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MINI-REVIEW

Chemodiversity in the genus *Aspergillus*

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Abstract Isolates of *Aspergillus* species are able to produce a large number of secondary metabolites. The profiles of biosynthetic families of secondary metabolites are species specific, whereas individual secondary metabolite families can occur in other species, even those phylogenetically and ecologically unrelated to *Aspergillus*. Furthermore, there is a high degree of chemo-consistency from isolate to isolate in a species even though certain metabolite gene clusters are silenced in some isolates. Genome sequencing projects have shown that the diversity of secondary metabolites is much larger in each species than previously thought. The potential of finding even further new bioactive drug candidates in *Aspergillus* is evident, despite the fact that many secondary metabolites have already been structure elucidated and chemotaxonomic studies have shown that many new secondary metabolites have yet to be characterized. The genus *Aspergillus* is cladistically holophyletic but phenotypically polythetic and very diverse and is associated to quite different sexual states. Following the one fungus one name system, the genus *Aspergillus* is restricted to a holophyletic clade that include the morphologically different genera *Aspergillus*, *Dichotomomyces*, *Phialosimplex*, *Polypaecilum* and *Cristaspora*. Secondary metabolites common between the subgenera and sections of *Aspergillus* are surprisingly few, but many metabolites are common to a majority of species within the sections. We call small molecule extrolites in the same biosynthetic family isoextrolites. However, it appears that secondary metabolites from one *Aspergillus* section have analogous metabolites in other sections (here also called heteroisoextrolites). In this review, we give a genus-wide overview of secondary metabolite production in *Aspergillus* species. Extrolites appear to have evolved because of ecological challenges rather than being inherited from ancestral species, at least when comparing the species in the different sections of *Aspergillus*. Within the *Aspergillus* sections, secondary metabolite pathways seem to inherit from ancestral species, but the profiles of these secondary metabolites are shaped by the biotic and abiotic environment. We hypothesize that many new and unique section-specific small molecule extrolites in each of the *Aspergillus* will be discovered.

Keywords Extrolites · Heteroisoextrolites · Secondary metabolites · *Aspergillus* · Chemodiversity

Introduction

The genus *Aspergillus* is rich in species and these species are able to produce a large number of extrolites, including secondary metabolites, bioactive peptides/proteins, lectins, enzymes, hydrophobins and aegerolysins. Extrolites are outward-directed chemical compounds from organisms that are secreted or anchored on the cell wall or in the membrane and accumulated. The word comes from extro (outwards directed and -ite: a chemical compound. The term is ecological rather than a metabolism term. The *Aspergilli* are also capable of biotransforming extrolites from other species. A xenoextrolite is an extrolite from another species than that in question. Because of the production of such diverse extrolites, many different *Aspergillus* species have been used in biotechnology, both for bulk and fine chemical production (Meyer et al. 2010), and also for exoenzyme production, and certain

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species stand out as *working horses* of biotechnology, especially *Aspergillus niger*, *Aspergillus oryzae* and *Aspergillus terreus*. *Aspergillus* species have also been used as heterologous producers of proteins and exometabolites and for bioremediation. Species of *Aspergillus* can also have negative effects and be pathogenic (Buzina 2013; Sugui et al. 2014a, b), give health problems in buildings (Miller and McMullin 2014) and deteriorate other materials.

Aspergillus species produces a wide array of small molecule extrolites (secondary metabolites or specialized metabolites, all abbreviated SM here), but also other bioactive molecules such as large peptide ribotoxins and lectins. The ribotoxins appear to be restricted to *Aspergillus* subgenus *Fumigati* sections *Fumigati* and *Clavati* (Ng and Wang 2006; Varga and Samson 2008; Abad et al. 2010), but bioactive peptides have also been reported from subgenus *Aspergillus*, for example eurocin production by *Aspergillus montevidensis* (Oeemig et al. 2012). Lectins have been found in phylogenetically distant subgenera of *Aspergillus* such as *Circumdati*, *Nidulantes*, *Fumigati* and *Aspergillus* (Singh et al. 2014a, b). Most known extrolites are small molecules, however, and these molecules will be emphasized here.

Specialized metabolites, as the name indicates, have evolved because of ecological challenges. Species with no competitors, such as the extremophile *Xeromyces bisporus*, do not produce any specialized metabolites and there are no gene clusters coding for such metabolites in the genome (Leong et al. 2015). Since *Aspergillus* species are usually very efficient specialized metabolite producers, we will also examine whether species in the different sections produce extrolites that have evolved with their species based on ecology or phylogeneny or both (Gibbons and Rokas 2013; Wisecaver and Rokas 2015).

Taxonomy and phylogeny of *Aspergillus*

The classification of *Aspergillus* has traditionally been based on morphology and colony colours including conidium colour, as was done in the latest full revision and identification-manual of *Aspergillus* by Raper and Fennell (1965) (Samson et al. 2006). A partial revision of some *Aspergillus* species by Kozakiewicz (1989) was heavily based on micromorphology, including conidium and ascospore characterization by scanning electron microscopy. Taxonomic characters based on ecophysiology, nutrition, secondary metabolites and extracellular enzymes were for many years used occasionally, but rarely incorporated into broad taxonomic schemes. However, all these ecologically relevant taxonomic features were promising, often giving clear-cut differences between closely related species. For example, the first use of secondary metabolites in *Aspergillus* taxonomy (Frisvad 1985; Frisvad and Samson 1990; Samson et al. 1990) was promising, as was the use of isoenzyme profiling (Cruickshank and Pitt 1990) and the use of simple ecophysiological and nutritional characters (Klich 2002; Pitt and Hocking 2009; Samson et al. 2010). It is now well established that profiles of small molecule extrolites are species-specific (Larsen et al. 2005; Frisvad 2015). In addition, large molecule extrolites appear also to be species specific (Varga and Samson 2008).

Cladistic analysis of the sequences of rDNA was used by Peterson (2000) to give an overview of potential phylogenetic relationships between species in *Aspergillus* and this has later been followed by a series of papers on sequence-based cladification of *Aspergillus* species, using nucleotide sequences of ITS1 and 2 from rDNA, β-tubulin, calmodulin and other genes (Geiser et al. 2007). Since analyses based on classification of functional characters were generally in agreement with sequence-based cladifications, a polyphasic approach using all these characters has been proposed for taxonomy, phylogeny, species descriptions and identifications (Frisvad et al. 2007a, b; Geiser et al. 2007; Samson et al. 2014).

Aspergillus species have widely different sexual states (Table 1), and it has been shown that *Aspergillus fumigatus* and allied species are nearly as molecularly divergent from *A. niger* and *Aspergillus flavus* as humans are from fish, based on average protein sequence identity (Fedorova et al. 2008). This is indeed reflected in the large differences between their sexual states: The small hard lightly-coloured sclerotioid ascomata of *Aspergillus fischeri* (Samson et al. 2007a, b) are very different from the black sclerotial stromatoid ascomata, in which many cleistothecial locules (2–8) are developing, in *Aspergillus alliaceus* (Raper and Fennell 1965), *A. flavus* (Horn et al. 2009a), *Aspergillus parasiticus* (Horn et al. 2009c) or *Aspergillus nomius* (Horn et al. 2009b). Furthermore, *Aspergillus* sensu *lato* as circumscribed by Raper and Fennell (1965) is paraphyletic, with a genus such as *Polypaecilum* (dichotomomyces-morph) placed between *Aspergillus* section *Fumigati* (neosartorya-morph) and *Aspergillus* section *Clavati* (neocarpenteles-morph) (Varga et al. 2007a, b, c; Houbraken and Samson 2011). With the accepted new nomenclatural system for fungi (one fungus one name) (Hawksworth 2011; Hawksworth et al. 2011), there have been discussions whether we should use the genus designation *Aspergillus* for all species in the monophyletic clade comprising *Aspergillus* sensu Raper and Fennell (1965), but including further species with different morphologies as dictated by DNA sequences (Samson et al. 2014) or to use the established names *Eurotium*, *Neosartorya*, *Emericella* etc. for distinct *Aspergillus* sections, as recommended by Pitt and Taylor (2014). If the latter solution to the nomenclatural problem in *Aspergillus* sensu Raper and Fennell (1965) was to be adopted, *Aspergillus* will have to be neo-typified, by for example *A. niger* (Pitt and Taylor 2014), because *Aspergillus* at

