Bee Venom Therapy For Cancer: A literature Review

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Abstract:

Background: Bee venom therapy is a sort of apitherapy - using bee products like honey, pollen, propolis, royal jelly and bee venom to prevent or cure illness and enhance healing – which was used to treat many diseases like rheumatism, arthritis, back pain, cancerous cells and skin diseases. Bee venom consists of peptides (like melittin and apamin), enzymes (like phospholipase A2) and small molecules.
Objectives: The objectives of this review article are to determine the mechanisms of actions, the therapeutic effects and the side effects of bee venom when used as a cancer treatment.
Review of the literature: Cancer is a serious health problem in developed countries . Complications connected with the use of chemotherapy and radiation therapy in cancer treatment might lower the effectiveness of such medication. So, using naturalistic yields in cancer treatment has become an important current topic. The bee venom have been found to have anticancer activities in different cancer cell lines involving breast, liver and prostate. Melittin links to some tumor cells at a higher affinity than to healthy cells and this is an interesting feature. Accordingly, bee venom has a possible anti-metastatic antiinvasive, and anti-angiogenesis impact which might earn future clinical research on its anti-tumor characteristics.
Keywords: Apamin ,Bee venom, Cancer, Melittin, Natural products, Normal cells, Toxins.

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Abbreviations list

The abbreviation	Stands for
BV	Bee Venom
BMD	Bone Mineral Density
bv-sPLA2	bee venom secretory Phospholipase A2
CDK	Cyclin Dependent Kinase
DRs	Death Receptors.
EMF	Electromagnetic Field
EAACI	European Academy of Allergy and Clinical Immunology
FADD	Fas-Associated Death Domain Protein

MMP-9	Matrix Metallopeptidase 9
NF-κB	nuclear factor kappa B
ROS	Reactive Oxygen Species
SRs	Systemic Reactions
UV	Ultraviolet

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Introduction:

Bees are well known flying insects. They have important role in producing many natural Products like, honey, beeswax, bee venom and royal jelly [1]. Bee products have been utilized in traditional medicine [2] and in Islamic medical system [3].

New studies have reported that bee products have a prospective effect against cancer in vivo and in vitro [4]. Suggesting the prospective application of these naturalize compositions as sort of an alternative medical therapy of human tumors [4]. Whereas while using radio- and chemo-therapy to get rid of cancerous cells, also they hurt normal cells and cause un-wanted side effects that restrict the treatment and effectiveness [2]. Accordingly, using natural products in substitutional anticancer medications research has turn into a current topic [2]. Although, naturalistic yields are weaker but they are much safer. naturalistic products differ in the way they interact by it with the body. For instance, some naturalistic yields are poisonous to healthy cells, and some others stimulate the immune responses then depend on the naturalistic immune differentiation among normal and infected or converted cells and therefore they do not immediately react with the cells. Also, a few naturalistic yields differentially work on Mutant and healthy cells [2].

Bee venom has been widely utilized to cure rheumatism, arthritis, back pain, cancer, and skin diseases [5]. Bee venom has antiviral, antibacterial and anti-inflammatory effects [6]. It consists of several active ingredients including peptides (like melittin and apamin),enzymes (like phospholipase A2) and small molecules [7]. In the bee venom, there are at least 18 different active ingredients possessing distinct pharmaceutical features [8]. One of these ingredients, is melittin, a small linear peptide contains 26 amino acids and it is the major active ingredient[9], which form ~50% of bee venom[10]. The activation of the native cellular immune reactions in lymph nodes by bee venom will prevent the propagation of cancer and tumor growth in vivo [2,11,12,13]. The bee venom affects the tumor by several mechanism including apoptosis ,necrosis, and lysis of the cancer cells[11],[12],[13].

Multiple researches have proved that bee venom and/or it's component melittin have potential impacts against cancer in different types of cancer such as prostate [11], liver [12],and breast cancer [13].

The objectives of this review article are to determine the mechanisms of actions, the therapeutic effects and the side effects of bee venom when used as a cancer treatment.

The literature review:

1.Background:

Cancer is a serious health problem in developed countries where it is the second cause of death mainly correlated with ageing and lifestyle [14].

