

The most widely recognized mushroom: Chemistry of the genus Amanita

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Abstract:

Many review papers have been published on mushrooms of the genus *Amanita*, as these are well known to both scientific and lay audiences, probably due to the toxic and/or hallucinogenic properties of some species. This article aims to supplement the content of previous reviews by categorizing all of the natural products isolated from any species in the genus *Amanita*. These compounds are subdivided into six major structural types, and references are provided for all species that have been examined chemically.

Keywords: *Amanita*; Mushrooms; Chemical structural classes

Article:

Introduction

Some of the morphological characteristics of the genus *Amanita* include white spore prints, gills free from the stem, and the presence of a universal veil ([Lincoff, 1981](#)). Species of this genus are found commonly throughout the world, and this includes mushrooms known to possess either toxic and/or hallucinogenic properties. Historical evidence suggests that at least three Roman emperors and a Pope may have been among the victims of mushroom poisoning ([Block et al., 1955](#)). Even in modern times, it has been estimated that nearly 90% of reported cases of lethal poisonings caused by the consumption of mushrooms, especially in Central Europe and North America, are due to two of the most poisonous species of this genus, the notorious death cap (*A. phalloides*) and destroying angel (*A. virosa*) ([Wieland, 1968](#)). Another important species of this genus, *A. muscaria*, also known commonly as ‘fly agaric,’ is one of the more beautiful and widely recognized mushrooms, due to its blood-red color and pyramidal, white patches ([Lincoff, 1981](#)). Consumption of *A. muscaria* for ceremonial and/or recreational purposes probably predates recorded history, due to its hallucinogenic effects, and there are many interesting descriptions of its use among Siberian tribesmen ([Schultes, 1969](#)). Idealized representations of this species permeate popular culture. Besides the well-known example of Lewis Carroll's *Alice in Wonderland* ([Carroll, 2000](#)), *A. muscaria* can be found in the background of many children's cartoons and as a major ‘obstacle’ in video games (e.g., the Smurfs and Super Mario Bros., respectively) besides numerous other depictions on album covers, greeting cards, t-shirts, etc. In short, mushrooms from this genus are heavily investigated scientifically and extremely well known conceptually; in many ways, they have become an integral part of human society.

The number of species of *Amanita* has been approximated at 900–1000, and new species are being discovered continuously, including recent examples in the last 2 years ([Sanmee et al., 2003](#), [Yang, 2003](#) and [Yang et al.,](#)

2004). However, a search of the literature suggests that only 17 identified species of *Amanita* have been screened chemically, which resulted in the description of more than 70 compounds, representing six major structural classes. The broad familiarity of this genus, coupled with the diverse chemical components isolated from it, especially the deadly toxins, have drawn the attention of chemists and mycologists. Quite a few reviews have been written on various aspects of *Amanita*, such as the chemotaxonomy (Beutler and Der Marderosian, 1981), the history and use of the hallucinogenic properties (Schultes, 1969), and a recent review specifically on *A. muscaria* (Michelot and Melendez-Howell, 2003). However, to the best of our knowledge, a review on the chemistry of compounds isolated from mushrooms of the genus *Amanita* has not been prepared.

Chemical investigation of *Amanita* toxins can be traced to 1899 (Schlesinger and Ford, 1907), and qualitative and quantitative analyses of *Amanita* toxins using chromatographic methods were reported about a half of a century later (Block et al., 1955 and Dubash and Teare, 1946). Yet, as evidenced by the references cited in the following sections, detailed structural analyses of compounds isolated from *Amanita* species, especially the peptides, only became achievable several decades later, probably due to recent advances in modern spectroscopic and spectrometric techniques. Broadly, the structures of the compounds reported from *Amanita* to date can be subdivided into the following six categories: peptides, amavadin, isoxazoles, simple amino acids and related derivatives, sterols, and ceramides.

