

Review

Biochemistry and metabolism of aflatoxins, fumonisins and trichothecenes

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The aim of this paper is to review the biochemistry and metabolism of aflatoxins, fumonisins and trichothecenes. Mycotoxins are secondary metabolites produced by toxigenic species of fungi, which can cause toxic effects in humans and animals. Food contamination by mycotoxins has been reported worldwide, mostly in foods that are susceptible to fungal growth, such as grains and cereals. Mycotoxins can lead to damage to health, and economic losses in agriculture. The most common mycotoxins found in routine food consumption and with consumption limits set by many countries, including Brazil, are: aflatoxins B₁, B₂, G₁ e G₂, ochatoxin A, zearalenone, deoxynivalenol, T-2 toxin and fumonisin. The better understanding of the biochemistry and metabolism of mycotoxins is necessary to avoid problems caused by them and minimize their negative effects on agriculture and health.

Key words: Aflatoxins, fumonisins, trichothecenes, biochemistry, metabolism, food contamination.

INTRODUCTION

Mycotoxins are produced mainly by the mycelial structure of filamentous fungi, or more specifically, the molds. Mycotoxins are secondary metabolites that have no biochemical significance in fungal growth and development (Moss, 1991). Toxigenic molds are known to produce one or more of these toxic secondary metabolites. It is well established that not all molds are toxigenic and not all secondary metabolites from molds are toxic. Examples of mycotoxins of high significance in public health and agro-economic are aflatoxins, ochratoxins, trichothecenes, zearalenone, fumonisins, tremorgenic toxins, and ergot alkaloids. These toxins account for loss of millions of dollars annually, worldwide in human health, animal health, and condemned agricultural products (Shane, 1994; Vasanthi and Bhat, 1998). Factors contributing to the presence or production of mycotoxins in foods or feeds include storage, environmental, and ecological conditions. Often times most factors are beyond human control (Hussein and Brasel, 2001). The hyphal structure of filamentous fungi has evolved to utilize solid substrates efficiently by growing over surfaces and penetrating into solid matrices. The moulds are able to secrete enzymes to break down complex macromolecular compounds and

utilize them for growth and metabolism. They are able to absorb low molecular weight nutrients and many also produce, and secrete, secondary metabolites, which are also relatively low molecular weight compounds but not obviously associated with the process of growth and primary metabolism (Bushell, 1989). Many of these secondary metabolites do have biological activity and may be toxic to microorganisms (antibiotics), plants (phytotoxins) or animals (mycotoxins) (Moss, 1996).

Mycotoxins that are produced by fungi belonging to *Fusarium* and *Aspergillus* genera (fusariotoxins/trichothecenes and aflatoxins, respectively) have received special attention, because they are most hazardous for humans and animals and are of economic significance. The terpenoid biosynthetic pathway is a characteristic of fusariotoxins (e.g., trichothecenes like toxin T2 and deoxynivalenol, the main precursors of which are mevalonic acid and farnesyl pyrophosphate). A large group of mycotoxins, including aflatoxin B₁ and zearalenone, are classified with polyketides, an important and large class of natural compounds, the initial stage of biosynthesis is the condensation of acetyl-CoA with several molecules of malonyl-CoA and subsequent multistage conversions of intermediate β -polyketones (Khomutov et al., 2011).

The major toxigenic species of fungi and their mycotoxins are presented in Table 1. Not all of these species and mycotoxins pose hazards to ruminants.

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Table 1. The major toxigenic species of fungi and their principal mycotoxins.

Fungal species	Mycotoxin
<i>Aspergillus flavus</i> ; <i>A. parasiticus</i>	Aflatoxins
<i>A. flavus</i>	Cyclopiazonic acid
<i>A. ochraceus</i> ; <i>Penicillium viridicatum</i> ; <i>P. cyclopium</i>	Ochatoxin A
<i>P. expansum</i>	Patulin
<i>Fusarium culmorum</i> ; <i>F. graminearum</i> ; <i>F. sporotrichioides</i>	Deoxynivalenol
<i>F. sporotrichioides</i> ; <i>F. poae</i>	T-2 toxin
<i>F. sporotrichioides</i> ; <i>F. graminearum</i> ; <i>F. poae</i>	Diacetoxyscirpenol
<i>F. culmorum</i> ; <i>F. graminearum</i> ; <i>F. sporotrichioides</i>	Zearalenone
<i>F. moniliforme</i>	Fumonisin
<i>Acremonium coenophialum</i>	Ergopeptine alkaloids

Source: (D'mello and Macdonald, 1997).

This review will focus on the biosynthesis and metabolism of aflatoxins, fumonisins and trichothecenes.

AFLATOXINS

Aflatoxins were discovered in *Aspergillus flavus* (hence the name "afla-toxin") about 50 years ago after an outbreak of Turkey X disease in England (Klich et al., 2000). Aflatoxins, a group of polyketide-derived furanocoumarins, are the most toxic and carcinogenic compounds among the known mycotoxins. There are only four major aflatoxins, B₁, B₂, G₁, and G₂ (AFB₁, AFG₁, AFB₂ and AFG₂), that contaminate agricultural commodities and pose a potential risk to livestock and human health (Jelinek et al., 1989; Bennett and Klich, 2003). Other significant members of the aflatoxin family, M₁ and M₂, are oxidative forms of AFB₁ modified in the digestive tract of some animals and isolated from milk, urine, and feces (Bhatnagar et al., 2002).

Chemically, aflatoxins have structures closely related to each other, forming a single group of highly oxygenated heterocyclic compounds (furocoumarines complex). Aflatoxins have a coumarin core connected to a bi-furan structure (Figure 1), whereas the aflatoxins B presents a cyclopentan ring, the group M result from hydroxylation of the previous and the group G contain the lactone ring in the molecule (Gourama and Bullerman, 1995).

