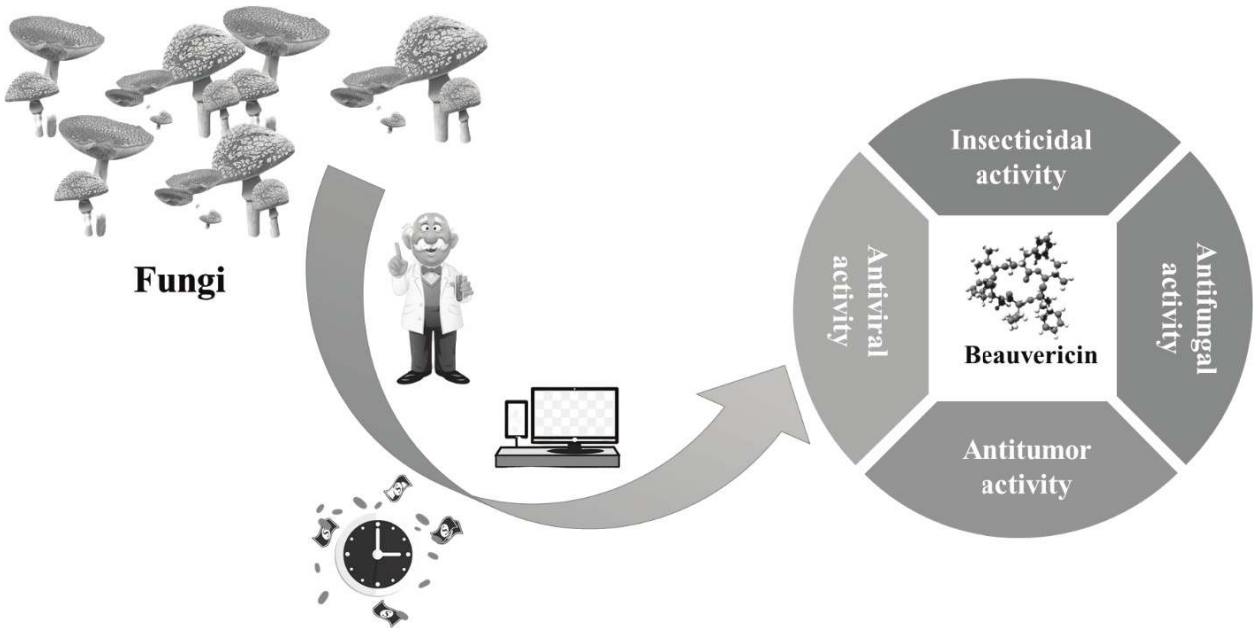
A Review of the Bioactivity of Beauvericin - A Bioactive Compound Produced by Fungi

Doan Manh Dung[a*], Tran Quang Huy[b]

Graphical abstract:



[a] Institute of Biotechnology and Environment, Tay Nguyen University; 567 Le Duan, Buon Ma Thuot City, Dak Lak Province, Vietnam. e-mail: dmdung@ttn.edu.vn

[b] University of Medicine and Pharmacy, Hue University; 6 Ngo Quyen, Vinh Ninh, Hue City, Thua Thien Hue Province, Vietnam. e-mail: quanghuymt27@gmail.com

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Abstract:

Beauvericin is a well-known insecticidal, antibacterial, antiviral and cytotoxic mycotoxin with a cyclic hexadepsipeptide structure that is a piece of the enniatin antibiotic family. It could be applied in several fields such as insecticides and pharmaceuticals. Other aspects of beauvericin like the toxicity and the determination techniques were mentioned in previous reports but there are seldom published about the bioactivity. Therefore, this is the first review discussing some various bioactivities of the fungal substance beauvericin such as insecticidal activity, and antitumor activity.

