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Apitherapy: A valuable gift from honey bee

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Abstract

Apitherapy is the use of bee products such as honey, pollen, propolis, bee wax, royal jelly and venom to prevent or to treat illness and promote healing. Apitherapy dates back to 460 BC, where Hippocrates utilized bee stings on his patients for the treatment of diseases. Its importance was highlighted with the publication of the First scientific paper by Desjardins, on the successful treatment and curative properties of bee venom for rheumatic disease. Filip Terc, who treated many of his patients with bee venom was considered as the “Father of Apitherapy”. Christopher Kim, patented the first standardized and federal regulated injectable form of honey bee venom known as Apitoxin. Bee products have been used for treatment of varieties of ailments. Honey is used for wound management, pediatric care, gastrointestinal disorder, pharyngitis, cough etc. Pollen that results from agglutination of honey is widely used for burn wounds, allergies and cosmetics. Propolis is used for gastrointestinal disorder and oncological treatment. Royal jelly is used for enhancing reproductive health and treating neurodegenerative disorders. Bee wax is effectively used as coating for slow drug release. Venom is used for treatment of Parkinson’s disease, neuralgia and cancer. “APILARNIL” and Bee hive airare also used for their beneficial effects on humans.

Keywords: Apitherapy, bee products, bee venom therapy, cosmetics, medicines

Introduction

Apitherapy is the science of wellbeing using bee products that come directly from honeybees such as honey, bee bread, bee venom, propolis, and royal jelly. These functional foods used both in conventional and modern medication, are researched extensively recently. These foods decidedly contribute to wellbeing and health.

Many workers defined apitherapy. According to Hellner *et al.* [26] apitherapy is the art and science of treatment and holistic healing through the honeybee and their products for the benefits of mankind and all animal kingdom. Gibbs *et al.* [14] defined it as the use of bee products such as honey, pollen, propolis, bees wax, royal jelly and venom to prevent or to treat illness and promote healing.

This review has been written with an idea to provide information on composition, health benefits and mechanisms of action of major bee products.

History of Apitherapy

460 – 370 BC – Hippocrates utilized bee stings on his patients for the treatment of diseases.

129 – 199 AD – Gelen mentioned the uses of bee venom in his 500 treatises on medicine.

1530 – 1584 – Ivan IV of Russia, who suffered from the gout was cured with bee stings

1600– 1634 – Monfat prescribed bee sting venom for reducing kidney stones and for strengthening urinary tract.

1859 – Dr. Desjardins, a French physician, published the first scientific paper on the curative properties of bee venom on rheumatic disease in journal “*Abellie Medical*”.

1888 – Dr. Phillip Terc, the “Father of Apitherapy” and his birthday 30th March celebrated as “World Apitherapy Day” was the first to apply the bee stings.

1912 – Dr. Rudolph Tertsch, the “Father of Modern Apitherapy” published research studies on the treatment of rheumatic fever with bee venom.

1928 – Dr. Franz Kretsky first invented an injectable form of bee venom.

1932 – Yoannovitch and Chahovitch both treated tumors with bee venom.

1935 – Dr. Bodog F. Beck coined the phrase “Bee Venom Therapy”.

2003 – Dr. Christopher Kim patented the first injectable form of bee venom, Apitoxin in Korea

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Bee Products that are used in Apitherapy

1. Honey

In India, therapeutic use of honey is documented in both *Veda* and *Ayurveda* texts about 4,000 years ago. It has been traditionally used by Egyptians, Greeks, Romans, and Chinese to heal wounds and diseases of the gut. It has also been used as remedy for cough, sore throat and earaches Rao *et al.* [45].

i. Chemical composition of honey

Natural honey is composed of minerals (mg/100g) viz., sodium (1.6 – 17), calcium (3–31), potassium (40 – 3500), magnesium (0.7 – 13), phosphorus (2 – 15), Selenium (0.002 – 0.01), Copper (0.02 – 0.6), Iron (0.03 – 4), Manganese (0.02 – 2), Chromium (0.01 – 0.3), Zinc (0.05 – 2) and Vitamins like Thiamine (B1), Riboflavin (B2), Niacin (B3), Panthothenic acid (B5), Pyridoxine (B6), Folic acid (B9), Ascorbic acid and Amino acids like Phenylalanine, Tyrosin, Lysine, Arginine, Glutamic acid, Histidine and Valine. In addition, honey consist of minor amounts of bioactive compounds, including phenolic acids, flavonoids, α -tocopherol, Ascorbic acid, Carotenoids and certain enzymes such as glucose oxidase and catalase Ferreres *et al.* [19] & Moniruzzaman *et al.* [40].

ii. Antimicrobial properties of honey

Natural honey exhibits bactericidal activity against many organisms including *Salmonella*, *Shigella*, *Escherichia coli*, *Helicobacter pylori* etc.