Biosynthesis of aflatoxins

A. flavus, *Aspergillus nomius* and *Aspergillus parasiticus* are the only fungal species known to produce aflatoxins (Cotty et al., 1994). However, as many as 20 different aspergilli, including *Aspergillus nidulans*, and species of *Bipolaris*, *Cbaetomiztm*, *Farrowia* and *Monocillizrm*, produce sterigmatocystin (ST), a highly toxic intermediate in the AFB₁ biosynthetic pathway (Barnes et al., 1994). The initial step in generation of the polyketide backbone

of AFB₁ is proposed to involve polymerization of acetate and nine malonate units (with a loss of CO₂) by a polyketide synthetase (PKS) in a manner analogous to fatty acid biosynthesis (Bhatnagar et al., 1992). An alternative and perhaps more plausible hypothesis involves the synthesis of a 6-carbon hexanoate starter unit by a fatty-acid synthase (FAS), which is then extended by a PKS (without further ketoreduction) to generate a 20-carbon decaketide, noranthrone (Townsend et al., 1991). In either scheme, noranthrone is then oxidized to the anthraquinone norsolorinic acid (NA) by a hypothesized oxidase (Bhatnagar et al., 1992). The rest of the proposed pathway is summarized in Figure 2 (Bhatnagar et al., 1992; Trail et al., 1995).

Versicolorin A (VA) is significant because it is the first molecule in the AFB₁ pathway that contains a double bond at the 2,3 position in the difuran moiety. This double bond is the target for microsomal cytochrome P450 enzymes which generate a highly reactive epoxide resulting in activation and adduct formation with DNA and proteins. In contrast, aflatoxin B₂ (AFB₂), which lacks this double bond, is hundreds of times less carcinogenic (Dvorackova, 1990).

Metabolism of aflatoxins

The system responsible for the biotransformation of AFB₁ basically has five mechanisms, represented by reactions of reduction, hydration, epoxidation, hydroxylation and ortho-demethylation. The aflatoxicol is produced by reduction of AFB₁ by an NADPH-dependent cytoplasmic enzyme present in the soluble fraction of the liver. The toxicity of aflatoxicol is apparently much smaller than AFB₁, but the conversion is reversible and the aflatoxicol can serve as a reservoir toxicity of AFB₁ in the intracellular space, it can be converted in this mycotoxin by microsomal dehydrogenase. The aflatoxicol can also be metabolized to AFM₁ and AFH₁ (Biehl and Buck, 1987). The hydration process results in a metabolite

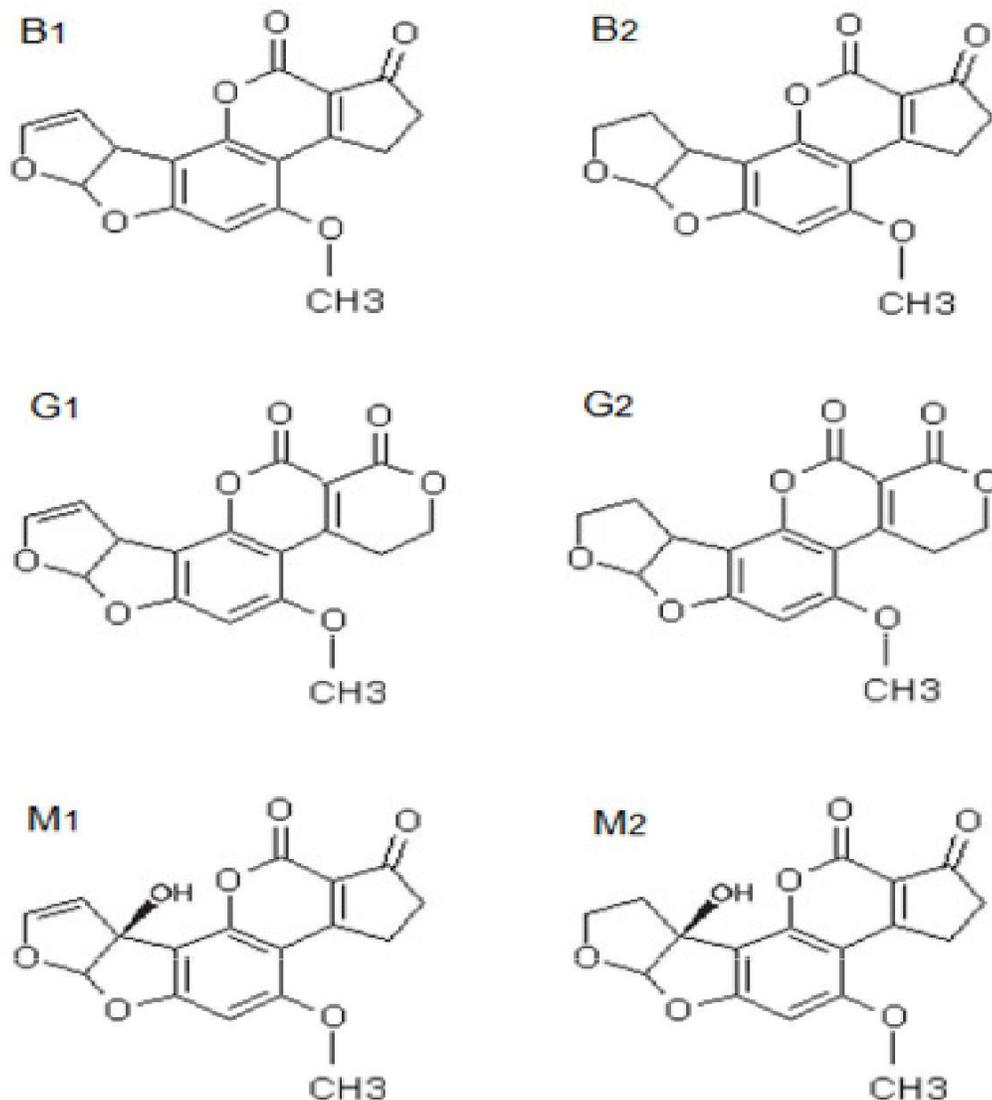


Figure 1. Chemical structure of aflatoxins (Biehl and Buck, 1987).