Key words: *beauvericin species; bioactive compound; antibiotic feature; mycotoxin; insecticidal feature*

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Introduction

Many fungi, including *Beaveria bassiana* and *Fusarium* spp., produce mycotoxin beauvericin (Hamill et al., 1969; Logrieco et al., 1998). Beauvericin is an antibiotic that belongs to the enniatin class and is a cyclic hexadepsipeptide. In an alternate pattern, it has 3 D-hydroxyisovaleryl (DHIV) and 3 NMPA (N-methylphenylalanyl) residues (Grove & Pople, 1980; Hamill et al., 1969). Beauvericin species are structurally like enniatins (denoted as ENTs), which are created by several Fusarium types, but the N-methylamino acid (denoted as NMAA) in beauvericin is dissimilar. The bioactivities of beauvericin, and the enniatins are plainly dissimilar because of this difference (Shin et al., 2009). *Beaveria bassiana*, a popular and economic entomopathogenic mycoinsecticide, was the first to produce Beauvericin (Hamill et al., 1969). One of the active ingredients of *B. bassiana*, beauvericin, was found to exhibit antibacterial and antitumor properties (Champlin & Grula, 1979; Hamill et al., 1969). As beauvericin is a mycotoxin, researchers have looked at its toxicity in normal human cells and improved determination techniques for food safety; these findings have been described elsewhere (Krska et al., 1996; Plattner & Nelson, 1994). However, there is no study that focuses on the beauvericin biological result activity; so, this paper is the first theoretical study to do so.

Bioactivity of beauvericin

There are four applications of bioactivity of beauvericin, in Figure 1.

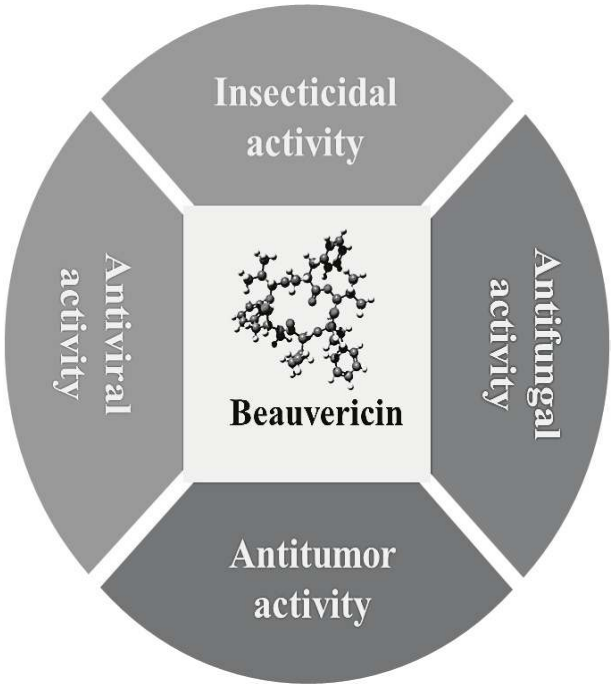

Figure 1. Four applications of bioactive Beauvericin

Insecticidal activity

Hamill and the team (Hamill et al., 1969) were the first to discover that beauvericin has insecticidal properties. The active ingredient from *B. bassiana* was verified to be Beauvericin against *Artemia salina*, which was used as a sample organism to examine insecticidal action. The insecticidal efficacy of beauvericin on *Calliphora erythrocephala*, *Aedes aegypti*, *Lygus* spp., *Spodoptera frugiperda* and *Schizaphis graminum* was then examined on a microgram level (Grove & Pople, 1980; Leland et al., 2005). Even though beauvericin has powerful insecticidal activity against to a wide range of insecticide pests, it has not been used as an economic insecticide for two reasons: first, due to insect movement, employing an entomopathogenic fungus that produces beauvericin as an insecticide acquires more benefits than applying the compound directly. The entomopathogenic fungus might multiply in the bodies of insects and spread over the world as a result of insect movement. Even if only a little amount of entomopathogenic fungus spores were utilized, the entomopathogenic fungus would provide effective pest control. Second, thorough monitoring of beauvericin output should verify that it does not exceed the EPA's threshold limitations (Leland et al., 2005). Beauvericin's insecticidal mechanism is

