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An amendment of *Aspergillus* section *Candidi* based on chemotaxonomical evidence

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Abstract

A novel 2,2′-epoxy-terphenyllin, candidusin C, in addition to the well known secondary metabolites terphenyllin, 3-hydroxyterpenyllin and chlorflavonin, has been isolated from the chemically unexplored fungus *Aspergillus campestris*. The latter three are known secondary metabolites from *Aspergillus candidus* and therefore a large number of Aspergilli were screened for production of these compounds to see whether they could be regarded as chemotaxonomical indicators of section membership in the monotypic *Aspergillus* section *Candidi*. The results indicated that *A. campestris* and *A. taichungensis* should be placed in *Candidi* and this was further confirmed by morphological and physiological similarities. Three species outside the section *Candidi* produced candidusin related secondary metabolites: *Aspergillus arenarius, A. ellipticus* and *Penicillium raistrickii*. Chlorflavonin, however, was only found in section *Candidi*.

Keywords: *Aspergillus candidus*; *A. campestris*; *A. taichungensis*; *Candidi*; Chemotaxonomy; 2,2′-Epoxy-terphenyllin; Candidusin C

1. Introduction

The genus *Aspergillus* has been subdivided into several subgenera and sections based on conidial colour and morphology. One of these sections, *Candidi*, contains only *Aspergillus candidus* (Gams, Christensen, Onions, Pitt & Samson, 1985; Raper & Fennell, 1965) which is a common cereal spoiling organism (Raper & Fennell, 1965). *A. candidus* has been reported to produce several secondary metabolites of the terphenyl-type (Marchelli & Vining, 1975; Kurobane, Vining, McInnes & Smith, 1979; Kobayashi, Takemoto, Koshimizu & Kawazu, 1985; Takahashi, Yoshihira, Natori & Umeda, 1976b) [including candidusins (Kobayashi, Takemura, Koshimizu, Nagano & Kawazu, 1982) and terprenins (Kamigauchi et al., 1998)], in addition to chlorflavonin (Bird & Marshall, 1969), dechlorochlorflavonin (Marchelli & Vining, 1973), xanthoascin (Takahashi et al., 1976b), kojic acid (Kinosita & Shikata, 1969; Cole & Cox, 1981), 3-nitropropionic acid (Kinosita, Ishiko, Sugiyama, Seto, Igarasi & Goetz, 1968), citrinin (Kinosita & Shikata, 1969; Cole & Cox, 1981; Timonin & Rouatt, 1944), and 6-sulfoaminopenicillanic acid (Yamashita et al., 1983).

Other *Aspergillus* sections are rich in species and we wanted to examine whether any newly described *Aspergillus* species with light coloured conidia might belong to section *Candidi* based on biochemical, morphological, and physiological evidence. Species such as *A. campestris* (Christensen, 1982) and *A. taichungensis* (Yaguchi, Someya & Udagawa, 1995) and other species with light conidia have been placed in the sections *Cervini, Flavipedes, Terrei* or *Circumdati* based on light (white, fawn, avellaneus, ochre or yellow) conidium colours, but this placement is based on ease of identification rather than on classificatory or phylogenetic relatedness (Peterson, 1995). There are examples of misidentified and misplaced isolates: an isolate

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(NRRL 1955) identified as *A. candidus* (subgenus *Circumdati* section *Candidi*) was reported to produce the nephrotoxic mycotoxin citrinin (Timonin & Rouatt, 1944), but that particular isolate was later shown to be *A. niveus* (subgenus *Nidulantes* section *Flavipedes*) (Raper & Fennell, 1965). Emphasising on species with white, or yellow conidia, our goal was to screen a large number of species in *Aspergillus* for secondary metabolites in order to see whether the results suggested another taxonomic placement of newly described species.

