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## REVIEW ARTICLE

# GYROMITRIN, MUSHROOM TOXIN OF *GYROMITRA* SPP.

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**Summary**

*Gyromitra esculenta* (Persoon ex Fries) mushrooms have been responsible for severe intoxications and even deaths. Clinical data are characterized primarily by vomiting and diarrhea and after a while by jaundice, convulsions and coma. Other *Gyromitra* species which may be of concern are *G. fastigiata* and *G. gigas*; nevertheless, recent advances in chromatography, biochemistry and toxicology have established that other species within the *Ascomycetes* may also prove toxic. Their toxins, mainly gyromitrin (N-methyl-N-formyl-N-acetyl-hydrazone) and their higher homologues are converted in the milieu of human stomach into N-methyl-N-formylhydrazine (MFH), then into N-methylhydrazine (MH). The toxicity of these latter chemicals, which are mainly hepatotoxic and even carcinogenic, has been established through *in vivo* and *in vitro* experiments with cell cultures and biochemical systems. Considering the chemical structure and the reactivity of these natural compounds, chemical and biochemical mechanisms are defined in order to explain their intrinsic biological activity. These findings imply that consumption of *G. esculenta* could present a carcinogenic as well as an acutely toxic health hazard.

*Key words: Gyromitra esculenta; mycotoxin; gyromitrin; N-methyl-N-formyl-N-acetyl-hydrazone; N-methyl-N-formyl-hydrazine*

## INTRODUCTION

*Gyromitra* is a genus of ascomycete mushrooms (*Ascomycota* phylum) found in the northern hemisphere. The genus *Gyromitra* contains about 18 species (Stephenson, 2010). Some types of *Gyromitra* are highly poisonous when raw, and these mushrooms have caused severe poisonings and even deaths in humans (Michelot and Toth, 1991). Clinical data are characterized primarily by vomiting and diarrhea, followed by jaundice, convulsions and coma (Hendricks, 1940). Gastrointestinal disorders distinguish this poisoning. Frequent consumption can cause hepatitis and neurological diseases (Köppel, 1993). The species of concern are mainly *G. esculenta*, as well as *G. gigas* (Kromb.). Nevertheless, recent advances in chromatography, biochemistry and toxicology have established that other *Gyromitra* species may also prove toxicity (Patowary, 2010), although some are edible when cooked.

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*G. esculenta* is very sought after in Scandinavian countries (Härkönen, 1998), while its sale or trading is illegal in some European countries (Ludolph, 2000). Consumption of false morel has been associated not only with acute poisoning, but also with a carcinogenic risk (Bergman and Hellenäs, 1992).

## Chemistry of toxic principles

Gyromitrin (ethylidene gyromitrin, acetaldehyde N-methyl-N-formylhydrazone) and its homologues are toxic compounds present in raw edible wild mushroom *G. esculenta*. They are converted *in vivo* into *N*-methyl-N-formylhydrazine (MFH), and then into *N*-methylhydrazine (MH) (Fig. 1), which is highly toxic (Nagel et al., 1977; List and Luft, 1968). In studies on volatile compounds in false morels it has been found that in addition to gyromitrin these mushrooms contain also other toxic hydrazones. They were identified as higher homologues of gyromitrin, i.e. N-methyl N-formyl hydrazones of pentanal, 3-methylbutanal, and hexanal (Fig. 2) (Pyysalo, 1975). The toxicity of these chemicals, which are mainly hepatotoxic and even carcinogenic, has been established through *in vivo* and *in vitro* experiments using animals, cell cultures and biochemical systems. Presumably all these compounds yield MH on hydrolysis, which is probably the highly toxic compound formed after false morels ingestion (Wright et al., 1978). The presence of these hydrazine derivatives has recently been confirmed at levels of 0.3% gyromitrin and 0.05% MFH in dried mushrooms (Schmidlin-Mészáros, 1974).

