Sphinganine-Analog Mycotoxins

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Sphinganine-analog mycotoxins (SAMs) including fumonisins and *Alternaria alternata* f. sp. *Lycopersici* (AAL) toxins are a group of related mycotoxins produced by plant pathogenic fungi in the *Fusarium* genus and in *A. alternata* f. sp. Lycopersici, respectively. SAMs have shown diverse cytotoxicity and phytotoxicity, causing adverse impacts on plants, animals, and humans, and are a destructive force to crop production worldwide.

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1. Introduction

Mycotoxins are secondary metabolites produced by various fungi. These metabolites have important ecological functions on living systems in their natural habitats. As secondary metabolites, mycotoxins are regarded as not essential for fungal growth or reproduction. However, their toxic effects to plants, animals, as well as humans are attracting increasing attention from chemists, biologists, food scientists, and healthcare professionals. Many fungi are capable of synthesizing mycotoxins, including certain saprophytic molds, poisonous mushrooms, human fungal pathogens, and plant fungal pathogens. Mycotoxins produced by plant pathogenic fungi can be divided into two groups: (i) host-selective (or host-specific) toxins (HSTs) and (ii) non-host-specific toxins (nHSTs), depending on whether they are specifically toxic to host plant (HSTs) or to a wide range of species (nHSTs). The known mycotoxins are typically low molecular-weight chemicals but with diverse structures and modes of actions. One group of mycotoxins are structurally analogous to sphingosine, the backbone precursor of sphingolipids that play essential structural and cellular roles in eukaryotic cells. These toxins are called sphinganine-analog mycotoxins (SAMs), with fumonisins and the *Alternaria alternata* f. sp. *Lycopersici* (AAL) toxins as the two most widely studied groups of SAMs. SAMs are toxic to plants and animals. They act by inhibiting the ceramide synthase (CerS), thereby influencing the sphingolipid metabolism and initiating apoptosis in animals and programmed cell death (PCD) in plants [1][2][3]. The paper provides an overview on the structural diversity, syntheses, modes of action, and health impacts of SAMs.

The discovery of fumonisin was first reported in 1988 and the organism producing it was *Fusarium verticillioides* (syn. *Gibberella fujikuroi* mating population A, syn. *G. moniliformis* Wineland, syn. *F. moniliforme* Sheldon) [4]. Fumonisins have since been found to be produced by at least 18 species of the *Fusarium* genus, with *F. verticillioides* and *F. proliferatum* being the most prominent, and by three unrelated fungal genera, *Aspergillus* section *Nigri* (such as *Asp. niger, Asp. Welwitschiae* (syn. *Asp. awamori*) and so on, known as black aspergilli), *Tolypocladium (T. inflatum, T. cylindrosporum,* and *T. geodes)*, and *Alternaria* (the tomato pathotype of *A. alternata,* formerly known as *A. arborescens*) [5][6][7][8][9][10]. Species of the *Fusarium* genus can be found as saprophytes in

soil and as endophytes and pathogens of many plants worldwide. A common group of diseases caused by *Fusarium* pathogens is rotting that can happen to all tissues during all stages of plant development [11][12]. In addition, the *Fusarium* species can infect crops at the post-harvest period during storage [13]. The fungal propagules surviving in the soil can also infect new crop plants and can be carried to new fields by wind or by anthropogenic activities, such as when seedlings are transplanted [14]. *Fusarium* strains can synthesize fumonisins during all stages of their growth, including the saprophytic stage in the soil, during their pathogenesis, and as endophytes in different parts of plants, as well as during crop storage after harvest [15].

Fumonisins, as a nHST, are major contaminants of cereals and grains, including corn, rice, wheat, barley, rye, oat, millet, and products made based on these crops [16]. The consumption of food contaminated by fumonisins significantly increases health problems for humans, leading to a variety of cancers such as esophageal cancer and neurological defects [17][18]. For example, the International Agency for Research on Cancer (IARC) characterized fumonisin FB_1 as a group 2B carcinogens for humans [16]. Fumonisins can also cause diseases and adverse effects in other species, especially in livestock when the feeds are contaminated [19]. Well-known diseases in livestock caused by fumonisins include leukoencephalomalacia in horses and pulmonary edema syndrome in pigs [20][21].