AFB_{2a}. This compound has the main action the inhibition of enzymes, in the liver and other tissues, causing a reduction in proteic synthesis (Ellis et al., 1991).

The pure form of AFB₁ has no mutagenic activity. The biotransformation of this compound through the reaction of epoxidation is that changes the AFB₁ in potent carcinogen compost. The compound formed by epoxidation is highly electrophilic and can react quickly, through covalently with nucleophilic sites of macromolecules, such as deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and proteins (Oliveira and Germano, 1997). The binding of 8,9 epoxide of aflatoxin with DNA is formed with the N7 of guanine, which determines the formation of adducts Af-N7-guanine in the target cell (Lillehoj, 1991). As a result of this adduct, the guanine-thymine (GT) pair suffers a transversion in

codon 249 of the p53 suppressor tumor gene (Wang and Groopman, 1999). These adducts formed in the DNA molecule can be removed from the molecule after its formation, leaving vacant sites, which tend to be filled with adenine, resulting in a mutation point. The compound 8,9 epoxide of aflatoxin is responsible by reduction in protein synthesis and the mutagenic, teratogenic and carcinogenic effects. The binding of 8,9 epoxide of aflatoxin with DNA or RNA of the liver has been demonstrated *in vivo* and *in vitro* (Biehl and Buck, 1987). The inhibition of synthesis of messenger RNA, the activity of DNA-dependent RNA polymerase, of protein synthesis in the liver and decrease in plasmatic proteins during aflatoxicosis cause a reduction of fat metabolism in the liver, causing necrosis and fatty degeneration, decrease bile flow and impaired absorption of nutrients, especially

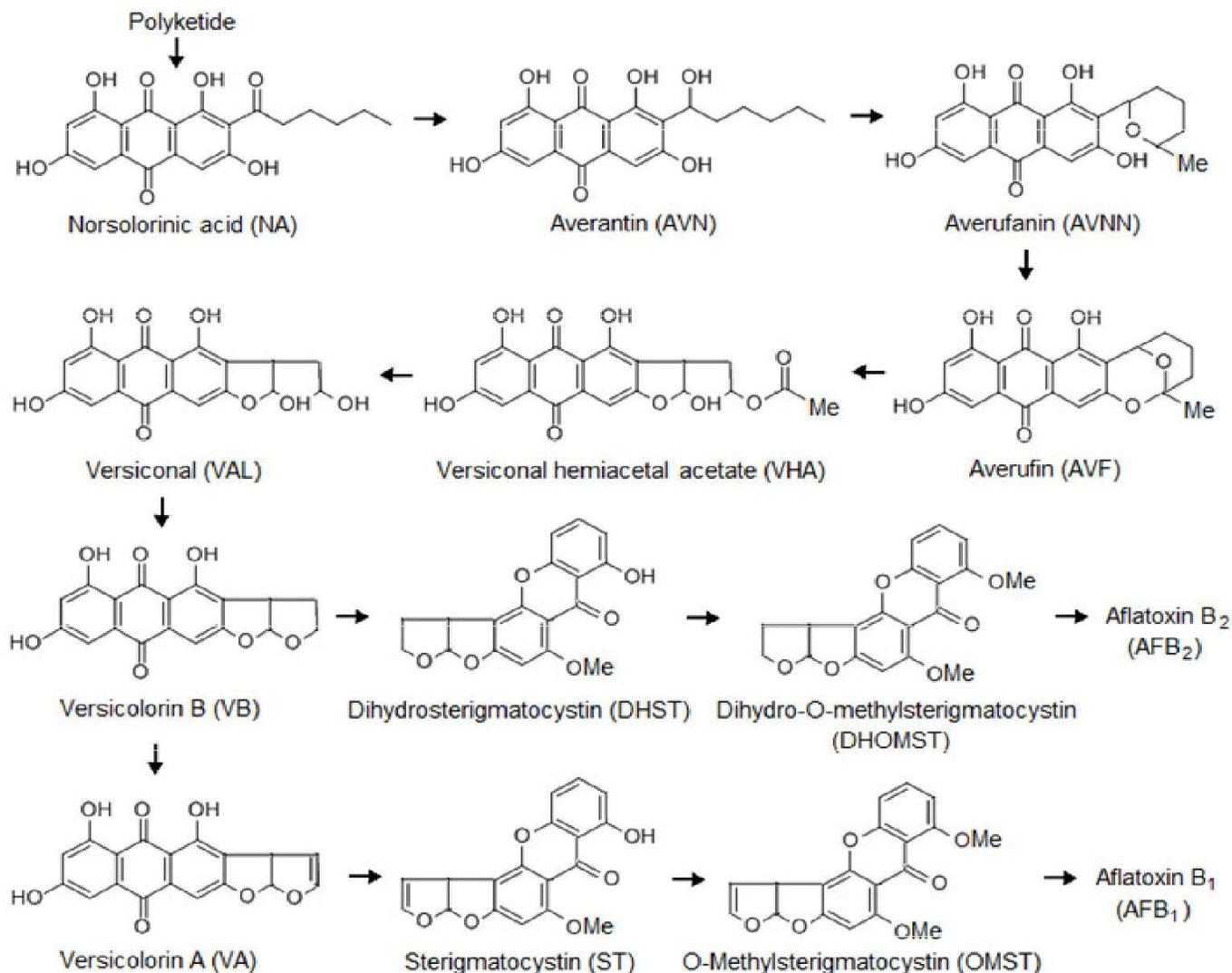


Figure 2. Aflatoxin B₁ and B₂ biosynthetic pathway (Trail et al., 1995).

