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Pharmacological and Therapeutic Potential of Beauvericin: A Short Review

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Abstract

An entomopathogenic fungus, *Beauveria spp*. has been known to have numerous pharmacological and therapeutic implications, especially, in terms of human health making it a suitable for ethnopharmacological use. Beauvericin is a cyclic hexadepsipeptide mycotoxin, a novel bio-metabolite derived from this fungus, exhibiting a very potent anticancer, cytotoxic activities, antiplatelet aggregation and antimicrobial activities. The current review discusses the therapeutic potential of beauvericin including pharmacological and biological activities which will certainly draw the attention of scientific community to improve the production of beauvericin for its use in medical fields.

Keywords: *Beauveria;* Therapeutic; Anticancer; Cytotoxic; Antiplatelet

Introduction

Bioactive secondary metabolites produced by entomopathogenic fungi play a key role as virulence factors for fungi infecting arthropods [1,2]. In addition beauvericin can also be synthesized by several other fungal genera such as *Paecilomyces, Polyporus, Isaria* and *Fusarium*. Several low toxic compounds are produced by entomopathogenic fungi *Beauveria bassiana* like destruxins, bassianolide, Beauvericin, efrapeptins, tenellin, oosporein [3-5]. The biometabolite beauvericin is first isolated from liquid fermented culture of *Beaveria bassiana*, which is a common and commercial entomopathogenic mycoinsecticide [6,7]. The genus *Beauveria* is well known mycoinsecticide and exhibits antimicrobial, antitumor, antifungal and antiviral activities [8]. The entomopathogenic fungus, *Beauveria bassiana belongs to Phylum* Ascomycota. It has been found and isolated from a wide variety of insects of different orders [9-12]. It is most widely used fungal species which is commercially available [13]. This fungus is widely found on infected insects both in temperate and tropical areas throughout the world [14]. In addition to beauvericin, *Beauveria* also produces varieties of other pharmacologically active compounds such as enniatins, ketone, alphahydroxy isovaleric acid, hydrocarbons, fatty acids, and wax ester.

Beauvericin is a cyclic trimer of a dipeptidol monomer synthesized from N-methyl phenylalanine and 2-hydroxyisovaleric acid which increases its potency for anti-cholesterol, and chemosensitizer activities, as well as repression of amyloid plaque formation in Alzheimer's disease [15]. Recent studies have shown that other than the above biochemical and molecular processes, other molecular mechanism of beauvericin is cell apoptosis [16,17] and other molecular targets of beauvericin are antiangiogenic activity, inhibition of metastasis prostate and breast cancer [18]. Therefore, these fungal natural products represent promising leading anticancer potential. However, the cure of diseases such as cancer still remains elusive despite the availability of a variety of chemotherapeutics agents that exhibit sophisticated mechanisms of action [6]. The Figure 1 illustrates various interactions of Beauvericin in biochemical processes, including metastasis, apoptosis, antiplatelet aggregation and antimicrobial activity.

Structure and Chemistry of Beauvericin

Beauvericin or cyclic hexadepsipeptide belongs to the family of enniatins with molecular formula $C_{45}H_{57}N_3O_9$, molecular weight 783.95, alkaline, needle like crystal, soluble in methanol, diethyl ether, chloroform, slightly soluble in water, melting point 95-97°C with a maximum absorption of 209 nm. The structure of beauvericin consists of three D-α-hydroxy-isovaleryl and N-methyl-L-phenylalanyl residues in alternating sequence as shown in Figure 2. Being a member of the enniatin family of antibiotics it has activity against Gram positive bacteria and mycobacteria, as well as against insects and brine shrimp. Its ion complexing capability allows beauvericin to transport alkaline earth metal and alkali metal ions across cell membranes [19,20]. Beauvericin has been shown to cause channel formation in patches of ventricular myocytes and synthetic membranes [21].

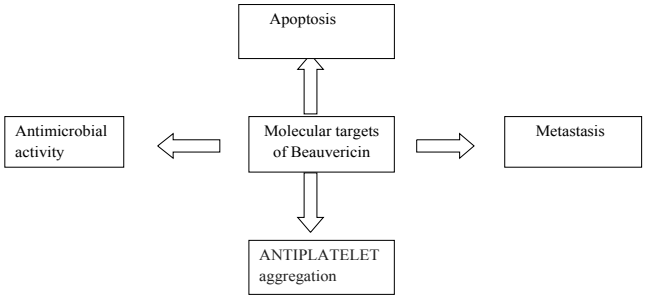

Figure 1: Illustration of the different interactions of beauvericin in biochemical processes, including metastasis, apoptosis, antiplatelet aggregation and antimicrobial activity.