Enzymatic production of hydrogen peroxide, low pH level and high osmo-molarity are found to be the reasons for antimicrobial property.

Inhibitory impact had been accounted on sixty types of microorganisms ranging from aerobes and anaerobes to gram positive and gram-negative bacteria Al-waili,^[6] Honey can function both as bacteriostatic and bactericidal based on the concentration used Bansal *et al.* [7] & Souza *et al.* [52]. In contrast to most regular anti-biotics, honey may be utilized consistently without the fear of development of resistance since it possesses a variety of anti-bacterial action as detailed below

- Firstly, honey with sufficiently high sugar content draws moisture out of the environment and thus dehydrate bacteria
- Secondly, acidic pH in the range of 3.2 and 4.5 is inhibitive for the microbial growth
- Thirdly, glucose oxidase mediated hydrogen peroxide production, a known anti-bacterial agent (Enzyme glucose oxidase oxidases glucose to gluconic acid and H₂O₂).
- Fourthly, presence of catalase and several other non-peroxide factors such as methyl syringate and methylglyoxal (MGO) (Al – waili, [5].

iii. Wound management

Molan^[39]documented honey as promotor of wound healing and as an antimicrobial agent. It was also shown that honey stimulates healing in wounds that do not respond to antibiotics and also to antibiotic-resistant bacteria such as methicillin-resistant *staphylococcus aureus* (MRSA) Honey also aids in autolytic debridement and accelerates the growth of healthy granulated wound bed Subrahmanyam [53] & Jalil *et al.*[32].

Wound management with honey led to quick healing, tissue regeneration, less inflammation and more comfort during

dressings because of lower degree of tissue adhesion Molan. [38] & Cooper *et al.* [14].

Diabetic Foot ulcer (DFU) coupled with microbial infections increases healing time and consumption honey, a low-cost treatment effectively treats DFU. Apart from that honey is used in effective management of locally infected wounds, charcot foot ulceration that have failed hospital management Basa *et al.* [9].

iv. Pediatric care

Pediatric dermatitis brought about by excessive and continuous use of diapers and psoriasis could be treated successfully with honey blended with beeswax and olive oil Jones *et al.* [33] Honey comprises of different nitric oxide metabolites which decreases the frequency of skin infection in psoriasis (Al – Waili [5].

v. Gastrointestinal disorders

Gastrointestinal Tract (GIT) contains many beneficial microbes called “Probiotics” as like lactic acid bacteria which sustain a healthy GI system. Studies have demonstrated that honey contains high number of prebiotics Abeshu and Geleta [3].

Intake of honey assists Gastroesophageal reflux disease by covering the Esophagus and forestalling the upward progression of gastric juice (Abdellah and Abderrahim^[1].

Peptic ulcer has been cured by strong inhibition of *Helicobacter pylori* Header *et al.* [25]. Glucose oxidase function as fibroblast and epithelial cell activators required for ulcer healing Abeshu and Geleta [3].

Oral Rehydration Solution (ORS) made with honey resulted in faster recovery of infantile gastroenteritis patients. High sugar content in honey helps rebuilding of electrolyte balance and water reabsorption in the gut Abdulrahman⁽²⁾. Inflammatory Bowel Syndrome (IBS) have also been treated successfully with Manuka honey on empty stomach Zhang *et al.* [58].

vi. Oral health

Honey prevents the growth of *Porphyromonas gingivalis*, that causes periodontitis Eick *et al.* [16]. Honey enters into the reddened Stomatitis tissues rapidly and heals it successfully Halim *et al.* [24]. Halitosis remedied by honey consumption due its potent antibacterial action resulting out of methylglyoxal part Shiga *et al.* [49].

vii. Pharyngitis and cough

Pharyngitis induced by *Streptococcus* spp. is treated effectively by Manuka honey. It possesses anti-inflammatory and anti-microbial properties. Gupta and Stangaciu^[23] & Patel and Cichello^[42]. A survey has demonstrated that honey is superior than dextromethorphan and diphenhydramine Shadkam^[48].

viii. Liver and pancreatic diseases

Anti-oxidant and hepato-protective activity of honey was revealed through its usage in the successful treatment of paracetamol – induced liver damage in rats (Wang *et al.* [56]. Another investigation detailed decrease in blood glucose level after treatment with Tualang honey Erejuwa *et al.* [17].

ix. Metabolic and Cardiovascular health

Honey consumption indicated a decrease in metabolic and cardiovascular maladies because of the presence of wide

range phenolic compounds. It displays cardioprotective actions like vasodilation, balancing vascular homeostasis and enhancements in lipid profile Bogdanov *et al.* [11].

