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Review

Biochemistry and metabolism of aflatoxins, fumonisins and trichothecenes

***Eduardo E. S., Romário G. O. and Sérgio Antônio**

Mycotoxin Laboratory, Chemistry and Food School, Federal University of Rio Grande, Rio Grande, Rio Grande do Sul, Brazil.

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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 B_1, B_2, G_1 e G_2, 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 agroeconomic 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 receive 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 B_1 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.

*Corresponding author. E-mail: Eduardo.se22@yahoo.com.br

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

Fungal species	Mycotoxin
Aspergillus flavus; A. parasiticus	Aflatoxins
A. flavus	Cyclopiazonic acid
A. ochraceus; Penicillium viridicatum; P. cyclopium	Ochatoxin A
P. expansum	Patulin
Fusarium culmorum; F. graminearum; F. sporotrichioides	Deoxynivalenol
F. sporotrichioides; F. poae	T-2 toxin
F. sporotrichioides; F. graminearum; F. poae	Diacetoxyscirpenol
F. culmorum; F. graminearum; F. sporotrichioides	Zearalenone
F. moniliforme	Fumonisins
Acremonium coenophialum	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, B_1, B_2, G_1, and G_2 (AFB_1, AFG_1, AFB_2 and AFG_2), 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, M_1 and M_2, are oxidative forms of AFB_1 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 ciclopentan 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 AFB_1 biosynthetic pathway (Barnes et al*.*, 1994). The initial step in generation of the polyketide backbone of AFB_1 is proposed to involve polymerization of acetate and nine malonate units (with a loss of CO_2) 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 AFB_1 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 B_2 (AFB_2), which lacks this double bond, is hundreds of times less carcinogenic (Dvorackova, 1990).

Metabolism of aflatoxins

The system responsible for the biotransformation of AFB_1 basically has five mechanisms, represented by reactions of reduction, hydration, epoxidation, hydroxylation and ortho-demethylation. The aflatoxicol is produced by reduction of AFB_1 by an NADPH-dependent cytoplasmic enzyme present in the soluble fraction of the liver. The toxicity of aflatoxicol is apparently much smaller than AFB_1, but the conversion is reversible and the aflatoxicol can serve as a reservoir toxicity of AFB_1 in the intracellular space, it can be converted in this mycotoxin by microsomal dehydrogenase. The aflatoxicol can also be metabolized to AFM_1 and AFH_1 (Biehl and Buck, 1987). The hydration process results in a metabolite

