كلية الصيدلة

Attahadi University, Faculty of Pharmacy

A study on the Knowledge of people on bee venom

A graduation project submitted to obtain a Bachelor's degree in Pharmaceutical Sciences

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كلمة شكر

لابد وانا أخطو خطواتي لأخيرة في الحياة الجامعية من وقفة أعود وفيها إلي أعوام قضيتها في رحاب كلية الصيدلة مع أساتذتي الكرام الذين قدموا لي الكثير إلي أن أصل إلي هذه المرحلة

" أعضاء هيئة التدريس "

"كن عالماً فإن لم تستطع . . . فكن متعلماً . . . فإن لم تستطع . . .
فأحب العلماء . . . فإن لم تستطع . . . فلا تبغضهم "

Profesor Dr. Fathi Sherif

الإهداء

إلي من شجعني على المثابرة طوال . إلي الرجل الأبرز في حياتي

﴿ والدي العزيز ﴾

إلي من بـــها أعلو ،وعليها أرتكز ، إلي القـــلب المعطاء

﴿ إخـــواني وأخـــواتي ﴾

إلي كل من ساهـــم ولو بحرف في حياتي الدراسية. . . .

إلي كل هؤلاء : أهدي هذا العمل ، الذي أسال الله تعالي أ يتقبله خالصا . . . .اً

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

{ يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ }

{ صدق الله العظيم }

{ سورة المجادلة: 11}

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APITHERAPY, or "bee therapy" (from the Latin apis which bee) is **.1**
.the medicinal use of products made by honeybees
Products of the Honeybee include bee venom, honey, pollen, royal jelly,
.propolis, and beeswax
Some of the conditions treated (not in any special order) are: multiple sclerosis, arthritis, wounds, pain, gout, shingles, burns, tendonitis, and
.infections
Therapies involving the honeybee have existed for thousands of years and some may be as old as human medicine itself. The ancient rock art of early hunter-gatherers depicts the honeybee as a source of natural medicine. Bee venom therapy was practiced in ancient Egypt, Greece, and China-three Great Civilizations known for their highly developed medical systems. Hippocrates, the Greek physician known as the "Father of Medicine", recognized the healing virtues of bee venom for treating arthritis and other joint problems. Today, growing scientific evidence suggests that various bee products promote healing by improving circulation, decreasing inflammation, and stimulating a healthy immune
.response
References to medical properties of bee products can be found in Chinese, Korean, Russian, Egyptian and Greek traditional medicine practices. (silva, al., 2015) Apitherapy has been practiced since the et times of Hippocrates and Galen. The more modern study of apitherapy, specifically using bee venom, was initiated by Austrian physician Philipp Terč (cs) in his 1888 article "About a Peculiar Connection Between the Bee stings and Rheumatism."(Terč and philipp,188)] More recent alternative medicine practice is attributed to the Hungarian physician Bodog F. Beck who coined the term "bee venom therapy" in 1935, and to beekeeper Charles Mraz (1905-1999) in the latter half of the twentieth century. In 1957, the USSR Ministry of Health sanctioned use of bee venom to treat certain ailments by approval of Nikolay Artemov's "Instruction for Bee Sting Venom Apitherapy."(Berenbaum, et al., 1988)

DEFINITION OF BEE VENOM.1.1

Apitherapy can include the usage of all products created naturally from
:honeybees. This includes

- Bee venom. Female worker bees produce bee venom. It can be delivered directly from a bee sting. The bee sting may be administered to the skin through a stainless steel micro mesh. This allows the venom to enter the skin, but prevents the stinger from being attached to the skin,
.which would kill the bee
- .Honey. Bees produce this sweet substance. It can also be harvested

- Pollen. This is the male reproductive material bees collect from plants. It contains a large number of vitamins and nutrients.
- Royal jelly. The queen bee feeds on this enzyme-enriched food. It contains a large number of beneficial vitamins.
- Propolis. This is a combination of beeswax, tree resins, honey, and enzymes made by bees to protect the hive from external threats, like bacteria or viruses. It contains strong antiviral, antifungal, anti-inflammatory, and antibacterial properties as a result.
- Beeswax. Honeybees create beeswax to build their hive and store both honey and pollen. It's commonly used in cosmetic products.

In our research, we focus and interested to study the bee venom and the clinical effect of venom on different medical condition.

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PHYSICAL CHARACTER OF BEE VENOM 1.2

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Honeybee venom is a transparent liquid dries up easily even at room temperature, odourless, ornamental pungent smell, a bitter taste, ydrolytic blend of proteins with basic pH (4.5 to 5.5) that is used by bees for defense (R. Krell, 1996), (J.O. Schmidt, et al, 1999). When coming into contact with mucous membranes or eyes, it causes considerable burning and irritation. Bee venom is soluble in water and insoluble in alcohol and ammonium sulfate. When it comes in contact with air it forms grayish-white crystals. Dried venom takes on a light yellow colour and some commercial preparations are brown, thought to be due to oxidation of some of the venom proteins. Bee venom contains a number of very volatile compounds which are easily lost during collection, it is considered a rich source of enzymes, peptides and biogenic amines, it is specific weight 1.1331 (J.O. Schmidt, et al., 1986).

COMPOSITION OF BEE VENOM.1.3

- There are 78 different components in the bee venom.
- But not all these components are consistently present in every bee's venom.

- There are five primary components which are through to provide the major therapeutic benefits of bee venom therapy (BVT).

Bee venom is made up of at least 18 pharmacological active compounds The amount of bee venom protein released in a sting is variable, ranging between 50 to 140 micrograms. Venom is what comes out of the protecting apparatus of the bee the pollen consumed / food Bee Venom keeps fresh and pure: in the live bee only! (ALI, M,2012).

