

Beauvericin Production by *Fusarium* Species†

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Beauvericin is a cyclohexadepsipeptide mycotoxin which has insecticidal properties and which can induce apoptosis in mammalian cells. Beauvericin is produced by some entomo- and phytopathogenic *Fusarium* species (*Fusarium proliferatum*, *F. semitectum*, and *F. subglutinans*) and occurs naturally on corn and corn-based foods and feeds infected by *Fusarium* spp. We tested 94 *Fusarium* isolates belonging to 25 taxa, 21 in 6 of the 12 sections of the *Fusarium* genus and 4 that have been described recently, for the ability to produce beauvericin. Beauvericin was produced by the following species (with the number of toxigenic strains compared with the number of tested strains given in parentheses): *Fusarium acuminatum* var. *acuminatum* (1 of 4), *Fusarium acuminatum* var. *armeniicum* (1 of 3), *F. anthophilum* (1 of 2), *F. avenaceum* (1 of 6), *F. beomiforme* (1 of 1), *F. dlamini* (2 of 2), *F. equiseti* (2 of 3), *F. longipes* (1 of 2), *F. nygamai* (2 of 2), *F. oxysporum* (4 of 7), *F. poae* (4 of 4), *F. sambucinum* (12 of 14), and *F. subglutinans* (3 of 3). These results indicate that beauvericin is produced by many species in the genus *Fusarium* and that it may be a contaminant of cereals other than maize.

Beauvericin is a toxic cyclic hexadepsipeptide first studied for its insecticidal properties (5, 7, 8). Beauvericin is a specific cholesterol acyltransferase inhibitor (20) and is toxic to several human cell lines (12). In particular, beauvericin induces programmed cell death similar to apoptosis and causes cytolysis accompanied by internucleosomal DNA fragmentation into multiples of 200 bp (12, 17).

In spite of the toxicological importance of beauvericin, the extent of human, animal, and plant exposure to this toxin has not been established. One approach is to screen fungal isolates for their abilities to produce beauvericin. Beauvericin was first reported to be produced by entomopathogenic fungi such as *Beauveria bassiana* (Balsamo) Vuill. and *Paecilomyces fumosoroseus* (Wize) Brown et Smith (8). In 1991, Gupta et al. (7) detected beauvericin in cultures of entomopathogenic strains of *Fusarium moniliforme* Sheldon var. *subglutinans* Wollenw. et Reinking and *F. semitectum* Berk et Rav. Beauvericin also is produced by *F. subglutinans* (Wollenw. et Reinking) Nelson, Toussoun, et Marasas isolated from maize ears from Austria, Canada, Italy, Poland, Peru, and South Africa, including some strains reported to be toxigenic to experimental animals (9, 10, 14). Beauvericin also is produced by *F. proliferatum* (Matsushima) Nirenberg isolated from maize and asparagus (13, 15, 18). In *Gibberella fujikuroi* (Sawada) Ito in Ito et K. Kimura, beauvericin was produced in large amounts by isolates belonging to mating populations B (*F. subglutinans*), C (*F. proliferatum*), D (*F. proliferatum*), and E (*F. subglutinans*), whereas isolates of mating populations A (*F. moniliforme* Sheldon) and F (*F. thapsinum* Klittich, Leslie, Nelson, et Marasas, sp. nov.) produce little, if any, of this toxin (15).

In the present study we measured the beauvericin production capabilities of *Fusarium* isolates representing 25 taxa, 21 in 6 of the 12 sections of *Fusarium* (16) and 4 that have been described recently.

Materials and methods. The strains we used (Table 1) are deposited in culture collections at the Institute of Plant Genetics (KF), Polish Academy of Sciences, Poznan, Poland (on autoclaved wheat kernels), and the Istituto Tossine e Micotossine da Parassiti Vegetali (ITEM), Bari, Italy, in sterile 18% glycerol at -75°C .

The abilities of different isolates to produce beauvericin were determined by analyzing maize kernel fungal cultures grown in duplicate as previously reported (11). Control maize meal was produced in the same way, except that it was not inoculated.

Samples of *Fusarium* cultures (15 g) were dried, ground (powdered), extracted overnight with 75 ml of solvent (acetonitrile-methanol-water, 16:3:1 [vol/vol/vol]), and filtered (Whatman no. 4 filter paper). The filtrate was defatted twice with 25 ml of heptane, and the bottom layer was evaporated to dryness. The residue was dissolved in 50 ml of solvent (methanol:water, 1:1 [vol/vol]) and extracted twice with 25 ml of methylene chloride. The methylene chloride phase (containing beauvericin) was collected and evaporated to dryness.

