

## Antineoplastic Effects of Honey Bee Venom

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Article information	Abstract
<p>Article history: Received: 12 Jul 2011 Accepted: 12 Mar 2011 Available online: 30 Dec 2012 ZJRMS 2013; 15(8): 1-5</p> <p>Keywords: Bee venom Cancer Apoptosis Neoplasm</p> <p>*Corresponding author at: Department of Cell and Molecular Biology, Faculty of Biological Sciences, Kharazmi University, Tehran, Iran. E-mail: nabiuni@tmu.ac.ir</p>	<p><b>Background:</b> Bee venom (BV), like many other complementary medicines, has been used for thousands of years for the treatment of a range of diseases. More recently, BV is also being considered as an effective composition for the treatment of cancer. Cancer is a major worldwide problem. It is obvious that the identification of compounds that can activate apoptosis could be effective on the treatment of cancer. BV is a very complicated mixture of active peptides, enzymes, and biologically active amines. The two main components of BV are melittin and phospholipase A<sub>2</sub> (PLA<sub>2</sub>). Of these two components, melittin, the major active ingredient of BV, has been identified to induce apoptosis and to possess anti-tumor effects. We tried to review antineoplastic effects of BV in this study.</p> <p><b>Materials and Methods:</b> The related articles were derived from different data bases such as PubMed, Elsevier Science, and Google Scholar using keywords including bee venom, cancer, and apoptosis.</p> <p><b>Results:</b> According to the results of this study, BV can induce apoptosis and inhibit tumor cell growth and metastasis. Results of in vivo experiments show that the anti-tumor effect of the BV is highly dependent on the manner of injection as well as the distance between the area of injection and the tumor cells.</p> <p><b>Conclusion:</b> The results obtained from the reported studies revealed that BV has anti-cancer effects and can be used as an effective chemotherapeutic agent against tumors in the future.</p> <p>Copyright © 2013 Zahedan University of Medical Sciences. All rights reserved.</p>

## Introduction

Bee venom has been used in different ways since the ancient times. The simplest method is natural stings of bee through stimulating the bee to sting in the desired area. BV injection or using this method together with the use of acupuncture is another common method for using this substance [1]. BV has been used as a traditional medicine to treat various diseases such as rheumatoid arthritis, multiple sclerosis (MS), gout, infection, burns, wound and pain [2]. BV together with acupuncture had been used by people of Korea in the treatment of immune-related diseases, particularly rheumatoid arthritis and was associated with satisfactory results [3]. Several recently conducted studies have proven the potential impact of BV on cancer therapy [2]. Honeybee with the scientific name of *Apis Mellifera* has clear venom which is stored in poison bag and it is used by the bee for personal defense [3-5]. This substance has at least 18 active components.

BV contains various peptides including melittin, apamine, adolapine, enzymes including hyaluronidase and phospholipase A<sub>2</sub>, biologically active amines such as histamine and epinephrine and non-peptide components with the numerous medicinal properties [5].

Melittin and phospholipase A<sub>2</sub> are considered as the two main components of BV [6]. Melittin that makes up 50-60% of the dry venom is a small protein with a weight of 2850 Dalton which is composed of 26 amino acids and is the main component of the toxic poison. When some

Melittin molecules penetrate the cell membrane, it broke phospholipids and caused cell lysis. In fact, this polypeptide leads to the loss of integrity of the two phospholipidic and synthesized layers. Melittin is found as a tetramer in the poison bag of the bee, but when influencing cell, it acts as a monomer [6]. It is reported that this substance is able to induce apoptosis and has antitumor effects [6]. Different types of cancer cells such as renal, liver, lung, prostatic, bladder, breast carcinoma and leukemia cancer cells can be targeted by melittin as one of the active ingredients of BV [5].

Phospholipase A<sub>2</sub> which makes up 15-20% of BV causes the collapse of phospholipids structure of the cell membrane and consequently leads to the membrane collapse [7].