:Bee venom composed of

Water-1

Peptides-2

Enzymes-3
Esters: volatile elements-4
Low molecular components-5

-:WATER.1.3.1

The water content varies between 55 and 70 % (DOTIMAS, EM and .HIDER, RC ,1987)

Peptides.1.3.2

Polypeptides are smaller in molecular weight than enzymes, made of 2 or more amino acids. BV has numerous polypeptides, the main one being .millitin, which is also the main component of BV

:The peptides content on bee venom

Millitin	40%- 50%
Apamin	2% -3%
Mast Cell Degranulating Peptide	2% -3%
Adolapin	1%

-:Millitin.1.3.2.1

Approximately 50% of honey bee venom is comprised of millitin, which .has a profound neuro-hormonal and immunological effect on the body

- It primarily stimulates the hypothalamus in the brain to release corticotrophin releasing hormone which triggers the pituitary gland .to secrete
- adrenocorticotrophic hormone (ACTH), which stimulate the .adrenal cortex to reproduces cortisol

-:Cortisol is

,A potent anti-inflammatory
,stimulates gluconeogenesis
activates anti-stress pathways

Millitin also stabilizes lysosomal cell membrane, protecting against inflammation and slows the production of interleukin-1 which has been .correlated to both arthritic pain and inflammation

- :Action
- Central
- Ganglions
- Neuro-muscular
- Heart
- Vessels' permeability
- Peripheral circulation
- :Effects
- ,Anti-fungal
- Activates Histamine
- Decreases surface tension
- Stimulates ACTH (Plasma Cortisol in rats)
- Provides the "outch" and the itch
- .Anti-bacterial (ASAFOVA, et al., 2001)

-Apamin.1.3.2.2

:Action

- Shortens neuronal action potential
- Anti-inflammatory
- Blocks calcium-dependent potassium channels
- Enhances long-term synaptic transmission

Apamin is an 18 amino acid peptide neurotoxin. Dry bee venom consists of 2-3 % of Apamin. It selectively blocks Small conductance calcium-

activated potassium channels (SK channels), a type of Ca^{2+} activated K .channel expressed in the central nervous system

These channels are a type of ion channel allowing potassium cations to cross the cell membrane and are activated (opened) by an increase in .intracellular calcium

Their activation limits the firing frequency of action potentials and is important for regulating after-hyperpolarization in the neurons of the central nervous system as well as many other types of electrically excitable cells. This hyperpolarization causes the membrane potential to .become more negative

Mast Cell Degranulating Peptide.1.3.2.3

Mast cell degranulation peptide is a potent anti-inflammatory, 100 times more effective than hydrocortisone in reducing inflammation, it blocks .arachidonic acid production and inhibits prostaglandin synthesis

-:Action

Vascular permeability increased-

Anti-inflammatory (not via Adrenals)-

(Hydrocortisone <100)

Mastocytolytic action: Histamine Inflammation(ASAFOVA, et al.,- .2001)

-:Adolapin.1.3.2.4

Adolapin has an anti-inflammatory and pain killing effect. It inhibits microsomal cyclooxygenase, platelet lipoxygenase, thromboxane and .prostacycline which are activated during inflammation

:Action

Anti-inflammatory,Analgesic and Antipyretic

,Secapin, tertiapin

,cardiopep, minimin

-:procamine 3-5%

.Peptides, with an uncertain role in the physiological action of BV

-:Enzymes.1.3.3

:Action

Phopspholipase A2

Blood pressure (normalization)

Cardiac rate (normalization)

Mastolytic action

Hylaruronidase

Increases tissue permeability

Together they do

Local clean-up

From Chronic to Acute

Phospholipase A2 (*Enzyme hydrolyzing phospholipids*)**.1.3.3.1**

Phospholipase A2 is an enzyme that catalyses the hydrolysis of natural lipids, deacylating at position 2 to produce lysophosphoglycerides and long chain fatty acids (systematic name, phosphatide 2-acylhydrolase). (The lysophospholipid product may be further broken down by).lysophospholipase

Hyaluronidase (*Catalyses hydrolysis of hyoloronic acid*)**.1.3.3.2**

The presence of a spreading factor in venoms generally is very common (Habermann). Hyaluronidase (properly called hyaluronoglucosaminidase) catalyses the hydrolysis of the viscous mucopolysaccharide hyaluronic acid, which is present in the interstitial ground substance of connective

.tissues

-:Acid Phosphomonoesterase .1.3.3.3

This enzyme, commonly called acid phosphatase, represents - 1% of the dried venom (w/w). The presence of both acid and alkaline phosphatases was reported by Benton (1967) as a result of analysis by disc electrophoresis but the isolation was not reported until later (Shkenderov, .et al., 1979)

-:a-D-Glucosidase .1.3.3.4

The presence of an a-D-glucosidase in the fraction from bee venom that was excluded on gel filtration along with the acid phosphomonoesterase was established by (Shkenderov, et al .,1979). The amount of this enzyme .in crude venom was estimated to be 0.6%

-:Lysophospholipase .1.3.3.5

A low Phospholipase B activity in bee venom was first detected by Doery and Pearson (1964). The substrate, commonly lysolecithin, is hydrolysed to form glycerophosphocholine, releasing the remaining fatty acid anion from the C3 position

Low molecular compounds .1.3.4

BV contains smaller quantities of low molecular compounds are different in nature: amino acids, catecholamine, sugars and minerals. Sugars have been identified in some BV preparations, but if BV is collected with a collector preventing the contamination by pollen and nectar, it does not .contain carbohydrates

:DOPAMINE.1.3.4.1

.controls different brain center

Neurotransmitters

The low concentrations in BV do not cause physiological effects in mammals, but active when injected in invertebrates

NOREPINEPHRINE.1.3.4.2

-important neurotransmitter regulating heart rate, suppresses neuro .inflammation, and increases blood flow to skeletal muscles

:HISTAMINE.1.3.4.3

Neurotransmitter

Dilates blood vessels, increasing the permeability of blood capillaries and increases blood circulation; Stimulates smooth muscles

displays a dual effect by directly suppressing allergen-stimulated T cells and increasing IL-10 production