Table 1 Sections of *Aspergillus* and their associated sexual states

Subgenus/section	Raper and Fennell (1965) group	Earlier name given to the sexual state in the two-name system	References on taxonomy, phylogeny and secondary metabolites
Circumdati/*Nigri*	*Aspergillus niger* group	*Saitoa*, now informally saitoa-morph	Parenicová et al. 2001; Abarca et al. 2004; Samson et al. 2004; De Vries et al. 2005; Serra et al. 2006; Perrone et al. 2007, 2008; Samson et al. 2007a, b; Varga et al. 2007a; Noonim et al. 2008; Nielsen et al. 2009; Varga et al. 2011a; Meijer et al. 2011; Perrone et al. 2011; Jurjevic et al. 2012a, b; Hong et al. 2013; Horn et al. 2013
Circumdati/*Flavi*	*Aspergillus flavus* group	*Petromyces*, now informally petromyces-morph	Frisvad and Samson 2000; Peterson et al. 2001; Pildain et al. 2008; Varga et al. 2011b
Circumdati/*Circumdati*	*Aspergillus ochraceus* group	*Neopetromyces*, now informally neopetromyces-morph	Varga et al. 2000a, b, c; Frisvad and Samson 2000; Frisvad et al. 2004a, b; Visagie et al. 2014a
Circumdati/*Terrei*	*Aspergillus terreus* group	Name not given, but sexual state found in *Asp terreus*	Varga et al. 1995; Balajee et al. 2009; Samson et al. 2011a; Arabatis and Velegraki 2013
Circumdati/*Flavipedes*		*Fennellia*, now informally fennellia-morph	Samson et al. 2011a, b; Visagie et al. 2014b Hubka et al. 2015
Circumdati/*Candidi*	*Aspergillus candidus* group	Not known, sclerotia present	Rahbæk et al. 2000; Varga et al. 2007b; Visagie et al. 2014b
Circumdati/*Jani*			Hubka et al. 2015
Circumdati/'*Arenarii*'	*A. arenarius*, *A. arenarioides*		Visagie et al. 2014a, b, c
Nidulantes/*Ochraceorosei*	–	Not known	Frisvad et al. 2005
Nidulantes/*Aenei*	*Aspergillus nidulans* group	*Emericella*, now informally emericella-morph	Varga et al. 2010a
Nidulantes/*Nidulantes*	*Aspergillus nidulans* groupclust	*Emericella*	Horie 1980; Frisvad 1985; Zalar et al. 2008; Matsuzawa et al. 2012
Nidulantes/*Versicolores*	*Aspergillus versicolor* group	(*Emericella*)	Klich 1993; Peterson 2000; Jurjevic et al. 2012a, b
Nidulantes/*Usti*	*Aspergillus ustus* group	*Emericella*	Houbraken et al. 2007; Samson et al. 2011b; Visagie et al. 2014b
Nidulantes/*Sparsi*	*Aspergillus sparsus* group	*Emericella*	Varga et al. 2010b
Fumigati/*Clavati*	*Aspergillus clavatus* group	*Hemicarpenteles*, now informally hemicarpenteles-morph	Varga et al. 2003a, b; 2007c
Fumigati/*Fumigati*	*Aspergillus fumigatus* group	*Neosartorya*, now informally neosartoya-morph	Geiser et al. 1998; Hong et al. 2005, 2006; Samson et al. 2007a, b; Hong et al. 2008; Frisvad et al. 2009; Barrs et al. 2013; Nováková et al. 2014; Sugui et al. 2014a, b
A. maritimus	(*Aspergillus maritimus*)	*Hemisartorya*	Rai and Chowdhery (1975)
Fumigati/*Cervini*	*Aspergillus cervinus* group	Not known	Peterson (2000)
Fumigati/*Dichotomomyces*: *Aspergillus cejpii*	*Dichotomomyces cejpii*		Houbraken and Samson 2011
Polypaecilum/*Phialosimplex*: *A. baarnensis*, *A. canicus*, *A. halophila*, *A. insolitus*, *A. salinarus*, *A. sclerotialis*	*Basipetospora halophila*, *Phialosimplex caninus*, *Ph insolitum*, *Ph salinarum*, *Ph sclerotialis*		Houbraken and Samson 2011
Polypaecilum/*Polypaecilum*: *A. pisci*	*Polypaecilum pisci*		Pitt and Hocking 1985
Aspergillus/*Aspergillus*	*Aspergillus glaucus* group	*Eurotium*, now informally eurotium-morph	Slack et al. 2009; Hubka et al. 2013; Visagie et al. 2014b
Aspergillus/*Restricti*	*Aspergillus restrictus* group	*Eurotium*	Peterson (2000)
'*Cremei*'/*Cremei* (incl. *Wentii*)	*Aspergillus wentii* and *Aspergillus cremeus* group	*Chaetosartorya*, now informally chaetosartorya-morph	Peterson (1995)

present is typified by *Aspergillus glaucus* and keeping the name *Eurotium* will require such a neo-typification. In this review, we have decided to follow the decision of Samson et al. (2014) to include species of *Aspergillus* in the monophyletic clade including *A. glaucus* (Hubka et al. 2013) and nearly all species accepted by Raper and Fennell (1965). This has had the consequences that *Penicillium inflatum* had to be transferred to *Aspergillus* as *Aspergillus inflatus*, *Aspergillus paradoxus*, *Aspergillus malodoratus* and *Aspergillus crystallinus* had to be transferred to *Penicillium* as *Penicillium paradoxum*, *Penicillium malodoratum* and *Penicillium crystallinum*, *Aspergillus zonatus* and *Aspergillus clavatoflavus* had to be excluded from *Aspergillus* and finally that the species in the genera *Dichotomomyces*, *Phialosimplex*, *Polypaecilum* and *Cristaspora* had to be transferred to *Aspergillus* (Houbraken and Samson 2011; Houbraken et al. 2012; Samson et al. 2014). In this system, 354 species of *Aspergillus* have been accepted (Samson et al. 2014). As an example of proper naming of the well-known species in the former two-names for a species system *A. fumigatus*/*Neosartorya fumigata* and *Aspergillus fischerianus*/*Neosartorya fischeri* should now be named *A. fumigatus* and *A. fischeri*. If the sexual state has been observed for an isolate, the name can be more informative in calling them *A. fumigatus* (neosartorya-morph) and *A. fischeri* (neosartorya-morph). In two species in *Aspergillus*, *Aspergillus monodii* and *Aspergillus arxii*, only the sexual state has been found, making it difficult to recognize these species as *Aspergillus*, and in such cases sequencing of several house-hold genes is necessary for correct cladification, classification and identification (Samson et al. 2014). Several *Aspergillus* species have been genome sequenced (Andersen et al. 2011; Baker 2006; Pel et al. 2007; Gibbons and Rokas 2013), and many clusters coding for new *Aspergillus* secondary metabolites have been discovered (Chiang et al. 2010; Brakhage 2013).

Being so different, the sections of *Aspergillus* could be hypothesized to produce widely different small molecule extrolites. Below, we will investigate whether this is the case.

Chemodiversity of *Aspergillus*

Chemotaxonomy based on secondary metabolites has been very valuable in *Aspergillus* taxonomy, and secondary metabolites are often included in species descriptions (Larsen et al. 2005; Frisvad et al. 2007a, b; 2008; references in Table 1). Independent analysis of *Aspergillus* species identified either using morphology plus physiology or using DNA sequences shows that the profile of secondary metabolites is species specific, while individual secondary metabolites may occur in closely related species, in less closely related species within a genus and even in completely unrelated species. Papers by Patron et al. (2007), Khaldi et al. (2008), Schmitt and Lumsch (2009), Ma et al. (2010), Slot and Rokas (2010), Khaldi and Wolfe (2011), Campbell et al. (2012), Wisecaver et al. (2014) and Wisecaver and Rokas (2015) indicate that at least in some cases horizontal gene cluster transfer is a possibility. Within a particular section of *Aspergillus*, often a large number of species share the ability to produce a given secondary metabolite. In *Aspergillus* section *Flavi* 14 out of 24 species can produce sterigmatocystins and 13/24 can produce aflatoxins (Fig. 1). In the same section all species except *A. avenaceus* can produce kojic acid (Varga et al. 2009; 2011b). Within a section the ability to produce a particular secondary metabolite seems to be laterally transferred (inherited from a common ancestor). Most secondary metabolites from *Aspergillus* are produced by species in only one or few sections. Some well know bioactive secondary metabolites, such as penicillin, viridivatin, mevinolin, pseurotin A and cyclopiazonic acid are present in phylogenetically different sections of *Aspergillus* (Fig. 1).

