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APITHERAPY

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Abstract: **Ethnoentomology is the study of the relationship between insects and people. "Ethno"-study of people and "entomology" –is the study of insects, so the focus of Ethnoentomology is on how insects have been or are being used in human societies around the world, which includes insects used for food rituals and medicine. While insects are commonly considered pests and a large part of man efforts are extended towards eradicating them, some insects have been counted as mankind s friend. Apitherapy is the one part of this field, is the medical use of honey bee products that includes the use of honey, pollen, bee bread, propolis, royal jelly, bee venom etc. The first use of apitherapy, the exact location is not traced but in general sense to ancient Egypt, Greece and China. Honey and other bee products have healing properties are included in many religious texts including the VEDA, BIBLE, and QURAN. The term apitherapy is use of bee venom not consumption of honey or other bee products. Whereas bee venom therapy is the use of live bee stings (or injectable venom) to treat various diseases such as arthritis, rheumatoid arthritis, multiple sclerosis (MS), lupus, sciatica, low back pain, and tennis elbow to name a few. It refers to any use of venom to assist the body in healing itself. Bee venom is a complex mixture of a variety of peptides and enzymes and amines some of which have strong neurotoxic and immunogenic effects. Such as melittin, has powerful anti inflammatory, anti bacterial, anti viral action. Sulfur is believed to be one of the main elements in inducing the release of cortisol from the adrenal glands and in protecting the body from infections. As because the therapeutic index of bee venom is median lethal dose i.e. adult person having weight 60 kg has a 50% chance of surviving injections totalling 168mg of bee venom. 560 stings could be lethal for such a person assuming 0.3mg venom per stings. Most human deaths result from bee stings due to allergic reactions, heart failure or suffocation from swelling around the neck or the mouth. So, apitherapy is very safe for human treatment.**

Keywords: **Apitherapy, bee venom, entomology, chemical composition, physical properties, medical use.**

1. INTRODUCTION

Though the exact location of apitherapy is not been traced but honey is used in various traditional medicines such as traditional Chinese medicine, Ayurveda medicine etc. According to the Ayurveda classic Ashtanga hridaya , written about 500 AD honey can be used against many diseases, e.g. healing and cleaning the wounds, against different internal and external infections. These are mostly attributed to nutritional benefits of consumption of bee products and not use of bee venom. The modern use of bee venom in apitherapy was initiated by Phillip Terc in his published results "report about a peculiar connection between the bee stings and rheumatism" in 1888. Over past 60 years, the most popularity can be drawn to Charles Mraz from Vermont, United States. He is called the "king of bee venom therapy". He practising with various arthritics but he got success in multiple sclerosis. He is one of the students of Dr. Bodog Beck; he started treating people in New York City in 1920. The insects in the order Hymenoptera can stings such as bee, ants, and wasps. During sting they inject venom. But only female can stings not male. Sting, the egg-laying apparatus is present at or near at abdomen not at head. Bee venom is the one of the pharmacological active component of the hive, which is synthesized in venom gland and stored in reservoir of workers and queen inject during stinging. The production increases at first two weeks for workers and maximum at the time when workers involved in hive defence and foraging. A mature defender contains 100-150 ug venom and injects 0.15-0.30 mg of venom via its stinger and queen contains highest quantity about 700ug.

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2. PROPERTIES

- Honey bee venom is transparent liquid, bitter taste, pH5.0-5.5, density 1.1313gm/cm3, soluble in water insoluble in alcohol ammonium sulphate, cause inflammation when comes in contact with mucous membrane .
- Honey is a semi fluid made from nectar.
- Royal jelly is 1:1 mixture of the gland secretion of workers and honey.
- Apilarnil contains the specific food content of larvae cell.
- Propolis is a resin like substance which is used to coat the inside of hive and honey comb cell, mixture of plant substance and glandular cell secretion.

3. COMPOSITION

➢ **Composition of bee venom:** - Bee venom is a complex mixture of protein, peptides and lower molecular compound.

TABLE 1

Substances group	Components
Proteins(enzymes)	PhospholipaseA2 Phospholipase B Hyaluronidase Phosphatase alpha- Glucosidase
Peptides	Melittin Apamine MCD peptide Secapine Pamine Minimine Adolapine Procamine A,B Protease inhibitor Tertiapine Cardiopep Melittin F
Phospholipids	
Biogenic amines	Histamine Dopamine Noradrenalin
Amino acids	Aminobutyric acid
Sugars	Glucose, fructose
Volatiles	Complex ethers
Minerals	P, Ca, Mg

Enzymes are higher molecular weight than polypeptides, polypeptides are made of two or more amino acids. Mellitin has molecular weight 2840 daltons it can reach 12500 dalton, they may form tetramer.