Interestingly, many observations have guided researches to a novel hypothesis (published in 2011) for cancer mechanism. The chief, that cancer occurs just on those multicellular creatures whose have complex wound-healing abilities. One more, wounds considered as risk factors in whole types of cancers in clinics (see table 1). Lastly, the activation of oncogene occurs in normal physiology and non-cancer pathology ways and not just in cancer. As stated in the novel hypothesis, cancer is related to the process of healing of natural wounds that occur in the body, which involves oncogene stimulations, cytokine secretions, stem cell recruitment differentiation, and tissue remodeling. Wounds stimulate oncogenes of some cells and the other release cytokines to induct stem cells to cure the wounds [15].

However, when wounds or when causes of the wounds continues, like under the constant ultraviolet and carcinogen exposures, the wounds healing activity will continue which will results in a tumor. If the wound occurs, there is absolutely no method can pause or invert the wound healing activity in the mid phase. Curing the wound or depleting the entire system are the possible results of the cancer mechanism. This novel hypothesis compatible with the justifications of the another physiological metabolisms of the body to survive. Moreover, it aids to comprehend several cancer problems resulting from the mutation theory, like why cancer occurs only in a small proportion of multicellular creatures ? although they are beneath possible mutation hazards through DNA replications. This hypothesis could be utilized to explain and direct cancer prohibition, retrieval, metastasis, *in vivo* and *in vitro* researches, and also personalized medications [15].

Chemotherapeutics antitumor impacts depend on the significant function of apoptosis in cancer. Activation of Death Receptors (DRs) expression is importantly involved in the creation of apoptosis in tumor cells, particularly chemoresistant one. DRs are stimulated by the interaction of DRs with their ligands [16]. While DRs bind to their ligands, death fields induct the intracellular adapter protein FADD (Fas-associated death domain protein) which conducts in the induction of caspases, involving caspases-3,-8 and -9, and a rise of Bax and reduce of BCl-2 to encourage apoptosis [17].

The nuclear factor kappa B (NF-κB) family has a significant function in many human tumor cell growths. Also, NF-κB gene productions have significance in proliferation. It have an important role against apoptosis which could participate to cancer development, progression, and resistance to treatment of cancer cells[18]. So, factors that are capable of holding NF-κB pathway perhaps potentially helpful in prevention and treatment of cancer growth and resistance [19].

Cancer metastasis is a complicated procedure including large interactions among the cancer cells and the normal tissues. It is the major cause of death in patients whose develop a cancer mass besides being the reason in the restriction of comparatively simple treatments (localized radio- and/or chemo-therapy or surgical tissue eradication) contrasted to systemic cancer therapy. Cancer metastasis can be splitted to four stages of (1) cancer cell dissociation, (2) intravasation and crudation, (3) arrest and extravasation and (4) adhesion, angiogenesis and proliferation[20].

Early diagnosis, global access to health care and progressions in personalized therapies has resulted in an important improvement of cancer survival, being evaluated that up to two thirds of cancer will be finally cured with striking variations among tumors [14].

2.Side effects of cancer therapy:

A variety of cancer treatments, involving hormonal therapy, chemotherapy, and glucocorticoids influence gonadal hormone production, which rises bone resorption and lowers bone mineral density (BMD). Such bone loss occurs more rapidly and to a greater grade than naturalistic age-related osteoporosis, rises the risk for fracture and other morbidities, and lowers survival [21] . Chemotherapy and radiation therapy are the most vastly used interventions for the treating of cancer. Although these therapies are employed to ameliorate the patient's quality of life, they are connected with many side effects. serious adverse reactions due to these treatments result in patient morbidity and mortality. In addition, they also participate to economic consequences of the affected patient [22]. Complications connected with the use of chemotherapy and radiation therapy may lower the effectiveness of

medication by the need to reduce the dose or increase of the interval between cycles [23].

3. Bee venom therapy:

Importantly, using naturalistic products in substitutional anticancer drugs research has become a current topic. One of the very effective naturalistic anticancer remedies is Bee Venom.

Bee venom is an extremely complex mixture of components (see table 2). It encourages membrane lysis and prevents tumor cell proliferation, and enhances cancer cell apoptosis by a rise in reactive oxygen species (ROS) and an increase in intracellular Ca2+. Bee venom therapy induces both caspase-dependent and caspase-independent apoptotic cell death through the stimulation of intracellular Ca (2+)-modulated intrinsic death pathway in human bladder tumor cells [16].

Furthermore , naturalistic toxin bee venom could be helpful as an anti-tumor factor through the overexpression of DR3 and inactivation of NF-κB for the treating of lung tumor cells and drug resistant tumor cells[19].