Flavonoids in honey diminishes the danger of Coronary Heart Disease and improves coronary vasodilation, diminishes the capacity of platelets to form clots, forestall oxidation of low-density lipoproteins and increases high density lipoproteins and improves endothelial functions (Khalil *et al.* [37].

x. Colorectal cancer

The outcomes of the study on the effect of honey on hydrogen peroxide induced inflammation showed that honey checked cancer cell inflammation. Another study carried out to explore the apoptotic effect of crude honey on colon malignant cell lines affirmed the antiproliferative impact of honey in these cells Germain *et al.* [20]. Flavonoid constituent of honey, quercetin, has appeared to trigger Mitochondrial external layer permeabilization that lead to malignant cell death (Erejuwa *et al.* [17].

Honey shows anticancer properties through anti-oxidant or pro-oxidant mechanism that are specifically reliant on the condition of oxidative stress in the malignant cells Fauzi *et al.* [18]

2. Bee Pollen

Bee pollen which results from agglutination of pollen, honey and bee's salivary substances is an essential ingredient of bee's nutrition both for current needs and future use. An important apitherapeutic item, it exhibits antimicrobial, anti-inflammatory, hepatoprotective, anti-cancer, immunostimulating and radical scavenging actions.

i. Composition of Bee Pollen

It contains 30.8 per cent Carbohydrates, 22.7 per cent proteins including 10.4 per cent essential amino acids, 5.1 per cent lipids, 0.4 per cent fatty acids, 1.6 per cent polyphenolics, 0.7 per cent vitamins and 1.6 per cent minerals. It is also rich in bio-active substances, *viz.*, phytosterols, phospholipids, nucleic acids, coenzymes and phenolic acids (Rzepecka – stojko *et al.* [46].

ii. Health benefits of bee pollen

In the treatment of burn wounds, bee pollen is a potential remedy Heller *et al.* [26]. In the treatment with bee pollen absence of side effect as noticed in silver sulfadiazine was reported Dai *et al.* [15]. It exhibits strong immune modulating, bacteriostatic, bactericidal, and anesthetic properties and quicken epithelialization process Kedzia [34].

Its anti-inflammatory action decreases the healing time and intensity of ailments. The histopathological observations revealed bee pollen's beneficial effect on re-epithelialization and wound closure. Anti-allergic activity of Bee Pollen Phenolic Extracts (BPPE) and the flavonoid myricetin (MYR) was ascertained in a murine model of ovalbumin (OVA) induced allergy in mice.

iii. Bee pollen in cosmetics

Bee pollen effectively enhance protective mechanism against skin ageing, dryness, oxidative damage and melanogenesis.

Carbohydrates of bee pollen such as (Alginates, Carrageenans, Ulvans, Fucoidans, Laminarans agar) are mainly used as thickeners, emulsion stabilizers, protective colloids, gelling, moisturizing and chelating agents. They also prevent skin aging and cutaneous disorders. It is believed that

the extra use of vitamins from bee pollen in cosmetics can better protect and possibly correct damage by neutralizing free radicals.

3. Propolis (Bee Glue)

Propolis is a resinous product collected by bees from various plant sources. It has a long history of being used in medicine. It is reported that propolis possess various biological activities such as anti-cancer, anti-oxidant, anti-inflammatory, anti-biotic, anti-microbial, anti-hepatotoxic and anti-septic Salatino *et al.* [47].

i. Chemical composition of Propolis

Propolis is composed of resin (50%), wax (30%), essential oil (10%), pollen (5%), and other organic compounds (5%) (Gomez- caravaca *et al.* 2006 [22]. Phenolic compounds like esters, flavonoids, phenolic acids, terpenes, beta- steroids, aromatic aldehydes and alcohols are some of the important organic compounds present in propolis. It also contains vitamins and minerals. A few enzymes like succinic dehydrogenase, glucose-6- phosphatase, adenosine triphosphate and acid phosphatase are also present in propolis Lotfy [36]

The following health benefits were reported for propolis

ii. Gastrointestinal disorder

Efficacy of propolis ethanolic extracts on giardiasis was proved in an *in vitro* impact study on the development and adherence of *Giardia duodenalis* trophozoites and through cure rate of 52 and 60 per cent among giardiasis affected children and adults respectively in a clinical trial where conventional medication demonstrated only a 40 per cent cure rate.

