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ARTICLE

Mycotoxin producers in the *Aspergillus* genus: an update

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ABSTRACT Mycotoxins are secondary metabolites of fungi. Species assigned to the *Aspergillus* genus produce a wide range of mycotoxins which can contaminate several agricultural products, and cause various human and animal diseases. In this review, we wish to give an overview of producers of *Aspergillus* mycotoxins in view of recent scientific data.
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KEY WORDS

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Introduction

Mycotoxins are fungal secondary metabolites which are harmful to animals and humans. *Aspergillus*, *Fusarium* and *Penicillium* are the most common mycotoxin-producing genera. Mycotoxins produced by Aspergilli have a serious impact on the health of humans and animals. The main mycotoxins produced by *Aspergillus* species include aflatoxins, sterigmatocystin, ochratoxins, fumonisins, patulin, gliotoxin and cyclopiazonic acid. The *Aspergillus* genus comprises 344 species (Samson et al. 2014), and the chemodiversity among these species is very high; according to Frisvad (2015), the average number of exometabolites is 5.77 per species in this genus, which is higher than that observed in *Penicillium* (3.77) or *Talaromyces* species (3.58). The same mycotoxin can be produced by unrelated species (*e.g.*, fumonisins by *Fusarium, Aspergillus, Tolypocladium* and *Bipolaris* species), and Frisvad and Larsen (2015) suggested that this phenomenon could be explained by either lateral or horizontal transfer of gene clusters between unrelated species. On the other hand, one species (or even a single isolate) can produce a variety of secondary metabolites (*e.g.*, *A. niger* produces both fumonisins and ochratoxins; Frisvad et al. 2011). In this respect, the so-called OSMAC (one strain many compounds) approach should be mentioned. Bode et al. (2002) clarified that using different media or altering other growth parameters (temperature, water activity, etc.) various exometabolites could be identified in *A. westerdijkiae* and other fungi. This observation was confirmed by van der Molen et al. (2013). However, the isolates of any examined fungal species seem to be chemoconsistent (Frisvad 2015), although even a single point mutation in a gene of the gene cluster responsible for the production of an exometabolite can lead to the loss of production of the compound (Susca et al. 2014).

In this review, we wish to give an overview of the *Aspergillus* species able to produce the most important mycotoxins in view of recent scientific data.

Aflatoxins

Aflatoxins are decaketide derived mycotoxins produced predominantly by certain strains whithin species of the *Aspergillus* genus (Fig. 1). They were first identified from peanut samples in 1961 as responsible for Turkey-X disease (Blout 1961; van der Zijden et al. 1962). The main causative agent was *A. flavus* (Fig. 2). Aflatoxin contamination of foods and feeds causes serious economic and health problem worldwide. Aflatoxin B_1 exhibits hepatocarcinogenic and hepatotoxic properties, it is the most potent naturally occurring carcinogen (Squire 1981; IARC 2012; Fig. 1a), and is usually the major aflatoxin produced by toxigenic strains. Other naturally occurring types of aflatoxins include aflatoxins B_2, G_1 and G_2 (Baranyi et al. 2013; Fig. 1b-d). The International Agency for Research on Cancer (IARC) assigned all aflatoxins to group 1 (carcinogenic to humans; IARC 2012). Aflatoxin M_1, a hydroxylated metabolite is also found primarily in animal tissues and fluids (milk and urine) as a metabolic product of aflatoxin B_1 (Varga et al. 2009; Fig. 1e).

Recent data indicate that aflatoxins are produced by at least 20 species assigned to three sections of the genus

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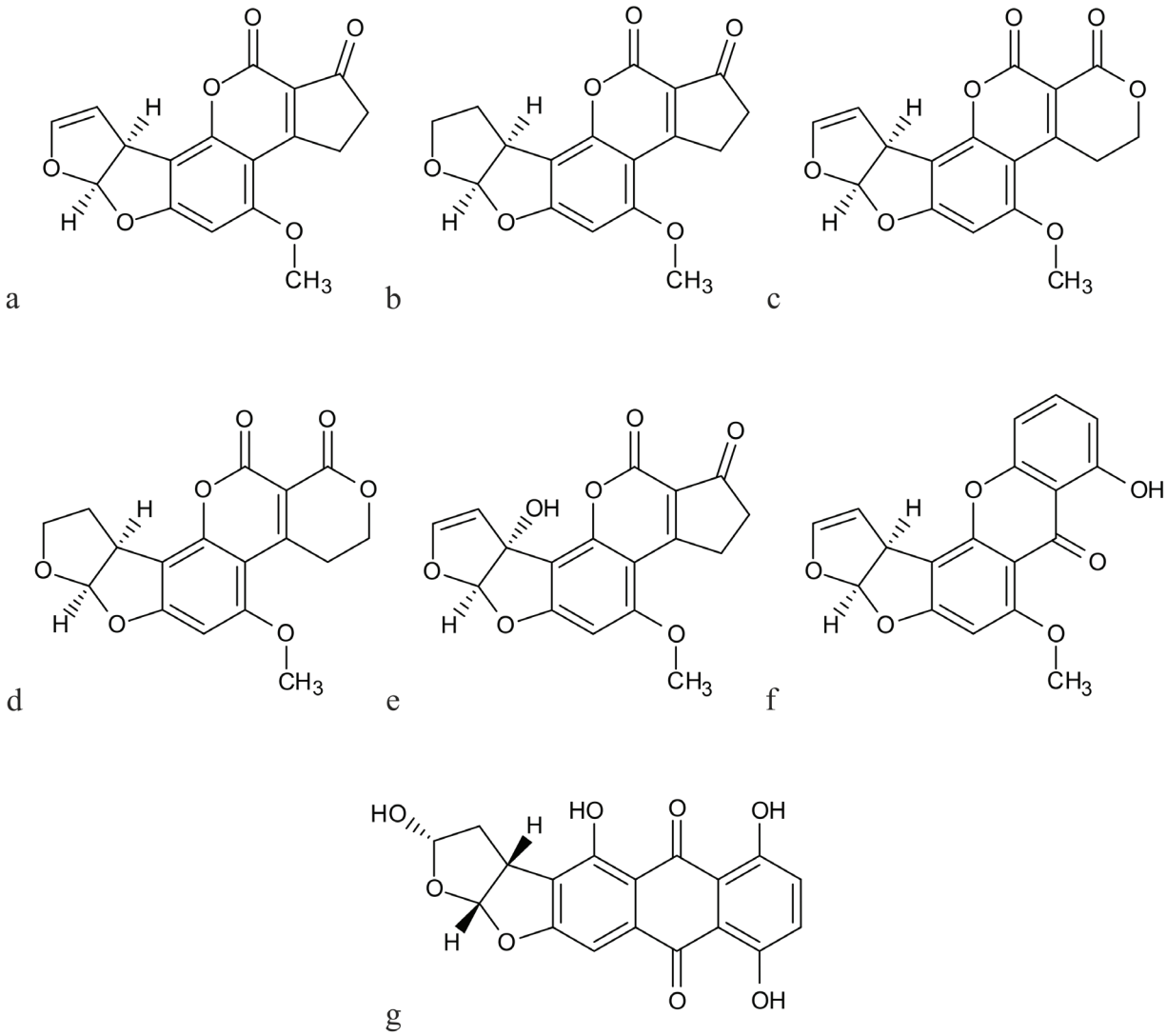

Figure 1. Structures of aflatoxins and related compounds. Aflatoxin B_1 (a), aflatoxin B_2 (b) aflatoxin G_1 (c), aflatoxin G_2 (d), aflatoxin M_1 (e), sterigmatocystin (f), dothistromin (g).

Aspergillus: sections *Flavi*, *Nidulantes* and *Ochraceorosei* (Varga et al. 2009; Fig. 3; Table 1) including the newly described *A. pseudonomius*, *A. pseudocaelatus* (Varga et al. 2011a), *A. togoensis* (Rank et al. 2011), *A. mottae, A. sergii, A. transmontanensis* (Soares et al. 2012) and *A. novoparasiticus* (Gonçalves et al. 2012). Recently, aflatoxins have also been identified in *Aschersonia coffeae* and *As. marganita* (Kornsakulkarn et al. 2012, 2013). Some aflatoxin producing species have been described as *Emericella* species (one of the sexual stages of the *Aspergillus* genus). However, according to the Amsterdam declaration on fungal nomenclature, only one name can be applied for a fungus (Hawksworth et al. 2011). Under the current rules of the International Code of Nomenclature for algae, fungi, and plants (so-called Melbourne Code; Hawksworth 2011; McNeill et al. 2012) and the discussions held by the International Commission on *Penillium* and *Aspergillus* (ICPA; http://www.aspergilluspenicillium.org/index.php/single-name-nomenclature/88-single-names/105-aspergillus-options), the *Aspergillus* name was chosen as the valid one for these species (Samson et al. 2014). Only B-type aflatoxins are produced by most species, although species related to *A. parasiticus* and *A. nomius* in section Flavi are usually able to produce G-type aflatoxins too (Fig. 3; Table 1). Although, aflatoxin production was claimed for several other species and fungal genera (and actually even for bacteria), none of these observations could have been confirmed (Varga et al. 2009). Recently, a *Fusarium kyushuense* isolate was also claimed to produce aflatoxins, but this report also could not be

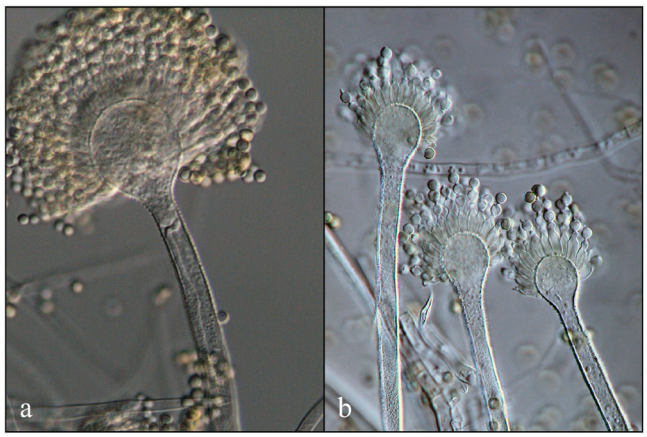

Figure 2. Bi- and monoseriate heads of *A. flavus*.

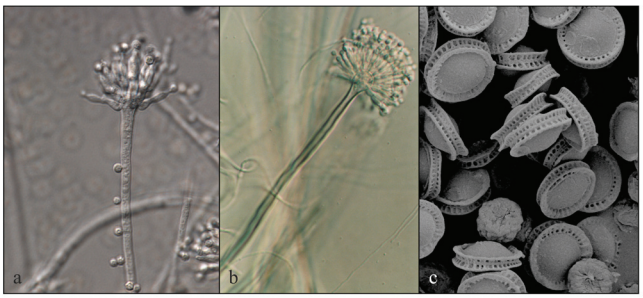

Figure 4. Conidial heads of the sterigmatocystin producers *A. versicolor* (a), *A. inflatus* (b), and ascospores of *A. nidulans* (c).

confirmed (Schmidt-Heydt et al. 2009; Varga et al. 2009). In *Aspergillus* section *Usti*, *A. ustus* produces versicolorins, *A. heterothallicus* is a sterigmatocystin-producer, while recently *A. pseudoustus* was described which was found to produce norsolonic acid, averufin and versicolorin C, indicating that this species also carries at least part of the aflatoxin biosynthetic gene cluster (Samson et al. 2011b).