2. Results and discussion

2.1. Isolation and characterization of compounds from Aspergillus campestris

Initial interest in *A. campestris* was based on the unusually large number of secondary metabolites produced by this species as judged by HPLC diode array analysis of extracts as part of a large chemotaxonomical study on species of the genus *Aspergillus*. Separation of the EtOAc extract of Petri dish cultures of *A. campestris* IBT 13382 resulted in the isolation of the new compound candidusin C (**1**), in addition to 3-hydroxyterphenyllin and chlorflavonin, previously reported from *A. candidus* (Kurobane et al., 1979; Bird & Marshall, 1969). The molecular formula of **1**, $C_{21}H_{18}O_6$, was established by NMR analysis in combination with HREIMS (M^+, 366.109, $C_{21}H_{18}O_6$, Δ −4 ppm). The characteristic UV-spectrum of **1** and ^1H NMR data indicated a structure similar to candidusin A (**2**) and B (**3**), two other metabolites produced by *A. candidus* (Kobayashi et al., 1982). Thus, the NMR analysis, including APT, HMQC and HMBC experiments, provided evidence for a 2,2′-epoxy-terphenyl-structure substituted with three methoxy and two hydroxy groups. The positions of the substituents were determined by comparison of the NMR data of **1** with those of **2**, 3′-demethoxy-6′-desmethyl-5′-methoxycandidusin B (**4**) (Belofsky, Gloer, Gloer, Wicklow & Dowd, 1998) and 6′-desmethyl-candidusin B (**5**) (Belofsky et al., 1998), in addition to analysis of long-range ^1H–^{13}C-correlations (from C1, C4 and C5 to H6, from C1′ to H5′, from C3′ to H5′ and 3′-OMe, from C4′ to H5′ and H2″/H6″, from C6′ to H5′and 6′-OMe, and from C4″ to 4″-OMe) observed in the HMBC spectrum of **1**. Thus, the structure of **1** was established as 2,2′-epoxy-3′,4″,6′-trimethoxy-1,1′:4′,1″-terphenyl-4,5-diol.

2.2. Examination of species and isolates with white and yellow conidia

Having found two biosynthetically different groups of secondary metabolites in common with metabolites reported from *Aspergillus candidus* (terphenyllins and chlorflavonins) prompted us to examine other species with white or light coloured conidia, as the results indicated that *A. campestris* might belong in section *Candidi* rather than in section *Circumdati* as previously suggested by Christensen (1982).

Ten isolates of *Aspergillus candidus*, including the culture ex type, were examined. They all produced terphenyllin and 3-hydroxyterphenyllin and seven of the ten isolates produced at least one of the terphenyllin derivatives candidusin A and/or B. In addition seven of ten isolates produced chlorflavonin and one produced xanthoascin in agreement with Takahashi, Sekita, Yoshihira and Natori (1976a). *A. campestris* produced terphenyllin and 3-hydroxyterphenyllin in common with *A. candidus*, but consistently produced candidusin C in contrast to candidusin A and B produced by *A. candidus* (see Table 1). Although some cultivations were performed up to 10 years ago the isolates were culti-

Table 1
Strains examined for production of *Aspergillus candidus* related secondary metabolites, kojic acid, and citrinin on CYA and YES agar (*x* means metabolite detected)[a]

Section *Candidi*		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
A. candidus	CBS 566.65[b]		*x*	*x*		*x*	*x*	*x*	*x*			
	CBS 567.65		*x*	*x*		*x*	*x*					
	CBS 102.13		*x*	*x*		*x*	*x*	*x*	*x*			
	CBS 266.81			*x*	*x*	*x*	*x*		*x*			
	IBT 21789		*x*	*x*		*x*	*x*	*x*				
	UAMH 1325[c]			*x*	*x*	*x*	*x*		*x*			
	NRRL 5214				*x*	*x*	*x*	*x*				
	IBT I 239y					*x*	*x*	*x*	*x*			
	IBT 12659				*x*	*x*	*x*					
	IBT as5		*x*	*x*		*x*	*x*			*x*		
A. campestris	CBS 348.81[b,d]	*x*				*x*	*x*	*x*				
	IBT 17867	*x*				*x*	*x*					
	UAMH 1324[e]	*x*				*x*	*x*					
	IBT I 174	*x*				*x*	*x*					
	IBT 16773	*x*				*x*	*x*					
A. taichungensis	IBT 19404[b,f]	*x*				*x*	*x*[g]					
Other sections												
A. ellipticus	CBS 707.79				*x*	*x*						
A. helicothrix	CBS 677.79				*x*	*x*						
A. flavus	ATCC 44054[a]										*x*	
A. niveus	NRRL 1955[b]											*x*
A. carneus	NRRL 527[b]											*x*