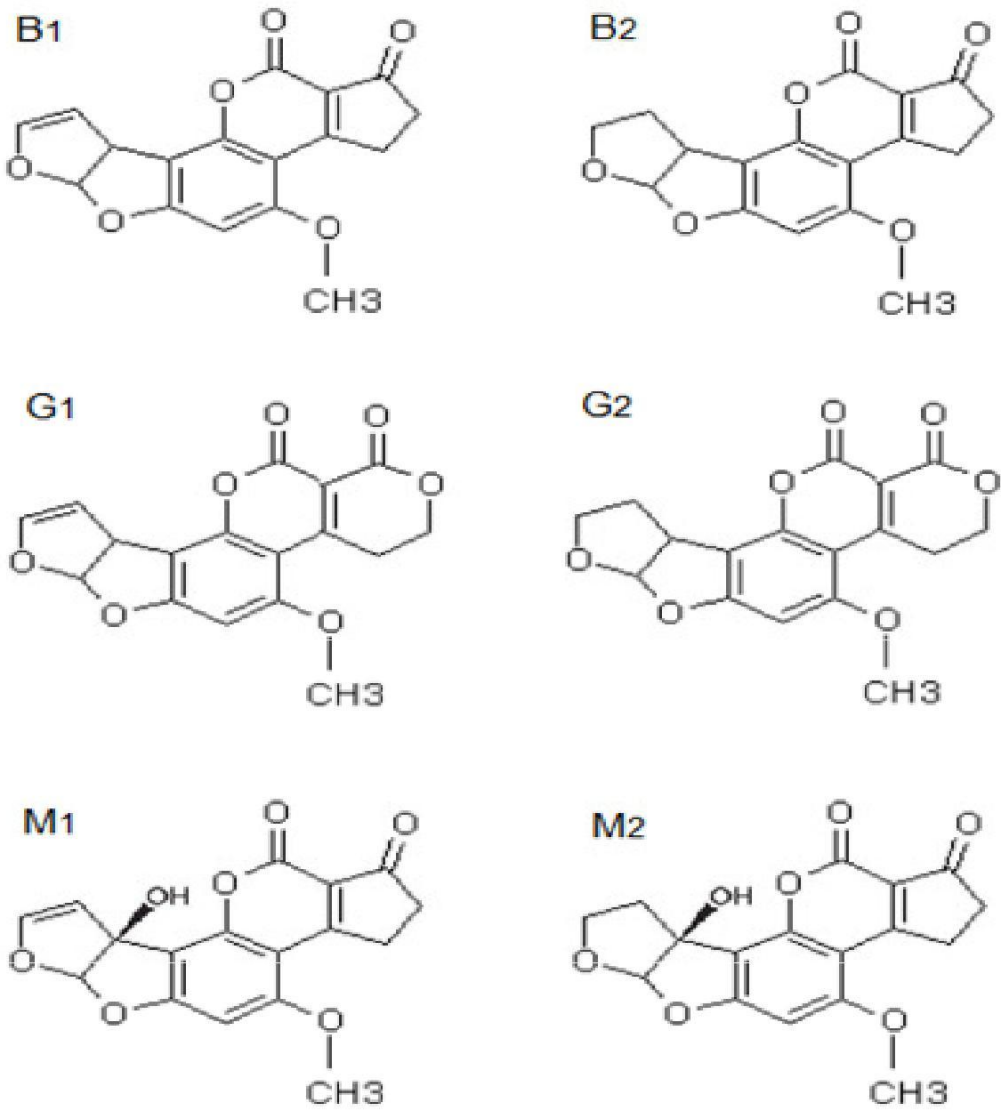

Figure 1. Chemical structure of aflatoxins (Biehl and Buck, 1987).

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 AFB_1 has no mutagenic activity. The biotransformation of this compound through the reaction of epoxidation is that changes the AFB_1 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 filed 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