Sterigmatocystin

Sterigmatocystin is a penultimate precursor of aflatoxin biosynthesis and also a toxic and carcinogenic substance produced by many *Aspergillus* species belonging mainly to sections *Versicolores, Usti, Aenei, Ochraceorosei, Cremei* and *Nidulantes* of the *Aspergillus* genus (Varga et al. 2010a; Rank et al. 2011; Fig. 1f). It is assinged to group 2b by IARC (possibly carcinogenic to humans; IARC 2012). While aflatoxin producing species assigned to section *Flavi* do not accumulate

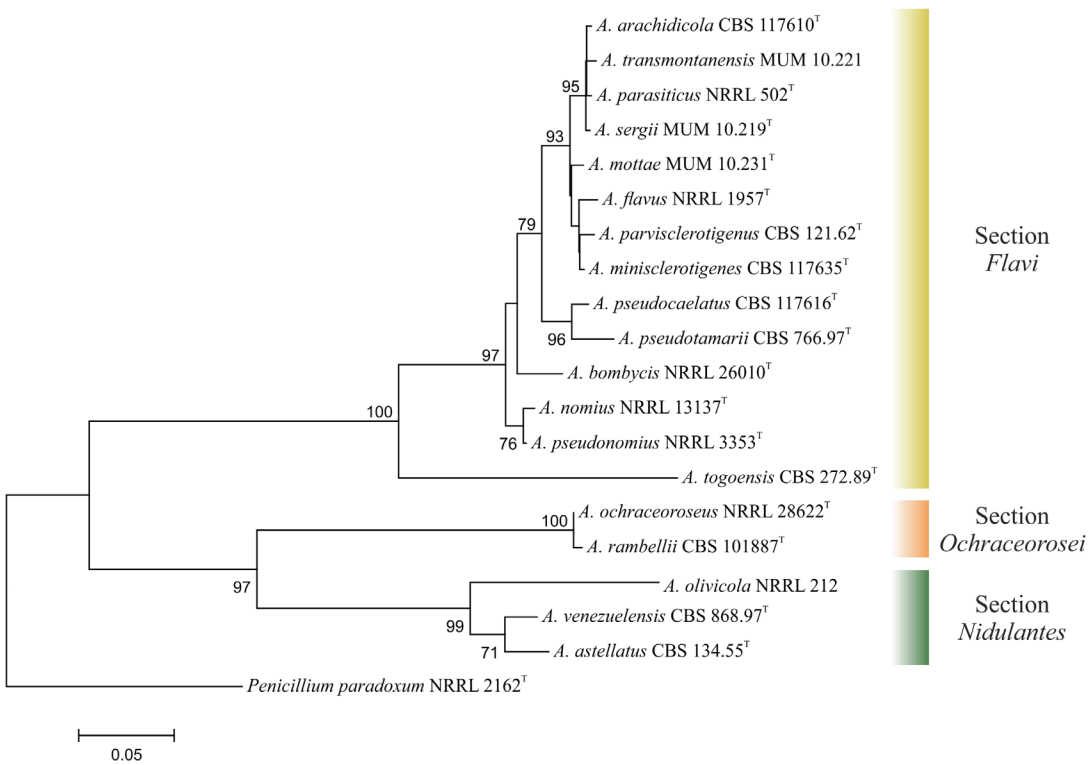

Figure 3. Phylogenetic tree of aflatoxin producing species based on neighbor joining analysis of partial calmodulin sequence data.

Table 1. *Aspergillus* species able to produce aflatoxins and other mycotoxins (modified after Baranyi et al. 2013).

Section	Species	Type of aflatoxins produced	Other mycotoxins
Flavi	*A. arachidicola*	Aflatoxins B_1, B_2 & G_1, G_2	kojic acid, aspergillic acid
	A. bombycis	Aflatoxins B_1, B_2 & G_1, G_2	kojic acid, aspergillic acid
	A. flavus	Aflatoxins B_1 & B_2	cyclopiazonic acid, kojic acid, aspergillic acid
	A. minisclerotigenes	Aflatoxins B_1, B_2 & G_1, G_2	cyclopiazonic acid, kojic acid, aspergillic acid
	A. nomius	Aflatoxins B_1, B_2 & G_1, G_2	kojic acid, aspergillic acid, tenuazonic acid
	A. novoparasiticus	Aflatoxins B_1, B_2 & G_1, G_2	kojic acid
	A. parasiticus	Aflatoxins B_1, B_2 & G_1, G_2	kojic acid, aspergillic acid
	A. parvisclerotigenus	Aflatoxins B_1, B_2 & G_1, G_2	cyclopiazonic acid, kojic acid
	A. pseudocaelatus	Aflatoxins B_1, B_2 & G_1, G_2	cyclopiazonic acid, kojic acid
	A. pseudonomius	Aflatoxins B_1, B_2 & G_1, G_2*	kojic acid
	A. pseudotamarii	Aflatoxin B_1	cyclopiazonic acid, kojic acid
	A. togoensis	Aflatoxin B_1	sterigmatocystin
	A. transmontanensis	Aflatoxins B_1, B_2 & G_1, G_2	aspergillic acid
	A. mottae	Aflatoxins B_1, B_2 & G_1, G_2	cyclopiazonic acid, aspergillic acid
	A. sergii	Aflatoxins B_1, B_2 & G_1, G_2	cyclopiazonic acid, aspergillic acid
Ochraceo-rosei	*A. ochraceoroseus*	Aflatoxins B_1 & B_2	sterigmatocystin
	A. rambellii	Aflatoxins B_1 & B_2	sterigmatocystin
Nidulantes	*A. astellatus (= Emericella astellata)*	Aflatoxin B_1	sterigmatocystin, terrein
	A. olivicola (= Emericella olivicola)	Aflatoxin B_1	sterigmatocystin, terrein
	A. venezuelensis (= Emericella venezuelensis)	Aflatoxin B_1	sterigmatocystin, terrein

*Although the type strain of *A. pseudonomius* produces only B-type aflatoxins (Varga et al. 2011a), other isolates came from Brazil nuts (Massi et al. 2014) and from maize (Baranyi et al. 2015) are able to produce G-type aflatoxins too.

sterigmatocystin, aflatoxin producing species belonging to sections *Ochraceorosei* and *Nidulantes* produce these compounds simultaneously (Rank et al. 2011; Samson et al. 2014). Members of *Aspergillus* section *Flavi*, which includes the major aflatoxin producers, efficiently convert sterigmatocystin through 3-methoxysterigmatocystin to aflatoxins (Rank et al. 2011; Fig. 4). An exception in this section is *A. togoensis*, which is able to produce both aflatoxins and sterigmatocystin (Wicklow et al. 1989; Rank et al. 2011). Sterigmatocystin was also detected in two other aflatoxin producers, *Aschersonia coffeae* and *Aschersonia marginata* (Kornsakulkarn et al. 2012, 2013), while glycosylated precursors of the sterigmatocystin biosynthesis were identified in *Staphylotrichum boninense* (Tatsuda et al. 2015). Sterigmatocystin production was also detected in the phylogenetically unrelated genera *Aschersonia, Aspergillus, Bipolaris, Botryotrichum, Chaetomium, Humicola, Moelleriella* and *Monicillium* (Rank et al. 2011). Sterigmatocystin production was also confirmed in *Podospora anserina* (Matasyoh et al. 2011), and the gene cluster responsible for the biosynthesis for sterigmatocystin was also identified (Slot and Rokas 2011). The authors suggested that horizontal gene transfer of the sterigmatocystin gene cluster took place beween the distantly related *Aspergillus nidulans* and *P. anserina*. Apart from sterigmatocystin, the immediate precursor of aflatoxin, o-methylsterigmatocystin was also found in *Chaetomium cellulolyticum, Chaetomium longicolleum, Chaetomium malaysiense* and *Chaetomium virescens* (Rank et al. 2011). Besides, the ex-type strain of the newly

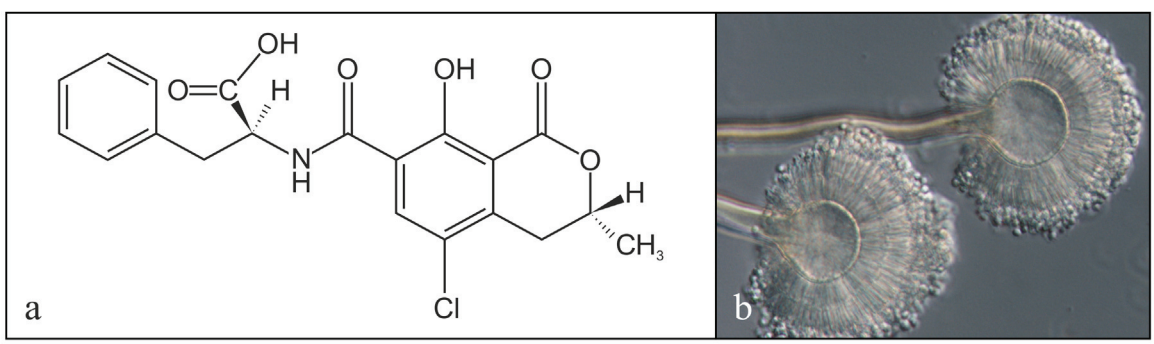

Figure 5. Structure of ochratoxin A (a), and conidial heads of *A. ochraceus* (b).

