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Economic Prospects in the Production of Bee Venom and Bee Venom Products from the Aspect of Application in Medical andCosmetological Therapies

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Abstract

Advances in the scientific field of molecular structure characterization, genomics and proteomics have intensified research into the variety of biologically active molecules from animal venoms. Their antimicrobial, anticancer properties, as well as neuroprotective characteristics are finding a wider range of applications in modern medicine. Bee and wasp venoms are known to be rich in neuroactive molecules that can be useful in the development of new drugs or act as pharmacological tools to study the normal and pathological functioning of the nervous system [38]. Many published studies indicate antimutagenic, radioprotective, anti-inflammatory and anti-cancer actions documenting the use of bee venom for the treatment of inflammation and diseases of the central nervous system, such as Parkinson's disease, Alzheimer's disease and multiple sclerosis, then arthritis and pain [40]. In recent history, there have been documented researches aimed at examining the antimicrobial and antiviral properties of some of the compounds in bee venom. Number of studies have described the biologically active components of bee venom, followed by preclinical trials to determine the potential use of bee venom and its constituents as potential next-generation drugs. A detailed characterization of the purified components of these compounds and a comprehensive analysis of the potential pharmacological effects creates a need for new research and their application in the development of new therapies, but on the other hand, the direction and dynamics are defined by the economic aspects of the production and use of bee venom.

The absence of generally established standards for classification, quality and application, as well as the low level of research that would increase applicability, limit the production and sale of bee venom. The potential is great, but the need has to be generated, created and developed in several directions, from new studies and areas of application, to modernization of production, innovation, standardization and opening of new markets and sales channels.

Keywords: Bee Venom, Pharmacology, Cosmetic and Medical Products, Economic Analysis

Introduction

Bee venom produced in the glands that are housed in the abdominal cavity of the honey bees (Lat. Apis mellifera) [8, 10] is a bitter, opalescent yellowish in color fluid produced by the toxic glands of the worker bee and is stored in the sacs connected to the sting apparatus. The water content of fresh bee venom varies and can reach 70% [6]. It is soluble in water and diluted acids, insoluble in alcohol, pH ranges from 4.5-5.5 (Nejash, 2016). Specific weight is about 1.13 g/cm3. The worker's bee produces about 0.150- 0,300 mg bee venom during its life and dies when it leaves the sting in the victim's tissue during the sting.

Bee venom or apitoxin is a complex mixture of at least 18 pharmacologically active components (see Table 1). Bee venom contains smaller amounts of low molecular compounds of different nature: amino acids, catecholamines (biogenic amines), sugars (as a result of contamination from pollen and nectar) and minerals. Pure bee venom does not contain carbohydrates.

Over 1700 scientific publications have been published on the composition and various effects of bee venom on animals and humans. Apitherapy as a term is usually associated with therapy compromised of direct sting contact with bee venom, which creates a complex cascade of reactions in the human body as a result of its active ingredients consisting of a complex mixture of proteins and peptides. However, recent clinical studies published findings of the bee venom positive effects on treatment against rheumatoid arthritis, on the therapeutic effects of bee venom in skin diseases and even some anticancer effects of the melittin peptide in breats cancer treatment.

The methods of the application of bee venom include natural bee stings, subcutaneous injections, electrophoresis, ointments, inhalations and tablets. Bee venom can be sold as a complete bee extract, pure liquid venom, or solution for injections. Most of the venom is sold in a dry crystal form. Although there is no available international standard, certain criteria should be satisfied when bee venom is used within the technological production processes in the pharmaceutical industry (Muller, 1988) [27] and (Shkenderov & Ivanov, 1986) [37, 12].

Concerning bee venom, there is no national legislation for its production, or marketing. The organized market is almost non-existent, and consumers are mainly pharma industries both in medical and cosmetical areas. Global bee venom market and price are steadily growing by single digit numbers dominated by few big international players. Depending whether is for cosmetic or for medical purposes, furure market supply and demand will heavily depend on the profound and extensive research activities, innovation and modernization of production of the bee venom. Aim and objective of this research is to indicate the need for more profound research in the areas where bee venom has shown results in medical treatments, to address the problems in stagnating and controlled supply and demand market, and to wider the scope to some alternative development paths for innovations, both in production technology of bee keepers and on the products for final use in cosmetology and medical treatments.

