African J. Biol. Sci., 18 (2): 43-57 (2022)
ISSN 1687-4870 **e- ISSN 2314-5501 (online)**
www.ajbs.journals.ekb.eg **E.mail: aasdjournal@yahoo.com**

Apitherapy as an Alternative medicine: Article review

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Received: June 23, 2022; Accepted: July 7, 2022; Available online: July 10, 2022.

ABSTRACT

Honey bees are the "Golden insects" that produce honey and other vital honeybee products. However, the best known primary products of honey bees are honey and bee wax, but pollen, propolis, royal jelly, bee venom, queen bees and their larvae are also marketable primary bee products. Worldwide the usage of such primary products as propolis, royal jelly and bee venom have increased mostly due to inclusion in cosmetics preparation. Medicinal use will increase once better and more detailed studies are completed, which however may not yet be in the very near future. Honey has medicinal uses like antiseptics and wound healing properties, while propolis is used to treat diabetes patients. Additionally, pollen has antioxidant property and anticoagulant and anti-inflammatory properties of bee venom serve to treat arthritis and other inflammatory conditions. Around the world, the most widely used hive products are honey and bees wax serving many functions, ranging from local beverage to different medicinal uses. Thus, this article review will summaries in brief life of honey bee, most important products especially bee venom and its uses as therapeutic agents.

Keywords: Anticoagulant -Apitherapy -Honey bee- Bee venom-Pollen-Arthritis.

1-**Honey Bee Life**

It is known that honey bees are social insects, that means the presence of group of individuals with specific characters, castes and roles live together in a common nest to complete their life cycle. This means that they tend to live in colonies where all the individuals are of the same family, often the offspring of one mother. In the more highly organized societies there is a division of labour in which individuals carry out particular duties (Johnson and Tsutsui, 2011). On the other side, there are solitary insects, male and female insect can complete their life cycle without the need for a specific nest or cooperation with other individuals (Gullan and Cranston, 2010).

1.1 Structure.

The bodies of bees are divided into head, thorax and abdomen, with three pairs of legs and two pairs of wings on the thorax. The fore and hind wings on each side are linked by hooks and grooves so that they move together in flight. The mouth parts consist of a "tongue" or labium, which can be enclosed near the head by the labial palps and maxillae. Nectar, from the nectaries of flowers, can be drawn up the grooved surface of the labium, partly by capillary attraction and partly by the pumping action of muscles in the head. When not in use, these elongated mouth parts are folded back under the head, leaving the shorter, stouter mandibles free in front to chew pollen, manipulate wax, attack intruders etc (Snodgrass and Erickson, 1992). The ovipositor through which the queen lays her eggs in the wax cell, is modified in the workers to form a sting (Winston, 1992).

1.2 Organization of the colony.

The Queen.

A queen bee may live from two to five years and, except for a short period at the end of her life when one of her daughters takes over the colony. She is the only egg-laying female. All members of the colony whether drones or workers are her offspring. She spends all her time lying eggs, perhaps up to 1500 a day, each one being placed in a wax cell made by the workers. The queen can feed herself but in the hive the nearest workers turn towards her, lick her body and feed her by regurgitating a special secretion of their salivary glands, called "royal jelly", on to their proboscis from which the queen can absorb it. The queen usually mates only once in her life (though second and third mating are known to happen) and stores the sperms received from the drone in a sperm sac in her abdomen. This store of sperms lasts her for the two or more years of egg-laying, a small quantity being released with each fertilized egg laid (Katzav-Gozansky *et al.,* 2002). When the store of sperms is used up she may continue to lay eggs but they are all unfertilized and will become drones. By this time one of her daughters has been reared as a queen and is ready to take over the egg-laying.

1.3 Life history.

Each egg is laid in one of the hexagonal wax cells and hatches into a tiny, white, legless larva. The larva feeds on substances deposited in the cell by the workers; it grows, pupates in the cell, hatches as an adult bee and finally emerges from the cell into the hive.

The eggs hatch after three to four days and by nine days are fully grown and ready to pupate. The workers put a capping over the cells at this time. Ten or eleven days later the capping is bitten away and the adult emerges. The times given above vary with changes of temperature and according to whether the bee is becoming a drone, worker or queen.