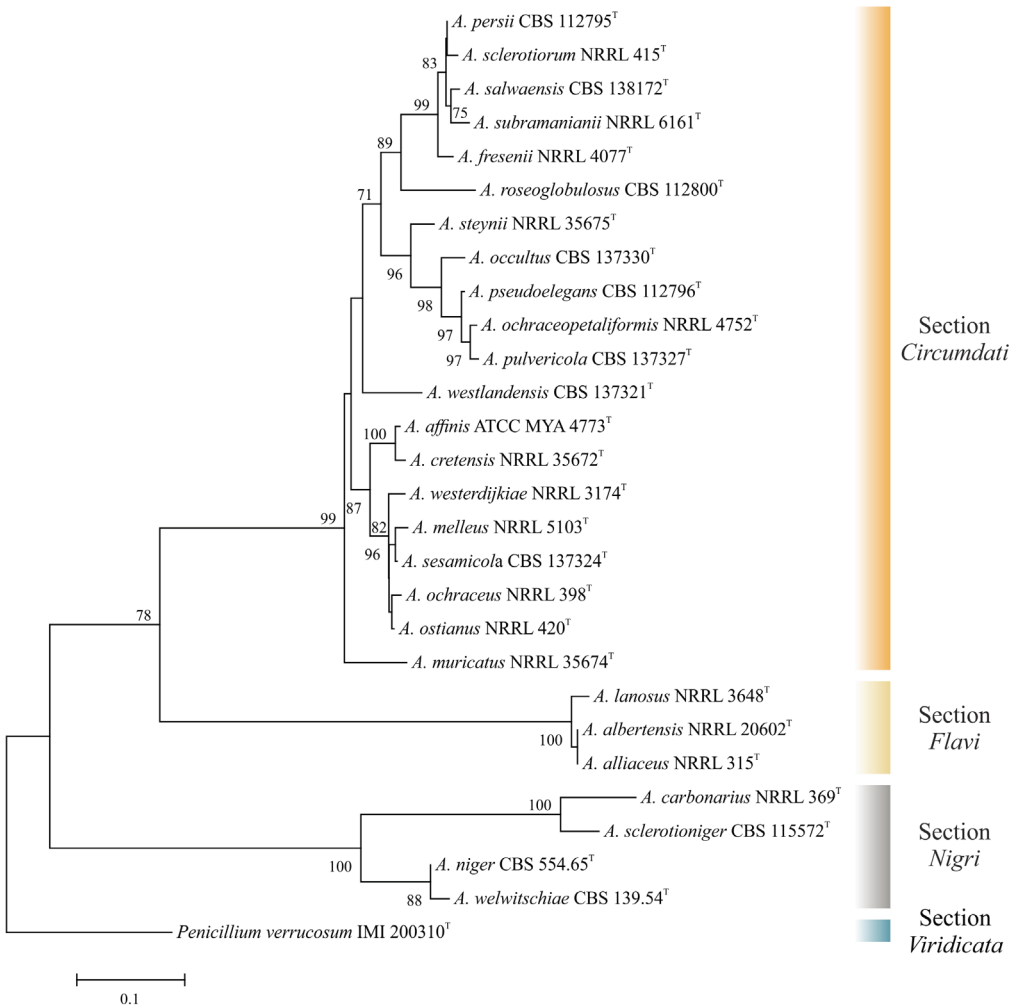

Figure 6. Phylogenetic tree of ochratoxin producing species based on neighbor joining analysis of partial calmodulin gene sequences.

described species *A. bertholletius* was also found to produce o-methylsterigmatocystin, indicating that the genome of this species also carries the aflatoxin biosynthetic gene cluster (Taniwaki et al. 2012).

The major source of sterigmatocystin in foods (cheese, cereals) and indoor environments is *Aspergillus versicolor* and its relatives (Samson et al. 2010; Jurjevi et al. 2012, 2013). On water-saturated materials, *A. versicolor* produces 5-methoxysterigmatocystin and sterigmatocystin in quantities up to 7 and 20 μg/cm^2, respectively (up to 1% of biomass; Nielsen 2003), whereas they are not produced at lower water activities ($a_w < 0.9$).

Another related compound, dothistromin is produced by *Dothistroma septosporum*, an important forest pathogen causing red band needle blight disease of pine trees (Bradshaw 2004; Fig. 1g). Dothistromin is similar in structure to versicolorin B, a precursor of aflatoxin biosynthesis. Full genome sequencing of *D. septosporum* made it possible to identify the genes taking part in the biosynthesis of this compound (Bradshaw et al. 2013). Interestingly, in contrast with other secondary metabolite biosynthesis genes which form gene clusters, most of the genes taking part in dothistromin biosynthesis were found to be spread over six separate regions of the pathogen (Bradshaw et al. 2013; Fig. 1).

Ochratoxins

Ochratoxins are cyclic pentaketids, dihydroisocoumarin derivatives linked to an L-phenylalanine moiety (Fig. 5). Ochratoxins were proved to exhibit nephrotoxic, immunosuppressive, teratogenic and carcinogenic properties (Varga et al. 2001a), and implicated in the etiology of animal and human diseases including Danish porcine nephropathy, Balkan endemic nephropathy, a syndrome characterized by contracted

Table 2. Ochratoxin and penicillic acid producing abilities of species assigned to *Aspergillus* section *Circumdati* (economically important ochratoxin producers in bold; modified after Visagie et al. 2014).

Species	Ochratoxins	Penicillic acid
A. affinis	+	+
A. auricomus	-	+
A. bridgeri	-	+
A. cretensis	+	+
A. elegans	-	-
A. fresenii (= A. sulphureus)	+	-/+
A. insulicola	-	+
A. melleus	-	+
A. muricatus	+	+
A. neobridgeri	-	+
A. occultus	+	+
A. ochraceopetaliformis (= A. flocculosus)	-/+	+
A. ochraceus	+/-	+
A. ostianus	-/+	+
A. pallidofulvus	-	+
A. persii	-/+	+
A. pseudoelegans	+	-
A. robustus	-	-
A. roseoglobulosus	+	+
A. salwaensis	+/-	+
A. sclerotiorum	+/-	+
A. sesamicola	+/-	-
A. steynii	+	-
A. subramanianii	+/-	+
A. westerdijkiae	+	+
A. westlandense	+/-	+

Abbreviations: +, most isolates produce the metabolite; +/-: the metabolite is produced in low quantities; -/+: only some isolates produce the metabolite; -: the isolates do not produce the given metabolite.

Table 3. Fumonisin producing fungi identified so far (modified after Rheeder et al. 2002).

Genus	Section	Species
Fusarium	*Liseola*	*F. verticillioides*
	Liseola	*F. proliferatum*
	Liseola	*F. fujikuroi*
	Liseola	*F. sacchari*
	Liseola	*F. subglutinans (?)*
	Liseola	*F. anthophilum*
	Liseola	*F. globosum*
	Liseola	*F. thapsinum*
	Liseola	*F. bulbicola*
	Dlaminia	*F. nygamai*
	Dlaminia	*F. dlamini*
	Dlaminia	*F. napiforme (?)*
	Dlaminia	*F. pseudonygamai*
	Dlaminia	*F. andiyazi*
	Elegans	*F. oxysporum*
	Arthrosporiella	*F. polyphialidicum*
Aspergillus	*Nigri*	*A. niger*
	Nigri	*A. welwitschiae*
Tolypocladium		*T. inflatum*
		T. cylindrosporum
		T. geodes
Bipolaris		*B. maydis (= Cochliobolus heterostrophus)*
		B. sorokiana (= Cochliobolus sativus)

kidneys with tubular degeneration, interstitial fibrosis and hyalinization of glomeruli chronic karyomegalic interstitial nephropathy and chronic interstitial nephropathy in Tunisia, and urothelial tumors (Varga et al. 2001b). Ochratoxin A is assinged to group 2b by IARC (possibly carcinogenic to humans; IARC 2012). Ochratoxins occur in various food products including cereals, spices, coffee, cocoa, grape-derived products and many others (Varga et al. 2001a). The most potent ochratoxin derivative, ochratoxin A (OTA) was first discovered in 1965 in an *Aspergillus ochraceus* isolate (van der Merwe et al. 1965). Since then, several *Aspergillus* and *Penicillium* species have been described as producers of this mycotoxin (Fig. 6). Among Penicillia, *P. verrucosum* and *P. nordicum* are able to produce ochratoxins (Frisvad and Larsen 2015). Regarding Aspergilli, species assigned to sections *Circumdati, Nigri* and *Flavi* are able to produce ochratoxins (Frisvad et al. 2004; Visagie et al. 2014; Table 2, Fig. 4). Among black Aspergilli, *A. niger, A. welwitschiae, A. carbonarius* and *A. sclerotioniger* are able to produce ochratoxins (Samson et al. 2007a). Interestingly, none of the uniseriate species of section *Nigri* are able to produce OTA (Varga et al. 2011b). Regarding section *Flavi*, *A. alliaceus, A. albertensis* and *A. lanosus* have been reported as ochratoxin producers (Varga et al. 2011a). Although, *A. ochraceus* was considered previously as the most important OTA producer in view of food safety, recent investigations clarified that other species (*e.g.*, *A. westerdijkiae* and *A. steynii* on coffee, *A. niger* and *A. carbonarius* on grapes, *A. welwitschiae* on onions, *P. verrucosum* on cereals; Noonim et al. 2007; Varga et al. 2012, unpublished results).

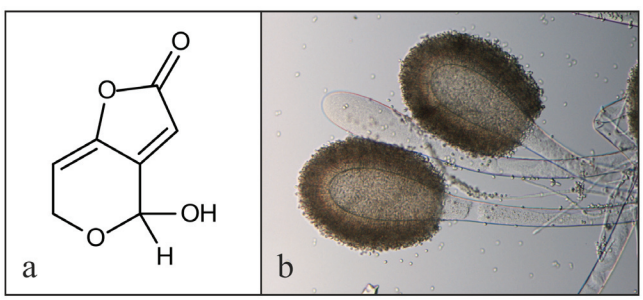

Figure 7. Structure of patulin (a), and conidial heads of an *A. clavatus* isolate (b).

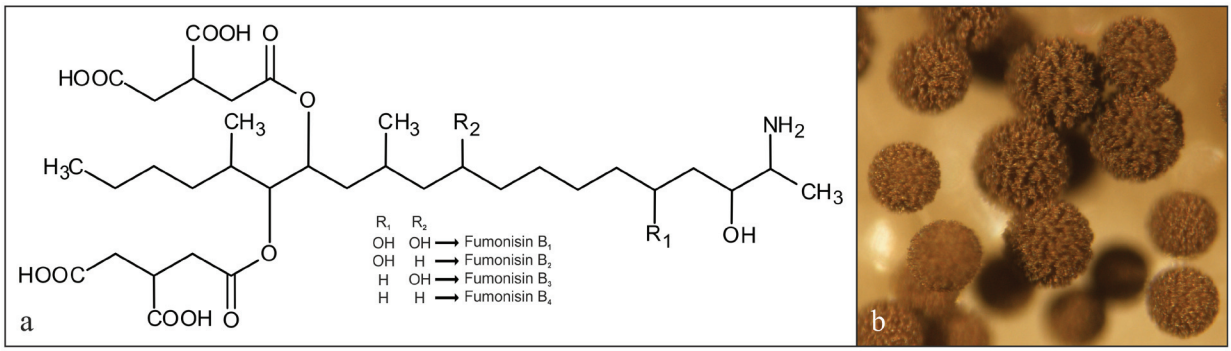

Figure 8. Structural formulae of fumonisins (a), and conidial heads of an *A. niger* isolate (b).

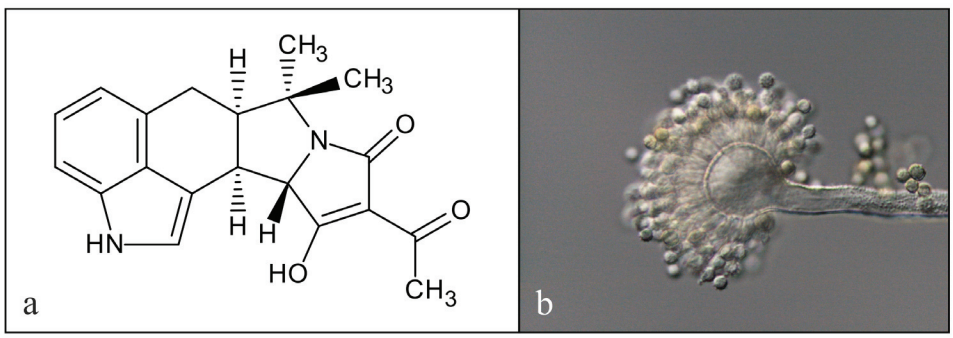

Figure 9. Structure of cyclopiazonic acid (a), and conidial head of *A. minisclerotigenes* (b).