Class of Molecule	*Apitoxin Component*	*Percent in dry Venom*
	Melittin	***40 - 50***
	Apamin	***1 - 3***
	Mast cell degranulating peptide	***2 - 3***
	Adolapin	***0,5 - 1***
Small proteins and peptides	***Tertiapin*** ***Cardiopep***	***0.1*** ***0.7***
	Procamine A, B	***1 - 2***
	Secapine	***0,5 - 2***
	Minimine	***2 - 3***
	Pamine	***- 3***
	Phospholipase A2	***10 - 12***
	Phospholipase B	***1***
Enzymes	***Phosphomonoesterase***	***1***
	Hyaluronidase	***1 - 2***
	Alfa glocsidase	***0.6***
	Histamine	***0,5 - 2***
Amines	***Dopamine***	***0,2 - 1***
	Noradrenalin	***0,1 - 0,7***
Sugars	***Glucose, fructose***	***2 - 4***
Minerals	***Phospate, calcium, magnesium***	***3 - 4***

Source: Bogdanov, Stefan. (2016). Bee Venom: Production, Composition, Quality [6].

Table 1: Composition of dry matter of bee venom

Artrithis	*Mulitple sclerosis*	*Premenstral syndrome*
Epilepsya	***Bursitis***	***Ligament injuries***
Chronic pain	*Some types of cancer*	*Sore throat*
Blood thinihg agent	***Migrane***	***General immunostimulator***
Neuroses	*Dilates capilares and arteries*	*Decreases blood cholesterol level*
Spondilitis	***Rhinosinusitis***	***Intercostal myalgia***
Polyarthritis	*Polyneuritis*	*Slowy healing wounds*
Myositis	***Neuralgia***	***Keratoconjuctivitis***
Thrombophiletritis	*Malaria*	*Asthma*
Iritis	***Tropical ulcer***	

Source: Studies on Bee Venom and Its Medical Uses, Mahmoud Abdu Al-Samie Mohamed Ali, Department of Plant Protection, Faculty of Agriculture, Ain Shams University, Cairo, Egypt. [1]

Table 2: List of diseases, health problems improved or cured, and effects on the body according to anecdotal reports

Materials and Methods

An extensive review of more than 1.200 of literature and scientific research publications published in last 40 years related to the subject of bee venom was made, with goal to provide adequate data and additional relevant information about the general effects, pharmacological, therapeutic effects and their potentials. Comparative analisys on regulations and regulative environment in some major markets in EU, USA, and Japan were done in the effort to find loopholes and make some policy recomendations. Complementing it with officially published data on produced quantities, regional distribution and pricing collected from number of bee venom traders, economic analysis and predictions have been made for short-term development and restructuring of production and application processes. Study selection period was 2018- 2022 and we have collected statistical data on the world number of bee hives in last 15 years published by Statista. We have also matched the results with the variables on the produced quantities are used to identify the market potential of suppliers of bee venom. Analysis based on information about standardization in the cosmetic and pharmaceutical industry is then used to project the business policies and investments related to the organized production of bee venom, the possibility of using the potential in beekeeping to increase local growth and development, as well as locating potentials for the production of final cosmetic and medical products as significant added value in organized production and purchase. Finally, using methods of correlation and causation we have made attempt to define potential for parallel growth of both supply and demand, both driven also by technological innovations and product development.

Results

Melittin is the main component and is the best characterized peptide in the composition of bee venom, constituting 40-50% of the dry venom. This linear peptide has 26 amino acid residues, alkaline features, a predominantly hydrophobic N-terminal region and a hydrophilic C-terminal, resulting in amphiphilic properties. It is thought to be the main ingredient responsible for the intense local pain, inflammation, itching and irritation caused by bee stings and bee venom injections. On the other hand, in very small doses, melittin can cause a wide range of central and systemic effects, including anti-inflammatory effects, increased capillary permeability, and lower blood pressure. Additionally, in vitro assays of melittin reveal potential as a neurodegenerative disease prevention agent, given its ability to inhibit apoptotic factor and cell death in neuroblastoma cells. Melittin also shows a potent effect of suppressing pro-inflammatory responses by reducing pro-inflammatory mediators and the production of nitric oxide, prostaglandins and cytokines. Thus, it is suggested that this compound may have significant therapeutic potential for the treatment of neurodegenerative diseases such as Parkinson's disease.