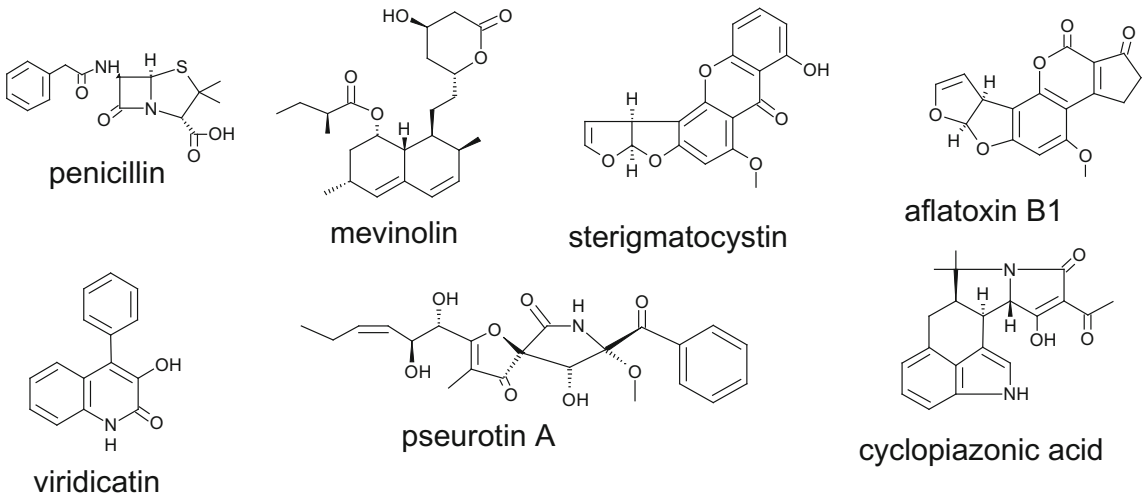

Fig. 1 Well-known secondary metabolites produced by *Aspergillus* species in different sections of the genus

Chemical uniqueness and differences between subgenera and sections of *Aspergillus*

There are six major subgenera in *Aspergillus*: *Circumdati*, *Nidulantes*, *Fumigati*, *Polypaecilum*/*Phialosimplex* (not officially named yet), *Cremei* (only named as a section at present) and *Aspergillus*. As mentioned by Fedorova et al. (2008), these are distantly related, but with the necessary transfers of misplaced Aspergilli and Penicillia (Samson et al. (2014); Visagie et al. 2014c), they form a monophyletic clade (Houbraken and Samson 2011; Houbraken et al. 2012; Samson et al. 2014). The last three *subgenera* have the common feature in that they grow well at very low water activities and often tolerate high concentrations of sodium chloride (most pronounced in subgenus *Aspergillus* section *Aspergillus* and *Restricti*, most of the species formerly in the genus *Eurotium*) (Pitt and Hocking 2009). Halotolerance or xerotolerance is also reflected in the halotolerant *Polypaecilum pisci* being transferred to *Aspergillus pisci*, and *Basipetospora halophile* = *Oospora halophile* = *Scopulariopsis halophilica* = *Phialosimplex halophila* (Pitt and Hocking 1985; Greiner et al. 2014) being transferred to *Aspergillus baarnensis* and *Phialosimplex salinarum* obviously also to be transferred to *Aspergillus* (Samson et al. 2014). Subgenus *Circumdati* and and its sister subgenus *Nidulantes* are closely related, for example hülle cells, aflatoxins, kojic acid, indole diterpenes, and bicyclo[2.2.2]diazaoctanes are found in both subgenera (Raper and Fennell 1965; Yaguchi et al. 1994; Varga et al. 2009; Finefield et al. 2012; Cai et al. 2013). Some known secondary metabolites, present in cladistically different sections of *Aspergillus*, are shown in Fig. 1.

Unique extrolites in subgenus *Circumdati*

The subgenus *Circumdati* contains most biotechnologically important *Aspergilli*, such as *A. niger*, *A. oryzae*, *Aspergillus. tamarii* and *A. terreus*. Apart from species in subgenus *Fumigati*, subgenus *Circumdati* also contains the most important pathogenic species and mycotoxin producers. Within subgenus *Circumdati*, the sections have quite few SMs in common, but they do have many analogous SMs in common. Section *Nigri* species can produce the unique compounds: calbistrins, fumonisins, malformins, naphtho-γ-pyrones, nigerloxins, nigragillins, okaramins, pyranonigrins, tensidols, and yanuthones (Nielsen et al. 2009 (Fig. 2)). Section *Flavi* species can produce the unique compounds asperfurans, asperlicins, cyclopiamins and griseofulvins (Varga et al. 2011a, b); section *Circumdati* species can produce the unique compounds aspochraceins/sclerotiotides, aspyrones, chlorocarolides, destruxins, melleins, ochrindols, penicillic acid, petromindols, preussins, sulpinins and xanthomegnins (Visagie et al. 2014a); section *Candidi* species can produce chloroflavonins and xanthoascins; and section *Terrei* and *Flavipedes* species can produce the unique compounds aspochalasins, asterriquinols, butyrolactones, citreoviridin, citrinins, geodins, mevinolins and terreic acids (Samson et al. 2011a) (Fig. 2). Species in these sections produce many more SMs, but some of these will be mentioned as similar or analogous SMs in different sections. An overview of SMs that are unique in the subgenus *Circumdati* sections *Nigri*, *Flavi*, *Circumdati*, *Terrei* and *Flavipedes* are presented in Fig. 2. A large number of these extrolites are very bioactive.

Unique extrolites in subgenus *Nidulantes*

Among the unique SMs in subgenus *Nidulantes* are aspernidins, asperugins, asteltoxins, austins, austocystins, cordycepins, echinocandins/mulundocandins, emecorrugatins, ethericins, falconensins, falconensons, emericellins, ophiobolins, shamixanthones, stromemycin, sydowinins and ustic acids (Fig. 3.) (Turner 1971; Turner and Aldridge 1983; Cole and Scheweikert 2003, Cole et al. 2003). However, many other SMs are shared with species in other *Aspergillus* subgenera and sections.

Unique extrolites in subgenus *Fumigati*

There are several unique SMs in subgenus *Fumigati* (Fig. 4) In section *Fumigati*, some important ones are fiscalins, fischerins, fumagillins, fumigaclavins, fumigatonins, fumiquinazolins, glabramycins, helvolic acids, pyripyropens, ruakuric acids, tryptoquivalins, viridicatumtoxins and viriditoxins and in section *Clavati* expansolides, cytochalasin E and patulin (Frisvad 1985; Varga et al. 2007a, b, c, Samson et al. 2007a, b; Hong et al. 2008; Frisvad et al. 2009).

Unique extrolites in subgenus *Aspergillus*, section *Cremei* and subgenus '*Polypaecilum*/*Phialosimplex*'

In section *Aspergillus* and *Restricti*, unique SMs include asperglaucide, asperentins, auroglaucins, echinulins, epiheveadride, flavoglaucins and neoechinulins (Fig. 5) (Slack et al. 2009; Turner 1971; Turner and Aldridge 1983; Cole and Scheweikert 2003, Cole et al. 2003), while section *Cremei* species can produce asperolides, anthraquinone-derived bianthrons, leuconic acid, citraconic anhydrides and wentilactones uniquely (Fig. 5) (Verchère et al. 1969; Turner 1971; Assante et al. 1979; Dorner et al. 1980; Selva et al. 1980; Turner and Aldridge 1983; Cole and Scheweikert 2003, Cole et al. 2003; Sun et al. 2012). Asperglaucide from *Aspergillus restrictus* and *Aspergillus penicillioides* (Itabashi