-:Esters.1.3.5

:Action

Antispasmodic, Anti-arrhythmic, Calming and Tonic (ASAFOVA, et al., .2001)

.Table 1: Composition of bee venom dry matter (ASAFOVA, et al.; 2001)

VENOM COLLECTION .1.4

Early collection methods required surgical removal of the venom gland or squeezing each individual bee until a droplet could be collected from the tip of the sting. Since the early 1960's, extraction by the electro-shock .method has been continuously improved and is now standard procedure Different extraction or collection methods result in different compositions of the final products Venom collected under water to avoid evaporation of very volatile compounds seems to yield the most potent venom (Pence, 1981). Venom collected from surgically removed venom sacs showed different protein contents from that collected with the electroshock method (Hsiang and Elliott, 1975). (Gunnison, 1966) used a cooling system with the standard electro-shock collecting apparatus in order to .preserve more of the volatile compounds

The standard electro-shock method (Morse and Benton, 1964a, b) cannot be recommended for venom collection from Africanized honeybees or the more defensive races in other parts of the world. Colony arousal can

become so overwhelming that bees start killing each other and alert other colonies or attack the beekeeper and bystanders. The mass reaction of Africanized honeybees may also result in contamination of the collected venom. Nevertheless, venom is collected by this method in Brazil and .Argentina, with only minor modifications

Even European colonies remain disturbed for up to a week after collection and it is said by (Mitev,1971) that colonies from which venom has been collected every three days produce 14% less honey. (Morse and Benton, 1964b) found no such evidence for reduced productivity, however. (Galuszka,1972) found that when using electro-shock treatment, the most efficient collection cycle was three 15-minute stimulations at intervals of three days, repeated after 2-3 weeks. An Argentinean beekeeper found that by modifying the electric stimulus, his collection .efficiency greatly increased and the bees remained disturbed for less time

The various trap designs stimulate bees by applying a mild electric shock through wires above the collecting tray. The most widely-used designs are modifications of the one first presented by (Benton, et al., 1963). A review by (Mraz,1983) discusses further developments. The trays are placed either between the bottom board and brood chamber at the hive entrance (see Figure 1) or in a special box between supers and the hive .cover

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Figure 1 a) Mr. Mraz with an electro-shock venom collector in his .beeyard

b) Placing the collector in front of the hive entrance. (Courtesy of B. Weeks)

When shocked, bees sting the surface on which they are walking. In some traps, this may be a glass plate or a thin (0.13 mm thick) plastic membrane, nylon taffeta or silicon rubber under which a collecting plate (preferably made of glass) or absorbent tissue receives the venom (see Figure 2). Venom dries rapidly on glass plates and can be scraped off with a razor blade or knife. Absorbent tissue is washed in distilled water to extract the venom, which then should be freeze-dried. Collection on glass is generally easier and produces a product which is easier to store, ship .and process

During handling of dry bee venom, protective gloves, glasses and dust masks should be worn to avoid any contact with, or inhalation of the .highly concentrated venom

It is unlikely that a bee will eject all the contents of its venom sac, even after repeated stinging. Therefore, typically, only 0.5 to 1.0 jil (0.2 j£l - Crane, 1990) of venom can be collected per bee, with an average of ten stings per bee (Mu-ller, 1939 and O'Connor, et al., 1967). This results in less than 0.1 ijg (0.11 jig - Crane, 1990) of dry venom per bee. Consequently, at least 1 million stings are required to make one gram of dry bee venom. (Dotimas and Hider, 1987) report that 1 g of venom can .be collected from twenty hives over a two hour period

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Figure 2: Close-up of collecting device with stings. The steel wires are approximately 6mm apart and suspended 1 to 3 mm above the thin silicon rubber film or directly abovethe glass plate in other models. The wires are alternately grounded and charged to amaximum of 33 volts. A lower voltage is effective, too. Preferably a collecting surfaceshould be used which does not make bees loose their sting. (Courtesy of B. Weeks)

Instead of collecting bee venom, adult bees may be used to sting the .patient directly
This is the way to apply the venom in its freshest, most complete and .cheapest form
To collect the bees, a small hole is made in the brood chamber, super or .inner cover
To avoid colony disturbance, the hole is opened and a collecting jar placed over it until a sufficient number of bees have come out. Small groups (10-100) of workers can maintained at home for up to 2 weeks. They should be kept in the dark, in a small box (with one side made of fly-screen) and with access to sugar syrup. Care needs to be taken to keep .ants away

VENOM PRODUCTS .1.5

Bee Venom Powder

Bee venom may be sold as whole bee extract, pure liquid venom or an injectable solution, but in either form the market is extremely limited. .Most venom is sold in a dry crystalline form
Since venom does not need to be processed, it can be prepared wherever bee venom therapy finds sufficient support. Production in small quantities is easy, as long as stringent sanitary controls and aseptic working conditions can be provided. The beekeeper has to work under extremely clean conditions, since most of the venom preparations will later be used .for injections into humans or animals
For injections, the venom can be mixed at the time of injection with injectable fluids, such as distilled (sterile) water, saline solutions and certain oils, or it may be taken from prepared ampoules. Ampoules with set doses of ready-to-inject venom should only be prepared by certified pharmaceutical laboratories, because of the need to maintain stringent .aseptic conditions and to measure the dosages very precisely

There are creams available which include bee venom (e.g. Forapin and Apicosan in Germany, Apivene in France and Immenin in Austria) which are used for external application on arthritic joints (BeeWell, 1993) (Sharma and Singh, 1983) but neither the ingredients nor their proportions are known to the author. Tablets can be impregnated with quantities of bee venom, but (Sharma and Singh, 1983) recommended the removal of toxic proteins, such as Millitin and the use of colors to indicate different dosages. The tablets should be placed under the tongue, but no indication is given to the effect or usefulness of such a preparation. Some specialized laboratories may be able to separate and purify different venom compounds and sell them to scientific and pharmaceutical laboratories. Phospholipase Ag and highly active peptides are among some of the proteins purified from bee venom for scientific suppliers or laboratories (Schmidt and Buchmann, 1992). Entry to this limited market requires a highly sophisticated laboratory and very well-trained .technicians and chemists
Though not directly related, bee sting emergency kits can be sold in some countries, particularly to people who are allergic. They also should be at hand for any beekeeper working with Africanized honeybees and at training centers, police and fire departments, in areas with Africanized honeybees. In the USA, they are now available only against a prescription. Such a kit (e.g. Anakit by Hollister Stier, USA) should :contain at least

