MMSL
Military Medical
Science Letters

Mil. Med. Sci. Lett. (Voj. Zdrav. Listy) 2016, vol. 85(2), p. 80-88
ISSN 0372-7025
DOI: 10.31482/mmsl.2016.015

## 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

Received 26th April 2016.
Revised 5th June 2016.
Published 14th June 2016.

**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

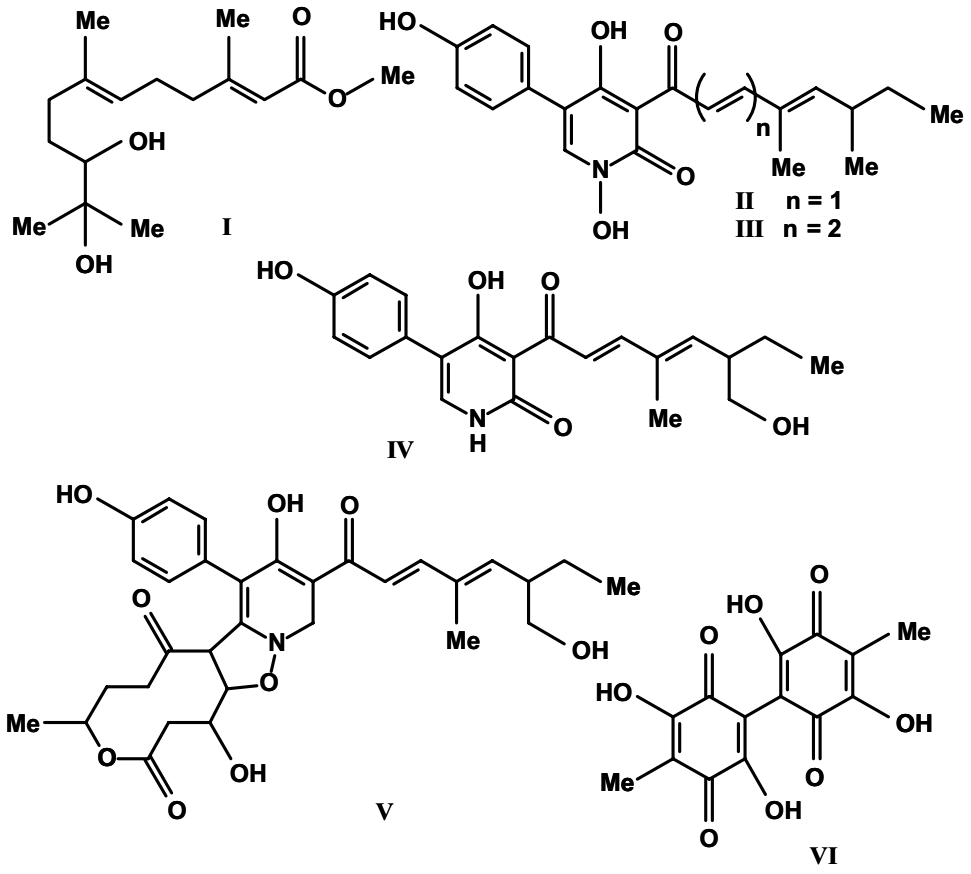


**Figure 1.** Biologically active metabolites of entomopatogenic fungi *Beauveria basssiana*.
**I** - S-(-)-10,11-dihydroxyfarnesic acid methyl ester,
**II** – tennelin,
**III** – bassianin,
**IV** – pyridovericin,
**V** – pyridomacrolidin,
**VI** – oosporein.

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).