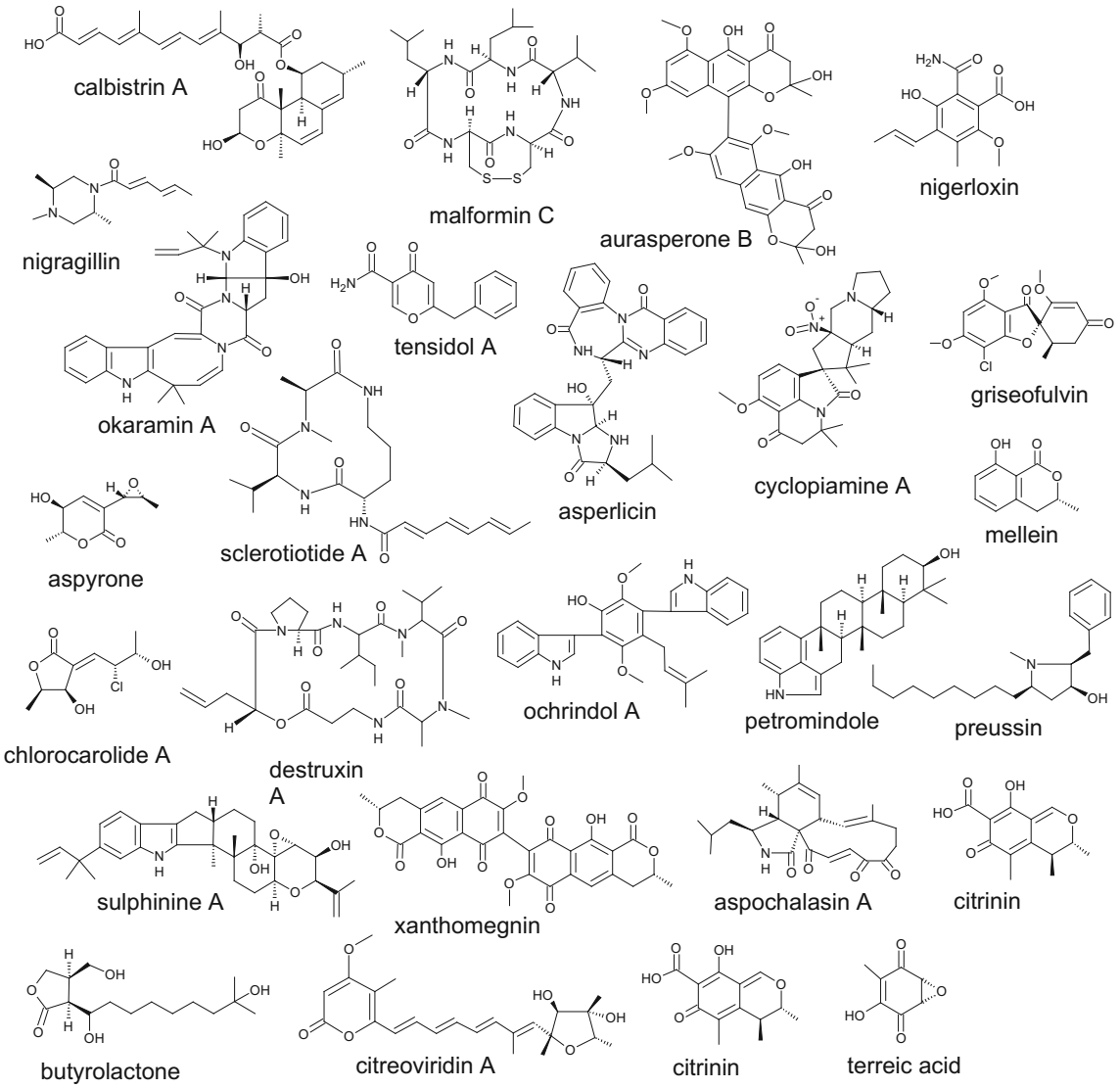

Fig. 2 A selection of *unique* secondary metabolites produced by species in *Circumdati*, sections *Nigri*, *Flavi*, *Circumdati*, *Flavipes* and *Terrrei*

et al. 2006) has a clear resemblance to asperphenamate found in *Aspergillus flavipes* in subgenus *Circumdati* section *Flavipedes* (Clark et al. 1977).

The same secondary metabolite produced in phylogenetically different subgenera and sections of *Aspergillus*

Despite the chemical differences between sections, there are several examples of the same SM being produced by species in different sections in *Aspergillus*, even phylogenetically more distantly related *Aspergilli*. This can be explained by lateral or horizontal SM gene cluster transfer or by reinvention of a gene cluster coding for the same secondary metabolite biosynthetic family. The results obtained so far indicate that lateral gene transfer is common within a series or section of a genus, while horizontal gene transfer (HGT) is more likely in phylogenetically more distant species in a genus or even very distantly related genera across the whole fungal kingdom (Rank et al. 2011; Campbell et al. 2012; Wisecaver and Rokas 2015). HGT of either a gene cluster or a whole mini-chromosome can then be a result of species occurring in the same habitat with a large degree of competition/collaboration and the same ecological challenge (Ma et al. 2010).

The polyketide sterigmatocystin (Fig. 1) has been found in widely different genera, including *Aschersonia*, *Aspergillus*, *Bipolaris*, *Botryotrichum*, *Chaetomium*, *Humicola*, *Moelleriella*, *Monicillium* and *Podospora* but also in widely different sections of *Aspergillus* including sections *Flavi*, *Ochraceorosei*, *Aenei*, *Nidulantes*, *Versicolores* and *Cremei*. Sterigmatocystin is most common in the two sister subgenera *Circumdati* and *Nidulantes* (Rank et al. 2011), while only *A. inflatus* in section *Cremei* produce it, and those *Aspergillus*

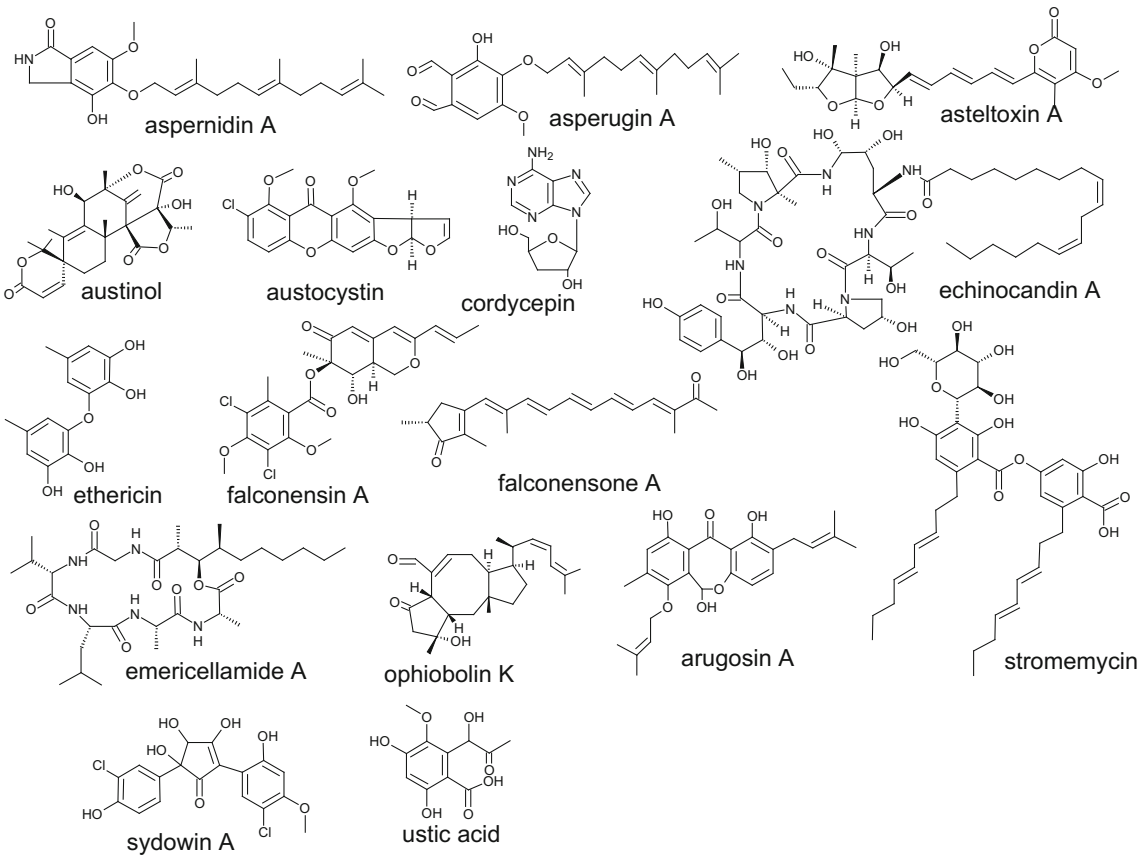

Fig. 3 A selection of *unique* secondary metabolites produced by species in subgenus *Nidulantes*, sections *Nidulantes*, *Aenei*, *Usti*, and *Versicolores*

sections are distantly related (Houbraken and Samson 2011). These genera span the Pezizomycotina, i.e. nearly all known filamentous ascomycetes. One further species *Staphylotrichum boninense* producer sterigmatocystin precursors, 5′-oxyaverantin, averantin and versicolorin B that are galactofuranosylated (Tatsuda et al. 2015), indicating that even sterigmatocystins and aflatoxins may be present as glycosides in foods (masked mycotoxins). Since it appears improbable that a common ancestor of all ascomycetes could produce sterigmatocystin or its precursors, the ability to produce this secondary metabolite must have evolved independently a large number of times, or the gene cluster or a chromosome carrying, it must have been horizontally transferred as suggested by Slot and Rokas (2011) for *Aspergillus* and *Podospora*. Secondary metabolites derived from sterigmatocystin, aflatoxins, are present in only two genera: *Aspergillus* (Varga et al. 2009) and *Aschersonia* (Kornsakulkarn et al. 2012, 2013). Within *Aspergillus*, there are some interesting differences between sections: Aflatoxins G_1 and G_2 has only been found in section *Flavi*, while species in other sections never produce aflatoxins G_1 and G_2, but accumulate both sterigmatocystin and aflatoxin B_1 (Frisvad et al. 2005). Concomitant accumulation of aflatoxin B_1 and sterigmatocystins is also seen in *Aschersonia coffeae* and *Aschersonia marginata* (Kornsakulkarn et al. 2012, 2013). Production of sterigmatocystin is restricted to the subgebera *Circumdati* section *Flavi* and *Nidulantes* sections *Aenei*, *Ochraceorosei*, *Versicolores* and *Nidulantes*, but has also been detected in the more distantly related *A. inflatus* in section *Cremei* (Rank et al. 2011; Samson et al. 2014). Interestingly sterigmatocystin and aflatoxins have never been found in *Penicillium*.