vitamins and essential amino acids (Quezada et al., 2000). AFM₁ and AFQ₁ are results of hydroxylation reaction of AFB₁. These compounds have a hydroxyl group, allowing their conjugation with glucuronic acid, sulfate and glutathione, making them very water-soluble substances that can be excreted in the bile, urine and milk (Biehl and Buck, 1987). Glutathione S-transferase is an isoenzyme that catalyzes the conjugation reactions with glutathione and protects tissues from toxic reactions. The sensitivity of a variety of animal species to the toxic effects of AFB₁, in large part depends on the ability of these species to detoxify the reactive metabolites of this toxin through the process of conjugation with glutathione (Neal et al., 1998).

Most of the aflatoxins are excreted between 72 to 96 h after the exposure, with the liver and the kidney retaining the waste for a longer period compare to other tissues (Biehl and Buck, 1987).

FUMONISINS

Fumonisin are polyketide mycotoxins produced primarily by *Fusarium verticillioides*. The fumonisins are found mainly corn crop, but several researches have reported the occurrence in other grains, such as rice (Park et al., 2005), wheat and oat (Mallmann et al., 2001). Fumonisin are structurally related molecules and 16 of which have been isolated and characterized: Fumonisin B₁ (FB₁), FB₂, FB₃, FB₄, A₁, A₂, A₃, AK₁, C₁, C₃, C₄, P₁, P₂, P₃, PH_{1A}, PH_{1B}, however, fumonisin B₁ and fumonisin B₂ are the most important and constitute up to 70% of the fumonisins found in naturally contaminated foods and feeds (Seo et al., 2001; Niderkon et al., 2009).

Contrary to most of the other mycotoxins, the fumonisins do not have cyclic structures, their structures are based on a long hydroxylated hydrocarbon chain. FB₁ is the diester of propane-1,2,3-tricarboxylic acid

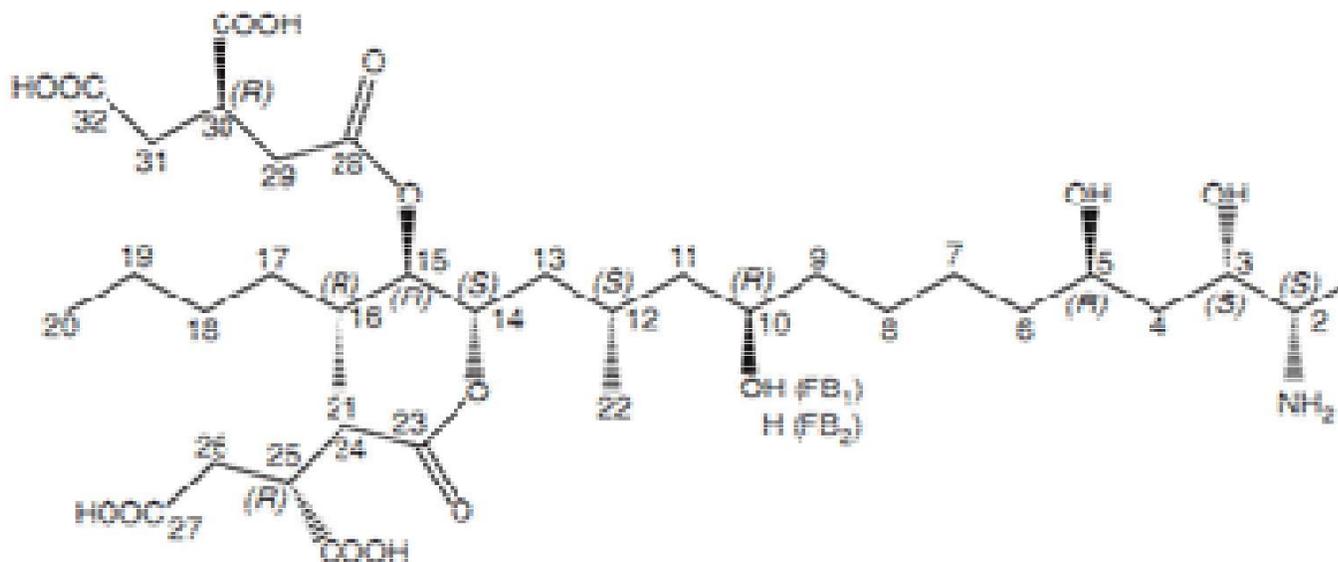


Figure 3. FB₁ and FB₂ configurations (Niderkon et al., 2009).

(tricarballic acid, TCA) and 2-amino-12,16-dimethyl-3,5,10,14,15-pentahydroxyeicosane, in which the C₁₄ and C₁₅ hydroxyl groups are esterified with the terminal carboxyl group of TCA. FB₂ is the C₁₀ deoxy analogue of FB₁, in which the corresponding stereogenic units on the eicosane backbone have the same configurations (Figure 3).

Firstly, fumonisins are found in measurable concentrations in corn grown all over the world. Secondly, the fungal toxins from *Fusarium* spp. have been epidemiologically associated with cancer. FB₁ has been classified by the International Agency for Research on Cancer (IARC) in Group 2B as a possible carcinogen to humans. In addition, FB₁ are frequently associated with animal diseases, including cancer and neural tube defects in mice (Menniti and Neri, 2010).