Havas in 1950 released the first study on bee venom and, after 3 decades, another researchers began to hold on attractive studies about the cytotoxicity of produces apoptosis in human leukemic cells, and not in murine bone marrow cells, by the inducement of Bcl-2 and caspase-3 expression out of the downregulation of mitogen-stimulated signal pathways[26]. Also, bee venom has been stated to induce apoptosis out of caspase-3 stimulation in synovial fibroblasts[27].

In addition, bee venom secretory phospholipase A2 (PLA2) (bv-sPLA2) and phosphatidylinositol-(3,4)-bisphosphate synergistically prevent cell proliferation by a mechanism including the maturation of immunostimulatory human monocyte-derived dendritic cells [28].

Melittin, a pore-forming peptide from Apis mellifera (Western honey bee) venom. Melittin constitute some 40%-60% of bee venom In addition to being the major protein component in the venom, it is also the responsible toxin bring about inflammation ,pain ,and sensitivity[29]. Melittin known as a cationic, water soluble, amphiphilic α-helical peptide of 26 amino acid residues that is recognized to do a set of membrane- perturbing impacts, like antimicrobial and hemolytic action [30]. Moreover, melittin is effective against many cancer types involving leukemia ,liver ,lung ,renal ,prostate ,bladder and mammary cancer. It has many important functions such as: calmodulin inhibitor [2],potent pore-forming factor, hyperactivates PLA2 in ras oncogene-transformed cells[25], produces cell membrane lysis and apoptosis[16], acts in different cell signaling pathways[26].In addition, recent studies have proved that melittin has properties against angiogenesis [24]. Bee venom has been displayed to immediately prevent the invasive and emigrating capacity of human breast cancer MCF-7 cells by the extinction of matrix metallopeptidase 9 (MMP-9) expression, and this probably stimulated by melittin, but not by apamin or PLA2. So, the specific suppression of MMP-9 by bee venom could be mediated through melittin only or probably in combination with other less familiar components [31]. These outcomes point that bee venom is a possible anti-metastatic and antiinvasive factor that might earn aftertime clinical study on its characteristics against tumors formation [2].

On the other hand , studies have point out that administration of melittin in high doses might cause hemolysis and hepatic injury [32]. It is interesting that melittin links to some tumor cells at a higher affinity than to healthy cells, and thus permitting a soft dose selectivity for working opposed to the converted cells than healthy cells[2].

Furthermore, apamin, a neurotoxin (i.e. toxins which attack the transmission of nerve impulses) from bee venom prevented vascular smooth muscle cell proliferation and migration through the regulation of Cyclin Dependent Kinase (CDK) [33].

3.1 Application strategies of bee venom in cancer:

In an in vivo study, Orsolic et al. (2003) reported that, while intravenously injected, bee venom importantly frustrated mammary carcinoma metastasis ($P < 0.001$) in murine injected also intravenously with this sort of cancer, when contrasted to control murine. Whist, no variations in metastasis formulation were noticed when the venom was subcutaneously administered. Also, the tumor reduced in size while the venom was administered intratumorally, and murine survived longer than control, suggesting that the in vivo venom action counts on how the venom is injected [34].Hu et al. (2006) stated that bee venom shows a cytostatic impact in a dose- and time-dependent manner, prevents proliferation and produces apoptosis of SMMC-7721 human hepatoma cells. The study confirmed that treatment with bee venom reduced expression of Ki67, a protein that is expressed in proliferating cells, and the proliferation rate of treated cells went from 97.0% to 10.2%[35]. Orsolic (2009) explored the possible growth-inhibiting impacts of bee venom exercised singly or in conjunction with a cytotoxic drug, bleomycin, on HeLa and V79 cells in vitro. The adjuvant medication caused a dose-dependent decline in cell survival due to DNA damage, indicating that bee venom may find a therapeutic benefit in enhancing cytotoxicity of the anticancer factor bleomycin[36].

Three strategies have been designed to reduce the adverse effects of melittin in not targeted tissues (1) coupling of melittin to an antibody or a targeting component; (2) development of shielded pro-cytolytic melittin systems; and (3) synthesis of melittin-transporting carriers[37]. Although melittin is the most studied and common bee venom peptide, its development for clinical applications stays at most in preclinical phases [24].