Patulin

Patulin is a tetraketide lactone which is produced by a variety of molds, in particular, *Aspergillus, Penicillium* and *Byssochlamys* species (Puel et al. 2010; Fig. 7). Patulin was originally used as an antibiotic against Gram-positive and Gram-negative bacteria causing common cold, but after the first trials, it is no longer used for that purpose. The main producer of patulin is *P. expansum*, which contaminates mainly apple and apple products, but also other fruits like cherry, blueberry, plums, bananas, strawberry and grapes. Other Penicillia are also able to produce this compound including *P. carneum*, *P. clavigerum*, *P. concentricum*, *P. coprobium*, *P. dipodomyicola*, *P. glandicola*, *P. gladioli*, *P. griseofulvum*, *P. marinum*, *P. paneum*, *P. roqueforti*, *P. sclerotigenum*, *P. vulpinum*, *Byssochlamys nivea* and *Paecilomyces saturatus* (Frisvad et al. 2004; Puel et al. 2010). However, patulin can also contaminate cereal products, which is suspected to be caused by Aspergilli. In this genus, the producers belong to section *Clavati*: *A. clavatus, A. giganteus* and *A. longivesica* (Varga et al. 2007c). The claims that *A. terreus* (Draughon and Ayres 1980), *A. candidus, A. amstelodami, A. echinulatus, A. fumigatus, A. parasiticus, A. repens, A. variecolor* and *A. versicolor* (Steiman et al. 1989) also produces patulin could not be confirmed (Varga et al. 2007b; Samson et al. 2011a; Frisvad and Nielsen 2015).

Fumonisins

Fumonisins are nonaketide derived mycotoxins produced mainly by *Fusarium* species (Fig. 8). They were discovered in 1988 in a *F. verticillioides* isolate (Gelderblom et al. 1988), and were show to be able to cause various disorders including lung oedema in pigs, leucoencephalomalacia (hole in the head disease) in horses, hepatocarcinoma in laboratory animals, and most importantly, esophaegal cacer in humans (Marin et al. 2013). Fumonisins are assinged to group 2b by IARC (possibly carcinogenic to humans; IARC 2012). Later several other Fusaria have been identified as fumonisin producers (Table 3). Recently, a survey of other species revealed that other species belonging to the genera *Aspergillus*, *Bipolaris* and *Tolypocladium* are also able to produce fumonisins (Frisvad

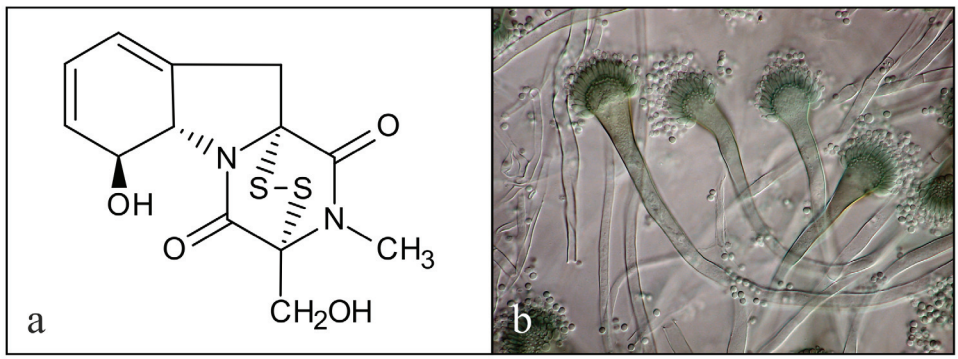

Figure 10. Structure of gliotoxin (a), and conidial heads of an *A. fumigatus* isolate (b).

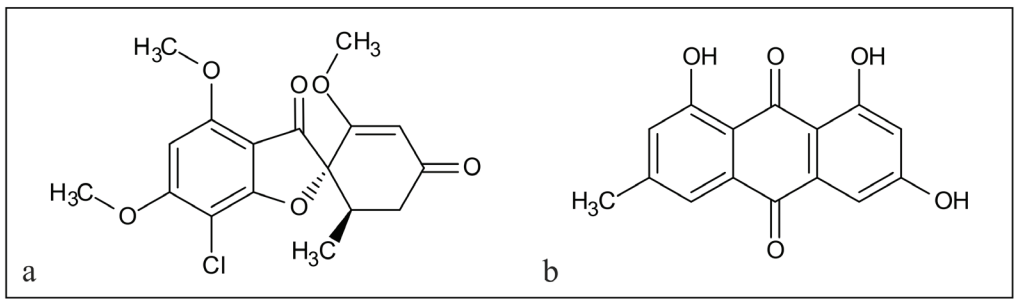

Figure 11. Structures of griseofulvin (a) and emodin (b).

et al. 2007, 2011; Mogensen et al. 2010, 2011; unpublished results). Among Aspergilli, *A. niger* and *A. welwitschiae* (formerly named as *A. awamori*) are fumonisin producers (Samson et al. 2007a; Hong et al. 2013). *A. niger* is frequently detected on grape-derived products (Varga et al. 2010), while *A. welwitschiae* infects onions and *Welwitschia mirabilis* (Varga et al. 2012; unpublished results). *A. fumigatus* was also predicted to produce fumonisins based on genomic studies (Takeda et al. 2014). *A. fumigatus* and *A. lentulus* produce sphingofungins and fumifungin (Larsen et al. 2007), which are structurally related to fumonisins. The host-specific AAL-toxins identified in *Alternaria alternata f. lycopersici* and fumonisins are also structurally related, and have similar mode of action on sphingolipid metabolism (Gilchrist and Grogan 1976; Abbas et al. 1994, 1996). Interestingly, homologs of the fumonisin gene cluster or its flanking regions have also been identified in other fungi have been identified in the genomes of several other fungi including *F. graminearum, Neurospora crassa, Magnaporthe grisea* and *A. nidulans* (Khaldi and Wolfe 2011). The authors suggested that horizontal transfer of the fumonisin biosynthetic gene cluster from an ancestor belonging to the Sordariomycetes resulted in the occurrence of fumonisin biosynthesis in *A. niger*.

Cyclopiazonic acid

Cylopiazonic acid is chemically an indole tetramic acid biosynthetised by a hybrid polyketide synthase-nonribosomal peptide synthetase (PKS-NRPS) enzyme (Fig. 9). It was originally isolated from *P. cyclopium* (Holzapfel 1968). Cyclopiazonic acid is a specific inhibitor of Ca^{2+}-dependent ATPase in the intracellular Ca^{2+} storage sites. The main producers of cyclopiazonic acid are Penicillia (*e.g.*, *P. camembertii, P. chrysogenum, P. commune, P. hirsutum, P. nalgiovense, P. puberulum, P. griseofulvum, P. urticae, P. verrucosum P. viridicatum*; Frisvad et al. 2004). Among Aspergilli, several species in section *Flavi* produce cyclopiazonic acid including *A. flavus, A. minisclerotigenes, A. oryzae, A. parvisclerotigenus, A. pseudocaelatus, A. pseudotamarii, A. tamarii, A. bertholletius* (Varga et al. 2011a; Taniwaki et al. 2012; Table 1), while *A. versicolor* from section *Versicolores*, and *A. lentulus* and *A. fumisynnematus* from the unrelated section *Fumigati* also produce this mycotoxin (Ohmomo et al. 1973; Larsen et al. 2007). Genomic studies could clarify the possible role of horizontal gene transfer or other mechanisms in the occurrence of this mycotoxin in such a diverse, taxonomically unrelated species. Further studies are needed to examine other

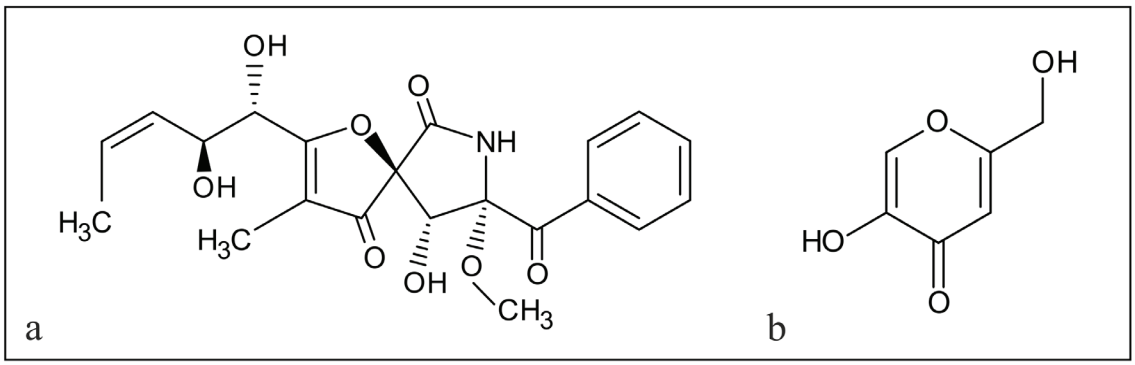

Figure 12. Chemical structures of pseurotin (a) and kojic acid (b).

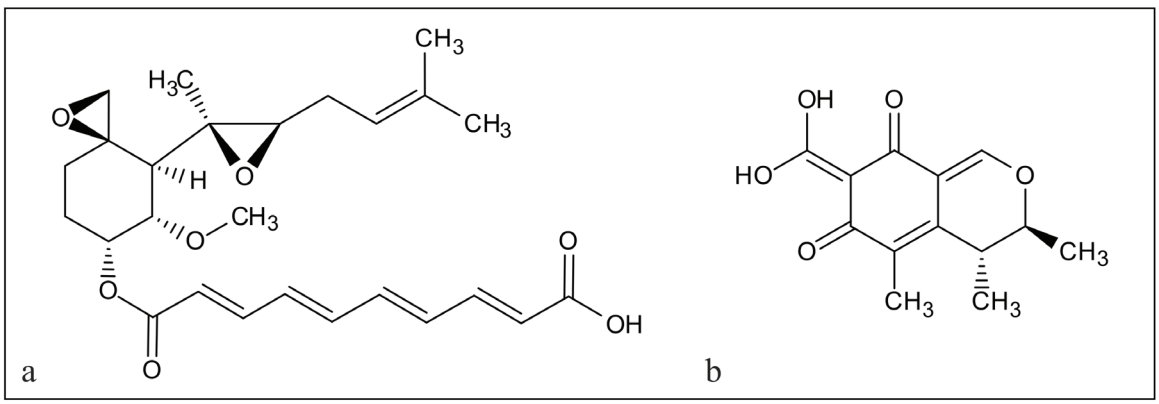

Figure 13. Structures of fumagillin (a) and citrinin (b).

species in section *Versicolores* to clarify if they are also able to produce cyclopiazonic acid.