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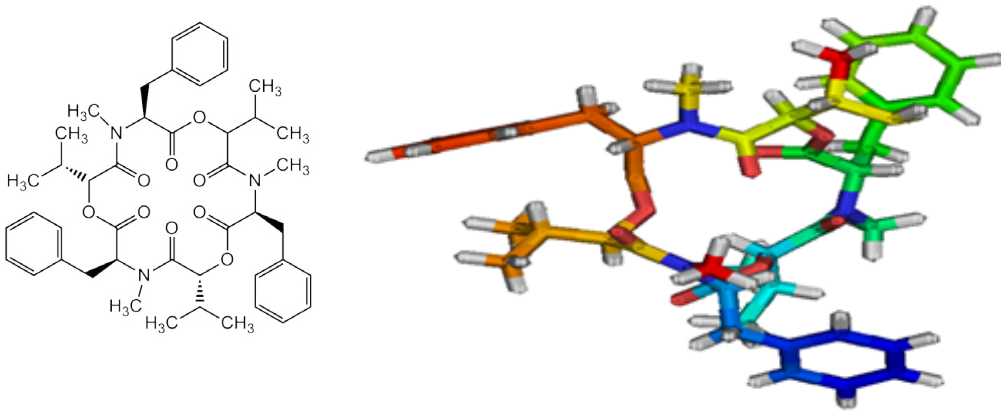

Figure 2: The chemical structure of the bioactive compound beauvericin produced by *Beauveria bassiana*.

Mechanism of Extraction, Separation and Detection of Beauvericin

For the extraction of beauvericin, cereal and corn samples were blended by using an acetonitrile-water mixture. In 1999, homogenised the sample with methanol [22]. After blending, the extract was placed into the Liquid chromatography–mass spectrometry without any further clean up and resulting in an LOD of 8 µg/kg. Liquid-liquid-partitioning with dichloromethane is often combined with solid phase extraction (SPE) columns for cleaning processes. Separation and detection of beauvericin are performed by using a High-Performance Liquid Chromatography with Photodiode Array Detection (HPLC-DAD) system with a reversed phase C^{18} column and an acetonitrile-water mixture as mobile phase. The absorbtion spectrum is calculated at 192 nm and 209 nm. Besides this Nuclear Magnetic Resonance (NMR) Spectroscopy is also used for identification purposes.

Another technique used for separation and detection is high performance thin layer chromatography (HPTLC), using precoated silica gel 60 plates that are spotted with methanolic extracts. Mobile phases are toluene/acetone, chloroform/2-propanol and ethyl acetate/hexane. Detection is performed at 365 and 254 nm after colouring with iodine vapours with a detection limit in the mg/kg range. It is concluded that Liquid Chromatography-Mass Spectrometry is a powerful tool for the determination and identification of beauvericin. The major disadvantages of liquid chromatography, mass liquid chromatography and mass spectrometry techniques are the high costs involved and the professional experience that is required [23].

Biosynthesis of Beauvericin

Wang and Xu reviewed the biosynthesis of bioactive secondary metabolite beauvericin [8]. A multifunctional enzyme beauvericin synthetase with a molecular mass of 250 kDa helps in the synthesis of BEA [24]. The fermentation process for the production of BEA is shown in Figure 3. BEA synthetase, AdoMet, ATP and Mg^{2+} are the important constituent's helps in the formation of cyclic ester of a trimer of (2*R*)-2-hydroxy-3-methylbutanoyl-*N*-methyl-L-phenylalanine. The nonribosomal peptide synthetase enzyme helps in the formation of cyclic ester of a trimer of (2*r*)-2-hydroxy-3-methylbutanoyl-*n*-methyl-l-phenylalanine [25]. The initial and important biosynthesis step involves transamination as L-phenylalanine and valine needs nitrogen and provided by any amino acids. The source of carbon can be pentose or hexose but the glucose was reported to be the most effective agent [26]. Beauvericin also requires several condensation, methylation and activation. S-Adenosyl methionine (AdoMet) acts as a source of methyl group for the L-phenylalanyl residues. Beauvericin biosynthesis is catalyzed by the beauvericin synthetase via a nonribosomal, thiol templated mechanism [7]. Beauvericin synthetase multienzyme activates the r-hydroxycarboxylic acid (2*r*)-2-hydroxy-3-methylbutanoate (d-hydroxyisovalerate, d-hiv) and the amino acid phenylalanine (l-phe) as adenylates, captures the activated substrates with peptide bond and finally releases the free cyclic trimeric lactone or the linear hexadepsipeptide is cyclised to make beauvericin with optimum pH for beauvericin formation pH 7.2, and the optimum temperature is 25-27°C [27].