Second most abundant peptide the neurotoxin apamin, is the smallest peptide, constituting less than 2% of bee venom, with 18 amino acids in its composition and a high content of the amino acid cysteine. It is well known for its pharmacological properties of irreversibly blocking calcium-activated potassium channels (known as SK channels) and is considered the most widely used blocker for this type of channel. Apamin has the unusual ability to cross the blood-brain barrier and act mainly on the CNS, where the mentioned channels are most pronounced. Apamin has also been evaluated for the treatment of Parkinson's disease using the motor score of the Unified Parkinson's Disease Rating Scale [2]. In this study, apamin showed primarily neurorestorative activity in Parkinson's disease, as well as symptomatic and neuroprotective activity. Apamin, however, reproduces these protective effects only partially, indicating that other components of bee venom enhance the protective effect of the peptide. Several electrophysiological studies have implicated apamin in the treatment of Alzheimer's disease, suggesting that blockade of SC channels by this compound may enhance neuronal excitability, synaptic plasticity, and long-term potentiation in the hippocampal region. Also, apamin is a valuable tool in the investigation of physiological mechanisms involved in higher brain functions, such as cognitive processes or mood control, and there is already a patented method for the early diagnosis of Alzheimer's using apamin [33]. However, it is important to emphasize that blocking SK channels can accelerate neurodegenerative processes, for which further additional research in this area is extremely important.

The pharmacological and biochemical properties of various stinging insect venoms are remarkably convergent. The biological diversity of these compounds is vital because drugs currently used to treat neurological disorders (ie, epilepsy, Parkinson's disease, and Alzheimer's disease) provide only symptomatic relief, with a note that the incidence of serious adverse effects is relatively high.

The peptides melittin and apamin, which is also a mild neurotoxin, have a strong effect and induce the production of cortisol in the body [16,17,41], suppressing edema, probably through an immunosuppressive mode of action. The phospholipase and hyaluronidase components in bee venom have the ability to block or inhibit the nervous system and stimulate the heart function and adrenal glands (R. Krell, 1996) [35]. Adolapin, which represents 2-5% of the peptide composition, has anti-inflammatory and analgesic effects because it blocks cyclooxygenase [21]. Phospholipase A2 with a share of 10-12% of the total enzymes is the most destructive component of apitoxin. It is an enzyme that degrades the phospholipids that make up cell membranes. It also causes decreased blood pressure and inhibits blood coagulation. Phospholipase A2 activates arachidonic acid, which is metabolized in the cyclooxygenase cycle and forms prostaglandins. Prostaglandins regulate the body's inflammatory response. Hyaluronidase in the composition of 1-3% of the total peptides peptides dilates the capillaries causing the spread of inflammation. Histamine (0.5-2%) is involved in the allergic response. Dopamine and norepinephrine in the composition of 1-2% increase the heart rate. Protease inhibitors in the composition of 2% act as anti- inflammatory agents and stop bleeding.

Other compounds contained in bee venom include formic acid, hydrochloric acid, ortho-phosphoric acid, mineral matter and volatile organic acids. Also, present are some antibiotics, phospholipase A, and two sulfur-rich amino acids methionine and cysteine. Sulfur is believed to be the main element in stimulating the release of cortisol from the adrenal glands. Due to its anticoagulant and anti-inflammatory properties, bee venom is mainly used to treat many inflammatory disorders such as arthritis, bursitis, tendinitis, scar treatment (eg keloids), herpes zoster, joint disease and rheumatoid arthritis, Lyme disease, multiple sclerosis and osteoarthritis. Diseases and problems that have been reported by patients or physicians as improved or cured by bee venom therapy are listed in Table 2. However, this does not constitute an endorsement of this type of therapy or a recommendation for treatment.

Melittin causes cell death by disrupting the structure of the biological membrane through the formation of pores and has a hemolytic effect, which indicates the high non-specific cytotoxicity of this peptide. Despite this well-characterized general cytotoxicity of melittin, some studies suggest that this substance specifically targets only cancer cells [5]. A more recent study indicates in vitro efficacy of melittin and bee venom in breast cancer [9]. Another study described the selective toxicity of whole bee venom against cancer cells [26]. Application of bee venom has been shown to have cytotoxic effects against various leukemia cells, but not against normal bone marrow cells. In contrast to these findings, a study [25] indicates a general toxicity of bee venom during treatment of normal human lymphocytes. One explanation for this discrepancy may be that melittin, due to its positive charge, shows affinity to bind to the surface of specific cancer cells that display an altered membrane lipid profile with an increased negative surface charge compared to non-transformed cells, making it more powerful against cancer cells, although healthy tissue is also affected. Despite the possibility of enhanced binding to cancer cells, the general and rather non-specific cytotoxicity of melittin has been documented in most studies, limiting the potential for further therapeutic approaches. However, chemical modifications of melittin and biotechnological approaches could represent one of the ways to overcome certain limitations of melittin, taking advantage of the potential anticancer effects of this peptide. Another approach to circumventing the general cytotoxicity of melittin involves encapsulating it in nanoparticles [43]. The idea behind these nanoparticles is to include a therapeutic substance in an inert carrier, which transports the substance to a specific location (for example, a specific tissue or cell type), where it is released and can change its function. Further research is needed to test these applications of melittin to confirm specificity, safety and anticancer effects.