BV is effective in the treatment of MS due to its anti-inflammatory properties and causes myelination of demyelinated areas through stimulating oligodendrocyte cells [8]. Our research group showed that the BV is effective on the improvement of MS induced with Ethidium Bromide in Wistar rats. In fact, BV can simulate the cell migration progenitor oligodendrocyte cells and increase in the production of myline in affected areas [9]. Suh et al. showed that the use of BV in acupuncture in the rats with rheumatoid arthritis induced with the type II collagen is followed with the 80% reduction in the activity of cytoplasm, lysosomes, and matrix proteases and also significant reduction in the levels of reactive

oxygen species (ROS) [6]. Considering that today cancer is a global problem and the second cause of mortality of human in developed countries and on the other hand, many of today's common therapeutic compounds have problems such as toxicity and drug resistance, discovering and development of new drugs effective against cancer seems logical [10]. Given that the researchers sought to evaluate the effects of BV on the treatment of various cancers in the recent years, we tried to evaluate the results of this study in this paper.

### Anti-cancer effects of bee venom

Liu et al. studied the effects of BV on melanoma cell line originated from rat (K1735M2) in the in vitro condition and the growth of melanoma induced in the rat in the in vivo condition. Results of in vitro studies have indicated that anti-proliferative effects of BV in a concentration-and time-dependent model, in this cell line, may cause cell cycle arrest in G<sub>1</sub> phase that will eventually lead to the occurrence of apoptosis. They also reported that the BV induces a specified morphological differentiation including dendrite-like structures and the formation of granules in this line. They caused formation of melanoma in these rats through B16 cells transplanted into the C57BL/6 female rats which was resulted in significant reduction in the tumor growth through peritoneal BV injection into their body [11].

Jang et al. also reported that BV is able to induce apoptosis and inhibit expression of cyclooxygenase 2 (COX-2) in human lung cancer cell line NCI-H1299. They showed that certain concentrations of BV is able to do DNA fragmentation following the activation of endonucleases, induction of morphological changes associated with the apoptosis such as the formation of apoptotic bodies, increase in the expression of Bax and Caspase 3 and reduction in the expression of Bcl-2, selective inhibition of COX-2 expression and reduction in the production of prostaglandins (PGs) [6]. COXs are key enzymes in the synthesis of PGs. COX-1 is an enzyme that is present in the most cells and is required for normal physiological functions, while the COX-2 is inducible and its expression in tumors, including lung cancer increases [12-14]. In this study, scientists proved that unlike non-steroidal anti-inflammatory drugs (NSAIDs) which cause many side effects like stomach ulcers and bowel dysfunction through inhibition of COX-1 expression, BV selectively reduces the expression of COX-2 and subsequently reduces the production of PGs [6].

Caspases is a family of cysteine proteases which are involved in different apoptotic pathways [15], so that caspase 3 decomposes agents such as from Poly ADP Ribose Polymerase (PARP) and Lamyn A and consequently many of the morphological changes associated with the apoptosis occur [16]. Bcl-2 family members are capable of forming complexes with Bax as Hetero-dimer or with themselves as hemo-dimer. When Bax expression is increased, apoptotic response to the death signaling is accelerated, but cell death is suppressed in response to the increased expression of Bcl-2 and its

hetero-dimerization by Bax. Thus the ratio of Bax to Bcl-2 determines whether apoptosis is occurring or not [17].

The effect of BV on the cell line of human Leukemia U937 has also been examined. These studies have shown that BV induces apoptosis by increasing expression of caspase 3 and inhibition of Akt/ERK, Bcl-2 expression and elevated levels of FAS/FASL and reduction in the level of HTert and Cox-2 in this category.

