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REVIEW ARTICLE

BIOACTIVE METABOLITES OF ENTOMOPATHOGENIC FUNGI *Beauveria bassiana*

Jiri Patocka [1,2]

[1] Institute of Radiology, Toxicology and Civil Protection, Faculty of Health and Social Studies, University of South Bohemia, Ceske Budejovice, Czech Republic
[2] Biomedical Research Centre, University Hospital, Hradec Kralove, Czech Republic

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Summary

Beauveria bassiana is a fungus which causes disease in insects. Currently it is used as an insecticide to control pest populations. Fungi are known to produce a vast array of secondary metabolites that are important for biotechnological applications. Furthemore, *B. bassiana* is an interesting source of biologically active molecules. There are alkaloids with the structure of 2-pyridone, dibenzoquinone pigments and different cyclodepsipeptides. Cyclodepsipeptides from *B. bassiana* are interesting for their neuroprotective properties. Interest of psychopharmacology is focused on the group of beauveriolides. Plant *B. bassiana* becomes a candidate for the prevention and treatment of neurodegenerative diseases.

Key words: Beauveria bassiana; entomopathogenic fungus; biologically active metabolites; alkaloids; cyclodepsipeptides

INTRODUCTION

Beauveria bassiana (Bb) is a fungus that grows naturally in soils throughout the world and acts as a parasite on various arthropod species. It is a fungus which causes a disease known as the white muscadine disease in insects; it thus belongs to the entomopathogenic fungi. It is being used as a biological insecticide to control a number of pests such as termites, thrips, aphids whiteflies, and different beatles (Feng et al., 1994). *Beauveria* infects the insect by contact and does not need to be consumed by their host to cause infection (Dembilio et al., 2010). Bb has a limited virulence in human and only rarely it is reported as a human pathogen (Tucker et al., 2004).

In research on the insect pathogenic filamentous fungus, Bb has witnessed significant growth in recent years from mainly physiological studies related to its insect biological control potential, to addressing fundamental questions regarding the underlying molecular mechanisms of fungal development and virulence. New studies of host–pathogen interactions (HPI) provide valuable insights into the dynamics of the highly aggressive coevolutionary arms race between entomopathogenic fungi (EPF) and their arthropod hosts (Butt et al., 2016). Interesting possibilities are offered Bb metabolites as potential drugs of various neurodegenerative diseases (Park et al., 2008; Schmid, 2015).

✉ University of South Bohemia České Budějovice, Faculty of Health and Social Studies, Institute of Radiology, Toxicology and Civil Protection, Jírovcova 24/1347, 370 04 České Budějovice, Czech Republic
toxicology@toxicology.cz

PAST AND PRESENT

Bb was discovered by Agostino Bassi de Lodi in 1835 when he was researching the heavy decline in larval silkworms, which are used to produce silk. He determined that the "muscardine" was caused by a fungus that multiplied in and on the host. This pathogen was later named after Agostino Bassi himself. Bb has a variety of characteristics that make it unique to other pathogens (Porter, 1973). It occurs naturally in soils throughout the world. It possesses many strains that exhibit considerable variation in virulence, pathogenicity and host range. A very unique characteristic is that it affects its host upon contact, unlike many other pathogens that need to be consumed to cause infection (But et al., 1994).

Bb is currently being used as an insecticide to control pest populations. A few of these pests include termites, fire ants, whiteflies, aphids and various beatles. For example, in China, approximately one million hectares a year are treated with Bb to control forest insects such as the pine caterpillar *Dendrolimus punctatus* (Wang et al., 2004). This fungal pathogen is also under current research together with its affects upon the malaria spreading mosquitoes (Lopez-Perez et al., 2015). Bb is also active against the larvae of *Aedes aegypti*, the main vector of dengue, yellow fever, chikungunya fever and zika fever (Shapshak et al., 2015). Current results support the use of Bb as a potential biocontrol agent against *Ae. aegypti* (Darbro et al., 2012).