A beauvericin standard was purchased from Sigma Chemical Co. (St. Louis, Mo.). Beauvericin was analyzed by high-performance thin-layer chromatography (13) and high-pressure liquid chromatography. Evaporated extract containing BEA was dissolved in 1 ml of methanol, and 0.5 ml was applied to the top of a column containing 2 g of silica gel 60 (200/400 mesh; Aldrich), activated for 2 h at 110°C . The column was preconditioned with 5 ml of chloroform-2-propanol (95:5 [vol/vol]). The extract on the column was washed with the same solvent (3 ml), and then beauvericin was eluted with another 5 ml of the same solvent. Beauvericin was quantified by using a Waters 501 apparatus with a C₁₈ Nova Pack column (3.9 by 300 mm) and a Waters 486 UV detector ($\lambda = 204 \text{ nm}$; $Y = 225$) at a flow rate of 0.6 ml/min; the retention time was 10.5 min and the

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TABLE 1. Production of beauvericin by species of *Fusarium* on autoclaved maize kernels

<i>Fusarium</i> species	Strain		Original host	Source ^b	Geographic origin	Beauvericin production (µg/g) ^c
	Original no.	Other designation(s)				
<i>Discolor</i>						
<i>F. culmorum</i>	KF-833		<i>Triticum aestivum</i>	JC	Poland	ND
	KF-838		<i>Triticum aestivum</i>	JC	Poland	ND
	KF-839		<i>Triticum aestivum</i>	JC	Poland	ND
	KF-1144		<i>Triticum aestivum</i>	JC	Poland	ND
	KF-1147		<i>Triticum aestivum</i>	JC	Poland	ND
	KF-1158		<i>Triticum aestivum</i>	JC	Poland	ND
	ITEM-478		<i>Zea mays</i>	AL	Italy	ND
	ITEM-627		<i>Triticum aestivum</i>	AL	Yugoslavia	ND
<i>F. cerealis</i>	KF-501		<i>Zea mays</i>	JC	Poland	ND
	KF-582		<i>Zea mays</i>	JC	Poland	ND
	KF-1154		<i>Triticum aestivum</i>	JC	Poland	ND
	ITEM-619		<i>Triticum aestivum</i>	AL	Yugoslavia	ND
	ITEM-667		<i>Solanum tuberosum</i>	AL	Italy	ND
<i>F. graminearum</i>	ITEM-644		<i>Panicum crusgalli</i>	AL	Italy	ND
	ITEM-646		<i>Triticum durum</i>	AL	Italy	ND
	KF-1413		<i>Zea mays</i>	JC	Poland	ND
	ITEM-645		<i>Triticum durum</i>	AL	Italy	ND
	ITEM-635		<i>Zea mays</i>	AL	Italy	ND
<i>F. sambucinum</i>	ITEM-847	BBA 64995	<i>Brassica oleracea</i>	HN	The Netherlands	2
	ITEM-934	BBA 64678	<i>Triticum aestivum</i>	HN	Switzerland	21
	ITEM-952	BBA 62433	<i>Beta vulgaris</i>	HN	Spain	53
	ITEM-954	BBA 64960	Soil	HN	The Netherlands	38
	ITEM-955	BBA 64737	<i>Solanum tuberosum</i>	HN	Germany	20
	ITEM-848	BBA 65009	<i>Solanum tuberosum</i>	HN	Italy	76
	ITEM-956	BBA 62434	<i>Solanum tuberosum</i>	HN	Iran	130
	ITEM-957	BBA 64226	<i>Solanum tuberosum</i>	HN	England	190
	ITEM-958	BBA 64998	<i>Solanum tuberosum</i>	HN	France	38
	ITEM-933	BBA 64996	<i>Solanum tuberosum</i>	HN	France	17
	ITEM-846	BBA 62397	<i>Solanum tuberosum</i>	HN	Germany	230
	ITEM-961	BBA 64480	<i>Solanum tuberosum</i>	HN	Finland	3
	ITEM-960	BBA 64262	<i>Glycine max</i>	HN	Brazil	ND
	ITEM-959	BBA 64484	<i>Solanum tuberosum</i>	HN	Finland	ND
<i>F. venenatum</i>	ITEM-831	BBA 64935	<i>Solanum tuberosum</i>	HN	Poland	ND
	ITEM-835	BBA 65030	<i>Zea mays</i>	HN	Germany	ND
	ITEM-836	BBA 64478	<i>Solanum tuberosum</i>	HN	Finland	ND
	ITEM-834	BBA 64757	<i>Humulus lupulus</i>	HN	Germany	ND
	<i>F. torulosum</i>	ITEM-838	BBA 64479	<i>Solanum tuberosum</i>	HN	Finland
ITEM-840		BBA 62398	<i>Betula verrucosa</i>	HN	Germany	ND
ITEM-841		BBA 64990	<i>Buxus</i> sp.	HN	The Netherlands	ND
ITEM-843		BBA 64988	<i>Hordeum vulgare</i>	HN	Hungary	ND
ITEM-844		BBA 64465	<i>Triticum</i> sp.	HN	Germany	TR
ITEM-953		BBA 64993	Unknown	HN	The Netherlands	ND
ITEM-839		BBA 63933	<i>Triticum aestivum</i>	HN	Australia	ND
<i>F. flocciferum</i>		KF-2108		Soil	JC	England
	KF-2109		Soil	JC	England	ND
<i>Gibbosum</i>						
<i>F. acuminatum</i> var. <i>acuminatum</i>	KF-332	ITEM-995	Potato	JC	Poland	8
	ITEM 728		<i>Zea mays</i> kernels	AL	Peru	ND
	ITEM-993	NRRL-13909	<i>Aspergillus sclerotia</i>	AL	United States	ND
	ITEM-1042	BBA 64641	Soil	HN	Denmark	ND
<i>F. acuminatum</i> var. <i>armeniicum</i>	ITEM-992	NRRL-6227	Fescue hay	SWP	United States	ND
	ITEM-797	MRC-3826	Oats	WFOM	South Africa	ND
	KF-359	NRRL-13334, ITEM-998		JC	Poland	2
<i>F. compactum</i>	ITEM-488		<i>Zea mays</i>	AL	Italy	ND
	ITEM-616		<i>Cicer arietinum</i>	AL	Italy	ND
	ITEM-1289		<i>Musa</i> sp.	AL	Cretan island	ND
<i>F. scirpi</i>	ITEM-1166	NRRL-13156, FRC-R6252	Soil	SWP	Australia	ND
<i>F. equiseti</i>	KF 403	R-7617	Corn feed	PEN	United States	ND
	KF-1011	ITEM 2892	<i>Lycopersicon esculentum</i> fruit	JC	Poland	12
	KF-1017	ITEM-2889	<i>Lycopersicon esculentum</i> fruit	JC	Poland	3