The protein and melittin electrophoretic patterns are typical in honey bee species. Bee venom contains smaller quantities of low molecular compounds are different in nature; amino acids, catecholamine, sugars and minerals but if bee venom is collected with a collected with a collector preventing the contamination by pollen and nectar, it does not contain carbohydrates. Low molecular weight peptides that are highly basic and have electric points ranging from pH 9-12. Apamine, a mild neurotoxin, increases cortisol production in the adrenal gland. Adolapin acts as an anti-inflammatory and

analgesic because it blocks cyclooxygenase. Phospholipase A2 degrades phospholipids of cellular membranes. It also decreased blood pressure and inhibits blood coagulation. It activates arachidonic which is metabolized in the cyclooxygenase cycle to form orostaglandins which regulate body's inflammatory response. Hyaluronidase dilates the capillaries causing the spread of inflammation. Histamine is responsible for allergic response. Dopamine and noradrenaline increase pulse rate. Protease –inhibitors comprise 2% and act as anti inflammatory agents and stop bleeding.

- **COMPOSITION OF HONEY:**

Honey composition includes sugars (sucrose, fructose, glucose, maltose, etc.), minerals (Fe, Ca, Mg, etc.), organic acids (acetic, butyric, gluconic, citric, formic, lactic, maleic, malic, oxalic, pyroglutamic, succinic, glycolic, 2,3 phosphoglyceric, alpha ceto-glutaric, piruvic and tartric), vitamins (B1, B2, B3, B5, B6, B9, B12, C, provitamin A, D, E, and K), pigments, aromatic substances, antibiotics (inhibine), antigerminative factors, enzymes(distase, invertase, sucrase, catalase, alpha and beta amylase, peroxydase, superoxide dismutase, superoxide oxydoreductase, alpha and beta glucosidase, tyrosinase), hormones, amino-acids (lysine, hystidine, treonine, arginine, valine, serine, methionine,glutamic acid, phenylalanine, tryptophane, prolyne, glycine, tyrosine and norleucine),fatty acids (palmitic, stearic, linoleic, oleic, lauric, miristoleic and linolenic), flavonoids and phenolic compounds (chrysin, kaempferol, quercetin, pinobanksin, naringenin, pinocembrin, luteolin, apigenin, genistenin,herperetin, p-coumaric acid, syringic acid, caffeic acid and vanillic acid.

- **COMPOSITION OF ROYEL JELLY:**

The chemical composition of royel jelly includes: proteins, glucides, gammaglobulin, gelatine, 10- hydroxi-2-decenoic acid with anti-tumoral properties, 9-hydroxidecenoic acid, formic,tartaric, citric, acetic, butyric acid, hydrosoluble and liposoluble vitamins and minerals.

- **COMPOSITION OF APILARNIL:**

Apliarnil contains proteins (9 -12%), glucides, lipids, hydrosoluble and liposoluble vitamins, minerals, enzymes, hormones and antiviral substances.

- **COMPOSITION OF PROPOLIS:**

Propolis contains resin and balms, volatile oils, aliphatic acid sterols, vitamins, minerals, amino acid, enzymes and flavonoids.

- **COMPOSITION OF POLLEN:**

Pollen contains enzymes, hormones, growth factors, reducing sugars (polein, fructose), non- reduceing sugars, azotate compounds (xantine, hypoxantine, geranine, trimethylamine), lipids, organic acids (citric, tartaric, malic, malonic, succinic, acetic, fumaric and alpha ceto-glutamic), proteins, essential amino-acids, liposoluble vitamins(A, D, E and K),B vitamins complex, C vitamin, minerals (calcium iron, magnesium and zinc), ribose, dezoxyribose, pectine, pigments (rutine, which increases the resistance of the capillaries), inositol, enzymes (amylase, invertase, protease lipase, phosphatase, catalase and lactase).