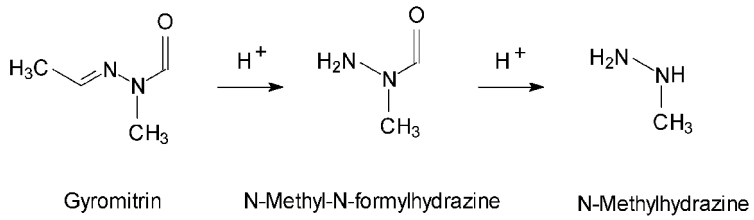


**Figure 1.** Gyromitrin (acetaldehyde N-methyl-N-formylhydrazone) is converted *in vivo* into *N*-methyl-N-formylhydrazine, and then into *N*-methylhydrazine.

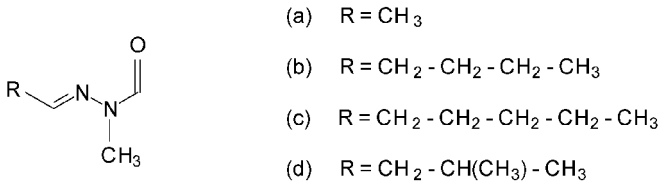


**Figure 2.** Structures of toxic compounds in fresh false morel (*Gyromitra esculenta*). (a) Acetaldehyde N-methyl-N-formyl hydrazone (gyromitrin), (b) pentanal N-methyl-N-formyl hydrazone, (c) hexanal N-methyl-N-formyl hydrazone, (d) 3-methylbutanal N-methyl-N-formyl hydrazone.

## Poisoning by Gyromitra

*Gyromitra* species are considered to be edible mushrooms although their potential toxicity has been long known. They have caused numerous accidents, sometimes lethal (Giusti and Carnevale, 1974; Michelot, 1989). Historical accounts of poisoning are reported and the authors describe the main characteristics: inconstant toxicity, influence of repetitive ingestions and variable individual sensitivity. Knowing that gyromitrin can be converted into MH, the authors suggest a relation between individual sensitivity to the mushrooms and variation of interhuman ability to carry out such a conversion. Several metabolites of gyromitrin can produce enzyme activation with subsequent synthesis

of MH. The cumulative activating role of consecutive ingestions is emphasized (Coulet and Guillot, 1982).

Acute poisoning by *Gyromitra* is scarce in Western Europe while it is the most frequent in Eastern Europe (Raszeja, 1959; Fiedorowicz-Fabrycy and Lapis, 1968; Eisner et al., 1973; Giusti and Carnevale, 1974; Garnier et al., 1978; Flammer, 1985; Kohn and Mot'ovská, 1997). Poisonings cases have been described in the American continent as well (Leathem and Dorran, 2007). A *G. esculenta* fatal hemolytic episode in a dog has also been described (Bernard, 1979).

Giusti and Carnevale (1974) reported a case of fatal poisoning by *G. esculenta* in a 53-year-old woman. Clinical data were characterized initially by vomiting and diarrhea, and subsequently by hypotension, anuria, jaundice, hemiplegia, and coma. Death followed on the third day. Prominent pathologic findings were brain edema, necrosis, fatty degeneration of the liver, nephrosis, scattered petechiae, and small hemorrhages.

*Gyromitra* poisoning clinical picture associating cytolytic hepatitis, seizures, and hemolysis reminds us of hydrazine poisonings (Mittmann, 1968; Garnier et al., 1978). Primary hemolysis induced by antigens and toxins of mushrooms must be distinguished from secondary hemolysis of shock and disseminated intravascular coagulation with disruption of erythrocytes (Flammer and Gallen, 1983). In the most severe cases, death occurs 3 or 5 days after ingestion. Hydrazine derivatives are also known to bind vitamin $B_6$, thus this could be the mechanism of action for some neurotoxic effects observed in *Gyromitra* poisonings (Ludolph, 2000). In fact, administration of vitamin $B_6$ is suggested to prevent seizures (Michelot and Toth, 1991).