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TABLE 1—Continued

<i>Fusarium</i> species	Strain		Original host	Source ^b	Geographic origin	Beauvericin production (μg/g) ^c
	Original no.	Other designation(s)				
<i>F. longipes</i>	KF-475	R-7459, ITEM-3202	String bean Soil	PEN SWP	Philippines Australia	200
	ITEM-870	NRRL-13368				ND
<i>Liseola</i>						
<i>F. subglutinans</i>	ITEM-805		<i>Musa</i> fruit	AL	Panama	10
	ITEM-807		<i>Musa</i> fruit	AL	Panama	300
	ITEM-817		<i>Musa</i> fruit	AL	Ecuador	300
<i>F. anthophilum</i>	KF-391	NRRL 13286 ITEM-3197	Sugarcane	JC	India	1,300
	KF-461	M-1134	<i>Plantago lanceolata</i>	PEN	United States	ND
<i>Elegans (F. oxysporum)</i>						
	KF-75	ITEM-2890	<i>Triticum aestivum</i>	JC	Poland	13
	KF-93	ITEM-2469	<i>Zea mays</i>	JC	Poland	83
	KF-1230	ITEM-2470	<i>Zea mays</i> stalk	JC	Poland	3,200
	ITEM-1508		<i>Zea mays</i>	AL	Italy	TR
	ITEM-1461		<i>Asparagus</i> sp.	AL	Italy	ND
	ITEM-1463		<i>Asparagus</i> sp.	AL	Italy	ND
	ITEM-1443		<i>Triticum durum</i>	AL	Italy	ND
<i>Sporotrichiella</i>						
<i>F. chlamyosporum</i>	KF-333	BBA 62169	<i>Triticum aestivum</i>	HN	Canada	ND
<i>F. poae</i>	KF-1404	ITEM-2891	<i>Zea mays</i>	JC	Poland	36
	KF-1409	ITEM-2893	<i>Zea mays</i>	JC	Poland	63
	ITEM-1446		<i>Triticum durum</i>	AL	Italy	TR
	ITEM-1523		<i>Zea mays</i>	AL	Poland	20
<i>F. sporotrichioides</i>	ITEM-550	KF-96, ATTC 62360	<i>Triticum aestivum</i>	JC	Poland	ND
	ITEM-710	NRRL-3510, FRC-T345, MRC 1704	<i>Panicum milaceum</i>	SWP	USSR	ND
<i>F. tricinctum</i>	KF-248	ITEM-706	<i>Triticum aestivum</i>	JC	Poland	ND
	KF-260	ITEM-649	<i>Triticum aestivum</i>	JC	Poland	ND
<i>Roseum (F. avenaceum)</i>						
	KF-203		<i>Triticum aestivum</i>	JC	Poland	ND
	KF-831		<i>Triticum aestivum</i>	JC	Poland	ND
	KF-1215	ITEM-3187	<i>Zea mays</i>	JC	Poland	7
	KF-1337	DAOM 170472	Pea pod	JC	Canada	ND
	ITEM-620		<i>Triticum aestivum</i>	AL	Yugoslavia	ND
	ITEM-859		<i>Triticum durum</i>		Italy	ND
Recently described species						
<i>F. polyphialidicum</i>	KF-464	M-2405, MRC-3389*	<i>Citrus</i> debris in soil	PEN	South Africa	ND
<i>F. beomiforme</i>	KF-1906	ITEM-3188	Soil	LWB	Australia	5
<i>F. dlamini</i>	KF-463	M-1637, MRC-3032*, ITEM- 3198	Plant debris in soil	PEN	South Africa	19
	KF-338	BBA 64596, ITEM-3199	<i>Vitis vinifera</i>	JC	Germany	94
<i>F. nygamai</i>	KF-434	M-1540, ITEM-3200	Soil debris	PEN	Australia	19
	KF-437	BBA-64375, ITEM-3201	<i>Cajanus indicus</i>	HN	India	3