The bioactive bicyclo[2.2.2]diazaoctanes, such as aspergamides, stephacidins, aspergillimides and notoamides are produced by several species in closely related sections *Circumdati*, *Nigri* and *Candidi* (Finefield et al. 2012; Cai et al. 2013), but also by species in subgenus *Nidulantes* section *Versicolores* (Finefield et al. 2012; Kato et al. 2015). Some *Aspergillus* species produce both enantiomers of these bicyclo[2.2.2]diazaoctanes, and in some cases, the final biosynthetic product is only of one configuration (Kato et al. 2015).

The aspergillic acids are also produced by species in several sections in subgenus *Circumdati*, but has not been found outside this subgenus yet. Many species in section *Flavi* produce aspergillic acids (White and Hill 1943; Varga et al. 2011a, b), species in section *Circumdati* can produce neoaspergillic acids (Maebayashi et al. 1978) and *A. flavipes* (section *Flavipedes*) produces flavipucin (Findlay and Radics 1972).

The nephrotoxin ochratoxin A is produced by species in the closely related sections *Circumdati*, *Flavi* and *Nigri* in

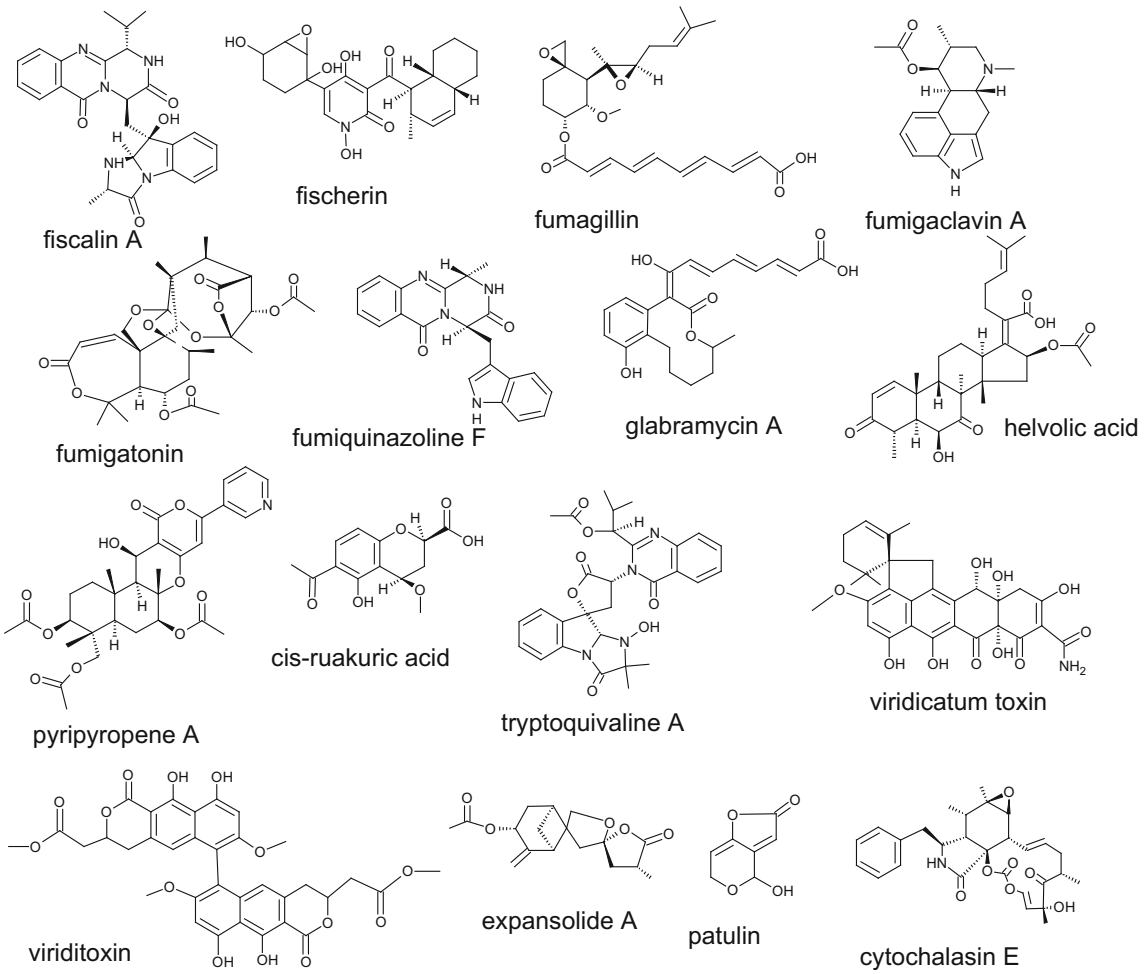

Fig. 4 A selection of *unique* secondary metabolites produced in subgenus *Fumigati*, section *Fumigati* and *Clavati*

subgenus *Circumdati* only (Frisvad et al. 2004a, Samson et al. 2004; Varga et al. 2011a, b; Visagie et al. 2014a). This mycotoxin has also been found in *Penicillium verrucosum* and *Penicillium nordium*, however (Frisvad et al. 2004b), but not in species in any other fungal genus.

In several cases, certain SMs are produced by quite unrelated species of *Aspergillus*, for example pseurotin A (Fig. 1) has been found in *A. fumigatus* (Wenke et al. 1993) in section *Fumigati*, while the distanly related *A. nomius* in section *Flavi* also produce it (Varga et al. 2011a, b). Similarly, several

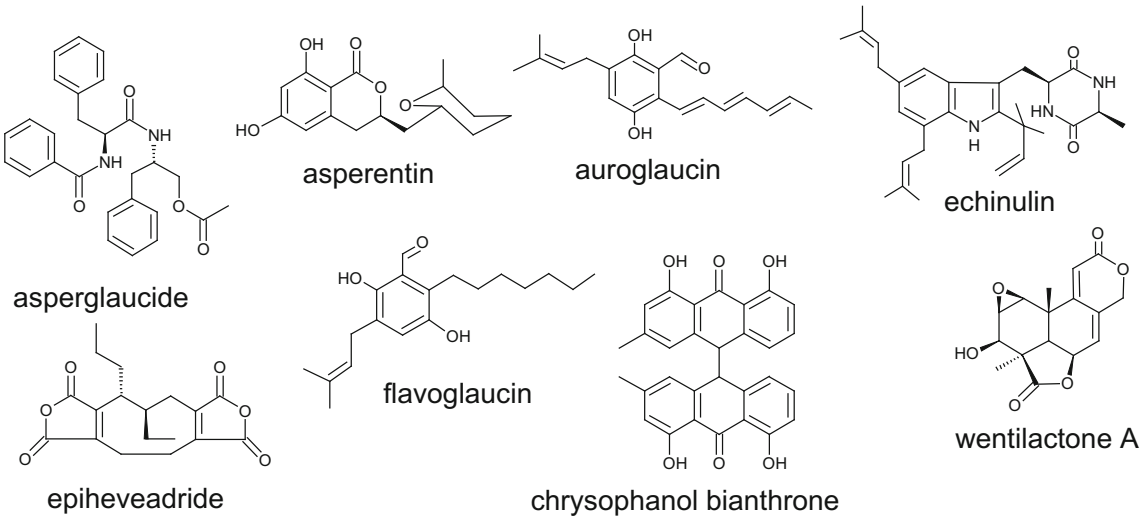

Fig. 5 A selection of *unique* secondary metabolites produced by species in subgenus *Aspergillus* sections *Aspergillus* and *Restricti*, and in section *Cremei*

species in section *Flavi* produce cyclopiazonic acid (Varga et al. 2011a, b), while *Aspergillus lentulus* and *Aspergillus fumisynnematus* in section *Fumigati* also produce this mycotoxin (Larsen et al. 2007).

Viridicatin (Fig. 1) and related compounds are produced by species in cladistically different sections of *Aspergillus*. It is produced by *Aspergillus sclerotiorum* in section *Circumdati* (Visagie et al. a, b, c), *Aspergillus jensenii* in section *Versicolores* (reported as *Aspergillus nidulans* by Ishikawa et al. 2014) and by *A. fumigatus* in section *Fumigati* (Frisvad and Dyer, unpublished).