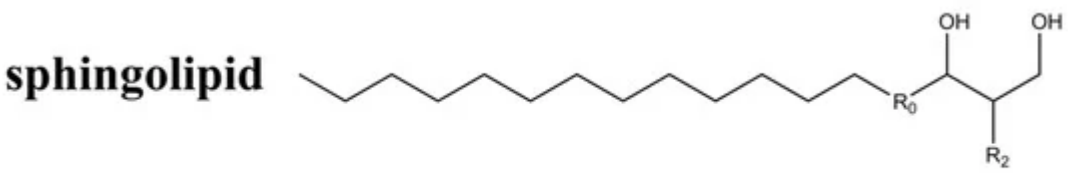
Similar to fuminisins, the AAL-toxins include a family of structurally analogous metabolites. AAL-toxins are a group of HST produced by the ascomycete fungal pathogen *A. alternata* f. sp. *Lycopersici*, the causal agent of tomato stem canker disease [22]. It should be noted that several other pathotypes of *A. alternata* could also produce other HSTs responsible for fungal pathogenesis on their specific host plants, respectively [23]. Unlike other HSTs produced by *A. alternata*, besides the susceptible tomato host, AAL-toxins can also affect many other weeds and crops of dicotyledonous species and at least 25 species of *Solanaceae* [24][25]. Furthermore, the tomato pathotype of *A. alternata* was also reported to produce fumonisins B (FBs) [8][26]. AAL-toxin and FBs were not only detected in the necrosis plant tissues and culture media inoculated by *A. alternata* but also in spores and mycelia of this pathogen [27]. However, AAL-toxin remains the only toxin as a pathogenicity factor for stem canker disease of sensitive tomato varieties, while fumonisins are toxigenic virulence factors [28].

2. Chemical and Structural Properties

2.1. Chemical and Structural Properties of Sphingolipids

SAMs have a distinct structural similarity to sphinganine (Figure 1). Sphinganine (dihydrosphingosine, DHS) is the simplest class of sphingolipids and has a backbone that consists of a linear aliphatic group with 18-carbon, an amino at C-2, and two hydroxyls (-OH) at C-1 and C-3, respectively. Phytosphingosine is obtained if a hydroxyl is introduced at C-4. Sphingosine consists of the sphinganine backbone but with a double bond at C-4. Ceramides are synthesized by linking an amide fatty acid at C-2 of sphingosine. Ceramides is a waxy lipid molecule, which is found in high concentrations in the membrane of eukaryotic cells. More complex sphingolipids can be formed by linking different chemical groups to hydroxyl (C1) of ceramides. Sphingolipids are one type of lipids widely found in their membranes in eukaryotes and a few prokaryotes, and they form complex and diverse interactions with other

molecules [29]. Sphingolipids play important structural and functional roles, they are involved in a variety of signal transductions and crucial cellular processes [30][31]. For example, in humans, ceramides help form the skin's barrier and regulate immune response, protecting the skin against environmental irritants, pollutants, and water loss. Without the proper ratio of ceramides on our epidermal cells, the barrier of the skin will be damaged, resulting in dryness, itching, and irritation [32].



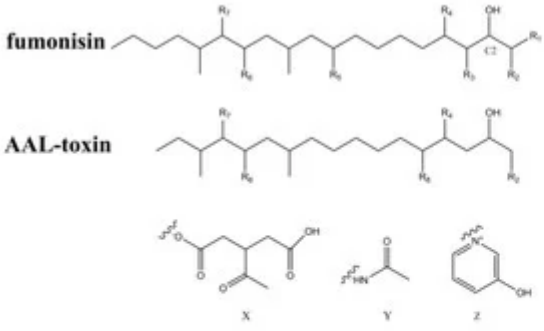
sphingolipid	R_0	R_2
sphingosine	CH=CH	NH_2
sphinganine	CH_2-CH_2	NH_2
phytosphingosine	CH_2-CHOH	NH_2
ceramide	CH=CH	Y-$(CH_2)_n$-CH_3

Figure 1. Chemical structure of sphingolipids. The table shows the different substituents in the chemical scaffold of the most essential sphingolipid.