## Toxic compounds

Gyromitrin is the main poisonous hydrazine derivative present in *G. esculenta*, but its metabolites MFH and MH are also very important toxic products (Coulet and Guillot, 1982).

### *Gyromitrin*

Gyromitrin (CAS Registry Number 16568-02-8) $LD_{50}$ acute oral toxicity is: 344 mg/kg in mice (Wright et al., 1978), 320 mg/kg in rats (Mäkinen et al., 1977), while in rabbits it varies from 50 mg/kg (Pyysalo, 1975) to 70 mg/kg (Mäkinen et al., 1977). No toxic effects were detected in chickens when given a dose of 400 mg/kg (Mäkinen et al., 1977). Gyromitrin had no detectable toxic effect on the bacterium *Escherichia coli* (Wright et al., 1977). The gyromitrin content of dried false mushrooms has been found to be between 0.05 and 0.3 percent. It is estimated that 99.9 % of the gyromitrin in a mushroom is lost by boiling and up to 99 % is lost by drying.

In rats gyromitrin caused an increased diuresis in which urine was produced with a weak alkaline pH, as well as a high excretion of sodium (530 %) and potassium (210 %). The observed increase lasted for about 12 h and was followed by a retention with regard to the volume and the sodium excretion for about 72 h. On the basis of [3H] inulin excretion, an increased glomerular filtration was observed followed by a decrease 12 h after application of gyromitrin (Braun et al., 1979).

Clonic-tonic convulsions, hypersensitivity, loss of activity, lack of appetite and severe weight loss were observed in rabbits and rats after administration of gyromitrin. Haemoglobinuria, proteinuria, bilirubinuria and a decrease in urinary pH were evident in affected rabbits and concentrations of creatine, bilirubin and activities of aspartate and alanine aminotransferases were abnormally high in the serum. Rabbits that died showed extensive fatty degeneration of the liver, but this effect was much less severe in rats (Mäkinen et al., 1977).

Gyromitrin was not shown to be mutagenic in bacteria (Wright et al., 1977), but some authors conclude that gyromitrin is carcinogenic in experimental animals (Braun et al. 1981). No data is available to establish carcinogenicity in humans. Although there are no case reports or epidemiological studies available to evaluate carcinogenicity in humans, it is reasonable to regard the compound as if it presented a carcinogenic risk (Anonymous, 1983).

### *N-Methyl-N-formyl hydrazine*

*N*-methyl-N-formyl hydrazine (MFH) (CAS Regisry Number 758-17-8) is formed from gyromitrin by hydrolytic cleavage *in vivo* and *in vitro* during food processing (Nagel et al., 1977), but it is also a stable constituent of the edible false morel mushroom *G. esculenta* (Toth and Patil, 1982). MFH

is hepatotoxic and carcinogenic (Braun et al., 1979, 1981; Toth and Patil, 1979). Its mode of action, however, is poorly understood. Gannet et al. (1991) found that microsome-mediated oxidation of MFH yielded formaldehyde and acetaldehyde. The formation of acetaldehyde requires (i) the oxidation of MFH to a diazenium ion or diazene and (ii) fragmentation of these ions to formyl and methyl radicals. It is suggested that these radical intermediates may be important in understanding and elucidating carcinogenesis by MFH (Gannett et al., 1991).

Continuous administration of 0.0078% MFH in drinking water to 6-week-old outbreed Swiss mice for life produced tumors of the liver, lung, gallbladder, and bile duct (Toth and Nagel, 1978; Toth et al., 1979). Histopathologically, the tumors were classified as benign hepatomas, liver cell carcinomas, angiomas and angiosarcomas of blood vessels, and adenomas and adenocarcinomas of lungs. From representative samples of these neoplasms detailed transmission electron microscopic investigations were also carried out. Since these hydrazine analogs induce tumors in animals and these mushrooms are consumed on a large scale by humans in various parts of the world, their hazardous nature should be considered (Toth, 1979; Toth and Patil, 1980a,b).