[a] **1** = Candidusin C, **2** = candidusin A, **3** = candidusin B, **4** = candidusin analogues, **5** = terphenyllin, **6** = 3-hydroxyterphenyllin, **7** = chlorflavonin, **8** = chlorflavonin analogue, **9** = xanthoascin, **10** = kojic acid, and **11** = citrinin.
[b] Type culture.
[c] Received as *A. niveus*.
[d] IBT 13382.
[e] Received as *A. sulphureus*.
[f] PF 1167.
[g] Received as *A. candidus*.

vated on the same media. However, variations in production of secondary metabolites may be due to variations in the composition of Difco yeast extract in the course of 10 years. For example *A. candidus* IBT as5 (no longer available in culture) was cultivated in 1989 and produced xanthoascin as the only strain out of the 10 strains examined (see Table 1).

An isolate claimed to be *A. candidus*, ATCC 44054, indicated to be a mutant of *A. flavus* with white conidia. It produced kojic acid, a metabolite commonly produced by isolates of *A. flavus* (Cole & Cox, 1981). Another isolate claimed to be *A. candidus*, NRRL 1955, proved to be *A. niveus*. This isolate produced citrinin and gregatins as three other isolates of *A. niveus* do (see Table 1). Other species related to *A. niveus* in sections *Flavipedes* and *Terrei*, including *A. carneus* and *A. terreus* also produce citrinin (Cole & Cox, 1981, see Table 1) confirming the close relatedness of these species as indicated by Raper and Fennell (1965).

Previously isolates have been referred to *Aspergillus* sections based primarily on conidium colour, presence of metulae, vesicle shape and arrangement of conidia (Raper & Fennell, 1965). For example section *Candidi* is characterized by conidial heads with persistently white conidia or conidia becoming yellowish cream in age (Raper & Fennell, 1965) and section *Circumdati* (formerly the *A. ochraceus* group) by yellow or ochraceous conidia (Christensen, 1982) and both sections by globose heads as opposed to the columnar heads in sections *Terrei* and *Flavipedes*. *A. campestris* was placed in section *Circumdati* because of its yellowish white conidia and it was not considered closely related to *A. candidus* by Christensen (1982). *A. taichungensis* was equivocally placed in either section *Versicolores, Terrei* or *Flavipedes* (Yaguchi et al., 1995). However, the chemotaxonomical evidence presented here in Table 1 indicates that both species belong to section *Candidi*. This is strongly supported by all the morphological characteristics that are characteristic of the section *Candidi*: slow growing colonies with globose conidial heads having white to yellowish conidia (amended description suggested here), conidiophores smooth, small conidiophores common, metulae present and covering the entire vesicle, some large *Aspergillus* heads with large metulae, conidia smooth or nearly so with a subglobose to ovoid shape (albeit slightly ellisoidal in *A. campestris*), and sclerotia present (dark brown) in *A. taichungensis*. Sclerotia have not been observed in *A. campestris*, but have been observed in *A. candidus* (light cream coloured turning purple to black in age).

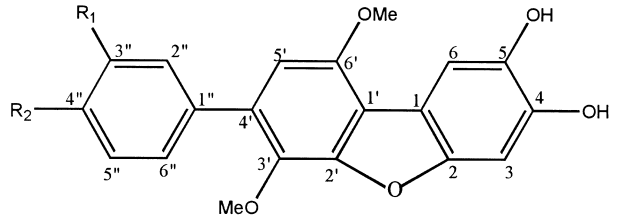
Thus, terphenyllin, 3-hydroxyterphenyllin and candidusins are common in all species in section *Candidi* as amended here, and chlorflavonin is produced by isolates in two species. However, kojic acid and citrinin were not produced by any of the examined strains of *A. candidus*.