^a From other collections. *, ex-holotype culture.

^b LWB, L. W. Burgess, Fusarium Research Laboratory, University of Sydney, Sydney, Australia; JC, J. Chelkowski; AL, A. Logrieco; WFOM, W. F. O. Marasas, Programme on Mycotoxins and Experimental Carcinogenesis, Medical Research Council, Tygerberg, South Africa; PEN, P. E. Nelson, *Fusarium* Research Center, Department of Plant Pathology, Pennsylvania State University, University Park, Pa.; HN, H. Nirenberg, Institut für Mikrobiologie, Biologische Bundesanstalt für Land und Forstwirtschaft, Berlin, Germany; SWP, S. W. Peterson, National Center for Agricultural Utilization Research, Peoria, Ill.

^c ND, not detected. TR, trace.

beauvericin detection limit was 0.07 μg/g at a λ of 204 nm and 0.8 μg/g at a λ of 225 nm. The production of beauvericin by *F. oxysporum* (ITEM-2470), *F. poae* (ITEM-1523), and *F. sambucinum* (ITEM-846) was confirmed by ¹H nuclear magnetic resonance (NMR) spectra and by low-resolution electronic-impact mass spectrometry (*m/z* 784) performed sep-

arately on the toxin purified from the fungal culture. In particular, the molecular peak at *m/z* 783 and the fragments at *m/z* 261 and 522 obtained by low-resolution electronic-impact mass spectrometry confirmed the trimeric structure of beauvericin. Proton and carbon NMR spectra were run in CDCl₃ (2 mg/ml) on a Bruker AMX600 spectrometer operating at 600.13 and

150.92 MHz, respectively. The ^1H and ^{13}C data were consistent with previous results (13).

Results. Results of beauvericin production by 94 *Fusarium* isolates on maize cultures are summarized in Table 1. In the *Discolor* section, 12 of 14 isolates of *F. sambucinum* Fuckel sensu stricto produced 2 to 230 μg of beauvericin/g.

In the *Gibbosum* section, beauvericin production was mostly at low levels. The highest beauvericin producer was one of the two tested strains of *F. longipes* Wollenw. et Reinking (ITEM-3202) (200 $\mu\text{g}/\text{g}$). Other beauvericin-producing species of this section were *Fusarium acuminatum* Ell. et Ev. var. *acuminatum* (one of four isolates), *Fusarium acuminatum* var. *armeniicum* Forbes et al. (one of three isolates), and *F. equiseti* (Corda) Sacc. (two of three isolates).