Several studies demonstrate the anti-inflammatory effect of melittin and bee venom in general, highlighting the potential of these natural compounds to alleviate the symptoms of rheumatoid arthritis. Hong et al. investigated the effect of bee venom as a treatment for patients with rheumatoid arthritis [13, 14]. The analysis showed that apitoxin caused apoptosis of synovial cells after 24 hours from the start of treatment as a result of the proliferation of rheumatoid synovial cells by activating certain signaling pathways.

To date, the skin diseases where the therapeutic application of bee venom has been investigated are: acne, alopecia, atopic dermatitis, melanoma, morphea, aging of the skin under the influence of sunlight, psoriasis, wounds, wrinkles and vitiligo. [19]. Recent *in vitro and in vivo* studies [22] show that the cytotoxic melittin can be used to treat inflammatory diseases by reducing the excessive immune response. The therapeutic efficacy of melittin as an alternative treatment for inflammatory skin diseases caused by *Propionibacterium acnes* (P. acnes) has been investigated. In one study, melittin significantly reduced the swelling and inflammatory response induced

by intradermal injection of *P. acnes*. These results indicate that the application of melittin has potential for the treatment of inflammatory skin disease caused by *Propionibacterium acnes*. [24].

Bee venom promotes the recovery of human skin fibroblasts from damage caused by UV radiation, at a concentration of one microgram per milliliter without a negative effect on cell viability and morphology. However, at concentrations higher than 10 micrograms per milliliter, bee venom treatment reduces cell viability by 90%. The results of another study [39] show that bee venom promotes wound healing by inhibiting cytokines associated with fibrosis, which in turn leads to a reduction in wound size and acceleration of epithelial formation. The study [15] in turn evaluates the beneficial effects of serum containing bee venom on facial wrinkles. The results of in-vitro research show that bee venom has a positive effect on the melanocyte proliferation, melanogenesis, dendriticity and migration. These results suggest that bee venom has potential for the treatment of vitiligo with skin repigmentation.

Discussion

The only legally accepted medical use of bee venom in Western European and North American countries is to desensitize people who are hypersensitive (allergic) to bee venom. This purified allergic bee venom extract for injection under the skin is approved by the FDA (US Food and Drug Agency), and a similar record of the same product in BNF (British National Formularies) is registered at the National Institute of Health Protection UK, NICE (The National Institute for Health and Care Excellence - United Kingdom). Allergen extracts are currently produced in two forms: standardized and non-standardized. For standardized allergen extracts, manufacturers compare the allergen extract with the US reference standard for potency. CBER - Center for Biologics Evaluation and Research (Center for Biological Drug Research and Assessment) maintains these reference standards and distributes them to manufacturers. There are currently 19 standardized allergen extracts in the United States. The European Drug Agency (EMA) prescribes a guide entitled "Allergen products: production and quality issues". This document provides quality recommendations for allergenic products of biological origin.

Although there is no international available standard, certain criteria should be satisfied when bee venom is used within the technological production processes in the pharmaceutical industry (Muller, 1988) [27] and (Shkenderov & Ivanov, 1986) [37, 12], water content to be less than 2%, water insoluble substances up to 0.8%, sugars up to 6.5% and satisfying biological activity of hyaluronidase, phospholipase, melitin and protease inhibitors. The LD50 for bee venom is 3.7 milligrams per kilogram of body weight (a dose of venom that when injected intravenously causes death in 50% of experimental animals) [44].

