**Additional Mycotoxins of Potential Importance to Human and Animal Health**

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To expand the list of mycotoxins, that have already been discussed, to include all of those of potential significance in human and animal disease, might require more insight into the future than one's crystal ball may allow. However, in the selection of additions to the list, there should be some justification for their inclusion in such a presentation other than the biases of this author. Perhaps, justification could be made for claiming the potentiality of any fungal secondary metabolite as important in human and animal disease but, I believe that some criteria should be established by the author before proceeding. Therefore, mycotoxins to be included as additions to the list are those that (a) frequently occur in commodities, (b) cause natural disease, (c) are produced by common food or feed inhabiting fungi, (d) are produced by human and animal pathogenic fungi, or (e) are known immunosuppressive agents. One additional important criterion is that any mycotoxin included in such a list should elicit its toxic response when given by a natural route.

The three mycotoxins or groups of mycotoxins that are included herein were selected because they are representatives within two or more of the above stated criteria.

**CITREOVIRIDIN**

**Historical Aspects**  
A disease of humans occurred for three centuries in Japan and Asian countries that was characterized by convulsions, paralysis, and respiratory arrest. The disease known as cardiac beriberi or "shoshin kakke" in Japan was investigated from the standpoint of being either an infection, an avitaminosis, or an intoxication. Discovery of the etiology of the disease began when Sakaki (1891) (cited in 1) demonstrated that an ethanol extract of naturally contaminated rice caused neurotoxic signs in mice, frogs, and rabbits. Later, a toxic fungus was isolated from "yellow rice" and named *Penicillium toxicarium* (Miyake & Igaku, 1943) (cited in 1), but later the name was changed to *P. citreoviride* (Naito 1964) (cited in 1). Subsequent studies on toxic metabolites of *P. citreoviride* yielded extracts that produced signs in animals similar to...
those in humans affected with cardiac beriberi. The yellow pigment, named citreoviridin, was isolated from culture extracts of the fungus by Hirata (2) and the structure (Fig. 1) was elucidated by Sakabe et al. (3). The causal relationship of citreoviridin to cardiae beriberi was finally demonstrated by Ueno and Ueno (4). Although cardiac beriberi is not an important disease in these modern times because of improved inspection for rice quality and the vitamin enriched diet of the consumer, citreoviridin still remains as a potential causal agent of disease because of its recognized occurrence in corn and other food and feedstuffs.

Occurrence. The fungi that have been reported to produce citreoviridin are: Aspergillus terreus (5); P. toxicarium, P. citreoviride, Eupenicillium ochrosalmoneum, (P. ochrosalmoneum, anamorph), P. pulvillorum, and P. fellutanum. However, P. toxicarium and P. citreoviride are considered to be synonymous with P. citreoviride, and P. pulvillorum is synonymous with P. simplicissimum (6). Generally, all of the species are soil borne organisms, although P. simplicissimum and P. fellutanum are seldom isolated from that source. Most isolates of these species are also obtained from contaminated grains or seeds of various plant species.

The organism described as P. citreoviride has been isolated from rice on numerous occasions and was detected in wheat flour and the Japanese food “miso” (1). However, there have been limited chemical surveys for the toxin, citreoviridin, in foods and feeds contaminated with species of fungi known to produce the compound.

Using an HPLC method of analysis (7), Wicklow and coworkers (8) examined maize infected with E. ochrosalmoneum and found concentrations of citreoviridin in bulk samples from five of eight Georgia fields, and the amounts found varied from 19 to 2,790 μg/kg. However, when yellow kernels were picked from bulk samples and analyzed, six of eight samples were positive for citreoviridin, and the concentrations ranged from 53,800 to 759,900 μg/kg. In maize that was wound inoculated with E. ochrosalmoneum, the concentrations of citreoviridin were demonstrated on body weight gains and histopathologic changes in liver, adrenal, or kidney tissues.