Gliotoxin

Gliotoxin is a sulfur-containing mycotoxin produced by several fungal species belonging to genera including *Penicillium*, *Gliocladium*, *Thermoascus* and *Aspergillus.* Gliotoxin was originally isolated from *Gliocladium fimbriatum* (Johnson et al. 1943), and it is an epipolythiodioxopiperazine metabolite derived from the amino acid pathway (Fig. 10a). Gliotoxin possesses immunosuppressive properties as it may suppress and cause apoptosis in certain types of cells of the immune system, and also exhibits antibacterial and antiviral properties. It is treated as an important virulence factor in invasive aspergillosis cases caused by *A. fumigatus* (Sugui et al. 2007; Fig. 10b). Regarding Aspergilli, gliotoxin is produced by *A. fumigatus* and related species in section *Fumigati* including *A. denticulatus, A. cejpii* and *A. pseudofischeri* (Samson et al. 2007b). Even though pathogenic Aspergilli including *A. niger, A. flavus* and *A. terreus,* and *A. chevalieri* were suggested to produce gliotoxin, these observations could not be confirmed (Wilkinson and Spilsbury 1965; Lewis et al. 2005; Kupfahl et al. 2008).

Other mycotoxins

Griseofulvin

Griseofulvin is a chlorine-containing pentaketide derivative which was first identified in *P. griseofulvum* in 1939 (Oxford et al. 1939; Fig. 11a). It is used against fungi causing dermatomycoses or onychomycoses as an antibiotic. Apart from several fungal species assigned to the genera *Penicillium*, *Nigrospora, Memnoniella* species (*e.g.*, *P. griseofulvum*, *P. dipodomyicola*, *P. aethiopicum*, *P. persicinum*, *P. sclerotigenum*, *P. coprophilum*, *M. echinata*), some species assigned to *Aspergillus* section *Versicolores* are also able to produce this metabolite including *A. versicolor* and *A. sydowii* (Frisvad and Larsen 2015). Further studies are needed to clarify if the recently described species assigned to this section are able to produce this metabolite.

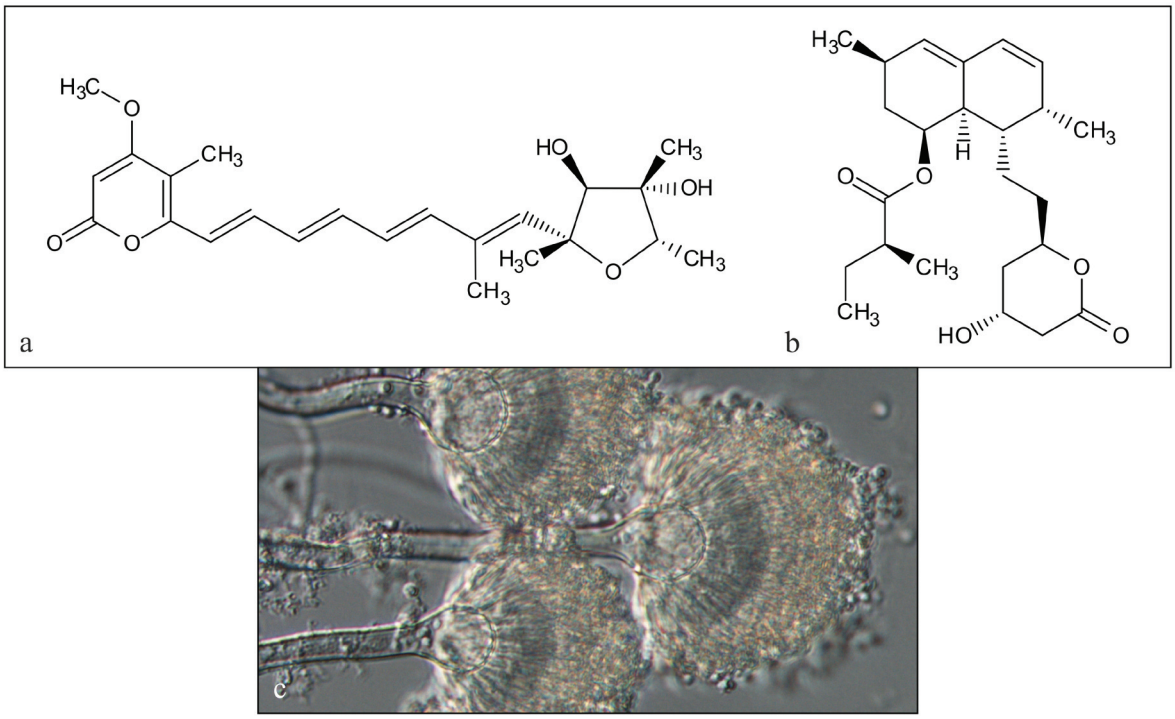

Figure 14. Structures of citreoviridin (a), lovastatin (b), and conidial heads of an *A. terreus* isolate (c).

Emodin

This and other structurally related compounds are anthraquinone derivatives, and have been found in many *Aspergillus* species across the whole genus, but is also common in *Penicillium, Talaromyces* species and in plants (Frisvad and Larsen 2015; Fig. 11b). Emodin has antibacterial, antifungal, antiparasitic and antiviral effects and is also an antioxidant (Izhaki 2002). Regarding the *Aspergillus* genus, emodin was first reported as a mycotoxin from *A. wentii* (section *Cremei*) (Wells et al. 1975). However, later emodin or its derivatives including anthrons, bianthrons, sulochrin, secalonic acid, emericillin or geodin have been identified in several other species assigned to sections *Aspergillus, Cremei, Circumdati, Terrei, Fumigati, Nidulantes* and *Nigri* (Frisvad and Larsen 2015).

Pseurotin

Pseurotin is synthetised by a hybrid PKS-NRPS enzyme in several fungal species. It was originally described in 1976 as a metabolite of *Pseudeurotium ovalis* (Bloch et al. 1976; Fig. 12a). It is a competitive inhibitor of chitin synthase, and suppresses the production of immunoglobulin E (Wenke et al. 1993). Regarding Aspergilli, pseurotin is produced by species assigned to section *Clavati* (*A. clavatus, A. longivesica, A. giganteus, A. cejpii*), section *Fumigati* (*A. fumigatus, A. duricaulis, A. aureolus, A. auratus, A. spinosus*; Samson et al. 2007a) and by *A. nomius* belonging to the unrelated section *Flavi* (Varga et al. 2011a).

Kojic acid

Kojic acid is a pyrone derivative which inhibits tyrosinase, so it is an inhibitor of the formation of pigments in plant and animal tissues, and is used in the food and cosmetic industries to preserve or change colors of substances (Fig. 12b). Kojic acid is mainly produced by species assigned to section *Flavi* (*A. arachidicola, A. bombycis, A. caelatus, A. flavus, A. lanosus, A. nomius, A. oryzae, A. parasiticus, A. parvisclerotigenus, A. pseudocaelatus, A. pseudonomius, A. pseudotamarii, A. sojae, A. tamarii;* Varga et al. 2011a; Table 1).

Fumagillin

Fumagillin is a terpene derivative which has antibiotic properties (Fig. 13a). Fumagillin has been used in the treatment of microsporidiosis in humans and honey bees as well (Molina et al. 2002), and its synthetic derivatives are investigated as angiogenesis inhibitors in the treatment of cancer (Ingber et al. 1990). It was first isolated from *A. fumigatus* in 1949

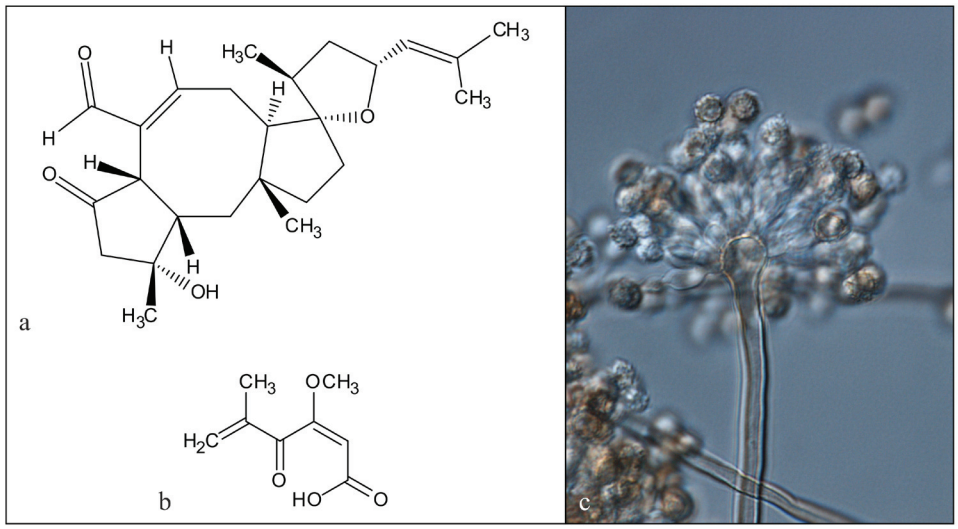

Figure 15. Structure of ophiobolin A (a), penicillic acid (b), and conidial heads of an *A. calidoustus* isolate (c).

(Hanson and Elbe 1949), and also produced by several other species assigned to section *Fumigati* (*A. duricalulis, A. aureolus, A. udagawae*).

Citrinin

Citrinin is a pentaketide derivative first isolated from *Penicillium citrinum* (Hetherington and Raistrick 1931; Fig. 13b). It is structurally similar to ochratoxins, and has nephrotoxic properties. Several species are able to produce it including Aspergilli assigned to sections *Terrei* and *Flavipedes* (*A. alabamensis*, *A. allahabadii*, *A. carneus*, *A. floccosus*, *A. hortai*, *A. neoindicus*, *A. pseudoterreus, A. niveus*, *A. flavipes*), *Monascus* (*e.g.*, *M. ruber, M. purpureus, M. pallens*) and *Penicillium* species (*P. expansum*, *P. radicicola*, *P. verrucosum;* Frisvad et al. 2004; Samson et al. 2011a). Previous claims that *A. candidus* produces citrinin could not be confirmed (Varga et al. 2007b).

Citreoviridin

Citreoviridin is a nonaketide derivative produced by several *Penicillium* (*e.g.*, *P. citreonigrum, P. ochrosalmoneum, P. citrinum* and *P. miczynskii*; Frisvad et al. 2004) and *Aspergillus* species assigned to section *Terrei* (*A. terreus, A. alabamensis, A. auroterreus, A. neoniveus;* Varga et al. 2011a; Fig. 14a). It is implicated in the etiology of yellow rice disease and cardial beri-beri.