Sumalee states that, fungi are presently considered to be in a broad range of biological activities such as medicines and pesticides [28]. It is studied for the production of beauvericin, the fermentation conditions and techniques are widely accepted and fed-batch method is accepted as the most efficient method. *B. bassiana, Fusarium spp., Paecilomyces fumoso-roseus* and *P. tenuipes* are feasible and promising fungi for the production of beauvericin [28-32].

In fed batch fermentation, glucose is the main source to feed the culture and is successfully used in BEA production. It is concluded that carbon is the major source of glucose. Among peptone and $NaNO_3$, peptone is the major source of nitrogen [33,34]. Being an intracellular product, only a small amount of BEA is exported into the medium [8,35]. Xu studied *F. redolens* Dzf2 mycelial culture along with macroporous polystyrene resin as sorbent increases the production of BEA from 194-265 mg/L. When the mycelial cuture is optimized with glucose and resin, the yield is increased upto 400 mg/L. It is concluded that the quantity of BEA was low as compared to those of industrial and commercial products. Hence, the BEA can be extracted by using an organic and non-polar solution in the fermentation process to enhance production.

Biological Activities

Beauvericin displays a diverse array of biological activities including antibiotic, insecticidal, herbicidal, antiretroviral, cytotoxic, anti-haptotactic, anti-cholesterol and chemosensitizer, as well as repression of amyloid plaque formation in Alzheimer's disease [32]. According to Jow et al. [16] beauvericin increases antiproliferative activity against

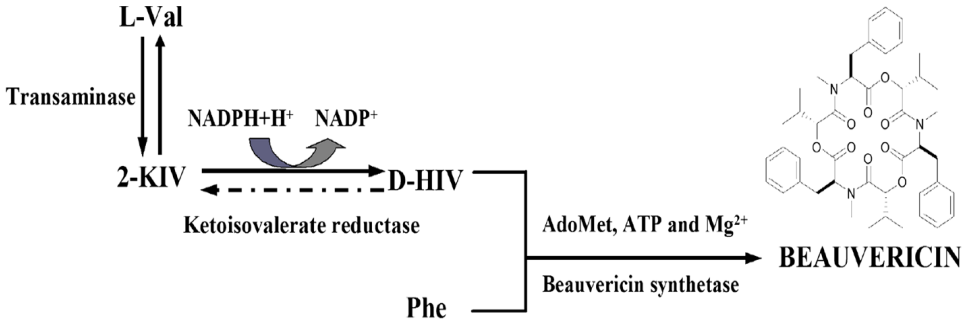

Figure 3: Fermentation process for the production of BEA [25].

various human cancer cell lines by activating calcium sensitive cell apoptotic pathways. On the other hand, it also inhibits the directional cell motility of cancer cells at subcytotoxic concentrations as haptotaxis (outgrowth of cells) is essential for the formation of new blood vessels in tumors (angiogenesis), invasion of other tissues by cancer cells, and metastasis to the distant organs [18,36].

Induction of Apoptosis and Cytotoxic and Antitumor Activity

Apoptosis is synonyms to programmed cell death, which leads to series of distinct changes such as DNA fragmentation, alteration in cell morphology, such as blebbing, loss of cell attachment, cytoplasmic contraction and other biochemical changes including the activation of caspases through extrinsic and/or intrinsic mitochondrial pathways [6]. Zhan demonstrated the role of beauvericin in the induction of apoptosis which involves various changes in the cellular and molecular pathways [18]. This process involves the activation of proteins which are involved in programmed cell death, for example, the *BCL2* family of proteins has both anti-apoptotic and pro-apoptotic members. Beauvericin has also been known to induce apoptosis in the human leukemia cell lines (CCRF-CEM) through nuclear fragmentation followed by the release of cytochrome C from mitochondrial membrane which leads to activation of caspase 3 and subsequent cellular changes in morphology [17]. Similarly the apoptotic effect of Beauvericin has also been investigated in human cell lines, HepG2 and MRC-5 to possess anticonvulsion and antirhythmic activities [37].