TRADITIONAL AND CURRENT MEDICINE

Bb appear in pharmacopoeias of Chinese and Korean traditional medicine as the silk moth fungus (batryticated silkworms, *Bombyx mori* larvae infected with *Beauveria bassiana*). For centuries it has been used mostly to treat stroke, hives and diabetes, and it is the most frequently prescribed and medically important arthropod drugs in oriental medicine (Pemberton, 1999; Hou et al., 2007). Currently there are no known credible information about Bb used in human medicine, like other ento-mopathogenic fungus such as *Cordyceps chinensis* or *C. militaris* (Das et al., 2010). However, BP is a rich source of numerous biologically active substances, some of which could find application in medicine as drugs. The medicinal potential of batryticated silkworms has been validated by modern technologies, e.g. water extract of batryticated silkworms protects against β-amyloid induced neurotoxicity (Koo et al., 2003).

PHARMACOLOGY

It is known that crude extract of Bb exhibited antibacterial activity by any concentration used on different strains of gram-positive and gram-negative bacteria. However, these antibacterial activities against *Bacillus cereus*, *B. subtilis*, *Micrococcus leteus*, *Streptococcus aureus*, and *Escherechia coli* are less active when compared to the control streptomycin and penicillin (Sahab, 2012). Recently Bb attracted attention for their neuroprotective and anti-age properties (Hu and Dong, 2015).

BIOLOGICALLY ACTIVE METABOLITES

Beauveria sp. is well known for producing a large array of biologically active metabolites (Kucera and Samsinakova, 1968). There are mainly volatile organic compounds, alkaloids (tennelin, bassianin, pyridovericin, pyridomacrolidin), non-peptide pigment (oosporein), non-ribosomally synthesized cyclodepsipeptides (beauvericins and allobeauvericins, bassianolides) and cyclopeptides (beauveriolides), and other metabolites involved in pathogenesis and virulence (BbL lectin) that have potential or realized industrial, pharmaceutical and agricultural uses (Xu et al., 2009).

Volatile organic compounds

The factors responsible for the initiation and development of mycosis in insects are extremely complex, involving fungal production of biologically active volatile and non-volatile metabolites that could be related to the mechanism of pathogenicity. Entomopathogenic fungi invade their insect host through the cuticle, covered by a thin layer of different lipids. These are composed of a mixture of very-long-chain hydrocarbons together with different fatty alcohols and fatty acids (Blomquist et al., 1987). Cuticle lipids play a major role in protecting insects from desiccation, penetration of toxic chemicals, as well as in chemical communication events (Juárez 1994). If the entomopathogenic fungus penetrates through the insect cuticle and acts as a pathogenic agent, fungi must disrupt the protective layer on the surface of the insects. Volatile organic compounds (VOCs) released by fungi can overcome this protective layer. Approximately 300 known VOCs are emitted by fungi (Hung et al., 2015). Among the VOCs released by Bb, diisopropyl naphthalenes (>57%) (2,3- and 2,6-isomers), ethanol (10.2%), and sesquiterpenes (6.4%) were detected. Minor amounts of benzeneacetaldehyde, straight

even-chain saturated hydrocarbons of 10–12 and 16 carbons (mainly n-decane), 1-pentadecene, alkyl-benzene derivatives, and methyl-alkyl ketones were also detected (Crespo et al., 2008).

S-(-)-10,11-dihydroxyfarnesic acid methyl ester

Between secondary metabolites of Bb, S-(-)-10,11-dihydroxyfarnesic acid methyl ester (**I**) was also found. (Fig. 1) This compound is a potent inhibitor of melanin synthesis and can be potentially used for cosmetic biomaterials (Baek et al., 2014). The irritation test proved the safety of this substance in cosmetics. It does not even irritate the skin or eyes (Son and Lee, 2013).