Mevinolin

Mevinolin (or lovastatin) is a cholesterol-lowering compound, which was first identified in 1979 (Endo 1979; Fig. 14b). It is produced by some *Aspergillus* species (*A. terreus, A. africanus*; Samson et al. 2011a; Fig. 14c) and many other fungi including *Pleurotus* and *Monascus* species, while *Penicillium solitum* produces mevistatin or compactin, which is structurally closely related to lovastatin. Previous reports on the production of lovastatin by other Aspergilli including *A. oryzae, A. flavus, A. niger, A. repens, A. flavipes* and *A. versicolor* could not be confirmed (Gunde-Cimerman et al. 1973; Shindiaa 1997; Samiee et al. 2003; Valera et al. 2005).

Ophiobolins

Ophiobolins are sesterterpene derivatives which induce cell death in human and animal cell cultures (Au et al. 2000; Fig. 15a). Mainly *Cochliobolus* and *Bipolaris* species produce this phytotoxin. Recently, ophiobolins G and H were identified in *A. calidoustus* (Fig. 15c), *A. insuetus* and *A. keveii* assigned to section *Usti*, ophiobolins C, H and K from a presumably new species of section *Usti*, and several ophiobolins in *A. variecolor* (Wei et al. 2004; Samson et al. 2011b; Bladt et al. 2013). Ophiobolin production could not be confirmed in *A. ustus* (Cutler et al. 1984).

Penicillic acid

Penicillic acid is a tetraketide derivative, and exhibits hepatotoxic, antibacterial, antiviral, cytotoxic, carcinogenic and phytotoxic properties (Keromnes and Thouvenot 1985; Fig. 15b). This compound was first identified in *P. puberulum* and *P. cyclopium* (Birkinshaw et al. 1936). Later it was found in several *Penicillium* (*e.g.*, *P. aurantiogriseum*, *P. carneum*, *P.*

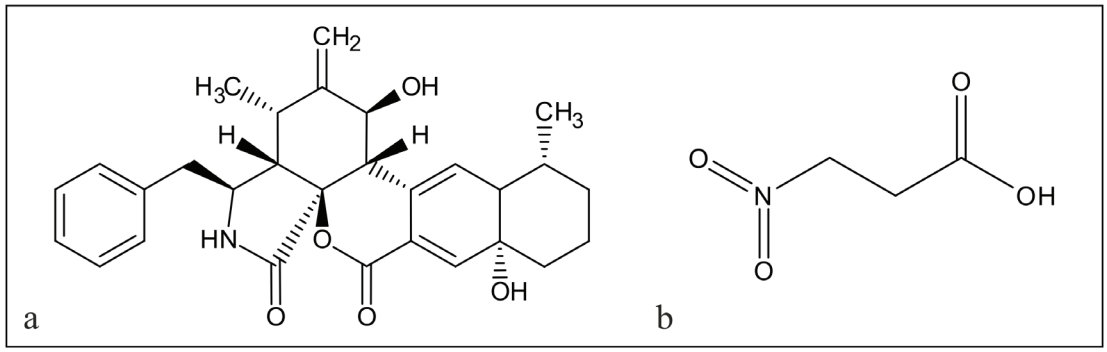

Figure 16. Chemical structures of cytochalasin A (a) and β-nitropropionic acid (b).

freii, *P. melanoconidium*, *P. neoechinulatum*, *P. polonicum*, *P. pulvillorum, P. radicicola*, *P. tulipae*, *P. viridicatum*; Ciegler and Kurtzman 1970; Frisvad et al. 2004) and *Aspergillus* species (*A. ochraceus, A. ostianus, A. melleus, A. sulphureus, A. westerdijkiae, A. westlandense, A. steynii, A. sclerotiorum, A. roseoglobulosus, A. pseudoelegans, A. persii, A. muricatus, A. flocculosus, A. auricomus, A. bridgeri, A. cretensis*) belonging to section *Circumdati* (Ciegler 1972; Samson et al. 2004; Visagie et al. 2014; Table 2). Interestingly, species belonging to other *Aspergillus* sections are unable to produce this metabolite (Frisvad and Larsen 2015).

Cytochalasins

Cytochalasins were discovered in 1964 during the screening of fungal culture filtrates for possible biological activity on cells (Carter 1967), and are synthetised by a PKS-NRPS hybrid enzyme (Fig. 16a). They are able to bind to actin filaments and block polymerization of actin, consequently cytochalasins can change cellular morphology, inhibit cellular processes such as cell division, and even can induce apoptosis (Cooper 1987). Several fungi can produce cytochalasins belonging to the genera *Phoma*, *Helminthosporium*, *Zygosporium*, *Metarrhizium*, *Chaetomium*, and *Rosellinia.* Regarding Aspergilli, several unrelated species are able to produce this compound including *A. clavatus, A. terreus, A. sclerotioniger, A. elegans* and *A. niveus* (Gebhardt et al. 2004; Varga et al. 2007c; Zhang et al. 2010; Zheng et al. 2013; Petersen et al. 2014).

β-nitropropionic acid

β-nitropropionic acid is derived from oxalacetic acid, which is a metabolic intermediate in many processes in living organisms including, *e.g.*, gluconeogenesis, amino acid synthesis, fatty acid synthesis and citric acid cycle (Fig. 16b). This compound was first identified in plants (Carter and McChensey 1949), later in several fungi including *Arthrinium* species (Wei et al. 1994), Penicillia (Raistrick and Stössl 1958) and Aspergilli. The producing species among Aspergilli include *A. oryzae* (Penel and Kosikowski 1990), *A. flavus* (Bush et al. 1951) and *A. wentii* (Steenkamp 1969). β-nitropropionic acid contamination occurs in sugarcane, and various oriental fermentation products including miso and soy sauce. It was implicated as a causative agent of sugarcane poisoning in China between 1972-1988 (Liu et al. 1992), and is used in several laboratories to examine the effects of Huntington's disease in animal models (Brouillet et al. 1999).

Aspergillus species are able to produce a range of other secondary metabolites, including, *e.g.*, the highly toxic rubratoxin produced mainly by *Talaromyces purpurogenus* (Yilmaz et al. 2012), and also by *A.* (*Dichotomomyces*) *cejpii* (Varga et al. 2007c). To date, 1984 extracellular metabolites (so-called exometabolites) have been identified in Aspergilli. These exometabolites include both secondary metabolites and other secreted metabolites including, *e.g.*, organic acids like itaconic acid in *A. terreus*, citric acid and oxalic acid in *A. niger*, or exoproteins including ribotoxins (Frisvad 2015). The clarification of the role of these compounds in human and animal diseases needs further examinations including genomic and metabolomic studies.

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References

Abbas HK, Duke SO, Shier WT, Riley RT, Kraus GA (1996) The chemistry and biological activities of the natural products AAL-toxin and the fumonisins. Adv Exp Med Biol 391:293-308.

Abbas HK, Tanaka T, Duke SO, Porter JK, Wray EM, Hodges L, Sessions AE, Wang E, Merrill AH, Riley RT (1994) Fumonisin- and AAL-toxin-induced disruption of sphingolipid metabolism with accumulation of free sphingoid bases. Plant Physiol 106:1085-1093.

Au TK, Chick WS, Leung PC (2000) The biology of ophiobolins. Life Sci 67:733-742.

Baranyi N, Kocsubé S, Varga J (2013) Current trends in aflatoxin research. Acta Biol Szeged 57:95-107.

Baranyi N, Jaksi Despot D, Palágyi A, Kiss N, Kocsubé S, Szekeres A, Kecskeméti A, Bencsik O, Vágvölgyi C, Segvić Klarić M, Varga J (2015) Identification of *Aspergillus* species in Central Europe able to produce G-type aflatoxins. Acta Biol Hung 66:339-347.

Birkinshaw JH, Oxford AE, Raistrick H (1936) Studies in the biochemistry of micro-organisms: Penicillic acid, a metabolic product of *Penicillium puberulum* Bainier and *P. cylopium* Westling. Biochem J 30:394-411.

Bladt TT, Dürr C, Knudsen PB, Kildgaard S, Frisvad JC, Gotfredsen CH, Seiffert M, Larsen TO (2013) Bio-activity and dereplication-based discovery of ophiobolins and other fungal secondary metabolites targeting leukemia cells. Molecules 18:14629-14650.

Bloch P, Tamm C, Bollinger P, Petcher TJ, Weber HP (1976) Pseurotin, new metabolite of *Pseudeurotium ovalis* Stolk having an unusual hetero-spirocyclic system. Helv Chim Acta 59:133-137.

Blout WP (1961) Turkey "X" disease. Turkeys 9:52-77.

Bode HB, Bether B, Hofs K, Zeeck A (2002) Big effects from small changes: possible ways to explore nature's chemical diversity. Chembiochem 3:619-627.

Bradshaw RE (2004) *Dothistroma* (red-band) needle blight of pines and the dothistromin toxin: a review. Forest Pathol 34:163–185.

Bradshaw RE, Slot JC, Moore GG, Chettri P, de Wit PJ, Ehrlich KC, Ganley AR, Olson MA, Rokas A, Carbone I, Cox MP (2013) Fragmentation of an aflatoxin-like gene cluster in a forest pathogen. New Phytol 198:525-535.

Brouillet E, Condé F, Beal MF, Hantraye P (1999) Replicating Huntington's disease phenotype in experimental animals. Progr Neurobiol 59:427-468.

Bush M, Touster O, Brockman JE (1951) The production of beta-nitropropionic acid by a strain of *Aspergillus flavus*. J Biol Chem 188:685-693.

Carter CL, McChesney WJ (1949) Hiptagenic acid identified as beta-nitropropionic acid. Nature 164:575.

Carter SB (1967) Effects of cytochalasins on mammalian cells. Nature 213:261-264.

Ciegler A (1972) Bioproduction of ochratoxin A and penicillic acid by members of the *Aspergillus ochraceus* group. Can J Microbiol 18:631-663.

Ciegler A, Kurtzman CP (1970) Penicillic acid production by blue-eye fungi on various agricultural commodities. Appl Microbiol 20:761-764.

Cooper JA (1987) Effects of cytochalasin and phalloidin on actin. J Cell Biol 105:1473-1478.

Cutler H, Crumley FG, Cox RH, Springer JP, Arrendale RF, Cole RJ, Cole PD (1984) Ophiobolins G and H: new fungal metabolites from a novel source, *Aspergillus ustus*. J Agric Food Chem 32:778-782.

Draughon FA, Ayres JC (1980) Insecticide inhibition of growth and patulin production in *Penicillium expansum, Penicillium urticae, Aspergillus clavatus, Aspergillus terreus*, and *Byssochlamys nivea*. J Agric Food Chem 26:115-1117.

Endo A (1979) Monacolin K, a new hypo-cholesterolemic agent that specifically inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase. J Antibiot (Japan) 33:334-336.

Frisvad JC (2015) Taxonomy, chemodiversity, and chemoconsistency of *Aspergillus, Penicillium* and *Talaromyces* species. Front Microbiol 5:1-7.

Frisvad JC, Frank JM, Houbrakren JAMP, Kuijpers AFA, Samson RA (2004) New ochratoxin A producing species of *Aspergillus* section *Circumdati*. Stud Mycol 50:23-43.

Frisvad JC, Larsen TO (2015). Chemodiversity in the genus *Aspergillus*. Appl Microbiol Biotechnol (*in press*).