Biosynthesis of fumonisins

The study of biosynthesis of fumonisins began in the past decade, which were cloned a cluster of genes called as cluster gene *FUM*, this cluster has, approximately, 42-Kb in length (Proctor et al., 2003).

Fumonisin polyketide synthase (*FUM₇*) was the first gene to be cloned and is the principal for the fumonisin biosynthesis. Since then, others cluster of genes required for fumonisin biosynthesis were identified, although some with function is not yet known (Desjardins and Proctor, 2007).

According to Seo et al. (2001), the fumonisins biosynthesis began with the linear molecule synthesis of 20 carbon called polyketide. This molecule consist of 18 carbon with methyl groups at C-12 and C-16, there is

evidence that polyketide formation is catalyzed by synthase-polyketide. Although the fumonisin biosynthetic pathway is poorly understood, precursor feeding studies have revealed that C-3 to C-20 of the backbone are derived from acetate, the amine group and C-1 and C-2 are derived from alanine, the methyl groups are derived from methionine.

Second to Lorenzetti et al. (2006), during the biosynthesis of fumonisins is not clear whether they are derived from a fatty acid or polyketide one, because both these compounds are derived from acetate.

The advances in understanding the biosynthesis of fumonisins were many, but studies aimed at better understanding of genes involved in this stage are still needed. Moreover, informations about the role these genes in toxin production are essential for better developing management strategies pre and post harvest in order to better quality products to be consumed in national and foreign markets (Lorenzetti et al., 2006).

Metabolism of fumonisins

The structure of fumonisin B₁ is very similar to that of the free sphingoid base sphinganine. This had led to the hypothesis that fumonisins exert their toxic effects through a disruption of sphingolipids metabolism or inhibition of the function of sphingolipids. The sphingolipids plays important roles in membrane and lipoprotein structure, cell-to-cell communication, interaction between cells and extracellular matrix and regulation of growth factor receptors and as second messengers for a wide range of factors, including the tumor necrosis factor and interleukin-1 (Soriano et al., 2005). The

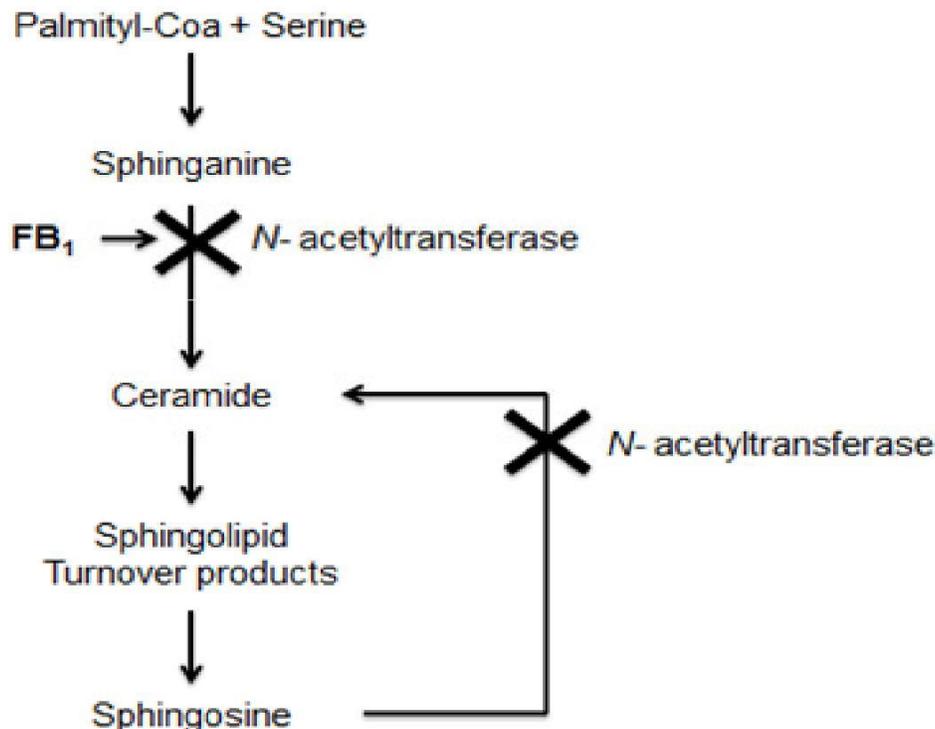


Figure 4. The disruption of sphingolipid pathway by fumonisins (Ramasamy et al., 1995).

fumonisin-induced disruption of sphingolipid metabolism is important in the cascade of events leading to altered cell growth, differentiation and injury observed both *in vivo* and *in vitro* (fumonisins disruption of ceramide). The disruption of sphingolipid pathway by fumonisins is shown in Figure 4. The fumonisins are competitive inhibitors with respect to both substrate (that is, sphinganine and fatty acyl coenzyme A) of sphinganine (sphingosine) *N*-acetyltransferase (ceramide synthase). The results of this inhibition includes: Blockage of complex sphingolipids biosynthesis, increase of free sphinganine and sphingosine, and reacylation of sphingosine derived from complex sphingolipid turnover and degradation of dietary sphingolipids (Enongene et al., 2000; Soriano et al., 2005).

The accumulation of free sphinganine induced of growth-inhibitory and cytotoxic to cells and increased cell death (apoptotic and oncotic) in liver and kidney. Moreover, in animals, consumption of fumonisin B₁ disrupts sphingolipid metabolism as indicated by the accumulation of high levels of free sphinganine in liver, kidney, serum and/or urine (Enongene et al., 2000).