Penicillins (Fig. 1) are also produce by phylogenetically different species in different sections: *A. nidulans* and other *Aspergilli* produce penicillins (Dulaney 1947a, b), while *A. parasiticus* and *A. flavus* in section *Flavi* and *Aspergillus clavatus* in section *Clavati* also produces penicillins (Arnstein and Cook 1947).

Analogous secondary metabolites are produced in different sections of *Aspergillus* (heteroisoextrolites)

The many secondary metabolites produced from one biosynthetic origin, a biosynthetic family of compounds, could be called small molecule isoextrolites. However, there are functionally and biosynthetically quite similar SMs that may be analogous. We call these metabolites for small molecule heteroisoextrolites. Given the large phylogenetic distance between the main subgenera of *Aspergillus* (Fedorova et al. 2008), it is to be expected that the species in those subgenera produce different versions of the functionally the same kind of secondary metabolite. An example is 6-methylsalicylic acid-derived antibiotically active secondary metabolites of similar, but not identical structures (Fig. 6). Species in section *Flavi* produce parasitenone (Son et al. 2002), in section *Nigri* some species produce the terpene-decorated yanuthones (Bugni et al. 2014; Holm et al. 2014), in section *Terrei* some species produce terreic acid (Guo and Wang 2014; Guo et al. 2014), in section *Fumigati* some species produce fumigatin oxide (Yamamoto et al. 1965), in section *Clavati* most species produce (+)-epoxydon and the *end-product* patulin is also produced (Varga et al. 2007c), while another species in the section, *Aspergillus acanthosporus*, produces (+)-isoepoxydon (Kontani et al. 1990). These epoxyquinones and epoxyquinols thus seem to be spanning the whole genus, except that species in sections *Aspergillus* and *Restricti* have not been reported to produce these compounds.

Small organic acids (Fig. 7) should be classified as secondary metabolites when they are secreted and accumulated (Frisvad 2015). The gene cluster for itaconic acid has been characterized (Van den Straat et al. 2014), and in *Aspergillus*, this acid has been found in *Aspergillus itaconicus* (Kinoshita 1931) and *Aspergillus gorakhpurensis* (Busi et al. 2009) in section *Cremei* and in *A. terreus* in section *Terrei* (Van den Straat et al. 2014). It appears that most sections of *Aspergillus* have a unique profile of organic acid production. In *Aspergillus* section *Flavi*, most species produce kojic acid (Varga et al. 2011b), which is glucose derived (Terebayashi et al. 2010) and malic acid as the main acids (Peleg et al. 1988; Knuf et al. 2014). In the phylogenetically closely related *Aspergillus* section *Nigri*, *A. niger*, *Aspergillus carbonarius* and *Aspergillus tubingensis* predominantly produce citric acid, oxalic acid and gluconic acid, depending on pH (Goldberg et al. 2006). *A. niger* was originally reported to produce citric acid consistently (Moyer 1953a, b), but some of the acid-producing strains were later re-identified to *A. carbonarius* and *A. tubingensis* (Frisvad et al. 2011). Furthermore a citric acid producing *Aspergillus wentii* (Moyer 1953a, b), was later shown to be *A. niger* (Frisvad et al. 2011). Deletion of the glucose oxidase gene in *A. carbonarius* resulted in the production of citric acid, oxalic acid and malic acid (Yang et al. 2014), but apparently malic acid is not *naturally* overproduced

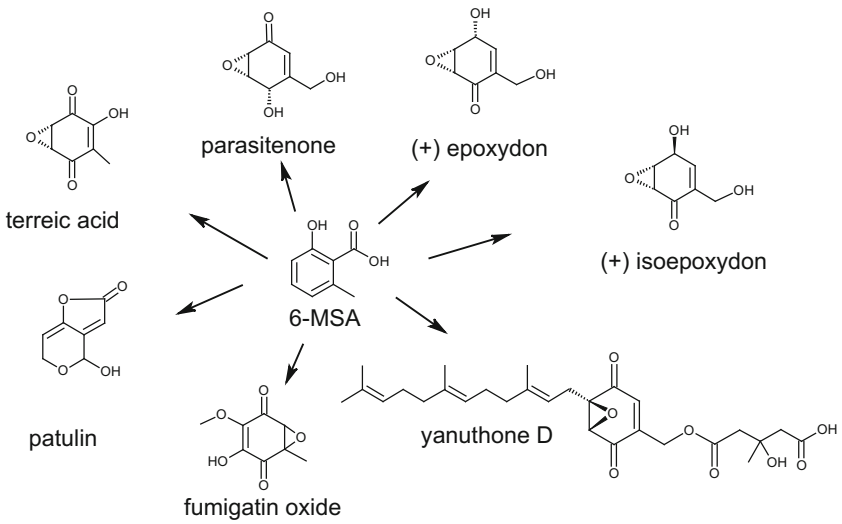

Fig. 6 Some 6-methylsalicylic acid (6-MSA)-derived secondary metabolites in different sections of *Aspergillus* (see text for the producers of each compound)

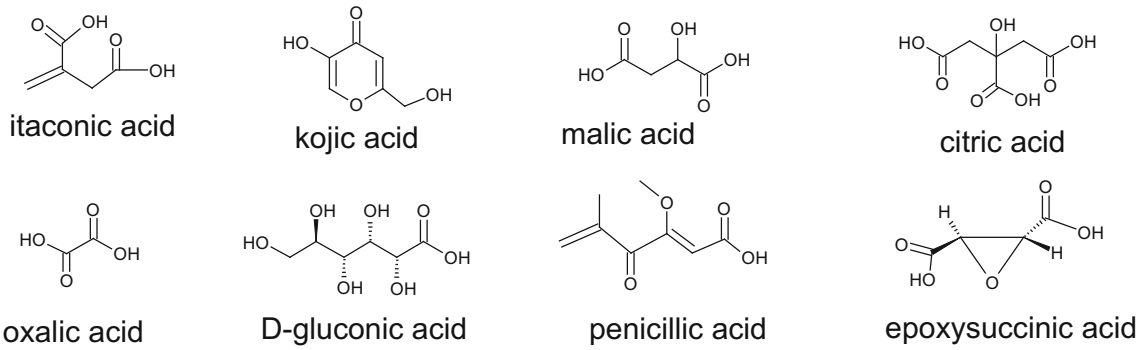

Fig. 7 Examples of small organic acids produced by species in different sections of *Aspergillus*

in *A. carbonarius*. Although seemingly a major small acid produced by *A. niger*, citric acid has also been reported from *Aspergillus lanosus* in section *Flavi*, *Aspergillus ochraceus* and *Aspergillus melleus* in section *Circumdati* and in *A. gorakhpurensis* in section *Cremei* (Srivastava and Kamal 1980). However, citric acid production is much stronger and more consistent in *A. niger*. In section *Circumdati*, the dominant small acid seems to be malic acid (Srivastava and Kamal 1980; West 2011), but most species in that section produce the small polyketide acid penicillic acid (Frisvad et al. 2004a, b; Visagie et al. 2014a, b, c), not produced by species in any other *Aspergillus* section. The main acid produced by *A. fumigatus* appear to be epoxysuccinic acid (Martin and Foster 1955), but in general species in the unrelated sections *Nigri*, *Terrei* and *Cremei* are the most efficient producers of small organic acids.

A systematic study of all species in section *Nigri* has not been performed yet, but preliminary studies indicate that while the biseriate species in section *Nigri* produce large amounts of citric acid/oxalic acid/gluconic acid, the uniseriate species are much less productive.

Fumonisins were discovered in *A. niger* in 2007 (Frisvad et al. 2007b, 2011) and in a recent paper a motif-independent method for prediction of secondary metabolite gene clusters, *A. fumigatus* was predicted to produce fumonisins (*top hit*) based on the gene cluster in *Fusarium graminearum* (Takeda et al. 2014). However, fumonisins have never been detected in *A. fumigatus*. Interestingly, *A. fumigatus* and *A. lentulus* produce sphingofungins and fumifungin (Larsen et al. 2007), structurally related to fumonisins (Fig. 8), so this is probably reflecting some sequence similarities in the two gene clusters. Sphingofungins and fumonisins may also be heteroisoextrolites.