3.2 Side effects of Bee Venom therapy:

Although the therapeutic advantages of bee venom has been established, its safety profile is an significant limiting consideration, because immune responses to bee venom therapy can extend from inconsiderable skin reactions that resolve over several days to life-threatening reactions such as anaphylaxis [38].

Venom concentration and frequency of venom administration can influence the severity and rate of incidence of adverse effects resulting from bee venom Acupuncture [32,38].

In 33 single-case studies and 13 case series of patients suffering from different diseases and treated by bee venom, they found that systemic reactions involved 51.72% on the adverse effects generated by bee venom. In addition, the specified severe adverse effects included14 cases of stage III systemic reaction and 1 case of stage IV systemic reaction (see table 3) .Also, they found that there have been significant adverse events associated with bee venom therapy that urgently needed subcutaneous adrenaline or steroid and an oxygen treatment , with death occurring in only 1 case [38].

Conclusion:

The bee venom have been discovered to have anticancer activities in different cancer cell lines involving breast, liver and prostate. Many bee venom components have a therapeutic effect on cancer cells for instance melittin, apamin and phospholipase A2. The mechanism of actions of bee venom activities that have been reported are lysis of the tumor cell membrane, inhibiting tumor cell proliferation and induces cancer cell apoptosis. Bee venom presents a cytostatic impact in a time- and dose-dependent pattern. Although, bee venom has a lot of therapeutic benefits, however, as any treatment it has side effects so it should be used with a great caution.

We hope and if we can recommend that researchers develop safe products of bee venom components that have proven effective against cancer.

Table 1Table 1. Some types of cancers and wounds that considered as cancer risk factors in humans by Meng X, Zhong J, Liu S, Murray M, Gonzalez-Angulo A in (2011) [19].

Cancer	% of whole sites	Wound related
Prostate cancer (M)	25%	Inflammation, chronic prostatitis, virus infections.
$$	27%	Virus infections, chronic inflammation, electromagnetic field (EMF), breast trauma.
Lung and bronchus	14.5%	Chronic inflammation and lesions by smoking, virus infection, trauma predispose to metastasis, particle.
Colon and rectum	10%	Inflammation, Crohn's disease and chronic ulcerative colitis.
Urinary bladder (M)	7%	Parasite infection, cystitis.
Skin cancer	4.5%	UV from the sun.
Leukemia (M)	3%	Virus infections, radiation, EMF.
Oral cavity and pharynx (M)	3%	Gingivitis, lichen planus.
Liver cancer	1.5%	Inflammation, sarcoidosis, parasite infection, alcohol intake.
Gastric cancer	1.4%	Gastric ulcers, helicobacter pylori infection.

The percentages were from the evaluated new cases in 2009 from reference [40]. M male, F female, and no indication represent both.

Table 2Table 2. main ingredients found in bee venom reported by Moreno M, Giralt (2015) [24] .

Bee venom	Type and MW (Da)	% Compound *	Toxic
Phospholipase A2	Enzyme (~18 kDa)	10–12	Yes
Phospholipase B	Enzyme (~26 kDa)	1	Yes
Hyaluronidase	Enzyme (~54 kDa)	1.5–2	Yes
Phosphatase	Enzyme (~60 kDa)	1	No
α-Glucosidase	Enzyme (~170	0.6	No
Melittin	kDa)	40–50	Yes
Apamin	Peptide (2847 Da)	2–3	Yes
	Peptide (2027 Da)		

** The percentages of ingredients correspond to the venom only and do not take into account the water content. This toxicity refers to the potential toxicity that each ingredient could have. It is based on the cytotoxic and immunologic impact .*

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Table 3Table 3. EAACI grading of systemic reactions (SRs) reported by Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling H-J, Valovirta E in 2006 [39] .

0 No symptoms	No symptoms or nonspecific symptoms.
I Mild systemic reactions	Symptoms: Localized urticaria, rhinitis or mild asthma (PF <20% decrease from baseline).
II Moderate systemic reactions	Symptoms: Slow onset (>15 min) of generalized urticaria and/or moderate asthma (PF < 40% decrease from baseline).
III Severe (non–life-threatening) Systemic reactions:	Symptoms: Rapid onset (<15 min) of generalized urticaria, angioedema, or severe asthma (PF >40% decrease from baseline).
IV Anaphylactic shock	Symptoms: Immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, hypotension, etc.

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(Placeholder1)

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