A note of interest is that aflatoxin occurred in all samples of Georgia corn examined by Wicklow and coworkers (8) and allows for possible interaction of aflatoxin and citreoviridin in producing animal disease.

The conditions for production of citreoviridin have been investigated with P. citreoviride grown on rice (10). Maximum yields of toxin were obtained on this substrate at low temperature (12 to 22°C) and high relative humidity. The importance of low temperature was confirmed using synthetic liquid media whereby toxin was demonstrated in the liquid broth as well as in the extracts of dried mycelium (420 mg from 127 g of dried mycelium).

Citreoviridin was isolated from pecan fragments that were contaminated with an organism identified at that time as P. charlesii (11) [later they apparently decided it was P. citreoviride (7)]. [Note: Pitt (6) considers P. charlesii to be a synonym of P. fellutanum.] The concentration of citreoviridin in pecans was 168.9 mg/kg.

Toxicity. Because of the ubiquitous nature and occurrence in agricultural products of Penicillium spp that produce citreoviridin, knowledge of the toxic nature of the compound is important.

Nishie and coworkers (12) have evaluated the toxicity of citreoviridin in mice and rabbits, and reported LD50 values as shown in Table 1.

![Citreoviridin](image)

**Table 1**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Sex</th>
<th>Route</th>
<th>LD50 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>M</td>
<td>SC</td>
<td>9.6, 11</td>
</tr>
<tr>
<td>Mouse</td>
<td>M</td>
<td>IP</td>
<td>7.5</td>
</tr>
<tr>
<td>Mouse</td>
<td>F</td>
<td>SC</td>
<td>11.8, 3.6</td>
</tr>
<tr>
<td>Mouse</td>
<td>M</td>
<td>PO</td>
<td>29</td>
</tr>
<tr>
<td>Rabbit</td>
<td>M</td>
<td>IP</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Rabbit</td>
<td>M</td>
<td>IV</td>
<td>&gt;5</td>
</tr>
</tbody>
</table>

The teratologic effects of citreoviridin were studied in Fisher rats (14). Rats were given doses of 0, 5, 10, or 15 mg citreoviridin/kg by gastric intubation on either days 8 to 11 or days 12 to 15 of pregnancy. Although there were developmental defects (cleft palates and dilated lateral ventricles), postimplantation loss, and skeletal retardation, three changes did not occur in the absence of maternal toxicity. No studies have been conducted whereby animals were fed the toxin at other times of or throughout the gestation period.

Cats given a total IV dose of 15.4 mg/kg of citreoviridin developed ascending paralysis followed by loss of eyesight at several days after dosing (1).
Other than those episodes that were mentioned in the first part of this discussion on citreoviridin, there are no known natural intoxications of animals. Moreau (15) reported a paralysis in sheep in France, where moldy cheese, particularly moldy cream cheese, was fed to the sheep. Although he indicated that he was doing additional investigations into this toxic syndrome, no further reports were found.

The development and use of newer analytical procedures for citreoviridin such as the liquid chromatographic method of Stubblefield and coworkers (7) may increase the incidence of detection of this mycotoxin and allow for identification of this compound in cases of mycotoxicosis of uncertain cause. These methods may be useful in detecting small amounts of the toxin or its metabolites in animal tissues. Ueno (10) showed that liver contained the greatest concentration of citreoviridin in dosed rats. Low recoveries of citreoviridin were found in feces, and none was detected in urine using spectrophotometric and TLC methods.

**Penitrems**

**Historical Aspects** Within a large group of chemically related fungal secondary metabolites known as tremorgens (named because they cause tremors or similar nervous signs when administered to or ingested by animals) is a group of toxic compounds known as penitrems (Figs. 2 and 3).