iii. Oral health

Mouth wash containing propolis is effective in healing surgical wounds Jain *et al.* [31]. Three per cent Propolis ethanolic extracts in toothpaste gel showed potency against gingivitis caused by dental plaque (Skaba *et al.* [51]. Propolis extracts also helped to cure halitosis.

iv. Oncological Treatment

Potential effectiveness of propolis against human breast cancer through apoptosis was reported. It was also identified that it has selective toxic property Xuan *et al.* [57]. Benguedouar *et al.* [10] reported that galangin, a common flavonoid present in propolis induces apoptosis and inhibit melanoma cells. Further, Turkish propolis showed the selective cytotoxic action on human lung cancer cells by inducing endoplasmic reticulum stress, apoptosis and caspase activity and reduce the mitochondrial membrane potential Shruthi *et al.* [50].

v. Diabetes

Long term propolis consumption in patients with Type 1 DM has the potential to reduce both macrovascular (diabetic neuropathy, retinopathy) and microvascular complications (coronary artery disease, peripheral arterial disease and stroke) and in patients with Type 2 DM decrease fasting glycemia.

4. Royal Jelly

Royal jelly is a white and viscous jelly like substance secreted from hypopharyngeal glands of worker bees. The main compound Royalactin has many pharmacological activities such as anti-bacterial, anti-tumor, anti-allergy, anti-

inflammatory and immunomodulatory effects.

i. Chemical composition of royal jelly

It has water (50 – 60%), proteins (18%), carbohydrates (15%), lipids (3-6%), mineral salts (1.5%) and vitamin B5, B6 and C. It is also composed of immunomodulatory compound *viz.*, 10-hydroxyl-2-decenoic acid (HAD) Sugiyama *et al* [54] and many other bio active compounds such as Fatty acids, adenosine monophosphate, adenosine, acetylcholine, polyphenols and hormones such as testosterone, progesterone, prolactin and estradiol Ramadan and Al-Ghamdi [44].

ii. Reproductive health

Royal jelly has been traditionally used to treat menopause symptoms by rebalancing the hormonal concentration in the blood, decreasing the follicle-stimulating hormones and increasing the estrogen concentration. A study showed that the changes in hormone level resulting from the royal jelly increased the number of ovulated oocytes and their quality in aged rats.

iii. Neurodegenerative and aging disease

Poor mental state and performance, experienced in Alzheimer's disease due to aging are corrected by royal jelly and improves elders' appetite and weight. It also exerts neuroprotective action in those patients. Another study revealed that royal jelly contains longevity promoting factors. It is demonstrated that consuming royal jelly @ 3g/day for six months improves the mental health in humans Kim *et al.* [35].

iv. Wound healing

Royal jelly exhibit protective actions on human skin against ultraviolet B- induced photoaging by promoting collagen production. It is also effective in treating diabetic foot ulcers. It dilates the blood vessels, enhance the blood flow and hasten the healing process. It also helps in preventing infections.

v. Anti – Tumor, Anti – Bacterial and Anti – Inflammatory activities

Studies with leukemia affected experimental mouse has revealed that Royal jelly possesses anti-tumor activity. Further, it also possesses anti-bacterial activity against gram - positive bacteria. It also prevents the cholesterol elevating effect of nicotine and has lowered serum cholesterol in animals and humans as well.

5. Bees Wax

Bees wax is produced from the bee's own body and it is a least allergic product.

i. Slow drug releasing function of bee wax

Bees wax is considered safe for human consumption. It is used as a coating for drugs. Beeswax retards dissolution of the enclosed compounds until they reach the digestive tract. It releases drug over a longer period of time and being an inert substance, it does not interact with the digestive system.

ii. Other benefits of beeswax

Chewing comb without honey, Brood or bee bread is effective against colds. when applied to skin it improves the elasticity and makes it look fresh and smooth. It can be chewed for strengthening the gingival and to increasing saliva and stomach juices.