Discussion

Peptides

Recent reviews have discussed the occurrence, chemistry and toxicology of peptides from *Amanita* (Fig. 1; amatoxins, phallotoxins and virotoxins) (Karlson-Stiber and Persson, 2003 and Vetter, 1998), especially those occurring in *A. phalloides*, which was one of the earliest identified toxic mushrooms, as one bite of this mushroom can kill an adult (Wieland, 1968). Interestingly, the toxicity of *A. phalloides* is relatively slow, emerging 10–15 h post-consumption, which may account for the grave consequences, since the toxins have been absorbed thoroughly in the body by then (Block et al., 1955). In addition, several other *Amanita* species, including *A. bisporigera*, *A. verna*, and *A. virosa*, have been found to produce toxic peptides as well (Preston et al., 1975, Seeger and Stijve, 1979 and Yocum and Simons, 1977).

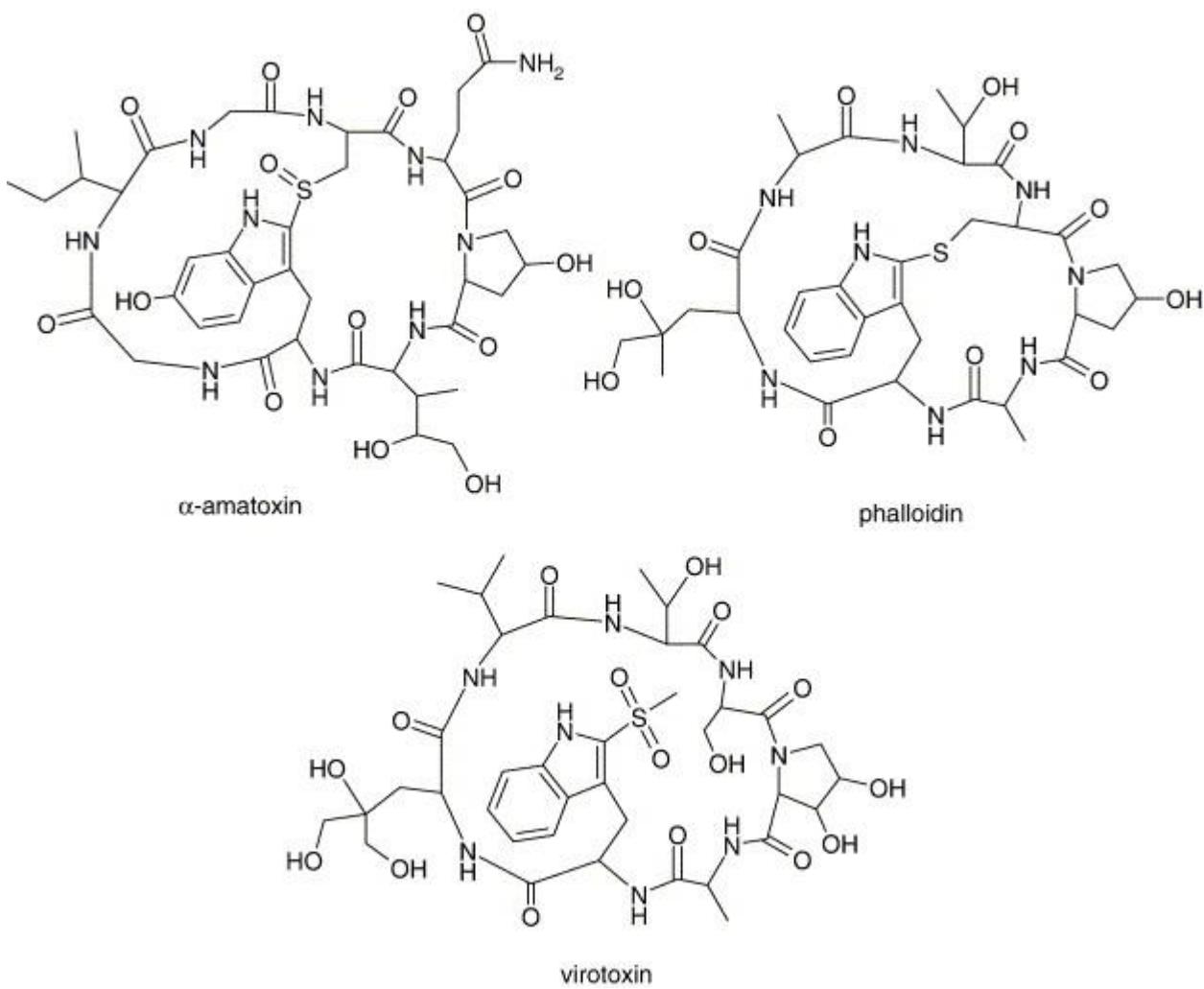


Fig. 1. Representative structures of amatoxins, phallotoxins, and virotoxins.

