

Mycotoxins that Affect the Human Cardiovascular System

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Abstract

Mycotoxins are toxic secondary metabolites produced by fungi in the field or during storage; these fungi are mainly saprophytic molds growing on foodstuffs or animal feeds. These molds produce chemical compounds of low molecular weight that are not detected by antigens and hence are insidious poisons with no obvious symptoms. Since 1960, mycotoxins have been considered responsible for diseases and death in domestic animals and humans. Mycotoxicoses, the diseases caused by mycotoxins, have been responsible for major epidemics in humans and domestic animals since agriculture was developed. Each of these diseases is caused by specific molds that produce one or more potent toxins, usually in one specific type of commodity or feed. Among the main mycotoxigenic fungi are the genera *Aspergillus* spp., *Penicillium* spp. and *Fusarium* spp.

The symptoms caused by mycotoxins can be acute or chronic, depending on the type of toxin and the dose. The symptoms of acute mycotoxicoses include liver and kidney damage, attacks on the central nervous system, skin disorders, hormonal effects, miscarriage, hemorrhage, vomiting, diarrhea and many others. Mycotoxins are eaten in trace quantities in the daily diet; some, such as aflatoxins, can accumulate, whereas others are quickly eliminated. Examples of chronic mycotoxicoses include Reye syndrome, Kwashiorkor, and cancers that develop in experimental animals or humans long after the mycotoxin is eaten. In the present review, we will describe some mycotoxins that cause circulatory problems, vein breakage, hemorrhage, and heart failure.

Keywords: Mycotoxins; Aflatoxins; Citreoviridin; Moniliformin; T-2 toxin; Cardiovascular system

Aflatoxins

Chemical name: 2,3,6aR,9aS-tetrahydro-4-methoxy-1H,11H-cyclopenta[c]furo[3',2':4,5]furo[2,3-h][1]benzopyran-1,11-dione (Figure 1).

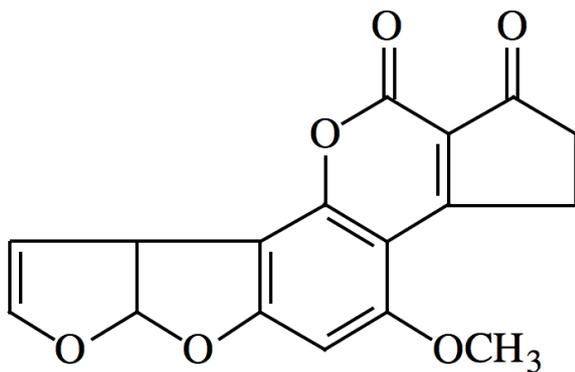


Figure 1: Aflatoxin B₁ structure [7].

The fungal asexual phase and producer of aflatoxins is *Aspergillus*, a green-yellowish mold of the species *A. flavus* Link ex Fries, *A. parasiticus* Speare [1], *A. bombycis* [2], *A. ochraceoroseus* [3-5], *A. nomius* Kurtzman Horn and Hesselst and *A. pseudotamarii* [6].

The structures, physicochemical properties [7], biosynthesis [8], production conditions and occurrence of aflatoxins are also well known [9,10]. One important property of aflatoxins is that they form links to DNA, RNA and proteins [11,12], and they accumulate over time as adducts of AFB1-formamidopyrimidine (AFB1-FAPY) [13] and AFB1-lysine albumin [14], which are active carcinogens.

Aflatoxins, the most powerful mycotoxins, were discovered in the

early 1960s with the outbreak of turkey "X" disease in England and high incidences of liver disease in ducklings in Kenya and hatchery-reared trout in the United States; the causes of all these problems were aflatoxins [15]. Aflatoxins are present in numerous foods, such as cereals, spices [16], oilseeds [17], and dry fruits. After these foods are consumed, the aflatoxins pass into milk, [18,19], all dairy products, eggs [20] and meat [21] derivatives. Aflatoxins are considered unavoidable toxins [22]. Biological control measures include lactic acid bacterial fermentation, which is known to render cereal-based foods and beverages safe [23], and the use of aluminosilicates, glucomannans and optimal storage conditions to prevent fungal growth.

Aflatoxin intake is related to kwashiorkor [24] and Reye syndrome [25], and aflatoxins induce liver damage in undernourished individuals [26]. Aflatoxins are classified as Group I carcinogens in humans [27]; they are potent mutagens and teratogens, and they cause abortions, immunosuppression and cardiovascular symptoms. These toxins weaken veins and arterial walls, break platelets and cause internal hemorrhaging [28]. Aflatoxin B1 (AFB1) may interfere with the normal process of protein synthesis and may inhibit several metabolic systems, thus causing damage to various organs, especially the liver, kidney and heart [29,30].