2.2. Chemical and Structural Properties of Fumonisins

SAMs consist of two main types of toxins, fuminisins and AAL-toxins. Fumonisins can be divided into seven groups (FA, FB, FC, FD, FP, FP_y, and FL_a). These groups differ in the nitrogen functional group and the length of the carbon backbone [5]. Most fumonisins contain a 19–20 (FD contain 17 or 18 carbon) linear backbone similar to sphinganine with one nitrogen functional group (except for FP_ys and FL_as), two to four hydroxyl, two methyl, and two propane-1,2,3-tricarboxylic acid (PTCA) side chains esterified to the backbones [26][33]. The structural features of the seven groups of fumonisins are shown in Figure 2. Among them, the B group is the dominant one. For example, FB_1 accounts for 70–80% of the total fumonisins produced by *F. verticillioides* and is the predominant toxic form [5]. FB_2 and FB_3 are isomers of each other but with one less hydroxyl group than FB_1. The B series of fumonisins (FBs) are also the main food contaminants. Group A fumonisins (FA) are acetylated derivates of group B toxins, with lower toxicity and bioactivity than their FB counterparts [34]. Group C fumonisins (FC) have the same nitrogen functional group as FB_1 but lack the terminal methyl group at C-1 [35]. Three forms of acetylated FC_1 have been discovered in *F. oxysporum* [36]. Group P fumonisins (FP) have a nitrogen functional group of 3-hydroxypyridinium instead of the amino group in FB at the R_2 position [37]. The FC and FP groups have similar phytotoxic and cytotoxic effects to those caused by FB_1 or AAL-toxin [38]. Aside from these four main groups, there are several other lesser-known fumonisin analogs, with one or two PTCA replaced by a hydroxyl or carbonyl or other carboxylic acids group at C-13 and/or C-14 of the backbone (for example, HFB_1, as show in Figure 2). Rheeder et al. summarized the 28 fumonisin analogs that have been characterized between 1988 and 2002 [5]. By reversed-phase high-performance liquid chromatography/electrospray ionization ion trap multistage mass

spectrometry (RP-HPLC/ESI-IT-MS^n), Bartok et al. detected 58 fumonisins (including FD) or fumonisin-like compounds from *F. verticillioides* in rice cultures, and 28 isomers of FB_1 [33][39]. Indeed, the recent application of a semi-targeted method revealed over 100 structurally related compounds from SAMs-producing fungi, including a hydroxyl-FB_1, and two new classes of non-aminated fumonisins (FP_ys and FL_as) [26].



Panel A

AAL-toxin	R_2	R_4	R_8	R_6	R_7
TA_1	NH_2	OH	OH	X	H
TA_2	NH_2	OH	OH	H	X
TB_1	NH_2	OH	H	X	H
TB_2	NH_2	OH	H	H	X
TC_1	NH_2	H	H	X	H
TC_2	NH_2	H	H	H	X
TD_1	Y	OH	H	X	H
TD_2	Y	OH	H	H	X
TE_1	Y	H	H	X	H
TE_2	Y	H	H	H	X