still worth exploring, even though it is not used as an economic insecticide. Beauvericin's insecticidal mechanism has received little attention. Despite having chemical structures that are comparable to those of other cyclic types of hexadepsipeptide mycotoxins types, beauvericin is more potent against to *Aedes aegypti* (Daniel et al., 2017; Grove & Pople, 1980) and might have an exclusive mechanism of action. The identification of beauvericin's anti-insect mechanism of action will aid in the development of new commercial insecticides, lessen the danger that these substances pose to human cells and shed light on the mechanism by which other mycotoxins work.

Antitumor activity

In recent times, beauvericin's anticancer activity has received increased attention (Table 1). Beauvericin's cytotoxicity to human leukemia cells has been well documented.

Table 1. Beauvericin's cytotoxic effects

Lineage of biological cells	IC_{50} (g/L)	REF.
Vero fibroblasts from African green colored monkey kidneys	10.12	(Nilanonta et al., 2002)
BC-1 is a kind of human breast cancer	15	
Individual epidermoid carcinoma KB	> 20.13	
Individual leukemia biological cell CCRF-CEM	1.02 – 2.34	(Jow et al., 2004)
People monocytic lymphoma cells U-937	24.2	(Calò et al., 2004)
Human promyelocytic leukemia HL-60	12	
Individual big biological cell lung cancer (NSCLC) A549	2.41 – 7.82	(Lin et al., 2005)
People breast cancer MCF-7	1.411	(Zhan et al., 2007)
People CNS cancer (glioma) SF-268	1.813	
People non-small cell lung cancer NCI-H460	1.104	
People pancreatic carcinoma MIA Pa Ca-2	1.302	
People retinoblastoma Y79	0.4 – 4	(Cheng et al., 2009)

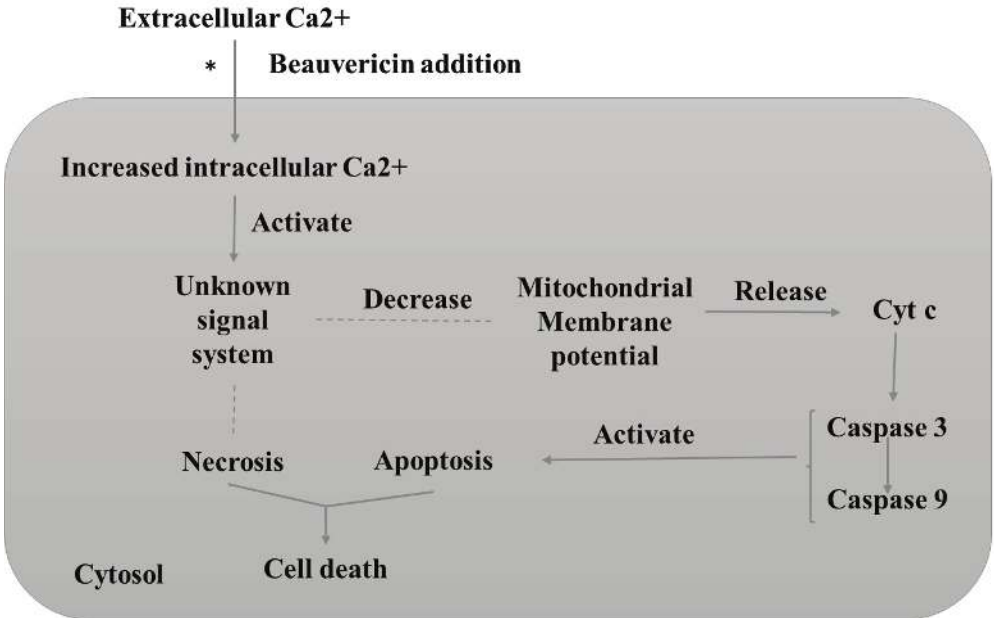

Figure 2. Mechanism of the lethal effects of beauvericin on a human leukemia cell (*beauvericin caused external Ca^{2+} to migrate inside the cell, increasing the quantity of internal cell Ca^{2+}; some dashed arrows show the particular mechanisms process that are uncertain).