6. Bee Venom

Bee venom is produced by two glands (acid and alkaline glands) associated with the sting apparatus of worker bees. It is also called as apitoxin. It contains mixture of proteins like melittin, apamin, adolapin, phospholipase A2, hyaluronidase, histamine, dopamine and protease inhibitor.

i. Ways of administering venom

- **Bee sting therapy**, also called Apipuncture is the technique of allowing a live bee to sting for the treatment of skin diseases and arthritis.
- **Bee venom therapy** - Apitoxin or Apitox applied intradermally up to 2ml. It has to be practised only by medical doctors. Patients should always undergo an allergy test. After injecting 1.0 mg of bee venom, the severity of the reaction is monitored. A patient is considered negative to the test if he/she does not develop any reactions within 15-30 mins. Depending on patient's ability to tolerate honeybee venom, dosage schedule varies.

ii. Health benefits of Bee venom

Bee venom acupuncture effectively protected dopaminergic neurons against MPTP (1-methyl-4 phenyl-1,2,3,6-tetrahydropyridine) toxicity in mouse models of Parkinson's Disease and it also protects SH- SY5Y human neuroblastoma cells from MRTP induced apoptotic cell death.

A 51-year-old post herpetic neuralgia patient was stung by three bees and it was reported that pain was relieved one day after the treatment and the relief lasted for one and half months.

Diluted bee venom (DBV) reduced the cold allodynia in sciatic nerve chronic constriction injury (CCI) in rats. Single or repetitive stimulation of DVB could alleviate CCI induced cold allodynia *via* activation of spiral $\alpha 2$ -adrenoceptor.

Anti-arthritis action of bee venom has the following two mechanism *viz.*, immune response alteration *via* antigen competition and anti-inflammatory action *via* corticosteroids Chang and Bliven [13].

Studies showed that bee venom injection into azusanil acupoint has both anti- inflammatory and anti-nociceptive effects on Freund's adjuvant induced arthritis in rats. A study showed that significantly higher proportion of people receiving bee venom through acupuncture were substantially relieved when compared with traditional needle acupuncture therapy.

A study reported that mellitin suppressed the expression of pro-inflammatory cytokines through the nuclear factor (NF- κ B) signaling pathway and prevents TAA-induced liver fibrosis Rajitha *et al.* [43].

Mellitin and phospholipase A2 can be used in the treatment of cancer. The cytotoxic effect through the activation of PLA2, caspase and matrix metalloproteinases by mellitin has been suggested as its anti-cancer mechanism. Studies opined that Mellitin may be a better choice than whole bee venom. Further, bee venom acupuncture and mellitin were used to control neuropathy caused by cancer chemotherapy Tagscherer *et al.* [55]

Venom Immunotherapy is highly effective for reducing allergic sensitivity in people and has been showed to reduce the risk of systematic reactions in people with bee sting allergies by more than 95 per cent.

7. Apilarnil

APILARNIL was first made by Nicolae V. Iliescu^[30] and Word “API-LAR-NIL” comes from (Bees - APIs, LAR - LARvae and NIL –from his name Nicolae ILiescu). It is obtained by taking the whole composition of 7 days old drone larvae comb cells (97% drone larvae and 3% larvae food – royal jelly, pollen, bee bread, honey). It is a homogenous, milky substance with yellowish grey colour and sour taste Barnutiu *et al.*^[8].

APILARNIL consists of water (65 – 75%), proteins (9 – 12%), carbohydrates (6 – 12%), fatty acids and lipids (3.5 – 8%), minerals (potassium, calcium, sodium, magnesium (11.5%), Essential amino acid (Threonine, leucine, Isoleucine, methionine). It is also rich in vitamins (A, B1, B2, B6, choline, beta-carotene) and sex hormones (Testosterone, prolactin, progesterone and Estradiol).

It possesses male sex characteristics strengthening effects Bogdanov *et al.*^[11] APILARNIL increases weight of the seminal glands, epididymis, improves ejaculate volume, germ cell density and mobility of sperms in boars. This research corroborates the idea of its usage as therapy for testosterone deficiency. It is due to the presence of methyl palmitate and methyl oleate. It is also used for the stomach ulcer and congestive liver treatment. Further, removal of drone cells decreases the occurrence of *Varroa jacobsoni* Q.

8. Apilarmel

It is a mixture of 10% apilarnil, 20% pollen and 70% honey. It is used effectively in the treatment of respiratory virosis of children.

9. Bee Hive Air Therapy

Austrian **Heinrich Huttner** developed the technique of using bee hive air for treatment. It is effective against respiratory illness and most effective against immune disorders. A hole drilled in the top of the beehive is fitted with a ventilator and air is blown through to a hose and mask from which the patient breathes^[27-29].

Conclusion

Bee products are rich in bioactive compounds and have biological functions in preventing diseases. However, Venom therapy should not be used for those with severe allergies, tuberculosis etc., Sometimes, even death due to anaphylactic shock in bee acupuncture therapy has been reported. Hence, it is necessary to conduct further studies to determine the critical mechanisms related to the pharmacological activities of these bee products and the appropriate amounts that can be taken in order to obtain promising health benefits.

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