The histopathological features of various abnormalities induced by different doses of ochratoxin A, AFB1, and their combination in rat fetuses have been studied [31]. Histological examination of fetal organs

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after AFB1 treatment revealed that the liver, brain, kidney, and heart were affected. The incidence of heart lesions, especially valvular defects, was higher in rats treated with the combination diets. There was an antagonist effect of ochratoxin A with the AFB1, which was responsible for the teratogenic effect [31].

In the case of poultry, serious pathological changes were noted in the heart when crude toxin preparations from *Aspergillus flavus* mixed with normal foodstuff were given to animals [32]. Some clinical effects of aflatoxins on the cardiovascular system are frequent hemorrhage in different organs in animals such as chickens [33,34], horses [35], dogs [36] and humans [37]. The effects of chronic oral exposure (28 days) to AFB1 and fumonisin B1 (FB1) were studied in weaned piglets. The heart/body weight ratio of the piglets was significantly greater in groups fed with 30 mg of FB1/kg of feed with or without 50 mg of AFB1/kg added to the feed. The heart effect was more strongly associated with fumonisins than with aflatoxins [38].

Aflatoxin poisoning occurred in Uganda in 1967, in a 15-year-old boy who was diagnosed as suffering from heart failure; he died 2 days after hospital admission. An autopsy revealed pulmonary edema, flabby heart, and interstitial edema of the heart, along with other symptoms, such as liver necrosis [39]. Aflatoxins have been detected in the heart muscle [40].

Cereals (e.g., maize, rice, and sorghum), nuts (e.g., walnut, pecan, pistachio, and cashew) and spices (e.g., black and green peppers and chili) cannot avoid *Aspergillus* fungal attacks; therefore, all of these foods are heavily contaminated with aflatoxins, and their consumption facilitates the development of human cancer. Physicians recommend maize, cereals and nuts in the diet, which have heavy loads of carcinogens, mutagens, and teratogens and inhibit immunological defenses. AFs are analyzed at the ng/g level, but the amount that a person consumes in cooked foods and desserts exceeds tolerance limits and, depending on frequency, can be considered a risk factor for chronic health effects.

However, maize and nuts have developed substances to inhibit the mutagenicity of the fungus and protect themselves. In this way, cereals and oilseeds have contradictory properties; maize has oleic acid to protect against aflatoxin mutagenicity, and walnuts are considered part of a "healthy" diet that provides oils, proteins, minerals, flavonoids, tannins, phenolic acids, polyphenols, and antioxidants, which protect against fat nodules (atheroma plaques) in the arteries, are anti-inflammatory and anti-mutagenic [41] and contain unsaturated fatty acids and vitamins [42], which protect against diabetes [43].

Additionally, pecans contain compounds that have protective effects on the heart [44] and are a source of monounsaturated fatty acids and heart-protective compounds, including vegetable sterols, vitamins A, B and E, folic acid, calcium, magnesium, phosphorus, zinc and fiber [44]. Pecans are a cholesterol-free food with high protein content, and its oleic acid is similar to that of olives [45].

Cashews contain cardol, which has antimicrobial activities [46]. They contain more ascorbic acid than oranges, vitamins B1 and B2, pantothenic acid, and minerals, such as magnesium [47], and they are rich in unsaturated fatty acids, such as oleic and linoleic acids. The cashew has raw protein and lysine levels comparable to those of peanuts [48] and soybean, and it has higher amounts of sulfur amino acids and oils and gums with cardol, which is a caustic and poisonous substance that evaporates when the nuts are heated [49]. The cashew contains a group of phenolic compounds known as "cashew nut shell liquid" (CNSL) [50-52], which includes anacardic acid, cardanol and cardol, the last of which has been reported to have antimicrobial activities [46],

possibly conferring resistance to *Aspergillus* invasion. Thus, a dialectic situation is established: the food that cures you has toxins that can also kill you, and life and death are united in a single nut or maize cob.

Aflatoxins have an effect on the cardiovascular system, with hemorrhage being the most frequent symptom, although their main symptoms are as liver carcinogens.

Citreoviridin

Chemical name: 2,5-anhydro-1,6-dideoxy-2-C-[(8-(4-methoxy-5-methyl-2-oxo-2H-pyran-6-yl)-2-methyl-1E,3E,5E,7E-octatetraen-1-yl)-4-C-methyl-D-Iditol (Figure 2).