These peptides, considered the major toxins from *Amanita*, can be classified into three groups: amatoxins, phallotoxins and virotoxins (Fig. 1). The phallotoxins and virotoxins act relatively quickly, inducing death in mice and rats often within 1–2 h. Conversely, the amatoxins are relatively slow-acting poisons, having a lethal interval of at least 15 h post-consumption. However, as amatoxins are 10–20 times more toxic than phallotoxins and virotoxins, it has been concluded that amatoxins are probably responsible for fatal human poisonings (Wieland and Faulstich, 1978). In fact, since phallotoxins and virotoxins do not exert any acute toxicity after ingestion, their effects in human poisoning may be negligible (Karlson-Stiber and Persson, 2003 and Wieland, 1983). Virotoxins were the most recently described peptides from *Amanita* (Faulstich et al., 1980), and to date, they have only been found in *A. virosa*. Conversely, amatoxins and phallotoxins have been observed even in other genera, including *Clitocybe*, *Galerina* and *Lepiota* species, and the relative differences in toxin content of these have been discussed (Klan, 1993 and Koppel, 1993).

Structurally, all three types of peptides are characterized as cyclopeptides containing a sulfur-linked tryptophan unit and some unusual hydroxylated amino acids. The amatoxins and phallotoxins are octapeptides and heptapeptides, respectively. These two groups of peptides have been investigated thoroughly, owing to the

novelty of being some of the earliest identified toxins. For example, more than 40 derivatives of amatoxin have been synthesized ([Wieland, 1983](#)), and the structure–activity relationships for some of these have been explored ([Shoham et al., 1984](#), [Shoham et al., 1989](#) and [Wieland et al., 1983](#)). Structurally related to the phallotoxins, the virotoxins are heptapeptides also. The conformation of viroisin, a representative of this class, was investigated by 2D NMR ([Bhaskaran and Yu, 1994](#)). All proton signals were assigned completely, and interproton distances were determined from ROESY studies. It has been proposed that the virotoxins are derived biosynthetically from the phallotoxins or from a common precursor molecule ([Wieland, 1983](#)).

Amavadin

Amavadin ([Fig. 2](#)) is a pale blue vanadium complex isolated originally from *A. muscaria* ([Bayer and Kneifel, 1972](#) and [Kneifel and Bayer, 1973](#)). In general, metal accumulation may be a means for organisms to protect against toxicity arising from an excess of metal in soil. However, the concentration of vanadium in some *Amanita* species is unusually high, often several hundred times more than those found in plants ([Berry et al., 1999](#)).

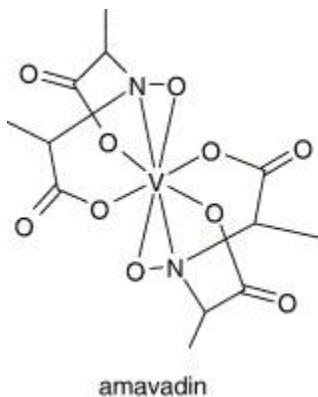


Fig. 2. Structure of amavadin.

The structure of amavadin includes a vanadium atom at the center, existing as an eight-coordinate and containing a 1:2 complex of V(IV):N-hydroxyimino-2,2'-dipropionic acid. This unique structure has garnered enormous interests from chemists, and its structure has been reviewed repeatedly ([Crans et al., 2004](#), [Harben et al., 1997](#), [Kneifel and Bayer, 1986](#) and [Koch et al., 1987](#)). A recent X-ray crystallographic study confirmed this novel structure ([Berry et al., 1999](#)), and another report, which utilized comprehensive spectroscopic experiments, including ¹H, ¹³C-NMR, COSY, NOE, and CD, showed that amavadin consists of nearly an equimolar mixture of the d- and l-isomers of [V(S,S-HIDPA)₂]²⁻ ([Armstrong et al., 2000](#)).