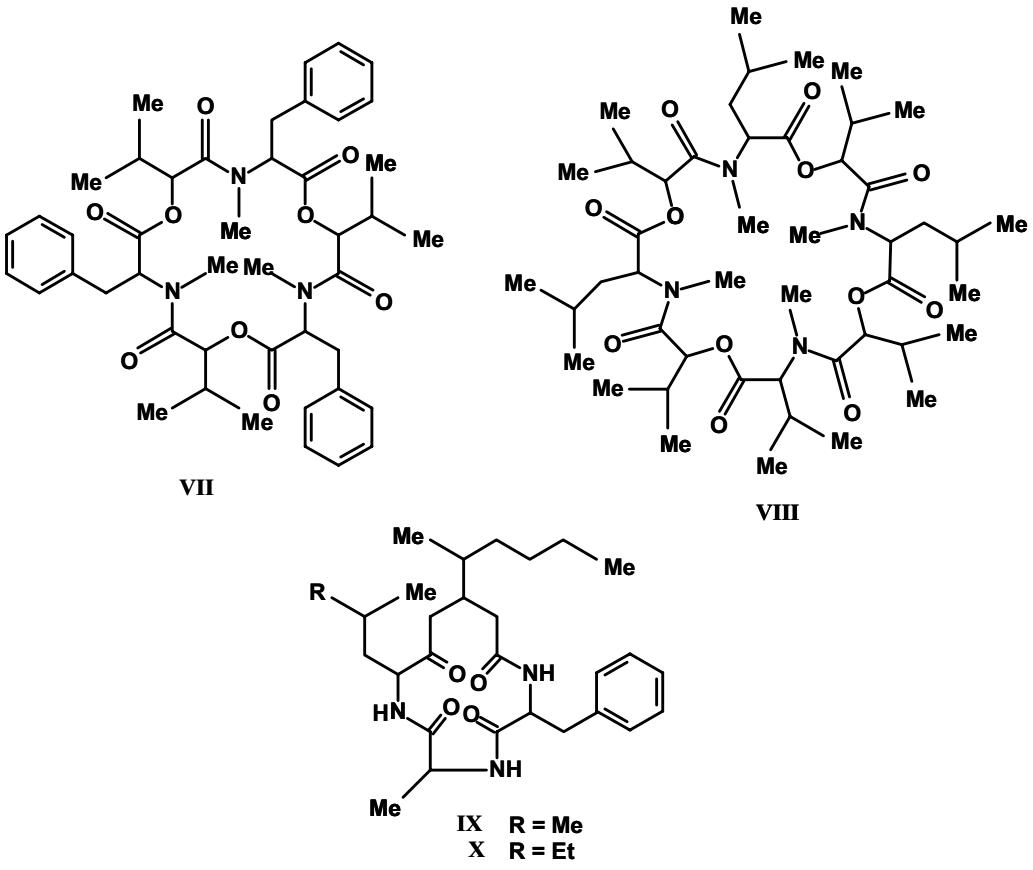


**Figure 2.** Biologically active metabolites of entomopatogenic fungi *Beauveria basssiana.*
**VII** -Beauvericin,
**VIII** – bassianolide,
**IX** – beauveriolide I,
**X** – beauveriolide III.

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.

## ACKNOWLEDGMENTS

This work was supported by the Agrokoncern a.s., Slušovice, Czech Republic. Project Healthy and Happy (Alzheimer’s Disease).