Panel B

fumonisin	R_1	R_2	R_3	R_4	R_5	R_6=R_7
FA_1	CH_3	Y	H	OH	OH	X
FA_2	CH_3	Y	H	OH	H	X
FA_3	CH_3	Y	H	H	OH	X
FA_4	CH_3	Y	H	H	H	X
isoFA[a]$_{1a,b}$	CH_3	Y	H	H	H	X
FC_1	H	NH_2	H	OH	OH	X
FC_2	H	NH_2	H	OH	H	X
FC_3	H	NH_2	H	H	OH	X
FC_4	H	NH_2	H	H	H	X
isoFC$_1$	H	NH_2	OH	H	OH	X
isoFC[b]$_{2,3}$	H	NH_2	H	H	H	X
FC_3OH	H	NH_2	OH	OH	OH	X
FD[c]	H	NH_2	H	H	OH	X
FP_1	CH_3	Z	H	OH	OH	X
FP_2	CH_3	Z	H	OH	H	X
FP_3	CH_3	Z	H	H	OH	X
FP_{y2}	CH_3	=O	H	OH	H	X
FP_{y4}	CH_3	=O	H	H	H	X
FP_{y8}	CH_3	=O	OH	OH	H	X
FL_{a2}	CH_3	OH	H	OH	H	X
FL_{a4}	CH_3	OH	H	H	H	X

fumonisin B	R_1	R_2	R_3	R_4	R_5	R_6=R_7
FB_1	CH_3	NH_2	H	OH	OH	X
FB_2	CH_3	NH_2	H	OH	H	X
FB_3	CH_3	NH_2	H	H	OH	X
FB_4	CH_3	NH_2	H	H	H	X
FB_6	CH_3	NH_2	OH	OH	H	X
isoFB$_1$	CH_3	NH_2	OH	H	OH	X
isoFB[b]$_{1a-d}$	CH_3	NH_2	H	H	OH	X
isoFB[b]$_{2,3a-e}$	CH_3	NH_2	H	H	H	X
FB[a]$_y$/ isoFB[a]$_{3a-d}$	CH_3	NH_2	H	H	OH	X
FB_1OH	CH_3	NH_2	OH	OH	OH	X
FBK$_1$ 2TCA[d]	CH_3	NH_2	H	OH	OH	X
FBK$_4$ 2TCA[d]	CH_3	NH_2	H	OH	H	X
HFB$_1$	CH_3	NH_2	H	OH	OH	OH
PHFB[a]$_{1a,b}$	CH_3	NH_2	H	OH	OH	X/OH

[a] There are two other OH groups on the backbone
[b] There is another OH group on the backbone
[c] C18 compound or C17 compound (C2:without OH, R_3:ketone, R_4:OH
[d] C2 ketone
[e] A PTCA (X) was removed by hydroxylation at C13 or C14

Figure 2. Chemical structure of sphinganine-analog mycotoxins (SAMs). Panel A shows the AAL-toxins, Panel B shows fumonisin. In the table of each panel, the different substituents present in the chemical scaffolds of individual compounds are shown.

2.3. Chemical and Structural Properties of AAL-Toxin

The AAL-toxins have a structural similarity to fumonisins (Figure 2). The main difference between fumonisins and AAL-toxins is that AAL-toxins have one fewer PTCA side chain than fumonisins. The AAL-toxins have been divided into five pairs based on their side chain structures: A, B, C, D, and E pairs (TA, TB, TC, TD and TE). These pairs differ in their nitrogen functional group and hydroxylation at C-4 or C-5 positions of the backbone [40][41][42]. Each pair of AAL-toxins is composed of two regioisomers with PTCA esterified to C-13 or C-14 of the backbone,

respectively. The TA pair is the major pair of toxins, with the TB and TC pairs formed by removing hydroxyl groups one by one from C-5 and C-4 of the TA pair. The TD and TE pairs were acetylated derivatives of TB and TC respectively, while the acetylated form of TA and keto derivatives of AAL-toxins (2-keto or 14-keto analogues predicted) were also found in 2015 [26]. These four regioisomeric pairs (TB, TC, TD, and TE) of AAL-toxins can all induce genotype-specific necrosis characteristics in tomato leaflets in the same pattern as that of the TA pair, but they differ as much as 1000-fold in their relative toxicity [42].