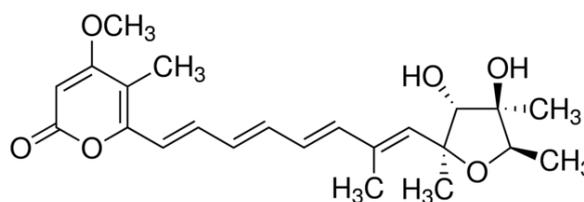


Figure 2: Structure of citreoviridin, a mycotoxin produced by *Penicillium citreoviride* [52].

The history of mycotoxin research in Japan began in 1891, when Sakaki demonstrated that moldy, unpolished rice was fatal to experimental animals, with symptoms indicating paralysis of the central nervous system (Shoshin-kakke) [53,54]. In 1920, Miyake and Takada first reported that *Penicillium commune*, known as a causal agent of "Mossy diseased rice", was toxic when fed to rabbits and rats [53]. Miyake and collaborators discovered the first sample of yellow rice grains from Taiwanese and domestic rice containing *Penicillium citreonigrum* (= *P. toxicarium*), which produced citreoviridin [53,55]. Among isolates from imported rice, Tsunoda et al. found *Penicillium islandicum*, which produced brownish, discolored rice containing two hepatotoxic metabolites: luteoskyrin and cyclochlorotine [53,56]. Toxic disturbances associated with the consumption of rice contaminated with *Penicillium* species occurred and became known as "Yellow rice syndrome" [56,57]. Although no human cases of poisoning have been recorded, mycotoxicologists recommended that the Japanese government take action to protect citizens against "yellow rice poisoning" caused by a metabolite of *Penicillium citreoviride* called citreoviridin. This disease, which is manifested in humans and experimental animals by respiratory and circulatory failure, paralysis, convulsions and death, is identical to beriberi, originally considered to be a thiamin nutritional deficiency [53,58].

Citreoviridin plays a major role in causing myocardial injury (degeneration and necrosis) in adult Wistar rats exposed to it, and citreoviridin combined with deficiencies in selenium and protein can aggravate the damage at the biochemical level [59]. Cardiac toxicity of citreoviridin in selenium-protein with citreoviridin group caused the intercalary discs of cardiac myocytes to become fragmented; the junctions between myocytes were broken; in some regions, cardiac myocytes became edematous and even dissolved; the structure of sarcomeres was not obvious; mitochondrial cristae were loosened; cavities in myocytes were occasionally observed; and there was substantial disseminated sarcoplasmic reticulum extension. In selenium-protein with no citreoviridin group, the change in cardiac myocytes' membrane structures was not obvious; the filament structure disappeared around the nucleus, and the deposition of mass floccule was observed. The authors concluded that citreoviridin is the main risk

factor for inducing myocardial damage [60].

Acute cardiac beriberi

Acute cardiac beriberi is caused by citreoviridin, a mycotoxin produced by *Penicillium citreonigrum*. Acute cardiac beriberi was a common disease in Japan, especially in the second half of the last century. This disease is characterized by difficulty breathing, nausea and vomiting, and, after 2 to 3 days, severe pain and distress. Progressive paralysis may lead to respiratory failure and death. There was also an outbreak of beriberi deaths reported in 2006 in the Maranhao State of Brazil, which was caused by citreoviridin from *Penicillium citreonigrum* strains and was associated with rice consumption [61].

Beriberi is the general name for vitamin deficiencies resulting from the consumption of polished rice. Acute cardiac beriberi may be a toxicosis rather than a vitamin deficiency [62]. In 1910, the incidence of acute cardiac beriberi suddenly decreased in Japan when government inspection led to a reduction in the sale of moldy rice. The incidence of true beriberi, resulting from the consumption of polished rice, was unaffected. The victims of acute cardiac beriberi were often young, healthy adults. This mycotoxicosis is characterized by precordial distress with palpitation and tachypnea; as the dyspnea worsens, nausea and vomiting are experienced. After a few days, the victim suffers severe anguish, pain, and restlessness and can become violently maniacal at times. The right heart is dilated, and the heart sounds are abnormal. In the final stages, as the dyspnea increases, the extremities become cold and cyanotic, the pupils dilate, and the person loses consciousness. The neurotoxic mycotoxins of *Penicillium citreo-viride* Biourge may also cause acute cardiac beriberi [62].