Some unique chlorinated PKS-NRPS-derived molecules have been detected in sections *Flavi*, *Circumdati*, *Nigri* and *Candidi*. While ochratoxin A, a phenylalanine PKS hybrid, is present in species in *Circumdati*, *Flavi* and *Nigri* (Frisvad et al. 2011; Varga et al. 2011a, b; Visagie et al. 2014a, b, c); it has never been found in section *Candidi*. Interestingly the only flavonoid-type SM known in fungi, chlorflavonin, is produced by *Aspergillus candidus* and is also derived from a phenylalanine and a PKS hybrid that is chlorinated (Fig. 9) (Burns et al. 1979). This indicates that different section-specific analogous secondary metabolites may be produced in *Aspergillus*. A comparison of the gene clusters coding for production ochratoxins and chlorflavonins may throw light upon this interesting observation.

Another group of antioxidative secondary metabolites abundant in species in section *Candidi* is terphenyllins and candidusins (Rahbaek et al. 2000; Yen et al. 2001), probably being overproduced to protect the white/yellow conidia of these fungi rather than via melanin, as opposed to species in section *Nigri* that produce very large amounts of melanins. However, the terphenyllins and candidusins have analogous SM molecules in section *Nigri*: cycloleucomelon and atromentin (Hiort et al. 2004) and aspulvinones in section *Terrei* (Gao et al. 2013). All these biosynthetic families are produced via the shikimic acid pathway (Turner 1971). Analogous alkaloidic shikimic acid derived SMs to the compounds in other sections of *Aspergillus* are emerin and epurpurins in section *Nidulantes* (Ishida et al. 1975;

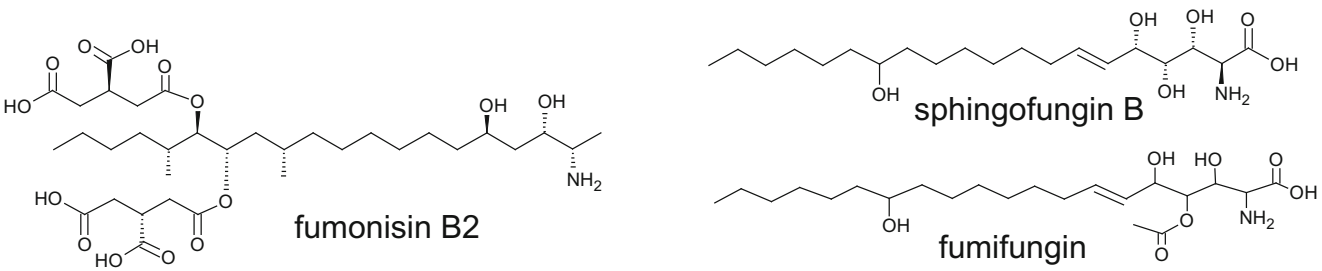

Fig. 8 Analogous compounds in *Aspergillus* in the distantly related sections *Nigri* and *Fumigati*: Fumonisin B_2 from *A. niger* and fumifungins and sphingofungins from *A. fumigatus* and *A. lentulus*

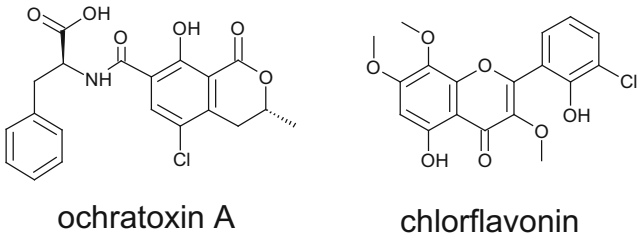

Fig. 9 Ochratoxin A is a chlorinated PKS-NRPS-derived secondary metabolites produced from phenylalanine and a polyketide by species in section *Nigri*, *Flavi* and *Circumdati*. Chlorflavonin is also derived from phenylalanine and a polyketide and is chlorinated, so an example of analogous biosynthetic pathways

Takahashi et al. 1996), xanthoascin in section *Candidi* (Takahashi et al. 1976) and fumiformamide in *Fumigati* (Zuck et al. 2011) (Fig. 10). Thus, it seems that shikimic acid derived functionally quite similar SMs are produced by species in the different sections of *Aspergillus*.

Gliotoxin is an important secondary metabolite produced by *A. fumigatus* and related species in section *Fumigati*. Even though this epidithiodioxopiperazine has been reported in trace amounts from other potentially pathogenic *Aspergilli*, including *A. niger*, *A. flavus* and *A. terreus* (Lewis et al. 2005; Kupfahl et al. 2008). The results obtained by latter two groups suffered from unavailability of strains, so the results could not be verified, and there is some doubt whether this was just transient or non-production. Gliotoxin seems to be only produced in high amounts by species in section *Fumigati* in *Aspergillus*. However, the other species produce biosynthetically closely related epidithiodioxopiperazines: *A. flavus*, *A. oryzae* and *A. tamarii* can produce aspirochlorine = oryzachlorin (Berg et al. 1976; Sakata et al. 1982; 1983; Monti et al. 1999; Chankhamjon et al. 2014), *A. terreus* can produce acetylaranotin (Miller et al. 1968; Cosulich et al. 1968; Guo et al. 2013) and *A. striatus* and six other species in section *Nidulantes* can produce emestrin (Seya et al. 1985; Terao et al. 1990; Kawahara et al. 1994; Ooike et al. 1997) (Fig. 11). Interestingly, both aspirochlorine and acetylaranotin is biosynthesized via a phenylalanyl phenylalanine diketopiperazine, while gliotoxin is biosynthesized via phenylalanyl serine diketopiperazine (Amatov and Jahn 2014).

Emodin has been found in many *Aspergillus* species across the whole genus, but is also common in *Penicillium*, *Talaromyces* and even in plants (Turner 1971; Turner and Aldridge 1983; Izhaki 2002; Yilmaz et al. 2014). It has multiple effects on other organisms; has an antibacterial, antifungal, antiparasitic and antiviral effects; is a feeding deterent on insects, birds and small mammals; and is also an antioxidant (Izhaki 2002). Regarding *Aspergillus*, it was early reported as a mycotoxin from *A. wentii* (section *Cremei*) (Wells et al. 1975), but usually emodin, biosynthesized via atrochrysone, is converted into more chemically elaborate end-products, depending on the *Aspergillus* section (Fig. 12). In subgenus *Aspergillus*, emodin is turned into anthrons (Turner 1971) and in section *Cremei*, several *Aspergillus* species turns emodin into emodin bianthrones and isosulochrin (Assante et al. 1980; Hamazaki and Kimura 1983; Rabie et al. 1986; Ji et al. 2014). In section *Nigri* and *Circumdati*, emodin is converted to secalonic acids (Yamazaki et al. 1971; Andersen et al. 1977; Turner and Aldridge 1983, Varga et al. 2011a). In *A. fumigatus*, emodin is converted to either trypacidin/3-*O*-methylsulochrin or into chloroanthraquinones (Yamamoto et al. 1968). In *A. terreus*, emodin is converted in to geodin

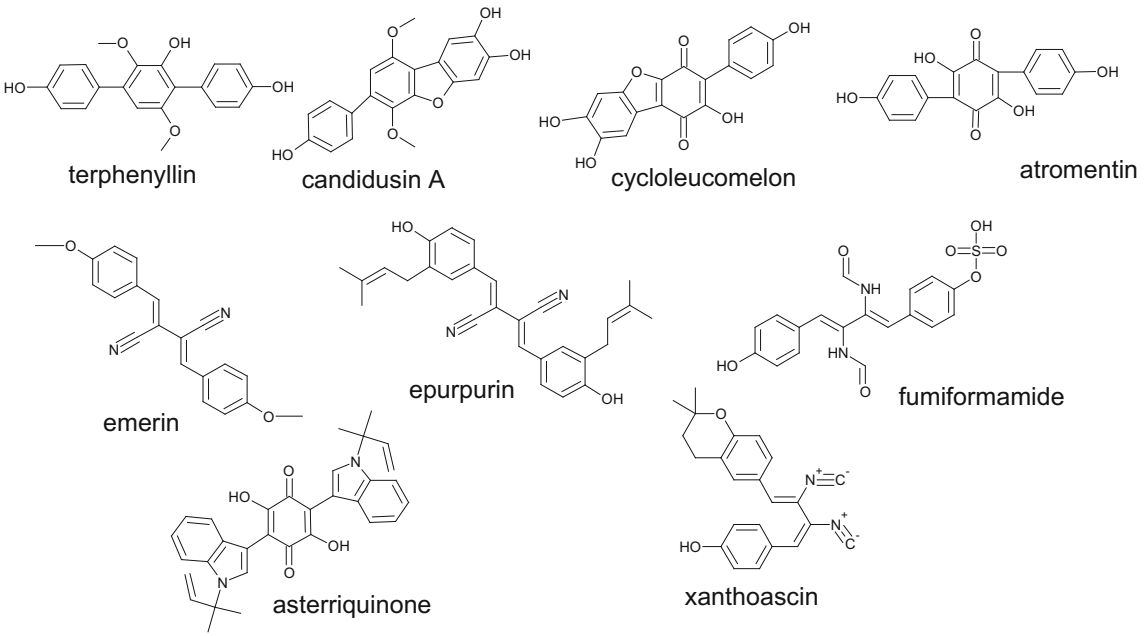

Fig. 10 Shikimic acid-derived analogous secondary metabolites from *Aspergillus* sections *Candidi* (terpenyillin, candidusin A, xanthoascin), *Nigri* (cycloleucomelon and atromentin), *Nidulantes* (emerin and epurpurin) and *Fumigati* (fumiformamide)