4. PHARMACOLOGICAL EFFECT

- Pollen stimulates cellular regeneration, haematopoiesis and has antioxidant, antianeamic and anti leukemic effects.
- Apliarnil has anti-anaemic, antileucemic,bio stimulant, immunomodulating, energizing properties and stimulates cell regeneration.
- Royel jelly stimulates cellular regeneration, the enzyme system and haematopoiesis; it also has antioxidant, immunomodulating, hepatoprotective, remineralizing, anti-anaemic, anti-leucemic and anti-tumoral properties.
- Honey can help dispel pathogenic heat, clear away toxins, relieve pain and combat dehydration according to traditional Chinese medicine and eating honey regularly resulted clear sight and rosy cheeks and help to prevent constipation and chronic coughing. According to Ayurveda honey mainly used for the treatment of eye diseases, cough, thirst ,phlegm,

hiccups, blood in vomit, leprosy, diabetes, obesity, worm infestation, vomiting, asthma, diarrhoea and healing wounds. It also used as a natural preservative and sweetener in many Ayurveda preparations. It also used as a vehicle along with some medicines to improve its efficacy or to mitigate the side effect of other medicines it is mixed with. Fresh honey helps to increase body mass while old honey produces constipation and decreases body mass. According to Ayurveda, there are eight different types of honey:

1. Makshikam: used in the treatment of eye diseases, hepatitis, piles, asthma, cough and tuberculosis.
2. Bhraamaram: used in the treatment when blood is vomited.
3. Kshoudram: used in the treatment of diabetes.
4. Pauthikam: used in the treatment of diabetes and urinary infections.
5. Chathram: used in the treatment of worm infestation.
6. Aardhyam: effective for eye disease, cough and anaemia.
7. Ouddalakam: used in leprosy and poisoning cases.
8. Daalam: It increases digestion and helps in the treatment of cough.

HONEY USED IN CANCER:-Honey consist several biologically active compounds which are exerts anti-inflammatory, antioxidant, anti proliferic, anti tumour, metastatic and anti cancer effect.

- **BREAST CANCER-**The circulating levels of estrogens and dysregulated estrogen signalling pathways play a predominant role in the development and progression of breast cancer. As a result, breast cancer therapy often targets the estrogen receptor (ER)-signalling pathway. The honey samples exhibited a biphasic activity in MCF-7 cells, the breast cancer cells, depending on the concentration—an antiestrogenic effect at low concentrations and an estrogenic effect at high concentrations. In the presence of estradiol, thyme and pine honey extracts were found to antagonize estrogen activity, while fir honey extract enhanced estrogen activity in MCF-7 cells. These dual effects of honey extracts are mostly likely due to their high contents of phenolic compounds such as kaempferol and quercetin. Phytoestrogens are phytochemicals which are structurally similar to mammalian estrogens and therefore can bind to estrogen receptors. Tualang honey was shown to induce apoptosis and reduce mitochondrial membrane potential by increased leakage of lactate dehydrogenase (LDH) from the cell membranes.

- **LIVER CANCER-**Hepatocellular carcinoma (HCC) is the most predominant liver cancer. The increased incidence of HCC is linked to various factors, mainly infection with hepatitis B or hepatitis C virus, as well as diabetes, obesity, hereditary and social risk factors such as excessive consumption of alcohol. Treatment of human hepatocellular carcinoma (HepG2) cells with honey markedly reduced the number of viable HepG2 cells and nitric oxide (NO) levels, while it enhanced the total antioxidant status (TAS). Based on these findings, it can be speculated that the viability or survival of HepG2 cells is sustained by reactive oxygen species (ROS). Moderate levels of ROS enhance cell proliferation, growth and differentiation. The reduced levels of NO following honey treatment lend credence to this view. By scavenging ROS, honey will invariably enhance TAS as shown in this study. Hence, decreased ROS and improved antioxidant defenses will consequently lead to inhibition of proliferation as evidenced by the reduced number of viable HepG2 cells. A recent study investigated the effect of honey on the development and progression of diethylnitrosamine (DEN)-induced hepatic cancer in rats. After treatment for six months, the liver of untreated DEN-injected rats showed a variety of lesions including inflammatory lymphocytic infiltration, fatty degeneration with displacement of the nucleus, oedema and injured hepatocytes with hyperchromatic nuclei. The liver of DEN-injected rats also showed the presence of neoplastic hepatic cells which were polyhedral to round with dense vesicular nuclei. Several strongnpositive stained nuclei for p53 and PCNA expressions were also observed in the liver of untreated DEN-injected rats. These abnormalities including neoplastic hepatic cells, stained nuclei for p53 and PCNA expressions were considerably reduced in the liver of honey-treated DEN-induced rats. These findings suggest that honey has an anticancer effect on liver cancer cells and exerts a protective effect against chemical-induced hepatocarcinogenesis in rats.