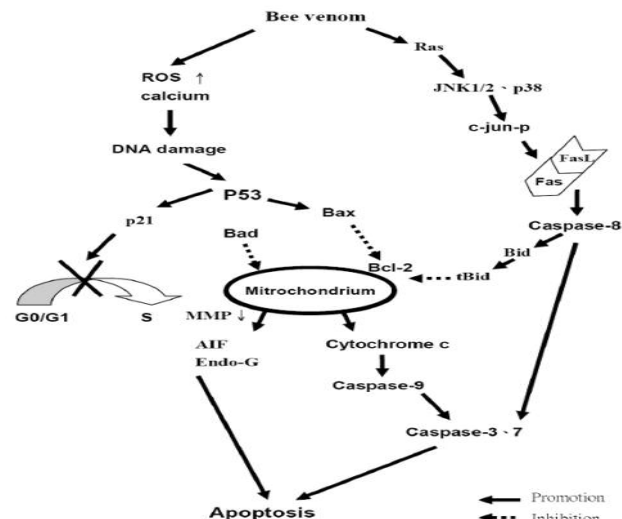
This study proved that BV is able to activate initial Caspases 8 and 9 as well as effector caspase and subsequently PARP decomposition. Also the expression of XIAP and cIAP-2 which belong to the family of proteins which are inhibitors of apoptosis as well as Bcl-2, as an anti-apoptotic molecule, are reduced affected by BV which this reduction may be involved in the activation of Caspase 3 and the occurrence of apoptosis [18]. Mitogen-activated protein kinase pathways (MAPK) play important roles in the cell survival and death, so that P38MAPK and JNK pathways lead to the cell death, but the ERK pathway leads to the cell survival [19]. AKT activation also induces cell proliferation and the increase in the resistance to apoptosis through regulating NF- $\kappa$ B signaling [20]. On the other hand, telomeres are structures at the ends of eukaryotic chromosomes that the shortening of their length causes the stop in the growth and induces apoptosis.

Many tumor cells prevent the telomeres from shortening and consequently prevent continuation of proliferation through telomerase. Telomere length is controlled by three main components of Htert, hTER and TEP-1 [21]. Lee et al. examined BV effects on human normal lymphoid cells and HL-60 human cancer cell line. They reported that the complete BV has selective cytotoxic characteristics on the normal and cancer cells. Applying this substance in a dose-dependent pattern reduces HL-60 cell survival up to 24 hours. They showed that phospholipase A<sub>2</sub> present in the BV causes loss of membrane integrity of HL-60 cells, while BV, induces morphological changes, somewhat similar to the apoptosis, in the normal human lymphoid cells. But in fact, it cannot be taught as a full apoptotic cell death. They reported the increase in the expression of phosphate and Tensin Homolog (PTEN) as a tumor suppressor protein in HL-60 cells, but not in normal lymphoid cells. They expressed that this increase in the expression of PTEN in HL-60 cells may induce cells to stop in S phase. Consequently, it can be considered as a reducing agent in the cell survival up to 24 hours in these cells. Genotoxicity that was decreased in the normal lymphocytic cells after treatment with BV which is due to the activation of the Forkhead transcription factors subfamily such as FKHR and FKHL1 in the normal lymphoid cells but not in the HL-60 cells has also been mentioned in this report. FKHL1 has the ability to repair DNA which confirms the team claims about the genotoxicity decreased in the normal cells [22]. Our research group began to examine the differentiation effects of BV for the first time, while noting that the differentiation therapy is one of the useful mechanisms of cancer treatment. We studied differentiation effects of bee

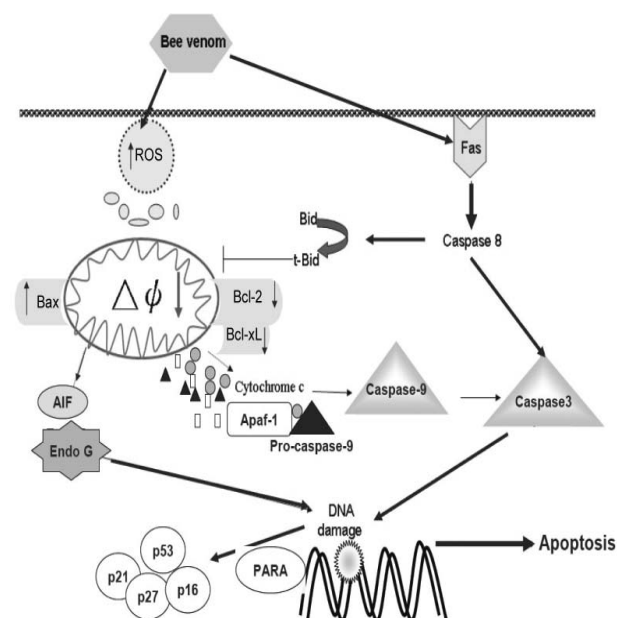
venom and 1, 25-dihydroxy vitamin D<sub>3</sub> and also bee venom and all-trans retinoic acid, as separately and combined, on HL-60 cells. The results of this study showed that BV doesn't have any differentiation effect on this line, but it is capable to increase the antiproliferation and differentiation effects of 1, 25-dihydroxyvitamin D<sub>3</sub> and all-trans retinoic acid [23-24].