Frisvad JC, Larsen TO, Samson RA (2004) Mycotoxins, drugs and other extrolites produced by species in *Penicillium* subgenus *Penicillium*. Stud Mycol 49:201-242.

Frisvad JC, Larsen TO, Thrane U, Meijer M, Varga J, Samson RA, Nielsen KF (2011) Fumonisin and ochratoxin production in industrial *Aspergillus niger* strains. PLoS One 6:e23496.

Frisvad JC, Smedsgaard J, Samson RA, Larsen TO, Thrane U (2007) Fumonisin B_2 production by *Aspergillus niger*. J Agric Food Chem 55:9727-9732.

Gebhardt K, Schimana J, Höltzel A, Dettner K, Draeger S, Beil W, Rheinheimer J, Fiedler HP (2004) Aspochalamins A-D and aspochalasin Z produced by the endosymbiotic fungus *Aspergillus niveus* LU 9575. I. Taxonomy, fermentation, isolation and biological activities. J Antibiot (Tokyo) 57:707-714.

Gelderblom WCA, Jaskiewicz K, Marasas WFO, Thiel PG, Horak MJ, Vleggaar R, Kriek NPJ (1988) Fumonisins -novel mycotoxins with cancer promoting activity produced by *Fusarium moniliforme*. Appl Environ Microbiol 54**:**1806-1811.

Gilchrist DG, Grogan RG (1976) Production and nature of a

hostspecific toxin from *Alternaria alternata* f. sp. *lycopersici*. Phytopathology 66:165-171.

Gonçalves SS, Stchigel AM, Cano JF, Godoy-Martinez PC, Colombo AL, Guarro J (2012) *Aspergillus novoparasiticus*: a new clinical species of the section *Flavi.* Med Mycol 50:152-160.

Gunde-Cimerman N, Friedrich J, Cimerman A, Benicki N (1973) Screening fungi for the production of an inhibitor of HMG CoA reductase: Production of mevinolin by the fungi of the genus *Pleurotus*. FEMS Microbiol Lett 111:203-206.

Hanson FR, Elbe TE (1949) An antiphage agent isolated from *Aspergillus* sp. J Bacteriol 58:527.

Hawksworth DL, Crous PW, Redhead SA, Reynolds DR, Samson RA, Seifert KA, Taylor JW, Wingfield MJ, Abaci O, Aime C, Asan A, Bai FY, de Beer ZW, Begerow D, Berikten D, Boekhout T, Buchanan PK, Burgess T, Buzina W, Cai L, Cannon PF, Crane JL, Damm U, Daniel HM, van Diepeningen AD, Druzhinina I, Dyer PS, Eberhardt U, Fell JW, Frisvad JC, Geiser DM, Geml J, Glienke C, Gräfenhan T, Groenewald JZ, Groenewald M, de Gruyter J, Guého-Kellermann E, Guo LD, Hibbett DS, Hong SB, de Hoog GS, Houbraken J, Huhndorf SM, Hyde KD, Ismail A, Johnston PR, Kadaifciler DG, Kirk PM, Kõljalg U, Kurtzman CP, Lagneau PE, Lévesque CA, Liu X, Lombard L, Meyer W, Miller A, Minter DW, Najafzadeh MJ, Norvell L, Ozerskaya SM, Oziç R, Pennycook SR, Peterson SW, Pettersson OV, Quaedvlieg W, Robert VA, Ruibal C, Schnürer J, Schroers HJ, Shivas R, Slippers B, Spierenburg H, Takashima M, Taşkın E, Thines M, Thrane U, Uztan AH, van Raak M, Varga J, Vasco A, Verkley G, Videira SI, de Vries RP, Weir BS, Yilmaz N, Yurkov A, Zhang N (2011) The Amsterdam declaration on fungal nomenclature. IMA Fungus 2:105-112.

Hetherington AC, Raistrick H (1931) On the production and chemical constitution of a new yellow colouring matter, citrinin, produced from glucose by *Penicillium citrinum* Thom. Phil Trans Royal Soc Biol Sci 220:269-295.

Holzapfel CW (1968) The isolation and structure of cyclopiazonic acid, a toxic metabolite of *Penicillium cyclopium* Westling. Tetrahedron 24:2101-2119.

Hong SB, Lee M, Kim DH, Varga J, Frisvad JC, Perrone G, Gomi K, Yamada O, Machida M, Houbraken J, Samson RA (2013) *Aspergillus luchuensis*, an industrially important black Aspergillus in East Asia. PLoS One 8:e63769.

Hylin JW, Matsumoto H (1960) The biosynthesis of 3-nitropropionic acid by *Penicillium atrovenetum*. Arch Biochem Biophys 93:542-545.

IARC (International Agency for Research on Cancer) (2012) A review of human carcinogens. Vol. 100F: Chemical agents and related occupations. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, Lyon, France.

Ingber D, Fujita T, Kishimoto S, Sudo K, Kanamaru T, Brem, Folkman J (1990) Synthetic analogues of fumagillin that inhibit angiogenesis and suppress tumour growth. Nature 348:555-557.

Izhaki I (2002) Emodin – a secondary metabolite with multiple ecological functions in higher plants. New Phytol 155:205-217.

Johnson JR, Bruce WF, Dutcher JD (1943) Gliotoxin, the antibiotic principle of *Gliocladium fimbriatum*. I. Production, physical and biological properties. J Am Chem Soc 65:2005-2009**.**

Jurjevi Z, Peterson SW, Horn BW (2012) *Aspergillus* section *Versicolores*: nine new species and multilocus DNA sequence based phylogeny. IMA Fungus 3:61-81.

Jurjevi Z, Peterson SW, Solfrizzo M, Peraica M (2013) Sterigmatocystin production by nine newly described species in section *Versicolores* grown on two different media. Mycotoxin Res 29:141-145.

Keromnes J, Thouvenot D (1985) Role of penicillic acid in the phytotoxicity of *Penicillium cyclopium* and *Penicillium canescens* to the germination of corn seeds. Appl Environ Microbiol 49:660-663.

Khaldi N, Wolfe KH (2011) Evolutionary origins of the fumonisin secondary metabolite gene cluster in *Fusarium verticillioides* and *Aspergillus niger*. Int J Evol Biol 2011:1-7.

Klich MA, Tang S, Denning DW (2009) Aflatoxin and ochratoxin production by *Aspergillus* species under *ex vivo* conditions. Mycopathologia 168:185-191.

Kornsakulkarn J, Saepua S, Laksanacharoen P, Rachtawee P, Thongpanchang C (2013) Xanthone and anthraquinone-type mycotoxins from the scale insect fungus *Aschersonia marginata* BCC 28721. Tetrahedron Lett 54:3813-3815.

Kornsakulkarn J, Saepua S, Srichomthong K, Supothina S, Thongpanchang C (2012) New mycotoxins from the scale insect fungus *Aschersonia coffeae* Henn. BBC 28712. Tetrahedron 68:8480-8486.

Kupfahl C, Michalka A, Lass-Flörl C, Fischer G, Haase G, Ruppert T, Geginat G, Hof H (2008) Gliotoxin production by clinical and environmental *Aspergillus fumigatus* strains. Int J Med Microbiol 298:319-327.

Kurtzman CP, Horn BW, Hesseltine CW (1987) *Aspergillus nomius*, a new aflatoxin- producing species related to *Aspergillus flavus* and *Aspergillus parasiticus*. Antonie van Leeuwenhoek 53:147-158.

Larsen TO, Smedsgaard J, Nielsen KF, Hansen MAE, Samson RA, Frisvad JC (2007) Production of mycotoxins by *Aspergillus lentulus* and other medically important and closely related species in section *Fumigati*. Med Mycol 45:225-232.

Lewis RE, Wiederhold NP, Lionakis MS, Prince RA, Kontoyiannis DP (2005) Frequency and species distribution of

gliotoxin-producing *Aspergillus* isolates recovered from patients at a tertiary-care cancer center. J Clin Microbiol 43:6120-6122.

Liu X, Luo X, Hu W (1992) Studies on the epidemiology and etiology of moldy sugarcane poisoning in China. Biomed Environ Sci 5:161-177.

Marin S, Ramos AJ, Cano-Sancho G, Sanchis V (2013) Mycotoxins: occurrence, toxicology, and exposure assessment. Food Chem Toxicol 60:218-237.

Massi FP, Vieira ML, Sartori D, Penha RE, de Freitas Munhoz C, Ferreira JM, Iamanaka BT, Taniwaki MH, Frisvad JC, Fungaro MH (2014) Brazil nuts are subject to infection with B and G aflatoxin-producing fungus, *Aspergillus pseudonomius*. Int J Food Microbiol 186:14-21.

Matasyoh JC, Dittrich B, Schueffler A, Laatsch H (2011) Larvicidal activity of metabolites from the endophytic *Podospora* sp. against the malaria vector *Anopheles gambiae*. Parasitol Res 108:561-566.

McNeill J, Barrie FR, Buck WR, Demoulin V, Greuter W, Hawksworth DL, Herendeen PS, Knapp S, Marhold K, Prado J, Prud'homme van Reine WF, Smith GF, Wiersema JH, Turland N (eds. & comps.) (2012) International Code of Nomenclature for algae, fungi, and plants (Melbourne Code), adopted by the Eighteenth International Botanical Congress Melbourne, Australia, July 2011. Koeltz Scientific Books, Königstein.

Mogensen JM, Frisvad JC, Thrane U, Nielsen KF (2010) Production of Fumonisin B_2 and B_4 by *Aspergillus niger* on grapes and raisins. J Agric Food Chem 58:954-958.

Mogensen JM, Møller KA, von Freiesleben P, Labuda R, Varga E, Sulyok M, Kubátová A, Thrane U, Andersen B, Nielsen KF (2011) Production of fumonisins B_2 and B_4 in *Tolypocladium* species. J Ind Microbiol Biotechnol 38:1329-1335.

Molina JM, Tourneur M, Sarfati C, Chevret S, de Gouvello A, Gobert JG, Balkan S, Derouin F; Agence Nationale de Recherches sur le SIDA 090 Study Group (2002) Fumagillin treatment of intestinal microsporidiosis. N Eng J Med 346:1963-1969.

Nielsen KF (2003) Mycotoxin production by indoor molds. Fungal Genet Biol 39:103-117.

Noonim P, Mahakarnchanakul W, Nielsen KF, Frisvad JC, Samson RA (2008) Isolation, identification and toxigenic potential of ochratoxin A-producing *Aspergillus* species from coffee beans grown in two regions of Thailand. Int J Food Microbiol 128:197-202.

Ohmomo S, Sugita M, Abe M (1973) Production of alkaloids and related substances by fungi. XI. Isolation of cyclopiazonic acid, cyclopiazonic acid imine and Bissecodehydrocyclopiazonic acid from the cultures of *Aspergillus versicolor* (Vuill.) Tiraboschi. Agric Chem Soc Japan J 47:57-63.

Oxford AE, Raistrick H, Simonart P (1939) XXIX. Studies in the biochemistry of microorganisms. LX. griseofulvin, 17H1706CI, a metabolic product of *Penicillium griseofulvum* Dierckx. Biochem J 33:240-248.