- **PROSTATE CANCER-**Honey reduced considerably the viability of PC-3 cells (Prostate cancer cells). Honey has been shown to induce apoptosis and inhibit proliferation of PC-3 cells. These findings suggest that honey exerts

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antiproliferative effect on prostate cancer cells. The data also reveal that not all honey samples exhibit antiproliferative effect. This seems to support previous findings that the effect of honey on cell proliferation is dependent on the concentration of honey as well as the cancer cell line.

MECHANISM OF ACTION OF HONEY IN CANCER:-

1. Inhibition of cell cycle- cell cyclecomprises four sequential phases—G1, S, G2 and M. DNA replication takes place at the S phase while the cell divides into two identical daughter cells at the M phase. The regulation of the cell cycle events is under the control of a cascade of protein kinases and checkpoints. In cancer cells, the cell cycle becomes dysregulated and this results in uncontrolled cell proliferation. Using various cancer cell lines, honey has been documented to induce cell cycle inhibition. Honey treatment of bladder cancer cell lines was shown to cause a considerable arrest of cell cycle in the sub-G1 phase.

2. Activation of mitochondrial pathways- The mitochondrial pathway involves a series of interactions between several stimuli including nutrients, physical stresses, oxidative stress and damage, during which several proteins (such as cytochrome c) usually located in the intermembrane mitochondria space (IMS) become released resulting in cell death. Honey rich in flavonoids that are capable of activating mitochondrial pathway and release of proteins such as cytochrome C are considered potential cytotoxic agents.

3. Induction of apoptosis- Apoptosis helps to regulate cell growth and eliminate damaged cells. The apoptotic pathway involves MOMP which leads to the release of IMS pro-apoptotic proteins such as cytochrome c which in turn activate caspase cascade resulting in mitochondrial dysfunction and cell death. Treatment of cancer cells with honey was shown to cause apoptotic cell death in breast cancer cells via induction of caspase-3/7 and -9 activation. Honey was also recently reported to enhance tamoxifen-induced apoptosis by activating caspase-3/7, -8 and -9. The effect of honey has also been demonstrated on several enzymes, genes and transcription factors related to apoptosis. Colorectal cancer cell lines HCT-15 and HT-29 treated with honey showed down-regulation of poly(ADP-ribose) polymerase (PARP) expression. The PARP is an enzyme that plays a vital role in apoptosis and DNA repair. The inhibition of PARP activity by honey will prevent DNA repair and thereby contribute to increased cytotoxicity of honey in cancer cells.

4. Modulation of oxidative stress- The role of reactive oxygen species (ROS) and oxidative stress in cancer growth and inhibition is controversial. Low levels of ROS enhance proliferation of cells. On the other hand, increased levels of ROS which cause oxidative damage are well documented in many forms of cancer such as colorectal cancer, breast cancer, lung cancer and gastric cancer. Therefore, the maintenance of redox homeostasis is important for normal cell growth and proliferation. Considering that ROS are double-edged sword, available evidence also suggests that selective exposure of cancer cells to increased levels of ROS and/or lipid per oxidation products may result in cancer cell death. Honey is a potent antioxidant and free radical scavengers. If survival of cancer cells is dependent on low level of ROS and oxidative stress, honey may act as a pro-oxidant to generate more ROS and increase oxidative stress. On the other hand, if cancer growth is sustained or enhanced by elevated levels of ROS and oxidative stress, honey acts as an antioxidant by scavenging ROS and reducing oxidative stress. In both cases, pro-oxidant and antioxidant effects of honey invariably result in cancer cell death. These dual effects of honey in cancer cells are mostly likely due to its phenolic constituents.