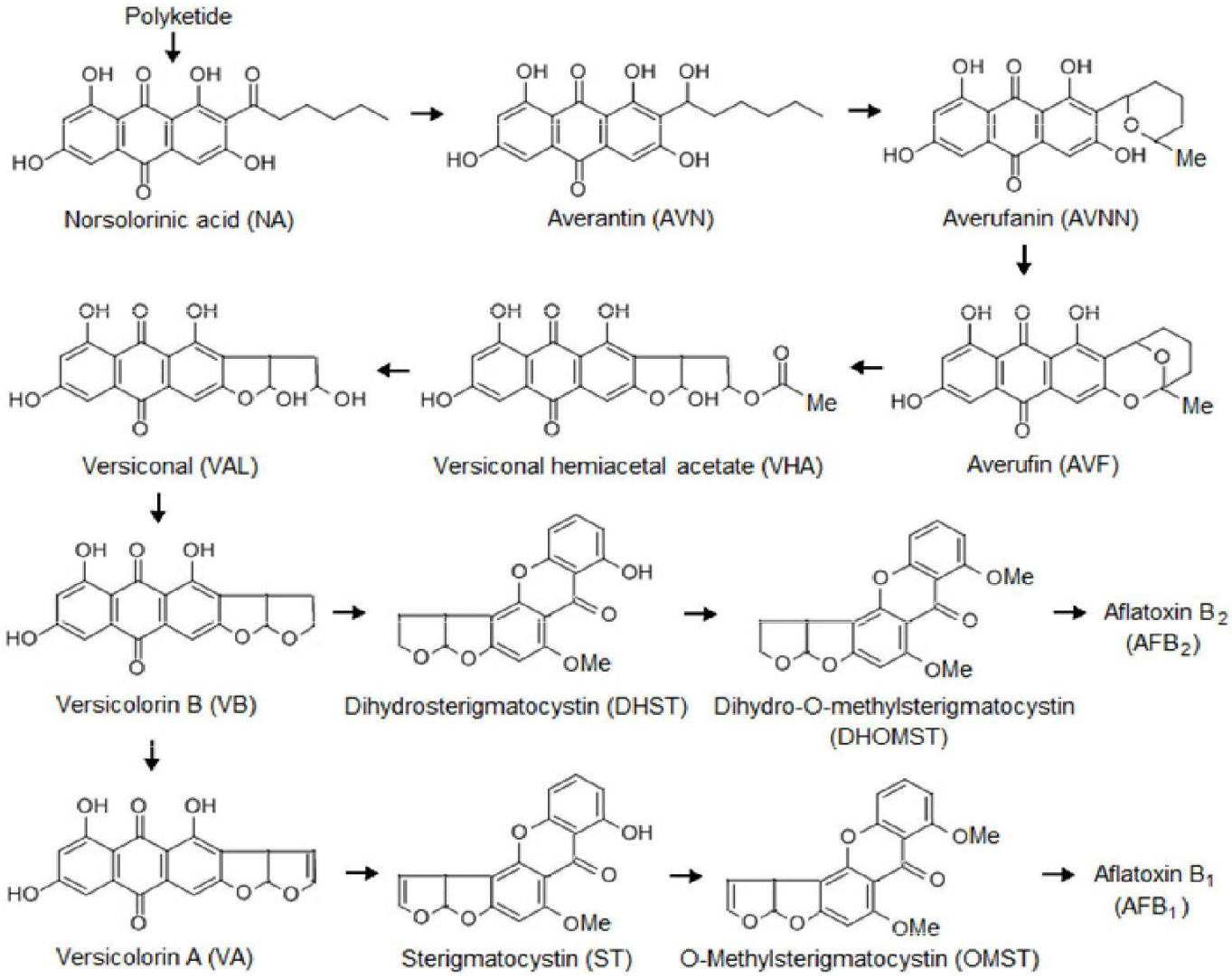

Figure 2. Aflatoxin B_1 and B_2 biosynthetic pathway (Trail et al., 1995).

vitamins and essential amino acids (Quezada et al., 2000). AFM_1 and AFQ_1 are results of hydroxylation reaction of AFB_1. 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 AFB_1, 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

Fumonisins 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). Fumonisins are structurally related molecules and 16 of which have been isolated and characterized: Fumonisins B_1 (FB_1), FB_2, FB_3, FB_4, A_1, A_2, A_3, AK_1, C_1, C_3, C_4, P_1, P_2, P_3, PH_{1A}, PH_{1B}, however, fumonisin B_1 and fumonisin B_2 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. FB_1 is the diester of propane-1,2,3-tricarboxylic acid