TRICHOHECENES

The trichothecenes mycotoxins comprise a vast group of over 100 fungal metabolites with the same basic

structure. Several fungal genera are capable of producing trichothecene mycotoxins, however, most of them have been isolated from *Fusarium* spp. All trichothecene contain an epoxide at the C12,13 positions, which is responsible for their toxicological activity (Figure 5). At the cellular level, the main toxic effect of trichothecene mycotoxins appears to be a primary inhibition of protein synthesis.

Trichothecene mycotoxins affect actively dividing cells such as those lining the gastrointestinal tract, the skin, lymphoid and erythroid cells. The toxic action of this mycotoxins results in extensive necrosis of the oral mucosa and skin in contact with the toxin, acute effect on the digestive tract and decreased bone marrow and immune function (Schwarzer, 2009). The trichothecene mycotoxins occur worldwide in grains and other commodities like corn, wheat, barley, oats, rice, rye, vegetables, and other crops.

Toxin production is greatest with high humidity and temperatures of 6 to 24°C. Examples of type A trichothecene mycotoxins include T-2 toxin (T-2) and HT-2 toxin (HT-2), and diacetoxyscirpenol (DAS). Deoxynivalenol (DON) and nivalenol (NIV) are some of the common naturally occurring type B (Table 2). Types A and B trichothecene are distinguished by the presence or absence of a carbonyl group at the C8 position, respectively (Wannemacher and Wiener, 1997; Schwarzer, 2009).

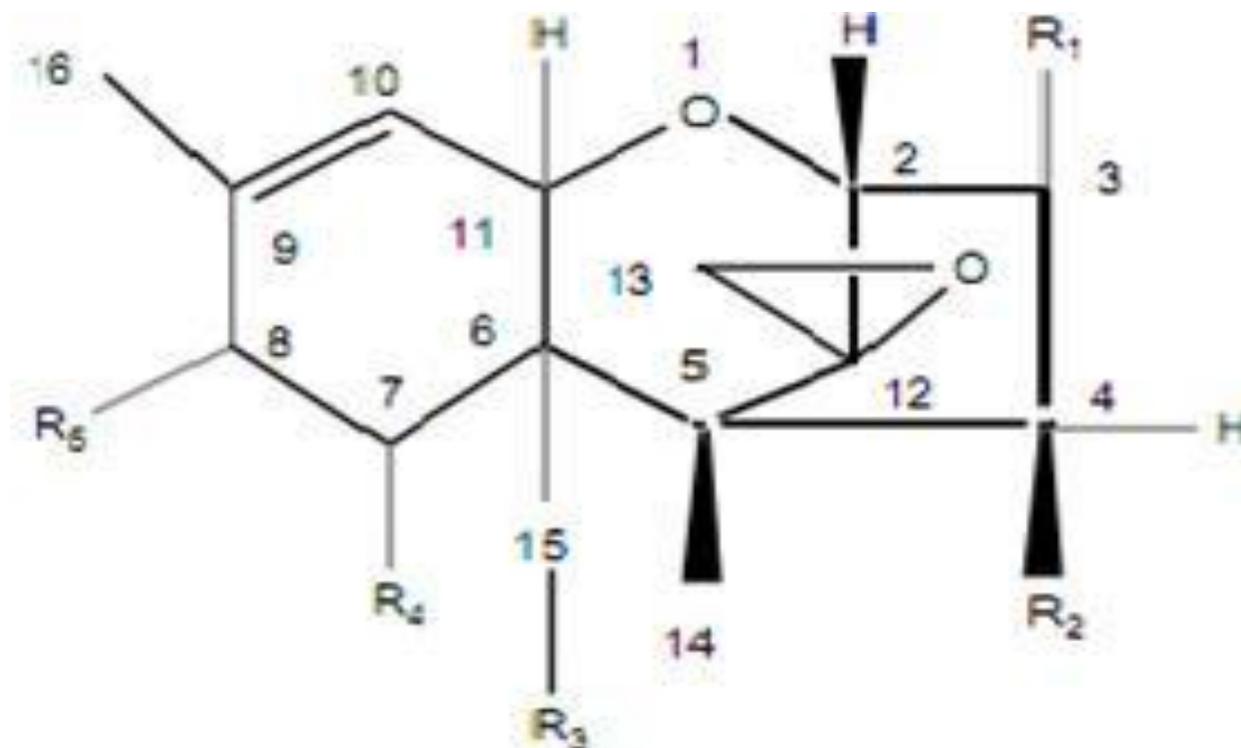


Figure 5. The general structure, numbering system, and variable side groups of the tetracyclic trichothecenes nucleus (Wannemacher and Wiener, 1997).

Biosynthesis of trichothecenes

Trichothecenes biosynthesis begins with the cyclisation of the isoprenoid farnesyl pyrophosphate (FPP) to hydrocarbon trichodiene by the enzyme trichodiene synthase (Figure 6) (Hohn and Van Middlesworth, 1986). The subsequent pathway involves a number of oxygenations, isomerisations, cyclisations and esterifications leading from trichodiene to diacetoxyscirpenol, T-2 toxin and 3-acetyl deoxynivalenol. All of the intermediates except those involved in the earlier steps of the non-macrocyclic biosynthetic pathway have been confirmed by feeding studies (Desjardins et al., 1993). In contrast, the macrocyclic biosynthetic pathway is much less understood; only the end products and late intermediates of the pathway have been isolated and characterized (Jarvis et al., 1991).