Alkaloids

Alkaloids produced by entomopathogenic fungus Bb are derivatives of 2-pyridine (Fig. 1). Until now, tennelin (**II**), bassianin (**III**) (Wat et al., 1977), pyridovericin (**IV**) and pyridomacrolidin (**V**) have been found (Takahashi et al., 1998a,b). All these alkaloids have also been prepared synthetically (Baldwin et al., 2002; Irlapati et al., 2004). Tenellin and bassianin are deduced from chemical and spectroscopic evidence to be the 3-[(E,E)-4,6-dimethylocta-2,4-dienoyl] and 3-[(E,E,E)-6,8-dimethyldeca-2,4,6-trienoyl] deriv-atives of 1,4-dihydroxy-5-(p-hydroxyphenyl)-2(1H)-pyridone. While their exact role in the fungal interaction with the host is not yet

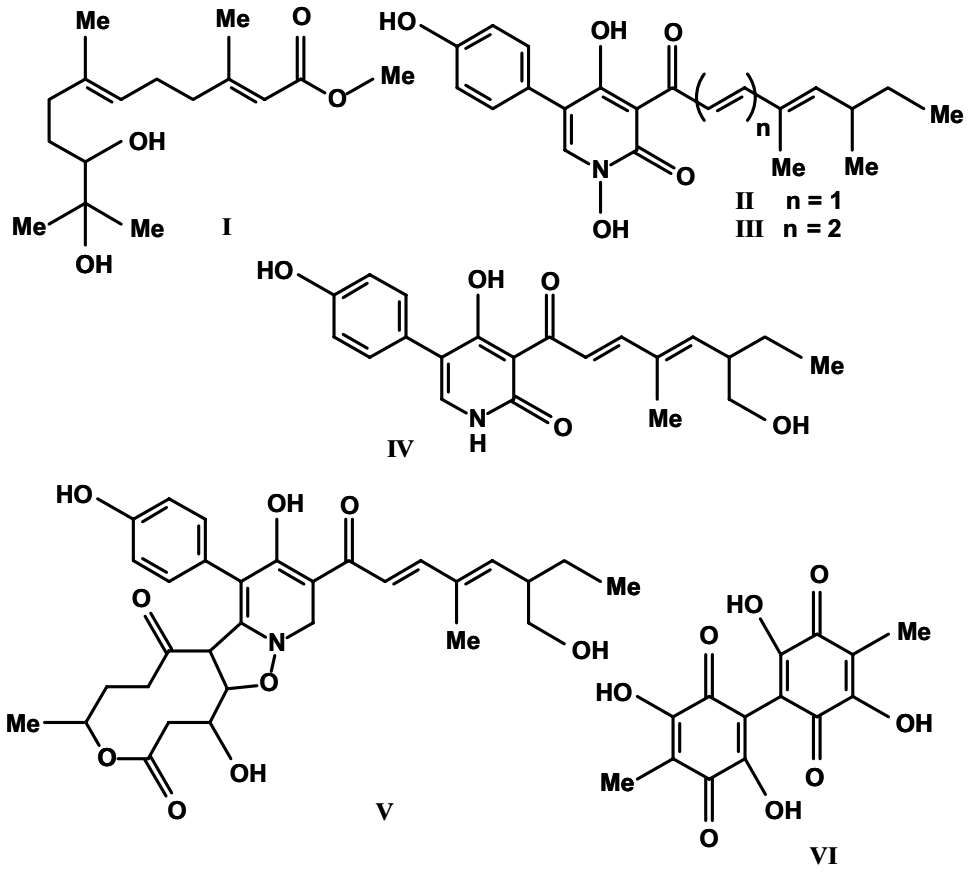

Figure 1. Biologically active metabolites of entomopatogenic fungi *Beauveria basssiana*.
I - S-(-)-10,11-dihydroxyfarnesic acid methyl ester,
II – tennelin,
III – bassianin,
IV – pyridovericin,
V – pyridomacrolidin,
VI – oosporein.

clarified, they have certainly received considerable attention in the biologi-cal and chemical community. Natural compounds with 2-pyridone core are frequently found in fungi and marine organisms (de Silva et al., 2009; Wang et al., 2015).

Many natural products have shown to possess neuritogenic activity in cell and animal models (Faulkner, 2000), and alkaloids with 4-hydroxy-2-pyridone core structure belong to this group of substances. These are selective ATP-competitive inhibitors of mitogen-activated protein kinase (MAP4K4) but not of the other stress pathway related kinases (Schröder et al., 2015). Numerous studies in recent years show that MAP4K4 may be a new target for the treatment of neurodegenerative diseases (Yang et al., 2011).