In the *Liseola* section, all three isolates of *F. subglutinans* from bananas and one of two isolates of *F. anthophilum* (A. Braun) Wollenw. produced beauvericin (from 10 to 300 $\mu\text{g}/\text{g}$ and 1,300 $\mu\text{g}/\text{g}$, respectively). Four of seven tested strains of *F. oxysporum* Schlecht. emend. Snyder et Hans (*Elegans* section) produced beauvericin, including ITEM-2470, the highest-producing strain of this study, which was isolated from Polish maize and produced 3,200 $\mu\text{g}/\text{g}$.

In the *Sporotrichiella* section, all four tested strains of *F. poae* (Peck) Wollenw. produced the toxin, ranging from traces (ITEM-1446 from wheat) to 63 $\mu\text{g}/\text{g}$ (ITEM-2893 from maize). One of the *F. avenaceum* (Fz.) Sacc. isolates (*Roseum* section) produced beauvericin at a very low level (7 $\mu\text{g}/\text{g}$).

Finally, of four recently described species, three produced beauvericin. In particular, one isolate of *F. beomiforme* Nelson, Toussoun, et Burgess, two isolates of *F. dlamini* Marasas et al., and two isolates of *F. nygamai* Burgess et Trimboli all produced low levels of beauvericin.

Discussion. Fourteen *Fusarium* species now are known to produce beauvericin. To our knowledge, this report is the first of beauvericin production by strains of *F. sambucinum*, *F. acuminatum* var. *acuminatum*, *F. acuminatum* var. *armeniicum*, *F. equiseti*, *F. longipes*, *F. anthophilum*, *F. oxysporum*, *F. poae*, *F. avenaceum*, *F. beomiforme*, *F. dlamini*, and *F. nygamai*.

The species that produce beauvericin occur worldwide and can grow in various ecological niches as well as on various host plants (3). Previous studies reported the natural occurrence of beauvericin only in maize (19) and identified *F. subglutinans* and *F. proliferatum* as the main beauvericin producers and the species responsible for its accumulation (9, 14, 15, 18). Our findings suggest that other species occurring on maize can contribute to beauvericin contamination, especially *F. poae*. We suspect that beauvericin could be a common wheat contaminant because *F. poae* is a common wheat pathogen (3).

Further study of beauvericin production by some species not commonly isolated from maize is needed. In this study, *F. oxysporum* ITEM-2470 was the highest beauvericin producer, even though some other strains in this species did not produce any detectable beauvericin. These differences suggest that beauvericin might play a role in the plant diseases induced by these fungi and that beauvericin might be specific for some formae speciales.

Most of the strains of *F. sambucinum* analyzed in this study were beauvericin producers. The highest producers (up to 230 $\mu\text{g}/\text{g}$) were isolated from European potatoes. The strains of *F. sambucinum* we used were previously studied in a European *F. sambucinum* project, and they produced trichothecenes (specifically diacetoxyscirpenol and/or neosolaniol and T-2 toxin) and enniatin B (1). The ability of these strains to synthesize beauvericin suggests that further studies should be made on the occurrence of beauvericin together with other toxins in infected potatoes.

The abilities of several species of the *Liseola* and *Elegans* sections and of three recently described species to produce beauvericin agree with their proposed taxonomic and molecular affinities (6). *F. beomiforme*, *F. nygamai*, and *F. dlamini* are often isolated from tropical and subtropical niches and plants (e.g., *Striga hermontica*, Sudan [21]; *Cajanus indicus*, India; soil debris, Australia). Thus, we suspect that beauvericin could be a potential contaminant of plants and commodities in those areas. This hypothesis is supported by the production of beauvericin by all three strains of *F. subglutinans* isolated from banana fruits in Ecuador and Panama. If the toxigenic ability of a fungal population from a specific plant host were known, it could indicate the possible toxin contaminants on the plant products as well as possible synergistic effects of the toxins on the plant.

Many strains analyzed in our study produced little, if any, beauvericin. Many of these have been maintained in culture collections for extended periods of time and may have lost their ability to produce toxins. As an example, *F. dlamini* ITEM-3198, which produced 19 μg of beauvericin/g (Table 1), was also received from another source, but that specimen failed to produce any detectable toxin. Studies of freshly isolated field strains may be necessary to accurately determine the abilities of some species to produce beauvericin.

In conclusion, beauvericin appears to be one of the toxins most widely produced by species of *Fusarium*. Additional data on its possible interactions with other toxins produced by these fungi, e.g., trichothecenes, enniatins, fumonisins, fusaric acid, moniliformin, and fusaproliferin (1, 2, 4, 9, 15), are needed to evaluate the potential toxicity and synergistic effects of beauvericin.

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