It is demonstrated in several laboratories that beauvericin induced apoptosis in different systems. It is reported that in CY-1 (monkey kidney) cells, beauvericin induces the stereotypical hallmarks of apoptosis, including the formation of DNA ladders, compaction of nuclear DNA and the subsequent appearance of apoptotic bodies [38]. Another study reported the apoptotic activity in neonatal human keratinocytes and human esophageal epithelial cells with beauvericin which has developed morphological changes in cell shrinkage and membrane blebbing [39]. Similar results are observed in a porcine kidney epithelial cell line when treated with beauvericin [40]. Nilanonta reported the cytotoxic effect of beauvericin on African green monkey kidney fibroblastin African Vero with IC_{50} 10 µg/ml [30]. Additionally he also reported its effect on human breast cancer cells BC-1 and human epidermoid at 20 µg/ml. Nuclear fragmentation in the cell by the release of cytochrome C from mitochondria with the activation of caspase 3 and cellular changes in morphology with IC_{50} 1-2 µg/ml leads to cytotoxic effect on the cell lines of leukemia (CCRF-CEM) [16]. Calo studied the effect of mycotoxin BEA in human cell lines of myeloid origin which includes human monocytic lymphoma cells U-937 with IC_{50} 10 µg/ml and human promyelocytic leukemia HL-60 with IC_{50} 12 µg/ml [41].

Lin demonstrated the induction of apoptosis by BEA in human non–small cell lung cancer-A549 [42] cell line which involves the BCL2 family, cytochrome C release and caspase 3 activation with IC_{50} of 2.4-7.8 µg/ml, whereas Zhan studied the anticancerous activity against human non-small cell lung cancer [18] NCI-H460 cell line with IC_{50} 1.1 µg/ml. Recently it was also demonstrated in human breast cancer MCF-7 cells, human CNS cancer (glioma) SF-268 cells and human pancreatic carcinoma MIA Pa Ca-2 cells with IC_{50} from 1.3 to 1.8 µg/ml which involves searching for cell motility and angiogenesis inhibitors with potential anticancerous activity. Similar antiproliferative results were observed in human retinoblastoma Y79 cells with IC_{50} 0.4-4 µg/ml [43].

In addition to its involvement in apoptotic pathways, beauvericin plays an important role in inhibition of cell cycle at certain check points. It is observed that beauvericin leads to the inhibition of P(I)3K-Akt phosphorylation during T-cell activation. It is also observed that these cell lines show antiangiogenic activity in Human Umbilican Vein Endothelial Cells (HUVEC) cells at sublethal concentrations [18]. Inhibition of angiogenesis is an effective cancer chemotherapy strategy, and thus may be a useful anticancer agent [44].

The first experimental study to demonstrate the anticancer properties of beauvericin is performed in mice that demonstrates that BEA leads to the inhibition of activated T cells via down regulation of the P(I)3-Akt signaling pathway [45]. Furthermore it is showed that BEA plays an important role in the etiology of plant diseases. Preliminary studies reported that BEA is highly toxic to melon protoplasts as compared with fusaric acid and fumonisin B1 [46].

Anti-Platelets Aggregation

Platelets play an important role in regulation of tumor angiogenesis, its growth and metastasis. Earlier it is reported that cancer cells have remarkable property to activating platelets, helping their survival in the blood circulation during hematogenous metastasis by preventing tumor cell lysis by natural killer (NK) cells and cytotoxic T lymphocyte cells [47,48]. A variety of molecular mechanisms such as GPIIb/IIIa, GP Ib-IX-V, P2Y receptors, and PAR receptors, have been proposed to describe tumor cell-induced platelet seggregation (TCIPA) [49,50].

Antimicrobial Activity

BEA showed a great antibacterial activity against many pathogenic Gram positive and Gram negative bacteria, which also includes human,

animal and plant pathogens mainly food crops. It was found that BEA targets the cell organelles such as ribosomes or cell nucleus and enzymes, as BEA is synthesized from amino acids. Unlike other antibiotics example as penicillin which blocks the peptidoglycan biosynthesis of Gram-positive bacteria whose cell wall is not the antibacterial mode of action of beauvericin, although these antibiotics and beauvericin are both from amino acids that are produced by fungi [8]. Bacterial strains which are inhibited by BEA are listed in Table 1. Till now investigation is going on, against the activity of drug resistant bacteria of BEA.