Metabolism of trichothecenes

Compared with some of the other mycotoxins such as aflatoxin, the trichothecenes do not appear to require metabolic activation to exert their biological activity (Busby and Wogan, 1981). After direct dermal application or oral ingestion, the trichothecene mycotoxins can cause

rapid irritation to the skin or intestinal mucosa. In cell-free systems or single cells in culture, these mycotoxins cause a rapid inhibition of protein synthesis and polyribosomal disaggregation (Busby and Wogan, 1981). Thus, we can postulate that the trichothecene mycotoxins have molecular capability of direct reaction with cellular components. Despite this direct effect, it is possible to measure the toxic kinetics and the metabolism of the trichothecene mycotoxins. The lipophilic nature of these toxins suggests that they are easily absorbed through skin, gut, and pulmonary mucosa (Wannemacher and Wiener, 1997). When trichothecene binds to active polysomes and ribosomes, the peptide linkages are interrupted, the initiation and termination sequences are diminished, and the ribosomal cycle is disrupted (Ueno, 1977).

Other toxic effects of trichothecenes include disruption of membrane transport and function, suppression of the immune response, and abnormal blood function. For example, the negative effects of T-2 toxin on cell membrane function were explained by disrupting the transport of amino acids, nucleotides, and glucose and activity of Ca-K channel (Bunner and Morris, 1988). Khachatourians (1990) demonstrated that mitochondrial electron transport is also inhibited by T-2 toxin as a result of suppression of succinate dehydrogenase activity. Lipid peroxidation through generation of free radicals during T-2 metabolism has also been suggested as a mode of