Keshan disease

Keshan disease is also caused by citreoviridin toxin [63]. An individual with Keshan disease will have an abnormally large heart. Keshan disease can also lead to higher rates of cancer, cardiovascular disease, hypertension, and stroke. In addition, an individual can experience eczema, psoriasis, arthritis, cataracts, alcoholism, and infections. There has been controversy because some authors initially thought that Keshan disease was caused by coxsackievirus B3 viral infection [64,65]. Currently, many other authors attribute Keshan disease to the mycotoxin citreoviridin [60,63,66,67]. Tsunoda et al. found that *P. citrinum* was responsible for yellowish rice, which was associated with the high nephrotoxic toxicity produced by citrinin [53,56].

Moldy millet or maize, but not wheat, eaten for 4-12 months produced an outbreak of Keshan disease. Rats fed with 4 mg/kg (body weight) of citreoviridin-contaminated grain every day for 4-6 weeks exhibited necrosis of myocardium and cell mitochondrial swelling, proliferation and damage, identical to what was observed in cases of death from Keshan disease.

A number of genes in peripheral blood mononuclear lymphocytes of patients with Keshan disease are significantly differently expressed from those of healthy people [67]. These genes are mainly involved in cell proliferation, apoptosis and cell function restoration, and they may play an important role in the development of Keshan disease. Keshan disease must not be confounded with Kashin-Beck disease, which is a permanent and disabling osteoarticular disease involving growth and joint cartilage with multifactorial etiology associated with selenium deficiency, inorganic (manganese and phosphate) and organic matter (humic acids and fulvic acids) in drinking water, and fungi on self-

produced storage grain (*Alternaria spp.* and *Fusarium spp.*), which produce trichothecene (T-2) mycotoxins.

The gene expression profiles of Kashin-Beck and Keshan diseases occurring within the same endemic areas of China were compared [66]. Total RNA was isolated from peripheral blood mononuclear cells from 36 patients and 28 controls, and gene expression profiles were analyzed using oligonucleotide microarrays. Sixteen genes that were differentially expressed in both Kashin-Beck and Keshan disease (versus controls) were identified, including nine genes with synchronous expression and seven with asynchronous expression. The comparative toxicogenomics database shows that the expression and biological function of these genes can be affected by multiple environmental factors, including mycotoxin and selenium content, which are potential environmental risk factors for the two diseases. Thus, these shared differentially expressed genes may contribute to the distinct organ lesions caused by the common environmental risk factors for Kashin-Beck and Keshan diseases [66].

Onyalai

Onyalai is an acute disease of the circulatory system characterized by hemorrhaging lesions in the mouth. Onyalai has been endemic in Africa, especially in Southern Sahara regions, for at least 80 years [68]. This disease is much more common in rural than in urban populations. Many of the people affected by onyalai subsist on millet; therefore, Rabie et al. (1975) [68] suggested a possible role of a mycotoxin in this cereal. Toxicogenic isolates of *Phoma sorghina* were found to be common in millet consumed by affected populations, and Rabie et al. (1975) [68] reproduced many of the symptoms of onyalai in rats fed maize and wheat on which *P. sorghina* had been grown.

Moniliformin

Chemical name: Sodium 3,4-dioxo-1-cyclobutenolate. The condensed formula of moniliformin is K or NaC₄H₃O₃ (Figure 3).

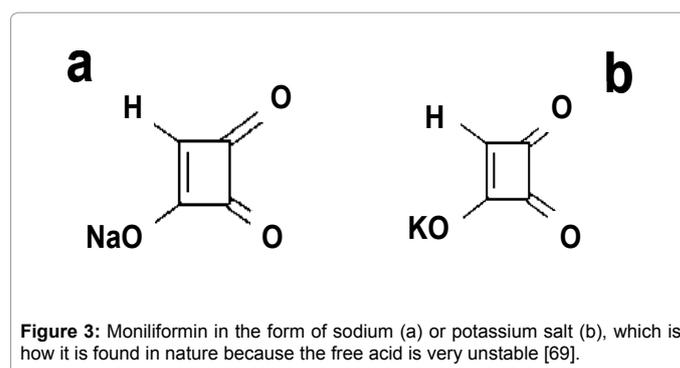


Figure 3: Moniliformin in the form of sodium (a) or potassium salt (b), which is how it is found in nature because the free acid is very unstable [69].