Viral infections lead to many fatal and epidemic diseases such as HIV, H1N1, SARS, AIV and HBV. Shin reported a new inhibitor of cyclic hexadepsipeptides i.e., BEA, which inhibits HIV type 1 integrase at IC_{50} 1.9 μM [51-55]. Along with antibacterial and antiviral activity, BEA being a fungal product it lacks antifungal activity. BEA showed the antifungal activity only in combination with ketaconazole at 0.5 mg/kg and miconazole at 0.5 mg/kg concentration against *Candida parapsilosis* which leads to high mortality rates especially in neonates [18,56]. Experimental research is still going on to study the effect of BEA in combination with other compounds as antifungal agent and as a result it can be utilized as therapeutic potential in many fields.

Insecticidal Activity

Hamill discovered firstly the insecticidal activity of BEA against a model organism *Artina salina* [7]. Similarly, various researchers investigated the insecticidal effect of BEA on *Aedes aegypti*, which is found to be more effective [57] and *Calliphora erythrocephala, Lygus spp., Spodoptra frugiperda* and *Schizaphus graminus* [58-60]. From the above listed functions the insecticidal activity of BEA is still under investigation and cannot be applied directly as commercial insecticidal agent.

Conclusion

BEA is a bioactive compound of a fungal product which shows different kinds of bioactivities (antimicrobial, anti-insecticidal, antitumor, and antiplatelet, etc.) at picogram level and with unique uncharacterized active mechanism [61-66]. BEA would be a great discovery in pharmacology, toxicology and medicines or pesticides because it is a therapeutic potential against deadly diseases such as cancer and viral or bacterial infections. Recent studies on medical ground and pharmaceutical industries indicates that it is impossible to find a perfect drug or compound without any side effects for a long time [30,67]. Since it has broad and significant bioactivities, BEA can become a commercial product from EPF in the future.

	Bacterial Strains	References
Gram Positive Bacteria	*Bacillus* spp.	Castlebury et al. [51]
	Bifidobacterium adolescentis *Eubaterium biforme* *Peptostreptococcus* spp. *Paenibacillus* spp.	Castlebury et al. [51]
	Clostridium perfringens	Castlebury et al. [51]; Meca et al. [52]
	Enterococcus faecium *Listeria monocytogenes*	Meca et al. [52]
	Mycobacterium tuberculosis	Nilanonta et al. [53]
	Staphylococcu haemolyticus	Xu et al. [54]
Gram negative Bacteria	*Agrobacterium tumefaciens* *Escherichia coli* *Pseudomonas lachrymans* *Xanthomonas vesicatoria*	Xu et al. [54]
	Escherichia coli CECT 4782 *Pseudomonas aeruginosa* *Salmonella enterica* *Shigella dysenteriae* *Yersinia enterocolitica*	Meca et al. [52]