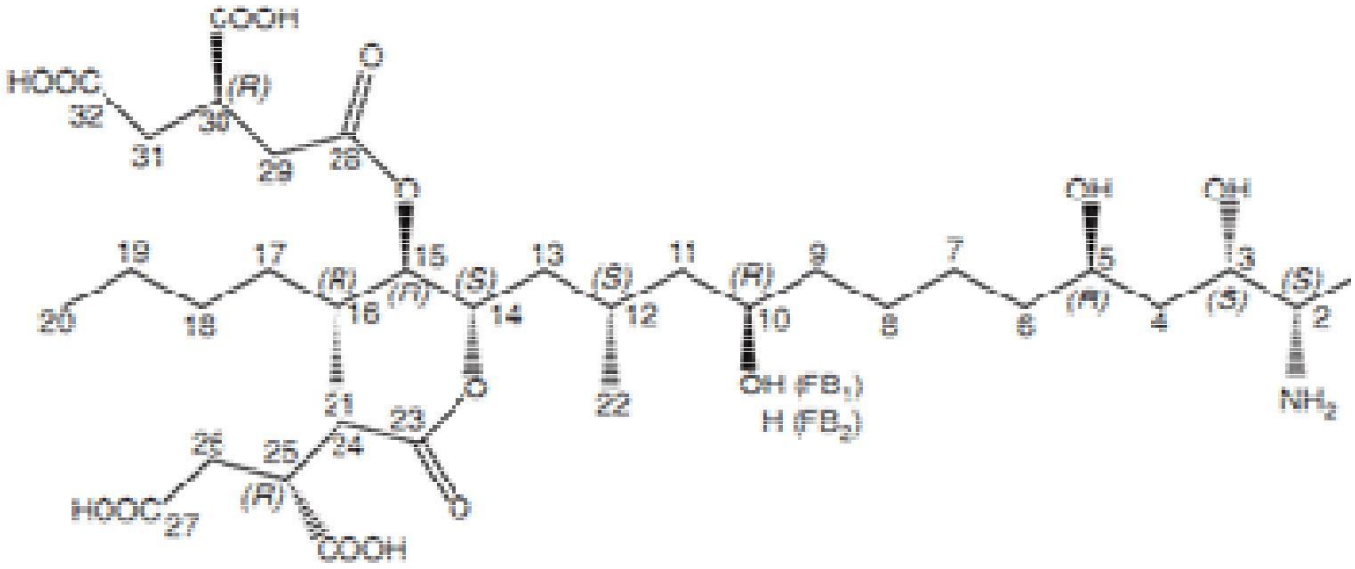

Figure 3. FB_1 and FB_2 configurations (Niderkon et al., 2009).

(tricarballylic acid, TCA) and 2-amino-12,16-dimethyl-3,5,10,14,15-pentahydroxyeicosane, in which the C_{14} and C_{15} hydroxyl groups are esterified with the terminal carboxyl group of TCA. FB_2 is the C_{10} deoxy analogue of FB_1, 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. FB_1 has been classified by the International Agency for Research on Cancer (IARC) in Group 2B as a possible carcinogen to humans. In addition, FB_1 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 (*FUM1*) 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, althought 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 Lorenzzetti 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 essencial for better developing management strategies pre and post harvest in order to better quality products to be consumed in national and foreign markets (Lorenzzetti et al., 2006).

Metabolism of fumonisins

The structure of fumonisin B_1 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 lipo-protein 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

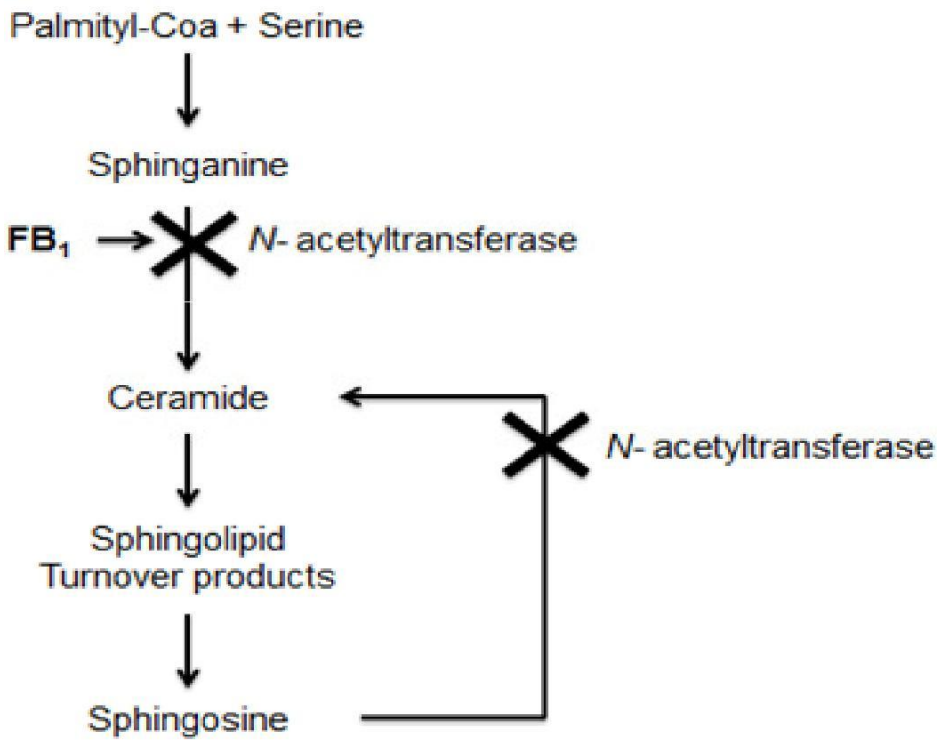

Figure 4. The disruption of sphingolipid pathway by fumonisins (Ramasamy et al., 1995).

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* (fumonisin 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 B_1 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).

TRICHOTHECENES

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).