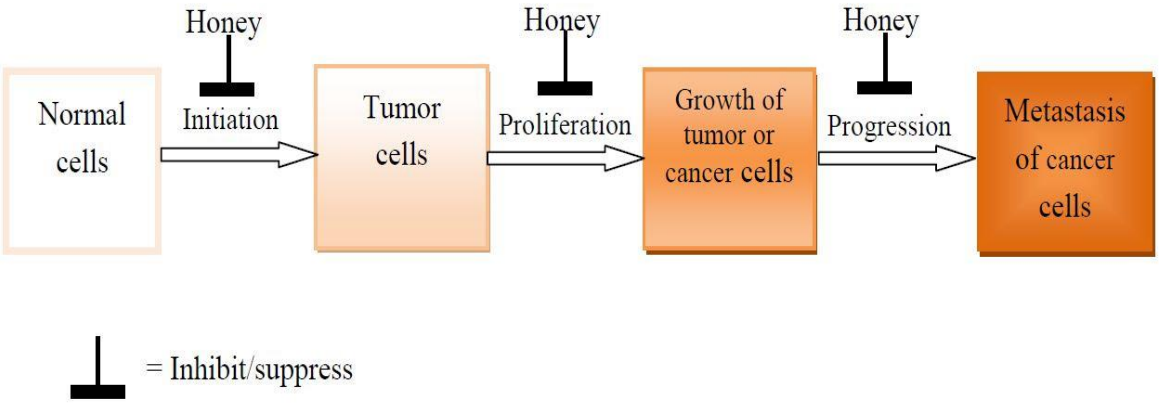

Figure 1: Honey blockage of the 3 stages of carcinogenesis.

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➢ **BENEFICIAL EFFECT OF BEE VENOM ON ANIMAL:-**

TABLE 2

OVERALL EFFECT	SPECIFIC EFFECT
Anti-inflammatory and arthritis	Glucocorticoid and aspirin effect
Anti-cancer effects	Antitumor effects on overy hepatoma, prostate, bladder,melanoma and renal cancers cells by different mechanism of action depending on the tumor type.
Affects the central and peripheral nervous system(CNS,PNS)	• Stimulates many peripheral chemoreceptor affecting flow to the CNS • Has cholinergic action • Blocks transmission of the vegetative synapse and the poly synaptic neuronal paths • Pain soothing aspirin like action. • Management of chronic and inflammation pain • Influence of brain EEG and behaviour patterns • Increase brain circulation • Anti-MS effect in rat models • Against oxaliplation – induced neuropathy
Heart and blood system	• Increases coronary and peripheral blood circulation improves the blood microcirculation • Slows down heart at lower doses and stimulates it at higher ones, lowers blood pressure, anti-arrhythmic • Against blood coagulation fibrinolytic stimulates the bulding of erythrocytes.
Action on immune system	Immunosuppressive and immune activating
Protection from radiation	Improves regeneration of leucoytes and erythrocytes
Antibiotic fungicide and anti-viral action	Bactericide action against different pathogens action against Candida albicans and inactivation of Herps Leukaemia and HIV viruses.
Antihyperthermic	Activates specific body system to overcome hyperthermia
Gall bladder intestive system	Increases fall flow and cholesterine and bilurubin concentration
Endicrinological system	Increases secretion of thyroid , hypophysis and of the hypothalamus hormones
Metabolic effects liver protecting	Increases protein and nucleotide metabolism potent suppressive effect on antiapoptotic responses of TNF-alpha/act-D treated hepatocytes
Growth increasing	Increase of growth of chicken broilers
Reno protecting	As tested in artificially induced nephrotoxicity in mice
Immunoprophylactic	BV spray reduces antibiotic use in broilers
Wound healing	Promotes skin cell regeneration
Against polycystic ovarian syndrome	Decreases the C-reactive protein
Antidiabetic	Lowers blood glucose and increases insulin secretion
Against skin itching	Inhibits the mast cell degradation and proinfammation cytokine expression

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5. MEDICAL APPLICATION OF BEE VENOM

DISEASE TYPE	APPLICATION
Arthristis	Both osteoarthritis and rheumatoid arthristis Rheumatic
Against frozen shoulder	BV acupuncture
Disease of the central and peripheral nervous system(CNS, PNS)	○ Multiple sclerosis ○ Dementia ○ Post-stroke paralysis ○ Polyneuritis ○ Ganglion nerve inflammation ○ Cerebella ataxy (muscular disfunction) ○ Syringomyelia(pain of extremeties, headache) ○ Inflammation of facial nerve ○ Myopathy ○ Trigeminal neuralgia ○ Posttraumatic inflammation ○ Inflammation of arachnoid CNS membrane ○ Parkinson ○ Against lower back pain
Heart and blood system	○ Hypertension ○ Arteriosclerosis ○ Endarteritis(chronic inflammation of the inner layer) ○ Angina pectoris ○ Arrhythmia
Skin disease	○ Eczema, dermatitis, psoriasis ○ Furunculosis(recurring boil) ○ Healing of cicatrices ○ Baldness
Other disease	○ Ophthalmology ○ Gastroenterology:colitis,ulcers ○ Pulmonology:asthma,bronchitis ○ Otorinolaringology: pharingytis, tonsillitis,ear nerve neuritis ○ Endocrinology: urology, gynaecology ○ Cancer