One syringe with a premeasured content of epinephrine (adrenaline) or (1 atropine, for immediate intramuscular injection usually 0. 3m1 of a diluted solution of epinephrine (1:1000) in saline solution. There are special, easy-to-use, syringes available from bee supply houses or through pharmacies, which can even be used through clothing (Epipen by .Centre Laboratories, USA)

.anti-histamine tablets .2

.tourniquet .3

instructions about when, where and how to use the syringe and anti- .4 histamine tablets; when not to use epinephrine, and where to seek medical help. Epinephrine injections should be given only in extreme emergencies when no other medical help is available. The sting emergency kit has a limited shelf-life and should be kept refrigerated .when not in use

The best way to buy bee venom is in the crystallized form, since it is more stable, impurities are easier to detect and adulteration is less likely. .The colour of both crystals and powder should be a very light yellow Liquid venom should be clear and colourless. Darker venom is slightly .oxidized and may have lost some of its effectiveness

As with all other products where immediate testing is not possible or is very expensive, the producer should be one who is well-known and who can be trusted to produce a high quality product. The producer as well as .the buyer should have adequate storage facilities

Even dried bee venom should be stored refrigerated or preferably frozen and it should always be kept in dark bottles in the dark. All producers and buyers should closely observe these conditions. Dried bee venom can be kept frozen for several months, but should not be kept refrigerated for more than a few weeks. Liquid venom and diluted venom can be stored .for similar periods if maintained in well sealed, dark glass containers

ADMINISTERING BEE VENOM .1.6

the venom can administered directly from bees via the bee's stinger. The lived bee is held by the person, who then places the bee on the part of the patient's body to be treated, at which point the bee reflexively stings. Also the venom could be given via a syringe, *rather than directly from the bee*

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-:APITOXIN

?What is Apitoxin

An injectable product obtained from bee venom

Quality depends on the producer

:At injection

Few volatile components conserved

Oxidation: esters acidified

Aqueous solution in ampoule for undetermined time

Therapeutic Dosages Bee Venom

one Bee delivers Bee Venom

one bee delivers in average - 150 µgr

A "micro-sting" sting left briefly delivering from

µgm on (1 sting used >100 times !) 1-2~

Doses vary from 1 micro-sting to> 100 stings

Therapeutic Dosages Apitoxine

one Syringe delivers Apitoxine

.one dose = 100 µgm=0.1 mg

.stings-30 doses = 3.0 mg 20

Amount Toxic-bee stings

Theoretical
LD=2.8 mg/Kg = 19 stings/Kg or 9 stings/lb
A man of 75 Kg (166 lb): 1,425 stings
A child of 30 Kg (66 lb): 570 stings
Death
by lung and/or kidney failure
-:Administration
:By injection
Intra-dermal
Bee sting or syringe
Sub-cutaneous
Deep Peri-articular
Intra-muscular
-:Administration
Trans-dermal

Salve: Rubbed in or moved in by electrophoresis
Liquid: Rubbed in with tool (China)
Inhalant
Oral: combined with honey
In eyewash
Toxic/Therapeutic Ratio
.Toxic amount (LD) = ~ 210 mgr

THE ALLERGIC FOR BEE VENOM .1.7

A bee sting is strictly a sting from a bee (honey bee, bumblebee, sweat bee, etc.).In people who are allergic to bee stings, a sting may trigger a .dangerous anaphylactic reaction that is potentially deadly

Allergic Reactions to Insect Stings

allergy is a general term that descriers a verity of human symptoms and reactions to diversity of materials including pollen, animal dander, foods, .drugs, dust mites (house dust), stinging insects and others

Stinging insect allergy refers to sting-induce systemic reactions of the .body that occur at body locations distant from the sting site

Allergic reactions do not include immediate pain caused by the sting itself or to the burning, redness, itching and swelling that might occur .around the sting site

Such reactions including very large local swelling are referred to as "local .reactions" (R. Krell, et al., 1996),(A.B. Phyllis, et al., 2000)

that most stings cause localized swelling, redness, and acute pain that may throb or burn. This is reaction to the insects venom. Whoever, some people are highly allergic to insect venom, and if they are stung, a very severe reaction can occur. People who are highly allergic to insect stings can experience anaphylactic shock, which can lead to unconsciousness and, in extreme International Journal of Advancements in Research & .Technology

Anaphylactic shock can cause symptoms such as bluish skin, coughing, difficulty breathing, dizziness, hives, nausea, severely swollen eyes, lips or tongue, stomach cramps, and wheezing. As cited by (R. Krell, et al., 1996) although, bee venom is safe for human treatment; it should only be used under the supervision of a qualified health care professional. Most experts recommend having an emergency sting kit available in case of .allergic reaction

This kit should include a syringe and a dose of epinephrine and .antihistamine tablets

The kit can get by prescription from the doctor, be sure you read the .directions on the package before you get your test sting