2.3. Examination of *Aspergillus* and *Penicillium* species with other conidium colours than white and yellow

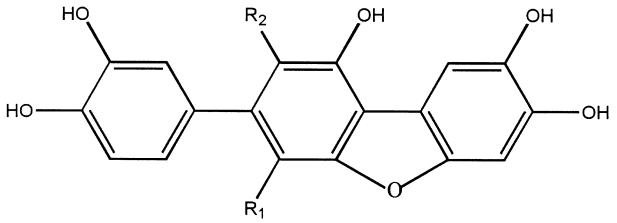
During a screening of approximately 2000 isolates of *Penicillium* and approximately 500 isolates of *Aspergillus*, terphenyllins and candidusins were found in the isolates listed in Table 1 inclusive *A. ellipticus* CBS 707.79 and a synonym of *A. ellipticus*: *A. helicotrix* CBS 677.79, in addition to *Penicillium raistrickii* FRR 1576 and CBS 215.71.

The terphenyl-type of secondary metabolites has also been found in the sclerotia of other species such as *A. arenarius* (Oh, Gloer, Wicklow & Dowd, 1998) and *Penicillium raistrickii* (Belofsky et al., 1998). Our screening confirmed that these compounds were present in those two species and were only found in one further species outside section *Candidi*: *A. ellipticus* in section *Nigri* of *Aspergillus*. These compounds were, however, not found in any of the other species of *Aspergillus* analyzed. For example, none of the several tested strains of all known species in the sections *Circumdati, Flavi, Wentii, Ornati, Usti, Flavipedes, Terrei, Aspergillus, Clavati, Fumigati* and *Cremei* were able to produce either terphenyllin and related compounds nor chlorflavonin under the culture conditions used. Several strains of species in *Nidulantes* and *Versicolores* were also examined and no producers of terphenyllins or chlorflavonins were found. However, it cannot be ruled out that other species not yet examined in the latter two sections or the section *Sparsi* produce these compounds. *A. arenarius* was placed in section *Versicolores*, since the dark yellow-green conidia and metulae covering only the upper part of the vesicle found in this species are too different from the characteristics of the three species in *Candidi* to be considered a member of this section. DNA sequence data could be useful in order to find out the correct phylogenetic placement of *A. arenarius*. In species of *Candidi* the production of terphenyllin like compounds is not dependent on sclerotium production: sclerotia were not observed in any of the cultures used for extraction. One family of secondary metabolites alone does not necessarily indicate close taxonomic or phylogenetic relationship (Geiser, Frisvad & Taylor, 1998). However, when chemotaxonomical and morphological characters are combined, the species in the section *Candidi* seem to be a natural, albeit polythetic (Sneath & Sokal, 1973), group of species that are closely related. Many secondary metabolites are known that occur in species in different genera (Frisvad, Thrane & Filtenborg, 1998), but it has also been shown that closely related species in

series or sections in *Penicillium* and *Aspergillus* produce several secondary metabolites in a polythetic fashion (Frisvad et al., 1998; Lund & Frisvad, 1994). Furthermore, secondary metabolite production is rather consistent in different isolates of the same species examined here, as have been shown for other fungal species previously (Lund & Frisvad, 1994).



1: R_1 = H, R_2 = OMe
2: R_1 = H, R_2 = OH
3: R_1 =OH, R_2 = OH



4: R_1 = H, R_2 = OMe
5: R_1 = OMe, R_2 = H

3. Experimental

NMR spectra were recorded in DMSO-d_6 solution on a Varian 400 FT-NMR spectrometer. EIMS spectra and high-resolution data were obtained on a JEOL AX505W instrument.