The first isolation of penitrems was reported in 1968 from isolates of *P. cyclopium* from feeds that were lethal to sheep, moldy horse feed, and peanuts (16). Subsequently, penitrems were implicated in naturally occurring disease, but a causal relationship was not established. In one case, a moldy commercial feed sample was suspected of being involved in mortalities of dairy cattle and a penitrem-producing isolate of *P. palitans* was obtained from the feed (17). Similarly, Dorner and coworkers (18) isolated a penitrem-producing isolate of *P. crustosum* from moldy corn involved in the intoxication of cattle in Michigan. However, analytical tests of the feed did not yield penitrem. The confirmed cases of penitrem toxicoses have all occurred in dogs. The first case was reported by Arp and Richard in 1979 (19), and involved two dogs that had consumed moldy cream cheese. They developed an acute neurologic episode characterized by severe muscle tremors, polypnea, hyperkinesia, ataxia, and clonic seizures with intermittent opisthotonos. Sodium pentobarbital treatment was followed by recovery in approximately 12 hr. Two other similar cases (20, 21) of toxicosis in dogs consuming moldy walnuts and a hamburger bun, respectively, have been reported.

**Occurrence** Penitrems are produced only by members of the fungal genus, *Penicillium*. Currently there are at least three taxonomic treatments of this genus resulting in some confusion among investigators that are unfamiliar with this group of organisms. An examination of the literature reveals the following species as producers of penitrem: *P. canescens*, *P. clavigerum*, *P. cyclopium*, *P. palitans*, *P. crustosum*, *P. nigricans*, *P. puberulum*, *P. commune*, and *P. lanosocoenuleum*. However, because of synonymy of some species by some taxonomists the reader is referred to Table 2. The most commonly encountered species capable of producing penitrems is *P. crustosum*, the species involved in all confirmed cases of penitrem toxicosis. In a survey of 1,400 isolates of *Penicillium*, it was the only species that produced penitrem (22).

The fungi that produce penitrems have been isolated from a wide variety of foods and feeds as well as from soil. Following isolation of tremorgenic fungi from soil, it was suggested that close grazing by livestock could potentially include ingestion of these fungi (23). Although it has not been demonstrated for penitrem, an intriguing concept is the production of toxin in soil by soil fungi followed by uptake and translocation of toxin by plants, a situation demonstrated with verruculogen (24). In confirmed cases of penitrem toxicoses, the compound was isolated from cheese, walnuts, and bread. A listing of sources from which penitrem-producing species of *Penicillium* were isolated is in Table 3.

**Toxicity** In an animal with natural or experimental intoxications with penitrem, there is a fine tremor produced that is initiated within a few minutes to an hr after ingestion of toxin. The tremor may be noted first peripherally in the ears, tail, and other appendages; subsequently, whole body tremors are noted, and are occasionally interrupted by periods of extensor rigidity, opisthotonos, and eventually the animal becomes recumbent with paddling of the legs. Often animals may be incoordinate, which may overshadow the tremorgenic response (25) or the tremor may...
The increase in these enzymes in calves was considered to be due to increased muscle activity, as were increases in plasma potassium and lactic and pyruvic acid concentrations. In guinea pigs given penitrem A, there were no significant changes in liver-specific enzymes. Hayes and coworkers (31) did demonstrate an hepatic effect of penitrem in mice based on decreased liver glycogen and DNA. Notably, penitrem A was not metabolized by the liver of sheep or by rat liver homogenates (32).

Historical Aspects In 1932, Weindling (38) noted the antifungal activity of Trichoderma lignosum, a parasitic soil fungus. He continued to evaluate the antibiotic nature of this fungus and, in 1937, reported that the fungus he was working with was a species of Gliocladium rather than Trichoderma (39). The toxic substance isolated from culture filtrates of the fungus thus became known as gliotoxin (Fig. 4). By 1942, gliotoxin had attracted much attention because of its antimicrobial properties (40), and production studies were undertaken to increase the yields of this potentially important antibiotic (41). Gliotoxin was produced by Trichoderma lignosum and was isolated as a crude mixture of several substances. The structure of gliotoxin is shown in Fig. 4.