Pigments

Yellow and red coloring substances were found in isolates of the fungus *Beauveria* (Basyouni et al., 1968). Yellov Bb pigments were identified as 2-pyridone alkaloids tennelin (**II**) and bassianin (**III**) and red pigment was identified as the dibenzoquinone pigment oosporein (**VI**) (Fig. 1). Yellow pigments were isolated from both *B. bassiana* and *B. tenella* cultures and found to be mixtures of similar com-pounds (Sohair et al., 1968). Red colored mycotoxin **VI** is also produced by *B. ossiana* (Eyal et al., 1994). Oosporein has antibiotic and cytotoxin properties (Alurappa et al., 2015).

The *Beauveria* pigments, tenellin, bassianin and oosporein, all inhibited total erythrocyte membrane ATPase activity (Jeffs and Khachatourians, 1997).

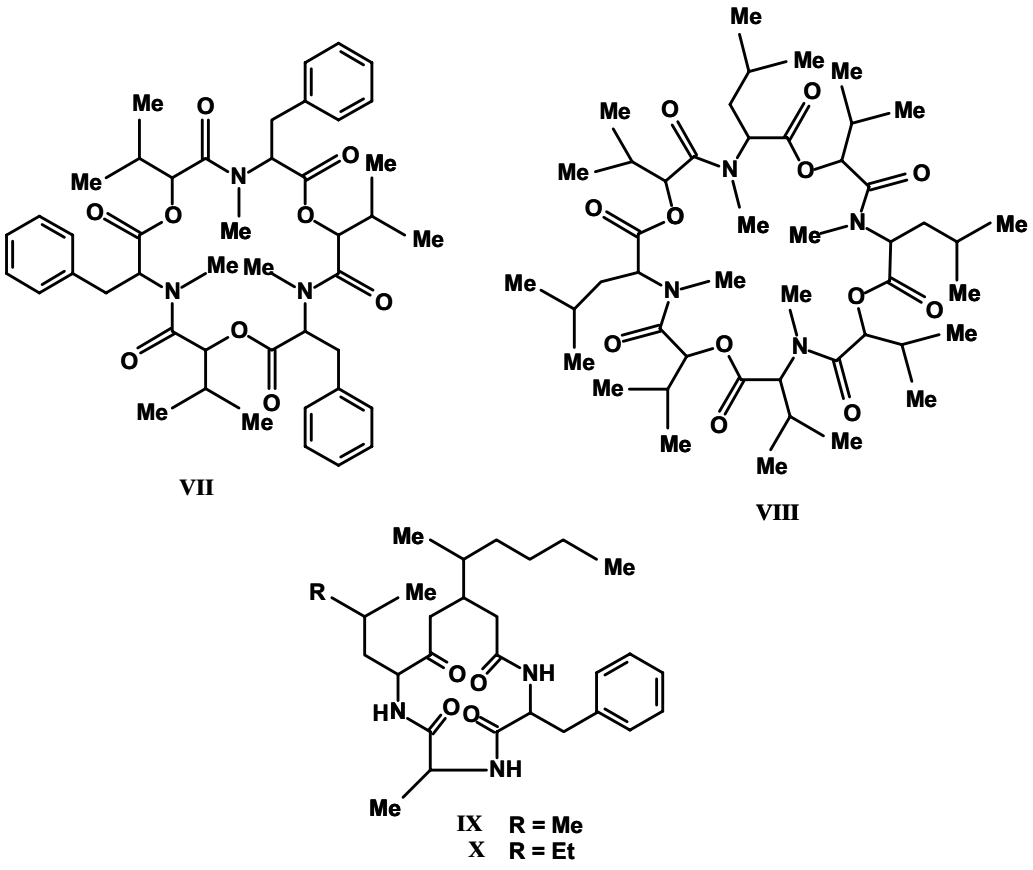

Figure 2. Biologically active metabolites of entomopatogenic fungi *Beauveria basssiana.*
VII -Beauvericin,
VIII – bassianolide,
IX – beauveriolide I,
X – beauveriolide III.