Beauvericin first causes external Ca^{2+} to migrate into the cytosol, which raises the intracellular Ca^{2+} level. A high Ca^{2+} concentration triggers the "unknown signal system", which causes *Cyt c* to be released from the mitochondria. Finally, apoptosis is brought on by the caspase that *Cyt c* activated. It is yet unknown how an elevated intracellular Ca^{2+} content controls the signaling process that results in cell death. Beauvericin's mechanism of cytotoxicity against additional cell lines has also been linked to Ca^{2+} flow, according to reports (Kouri et al., 2003; Ojcius et al., 1991; Que et al., 1997; Wu et al., 2002). The unidentified component in Figure 2, therefore, requires more research. Beauvericin's cytotoxic mechanism for leukemia cells may be exploited to identify other beauvericin cytotoxic mechanisms, such as its function as an insect reagent as well as an anti-fungal agent.

Antifungal feature

Beauvericin is a fungus, which would explain why it does not have much antifungal activity on its own. Beauvericin, when combined with miconazole or ketoconazole, exhibits antifungal action, according to Zhang and his team (Zhang et al., 2007) and Fukuda's team (Fukuda et al., 2004). The antifungal effect of beauvericin (0.5 mg/kg) and ketoconazole (0.5 mg/kg) against *Candida parapsilosis*, which could swiftly result in massive mortality

percentage rates, notably in neonates, was outstanding. Ketoconazole and beauvericin by themselves have negligible to no impact on *C. parapsilosis*. Beauvericin's antifungal effect might be comparable to leukemia cell's cytotoxic effect, which suggests that the fungus might be able to block the "not found signal system" (in Figure 2) and could until a different drug, such as ketoconazole, is introduced to activate the signaling system. Beauvericin's biological action could be developed and used in novel ways by combining it with another chemical. Much research (Shekhar-Guturja et al., 2016; Tong et al., 2016) has examined the mechanism underlying beauvericin's antifungal activity. It has been disclosed that beauvericin species could combat multimedication-resistant *Candida albicans* by blocking ABC transfer agents, confirming that their energetic influence is not the result of their pharmacokinetic reactions (Tong et al., 2016). By inhibiting the ATP-binding cassette transporters, beauvericin, a medication efflux pump modulator, reverses the multi-medication resistant phenotype of Albicans. By increasing intracellular Ca^{2+} and ROS, beauvericin demonstrates fungicidal activity (Tong et al., 2016). Beauvericin was currently used to examine a potent method to increase antifungal efficacy against fungal infection.

Antiviral activity

Additionally, beauvericin's antiviral activity (IC50 1.9 M) (Shin et al., 2009) has been identified. Beauvericin is the most efficient inhibitor of the cyclic hexadepsipeptides that inhibit HIV-1 integrase, according to the Shin team (Shin et al., 2009). Despite having a similar structure, enniatins have relatively poor activities, suggesting that the activity of beauvericin might be caused by the main structural variation, N-methylation. Diseases that are deadly and endemic can be brought on by viral infections. Beauvericin's antiviral activity should therefore be examined for any potential clinical implications as well as its effectiveness against other dangerous viruses like HBV, SARS, H1N1 and AIV. The anti-virus activity of beauvericin differs from other antibiotics in terms of its antibacterial mechanism. The capsid of a virus is not the antibacterial mode of beauvericin activation, in contrast to most medications. The targets of beauvericin include enzyme systems or cell organelles. According to (L. Xu et al., 2010), beauvericin has antivirus action against plant pathogens and might be used to combat drug resistance issues and control illnesses in non-food crops.