Pathologic changes have not been detected in tissues of any animals experimentally intoxicated with penitrems (33). The mode of action of penitrem is not completely understood, however. Stern (34) described tremors as caused by an inhibition of the inhibitory interneurons.

Glycine, known as a neurotransmitter of inhibitory neurons in the CNS of vertebrates (35), was reduced in concentration in brain tissues of penitrem A-treated mice (36). Substances that increase glycine levels in the CNS such as mephenesin and nalorphine, abolished tremors due to penitrem A in mice. Thus, changes induced by penitrem appear to be chemical (glycine reduction) rather than morphological.

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active against a wide range of Gram positive bacteria (42), and the relative activity of gliotoxin and its structural analogues against Bacillus subtilis were subsequently studied (43). Although some studies continued with gliotoxin, interest in this compound as an antibiotic waned when it was reported to be toxic in mammals (41), and its toxicity has precluded its use clinically. However, there has been a renewed interest in gliotoxin after discovery of an immunomodulating compound (later shown to be gliotoxin) produced by a fungus, identified as A. fumigatus, that had contaminated laboratory cell cultures (44).

Occurrence Subsequent to the finding that Gliocladium was capable of gliotoxin production by Weindling (38), several species among four genera of fungi have been shown to be capable of producing gliotoxin. Although there is disagreement among taxonomists about classification of some of these organisms, the species that have been described as gliotoxin producers are listed in Table 5.

Only recently has a sensitive method been developed whereby gliotoxin can be analyzed by HPLC (45). Therefore, to date, gliotoxin has not been found to occur in commodities or other matrices except under culture conditions.

Because both pathogenic and saprophytic fungi are capable of gliotoxin production, interaction of this mycotoxin in pathogenesis of certain mycotic diseases, as well as gliotoxin functioning as the etiologic agent in toxic disease, is potentially important.

Richard and coworkers (45) found that all nine isolates of A. fumigatus tested were capable of gliotoxin production. Similarly, they have found that 13 of 15 isolates of A. fumigatus, from cases of avian aspergillosis, produced gliotoxin (unpublished).

In 1930, Henrici (46) wrote in his classic tome entitled "Molds, Yeasts and Actinomycetes". "It is not clearly understood how the pathogenic fungi injure the tissues. Although fibrosis and giant cell reactions about some lesions bear a resemblance to a foreign body reaction, the extensive necrosis and suppuration which occur in the center of most lesions cannot be readily explained in this way. Moreover, the experimental lesions produced with freshly isolated and highly virulent strains of some species, as Aspergillus fumigatus and Candida albicans, are so acute as to suggest that these diseases may be caused by the same mechanisms as those found in bacterial infections."

During the ensuing 50 years, this concept has received little attention. However, Eichner and Mullbacher (47) hypothesized that gliotoxin may be produced during the pathogenic state of A. fumigatus, and they subsequently demonstrated the fungus and gliotoxin in peritoneal fluid from infected mice (48). Although Richard et al. (45) did not find gliotoxin production by a pathogenic isolate of A. fumigatus on rice at temperatures above 35°C, perhaps the nutrient state could influence the ability of isolates to produce gliotoxin at body temperatures.

Most of the fungi that produce gliotoxin are soil-borne fungi. The ability of isolates to produce gliotoxin is considered by some (49) as a means to compete with and displace other organisms.

Gliotoxin is a member of a group of fungal secondary metabolites known as epipolythiodioxopiperazines and, thus, is closely related to the mycotoxin sporidesmin, the agent of facial eczema in New Zealand. The latter compound is produced by Pithomyces chartarum, and is contained within the conidia of the fungus (50). However, we could not find any evidence of gliotoxin from 2.5 g of A. fumigatus conidia analyzed by an HPLC method (45).