➢ **USE IN ARTHRITIS:-**

There are various types of arthritis such as rheumatoid arthritis, psoriatic arthritis, septic arthritis, juvenile idiopathic arthritis, osteoarthritis etc. Arthritis is very old human disease and that Homo sapiens has probably found relief after bee stings, bee stings, bee stinging is probably the first apitherapy received by human. Among those types of arthritis rheumatoid arthritis and osteoarthritis is most epidemic. Rheumatoid arthritis is a complex autoimmune and progressive inflammatory disease that involves the joints and its progression leads to their destruction. About 1% of the world's population is afflicted by rheumatoid arthritis. Women are 3 times susceptible than men and can start at any age, although the mean age at the onset is 40 to 60 years. Like other autoimmune disease rheumatoid arthritis also cause of variable combination of genetic susceptibility, environmental factors and the inappropriate activation of the immune response that eventually result in clinical signs of arthritis. Rheumatoid arthritis is a systemic disease characterized by progressive, erosive and chronic, polyarthritis. Cellular proliferation of the synoviocytes and neoangiogenesis leads to formation of pannus which destroys the articular cartilage and bone. Increased oxidative stress and/or defective antioxidant contribute to the pathology of RA (Rheumatoid Arthritis). The study showed raised levels of malondialdehyde and low levels of endogenous antioxidant in the patients of RA. Another study showed that an impaired glutathione reductase activity in synovial fluid in RA patient.

The mechanism of action of BV in treating arthritis is clarified:

- BV blocks the building of the pro inflammarory substances *c*ytokinine, PGE-2, NO, Tumor Necrosis Factor TNF-2 and Enzyme COX-2
- BV inhibits the proliferation of rheumatoid synovial cells.

Osteoarthritis (OA) is the disease process by which joints wear out. As the joint surface wears away it sheds wear particles which stimulate the joint lining to produce fluid, causing the knee to swell. When the articular cartilage wears through, the underlying bone becomes exposed. The exposed bone rubs against exposed bone when walking and this causes pain - often described as a toothache type pain. It is a common disease in adults with a prevalence of about 0.5 %.

Different BV treatments have been used: bee stings (BS), api puncture (AP), injections, electrophoresis and phonophoresis (application with ultrasound waves), the success rates are generally good, lying generally between 60 and 90 %. BV was used in the treatment of different pain conditions: Neck pain, low back pain, herniated lumbar pain, disc pain, shoulder pain after stroke, acute ankle sprain, wrist sprain, rheumatoid arthritis and knee osteoarthritis. BS and AP therapy was useful in all these conditions. AP relieves pain more effectively than acupuncture. Herbal acupuncture is a new method of acupuncture where a distilled herbal decoction is extracted and purified to be administered on acupoints for stimulation. Bee venom acupuncture i.e. apipuncture is one of the kind of herbal acupuncture but having advantages of diluted bee venom instead of distilled herbal decoction.

- **USE IN NERVOUS SYSTEM:-**

BV used in Multiple sclerosis (MS), Alzheimer, Parkinson. The changes of release and uptake of glutamate, excitatory neurotransmitter of CNS, due to alteration in the activity of glutamate transporters cause many neuro degenerative disease. BV significantly inhibited the cellular toxicity of glutamate in neuronal cells and microglial cells.

- **MULTIPLE SCLEROSIS:-**

Multiple sclerosis (MS) ,also known as disseminated sclerosus or encephalomyelitis disseminate, is a chronic inflammatory disease of the central nervous system that leads to substantial disability through deficits of sensation and of motor, autonomic, and neuro-cognitive function. It is a demyelinating disease in which the insulting covers of nerve cells in the brain and spinal cord are damaged. Bee venom (BV) has been used in the practice of oriental medicine and evidence from the literature indicates that BV plays an anti-inflammatory or anti-nociceptive role against inflammatory reactions associated with arthritis and other inflammatory diseases. BV treatment increased the population of CD4 (+) CD25 (+) Foxp3 (+) T cells and inhibited CD4(+) T-cell proliferation in vitro. In vivo, BV treatment increased the population of CD4(+)CD25(+)Foxp3(+) T cells. Furthermore, BV administration reduced the severity of experimental autoimmune enphalomyelitis(EAE) while concurrently decreasing INF-gamma producing CD4(+) T cells, IL-17A producing CD4(+) T cells and inflammatory cytokine production including INF-gamma, IL-17A, TNF and IL-6. BV treated animals exhibited less infiltration and preserved morphology compared to saline-treated animals. Interestingly, the therapeutic effects of BV on EAE disappeared when CD4 (+) CD25 (+) Foxp3 (+) T cells were depleted by using anti-CD25 antibody. Our research suggests that BV could be a potential therapeutic agent for anti-inflammatory effects in an animal model of EAE.