It is also advisable that a test sting be performed before undergoing a

treatment (A.Rose, et al.; 1994)
Those who are sensitive to the test sting can be de-sensitized to bee venom in order to undergo apitherapy. It is estimated that 1% of the .population is allergic to bee stings
Only a small percentage of those allergic to a honeybee sting will suffer anaphylactic shock (A. Rose, et al., 1994) A severe reaction just after a .few stings is rare, but the danger grows with the number of stings
A person who is having a severe reaction to a bee sting may develop .hives on the skin and swelling around the eyes, lips, throat, and tongue
The person may vomit, slur words, show signs of mental confusion and even struggle to breathe. This is usually followed by the loss of .consciousness
If any of these signs are present, immediately consult with an emergency medical professional. In theory any stinging insect species can cause allergic reaction in humans. This because an insect sting introduces venom which essentially is a blend of foreign proteins- into the body where it contacts the immune system and can induce production of .allergy-causing antibodies (J.O. Schmidt, 1999)
An allergic reaction typically occurs after the second or subsequent .stinging event by the same or a closely related species
The first sting, (or stings), induces the production of the allergy causing antibody, immunoglobulin E (IgE), by the body resulting in the .sensitization of the individual to the venom
Later when the now hipper sensitive individual is stung again, the venom .causes an IgE-mediate allergic reaction

Table 2:Normal and allergic reaction to stings can vary enormously from individual to individual

Case of allergic	Symptoms
Normal , non – allergic reaction at the time of the sting	Pain, sometimes sharp and piercing
	Burning, or itching burn
	Readiness (erythema) around the sting site
	A wide area (wheal) immediately surrounding the sting puncture mark
	Swelling (edema)
	Tenderness to touch
Normal , non -allergic reaction hours or	Itching
Days after sting	Residual readiness
	A small brown or red damage spot at the puncture site
	Swelling at the sting site
Large local rection	Massive swelling (angioedema)around the sting site
	Extending over an area of 10 cm or more and frequently increasing insize 24 to 72 hours, sometimes lasting up to a week in duration
Cutaneous allergic reaction	Urticaria (hives, nettle rash) anywhere on the skin
	Angiodema (massive swelling) remote

	from the sting site
	Generalized pruritis (itching) of the skin
	Generalized erythema (redness) of the skin
	remote from the sting site
Non life -threatening systemic allergic reaction	Allergic rhinitis or conjunctivitis
	Minor respiratory symptoms
	Abdominal cramps
	Severe gastrointestinal up set
	Weakness
	Fear or other subjective feeling
life -threatening systemic allergic reaction	life-threatening systemic allergic reaction Shock
	Unconsciousness
	Hypotension or fainting
	Respiratory distress (difficulty in breathing (Laryngeal blockage (massive swelling in (the throat

Normal reactions are those that virtually everybody .(J.O. Schmidt, 1999) experiences and are characterized mainly by pain and burning that typically are in tense for a few minutes and then decrees over time. After the intense pain decreases a redness and swelling are oven observed and .this can last several hours to a day or more

Like normal (non-allergic) reactions, large local reaction is nothing to be feared. Though they are thought to be immunologically based reactions (P.M. Mauriello, et al., 1984) they rarely progress to systemic

QUALITY CONTROL OF BEE VENOM .1.8

As cited by (R. Krell,1996) there are no official quality standards, since bee venom is not recognized as an official drug or as a food. Purity analysis may be carried out by quantitative analyses of some of its more stable or more easily measured components such as millitin, dopamine, histamine, noradrenaline or those for which contamination is suspected. A nematode, Panagrellusredivivus was reported to react selectively and specifically to bee venom and a quantitative analysis of the venom in pharmaceutical preparations was developed by (A.A. Tumanov, et al., 1996) using this organism. (R.J. Pence, 1981) describes a method for testing the biological activity of bee venom by measuring electric pulses from muscles of excised honeybee abdomens in response to the volatile materials from bee venom. (M.W. Guralnick, et al., 1986) described standardization and quality control methods for purity and effectiveness .of Hymenoptera venom, including honeybee venom

:CHAPTER TWO

CLINICAL USES OF BEE VENOM

AND

LITERATURE REVIEW

THERAPEUTIC USE

When use in a normal doses, bee venom can be of benefit in treating .many number of ailments

Rheumatoid arthritis -.2.2

Is a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks the joint, ending with the destruction of the articular cartilage and ankylosis of the joints (ankylosis a stiffness of a joint due to abnormal adhesion and rigidity of the bones of the joint, which may be the result of injury or disease)

Almost 1% of the world population is afflicted by rheumatoid arthritis, .women three times more often than men

Mechanism of action: Bee venom is composed of several substance, primary phospholipase A and melittin, but also hyaluronidase, apamin, mast degranulating peptide, and adolapin. (Graham EJ, 1983)

The melittin component of bee venom has been shown to inhibit neutrophil superoxide and hydrogen peroxide production in a dose-dependent manner. (Somerfield SD, 1988)

This could explain some anti-inflammatory activity since oxygen radicals contribute to inflammatory tissue damage melittin may also inhibit macrophage production of interleukin-1 (Hadjipetrou-Koutounakis L, et

al., 1988)

It has also been postulated that bee venom may work by stimulating the adrenals to release endogenous steroid. one study showed that whole bee venom, melittin, and apamin resulted in markedly increase plasma cortisol level (Vick JA, et al., 1972)

ARTHRITIS According to scientist Stefan Bogdanov, who worked for 26 years at the Swiss Bee/Research, the mechanism of action of bee venom in treating arthritis clarified is clarified bee venom blocks the building of the pro inflammatory substances cytokinome, PGE 2, NO, Tumor Necrosis Factor TNF-2 and Enzyme COX-2 Bee venom inhibits the proliferation of rheumatoid synovial cells. Bee venom does not seem to influence rheumatoid deformation, as shown by patients X-rays, but it does control pain and inflammation. The success rates are generally good, . lying generally between 60 to 90%

Tested on arthritic rats, bee venom apipuncture was as effective as % .cortisol treatment

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From doctor Ludyansky's vast experience in Russian hospitals and general practitioners, as well as his own experience treating arthritis, bee venom apipuncture is better against rheumatoid arthritis than against .osteoarthritis

There are different bee venom treatments that can be used: bee stings (BS), apipuncture (AP), injections, electrophoresis and phonophoresis .(application with ultrasound waves)

examined the use of apipuncture in musk skeletal pain. (Lee, et al., 2005)