Toxicity and Biological Effects Gliotoxin has varying effects on a number of biological systems including the antibiotic effects already mentioned. The earliest known effects of this mycotoxin was associated with its antifungal effects (41), and the antibacterial nature of gliotoxin was reviewed by Boutilbannes and coworkers (51). However, the major effects of gliotoxin on B. subtilis was an extension of the growth lag phase (43).

Antiviral activity of gliotoxin was reported in 1964 and 1965 (52, 53) and this subject has been thoroughly reviewed (40, 54).

Gliotoxin is known to interact with nucleic acids as determined by blocking of viral RNA synthesis (55) and modification of B. subtilis DNA as measured by a "Rec" assay for genotoxicity (51). The compound is capable of both plasmid (Escherichia coli) and cellular (mouse) DNA damage in a cell-free system. In macrophage DNA, there was a discrete fragmentation pattern caused by gliotoxin and this characteristic, along with morphologic changes in the cellular chromatin, suggested similarities with cellular changes associated with apoptosis (56, 57).

Interest in the immunosuppression related activity of gliotoxin came from the discovery that it inhibited macrophage adherence to plastic (44, 58); a phenomenon related to phagocytic capacity of these cells. Gliotoxin also inhibited mitogenic stimulation of lymphocytes in vitro (59) and this inhibition occurred with mature hematopoietic cells, but pluripotent stem cells still responded (50, 60). The nature of this response may be related to observed cellular changes associated with those of apoptosis; however, another mechanism of action of gliotoxin would appear to be initiated by blocking of membrane thiol groups (49). This may be involved particularly in inhibiting adherence of macrophages, as it is known that cellular adherence is inhibited by thiol reagents (61). Waring and coworkers (56) noted that disulphide forms of epipolythiodioxopiperazines (e.g., gliotoxin) were required for antiphagocytic activity of macrophages, but not for DNA fragmentation.

Additional immunosuppressive activity of gliotoxin has been demonstrated by its ability to inhibit allograft rejection. Although in early studies murine lymphosarcoma cells exposed to gliotoxin and transplanted into syngeneic recipient mice failed to grow (62), recent studies determined that thyroid tissue from mice placed in media containing 1 μM gliotoxin for 16 hr and then transplanted in an allogeneic strain of mice, resulted in a 60-70% graft success rate (63). Such activity could be important in transplant technology, because the recipient or host need not be placed at an increased risk because of immunosuppressive therapy.

Toxicity of gliotoxin to animals has been demonstrated.
Mice given 50 mg gliotoxin/kg either orally or intraperitoneally died within 24 hr (41). Similar results were obtained with similar dosages in the rat, and a rabbit given an IV injection of 45 mg gliotoxin/kg died in 4 hr. Monkeys tolerated 0.2 mg/kg dosages of gliotoxin given intramuscularly for 15 days (52). Since that time, there has been little information available in the literature concerning the toxicity of gliotoxin in vivo. Recently, we determined that an oral dosage of 7.5 mg gliotoxin/kg in day-old turkey poults caused 100% mortality within 24 hr, only one of 8 poults given 5 mg/kg died. Also, Frame and Carlton (64) have determined that 25 and 35 mg gliotoxin/kg given as single oral dosages to hamsters caused 0.2 mg gliotoxin/kg either orally or intraperitoneally within 24 hr.

SOME ADDITIONAL CONSIDERATIONS

Obviously, the list of additional mycotoxins that have potential for involvement in human and animal health could be expanded beyond these mycotoxins, but I believe citreoviridin, penitrem, and gliotoxin would be near the top of any prioritized listing. If one reexamines the criteria, from my introductory commentary, for including the mycotoxins discussed herein and attempted to list other mycotoxins, the following would likely be included: ergot alkaloids, sporidesmins, cytchalasins, citrinin, aflatoxins, ochratoxins, and phomopsins. Unfortunately, neither time nor space would allow for adequate discussion of these mycotoxins.