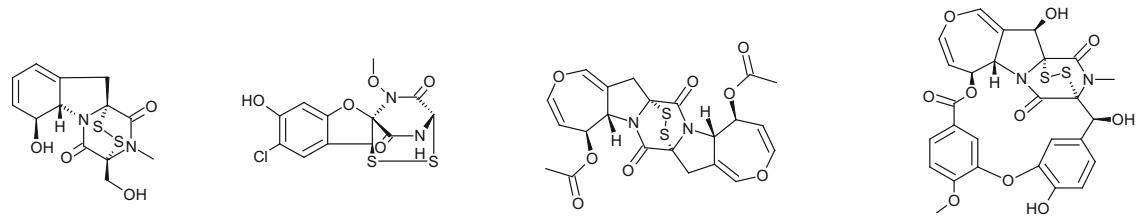

Fig. 11 Analogous secondary metabolites in different *Aspergillus* sections. Gliotoxin, aspirochlorin, acetylaranotin and emestrin. Emestrin is fused with a polyketide and so differs from the others that are only derived from amino acids (phenylalaninyl phenylalanine diketopiperazine for aspirochlorin and acetylaranotin and phenylalanine and serine in gliotoxin

(Nielsen et al. 2013). In subgenus *Nidulantes*, emodin is converted to emericellin and shamixanthones (Nielsen et al. 2011; Sanchez et al. 2011; Simpson 2012) and may also be involved in biosynthesis and the specific allocation of asperthecin in the ascomata (Brown and Salvo 1994; Szewczyk et al. 2008).

Dimeric diketopiperazines are also produced by fungi in different sections of *Aspergillus*: asperazine and similar compounds were isolated from *A. tubingensis*, *Aspergillus vadensis* and *Aspergillus luchuensis* in section *Nigri* (Varoglou et al. 1997; Varga et al. 2011a; Li et al. 2015) ditryptophenaline by *A. flavus* in section *Flavi* (Springer et al. 1977), aspergilazine A is produced by *Aspergillus taichungensis* in section *Candidi* (Cai et al. 2012), WIN 64821, probably from *A. flavipes* in section *Flavipedes* (Barrow et al. 1993), and eurocristatine is produced by by *Aspergillus cristatus* in section *Aspergillus* (Gomes et al. 2012).

The indoloterpenes are often produced in sclerotia only and occur in section *Flavi*, *Nigri*, *Circumdati*, *Candidi* and *Nidulantes*: Aflavinins are produced in sclerotia of section *Flavi* (Gallagher et al. 1980; Cole et al. 1981), 10,23-dihydro-24,25-dehydroaflavinins are produced in sclerotia by species in section *Nigri* (Tepaske et al. 1989, Frisvad et al. 2014), radarins and secopenitrems are produced in the sclerotia of species in *Circumdati* (Laakso et al. 1992) and emindole SB and similar compounds are produced in ascomata by species in section *Nidulantes* (Nozawa et al. 1988) and in *Aspergillus cejpii* in subgenus *Fumigati* (Harms et al. 2014), in addition to fischerindoline in *Aspergillus thermomutatus* in section *Fumigati* (Masi et al. 2013).

The bicoumarins, kotanins, aflavarins, isokotanins and desertorins are similar polyketides produced in the sclerotia of species in several sections of *Aspergillus*. Species in section *Flavi*, *A. alliaceus* and *A. flavus* produce isokotanins and aflavarins (TePaske et al. 1992; Laakso et al. 1994), *A. clavatus* in section *Clavati* and *A. niger* in section *Nigri* produce kotanins (Cutler et al. 1979; Varga et al. 2007c; Nielsen

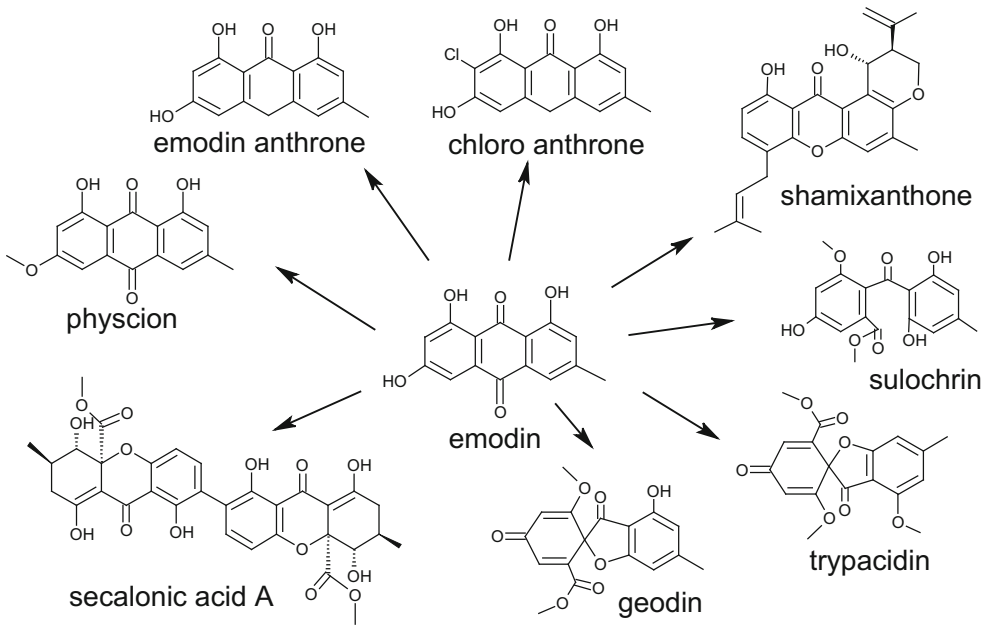

Fig. 12 Some emodin-derived secondary metabolites in different sections of *Aspergillus*. Secalonic acid A is produced by *A. sclerotiorum* in section *Circumdati*, and the optical antipode secalonic acid D is produced by several uniseriate *Nigri* species, sulochrin is produce by *A. wentii* in section *Cremei*, while geodin is produced by *Aspergillus terreus* in section *Terrei*, anthrons and bianthrons are produced by species in sections *Aspergillus* and *Cremei* and shamixanthone is produced by species in section *Nidulantes*. The chloro anthrone is produced by *A. fumigatus* in section *Fumigati* in addition to 3-*O*-methylsulochrin and trypacidin

et al. 2009) and *Aspergillus desertorum* in section *Nidulantes* produces desertorins (Nozawa et al. 1987). However, the kotanins are produced in isolates of *A. niger* without sclerotia being produced (Frisvad et al. 2014), so there is no strict correlation between ascoma or sclerotium in different *Aspergillus* sections and these bicoumarins.

Other analogous specialized metabolites including siderophores (Yin et al. 2013) have been found in several sections of *Aspergillus*, but the examples above show that these heteroisoextrolites are shared by sections covering the whole genus *Aspergillus*.

Conclusions

The genus *Aspergillus* contains a large number of species that are capable of producing a large number of specialized metabolites. Some of these metabolites are produced on most common substrates, while others need special chemical signals (xenoextrolites) in order to be produced. In the different sections of *Aspergillus*, the species produce many specialized metabolites in species-specific profiles. These profiles contain unique SMs, SMs shared with related and distantly related *Aspergilli* and analogous SMs (heteroisoextrolites) which are biosynthetically related and often functionally similar extrolites. The many shared similar and analogous secondary metabolites across the genus *Aspergillus* indicates that this genus is broad, yet has similarities indicating it should not be split into several smaller genera. The *unique* metabolites in many of these sections of *Aspergillus* are only unique within the genus *Aspergillus*, as several of those occur in *Penicillium* species also. However, we hypothesize that many more unique secondary metabolites will be discovered in each of the *Aspergillus* sections, based on genome sequencing evidence. The ability to accumulate and secrete small molecule extrolites, therefore, is a reaction to challenges in the environments and competition and collaboration in species consortia, rather than being determined only by phylogeny. The secondary metabolites have probably evolved based on gene duplications, horizontal gene transfer and new gene cluster formations as a reaction to the environment.

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Conflict of interest The authors declare that they have no competing interests.

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