Isoxazoles

Although not very complex structurally, this class of compounds is important pharmacologically, because these CNS-active constituents are responsible for the hallucinogenic effect of *A. muscaria* ([Fig. 3](#)). Ibotenic acid and muscimol, both of which were identified nearly simultaneously by several groups in the mid-1960s, are the two

best known representatives ([Eugster and Takemoto, 1967](#), [Good et al., 1965](#), [Mueller and Eugster, 1965](#), [Takemoto and Nakajima, 1964](#) and [Takemoto et al., 1964](#)). These two compounds have been reported largely from *A. muscaria* and *A. pantherina* ([Benedict et al., 1966](#) and [Michelot and Melendez-Howell, 2003](#)), although at least one study noted their presence in *A. cothurnata* and *A. gemmata* ([Chilton and Ott, 1976](#)). Ibotenic acid acts as an excitatory amino acid at glutamate receptors, and muscimol is a γ -aminobutyric acid (GABA) receptor agonist. Their hallucinogenic effects have been discussed in recent review articles ([Halpern, 2004](#) and [Michelot and Melendez-Howell, 2003](#)). Chemotoxic studies have been completed on a large number of *Amanita* species, and the purification and analysis of isoxazoles using gas chromatographic methods were reviewed ([Beutler and Der Marderosian, 1981](#)). In addition, numerous studies to synthesize structurally related analogues have been conducted, and most of this research has been reviewed recently ([Michelot and Melendez-Howell, 2003](#)). Even today, 40 years after their initial description, recent studies continue to explore this interesting class of compounds, especially with respect to their effects in the brain ([Shirakawa and Ichitani, 2004](#)).

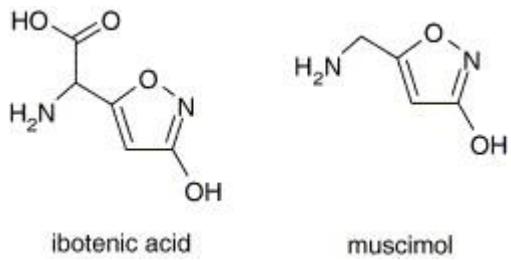


Fig. 3. Structures of the CNS-active isoxazoles.

Simple amino acid derivatives and polyketides

Most low molecular weight compounds fall into this category, generally having molecular weights below 200 a.m.u. ([Fig. 4](#)). These structures include triple bond-containing compounds, chlorinated compounds, cyclopropyl-containing compounds, tryptophan-containing compounds, and polyketide-derived pigments ([Chilton and Drehmel, 2001](#)). Most of these are considered as pigments, along with the above-mentioned amavadin, and their structures have been reviewed earlier ([Gill, 1994](#) and [Michelot and Melendez-Howell, 2003](#)). The most studied pigment is muscarufin, which is responsible for the bright color of *A. muscaria* ([Musso, 1982](#)).