Bee venom was used in the treatment of different pain conditions: neck pain, low back pain, herniated lumbar pain, dise pain shoulder pain after

stroke, acute ankle sprain, wrist sprain, rheumatoid arthritis and knee osteoarthritis. Bee stings, apipuncture therapy was useful in all these conditions. Apipuncture relieves pain more effectively than acupuncture. There is need for more studies on the effects of bee venom stinging in acupuncture points as compared to stinging in other body points. Today .only stinging in acupuncture points is used in treatment

Any studies? There are experimental studies and clinical trials of apipuncture for arthritis in the databases of PUBMED, EMBASE and the Cochrane Library. There are over 1700 scientific publications on the composition and various effects of bee venom in animals and humans .have been published

Almost all recent studies are conducted in South Korea, two leading Korean journals, "The Journal of Korean Society for Acupuncture and Moxibustion" and "The Journal of Korean Oriental Medicine" are publishing the studies. Many of them are open to public and we can find them published in scientific pages, like nebi.nlm.nih.gov. Here are some :of them

In 2004, the study "Acupoint stimulation with diluted bee venom (apipuncture) alleviates thermal hyperalgesia in a rodent neuropathic pain model: involvement of spinal alpha 2-adrenoceptors." was conducteed by Roh DH et al.,2004) from the Department of Veterinary Physiology, College of Veterinary Medicine, Seoul National University, South Korea. The was publishedby(ncbi.nlm.nih.gov.)

It investigated the potential antihyperalgesic and antiallodynic effects of apipuncture in a rat neuropathic pain model. Their conclusion was: "The relieving effect of apipuncture on thermal hyperalgesia was found to be mediated by spinal alpha2-adrenoceptors, but not opioid receptors. These data suggest that apipuncture might be an effective alternative therapy for patients with painful peripheral neuropathy, especially for those who are ".poorly responsive to opioid analgesics

from South Korea studied "Antinociceptive effect (Back YH, et al., 2006) and the mechanism of bee venom acupuncture (Apipuncture) on inflammatory pain in the rat model of collagen-induced arthritis: Mediation by alpha2-Adrenoceptors." The results showed that bee venom apipuncture can relieve inflammatory pain in collagen induced arthritis rats and the antinociceptive effect of bee venom acupuncture can be .mediated by alpha2-adrenergic receptor

published the study "Apipuncture treatment (In 2010, ncbi.nlm.nih.gov) for central post-stroke pain", conducted by Yun SP, Sun BC, from aint Paul's Oriental Medical Center, Seoul, Korea, assessed the effectiveness of apipuncture treatment for central post-stroke pain. The results showed that apipuncture was an effective and safe intervention to treat central .post-stroke pain

Diabetes mellitus 2.4

is a serious disease in which the body cannot control the amount of (DM) sugar in circulation due to either a deficiency of insulin secretion or a decreased sensitivity of the tissues to insulin. There are two main types of diabetes as follows: Type 1 and Type 2 .Both types can cause serious health complications, including kidney failure, heart disease, blurred vision, ketoacidosis, peripheral neuropathy, itchiness, fatigue, and even coma (M. Stolar, et al., 2010)

An insulin deficiency leads to elevations of cholesterol, phospholipids, and free fatty acids. Therefore, it is important that an ideal DM therapy should not only involve maintaining blood glucose levels but also involve the regulation of the lipid profile. To treat DM, several Antidiabetics drugs are used. However, these drugs are not without side effects and pose an economic burden to the patient. Therefore, scientists have turned to natural remedies, including honey and bee products, such as bee venom (BV). BV is a complex mixture of proteins, peptides, and low

molecular components secreted by the worker and the queen bees. The main active constituent of BV (apitoxin) is melittin, which has a relatively low toxicity (1 S. Bogdanov, 2015)

It exerts important effects on cells, such as hemolysis, membrane depolarization and muscle contraction, cytotoxicity, and phospholipase C and arachidonic acid following phospholipase A2 activation. Insulin activates the enzyme lipoprotein lipase and hydrolysis triglycerides (Frayn, 1993). According to the obtained results, bee venom decreased blood TG content. One could explain the observed decline as follows: bee venom improves glycemic control and decreases blood glucose level. Also glucose consumption is increased instead of lipids. Acetyl coA derived from pyrovic acid enters Krebs cycle which finally leads to glucose metabolism, however Acetyl CoA can enter TG synthesis pathway in usual condition (Zhang and Tan, 2003). Probably cholesterol lowering effect is largely due to inhibition of its absorption in small intestine and promoting its hepatic release. The liver plays a critical role .in discharging cholesterol via bile secretion (Reinner, et al., 1989)

Skin and eye diseases .2.8

Bee venom use against skin diseases has a long tradition and has been used since the beginning of the 20th century. Following skin diseases have been successfully treated eczemas like dermatitis, psoriasis, for the healing of cicatrices and against baldness. For skin application BV is .applied in the form of creams and ointments and also in electrophoresis Six weeks of treatment with PBVTM serum was found to be effective in the treatment of mild-to-moderate acne vulgaris, with no incidence of .serious side effects or irritation (HAN, SM et al., 2016)

Interestingly enough BV has been used also in ophthalmology. Especially, it has been used for the treatment of acute and chronic rheumatic iritis and neuritis of the eye nerve. Aqueous BV solutions are .used as drops and injections

BEE VENOM AND COSMETICS.2.9

Bee venom has been claimed to be the new Botox. This claim has a new prominent support in the name of Camilla Parker-Bowles, Duchess of Cornwall and wife of Prince Charles Honey bee venom is used cosmetically to 'fool' the skin into thinking it
has been lightly stung with the toxin melittin. This causes the body to direct blood towards the area and stimulates the production of the naturally-occurring chemicals collagen and elastin. Collagen strengthens body tissue while elastin is the protein that helps the skin to remain taut and bounce back into shape after being pressed or pinched. The venom also has the effect of relaxing the muscles, it is claimed Theantiaging :Heaven BV mask should be used as follows