## REFERENCES

1. Alurappa R, Venkataramana M, Nirmaladevi D, Gupta VK, Chandranayka S, Srinivas C.

Cytotoxic effects of oosporein isolated from endophytic fungus Cochliobolus kusanoi. *Front Microbiol*. **2015**, 6, 870.
2. Baek SH, Ahn JW, Nam SH, Yoon CS, Shin JC, Lee SH. S-(-)-10,11-Dihydroxyfarnesoic acid methyl ester inhibits melanin synthesis in murine melanocyte cells. *Int J Mol Sci*. **2014**, 15, 12750–12763.
3. Baldwin JE, Adlington RM, Conte A, Irlapati NR, Marquez R, Pritchard GJ. Total synthesis of pyridovericin: Studies toward the biomimetic synthesis of pyridomacrolidin. *Organic Letters*. **2002**, 4(13), 2125-2127.
4. Basyouni SHE, Brewer D, Vining LC. Pigments of the genus Beauveria. *Canad J Botany*. **1968**, 46(4), 441-448.
5. Blomquist GJ, Nelson DR, de Renobales M. Chemistry, biochemistry and physiology of insect cuticular lipids. *Arch Insect Biochem Physiol*. **1987**, 6, 227–265.
6. Brahmachari G. Bioactive Natural Products: Chemistry and Biology. John Wiley & Sons. **2015**, p. 286.
7. Butt TM, Coates CJ, Dubovskiy IM, Ratcliffe NA. Entomopathogenic Fungi: New Insights into Host–Pathogen Interactions. Advances in Genetics, **2016**. In press. Available online at http://www.sciencedirect.com/science/article/pii/S0065266016300062
8. Butt TM, Ibrahim L, Ball BV, Clark SJ. Pathogenicity of the entomogenous fungi Metarhizium anisopliae and Beauveria bassiana against crucifer pests and the honey bee. *Biocontrol Sci Technol*. **1994**, 4(2), 207-214.
9. Champlin FR, Grula EA. Noninvolvement of beauvericin in the entomopathogenicity of Beauveria bassiana. *Appl Environ Microbiol*. **1979**, 37(6), 1122-1126.
10. Crespo R, Pedrini N, Juárez MP, Dal Bello GM. Volatile organic compounds released by the entomopathogenic fungus Beauveria bassiana. *Microbiol Res*. **2008**, 163(2), 148-151.
11. Darbro JM, Johnson PH, Thomas MB, Ritchie SA, Kay BH, Ryan PA. Effects of Beauveria Bassiana on survival, blood-feeding Access, and fecundity of Aedes aegypti in laboratoř and semi-field conditions. *Am J Trop Med Hyg*. **2012**, 86(4), 656-664.
12. Das SK, Masuda M, Sakurai A, Sakakibara M. Medicinal uses of the mushroom Cordyceps militaris: current state and prospects. *Fitoterapia*. **2010**, 81(8), 961-968.
13. Dembilio O, Quesada-Moraga E, Santiago-Álvarez C, Jacas JA. Potential of an indigenous strain of the entomopathogenic fungus Beauveria bassiana as a biological control agent against the Red Palm Weevil, Rhynchophorus ferrugineus. *J Invertebrate Pathol*. **2010**, 104(3), 214-221.
14. de Silva ED, Geiermann AS, Mitova MI, Kuegler P, Blunt JW, Cole ALJ, Munro MH G. (2009). Isolation of 2-Pyridone Alkaloids from a New Zealand Marine-Derived Penicillium speces⊥. *J Nat Prod*. **2009**, 72(3), 477-479.
15. Elsworth JF, Grove JF. Cyclodepsipeptides from Beauveria bassiana Bals. Part 1. Beauverolides H and I. *J Chem Soc Perkin Transactions 1*, **1977**, (3), 270-273.
16. Elsworth JF, Grove JF. Cyclodepsipeptides from Beauveria bassiana. Part 2. Beauverolides A to F and their relationship to isarolide. *J Chem Soc Perkin Transactions 1*, **1980**, (1), 1795-1799.
17. Eyal J, Mabud MA, Fischbein KL, Walter JF, Osborne LS, Landa Z. Assessment of Beauveria bassiana Nov. EO-1 strain, which produces a red pigment for microbial control. *Appl Biochem Biotechnol*. **1994**, 44(1), 65-80.
18. Faulkner DJ. Marine natural products. Natural Product Reports **2000**, 17(1), 7-55.
19. Feng MG, Poprawski TJ, Khachatourians GG. Production, formulation and application of the entomopathogenic fungus Beauveria bassiana for insect control: current status. *Biocontrol Sci Technol*. **1994**, 4(1), 3-34.
20. Hou L, Shi Y, Zhai P, Le G. Antibacterial activity and in vitro anti-tumor activity of the extract of the larvae of the housefly (Musca domestica). *J Ethnopharmacol*. **2007**, 111(2), 227-231.
21. Hung R, Lee S, Bennett JW. Fungal volatile organic compounds and their role in ecosystems. *Appl Microbiol Biotechnol*. **2015**, 99(8), 3395-3405.
22. Hu Q, Dong T. (2015). Non-ribosomal Peptides from Entomogenous Fungi. In *Biocontrol of Lepidopteran Pests* Springer International Publishing, **2015**, pp. 169-206.
23. Irlapati NR, Adlington RM, Conte A, Pritchard GJ, Marquez R, Baldwin JE. Total synthesis of pyridovericin. *Tetrahedron*, **2004**, 60(41), 9307-9317.
24. Jeffs LB, Khachatourians GG. Toxic properties of Beauveria pigments on erythrocyte membranes. *Toxicon*. **1997**, 35(8),1351-1356.
25. Jirakkakul J, Cheevadhanarak S, Punya J, Chutrakul C, Senachak J, Buajarern T, Tanticharoen M, Amnuaykanjanasin, A. Tenellin acts as an iron chelator to prevent iron-generated reactive oxygen species toxicity in the entomopathogenic fungus Beauveria bassiana. *FEMS Microbiology Letters*. **2015**, 362(2), 1-8.