- Bhatnagar D, Yu J, Ehrlich KC (2002). Toxins of filamentous fungi. *Chem. Immunol.*, 81: 167-206.
- Biehler ML, Buck WB (1987). Chemical contaminants: their metabolism and their residues. *J. Food Nutr.*, 50: 1058-1073.
- Bunner DL, Morris ER (1988). Alteration of multiple cell membrane functions in L-6 myoblasts by T-2 toxin: An important mechanism of action. *Toxicol. Appl. Pharmacol.*, 92: 113-121.
- Busby WF, Wogan GN (1981). Trichothecenes. In: *Mycotoxins and N-Nitroso Compounds: Environmental Risks*. Shank RC (Eds.). CRC Press, Florida, U.S.A., pp. 29-41.
- Bushell ME (1989). The process physiology of secondary metabolite production. In: *Microbial Products: New Approaches* (Society for General Microbiology Symposium no. 44). Baumberg S, Hunter IS, Rhodes PM (Eds.). Cambridge University Press, Cambridge, USA., pp. 95-120.
- Cotty PJ, Bhatnagar D (1994). Variability among toxigenic *Aspergillus flavus* strains in ability to prevent aflatoxin contamination and production of aflatoxin biosynthetic pathway enzymes. *Appl. Environ. Microbiol.*, 60: 2248-2251.
- Desjardins AE, Proctor RH (2007). Molecular biology of *Fusarium* mycotoxins. *Int. J. Food Microbiol.*, 119: 47-50.
- Desjardins AE, Hohn TM, McCormick SP (1993). Trichothecene biosynthesis in *Fusarium* species: chemistry, genetics and significance. *Microbiol. Rev.*, 57: 595-604.
- Dvorackova I (1990). Aflatoxins and Human Health. CRC Press, Florida, U.S.A., pp. 135-150.
- Ellis WO, Smith JP, Simpson BK, Oldham JH (1991). Aflatoxins in food: occurrence, biosynthesis, effects on organisms, detection, and methods of control. *Crit. Rev. Food Sci. Nutr.*, 30: 403-439.
- Enongene EN, Sharma RP, Bhandari N, Voss KA, Riley RT (2000). Disruption of shingolipid metabolism in small intestines, liver and kidney of mice dosed subcutaneously with fumonisin B₁. *Food Chem. Toxicol.*, 38: 793-799.
- Faifer GC, Zabal O, Godoy HM (1992). Further studies on hematopoietic damage produced by a single dose of T-2 toxin in mice. *Toxicol.*, 75: 169-174.
- Gourama H, Bullerman LB (1995). *Aspergillus flavus* and *Aspergillus parasiticus*: aflatoxigenic fungi of concern in foods and feeds. *J. Food Protect.*, 58: 1395-1404.
- Hohn TM, Van Middlesworth F (1986). Purification and characterization of the sesquiterpene cyclase trichodiene synthase from *Fusarium sporotrichioides*. *Arch. Biochem. Biophys.*, 251: 756-761.
- Hussein SH, Brasel JM (2001). Toxicity, metabolism, and impact of mycotoxins on humans and animals. *Toxicol.*, 167: 101-134.
- Jarvis BB, Mokhtan-Rejali N, Schenkl E, Barros CS, Matzenbacher NI (1991). Trichothecene mycotoxins from Brazilian Baccharis species. *Phytochem.*, 30: 789-797.
- Jelinek CF, Pohland AE, Wood GE (1989). Worldwide occurrence of mycotoxins in foods and feeds - an update. *J. Assoc. Off. Anal. Chem.*, 72: 223-230.
- Johannisson A, Bjorkhag B, Hansson W, Gadhasson IL, Thuvander A (1999). Effects of four trichothecene mycotoxins on activation marker expression and cell proliferation of human lymphocytes in culture. *Cell Biol. Toxicol.*, 15: 203-215.
- Khachatourians GG (1990). Metabolic effects of trichothecene T-2 toxin. *Can. J. Physiol. Pharmacol.* 68: 1004-1008.
- Khomutov RM, Dzhevakhlyab VG, Khursa EN, Osipovaa TI, Shcherbakovab LA, Zhemchuzhinab NS, Mikityukb OD, Nazarova TA (2011). Chemical regulation of mycotoxin biosynthesis. *Dokl. Biochem. Biophys.*, 436: 25-28.
- Klich MA, Mullaney EJ, Daly CB, Cary JW (2000). Molecular and physiological aspects of aflatoxin and sterigmatocystin biosynthesis by *Aspergillus tamarii* and *A. ochraceoroseus*. *Appl. Microbiol. Biotechnol.*, 53: 605-609.
- Lautraite S, Parent-Massin D, Rio B (1997). *In vitro* toxicity induced by deoxynivalenol (DON) on human and rat granulomonocytic progenitors. *Cell. Biol. Toxicol.*, 13: 175-183.
- Lillehoj EB (1991). Aflatoxins: an ecologically elicited genetic activation signal. In: *Mycotoxins and Animal Foods*. Smith JE, Henderson S (Eds.). CRC Press, Florida, U.S.A., pp. 1-35.
- Lorenzetti RS, Vilas-boas IA, Garcia JE (2006). Genetic aspects of biosynthesis of fumonisins. *Sci. Biol. Health*, 8: 63-70.
- Mallmann CA, Santurio JM, Almeida CA, Dilkin P (2001). Fumonisin B₁ levels in cereals and feeds from Southern Brazil. *Arq. Inst. Biol.*, 68: 41-45.
- Menniti AM, Neri RGF (2010). Activity of natural compounds on *Fusarium verticillioides* and fumonisin production in stored maize kernels. *Int. J. Food Microbiol.*, 136: 304-309.
- Moss MO (1996). Mycotoxins. *Mycol. Res.*, 100: 513-523.
- Moss MO (1991). The environmental factors controlling mycotoxin formation. In: *Mycotoxins and Animal Foods*. Smith JE, Anderson RA (Eds.). CRC Press, Florida, U.S.A., pp. 37-56.
- Neal GE, Eaton DL, Judah DJ, Verma A (1998). Metabolism and toxicity of aflatoxins M₁ and B₁ in human-derived *in vitro* systems. *Toxicol. Appl. Pharmacol.*, 151: 152-158.
- Niderkon V, Morgavi DP, Aboab B, Lemaire M, Boudra H (2009). Cell wall component and mycotoxin moieties involved in the binding of fumonisin B₁ and B₂ by lactic acid bacteria. *J. Appl. Microbiol.*, 106: 977-985.
- Oliveira CAF, Germano PML (1997). Aflatoxins: Current concepts on mechanisms of toxicity and its involvement in the etiology of hepatocellular carcinoma. *Rev. Saúde Públ.*, 31: 417-424.
- Park JW, Choi SY, Hwang HJ, Kim YB (2005). Fungal mycoflora and mycotoxins in Korean polished rice destined for humans. *Int. J. Food Microbiol.*, 103: 305-314.
- Proctor RH, Brown DW, Plattner RD, Desjardins AE (2003). Co-expression of 15 contiguous genes delineates a fumonisin biosynthetic gene cluster in *Gibberella moniliformis*. *Fungal Genet. Biol.*, 38: 237-249.
- Quezada T, Cuellar H, Jaramillo-Juarez F, Valdivia AG, Reyes JL (2000). Effects of aflatoxin B₁ on the liver and kidney of broiler chickens during development. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.*, 125: 265-272.
- Rio B, Lautraite S, Parent-Massin D (1997). *In vitro* toxicity of trichothecenes on human erythroblastic progenitors. *Hum. Exp. Toxicol.*, 16: 673-679.
- Schwarzer K (2009). Harmful effects of mycotoxins on animal physiology. In: *17th Annual ASAAM SEA Feed Technology and Nutrition Workshop*, Hue, Vietnam.
- Seo JA, Proctor RH, Plattner MR (2001). Characterization of four clustered and co regulated genes associated with fumonisin biosynthesis in *Fusarium verticillioides*. *Fungal Genet. Biol.*, 34: 155-165.
- Shane SH (1994). Economic issues associated with aflatoxins. In: *The Toxicology of Aflatoxins: Human Health, Veterinary, and Agricultural Significance*. Eaton DL, Groopman JD (Eds.). Academic Press, San Diego, U.S.A., pp. 513-527.
- Soriano JM, González L, Catalá AL (2005). Mechanism of action of sphingolipids and their metabolites in the toxicity of fumonisin B₁. *Prog. Lipid Res.*, 44: 345-356.
- Suneja SK, Wagle DS, Ram GC (1989). Effect of oral administration of T-2 toxin on glutathione shuttle enzymes, microsomal reductase and lipid peroxidation in rat liver. *Toxicol.*, 27: 995-1001.
- Townsend CA, McGuire SM, Brobst SW, Graybill TL, Pal K, Barry CE (1991). Examination of tetrahydro- and dihydrobisfuran formation in aflatoxin biosynthesis: from whole cells to purified enzymes. In: *Secondary-Metabolite Biosynthesis and Metabolism*. Petroski RJ, McCormick SP (Eds.). Plenum Press, New York, U.S.A., pp. 141-154.
- Trail F, Mahanti N, Linz J (1995). Molecular biology of aflatoxin biosynthesis. *Microbiol.*, 141: 755-765
- Ueno Y (1977). Mode of action of trichothecenes. *Pure Appl. Chem.*, 49: 1737-1745.
- Vasanthi S, Bhat RV (1998). Mycotoxins in foods-occurrence, health and economic significance and food control measures. *Ind. J. Med. Res.*, 108: 212-224.
- Wang JS, Groopman JD (1999). DNA damage by mycotoxins. *Mutat. Res.*, 424: 167-181.
- Wannemacher RW, Wiener S (1997). Trichothecene mycotoxins. In: *Medical Aspects of Chemical and Biological Warfare*. Sidell FR, Takafugi ET, Franz DR (Eds.). TMM Publications, Washington, U.S.A., pp. 655-676.