3.1. Collection strains and growth conditions

2000 isolates of *Penicillium* (covering all accepted species in the genus) and 500 isolates of *Aspergillus* (covering all species accepted and publically available, except tropical species in the sections *Nidulantes*, *Versicolores* and *Sparsi*) were screened for terphenyllin, candidusins, xanthoascin and chlorflavonin screened using HPLC with diode array detection according to the method of Frisvad and Thrane (1987, 1993). A number of strains (the culture ex type and when available from culture collections more isolates of each taxon) in each of most species in the genus *Aspergillus* were screened for production of chlorflavonins and terphenyllin like compounds with an emphasis on the species in sections *Circumdati, Terrei* and *Flavipedes*. The isolates examined in section *Candidi* are listed in Table 1. The following further isolates with white conidia were examined: CBS 115.27, CBS 114.33, IMI 165060, IBT 16747, IBT 16357, and IBT 18518 (all *A. niveus*). Furthermore the *Aspergillus* isolates examined included cultures ex type listed in Pitt & Samson (1993).

The strains examined were all from the IBT collection of the Dept. of Biotechnology, Technical University of Denmark, Lyngby, Denmark and from other major fungal culture collections such as CBS (Centraalbureau voor Schimmelcultures, Baarn, the Netherlands; ATCC (American Type Culture Collection, Rockville, Maryland, USA; NRRL (National Center for Agricultural Utilization Research, Peoria, Illinois, USA); IMI (CABI Bioscience, Egham, UK) and UAMH (University of Alberta Microfungus Collection and Herbarium, Edmonton, Alberta, Canada). All strains were grown on Czapek yeast autolysate agar (CYA) (Samson, Hoekstra, Frisvad & Filtenborg, 1995), Blakeslee malt extract agar (MEA) (Raper & Fennell, 1965; Samson et al., 1995), yeast extract sucrose agar (YES) (Samson et al., 1995) at 25°C and CYA at 37°C for morphological examinations. CYA and YES agar were used in combination for extraction of secondary metabolites as detailed by Frisvad and Thrane (1987, 1993) and analyzed by HPLC-DAD. One culture of *A. candidus* (IBT 21789) from a salt pan in Slovenia was grown on CYA and YES agar and analyzed separately for each medium as detailed by Smedsgaard (1997).

Five strains of *A. campestris* were examined (see Table 1). The strain used for isolating pure candidusin C (**1**), terphenyllin 3-hydroxyterphenyllin and chlorflavonin was ex type culture, CBS 348.81 = IBT 13382, which was originally isolated from prairie soil, North Dakota (Christensen, 1982). The fungus was cultivated in large scale on 440 Petri dishes with yeast extract sucrose (YES) agar (total 1200 ml) with an incubation time of 12 days at 25°C.

3.2. Extraction and separation of secondary metabolites

The culture (*A. campestris* ex type culture, CBS 348.81 = IBT 13382) and growth media were extracted two times with EtOAc containing 0.5% formic acid giving 13.61 g of crude extract. The extract (13.56 g) was partitioned between 10% aq. MeOH and hexanes and then between 50% aq. MeOH and CH_2Cl_2. A fraction of the CH_2Cl_2 soluble part (1.38 g) was separated using vacuum liquid chromatography with a 5 × 4 cm column packed with Silica gel 60G from Merck and eluted with mixtures of EtOAc/heptane of rising polarity. All separations were guided by the UV spectra of the candidusin analog using analyti-

Table 2
^{13}C and ^{1}H NMR data for **1**

No.	^{13}C	^{1}H
1	114.6	
2	156.7	
3	96.2	7.38 (*s*)
4	148.6	
5	143.5	
6	106.9	7.40 (*s*)
1′	113.8	
2′	149.5	
3′	136.0	
4′	128.6	
5′	105.7	6.73 (*s*)
6′	149.3	
1″	130.9	
2″	115.1	6.85 (*d*, 8.8)
3″	130.4	7.43 (*d*, 8.8)
4″	148.0	
5″	130.4	7.43 (*d*, 8.8)
6″	115.1	6.85 (*d*, 8.8)
3′-OMe	60.6	3.78 (*s*)
6′-OMe	55.9[a]	3.98 (*s*)
4″-OMe	56.1[a]	3.88 (*s*)

