Gyromitrin poisoning: more questions than answers

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"It is perhaps ironic for a mushroom, Gyromitra esculenta*, whose very name means edible, to be so poisonous under certain circumstances. Surprisingly, the toxins were only characterized as recently as 1968. A number of factors conspired against the investigators of this mushroom poison (Lincoff and Mitchel, 1977). The first was the observation that only a few of the participants eating the same quantity of the same mushroom would become ill. Because of this, the poisoning was immediately ascribed to 'allergy' or 'individual idiosyncrasy.' The next problematic observation was that some dedicated mycophagist, who had eaten the mushroom for many years without any ill effects, would suddenly and unaccountably take ill. This too was passed off as the development of an allergy in the unfortunate individual, that the mushrooms had been mistaken for a poisonous variety, or a rotten batch had been eaten. To compound the difficulties,* Gyromitra esculenta *caused many poisonings in Europe, while in the western USA, the seemingly identical species appeared largely harmless. All sorts of explanations were proposed to explain this discrepancy, including such fanciful ones as suggesting that Americans cook their vegetables better. Many of these clues to the toxin never made any coherent sense, even though it was known for some years that the toxins could be destroyed by cooking." (From Benjamin, 1995.)*

***Gyromitra esculenta* from Washington, courtesy M. Beug.**

All the enigmas related to this toxin remain unresolved. The current literature merely repeats what was published before 1990. A deluge of "cut and paste." No meaningful research has been done in the past three decades. This is due to a number of factors. The first was the demise of academic pharmacognosy departments, responsible for investigating the biology and chemistry of products found in nature. Patent law does not issue patents on "natural" products so they cannot be monetized. The pharmaceutical industry seized this opportunity to create designer molecules, ignoring those produced by plants and fungi. Mycology research has been swallowed up by cell biology and lately molecular biology, so few scientists remain to do the field work or the chemistry. Funding for these types of investigations is almost nonexistent. The final issue was the passage of the HIPAA regulations. Obtaining reliable and comprehensive medical information from suspected poisonings is virtually impossible.

What is known

The main toxin in *Gyromitra esculenta*, and a few of its relatives, is gyromitrin. It is a highly volatile and unstable molecule. After ingestion this compound is converted into monomethylhydrazine (MMH) in the acid environment of the stomach and passage through the liver. A number of other hydrazine and hydrozone

***Gyromitra korfii* (*G. gigas*) from Wisconsin, courtesy B. Bunyard.**

molecules are also present in varying amounts, and probably contribute to the toxicity. The chemistry and effects of hydrazines are well studied, as they are used in the aerospace industry as propellants. However it should be noted that there are significant species differences, such that data derived from animals cannot be extrapolated to humans. For example, dogs frequently develop methemaglobinemia, while this is quite rare in humans. It is also known that the therapeutic/toxic range is very narrow, varying from one person to the next, depending on one's individual metabolism. This means that no two people may have the same reaction to the identical dose of toxin. There is no relationship between the dose and the response. "Thus, like rockets, MMH-containing mushrooms have the potential of moving the human body from an earthly existence to heaven" (Trestrail, 1994).

Compounding the problem, gyromitrin has a number of pharmacological effects that may manifest themselves in different ways from one person to the next. Symptoms of toxicity usually occur after six hours. Mild cases may be delayed even further, up to 48 hrs. In most people, the GI tract is the first and only organ to be affected, with a sense of bloating, nausea, vomiting, abdominal pain, and diarrhea. In more severe cases the liver may be damaged resulting in jaundice, which develops after 48–72 hours. This may progress to liver failure. Very rarely kidney failure may occur. In some cases there are serious neurological effects (confusion, convulsions, coma) due the effect of MMH interfering with enzymes that rely on pyridoxal 5-phosphate (vitamin B6). In the brain this inhibits the synthesis of the important neurotransmitter, GABA (Michelot and Toth, 1990).

***Gyromitra caroliniana* in Missouri, courtesy B. May.**

In rare circumstances patients have succumbed, although no deaths have been reported in the USA in the past 30 years. Other pharmacological effects mentioned in reviews, but poorly documented in human cases, include red cell hemolysis and methemoglobinemia.

Treatment is largely supportive. When neurological effects are present, the use of pyridoxal phosphate is advised. It should not be employed in mild toxicity. Mild cases usually recover in 48–72 hours.