Apply BV mask to cleansed skin, leave for 20 minutes then wash off, thereafter daily use massage a small amount onto the skin morning or evening or apply a thin layer under make-up for a flawless finison. A Skin sensitization study of BV was carried in guinea pigs and rats which showed that that BV was well tolerated and exhibited no dermal irritation potential in guinea pigs and rats. The findings may provide a developmental basis of BV for a cosmetic ingredient or external application for topical use The positive effect of BV against aging related . human face wrinkles has been scientifically proven

REFERENCES

ASAFOVA, N; ORLOV, B; KOZIN, R (2001) Physiologically active bee products (in Russian). YA.Nikolaev Nijnij Novgorod; 360 pp Email:

stefeug@gmail.com
ALL, M (2012) Studies on Bee Venom and Its Medical Uses, UART 1 (2)
A (2013) Bee Venom and Its Component Apamin as Neuroprotective Agents in a Parkinson Disease Mouse Model. Plos One 8 (4)
A .Rose, "Bees in balance". Starboint Enterprises, Ltd, Bethesda, .Maryland, 1994
W. Green, R.E. Reisman, and C.E. Arbesman, "Clinical and immunologic studies of patients with large local reactions following insect stings". J. Allergy Clin. Immunol 66:185-189, 1980
Hood JL et al. Cytolytic nanoparticles attenuate HIV-1 infectivity. Antiviral Thera 2013; 19: 95-1038ee Product Science, www.bee-hexagon.net, April 2016
BECK, 8F (1935) Bee venom therapy. D. Appleton-Century Company New York and London
Berenbaum, May R. (January 1995). Bugs in the System: Insects and Their Impact on Human Affairs. Helix Books. p. 175. ISBN 978-0-201-.62499-1
Benton, R.A. Morse, and J.D. Stewart, "Venom collection from .honeybees". Science 142: 228-230, 1963
BBerlin Veterinary Weekly. Graham EJ. The Hive and the Honey Bee. Hamilton, IL: Dadant and Sons; 1992ee J., 121(10): 726-731, 1981 Amer. .R.J. Pence

Bogdanov, "Bee venom: composition, health, medicine: a review," Bee .Product Science, 2015
Croatian et al. Honey Bee products potent in cancer prevention, .treatment. J Sci Food Agri 2004; 3: 154-89
CASTRO, HJ; MENDEZ-INOCENCIO, JI; OMIDVAR, B; OMIDVAR, J; SANTILLI, J; NIELSEN, HS;PAVOT, A P; RICHERT, JR; BELLANTI, JA (2005) A phase study of the safety of honeybee venom extract as a possible treatment for patients with progressive forms of .multiple sclerosis Allergy and Asthma Proceedings 26 (6): 470- 476
DOTIMAS, E M; HIDER, RC (1987) Honeybee venom. Bee World 68 .(2): 51-70
D.F.K.C. Graft, A. Schhuberth, K.A. Kagey-Sobotka, Y. Kwiterovich, L. Niv, M. Lichtenstein, and M.D. Valentine, "A. prospective study of the natural history of large local reactions after Hymenoptera stings in .children". J. Pediatr 104: 664-668, 1984
Gunnison, "An improved method for collecting the liquid fraction of bee .venom". J. Apic. Res. 5 (1): 33-36, 1966
Gajski, G.; Garaj-Vrhovac, V. Melittin: A lytic peptide with anticancer properties. Environ. Toxicol. Pharmacol. 2013, 36, 697-705
Gerst, J.E.; Salomon, Y. Inhibition by melittin and fluphenazine of melanotropin receptor function and adenylate cyclase in M2R melanoma .cell membranes
.Endocrinology 1987, 121, 1766-1772

G. Lee and H. Bae, "Anti-inflammatory applications of melittin, a major component of bee venom: Detailed mechanism of action and adverse .effects," Molecules, vol. 21, no. 5, article no. 616, 2016
Galuszka, "The research on a most effective method of the collection of bee venom by means of electric current". Zoologica Pol. 22 (12): 53-69, 1972
HAN, SM; PAK, SC; NICHOLLS, Y M; MACFARLANE, N (2016) Evaluation of anti acne
property of purified bee venom serum in humans. Journal of cosmetic .dermatology
.DOI: 10.1111/jocd.12227