These pigments inhibited Ca^{2+}-ATPases to a greater extent than $Na^{+}/K(^{+})$-ATPase activity. The ATPase inhibitory activity for these pigments was not specific but was probably a consequence of membrane disruption, since all pigments caused alterations in erythrocyte morphology and promoted varying degrees of cell lysis (Jeffs and Khachatourians, 1997). Jirakkakul and his co-workers (2015) recently demonstrated that tenellin formed a 3:1 complex with iron.

Cyclopeptides and cyclodepsipeptides

Entomopatogenic fungus Bb is the source of a series of cyclic biologically active nonribosomally synthesized depsipeptides (Elsworth and Grove, 1977, 1980). These compouds have cytotoxin activity (Valencia et al., 2011) and they are most important biologically active substances of *Beauveria* Sp. Several kinds of similar cyclodepsipeptides was found in Bb and other fungi *Beauveria* sp.: beauvericins and allobeauvericins, bassianolides and beauveriolides (Fig. 2).

Beauvericins and allobeauvericins

Beauvericins and allobeauvericins are a class of cyclohexadepsipeptides with a core structure made of free L-N-methylphenylalanine units connected alternately with three D-2-hydroxyisovaleric acid residues. They are primarily isolated from Beauveria sp., but were found in several other fungi. Currently seven different beauvericins are known: beauvericin (**VII**), beauvericins A, B, and C, and allobeauvericins A, B, and C (Brahmachari, 2015). All these compounds have properties of ionophoric abtibiotics (Champlin and Grula, 1979).

Beauvericins are highly toxic against different cancer cell lines with IC_{50} values in low micromolar range (Wätjen et al., 2014). Beauvericins induced apoptosis through mitochondrial pathway, including decrease of relative oxygen species generation, loss of mitochondrial membrane potential, release of cytochrome c, activation of Caspase-9 and -3, and cleavage of poly (ADP-ribose) polymerase (PARP), the family of proteins involved in a number of cellular processes involving mainly DNA repair and programmed cell death (Tao et al., 2015). Beauvericins inhibit cell proliferation by arresting cells in G0/G1 and increasing apoptosis. Moreover, at higher exposure times, beauvericins induce differ-entiation of CHO-K1 cells through G2/M arrest, preventing that cells entry into mitosis (Mallebrera et al., 2016).

Beauvericin (**VII**) in an isolated neuromuscular mouse hemidiaphragm preparation significantly inhibits indirectly elicited twitch amplitude (at 5 μM) and at higher concentrations (7.5 and 10 μM) produces a significant reduction of directly elicited, or complete block of indirectly evoked, muscle contraction. The **VII** also appears to be myotoxic, as indicated by a slowly developing muscle contracture. Development of neuromuscular blockade and contracture is concentration dependent. This mycotoxin acted by presynaptically depressing spontaneous acetylcholine release as indicated by the reduction in the frequency of spontaneous miniature endplate potentials (MEPPs), while the membrane potential of muscle fibers remained unchanged. At higher concentrations (7.5 and 10 μM), BEA progressively reduces or completely blocks MEPPs and EPPs amplitudes. Changes in MEPPs and EPPs are associated with substantial depolarization of muscle fibers when exposed to 7.5 and 10 μM of **VII**. These results indicate that VII has neurotoxic and myotoxic effects, which overlap in a narrow range of concentrations (Žužek et al., 2015).

Bassianolide

Bassianolide (**VIII**) is cyclotetradepsipeptide isolated from cultured mycelia of Bb and is pathogenic to insects. In a longitudinal muscle preparation from guinea pig ileum, bassianalodie almost irreversibly inhibited an isotonic contraction induced by acetylcholine and made the dose-response curve shift in parallel to the right (pA = 7.6). It also inhibited the contractions induced by carbachol, pilocarpine, histamine, 5-hydroxytriptamine, and prostaglandin E2, but did not inhibit the contraction induced by barium or a high concentration (40-60 mM) of potassium (Nakajyo et al., 1982). Bassianolide as a highly significant virulence factor of Bb (Xu et al., 2009) and an interesting candidate for future structural modification (Jirakkakul et al., 2008).