Table 1: Strains of bacteria inhibited by Beauvericin.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Molnar I, Gibson DM, Krasnoff SB (2007) Secondary Metabolites from Entomopathogenic Hypocrealean Fungi. Nat Prod Rep 27: 1241-1275.
2. Rohlfs M, Churchill ACL (2011) Fungal Secondary Metabolite as Modulators of Interactions with Insects and Other Arthropods. Fungal Genet Biol 48: 23-34.
3. Strasser H, Vey A, Butt TM (2000) Are There Any Risks in Using Entomopathogenic Fungi for Pest Control, with Particular Reference to the Bioactive Metabolites of *Metarhizium*, *Tolypocladium* and *Beauveria* Species? Biocontrol Sci Technol 10: 717-735.
4. Vey A, Vago C (1971) Reaction Anticryptogamique de Type Granulome chezles Insectes. Annales Institute of Pasteur Microbiology 121: 527-532.
5. Safavi SA (2013) *In vitro* and *In vivo* Induction, and Characterization of Beauvericin Isolated from *Beauveria bassiana* and Its Bioassay on *Galleria mellonella* Larvae. J Agri Sci Technol 15: 1-10.
6. Tuli HS, Sharma AK, Sandhu SS, Kashyap D (2013) Cordycepin: A bioactive metabolite with therapeutic potential. Life Sci 93: 863-869.
7. Hamill RL, Higgens GE, Boaz HE, Gorman M (1969) The structure of Beauvericin, a new desipeptide antibiotic toxic to *Artemia salina*. Tetrahedron Letters 49: 4255-4258.
8. Wang Q, Xu L (2012) Beauvericin, a Bioactive Compound Produced by Fungi: A Short Review. Molecules 17: 2367-2377.
9. MacLeod DM (1954) Investigations on the Genera *Beauveria* Vuill. and *Tritirachium Limbe*. Can J Botany 32: 818-890.
10. Leatherdale D (1970) The Arthropod Hosts of Entomogenous Fungi in Britain. Entomophaga 15: 419-435.
11. Li Z (1988) List on the Insect Hosts of *Beauveria bassiana* In: Study and application of Entomogenous Fungi in China. Beijing Academic Periodical Press pp: 241-255.
12. Jaronski ST, Goettel MS (1997) Development of *Beauveria bassiana*for control of grasshoppers and locusts. Memoirs of the Entomological Society of Canada 129: 225-237.
13. Goettel MS, Eilenberg J, Glare T (2010).Entomopathogenic Fungi and Their Role in Regulation of Insect Populations. In: Gilbert LI and Gill (eds.) Insect Control: Biological and Synthetic Agents. Amsterdam: S. S. Academic Press, pp: 387-432.
14. Zimmermann G (2007) Review on Safety of the Entomopathogenic Fungi *Beauveria bassiana* and *Beauveria brongniartii*. Biocontrol Sci Technol 17: 553-596.
15. Xu Y, Orozco R, Wijeratne EMK, Gunatilaka AAL, Stock SP (2008) Biosynthesis of the cyclooligomer depsipeptide beauvericin, a virulence factor of the entomopathogenic fungus *Beauveria bassiana*. Chem Biol 15: 898-907.
16. Jow G, Chou C, Chen B, Tsai J (2004) Beauvericin induces cytotoxic effects in human acute lymphoblastic leukemia cells through Cytochrome C release, Caspase 3 activation: The causative role of calcium. Cancer Lett 216: 165-173.
17. Hen BF, Tsai MC, Jow GM (2006) Induction of calcium influx from extracellular fluid by Beauvericin in human leukemia cells. Biochem Biophys Res Commun 340: 134-139.
18. Zhan J, Burns AM, Liu MPX, Faeth SH, Gunatilaka AAL (2007) Search for cell motility and angiogenesis inhibitors with potential anticancer activity: Beauvericin and other constituents of two endophytic strains of *Fusarium oxysporum*. J Nat Prod 70: 227-232.
19. Steinrauf LK (1985) Beauvericin and the other Enniatins. Metals Ions in Biological System 19: 139-171.

20. Braden B, Hamilton JA, Sabesan MN, Steinrauf LK (1980) Crystal structure of a beauvericin-barium picrate complex. J Am Chem Soc 102: 2704-2709.

21. Kouti K, Lemmens M, Gruber LR (2003) Beauvericin induced channels in ventricular myocytes and liposomes. Biochim Biophys Acta 1609: 203-210.

22. Shephard GS, Sewram V, Nieuwoudt TW, Marasas WFO, Ritieni A (1999) Production of the mycotoxins fusaproliferin and beauvericin by South African isolates in the *Fusarium gibberella fujikuroi* species complex. J Agric Food Chem 47: 5111-5115.

23. Fotso J, Leslie JF, Smith JS (2002) Production of Beauvericin, Moniliformin, Fusaproliferin, and Fumonisins B1, B2, and B3 by Fifteen Ex-Type Strains of Fusarium Species. Appl Environ Microbiol 68: 5195-5197.

24. Peeters H, Zocher R, Madry N, Kleinkauf H (1983) Incorporation of radioactive precursors into beauvericin produced by *Paecilomyces fumoso-roseus*. Phytochemistry 22: 1719-1720.

25. Xu L, Liu Y, Zhou L, WuJ (2011) Modeling of *Fusarium redolens* Dzf2 mycelial growth kinetics and optimal fed-batch fermentation for beauvericin production. J Ind Microbiol Biotechnol 38: 1187-192.

26. Xu L, Liu Y, Zhou L, Wu J (2010) Optimization of a liquid medium for beauvericin production in *Fusarium redolens* Dzf2 mycelial culture. Biotechnol Bioprocess Eng 15: 460-466

27. Peeters H, Zocher R, Kleinkauf H (1988) Synthesis beauvericin by a multifunctional enzyme. J Antibiot 12: 352-359

28. Supothina S, Srisanoh U, Nithithanasilp S, Tasanathai K, Jenniferluangsa AJ (2011) Beauvericin production by the Lepidoptera pathogenic fungus *Isariatenuipes*: Analysis of natural specimens, synnemata from cultivation, and mycelia from liquid-media fermentation. Nat Prod Bioprospect 1: 112-115.