The epidemiology of gyromitrin poisoning

The epicenter for *Gyromitra esculenta* consumption is the Nordic countries, especially Finland, where this mushroom is regarded as a delicacy. The collection, processing and sale is carefully regulated, and the Finnish health department publishes explicit guidelines about methods of preparation (www.ruokavirasto.fi). Poisoning is extremely rare. In over 100 years (from 1875–1988) only four fatalities were recorded, and in each case the mushrooms were eaten raw (www.dlc.fi/~marian1/gourmet/morel.htm#instrc). The instruction pamphlet produced by Evira, the Finnish Food Safety Authority, explicitly states that this preparation should only be used for Finnish mushrooms. Either they don't trust the rest of us to follow instruction or are concerned about liability, or both.

The largest number of reported cases of poisoning are from eastern Europe, where *Gyromitra* is both abundant and widely consumed. This is followed by western Europe, with only a small number of cases documented in North America. Most of these have occurred in the Midwest. Despite claims that *G. esculenta* does not contain gyromitrin west of the Rocky Mountains, there is at least one well documented example in which a couple was sickened after eating raw specimens of *G. esculenta* (Leathem, 2007). The files of the toxicology committee of the North American Mycological Association (NAMA) have reports of cases in Idaho, California, and Alaska (Beug et al., 2005). The most recent "outbreak" of poisonings in the USA occurred in Michigan in the spring of 2011, when at least 11 people were sickened.

Gyromitrin-producing fungi

Gyromitra esculenta is the most important fungus responsible for poisonings. Other *Gyromitra* species harboring this toxin include, *G. gigas* and *G. fastigiata*. However there is considerable taxonomic confusion with these in North America, none of which have been formally tested for gyromitrin. This includes the so-called "snow bank" mushroom (*G. gigas* complex, including the western *G. montana* and the midwestern/eastern *G. korfii*). The toxin also has been detected in some related species in Europe, including *Cudonia circinans* and *Leotia lubrica*, *Helvella crispa*, *H. lacunosa*, *H. elastica*, and *H. macropus* (Andary and Privat, 1985). This latter group is seldom collected for the table except by exceptionally adventurous mycophagists.

The experiences of toxicity with this group of mushrooms in North America was well reviewed by Dr. Michael Beug (2014). This was based on reports he received through the toxicology program of NAMA, as well as his expertise with ascomycetes in general. Beug highlighted some of the taxonomic and identification difficulties, as well as the lack of reliable information in a number of cases. Most striking was the absence of convincing evidence of toxicity with well-cooked *G. montana*. Beug (2014) suggested that *G. korfii* is similarly safe if appropriately prepared, although cautioned that there may be unreported cases of toxicity.

Importantly, there is no documented evidence of gyromitrin in morels or *Verpa* species. Claims to the otherwise are based on speculation, not fact.

Questions needing answers

There is only one study on the presence and concentration of gyromitrin in collections of *G. esculenta* in North America, but this was limited to counties in Michigan (Liang et al., 1998). For the rest of North America and for other species, there is an absolute dearth of data. That has not stopped unbridled speculation. It would be most beneficial if we had satisfactory answers to the following questions:

1. Which collections of *Gyromitra esculenta* from different ecological regions contain gyromitrin? Are there different genetic or chemotaxonomic strains?
2. How does toxin production and concentration vary by location, from season to season, change during the growth cycle?
3. What is the influence of substrate on toxin production? Although conventionally regarded as a saprobe, *G. esculenta* may also establish mycorrhizal relationships. The importance and frequency of this has yet to be determined.
4. Which other species of *Gyromitra* and *Helvella* contain gyromitrin, and in what concentration?
5. Does the altitude at which they grow determine the amount of toxin, as suggested in a single study in France (Andary and Privat, 1985)?
6. As hydrazines are known carcinogens, is there any evidence that occasional consumption of properly prepared *G. esculenta* poses any human health risk? And if so, is it any different from eating many other mushrooms known to contain hydrazines, such as *Agaricus bisporus* (Chiarelli et al., 1984; Toth, 1979)?
7. Why do some people develop hemolysis and not others?
8. Although the possibility of methemaglobinemia is mentioned in many reviews, documentation that it occurs is marginal. Careful evaluation of future poisoning cases could settle this issue.
9. Is the toxin cumulative?

With so little known about this mushroom in North America and its legendary vagaries, it is prudent to avoid its consumption. For those that insist, or have eaten it for years, the pejorative Australian "good-on-ya" is appropriate—you are winning in a game of Russian roulette. But as John Trestrail, a past chairman of the NAMA toxicology committee has written (1993): "Persons who decide to continue with this gastronomic gamble should have the numbers of their regional poison centers permanently engraved on their eating utensils."

General reviews

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***Gyromitra brunnea* in Wisconsin, courtesy B. Bunyard.**

***Gyromitra montana* from Washington, courtesy S. Trudell.**