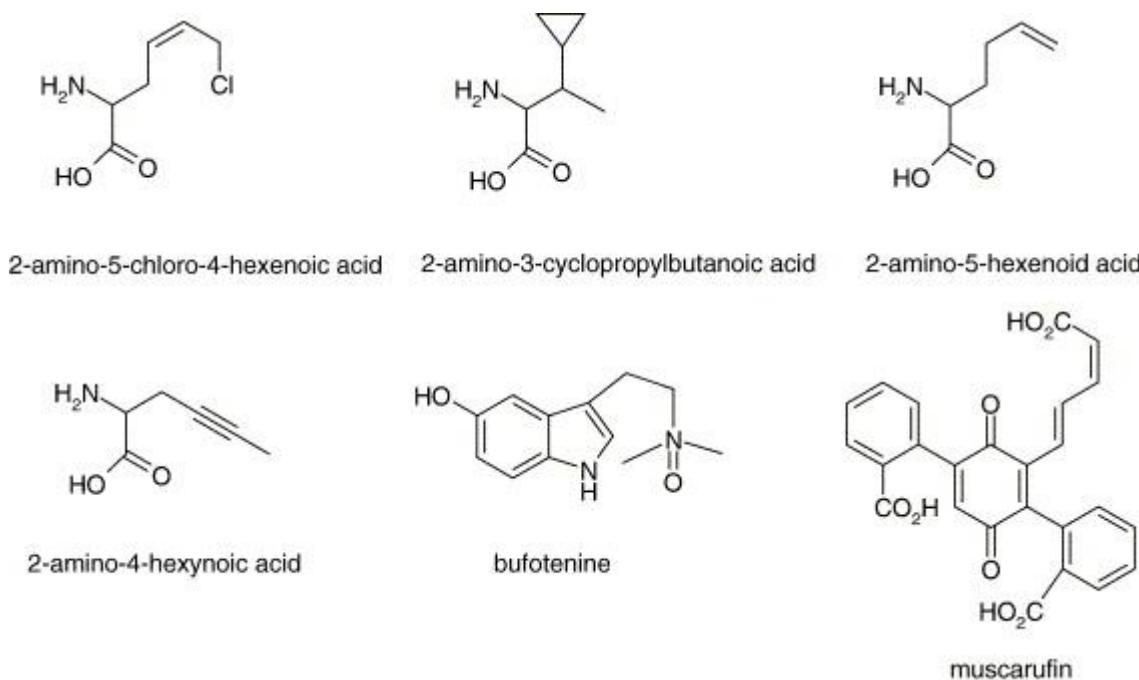


Fig. 4. Structures of representative amino acid derivatives and polyketides.

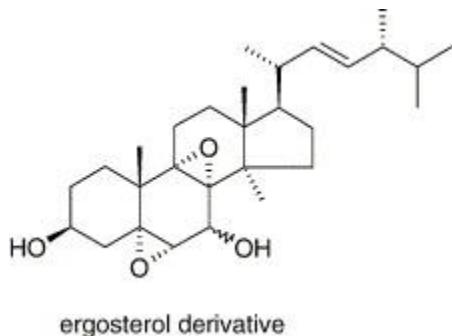


Fig. 5. An ergosterol derivative [5 α ,6 α ,8 α ,9 α -diepoxy-(22E,24R)-ergost-22-ene-3 β ,7 α -diol)], as one example of a sterol isolated from *A. pantherina* and *A. virgineoides* ([Yaoita et al., 1999](#)).

Ceramides

Several ceramides were isolated via an investigation of mushrooms from five different genera, including *A. pantherina* ([Fig. 6](#)) ([Yaoita et al., 2002](#)). Among the series of isolated compounds, three were from this species, and these structures were elucidated via spectrometric and spectroscopic data, including HRMS and 2D NMR. This class of compounds can be described as having a polyketide-like moiety that is linked through a secondary amine to an oxygenated aliphatic chain of variable length, and they appear to be the most recently described structural class reported from *Amanita* species.

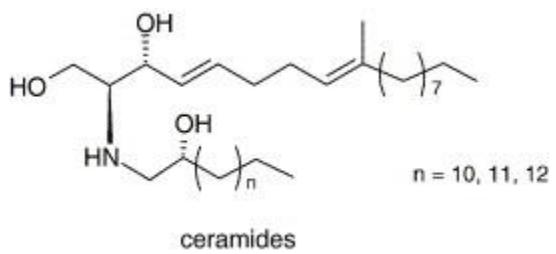


Fig 6. Ceramides, which vary based on the number of methylene units ($n = 10, 11$, or 12), from *A. pantherina*.