- **PARKINSON'S DISEASE:-**

Parkinson's disease is a progressive disorder of the nervous system that affects movement. It causes stiffness or slowing of movement. The BV-peptide Apamin has a neuro protective effect and can affect positively Parkinson. The blood supply and the supply of dopamine in the brain is improved by the BV, it increases the brain blood vessels and reduces blood coagulation. A neuroprotective effects of bee venom phospholipase 2 is postulated by suppression of neuroinflammatory responses in mouse model of Parkinson's disease. The Michael Fox Parkinson Foundation supports clinical research on the use of BG against Parkinson at the Pitie-Salpetriere hospital in Paris. On the basis of the clinical research an patient for the application using the injection of Apamin against Parkinson was submitted in January 2011 (Patent application number: 20110009330 from 01/13/2011).

- **ALZIEMAR:-**

Alzheimer is a type of dementia that causes problems with memory,thinking and behaviour. The brain have nerve cells which are join with each others to form communication networks. Scientist believe Alzhemier's disease prevents parts of a cell's factory from running well.they are not sure where the trouble starts but like a real factory, backup and breakdowns in one system cause problems in other areas.as damage spreads, cells lose their ability to do their jobs and eventually die, causing irreversible changes in the brain. Several behavioral and electrophysiological studies indicate that small conductance calcium-activated potassium channels-blockade by apamin may enhance neuron excitability, synaptic

plasticity, and long-term potentiation in the CA1 hippocampal region, and, for that reason, apamin has been proposed as a therapeutic agent in Alzheimer's disease treatment. A method for early diagnosis of Alzheimer with the help of apamin has been patented (US Patent documents 5580748; 5705401; 5778893 from 1999).

- **CANCER:-**

Melittin present in BV, a powerful anticancer peptide might be the better choice than whole BV. On the other hand bee venom acupuncture and melittin were used to control neuropathy caused by cancer chemotherapy. The cell cytotoxic effects through the activation of PLA2 by melittin have been suggested to be the critical mechanism for the anticancer activity of BV. The induction of apoptic cell death through several cancer cell death mechanisms, including the activation of caspase and matrix metalloproteinase, is important for the melittin induced anticancer effects. In prostate cancer and breast cancer the conjugation of cell lytic peptide with hormone receptors and gene therapy carrying melittin can be useful.

- **HIV:-**

Although melittin destroys the infectivity of HIV particles, the utility of this toxin is limited by its nonspecific cytotoxic effects: melittin kills cells by disrupting membrane structure and function. If administered directly to humans, melittin would kill any cell it encounters, causing widespread tissue damage. Therefore, researchers developped a method to deliver melittin by nano-particles so that it comes into contact with HIV particles but not human cells That because hood added protective bumpers to the nano particle surface. When the nano particles come into contact with normal cells, which are much larger in size, the particles are simply off. HIV is even smaller than the nanoparticle, so HIV fits between the bumpersand makes contact with the surface of the nano particles, where bee toxin awaits.

- **SKIN AND EYE DISEASE:-**

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, furunculosis (recurring boil), 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. 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.

6. ALLERGIC REACTION OF BEE VENOM

Allergy is a general term that describes a Varity 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" . 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 circumstances, death. 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.

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. 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 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. 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. Normal and allergic reaction to stings can vary enormously from individual to individual. Normal reactions are those that virtually everybody 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, they rarely progress to systemic reaction. Moreover, the frequency of individual who experience large local reaction later having systemic reactions is no greater than that of people not experiences large local.

NORMAL AND ALLERGIC REACTION TO INSECT STINGS:-

TABLE 5

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 days after sting	Itching Residual readiness A small brown or red damage spot at the puncture site Swelling at the sting site
Large local reaction	Massive swelling (angioedema)around the sting site Extending over an area of 10 cm or more and frequently increasing in size 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 ,allergic rhinitis or conjunctivitis
Non life-threatening systemic allergic reaction	Minor respiratory symptoms, Abdominal cramps severe gastrointestinal up set weakness, fear or felling shock.
life-threatening systemic allergic reaction	Unconsciousness Hypotension or fainting Respiratory distress (difficulty in breathing) Laryngeal blockage (massive swelling in the throat)

Bee stings are especially dangerous for allergic people. According to different studies 1 to 5 % of the people worldwide are allergic to bees or other insects like wasps and hornets but a 2012 review on the subject states that the numbers are higher, upto 25 % of the population, while aphylalaxys is about 3.5 %. In Switzerland, one person dies every year after a sting of a bee or a wasp. Beekeepers are specially exposed to bee stings. The development of a bee venom allergy is less probable if they are stung more often.