29. Gupta S, Montllor C, Hwang Y (1995) Isolation of novel beauvericin analogues from the 25 fungus *Beauveria bassiana.* J Nat Products 58: 733-738.

30. Nilanonta C, Isaka M, Kittakoop P, Trakulnaleamsai S, Tanticharoen M (2002) Precursor-directed biosynthesis of beauvericin analogs by the insect pathogenic fungus *Paecilomyces tenuipes* BCC 1614. Tetrahedron 58: 3355-3360.

31. Moretti A, Mule G, Ritieni A, Logrieco A (2007) Further data on the production of beauvericin, enniatins and fusaproliferin and toxicity to *Artemia salina* by *Fusarium* species of *Gibberella fujikuroi* species complex. Int J Food Microbiol 118: 158-163.

32. Suessmuth R, Mueller J, Von DH, Molnar I (2011) Fungal cyclooligomer depsipeptides: From classical biochemistry to combinatorial biosynthesis. Nat Prod Rep 28: 99-124

33. Vesonder RF, Wu W, Alpin MCE (1999) Beauvericin not an acute toxin to duckling bioassay. Phytopathology 89: 80.

34. Eley KL, Halo LM, Song Z, Powles H, Cox RJ (2007) Simpson Biosynthesis of the 2-pyridone tenellin in the insect pathogenic fungus *Beauveria bassiana*. Eur J Chem Biol 8: 289-297.

35. Lee HS, Song HH, Jeong JH, Shin CG, Choi SU (2008) Cytotoxicities of enniatins H, I, and MK1688 from *Fusarium oxysporum* KFCC 11363P. Toxicon 51: 1178-1185.

36. Carmeliet P (2003) Blood vessels and nerves: common signals, pathways and diseases. Nat Rev Genet 4: 710-720.

37. Ivanova L, Skjerve E, Eriksen GS, Uhlig S (2006) Cytotoxicity of enniatins A, A1, B, B1, B2 and B3 from *Fusarium avenaceum*. Toxicon 47: 868-876

38. Wang H, Jones C, Zannella CH, Holt T, Gilchrist DG, et al. (1996) Sphinganine analog mycotoxins induce apoptosis in monkey kidney cells. P Natl Acad Sci USA 93: 3461-3465.

39. Tolleson WH, Melchior WBJ, Morris SM, McGarrity LJ, Domom OE (1996) Apoptosis and antiproliferative effects of fumonisim B1 in human keratinocytes, Fibroblasts, eosphageal epithelial cells, and hepatom cells. Carcinogenesis 17: 239.

40. Kegvi T, Klarit M, Pepeljnjak S, Domijan AM, Petrik J (2007) Lipid peroxidation and glutathione levels in porcine kidney PK15 cells after individual and combined treatment with fumonisin B1, beauvericin and ochratoxin A. Basic Clin Pharmacol Toxicol 100: 157-164.

41. Calo L, Fornelli F, Ramires R, Nenna S, Tursi A, et al. (2004) Cytotoxic effects of the mycotoxin Beauvericin to human cell lines of myeloid origin. Pharmacol Res 4: 73-77.

42. Lin H, Chen LY, Tsai B, Lu M, Chou J, et al. (2004) Involvement of Bc1-2 family, Cytochrome C and Caspase 3 in induction of apotosis by beauvericin in human non-small cell lung cancer cells. Cancer Lett 230: 248-259.

43. Ojcjus DM, Zychlinsky A, Zheng LM, Young JD (1991) Inophore-induced apoptosis: Role of DNA fragmentation and calcium fluxes. Exp Cell Res 197: 43-49.

44. Jirakkakul J, Punya J, Pongpattanakitshote S, Paungmoung P, Vorapreeda N, et al. (2008) Identification of the nonribosomal peptide synthetase gene responsible for bassianolide synthesis in wood-decaying fungus *Xylaria sp.* BCC1067. Microbiology 154: 995-1006.

45. Wu XF, Xu R, Ouyang ZJ, Qian C, Shen Y (2013) Beauvericin Ameliorates Experimental Colitis by Inhibiting Activated T Cells via Downregulation of the PI3K/Akt Signaling Pathways. PLoS One 8: e83013.

46. Sagakuchi M, Moretti A, Endo E, Matsuda Y, Toyoda H, et al. (2000) An approach to the use of plant sensitivity for simple detection of mycotoxin. Proceedings of First Asian Conference of Plant Pathology, Kuala Lumpur, Malaysia, pp: 262-279.