26. Jirakkakul J, Punya J, Pongpattanakitshote S, Paungmoung P, Vorapreeda N, Tachaleat A, Klomnara C, Tanticharoen M, Cheevadhanarak S. Identification of the nonribosomal peptide synthetase gene responsible for bassianolide synthesis in wood-decaying fungus Xylaria sp. BCC1067. *Microbiology*. **2008**, 154(Pt4), 995-1006.
27. Joyner PM, Cichewicz RH. Bringing natural products into the fold–exploring the therapeutic lead potential of secondary metabolites for the treatment of protein-misfolding-related neurodegenerative diseases. *Natural Prod Reports*. **2011**, 28(1), 26-47.
28. Juárez MP. Inhibition of insect surface lipid synthesis, and insect survival. *Arch Insect Biochem Physiol*. **1994**, 25, 177–191.
29. Koo BS, An HG, Moon SK, Lee YC, Kim HM, Ko JH, Kim CH. Bombycis corpus extract (BCE) protects hippocampal neurons against excitatory amino acid-induced neurotoxicity. Immunopharmacol *Immunotoxicol*. **2003**, 25(2),191-201.
30. Kossowska B, Lamer-Zarawska E, Olczak M, Katnik-Prastowska I. Lectin from Beauveria bassiana mycelium recognizes Thomsen-Friedenreich antigen and related structures. *Comp Biochem Physiol B Biochem Mol Biol*. **1999**, 123(1), 23-31.
31. Kucera M, Samsinakova A. Toxins of the entomophagous fungus Beauveria bassiana *J Invertebr Pathol*. **1968**, 12, 316–320.
32. Lopez-Perez M, Rodriguez-Gomez D, Loera O. Production of conidia of Beauveria bassiana in solid-state culture: current status and future perspectives. *Crit Rev Biotechnol*. **2015**, 35(3), 334-341.
33. Mallebrera B, Juan-Garcia A, Font G, Ruiz MJ. Mechanisms of beauvericin toxicity and antioxidant cellular defense. *Toxicol Lett*. **2016**, 246, 28-34.
34. Nagai K, Doi T, Ohshiro T, Sunazuka T, Tomoda H, Takahashi T, Omura S. Synthesis and biological evaluation of a focused library of beauveriolides. *Bioorg Med Chem Lett*. **2008**, 18(15), 4397-4400.
35. Nakajyo S, Shimizu K, Kometani A, Kato K, Kamizaki J, Isogai A, Urakawa N. Inhibitory effect of bassianolide, a cyclodepsipeptide, on drug-induced contractions of isolated smooth muscle preparations. *Jpn J Pharmacol*. **1982**, 32(1), 55-64.
36. Ohshiro T, Matsuda D, Nagai K, Doi T, Sunazuka T, Takahashi T, Rudel LL, Omura S, Tomoda H. The selectivity of beauveriolide derivatives in inhibition toward the two isozymes of acyl-CoA: cholesterol acyltransferase. *Chem Pharm Bull* (Tokyo). **2009**, 57(4), 377-381.
37. Park SY, Song HH, Lee YG, Yoon CS, Lee C. (2008). Biological activities and partial characterization of Beauveria bassiana mycelium. *Food Sci Biotechnol*. **2008**, 17(1), 95-101.
38. Pemberton RW. Insects and other arthropods used as drugs in Korean traditional medicine. *J Ethnopharmacol*. **1999**, 65(3), 207-216.
39. Porter JR. Agostino Bassi bicentennial (1773-1973). *Bacteriol Rev*. **1973**, 37(3), 284.
40. Sahab AF. Antimicrobial activity of secondary metabolites of Beauveria bassiana against selected bacteria and phytopathogenic fungi. *J Appl Sci Res*. **2012**, 8(3), 1441-1444.
41. Schmid F. Total Synthesis of (–)-Pyridovericin and Synthetic Studies towards Aetheramide B. University Basel, Doctoral dissertation, **2015**, 269 pp.
42. Schröder P, Förster T, Kleine S, Becker C, Richters A, Ziegler S, Rauth D, Kumar K, Waldmann H. Neuritogenic Militarinone-Inspired 4-Hydroxypyridones Target the Stress Pathway Kinase MAP4K4. *Angewandte Chemie*. **2015**, 127(42), 12575-12580.
43. Shapshak P, Somboonwit C, Foley BT, Alrabaa SF, Wills T, Sinnott JT. Zika Virus. In Global Virology I-Identifying and Investigating Viral Diseases. Springer New York, **2015**, 477-500.
44. Sohair H, El Basyouni D, Brewer LC. Vining Pigments of the genus Beauveria. *Canad J Botany*, **1968**, 46(4): 441-448.
45. Son HU, Lee SH. Evaluation of eye irritation by S-(-)-10,11-dihydroxyfarnesic acid methyl ester secreted by Beauveria bassiana CS1029. *Rxp Ther Med*. **2013**, 6(4), 909-912.
46. Takahashi S, Kakinuma N, Uchida K, Hashimoto R, Yanagisawa T, Nakagawa A. 1998). Pyridovericin and pyridomacrolidin: novel metabolites from entomopathogenic fungi, Beauveria bassiana. *J Antibiotics.* **1998a**, 51(6), 596-598.
47. Takahashi S, Uchida K, Kakinuma N, Hashimoto R, Yanagisawa T, Nakagawa A. The structures of pyridovericin and pyridomacrolidin, new metabolites from the entomopathogenic fungus, Beauveria bassiana. *J Antibiotics*. **1998b**, 51(11), 1051-1054.
48. Tao YW, Lin YC, She ZG, Lin MT, Chen PX, Zhang JY. Anticancer activity and mechanism investigation of beauvericin isolated from secondary metabolites of the mangrove endophytic fungi. *Anticancer Agents Med Chem*. **2015**, 15(2), 258-266.