7. APPLICATION OF BEE VENOM

The therapeutic dose of BV is much lower than the toxic one. Apitherapy with BV should be applied by medical doctors, because of the dangers connected with this treatment. For apitherapy purposes different applications forms have been used:

- Puncture with whole bees: in non specific or in specific points and zones
- The Iorish technique: stings are applied to the outer surface of shoulders and thighs. Number of bees is gradually increased to 10 bees to the 10th day, and then takes a break of 3-4 days. After the break the number of bees is decreased from 10 to 1 during 10 days.
- The Kuzmina technique: The numbers of bees is gradually increased to 10 bees to the 10th day, and then take a break of 3-4 days. Then the number of bees is increased by 3 in every session (3, 6, 9,12, 15….. 30)
- Micro puncture with the BV stinger
- Injections with pure, sterile BV
- Apipuncture (api toxinreflexotherapy)
- BV ointments, creams, pills, drops
- Apis homeopathic preparations
- Electrophoresis, phonophoresistreatment.

Two of the principal and biologically active BV components melittin and apamin are commercially available and can be used for therapy instead of the whole BV. Melittin can be combined to a low molecular polysaccharide fucoidan for a reduced toxicity. Dose for adults are generally between 0.1-3 mg BV per treatments, the dose depending on the disease, higher doses (until 2-2.5 per treatment) being used in arthritis treatments. In one sting the maximum of about 50 to 100 mg per are applied, in micro puncture much less BV is applied, depending on the stinging time about 1 to10 mg can be applied. The lethal dose is about 2.8 mg/kg or 19 stings per kg, for a man of 75 kg meaning about 1400 stings.

8. CONCLUSION

Apitherapy is the use of honey bee products for medical purposes, this include bee venom, raw honey, royal jelly, pollen, propolis, and beeswax. Whereas bee venom therapy is the use of live bee stings (or inject able venom) to treat various diseases such as arthritis, rheumatoid arthritis, multiple sclerosis (MS), lupus, sciatica, low back pain, and tennis elbow to name a few. In documents dating back to 4000 years we can find reference to the use of honey. In Egypt honey used to embalm their death. Even Hippocrates, the great Greek physician renowned as “father of medicine”, used bee venom for treating joint pain and arthritis. A roman scholar Pliny had written about healing properties of propolis in his book, claiming, that it reduce swelling, soothes pain, and heals sores .Studies conducted in 1919 confirmed that honey had antibiotic properties. Venom from other Apis species is similar, but even the venoms from the various races within each species are slightly different from each other. The toxicity of *Apis cerana* venom has been reported to be twice as high as that of *A. mellifera*. BV consists of a variety of different peptides including melittin, apamin, adolapin, and mast cell degenerating peptides (MCD). Although adolapin (1mg/kg) and purified MCD peptides (1mg/kg) have inflammatory activity, these substances are present in very low concentration (1-2%) in whole bee venom. Melittin (50% of dry weight of bee venom) binds to secretary PLA2 and inhibits its enzymatic activity. Because PLA2 is a major inflammatory trigger (i.e. it cause arachidonic acid release) whose activity is enhanced in RA. It is possible that the formation of melittin PLA2 complex by BV injection is able to suppress some of the symptoms associated with the development of arthritis. Honey’s antiproliferative, antitumor, antimetastic and anticancer effects are mediated via diverse mechanisms, including cell cycle arrest, activation of mitochondrial pathway, induction of mitochondrial outer membrane permeabilization, induction of apoptosis, modulation of oxidative stress, amelioration of inflammation, modulation of insulin signaling, and inhibition of angiogenesis in cancer cells. Honey is highly and selectively cytotoxic against tumor or cancer cells while it is non-cytotoxic to normal cells. It can inhibit cancerogenesis by modulating or interfering with the molecular processes or events of initiation, promotion, and progression stages. It, therefore, can be considered a potential and promising anticancer agent which warrants further research—both in experimental and clinical studies.

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