Hadjipetrou-Hsiang, and W.8. Elliott, "Differences in honeybee (Apis mellifera) venom obtained by venom sac extraction and electrical .milking". Toxicon 13: 145- 148, 1975
Hu, H.; Chen, D.; Liu, Y.; Deng, Y.; Yang, S.; Qiao, M.; Zhao, J.; Zhao, X. Target ability and therapy efficacy of immunoliposomes using a humanized antihepatoma disulfide-stabilized Fv fragment on tumor cells. .J. Pharm. Sci. 2006, 95, 192-199
HAUSER, RA; DAGUIO, M; WESTER, D; HAUSER, M; KIRCHMAN, A; SKINKIS, C (2001) Bee-venom therapy for treating multiple sclerosis: a clinical trial. Alternative & Complementary Therapies (Feb.):37-45
IKEDA, M; DEWAR, D; MCCULLOCH, J (1991) Selective reduction of [<sup(125)>]- apamin binding sites in Alzheimer hippocampus: a quantitative autoradiographic study 1119. Brain Research 567 (1): 51-56
I. Aprechc, G. Eichler, U. Miller and R. Hoigne, "On the significance of severe local reactions to Hymenoptera stings". Clin. Allergy, 10:675-682, .1980
J.O. Schmidt, "Allergy to venomous insects" (in. The Hive and the Honey Bee, Edited by Joe M.Graham, Dadant and Sons, Hamilton, Illinois, .1999")
Koutounakis L, Yiangou M. Bee venom, adjuvant-induced disease and .interleukin production. J Rheumatol 1988;15:1126-1128
KRYLOV, V (1995) Pcelni yad (Bee venom in Russian). Nizhny Novgorod University
Nizhny Novgorod; 221 ALI, M (2012) Studies on Bee Venom and Its Medical Uses UART 1 http://en.wikipedia.org/wiki/Osteoarthriti
KIM, JI; YANG, EJ; LEE, MS; KIM, YS; HUH, Y: CHO, H; KANG, S: KOH, HK (2011) Bee Venom Reduces Neuroinflammation in the MPTP-Induced Model of Parkinson's Disease. International Journal of .Neuroscience 121 (4): 209-217
Mitev, "Collection of bee venom using a weak electric current - its effect on the condition and the performance of the colony". Zhivot. Nauki 8 (1): .103-108, 1971
Mraz, "Methods collecting bee venom and its utilization". Apiacta 18: 33- .34, 54, 1983
M. Stolar, "Glycemic control and complications in type 2 diabetes mellitus," American Journal of Medicine, vol. 123, no. 3, pp. $3-$11, 201Morse, and A.W. Benton, "Notes on venom collection from honeybees". Bee World 45 (4): 141-143, 1964a. O'Connor, W. Rosenbrook Jr, and R. Erickson, "Hymenoptera: pure venom from bees, wasps, and hornets". Science 139:420, 1963 (by Schmidt and Buchmann "In. The Hive and the Honey Bee, Edited by Joe M. Graham, Dadant and .Sons, Hamilton, Illinois, 1999")
Pence, "Methods for producing and bio-assaying intact honeybee venom .for medical use". Amer. Bee J., 121(10): 726-731, 1981
P.M. Mauriello, S.H. Barde, J.W. Georgitis, and R.E. Reisman, "Natural history of large local reactions from stinging insects". J. Allergy Clin. .Immunol 74: 494-498, 1984
P. Vigneri, F. Frasca, L. Sciacca, G. Pandini, and R. Vigneri," Diabetes and cancer," Endocrine-Related Cancer, vol. 16, no. 4, pp. 1103-1123, .2009
Rome, 1996 R. Krel Rome, Italy, 1996, A.A. Tumanov, and N.I. *Osipova
R. Krell, "Value-added products from beekeeping". SAO Agricultural Services Bulletin. Food and Agriculture Organization of the United .Nation, Rome, 1996
Silva, J; Monge-Fuentes, V; Gomes, F; Lopes, K; Dos Anjos, L; Campos, G; Arenas, C; Biolchi, A; Gonçalves, J; Galante, P; Campos, L; Mortari, M (2015). "Pharmacological Alternatives for the Treatment of

Neurodegenerative Disorders: Wasp and Bee Venoms and Their Components as New Neuroactive Tools". Toxins. 7 (8): 3179-3209
Somerfield SD. Bee venom and arthritis: Magic, myth or medicine? NZ .Med J 1986;99:281-283
Stefan Bogdanov, Bee Venom: Composition, Health, Medicine: A Review, bee- hexagon.net; Lee JD et al, An Overview of Bee Venom Acupuncture in the Treatment of Arthritis, (2005)
Song. C.C.; Lu, X.; Cheng, B.B.; Du, J.; Li, B.; Ling, C.Q. Effects of melittin on growth and angiogenesis of human hepatocellular carcinoma .BEL-7402 cell xenografts in nude mice. Al Zheng 2007, 26, 1315-1322
Shin, J.M.; Jeong, Y.J.; Cho, H.J.; Park, K.K.; Chung, I.K.; Lee, I.K.; Kwak, J.Y.; Chang, H.W.; Kim, C.H.; Moon, S.K.; et al. Melittin suppresses HIF-1alpha/VEGF expression through inhibition of ERK and mTOR/p70S6K pathway in human cervical carcinoma cells. PLoS One .2013, 8, e69380
Soman, N.R.; Baldwin, S.L.; Hu, G.; Marsh, J.N.; Lanza, G.M.; Heuser, J.E.; Arbeit, J.M.; Wickline, S.A.; Schlesinger, P.H. Molecularly targeted nanocarriers deliver the cytolytic peptide melittin specifically to tumor cells in mice, reducing tumor growth. J. Clin. Investig. 2009, 119, 2830-.2842
Terc, Philipp (26 August 1888). "Ueber eine merkwürdige Beziehung des Bienenstichs zum Rheumatismus
USA. Fourth Printing 952-960, 1999) J.O. Schmidt, and S.L. *,Buchmann
Vick JA, Shipman WH. Effects of whole bee venom and its fractions (apamin and melittin) on plasma cortisol levels in the dog. Toxicol 1972;10:377-380 WESSELIUS, T; HEERSEMA, DJ; MOSTERT, JP; HEERINGS, M; ADMIRAAL-BEHLOUL, FTALEBIAN, A; VAN BUCHEM, MA; DE KEYSER, J (2005) A randomized crossover study of bee sting therapy for multiple sclerosis. Neurology 65 (12): 1-5
Wiener Medizinische Press (in German). Urban & Schwarzenberg, 29 ..(35): 1261- 1263
*.Toxicon 24: 907-921, J.O. Schmidt, M.S. Blum, and W.L .1986
*,New Engl. J. Med. 299:157-161, K.J. Hunt .1978
Yadav, K. Moorthy, and N. Z. Baquer, "Effects of sodium-orthovanadate and Trigonella foenum-graecum seeds on hepatic and renal lipogenic enzymes and lipid profile during alloxan diabetes," Journal of Biosciences, vol. 29, no. 1, pp. 81-91, 20
Zhang, Z.; Cao, W.; Jin, H.; Lovell, J.F.; Yang, M.; Ding, L.; Chen, J.; Corbin, I.; Luo, Q.; Zheng, G. Biomimetic nanocarrier for direct cytosolic .drug delivery. Angew. Chem
Int. Ed. Engl. 2009, 48, 9171-9175. [About a Peculiar Connection .(Between the Bee stings and Rheumatism