Penel AJ, Kosikowski FV (1990) Beta-nitropropionic acid production by *Aspergillus oryzae* in selected high protein and carbohydrate-rich foods. J Food Protect 4:282-350.

Petersen LM, Bladt TT, Dürr C, Seiffert M, Frisvad JC, Gotfredsen CH, Larsen TO (2014) Isolation, structural analyses and biological activity assays against chronic lymphocytic leukemia of two novel cytochalasins - sclerotionigrin A and B. Molecules 19:9786-9797.

Puel O, Galtier P, Oswald IP (2010) Biosynthesis and toxicologial effects of patulin. Toxins 2:613-631.

Raistrick H, Stossl A (1958) Studies in the biochemistry of microorganisms, 104. Metabolites of *Penicillium atrovenetum* G. Smith: beta-nitropropionic acid, a major metabolite. Biochem J 68:647-653.

Rank C, Nielsen KF, Larsen TO, Varga J, Samson RA, Frisvad JC (2011) Distribution of sterigmatocystin in filamentous fungi. Fungal Biol 115:406-420.

Rheeder JP, Marasas WF, Vismer HF (2002) Production of fumonisin analogs by *Fusarium* species. Appl Environ Microbiol 68:2101-2105.

Samiee SM, Moazami N, Haghighi S, Mohseni FA, Mirdamadi S, Bakhtiari MR (2003) Screening of lovastatin production by filamentous fungi. Iran Biomed J 7:29-33.

Samson RA, Hong SB, Peterson SW, Frisvad JC, Varga J (2007b) Polyphasic taxonomy of *Aspergillus* section *Fumigati* and its teleomorph *Neosartorya*. Stud Mycol 59:147-203.

Samson RA, Houbraken J, Thrane U, Frisvad JC, Andersen B (2010) Food and Indoor Fungi. CBS KNAW Fungal Biodiversity Center, Utrecht.

Samson RA, Noonim P, Meijer M, Houbraken J, Frisvad JC, Varga J (2007a) Diagnostic tools to identify black Aspergilli. Stud Mycol 59:129-145.

Samson RA, Peterson SW, Frisvad JC, Varga J (2011a) New species in *Aspergillus* section *Terrei*. Stud Mycol 69:39-55.

Samson RA, Varga J, Meijer M, Samson RA (2011b) New taxa in *Aspergillus* section *Usti*. Stud Mycol 69:81-97.

Samson RA, Visagie CM, Houbraken J, Hong S-B, Hubka V, Klaassen CHW, Perrone G, Seifert KA, Susca A, Tanney JB, Varga J, Kocsubé S, Szigeti G, Yaguchi T, Frisvad JC (2014) Taxonomy, identification and nomenclature of the genus *Aspergillus*. Stud Mycol 78:141-173.

Schmidt-Heydt M, Häckel S, Rüfer CE, Geisen R (2009) A strain of *Fusarium kyushuense* is able to produce aflatoxin B_1 and G_1. Mycotoxin Res 25:141-147.

Shindia AA (1997) Mevinolin production by some fungi. Folia Microbiol 42:477-480.

Slot JC, Rokas A (2011) Horizontal transfer of a large and highly toxic secondary metabolic gene cluster between

fungi. Curr Biol 21:134-139.
Soares C, Rodrigues P, Peterson SW, Lima N, Venâncio A (2012) Three new species of *Aspergillus* section *Flavi* isolated from almonds and maize in Portugal. Mycologia 104:682-697.
Squire RA (1981) Ranking animal carcinogens: a proposed regulatory approach. Science 194:877-880.
Steenkamp CH (1969) Identification of beta-nitropropionic acid as the main toxic metabolite of *Aspergillus wentii* Wehm. PhD Thesis, Universiteit van Pretoria.
Steiman R, Seigle-Murandi F, Sage L, Krivook S (1989) Production of patulin by Micromycetes. Mycopathologia 105:129-133.
Sugui JA, Pardo J, Chang YC, Zarember KA, Nardone G, Galvez EM, Müllbacher A, Gallin JI, Simon MM, Kwon-Chung KJ (2007) Gliotoxin is a virulence factor of *Aspergillus fumigatus: gliP* deletion attenuates virulence in mice immunosuppressed with hydrocortisone. Eukaryot Cell 6:1562-1569.
Susca A, Proctor RH, Butchko RAE, Haidukowski M, Stea G, Logrieco A, Moretti A (2014) Variation in the fumonisin biosynthetic gene cluster in fumonisin-producing and nonproducing black aspergilli. Fungal Genet Biol 73:39-52.
Takeda I, Umemura M, Koike H, Asai K, Machida M (2014) Motifindependent prediction of a secondary metabolite gene cluster using comparative genomics: application to sequenced genomes of *Aspergillus* and ten other filamentous fungal species. DNA Res 21:447-457.
Taniwaki MH, Pitt JI, Iamanaka BT, Sartori D, Copetti MV, Balajee A, Fungaro MH, Frisvad JC (2012) *Aspergillus bertholletius* sp. nov. from Brazil nuts. PLoS One 7:e42480.
Tatsuda D, Momose I, Someno T, Sawa R, Kubota Y, Iijima M, Kunisada T, Watanabe T, Shibazaki M, Nomoto A (2015) Quinofuracins A-E, produced by the fungus *Staphylotrichum boninense* PF 1444, show p53-dependent growth suppression. J Nat Prod 78:188-195.
Udagawa T, Yuan J, Panigrahy D, Chang YH, Shah J, D'Amato RJ (2000) Cytochalasin E, an epoxide containing *Aspergillus*-derived fungal metabolite, inhibits angiogenesis and tumor growth. J Pharmacol Exp Ther 294:421-427.
Valera HR, Gomes J, Lakshmi S, Gururaja R, Suryanarayan S, Kumar D (2005) Lovastatin production by solid state fermentation using *Aspergillus flavipes*. Enz Microb Technol 37:521-526.
van der Merwe KJ, Steyn PS, Fourie L, Scott DB, Theron JJ (1965) Ochratoxin A, a toxic metabolite produced by *Aspergillus ochraceus* Wilh. Nature 205:1112-1113.
van der Molen KM, Raja HA, El-Elimat T, Oberlies NH (2013) Evaluation of culture media for the production of secondary metabolites in a natural products screening program. AMB Press 3:71.
Van der Zijden ASM, Blanche Koelensmid WAA, Boldingh J, Barrett CB, Ord WO, Philip J (1962) *Aspergillus flavus* and Turkey X disease: isolation in crystalline form of a toxin responsible for Turkey X disease. Nature 195:1060-1062.
Varga J, Due M, Frisvad JC, Samson RA (2007c) Taxonomic revision of *Aspergillus* section *Clavati* based on molecular, morphological and physiological data. Stud Mycol 59:89-106.
Varga J, Frisvad JC, Kocsubé S, Brankovics B, Tóth B, Szigeti G, Samson RA (2011b) New and revisited species in *Aspergillus* section *Nigri*. Stud Mycol 69:1-17.
Varga J, Frisvad JC, Samson RA (2007b) Polyphasic taxonomy of *Aspergillus* section *Candidi* based on molecular, morphological and physiological data. Stud Mycol 59:75-88.
Varga J, Frisvad JC, Samson RA (2009) A reappraisal of fungi producing aflatoxins. World Mycotoxin J 2:263-277.
Varga J, Frisvad JC, Samson RA (2010a) *Aspergillus* sect. *Aenei* sect. nov., a new section of the genus for *A. karnatakaensis* sp. nov. and some allied fungi. IMA Fungus 1:197-205.
Varga J, Frisvad JC, Samson RA (2011a) Two new aflatoxin producing species, and an overview of *Aspergillus* section *Flavi*. Stud Mycol 69:57-80.
Varga J, Kocsubé S, Suri K, Szigeti G, Szekeres A, Varga M, Tóth B, Bartók T (2010) Fumonisin contamination and fumonisin producing black Aspergilli in dried vine fruits of different origin. Int J Food Microbiol 143:143-149.
Varga J, Kocsubé S, Szigeti G, Man V, Tóth B, Vágvölgyi C (2012) Black Aspergilli and fumonisin contamination in onions purchased in Hungary. Acta Aliment 41:414-423.
Varga J, Rigó K, Téren J, Mesterházy Á (2001a) Recent advances in ochratoxin research I. Production, detection and occurrence of ochratoxins. Cereal Res Commun 29:85-92.
Varga J, Rigó K, Téren J, Mesterházy Á (2001b) Recent advances in ochratoxin research I. Biosynthesis, mode of action and control of ochratoxins. Cereal Res Commun 29:93-100
Visagie CM, Varga J, Houbraken J, Meijer M, Kocsubé S, Yilmaz N, Fotedar R, Seifert KA, Frisvad JC, Samson RA (2014) Ochratoxin production and taxonomy of the yellow aspergilli (*Aspergillus* section *Circumdati*). Stud Mycol 78:1-61.
Wei DL, Chang SC, Lin SC, Doong ML, Jong SC (1994) Production of 3-nitropropionic acid by *Arthrinium* species. Curr Microbiol 28:1-5.
Wei H, Itoh T, Kinoshita M, Nakai Y, Kurotaki M, Kobayashi M (2004) Cytotoxic sesterterpenes, 6-epi-ophiobolin G and 6-epi-ophiobolin N, from marine derived fungus *Emericella variecolor* GF10. Tetrahedron 60:6015-

6019.

Wells JM, Cole RJ, Kirksey JW (1975) Emodin, a toxic metabolite of *Aspergillus wentii* isolated from weevil-damaged chestnuts. Appl Microbiol 30:26-28.

Wenke J, Anke H, Sterner O (1993) Pseurotin A and 8-O-methylpseurotin A from *Aspergillus fumigatus* and their inhibitory activities on chitin synthase. Biosci Biotech Biochem 57:961-964.

Wicklow DT, Vesonder RF, Mcalpin CE, Cole RJ, Roquebert MF (1989) Examination of *Stilbothamnium togoense* for *Aspergillus flavus* group mycotoxins. Mycotaxon 34:249-252.

Wilkinson S, Splisbury JF (1965) Gliotoxin from *Aspergillus chevalieri* (Mangin) Thom et Church. Nature 206:619.

Yilmaz N, Houbraken J, Hoekstra ES, Frisvad JC, Visagie CM, Samson RA (2012) Delimitation and characterisation of *Talaromyces purpurogenus* and related species. Persoonia 29:39-54.

Zhang HW, Zhang J, Hu S, Zhang ZJ, Zhu CJ, Ng SW, Tan RX (2010) Ardeemins and cytochalasins from *Aspergillus terreus* residing in *Artemisia annua*. Planta Med 76:1616-1621.

Zheng CJ, Shao CL, Wu LY, Chen M, Wang KL, Zhao DL, Sun XP, Chen GY, Wang CY (2013) Bioactive phenylalanine derivatives and cytochalasins from the soft coral-derived fungus, *Aspergillus elegans*. Mar Drugs 11:2054-2068.