In another study we studied the effect of bee venom and retinoic acid on the induction of neuronal differentiation in P<sub>19</sub> embryonic carcinoma cells of the rats. Our findings showed that concentrations higher than 5 ml/μg of BV is a lethal dose for the cells after 5 days of treatment and concentrations less than this amount induces neuronal differentiation in P<sub>19</sub> cells and their differentiating effects on the cell line was increased when the bee venom and retinoic acid were used simultaneously [25]. TU et al. examined the effects of BV on A2058 cell line which is a cell line related to the human melanoma. Melanoma is a tumor with melanocytic origin that often can be found in the skin, intestines and eyes. This research team acknowledged that the bee venom induces cell death of apoptosis type in this line in a calcium-dependent and caspase-independent pathway, but it doesn't have such an effect on normal fibroblasts Detroit 551. BV causes very rapid increase in the intracellular calcium which in turn leads to the ROS production and changes in the potential of mitochondrial membrane. This pathway is followed by the release of apoptosis inducing factor (AIF) and Endonuclease G (Endo-G) inside the nucleus that ultimately trigger apoptosis in a caspase-independent pathway. On the other hand, BV caused JNK activation and deactivation of the AKT. This group also reported that the melittine, as the main component of BV, has a stronger lethal effect compared to bee venom [26]. It has known that changes in calcium ion homeostasis in the mammalian cells trigger apoptosis or necrosis. BV-induced increase in intracellular calcium concentration leads to the activation of calcium- and magnesium-dependent endonucleases that break the DNA strands and produce ROS and subsequent oxidative stress [27]. There is much evidence suggesting that AIF and Endo-G, as mitochondrial proteins, are the main factors triggering apoptosis in a caspase-independent pathways. These two factors are displaced from mitochondria to the nucleus using materials inducing apoptosis which in a wide range leads to DNA fragmentation [28]. In another study conducted in 2008, the effect of BV on Ca Ski cell line of human cervix carcinoma was studied.

BV causes DNA fragmentation through decreasing the expression of Bcl-2, increasing the expression of Bax, P<sub>21</sub>, P<sub>53</sub> and Fas, mitochondrial dysfunction (loss of membrane potential) and consequently the release of cytochrome c from mitochondria, production of ROS and Ca and activation of 8 and 9 initial caspases and the subsequent acting caspase 3. Therefore, BV-induced apoptosis is mitochondria and caspase-dependant and on the other hand, BV induces apoptosis through caspase-independent pathway in this category through inducing the expression of AIF and Endo-G (Fig. 1) [29].



**Figure 1.** Proposed model for the mechanism of the effect of BV on apoptosis induction in the Ca Ski cell line [29]



**Figure 2.** Model proposed for the mechanism of the effect of 31MCF-7

Two groups of researchers independently studied the effect of BV on MCF-7 cell line (breast cancer). They proved that BV in a dose- and time-dependent model inhibits proliferation, occurrence of morphological changes, DNA damage through the receptor Fas, production of ROS, decrease in the mitochondrial membrane potential and the release of cytochrome C, increase in the expression of Bax and decrease in the expression of Bcl-2, and AIF and Endo-G release from mitochondria. In summary it can be said that BV induces apoptosis in a mitochondria- and caspase-dependant or independent path (Via AIF and Endo-G) (Fig. 2) in MCF-7 cell line [30, 31].