2.4. Chemical and Structural Properties of Analogs of SAMs

In addition to fumonisins and AAL-toxins, several fungal secondary metabolites have also been identified as structural analogs of sphinganine and CerS inhibitors (summarized in Figure 3 and Table 1). These metabolites include myriocins, sphingofungins, viridiofungins, 2-amino-14,16-dimethyl-octadecan-3-ol (2-AOD-3-ol), and a new C17-SAM identified from mussels contaminated by marine fungi including *Aspergillus, Fusarium,* and *Trichoderma. Australifungin*, a structurally unrelated mycotoxin produced by *Sporormiella australis,* was also shown to inhibit sphingolipid synthesis in plants, similar to those of SAMs.

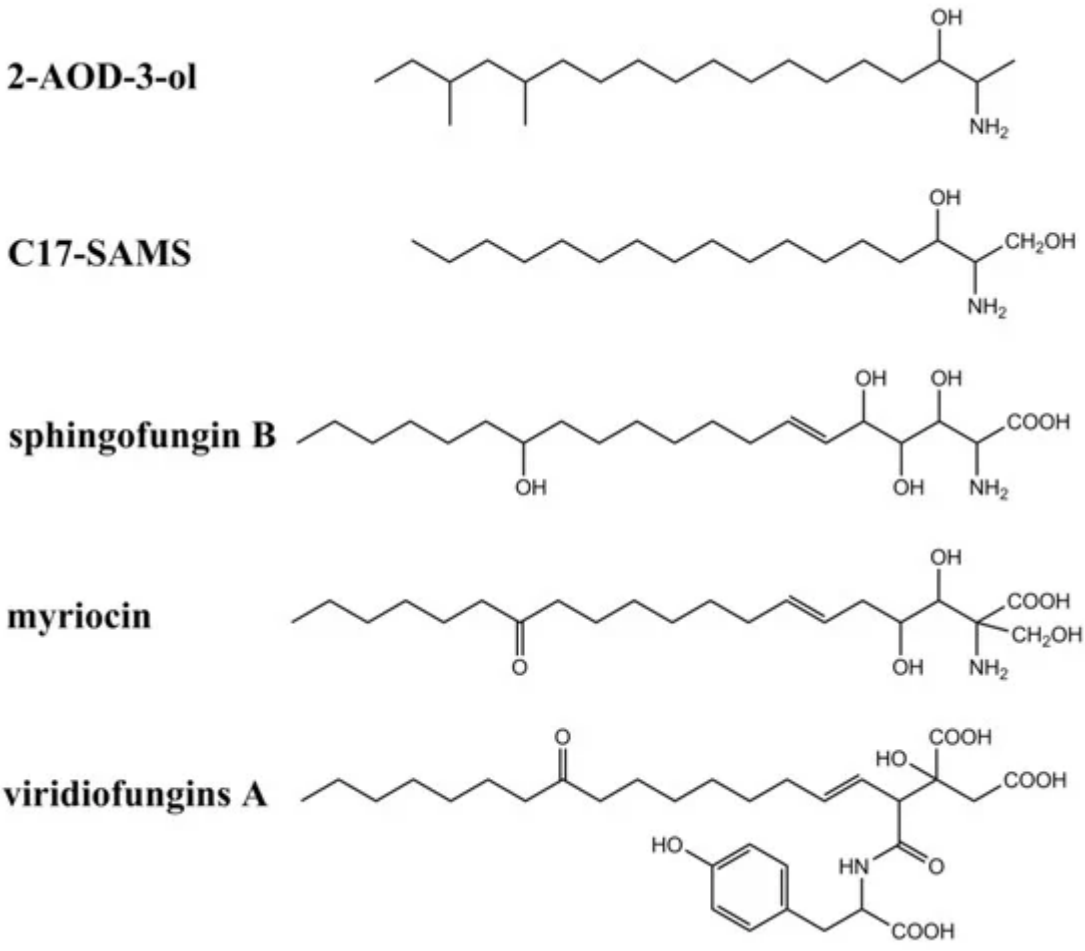


Figure 3. Chemical structures of other sphinganine-analog metabolites.