[a] Assignments may be interchanged.

cal or preparative HPLC systems coupled to a photodiode-array detector. The fraction containing **1** (ca. 512 mg, EtOAc/heptane 1:3) was further separated on a Lobar LiChroprep Si 60 (40–63 m) size B column from Merck (EtOAc:$CHCl_3$:heptane 50:5:45, 254 nm, 7 ml/min). A part of the 118 mg sample including **1** was separated on a NP semi-preparative column from Waters (Prep Nova-Pak HR silica 6 m 60 Å 25 × 100 mm Prep-Pak Cartridge, EtOAc/heptane 3:7, 10 ml/min, PDA detector) giving pure **1** (11 mg).

Candidusin C (**1**). Solid; λ_{max}^{MeOH} nm (log): 334 (4.39) 295 (4.29) 280 (4.31) 213 (4.61); EIMS *m*/*z* 366; $C_{21}H_{18}O_6$, ^{1}H and ^{13}C NMR data see Table 2.

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References

Belofsky, G. N., Gloer, K. B., Gloer, J. B., Wicklow, D. T., & Dowd, P. F. (1998). New *p*-terphenyl and polyketide metabolites from the sclerotia of *Penicillium raistrickii*. *Journal of Natural Products*, *61*, 1115–1119.

Bird, A. E., & Marshall, A. C. (1969). Structure of chlorflavonin. *Journal of the Chemical Society (C)*, 2418–2420.

Christensen, M. (1982). The *Aspergillus ochraceus* group: two new species from western soils and a synoptic key. *Mycologia*, *74*(2), 210–225.

Cole, R. J., & Cox, R. H. (1981). *Handbook of toxic fungal metabolites*. New York: Academic Press.

Frisvad, J. C., & Thrane, U. (1987). Standardized high-performance liquid chromatography of 182 mycotoxins and other fungal metabolites based on alkylphenone retention indices and UV-VIS spectra (diode array detection). *Journal of Chromatography*, *404*, 195–214.

Frisvad, J. C., & Thrane, U. (1993). Liquid chromatography of mycotoxins. In V. Betina, *Chromatography of mycotoxins: theory and applications* (pp. 253–372). In *Journal of Chromatography Library*, *Vol. 54*. Amsterdam: Elsevier.

Frisvad, J. C., Thrane, U., & Filtenborg, O. (1998). Role and use of secondary metabolites in fungal taxonomy. In J. C. Frisvad, P. D. Bridge, & D. K. Arora, *Chemical fungal taxonomy* (pp. 289–319). New York: Marcel Dekker.

Gams, W., Christensen, M., Onions, A. H. S., Pitt, J. I., & Samson, R. A. (1985). In R. A. Samson, & J. I. Pitt, *Advances in Penicillium* and *Aspergillus systematics* (pp. 55–62). New York: Plenum Press.

Geiser, D. M., Frisvad, J. C., & Taylor, J. W. (1998). Evolutionary relationships in *Aspergillus* section *Fumigati* inferred from partial β-tubulin and hydrophobin DNA sequences. *Mycologia*, *90*(5), 831–845.

Kamigauchi, T., Sakazaki, R., Nagashima, K., Kawamura, Y., Yasuda, Y., Matsushima, K., Tani, H., Takahashi, Y., Ishii, K., Suzuki, R., Koizumi, K., Nakai, H., Ikenishi, Y., & Terui, Y. (1998). Terprenins, novel immunosuppressants produced by *Aspergillus candidus*. *Journal of Antibiotics*, *51*(4), 445–450.

Kinosita, R., Ishiko, T., Sugiyama, S., Seto, T., Igarasi, S., & Goetz, I. E. (1968). Mycotoxins in fermented food. *Cancer Research*, *28*, 2296–2311.

Kinosita, R., & Shikata, T. (1969). On toxic moldy rice. In G. N. Wogan, *Mycotoxins in foodstuffs* (pp. 111–132). Cambridge, MA: MIT Press.