49. Tomoda H, Doi T. Discovery and combinatorial synthesis of fungal metabolites beauveriolides, novel antiatherosclerotic agents. *Acc Chem Res.* **2008**, 41(1), 32-39.
50. Tucker DL, Beresford CH, Sigler L, Rogers K. Disseminated Beauveria bassiana infection in a patient with acute lymphoblastic leukemia. *J Clin Microbiol*. **2004**, 42(11), 5412-5414.
51. Valencia JW, Gaitán Bustamante AL, Jiménez AV, Grossi-de-Sá MF. Cytotoxic activity of fungal metabolites from the pathogenic fungus Beauveria bassiana: an intraspecific evaluation of beauvericin production. *Curr Microbiol.* **2011**, 63(3), 306-312.
52. Wang CS, Fan MZ, Li ZZ, Butt TM. Molecular monitoring and evaluation of the application of the insect-pathogenic fungus Beauveria bassiana in southeast China. *J Appl Microbiol*. **2004**, 96, 861–870.
53. Wang J, Wei X, Qin X, Lin X, Zhou X, Liao S, Yang B, Liu J, Tu Z, Liu Y. Arthpyrones A–C, Pyridone Alkaloids from a Sponge-Derived Fungus Arthrinium arundinis ZSDS1-F3. *Organic Letters*. **2015**, 17(3), 656-659.
54. Wat CK, Mcinnes AG, Smith DG, Wright JLC, Vining LC. The yellow pigments of Beauveria species. Structures of tenellin and bassianin. *Canad J Chem*. **1977**, 55(23): 4090-4098.
55. Wätjen W, Debbab A, Hohlfeld A, Chovolou Y, Proksch P. The mykotoxin beauvericin induces apoptotic cell death in H4IIE hepatoma cells accompanied by an inhibition of NF-κB-activity and modulation of MAP-kinases. *Toxicol Lett*. **2014,** 231(1), 9-16.
56. Witter DP, Chen Y, Rogel JK, Boldt GE, Wentworth P Jr. The natural products beauveriolide I and III: a new class of beta-amyloid-lowering compounds. *Chembiochem*. **2009**, 10(8), 1344-1347.
57. Xu Y, Orozco R, Kithsiri Wijeratne EM, Espinosa-Artiles P, Leslie Gunatilaka AA, Patricia Stock S, Molnár I. Biosynthesis of the cyclooligomer depsipeptide bassianolide, an insecticidal virulence factor of Beauveria bassiana. *Fungal Genet Biol*. **2009**, 46(5), 353-364.
58. Yang X, Luo C, Cai J, Powell DW, Yu D, Kuehn MH, Tezel G. Neurodegenerative and inflammatory pathway components linked to TNF-α/TNFR1 signaling in the glaucomatous human retina. *Investigative Ophthalmology Visual science*. **2011**; 52(11), 8442-8454.
59. Žužek MC, Grandič M, Jakovac Strajn B, Frangež R. Beauvericin inhibits neuromuscular transmission and skeletal muscle contractility in mouse hemidiaphragm preparation. *Toxicol Sci*. **2015** Dec 29. pii: kfv326. [Epub ahead of print]