47. Tsuruo T, Fujita N (2008) Platelet aggregation in the formation of tumor metastasis. Proc Jpn Acad Ser B Phy Biol Sci 84: 189-198.

48. Goubran HA, Burnouf T (2012) Platelets, coagulation and cancer: multifaceted interactions. Am J Med 3: 130-140.

49. Jackson SP (2007) The growing complexity of platelet aggregation. Blood 109: 5087-5088.

50. Bambace NM, Holmes CE (2011) The platelet contribution to cancer progression. J Thromb Haemost 9: 237-249.

51. Castlebury LA, Sutherland JB, Tanner LA, Henderson AL, Cerniglia CE (1999) Use of a bioassay to evaluate the toxicity of Beauvericin to bacteria. World J Microbiol Biotechnol 15: 119-121.

52. Meca G, Sospedra I, Soriano JM, Ritieni A, Moretti A (2010) Antibacterial effect of the bioactive compound beauvericin produced by *Fusarium proliferatum* on solid medium of wheat. Toxicon 56: 349-354.

53. Nilanonta C, Isaka M, Kittakoop P, Palittapongarnpim P, Kamchonwongpaisan S (2000) Antimycobacterial and antiplasmodial cyclodepsipeptides from the insect pathogenic fungus *Paecilomyces tenuipes* BCC1614. Planta Med 66: 756-775.

54. Xu L, Wang J, Zhao J, Li P, Shan T (2010a) Beauvericin from the endophytic fungus, *Fusarium redolens,* isolated from *Dioscorea zingiberensis* and its antibacterial activity. Nat Prod Commun 5: 811-814.

55. Shin CG, An DG, Song HH, Lee C (2009) Beauvericin and enniatins H, I and MK1688 are new potent inhibitors of human immunodeficiency virus type-1 integrase. J Antibiot 62: 687-690.

56. Fukuda K, Arai M, Yamaguchi Y, Masuma R (2004) New Beauvericins, potentiators of antifungal miconazole activity produced by *Beauveria* sp. FKI-1366. J Antibiot, pp: 110-116.

57. Grove JF, Pople M (1980) The insecticidal activity of beauvericin and the enniatin complex. Mycopathologia 70: 103-105.

58. Jestoi M (2008) Emerging *Fusarium* -Mycotoxins Fusaproliferin, Beauvericin, Enniatins, And Moniliformin—A Review. Crit Rev Food Sci Nutr 48: 21-49.

59. Fornelli F, Minervini F, Logrieco A (2004) Cytotoxicity of fungal metabolites to lepidopteran (*Spodoptera frugiperda*) cell line (SF-9). J Invertebr Pathol 85: 74-79.

60. Leland JE, McGuire MR, Grace JA, Jaronski ST, Ulloa M (2005) Strain selection of a fungal entomopathogen, *Beauveria bassiana,* for control of plant bugs (*Lygus spp.*) (Heteroptera: *Miridae).* Biol Control 35: 104-114.

61. Plattner RD, Nelson PE (1994) Production of beauvericin by a strain of *Fusarium proliferatum* isolated from corn fodder for swine. Appl Environ Microbiol 60: 3894-3896.

62. Krska R, Schuhmacher R, Grasserbauer M, Scott PM (1996) Determination of the *Fusarium mycotoxin* beauvericin at µg/kg levels in corn by high-performance liquid chromatography with diode-array detection. J Chromatogr 746: 233-238.

63. Logrieco A, Rizzo A, Ferrancane R, Ritieni A (2002) Occurrence of beauvericin and enniatins in wheat affected by *Fusarium avenaceum* Head Blight. Appl Environ Microbiol 68: 82-85.

64. Ambrosino P, Galvano F, Fogliano V, Logrieco A, Fresa R, et al. (2004) Supercritical fluid extraction of beauvericin from Maize. Talanta 62: 523-530.

65. Sorensen JL, Nielsen KF, Rasmussen PH, Thrane U (2008) Development of a LC-MS/MS method for the analysis of enniatins and beauvericin in whole fresh and ensiled maize. J Agr Food Chem 56: 10439-10443.

66. Ganassi S, Moretti A, Pagliai AMB, Logrieco A, Sabatini MA (2002) Effects of beauvericin on *Schizaphis graminum* (Aphididae). J Invertebr Pathol 8: 90-96.

67. Luangsaard JJ, Berkaew P, Ridkaew R, Hywel JNL, Isaka M (2009) A beauvericin hot spot in the genus *Isaria*. Mycol Res 113: 1389-1395.