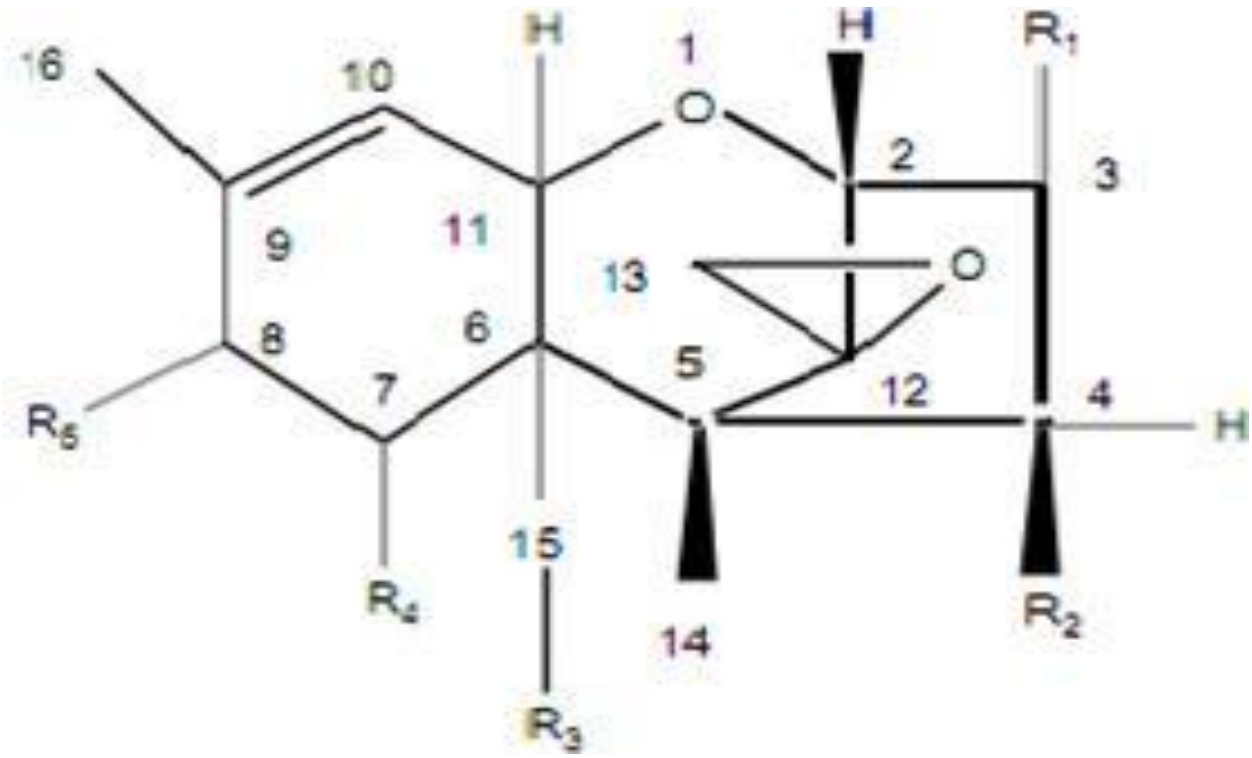

Figure 5. The general structure, numbering system, and variable side groups of the tetracyclic trichothecenes nucleus (Wannemacher and Wiener, 1997).