Studies conducted in 2009 indicated that BV can increase the cytotoxic effects of anti-tumor calmoduline inhibiting factors. Orsolio showed that the lethal effect of bleomycin in Hela and V79 cells is increased in the presence of B and acknowledged that BV inhibits cell

growth; cell proliferation and cloning in these two categories and possibly these effects are realized through inhibition of the calmodulin and apoptosis or necrosis induction.

BV also acts as an inhibitor of DNA repair and this hypothesis could be the probable mechanism for the toxicity of bleomycin. Researches conducted so far indicate that calmodulin inhibiting medications are able to inhibit DNA synthesis in glioblastoma, to inhibit the growth of Chinese hamster ovary cells and to block the movement of chromosomes during the metaphase and they can increase the toxicity of chemical drugs such as Vincristine and have systotoxic effects on malignant cells both in the in vitro and in-vivo conditions [32]. This researcher along with his colleagues studied the effects of BV on the in-vitro inhibition of the proliferation of breast carcinoma and in-vivo tumor growth inhibition. They proved that anti-tumor and anti-metastatic effects of BV greatly depends on the method of injection and the distance between tumor and the injection area for the induction of apoptosis and necrosis or inhibition of calmodulin. BV significantly reduced metastases only when it was used by the same method used in tumor inoculation (intra peritoneal), so, it can be concluded that the intratumoral injection of BV can greatly inhibit tumor growth and is used in cancer treatment.

Their findings show that BV has direct and indirect effects on tumor cells by stimulating the host cells especially macrophages and T lymphocytes. In other words one can say that BV is a strong activator of lymphoid cells derived from local lymph nodes near the area of BV injection. Also after the effect of BV on Mca cells in the in-vitro model it was observed that the cell growth inhibition in the presence of BV is dose-dependent up to 24 hours and this issue is justifiable with the instability of BV elements in the medium after this period of time [33]. The newest study about the effect of BV on the cancer cell line has been conducted by Park et al. on the prostate cancer [34]. Prostate cancer is the second cause of cancer death in men after lung cancer [35]. Among the various methods of treatment, chemotherapy is an important treatment for the advanced prostate cancer [36]. Therefore, evaluating and creating a new chemotherapy agent that effectively inhibit prostate cancer seems logical [37]. Researches has shown that family members of nuclear factor  $\beta$ k (NF- $\beta$ k: Nucleus

Factor- $\beta$ k) are activated in androgen-independent cancer cells. On the other hand, activation of caspases through deactivation of NF- $\beta$ k for the induction of apoptosis is very important in prostate cancer [38].

It has been also reported that some chemotherapy agents induce activation of NF- $\beta$ k in the prostate cancer cells which leads to the drug resistance [39]. Thus, agents capable of inhibiting the NF- $\beta$ k, may be useful in treating prostate cancer. This group showed that the BV and Melitinne inhibit LNCap, DU145 and PC-3 cancer cell growth through the induction of apoptosis. This inhibitory effect on the growth is realized through reducing expression of the various anti-proliferative and anti-apoptotic gene products including Bcl-2, Xiap, Ciap, COX-2 and cPLA<sub>2</sub> which are regulated by  $\beta$ NF-k.

These two substances also reduce the transcription of and binding DNA,  $\beta$ NF-k. In-vivo studies on this group showed that the BV significantly inhibits tumor growth in a dose-dependent pattern [34].

## Discussion

Based on these findings, it can be proved that the low concentration of BV is able to induce cell death (in most cases of apoptosis) in both in-vitro and in-vivo studies, considering this fact that today's conventional therapeutic compounds that are prescribed for various types of cancers have problems such as toxicity and drug resistance and on the other hand, apoptosis inducing compounds can be useful in cancer treatment. If further studies to be conducted at the in-vitro and in-vivo levels, and also clinical and definitive studies demonstrate the anticancer effects of this compound, BV can be an appropriate candidate for the treatment of various cancers and can be promising for the production of new drugs based on its effective composition and benchmarking of its chemical composition or structure in the near future for the treatment of different cancers specially those species resistant to the chemotherapy.

### Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

### Conflict of Interest

The authors declare no conflict of interest.

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