Conclusion

Table 1 summarizes the chemistry of *Amanita* by providing the scientific names of those species that have been investigated, the number and type of compounds isolated from each species, and references for the description of the isolation and/or structure elucidation studies and pertinent review papers. These data reveal that the majority of compounds come from *A. phalloides*, *A. virosa*, *A. muscaria*, and *A. pantherina*, a result that is not surprising given the toxic and/or hallucinogenic properties of these species. Thus, it is recognized that this analysis does not represent the full chemical composition of the entire genus, *Amanita*. Typically, other, less well-known species, have been screened only to analyze for the known toxins. Therefore, given the large number of species of *Amanita*, these data suggest that this genus is under explored and ripe for future investigations, especially from the viewpoint of chemistry.

Table 1.

Summary of compounds from *Amanita* species^a

Table 1. Summary of compounds from *Amanita* species^a

Species Name	Number of compounds reported	Structural types of the compounds	Corresponding references
<i>A. abrupta</i>	2	simple amino acids	(Ohta et al., 1987 and Yamaura et al., 1986)
<i>A. bisporigera</i>	1	peptide	(Wieland and Faulstich, 1978)
<i>A. castanopsisidis</i>	3	simple amino acids	(Yoshimura et al., 1999)
<i>A. cothurnata</i>	2	isoxazoles	(Chilton and Ott, 1976)
<i>A. gemmata</i>	4	isoxazoles, simple amino acids	(Chilton and Ott, 1976)
<i>A. gymnoporus</i>	1	simple amino acid	(Hatanaka et al., 1994)

Species Name	Number of compounds reported	Structural types of the compounds	Corresponding references
<i>A. miculifera</i>	1	simple amino acid	(Hatanaka et al., 1998)
<i>A. muscaria</i>	11	amavadin, isoxazoles, simple amino acids, polyketides	(Berry et al., 1999, Eugster and Takemoto, 1967, Eugster, 1969, Gill, 1994, Good et al., 1965, Michelot and Melendez-Howell, 2003, Mueller and Eugster, 1965, Takemoto and Nakajima, 1964 and Takemoto et al., 1964)
<i>A. pantherina</i>	10	ceramides, isoxazoles, sterols, simple amino acids	(Chilton et al., 1974, Chilton and Ott, 1976, Eugster and Takemoto, 1967, Good et al., 1965, Gu et al., 1998, Konda et al., 1985, Mueller and Eugster, 1965, Onda et al., 1964, Takemoto and Nakajima, 1964, Takemoto et al., 1964, Yaoita et al., 1999 and Yaoita et al., 2002)
<i>A. phalloides</i>	22	peptide, sterols, simple amino acids	(Buku and Wieland, 1974, Faulstich and Weckauff-Bloching, 1974, Frimmer, 1971, Kamp and de Wit, 1968, Michelot and Melendez-Howell, 2003, Thevenin et al., 1976, Vetter, 1998, Wieland and Wieland, 1959, Wieland, 1967, Wieland, 1972 and Wieland et al., 1969)
<i>A. pseudoporphryia</i>	3	simple amino acids	(Hatanaka et al., 1974, Hatanaka, 1975, Hatanaka et al., 1985 and Moriguchi et al., 1987)
<i>A. solitaria</i>	1	simple amino acid	(Chilton and Tsou, 1972 and Chilton et al., 1973)
<i>A. vaginata</i>	1	simple amino acid	(Vervier and Casimir, 1970)
<i>A. vergineoides</i>	1	simple amino acid	(Ohta et al., 1995)
<i>A. virgineoides</i>	1	simple amino acid, sterols	(Ohta et al., 1986 and Yaoita et al., 1999)
<i>A. verna</i>	2	peptide, simple amino acids	(Benedict et al., 1970, Gurevich et al., 1995 and Zhang et al., 1998)
<i>A. virosa</i>	12	peptide, simple amino acids	(Bhaskaran and Yu, 1994, Buku et al., 1980, Faulstich et al., 1979, Gurevich et al., 1995, Malak, 1976 and Zhang et al., 1998)

^a Although certainly not comprehensive, this table was developed largely by analyzing the database of Dictionary of Natural Products (Chapman & Hall/CRC Press LLC, web version 2005); additions and/or deletions to these data were implemented based on the content of some of the references.

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