The methods of application of bee venom include natural bee stings, subcutaneous injections, electrophoresis, ointments, inhalations and tablets. Bee venom can be sold as a complete bee extract, pure liquid venom or solution for injections. Most of the venom is sold in a dry crystal form. Depending on the disease being treated, the bee venom can be used in the form of cream, lining, ointment or injection. Phospholipase A2 and highly active peptides are among some of the proteins purified by bee venom for scientific suppliers or laboratories. The last subgroup of products of interest is the extracts of bee venom for the purpose of preparing a solution for injection, which can be further used for medical purposes in the treatment of Lyme disease, arthritis, rheumatic diseases, chronic inflammatory diseases, for inflammatory diseases and autoimmune diseases and for desensitization.

Lack of regulative, legislation and undefined standardization of the bee venom and its products are limiting both the production and demand side. Market uncertainty is further coupled with wide range of prices that are not directly dependent on market forces but on quality and most important, on purpose of use. When bee venom is used for cosmetic purposes and is exclusively for external use (Class II), price is about US$100/g. But when bee venom is used for medical purposes (Class I), which implies a high degree of purity and guaranteed defined quality using pharmaceutical-technological processes and production conditions, price amounts to US$3,900 /g. The final product, an injectable bee venom extract, costs $100 for 10mg, or US$10,000/g. of bee venom formulated in this way.

Therefore, while analyzing the potential and doing sensitivity analysis we cannot simply apply market rules, but observe the numbers considering the specifics of bee venom collection and areas of use. Prime focus will be the so called "created" demand, i.e. demand which is directly influenced by group of major players and the number of confirmed medical studies and innovative cosmetic products. Analyzing the data that in 2018 [3], when supply grew by 1.5%, it can be concluded that the market is almost saturated in terms of expansion possibilities. However, this small growth is due to the presence of a limited number of buyers in the global market of bee venom extracts, among which the largest stand out: Bee Whisper, ApiHealth NZ Ltd, Fernz, and Abeeco Pure, whose market share is almost 30% .

Observing the numbers, the bee venom market is valued at US$693 million and is experiencing constant growth of around 10% yoy in period 2014 - 2019. (see Figure 1). If we calculate an average price of US$100 per gram, then it follows that the annual world production of bee venom amounts to only 7 tons. Using the old traditional method of collection, this amount of production would be obtained from about 2 million bee colonies which represents only 2% of the number of colonies worldwide, estimated at around 94 million bee hives [36].

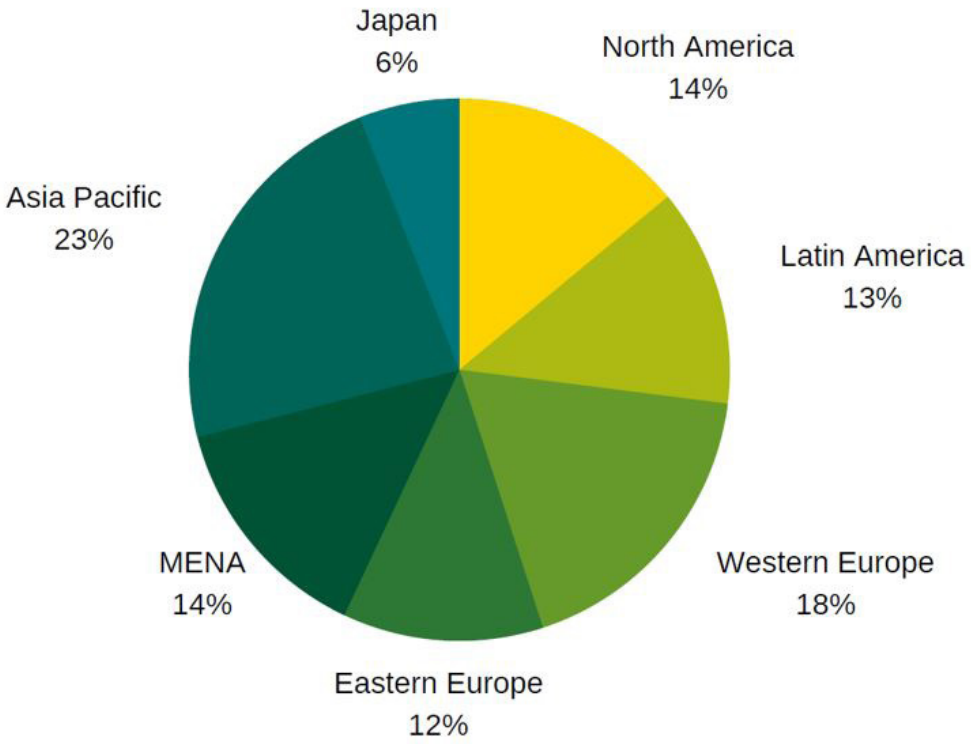
(https://www.statista.com/statistics/818286/number-of-beehives-worldwide/#:~:text=This%20statistic%20shows%20the%20total,beehives%20in%20the%20previous%20year)