Table 1. Analogs of sphinganine-analog mycotoxins (SAMs), their fungal producer(s), and their activities.

Analog of SAMs		Fungi/Origin	Activities	Scopus Citation (Review)	Reference
Myriocins (thermozymocidin, ISP-I)		*Myriococcum albomyces* *Melanconis flavovirens* *Isaria sinclairii*	Antifungal activity Inhibitor of serine palmitoyltransferase (SPT) Immunosuppressive activity Protective effect on hepatotoxicity Relieve fumonisin B_1 (FB_1)-induced toxicity and cell death Multi-pharmacological function on human	421(34)	[46][47][48][49] [50][51][52][53]
Sphingofungins	E/F	*Paecilomyces variotii*	Inhibitor of SPT Antifungal activity	65(15)	[54][55][56][57] [58]
	A/B/C/D/I	*Asp. fumigatus*			
	G/H	*Asp. penicilliodes*			
Viridiofungins	A/B/C	*Trichoderma viride Pers*	Inhibitors of SPT and squalene synthase Antifungal but lack antibacterial activity	21(5)	[59][60][61]
		Tri. harzianum			
Australifungin		*Sporormiella australis*	Inhibitors of sphinganine-N acyl transferase Antifungal activity, phytotoxicity	26(7)	[62][63]
2-AOD-3-ol		*F. avenaceum*	Animal cell toxicity as fumonisin B	5	[64]
C17-sphinganine analog mycotoxin		*Contaminated mussels*	Blocking skeletal muscle contraction	1	[65]

Myriocins, sphingofungins, and viridiofungins inhibit serine palmitoyltransferase (SPT), while fumonisins, AAL-toxin, and australifungin inhibit sphinganine-N acyltransferase. Serine palmitoyl transferase, one of the key enzymes in the synthesis of sphingolipids, was also reported to play a positive role in PCD regulation. The increase of SPT activity promoted PCD in plants. In contrast, by inhibiting SPT activity, the excessive accumulation of sphingosine can be alleviated, leading to reduced PCD [43]. Therefore, myriocin are usually used as a SPT inhibitor to pretreat *Arabidopsis thaliana* and tomato plants to induce their resistance to FB_1 and AAL-toxin, respectively [44][45].

3. Relationships between SAMs' Structure and Biological Activities

The biological effects of SAMs, such as their toxicity, are similar among different SMAs. Many SAMs have a similar spectrum of susceptible plant species [34]. Tomato tissues and cells are similarly sensitive to AAL-toxins and to FB_1 and FB_2 toxins. In some other plants, AAL-toxins can cause necrotic cell death, similar to that of fumonisins [66]. For animal tissue cultures, the TA toxins can induce cytotoxicity in both rat liver and dog kidney cells as FB_1 toxin [67] [68]. Besides, AAL-toxin and *F. verticillioides* could also inhibit larval growth and reduced pupal weights of tobacco budworrn *Heliothis virescens* [69]. Such similarities have been attributed to the structural similarities between the SAMs and sphinganine. However, there are differences among SAMs in their biological effects and those differences are related to their structural differences. Below, we summarize the main findings in this area.

The amino functional group of SAMs is essential for their toxic activity. The peracetylated derivatives of AAL-toxins and FB_1 are biologically inactive or have significantly reduced toxicity in both the plant bioassay and the animal tissue culture systems [66][70][71]. These results were consistent with initial reports on these toxins showing that blocking the free primary amines of AAL-toxins by specific reagents could abolish the biological activities of these toxins in plants [72]. In an in vitro test of rat primary hepatocytes, it was noted that the N-acetyl analogue of FB_1, FA_1, also showed CerS inhibition [68]. Later, FA was found to spontaneously undergo isomerization, rearranging its O-acetylation group to form different analogs. The impact of these rearrangement products on inhibition of CerS in rat liver slices also supported the important role of a primary amino for both CerS inhibition and toxicity [73]. Derivatization of the amino group with fluorogenic reagents also makes the FBs' detection possible by the high-performance liquid chromatography (HPLC) assay [74]. FBs can bind covalently to proteins by reacting with amino groups in abiogenic conversions, which may increase the toxicity of those conversion products [75]. Similarly, the terminal amino group of FB_1 can conjugate to bovine serum albumin (BSA) and work as an immunogen to produce monoclonal antibodies for enzyme-linked immunosorbent assay (ELISA) detection [76]. Amino group of fumonisins can also work as an electron donor and react with the electrophilic carbon within the isothiocyanate (ITC) group. Consequently, FBs can be degraded by fumigation treatment with ITC-containing compounds [77].