Moniliformin or semiquaric acid is a mycotoxin formed by 3-hydroxy-3-cyclobutene-1,2 dione acid. This toxin was discovered in 1973 in maize in the USA [69], and the fungus was incorrectly identified as *Fusarium moniliforme* Sheldon emend. Snyd. and Hans., leading to its being named moniliformin. The following *Fusarium spp.* produce moniliformin [70,71]:

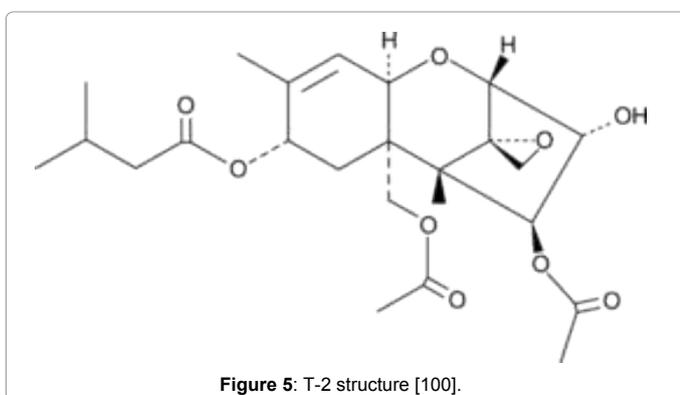
I. Section Liseola: *F. anthophilum* (A. Braun) Wollenw., *F. dlamini*, *F. napiforme*, *F. nygamai*, *F. proliferatum* (Matsushima) Nirenberg [72], *F. subglutinans* (Wollenw. and Reinking) Nelson, Toussoun and Marasas. [73-75].

II. Section Arthrosporiella: *F. concolor*, *F. semitectum* Berk. and

The teratogenic, embryopathic and embryocidal effects of purified fumonisin B1 and moniliformin on chicken embryos were studied. Early embryonic changes in the exposed embryos included hydrocephalus, enlarged beaks and elongated necks. Pathologic changes were noted in the liver, kidneys, heart, lungs, musculoskeletal system, intestines, testes and brains of the toxin-exposed embryos [99].

T-2

Formal name: (3 α ,4 β ,8 α)-12,13-epoxy-4,15-diacetate 8-(3-methylbutanoate) trichothec-9-ene-3,4,8,15-tetrol (Figure 5) T-2 (synonyms are Fusariotoxin T-2, Insariotoxin and Mycotoxin T-2) is a trichothecene mycotoxin. T-2 is a naturally occurring mold that is a byproduct of *Fusarium* spp. fungi and is toxic to humans and animals. The clinical condition caused by T-2 is alimentary toxic aleukia (ATA) [100], with symptoms in diverse organs such as the skin and airway, and stomach ingestion, which may come from the consumption of moldy whole



grains. T-2 can also be absorbed through human skin [101]. Skin contact with T-2 causes acute disturbances in the circulatory system (hypotension and arrhythmia), which may result from general pathophysiological responses to the T-2 toxin, including a central effect on blood pressure and catecholamine elevation, which have been reported in pigs and rats [102,103]. General arteriosclerosis and hypertension have been reported as delayed sequelae of repeated exposure to T-2 toxin [104]. In a series of studies of rats exposed to a limited course of T-2 toxin, doses caused the thickening of coronary arteries, including myocardial changes. Four injections of 3 mg of T-2 toxin/kg bw on alternate days led to vacuolization and swelling of endothelial cells, basement membrane changes and enlarged medial smooth muscle cells. After the topical application of T-2 toxin (1-20 μ g) to rat skin, dilated microvessels packed with erythrocytes and an increased number of degranulated mast cells were observed [105-107]. In experimental animals, cardiovascular responses to T-2 toxin administration included tachyarrhythmia, hypotension, and shock [104,108].

T-2 mycotoxin has been used as biological weapon: flour contaminated with *Fusarium* was produced and distributed in bread, causing significant morbidity and mortality [101]. T-2 was also used in Vietnam and was known as "yellow rain" [109].

Conclusions

Among the most important mycotoxins that cause cardiovascular problems, aflatoxins have the risk of forming adducts and being stored for years in the DNA of all cells, causing hemorrhage and heart malformations. Among the typical cardiotoxic mycotoxins, the two potent toxins that cause the worst damage are citreoviridin and

moniliformin. Considering the worldwide occurrence of moniliformin together with its high acute toxicity, research into the subchronic toxicity is of vital importance to identify the possible risk in human or animal health. Fumonisin are very frequent and related to malformations as has been reported here. It is impossible to produce food completely free of mycotoxins, improvements in storage and handling of grains, can minimize mold growth, and so reduce the risk of mycotoxin contamination in food supplies.

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