Manufacture of beauvericin compound from fungal souring progress

Nowadays, several chemicals that were extracted from fungi are employed as medications and pesticides. This beauvericin is a powerful commercial fungal item, hence

souring conditions for its manufacture have recently been examined. According to the results of the screening of carbon and nitrogen sources for the manufacture of beauvericin, glucose, peptone and sodium nitride were the best options for providing carbon and nitrogen, respectively (Lee et al., 2008; L.-J. Xu et al., 2010). When an ideal medium was utilized, the fungus provided adequate precursors for beauvericin production on its own, indicating that employing $C_5H_{11}NO_2$ (valine) and $C_9H_{11}NO_2$ (phenylalanine) as N (nitrogen) origins did not boost beauvericin production. Using *F. redolens* Dzf2, substrate (means glucose sample) inhibition in the souring of beauvericin was discovered. Beauvericin was successfully fermented using the fed-batch method, which decreased substrate inhibition and provided enough substrates for beauvericin synthesis (L.-J. Xu et al., 2011). Only a little amount of the intracellular substance beauvericin is sent out to the medium part. Fascinatingly, beauvericin may be effectively extracted from mycelium cells via microporous polystyrene. To significantly improve beauvericin recovery exists in the mycelial liquid civilization, an integrated souring with an *in-situ* item recovery procedure employing microporous polystyrene was adopted (L.-J. Xu et al., 2009). Beauvericin was easier to remove and separate from the fungus mycelia thanks to it. To fungus produce beauvericin efficiently, a changed Monod sample of the fed-batch approach was created. The operation strategy for fed-batch souring may be predicted using this sample with analyte (means glucose) inhibition and the stoichiometric equations for biomass item, analyte and items. Overall, the generation of beauvericin through mycelial souring of fungi like *Fusarium* spp. is a viable and encouraging method. Beauvericin production in the mycelial liquid culture was grew to 400 mg/l by optimizing the souring progress (L.-J. Xu et al., 2009), however, the levels of beauvericin produced were lower than those of other commercial and industrial antibiotics. To increase the production of beauvericin, research into the fermentation process and biosynthesis should be kept up. For instance, 2-phase souring process might be examined to boost the item of beauvericin. To boost item rate, it is feasible to extract intracellular beauvericin by utilizing an organic compound, non-polar aqueous solution in the souring progress.

Conclusion and future sights

The determination of beauvericin has been thoroughly investigated (at the picogram level) (Krska et al., 1996; Plattner & Nelson, 1994), but we believe that the bioactive improvement of beauvericin has been largely overlooked. In the long run, studies on medications and pesticides reveal that finding a "perfect chemical" with adverse influences would be difficult. As a result, we argue that repurposing existing molecules (beauvericin) may be considered the most effective strategy to find novel medications and

insecticides. Beauvericin has been certified to be a fungal item with not only a wide range of bioactivities scope, but also unidentified activation mechanisms.

Since beauvericin is a naturally occurring contaminant agent of many food products and feed matrices, it poses a main concern to both animal and individual's health. The precise mechanism of action is still not fully understood, though. After exposing beauvericin, cell viability is reduced, and mammalian cells exhibit apoptosis induction and cell cycle blockade. Combining the two events can also make it more poisonous. Endogenous and exogenous antioxidants could be effective defenses against beauvericin toxicity, but studies on this topic are conflicting. Oxidative stress might be a factor in beauvericin toxicity. Furthermore, a risk evaluation of beauvericin in food items and feed must consider its estrogenic, genotoxic and immunotoxin effects in vitro. Due to the scant scientific research on its toxicity in animals, a risk evaluation is still not attainable despite its numerous toxicological impacts. Therefore, future research should focus on expanding existing studies on the toxicology of beauvericin and toxicokinetic behavior in both animals and individuals. Beauvericin species could be a contender for an anticancer medication based on these most recent discoveries. For the clear and obvious function of its quite potential to be understood, more research on its mechanism is needed.

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