Kobayashi, A., Takemoto, A., Koshimizu, K., & Kawazu, K. (1985). *p*-Terphenyls with cytotoxic activity toward sea urchin embryos. *Agricultural and Biological Chemistry*, *49*(3), 867–868.

Kobayashi, A., Takemura, A., Koshimizu, K., Nagano, H., & Kawazu, K. (1982). Candidusin A and B: new *p*-terphenyls with cytotoxic effects on sea urchin embryos. *Agricultural and Biological Chemistry*, *46*(2), 585–589.

Kurobane, I., Vining, L. C., McInnes, A. G., & Smith, D. G. (1979). 3-Hydroxyterphenyllin, a new metabolite of *Aspergillus candidus*. *Journal of Antibiotics*, *32*(6), 559–564.

Lund, F., & Frisvad, J. C. (1994). Chemotaxonomy of *Penicillium aurantiogriseum* and related species. *Mycological Research*, *98*(5), 481–492.

Marchelli, R., & Vining, L. C. (1973). Biosynthesis of flavonoid and terphenyl metabolites by the fungus *Aspergillus candidus*. Journal of the Chemical Society. Chemical Communications, 555–556.

Marchelli, R., & Vining, L. C. (1975). Terphenyllin, a novel *p*-terphenyl metabolite from *Aspergillus candidus*. *Journal of Antibiotics*, *28*(4), 328–331.

Oh, H., Gloer, J. B., Wicklow, D. T., & Dowd, P. F. (1998). Arenarins A–C: new cytotoxic fungal metabolites from the sclerotia of *Aspergillus arenarius*. *Journal of Natural Products*, *61*(5), 702–705.

Peterson, S. W. (1995). Phylogenetic analysis of *Aspergillus* sections *Cremei* and *Wentii*, based on ribosomal DNA sequences. *Mycological Research*, *99*, 1349–1355.

Pitt, J. I., & Samson, R. A. (1993). Species names in current use in the Trichocomaceae (Fungi Eurotiales). *Regnum Vegetabile*, *128*, 13–57.

Raper, K. B., & Fennell, D. I. (1965). *The genus Aspergillus*. Baltimore: Williams and Wilkins.

Samson, R. A., Hoekstra, E. H., Frisvad, J. C., & Filtenborg, O. (1995). *Introduction to food-borne fungi* (4th ed). Centraalbureau voor Schimmelcultures.

Smedsgaard, J. (1997). Micro-scale extraction procedure for standardized screening of fungal metabolite production in cultures. *Journal of Chromatography A*, *760*, 264–270.

Sneath, P. H. A., & Sokal, R. R. (1973). *Numerical taxonomy*. New York: Freeman.

Takahashi, C., Sekita, S., Yoshihira, K., & Natori, S. (1976a). The structures of toxic metabolites of *Aspergillus candidus*. Part II: the compound B (xanthoascin), a hepato- and cardio-toxic xanthocillin analog. *Chemical and Pharmaceutical Bulletin*, *24*(10), 2317–2321.

Takahashi, C., Yoshihira, K., Natori, S., & Umeda, M. (1976b). The structures of toxic metabolites of *Aspergillus candidus*. Part I: the compounds A and E, cytotoxic *p*-terphenyls. *Chemical and Pharmaceutical Bulletin*, *24*(4), 613–620.

Timonin, M. I., & Rouatt, J. W. (1944). Production of citrinin by *Aspergillus* sp. of the *Candidus* group. *Canadian Journal of Public Health*, *35*, 80–88.

Yaguchi, T., Someya, A., & Udagawa, S. (1995). *Aspergillus taichungensis*, a new species from Taiwan. *Mycoscience*, *36*, 421–424.

Yamashita, M., Hashimoto, S., Ezaki, M., Iwami, M., Komori, T., Kohsaka, M., & Imanaka, H. (1983). FR-900318, a novel penicillin with β-lactamase inhibitory activity. *Journal of Antibiotics*, *36*(12), 1774–1776.