin because of its rapid metabolization in vivo. To our knowledge, no technique using liquid chromatography to identify and quantify gyromitrine or its metabolites was published.

No data have been published to date on the quantification of gyromitrin in human biological matrices following G. esculenta poisoning.
Table 9. Analytical methods for gyromitrine detection.

| Ref. | Matrix                        | Separation | Detection                  | Qualitative/Quantitative | LOD       | LOQ       | Linearity | Extraction Recovery | Additional Analytical Information |
|------|-------------------------------|------------|----------------------------|--------------------------|-----------|-----------|-----------|--------------------|-----------------------------------|
| [206] | Viscera                       | TLC        | UV (254–277 nm) IR (NC)    | Qualitative and quantitative | NC        | NC        | 0.1–0.5 g/L | NC                 | -                                |
| [219] | Mice gastric content          | GC         | UV and IR                  | Quantitative             | NC        | NC        | NC        | NC                 | Column: (2 mm × 2 mm) Chromosorb 103; T column: 160 °C; Helium flow rate: 20 mL/min; RT: GYRO: 17 min, MFH: 15.7 min |
| [220] | Mushrooms                     | GC         | MS                         | Quantitative             | NC        | NC        | NC        | NC                 | Column: 50 m FFAP                  |
| [221] | Mice peritoneal fluids        | GC         | Spectrofluorimetry         | Quantitative (MH)        | NC        | NC        | NC        | NC                 |                                   |
| [222] | Mushrooms                     | TLC        | Spectrofluorimetry         | Quantitative             | NC        | NC        | 0.43–2.17 ng | NC                 | -                                |
| [223] | Mushrooms                     | GC         | FID                        | Quantitative             | NC        | NC        | NC        | 30–74% GYRO 96–124% MH | Column: (25 mm × 0.31 mm) SE-54; Helium flow rate: 1 mL/min; RT: 7.3 min |
| [224] | Mushrooms                     | GC         | EI-MS (Full-scan 35–650 m/z) | Quantitative MH: 12 µg/L = 0.3 µg/g of gyromitrin | NC | NC–1.2 mg/L | 36–55% | Column: (30 mm × 0.25 mm) 0.25 µm HP5-MS |
| [56]  | Standard solution             | -          | PSL-HR-MS/MS               | Qualitative              | NA        | NA        | NA        | NA                 | -                                |

NA: not applicable; LOD: limit of detection; LOQ: limit of quantification; NC: not communicated; GYRO: gyromitrin; MFH: N-methyl-N-formylhydrazine; MH: methylhydrazine.
8. Conclusions

This review of the literature took an analytical perspective, and focused on highly toxic mycotoxins (orellanine, α- and β-amanitin, muscarine, ibotenic acid, muscimol, and gyromitrin). It identifies a set of knowledge gaps. There is indeed a lack of scientific data, particularly regarding the metabolism of mycotoxins in biological matrices, but there is also a lack of analytical tools. There is a real need for the development and validation of specialized analytical methods adapted for the analysis of these mycotoxins in various matrices. Their implementation in the context of a clinico-biological study comparing the results of biological samples analysis (identification and assay) with the case history and clinical signs of confirmed or suspected poisoning victims could strengthen our understanding and treatment of these poisonings.

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