Finally, the reader should be aware that, although certain mycotoxins are included in such a discussion as being potentially important in human or animal health, some are demonstrably involved in disease, while the involvement of others is only conjectural.

REFERENCES


We have another question: With respect to the toxins that were discussed this afternoon, is there evidence that residues of these toxins in meat, milk or eggs could be immunosuppressive in the human consumers?

Dr. Richard: I think a general statement could be made that...and it’s not really answering this question either...that the immunosuppressive effects are often found, generally (for mycotoxins that are immunosuppressive), at levels that are lower...
than you'd find with other toxic effects. So you'd have to take this on an individual basis, that is to say, what are the levels that occur in meat, milk or eggs, and are those levels immunosuppressive? And I think that if you looked at most of the literature on immunosuppression, the work has been done at given levels, but they really haven't gone down to see how far they can go and still get immunosuppression.

Dr. Finke-Gremmels: When you go down to low levels of ochratoxin-a or T-2 toxin, you easily come to a level where you have immune stimulation, so that's one reason why we have so much difficulty in an effort to interpret our results.

Dr. Richard: And it depends on what immunologic phenomena you happen to be looking at.

Dr. Finke-Gremmels: It was IGM expression and the inhibition of the thymidine incorporation rate. And with the first test you can see easily that you can come to a level, to a very minimal dose, where you have immune stimulation.

Dr. Richard: You can see lymphoblastogenesis with T-2 toxin.

Audience: My comment is that it was shown with a few mycotoxins that you can have immune stimulation, but it depends on how long you continue the experiment because in the same experiment after immunostimulation you can have immunosuppression.

Chair (Dr. Blodgett): Good comment. It all goes back to design then, how long, what doses. Another question for Dr. Richard: Do you see the possibility that gliotoxin can be used in humans for prevention of allograft rejection?

Dr. Richard: I think that is the premise under which the people in Australia are working. That's about all I can say.

Chair (Dr. Blodgett): Anybody want to tackle that one? Personally, I haven't read too many studies that have looked at the interactions in dosed combinations. There have been studies which were more or less case reports, where they used the naturally contaminated feed which probably had several different mycotoxins in it, but usually they don't elaborate on too many concentrations other than say, vomitoxin, and zearalenone and Dr. Beasley would know more on the synergism in that aspect.

Dr. Beasley: Well, I think there is probably not too much there as far as those two are concerned. Some of the work with aflatoxin and trichothecenes has indicated additive or less than additive toxicity. I haven't seen that much in the way of synergism. Anybody else have any experience?

Dr. Kuiper-Goodman: I think zearalenone is protective or antagonistic to the effect of ochratoxin. It is a species and sex related effect.

Dr. Robens: Bill Huff at the Veterinary Toxicology and Entomology Lab at College Station, Texas, has looked at a fair number of interactions in poultry. Its too bad that the Texas group could not be here (weather interfered with travel) because they could elaborate on that.

Dr. Chu: There are some earlier studies which show that aflatoxin and rubratoxin have a synergistic effect and there are some reactions with the trichothecenes, DAS and DON in combination. I think some of your Canadian colleagues such as Dr. Schiefer's lab may have worked on that.

Dr. Richard: If you recall, the slide that I showed earlier today with respect to aflatoxin and rubratoxin in combination, there was synergism.

Audience: In our laboratory we have investigated interactions of ochratoxin and citrinin, and we found very weak interactions, but there was something there.

Chair (Dr. Blodgett): So, I take it, most of the interactions have been with mycotoxins that effect the same target organ.

Dr. Norred: We've done one study of rodents looking at the combined effects of aflatoxin and cyclopiazonic acid. This was an acute study and we saw just additive effects without synergism. One reason that we don't see many of these types of studies is that they are very difficult studies to design especially with regard to meaningful levels and meaningful dosing regimens.