$LD_{50}$ acute oral toxicity of MFH in mouse is 118 mg/kg (Wright et al., 1978) and in rat 400 mg/kg (Kreybig et al., 1970). MFH is an inhibitor of human intestinal diamine oxidase (Biegański et al., 1980), but this effect is not probably important for the toxic effect of MFH.

***N-Methylhydrazine***

N-Methylhydrazine (MH) (CAS Registry Number 60-34-4) is a metabolite of gyromitrin, but is also a stable component of *G. esculenta*. MH has many industrial and commercial uses. For example, it has military applications as a rocket propellant in bipropellant rocket engines. Table 1 summarizes acute toxicity parameters ($LC_{50}$ and $LD_{50}$ values) for MH in different laboratory animals experiments.

**Table 1**. Toxic parameters of N-methylhydrazine acute toxicity.

| Organism | Test type | Route | Reported Dose | Source |
|---|---|---|---|---|
| Dog | $LC_{50}$ | inhalation | 96 ppm/1 hour | Haun et al., 1970 |
| Dog | $LD_{50}$ | intravenous | 12 mg/kg | Smith et al., 1969 |
| guinea pig | $LD_{50}$ | skin | 48 mg/kg | Smith et al., 1969 |
| Hamster | $LD_{50}$ | intraperitoneal | 21 mg/kg | Gregory et al., 1971 |
| Hamster | $LD_{50}$ | oral | 22 mg/kg | Gregory et al., 1971 |
| Hamster | $LD_{50}$ | skin | 239 mg/kg | Gregory et al., 1971 |
| Monkey | $LC_{50}$ | inhalation | 82 ppm/1 hour | Haun et al., 1970 |
| Mouse | $LD_{50}$ | intraperitoneal | 15 mg/kg | Furst et al., 1967 |
| Mouse | $LD_{50}$ | subcutaneous | 25 mg/kg | Hawks et a., 1974 |
| Rabbit | $LD_{50}$ | intravenous | 12 mg/kg | Smith et al., 1969 |
| Rabbit | $LD_{50}$ | skin | 95 mg/kg | Smith et al., 1969 |
| Rat | $LD_{50}$ | intraperitoneal | 21 mg/kg | Gregory et al., 1971 |
| Rat | $LD_{50}$ | intravenous | 17 mg/kg | Gregory et al., 1971 |
| Rat | $LD_{50}$ | skin | 183 mg/kg | Gregory et al., 1971 |
| Rat | $LD_{50}$ | subcutaneous | 35 mg/kg | Hawks et al, 1974 |

Acute inhalation exposure to high levels of MH may cause lacrimation, eye redness, nasal and respiratory irritation, headache, malaise, vomiting, diarrhea, ataxia, anoxia, cyanosis, tremors, and convulsions in humans (George et al., 1982). Acute exposure to MH in humans has also been observed to affect the blood, kidneys, and liver (Mori et al., 1988). MH is highly corrosive and irritating to

the skin, eyes, and mucous membranes of the respiratory system in humans and animals (Haun et al., 1970).

Chronic inhalation exposure to MH has been observed to impair function of the kidneys and liver, affect the blood and spleen, and cause convulsions in animals. MH significantly increased the incidence of lung tumors in Swiss mice (Toth, 1972). Nevertheless, the US Environmental Protection Agency has not classified MH for carcinogenicity (Reddy et al., 2010) and teratogenicity (Keller et al., 1984; Slanina et al., 1993).

## CONCLUSIONS

Consumption of false morel has been associated not only with acute poisoning, but also with a carcinogenic risk. Gyromitrin, acetaldehyde *N*-methyl-*N*-formylhydrazone, and N-methylhydrazine are toxins present in edible wild mushroom *G. esculenta*. N-methylhydrazine is a tumor inducer in mice and hamsters, through an intermediate, *N*-methyl-*N*-formylhydrazine. In addition, methylhydrazine is formed in a mouse stomach after p.o. administration of gyromitrin. These findings imply that consumption of *G. esculenta* could present a carcinogenic as well as an acutely toxic health hazard.

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