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

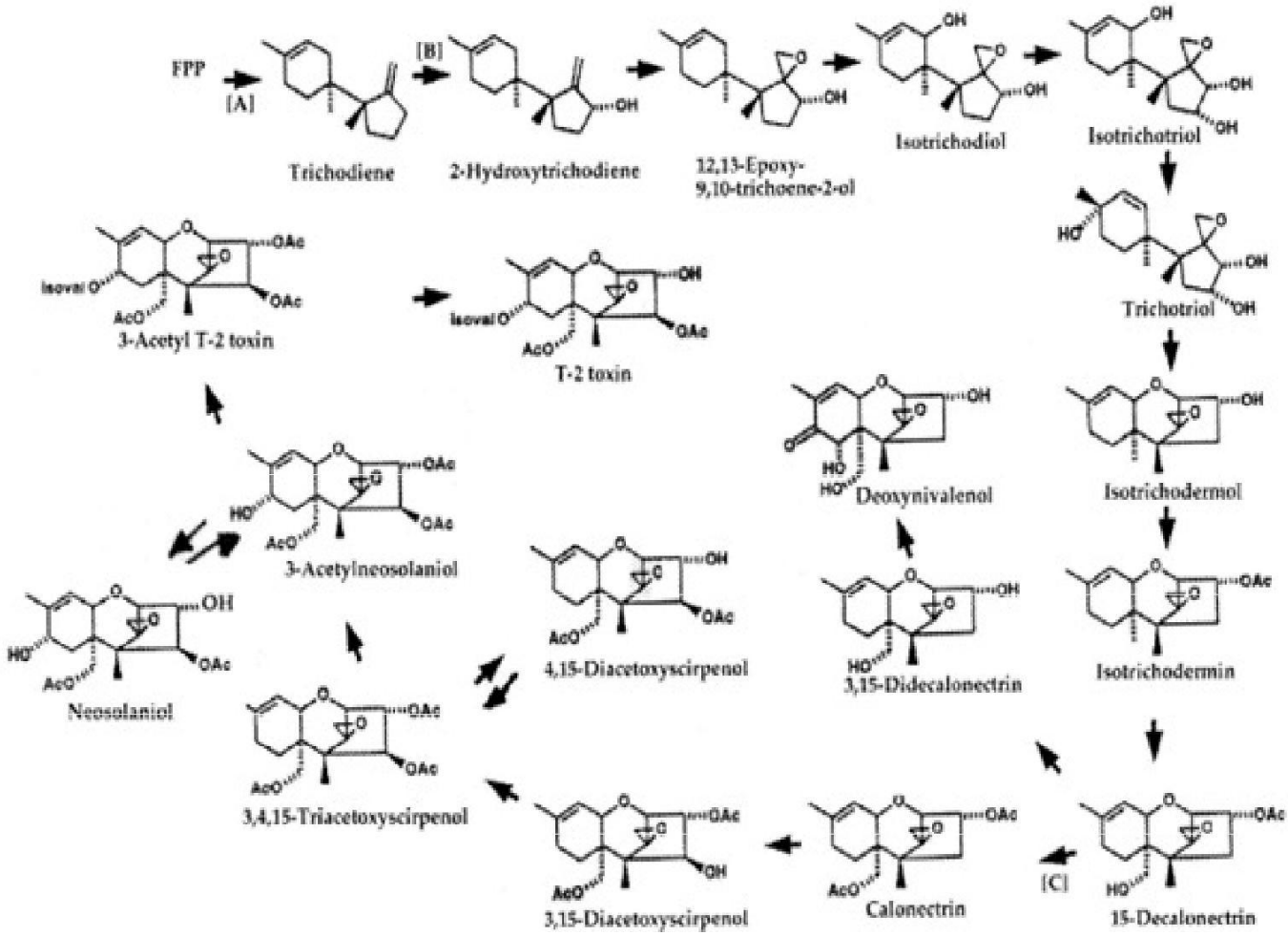

Figure 6. Trichothecene biosynthetic pathway in *Fusarium* species (Alexander et al., 1998).

trichothecene action in rat liver (Suneja et al., 1989; Johannisson et al., 1999). With regard to the immune response, proliferation of human lymphocytes in cultures was shown to be inhibited by T-2 toxin, DON, and DAS (Suneja et al., 1989). In another *in vitro* study where murine peritoneal macrophages were used (Ayral et al., 1992), DON and DAS were shown to inhibit the phagocytic activity, microbicidal activity, and superoxide anion production. The actions of trichothecenes at the hematological level have been illustrated in several studies (Faifer et al., 1992; Lautraite et al., 1997; Rio et al., 1997). For example, T-2 toxin reduced granulocyte macrophage colony-forming cells in the bone marrow of mice (Faifer et al., 1992). In another study (Lautraite et al., 1997), DON inhibited granulo-monocytic progenitors. Both T-2 toxin and DAS also inhibited human erythrobalstic progenitors (Rio et al., 1997). In summary, very little of the parent trichothecene mycotoxin is excreted intact. Rather, elimination by detoxification of the toxin is the result of extensive and rapid biotransformation (Wannemacher and Wiener, 1997).

CONCLUSION

In view of the toxic effect of mycotoxins to humans and animals, 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.

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