Beauveriolides

Beauveriolides (beauveriolide I (**IX**) and beauveriolide III (**X**)) are 13-membered cyclopeptides consisting of L-phenylalanine, L-alanine, D-leucine/D-allo-isoleucine, and (3S,4S)3-hydroxy-4-methyloctanoic acid, respectively. The 3-hydroxy-4-methyloctanoic acid moiety, the 3S configuration of the hydroxyl group is important for the inhibitory activity because 3R isomers lose this activity due to ganges in this group, while the stereochemistry of the methyl group at C-4 did not affect the inhi-

bition of cholesterol ester synthesis in macrophages, which is important biological effect of beauveriolides (Ohshiro et al., 2009).

It has been definitively shown that the generation and clearance of amyloid-beta peptide (Abeta) in specific regions of the brain is regulated by cholesterol homeostasis. Compounds that perturb cellular free cholesterol homeostasis such as acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors have been shown both in vitro and in vivo to reduce Abeta production and secretion. However, it is generally the case that ACAT inhibitors exhibit poor oral activity. The beauveriolides are a new class of fungal metabolites that have been shown to be orally active ACAT inhibitors and are currently being investigated as potential therapeutics for atherosclerosis.

Therefore, certainly in the context of atherosclerosis and now with ad, there is an unmet need for potent ACAT inhibitors with good bioavailability. It is the rationale of this proposal that beauveriolides are tested as a new class of anti-Alzheimer's drugs. It is given that the beauveriolides are orally active inhibitors of ACAT-1 and ACAT-2, that they should be investigated and optimised structurally for their ability to reduce Abeta production in vitro (Witter et al., 2009). Certain synthetically prepared beauveriolides are more efficient than natural metabolites of Bb (Nagai et al., 2008, Tomoda and Doi, 2008).

Boveria bassiana lectin

Boveria bassiana lectin (BbL) was isolated from the mycelium of the stationary growing Bb by extraction, chromatography on QAE-Sephadex A-25, salt precipitation, and hydrophobic chromatography on Phenyl-Sepharose 4B. The BbL is a 15 kDa glycoprotein rich in hydrophobic amino acids, without detectable amount of methionine. It contains 12.6% of carbohydrates including galactose and mannose. The lectin is stable between pH 6 and 11, and at temperature under 50 degrees C. Its isoelectric point was found at pH 7.1.

The activity of the BbL was not dependent on Ca^{2+}, Mg^{2+}, and Mn^{2+} cations and was appar-ently not blood group ABO specific. The hemagglutination caused by the lectin was inhibited by alpha lactose, but not by beta lactose. These results indicate that BbL exhibits sugar binding specificity towards glycotope corresponding to Thomsen-Friedenreich antigen and its related sequences (Kossowska et al., 1999).

Boveria bassiana AS A CANDIDATE FOR THE PREVENTION AND TREATMENT OF NEURODEGENERATIVE DISEASES

Bb and some of its metabolites represent a serious candidate for the prevention and treatment of neurodegenerative diseases such as e.g. Alzheimer's disease or Parkinson's disease (Joyner and Cichewicz, 2011). Mainly some cyclodepsipeptides, as for example natural beauveriolides or their synthetically prepared derivatives, represent an interesting way in the fight against neurodegenerative diseases (Tomoda and Doi, 2008).

It is not yet clear whether it would be better to use entire fungus, or some isolated metabolites in assays. Throughout the fungus there are some toxic substances present, but on the other hand, they may have additive effects in a mixture. For example, the methanolic extract of Bb increased acetylcholinesterase (AChE) activity and reactive oxygen species (ROS) scavenging activity, which would be beneficial for the suppression of neurodegenerative disorders (Park et al., 2008).

CONCLUSIONS

Beauveria bassiana is a fungus that grows naturally in soils throughout the world and acts as a parasite on various arthropod species. This patogene has a variety of characteristics that make it unique to other pathogens. It is currently being used as an insecticide to control pest populations. Since *B. bassiana* is a fungal pathogen, it does not harm humans. *B. bassiana* is well known for producing a large array of biologically active metabolites, which are being studied with a view to their practical use in medicine.

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