Another study published by Future market insigns in 2022, states that the global market for bee venom extract is estimated at US$ 327.5 million. The market is likely to reach nearly US$ 540 Million by 2032, with a growing CAGR of 5.1% from 2022 to 2032.

https://www.futuremarketinsights.com/reports/bee-venom-extract-market. Converted into produced qualities, market for bee venom extract where the average price per gram is US$ 3.900, will reach to around 140 kg per year in 2032. Obviosly, there is huge grow potential.

Source: Apitoxin market Trends 2018, Market Solutions [3].

Figure 1: Bee venom market value in millions of USD



Source: Apitoxin market Trends 2020, Market Solutions.

Figure 2: Graphic representation of bee venom market share worldwide by region for 2020

On the supply side, technology for collection, storing and transportation of bee wenom, are on constantly low and underdeveloped level, something that needs to be changed in parallel by education and investments. The study (Pocol, C. 2011) [32] conducted on 290 subjects examines the methods and ways of commercialization and notes that most of the bee venom is sold by direct placement on the market (30%) and 27% through intermediary production contracts, of which 14% are without a pre-production contract. A small percentage of sales is realized through bee associations, 5%, and less than that, only 4% are intermediary contracts with a pre-production contract. Only 2% of sales are through friends and acquaintances, and classic export sales are only 1%. Therefore, one of the primary focus of producers is to work on development of distribution channels and faster "production to market" access. Another segment of improving and increasing supply is modernizing production. Traditional methods require low investments in the equipment that is ussualy individualy hand made collectors placed outside the bee hive. With this methods, purity of bee venom is low and death rate of bees is on a high range. New modernized innovative system of bee venom collection, where collector is placed inside the beehive and not outside and is covering 1584 sm2 of contact area increases yield from 0.272 g. per bee colony per month with a standard collection method, to 4.25 g. of bee venom per bee colony in a period of one month (15 times higher yield), (Vera S, Sergio D. and Gastao M. 2019) [20, 34, 36]. Although in terms of investments, new collection system is twice more expensive than the traditional one, significantly higher yield and better quality of bee venom shortens the return of investment significantly.

Accordingly, both suppliers and buyers including the scientific community, all need to increase the investments in R&D, modernization of the production, innovations, distribution channels, logistics and education in the primary production that will bring the total bee venom market on a whole new level, with long term sustainable perspective.

Conclusion

- Potential use of bee venom in the medical and cosmetical industry in starting to be widely acknowledged

- There are various bee venom products, products intended for cosmetic use, products for external use intended for the treatment of certain conditions, medical products for injection application mostly for desensitization in case of allergy from bee stings and for bee venom therapy for certain conditions. This wide spectrum of potential use of bee venom needs multiple actions of the key players, producers, buyers, researchers, sellers.

- Sensitivity analysis needs to be performed that will show how much the market is "controlled" or free, and to ensure market development in which all participants in the chain and commercialization of products will function according to clear market rules and financial interest.

- The global market for bee venom products is estimated to be $693 million. The steadily growth of the market on an annual basis ranges between 4-6% in the last few years. This trend is expected to continue in the next years with higher dynamic if some preconditions are met. Still, this is very low level of underutilization of bee hives in produvtion of bee venom. For the purpose of further relevant conclusions it is necessary to obtain accurate data on the world number of bee hives, as a basis for planning production and market potential.

- Market needs to develop with greater dynamics. The primary priority is the adoption of a Regulation that will standardize licensing, production processes, quality control, and professional staff. In this way, the production will be better planned, the method of collection will be improved, the technology will become more accessible, the storage, the method of keeping and the transportation of the collected bee venom before it goes to the production facilities that would further include it into cosmetic grade or medical grade formulations.

- It is necessary to significantly increase the funding of new research and to confirm and expand certain therapeutic areas of action

- Efforts are needed to raise knowledge, awareness, modernize the bee venom collection process and build capacities for local production of specialized preparations for cosmetic and medical use. The creation of final products at the local level will allow the benefits to be directly felt by individual producers, national economies and through synergies to realize a wider economic and medical benefit.

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