The hydrolysis product of FB_1 (HFB_1) was shown as less toxic than both FB_1 and TA to plants [78]. Neither HFB_1 nor the yeast sphingolipids (completely acetylated) contain PTCA. While both had adverse effects on duckweed growth, they showed lower phytotoxicity than TA and FB_1 that contained one and two PTCA, respectively [79]. In contrast, the hydrolysis products of AAL-toxins largely maintain the toxicities of their parental compounds to the susceptible tomato lines [66]. These results indicate that PTCA is important to phytotoxicity of FBs and there is specificity of interaction between AAL-toxins and tomatoes.

Different from those in plants, an in vitro test using primary hepatocytes of rat showed that the HFBs had greater cytotoxicity than FBs. However, the HFBs could not initiate cancer development due to the lack of PTCA moiety, which was proposed to play an active role in the fumonisins absorption from the gut [70]. In the pregnant LM/Bc mouse model, HFB_1 did not cause neural tube defects. In contrast, 10 mg of FB_1/kg body weight of mice disrupted maternal sphingolipid metabolism, caused hepatic apoptosis in the female mice, increased fetus mortality, and reduced fetus weight [80]. In the SAMs-sensitive pig model, HFB_1 was shown to have limited intestinal or hepatic toxicity but only slightly disrupted sphingolipids metabolism [81]. The toxic effects of FB_1 and HFB_1 exposure on intestinal barrier function and immunity in a pig intestinal porcine epithelial cells and porcine peripheral blood

mononuclear cells co-culture model was also investigated. FB_1 aggravated lipopolysaccharide (LPS)/deoxynivalenol (DON)-induced intestinal inflammation, while HFB_1 showed less toxicity to the immune system [82]. In addition, when HFB_1 and HFB_2 were acylated by CerS, the N-acyl-metabolites were toxic in vitro to the human colonic cell line and in vivo to the intraperitoneal rat tissues [83].

Fumonisins are capable of binding to polysaccharides and proteins via their two PTCA side chains in thermal-treated food and form fumonisin artifacts [84]. The activities of SAMs vary depending on where hydroxylation occurs along the carbon backbone. For example, FB_2 had a greater cytotoxic effect than FB_3 and FB_1 in primary rat hepatocytes [70]. However, different from most other side groups, the C-1 terminal methyl group, which differed between FC and AAL-toxin from other fumonisins, seemed not required for the biological activity in SAMs.

Similar symptoms but less phytotoxicities of SAMs were observed when long-chain sphingoid bases or simple sphingolipids were applied to duckweed, which indicated that the phytotoxicity of SAMs might be resulted from the accumulation of phytotoxic sphingolipid intermediates [71][85]. This result was consistent with the induction of PCD through ceramide-based signaling pathways (described below).

Although AAL-toxins and fumonisins are structurally related chemicals with similar phytotoxicity, the latter are 10 times less efficient. AAL-toxins have been considered to serve as a herbicide at a very low dosage against a wide variety of broadleaf weeds (e.g., jimsonweed, prickly sida, and black nightshade). However, monocotyledonous crops (e.g., maize and wheat) are tolerant to AAL-toxins [24][86][87]. Until 2013, the mode of action through CerS inhibition was not among the 21 molecular target sites of the commonly used herbicides. Using AAL-toxin as a lead compound has the potential to develop novel and safe bio-herbicide, which has phytotoxicity but reduced or no mammalian toxicity [88][89].

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