Drones

The drones, who live for about four to five weeks and do not work inside the hive, are fed by the workers or help themselves from the store of pollen and nectar in the combs. Their function is to fertilize a new queen. In the autumn, or when conditions are poor, they are turned out of the hive where, unable to find food for themselves, they soon die.

Workers

They are female bees whose reproductive organs do not function. Among many other tasks they collect food from outside the hive and store it, make the wax cells and feed the developing larvae.

1.4 Origin of the three types of bee

The wax combs are built hanging vertically with a gap of about half an inch separating each one. The cells in each comb thus lie horizontally. The workers prepare three kinds of cell: worker cells about 5 mm across, drone cells about 6 mm across, and queen cells quite different from the others. The queen cells are larger and made individually, pointing downwards like small acorns from the surface or bottom of the comb. The relative numbers of these three kinds of cell seem to depend on the time of the year, the temperature, the abundance of food and condition of the colony. Normally, the worker cells predominate (Gullan and Cranston, 2010).

Eggs are laid by the queen in the brood area. This is where the temperature is about 32°C, kept so by the heat given out by the bees' bodies. The area varies, diminishing in the winter and expanding in the summer. The queen moves over the brood area, laying eggs indiscriminately in any of the three types of cell she encounters, by placing her abdomen in the cell and depositing a single egg. The eggs placed in the larger, drone cells, are not fertilized, and this results in the eggs developing into a male bee or drone. In the queen and worker cells, fertilized eggs are laid.

For the first three days after hatching, all the larvae are fed on a protein-rich, milky secretion, called royal jelly, which comes from the salivary glands of workers of a certain age. The grubs in queen cells continue to be fed on royal jelly for the rest of their lives, but those in drone or worker cells are "weaned" onto a mixture of dilutenectar and pollen. If a one-to-three-day old larva is transferred from a worker to a queen cell, it will receive the diet of royal jelly and develop into a queen. Thus, though there is no difference between the eggs and young larvae in queen and worker cells, their different treatment by the workers results in their becoming quite distinct types of bee.

Exactly what aspects of their feeding cause this is not known for certain. It may be the absence of pollen from the queen's diet, the cessation of royal jelly in the worker's diet, the super-abundance of food placed in the queen cells or a vitamin-like chemical fed to the queen larvae in the early stages. After three days, worker grubs cannot be reared as queens, even if they are placed in queen cells and fed on royal jelly (Johnson and Tsutsui, 2011). Drones, then, develop from unfertilized eggs in wide cells, queens and workers from fertilized eggs which are fed differently as larvae.

1.5 Life of a queen.

When a new queen emerges she is fed by the workers. She bites a hole in any other occupied queen cells that she finds and some observers believe she stings the occupants. In any event, the workers usually tear down the other queen cells that have been bitten into and destroy the occupants. For a few days the queen leaves the hive for short flights lasting, at first, only a minute but gradually lengthening to about 15 minutes. During these flights she learns the geography of the district around the hive. On one of these flights she is pursued by drones, but not necessarily from her own hive; in fact, they do not follow her from the hive but are already waiting outside. One of them catches the queen and mates with her, depositing in her vagina sperms which eventually find their way into her sperm sac. She now returns to the hive, and soon after begins to lay eggs (Johnson and Tsutsui, 2011).

From glands in her head, the queen produces a mixture of chemicals called pheromones (‘queen substance’). When the workers ‘lick’ her body, the pheromones suppress their fertility. When, at the end of her life, the queen ceases to produce these pheromones, some workers start to lay eggs which, being unfertilised, produce only drones. They do, however, start building new queen cells.

1.6 Food.

The foraging workers collect nectar from the nectaries of flowers. The nectar is drawn off from the nectarines by the long labium. It is pumped up and swallowed into the honey sac, a region of the gut from which it can be regurgitated on reaching the hive. Nectar is a watery sugar solution when collected, but it is processed by the house bees to whom it is passed. These workers repeatedly swallow it, mix it with enzymes and regurgitate it. The enzyme action and the evaporation of water result finally in its conversion to honey. Nectar contains very little protein, and the pollen collected by the foragers makes up this deficiency.

Pollen is collected by combing off with the legs the grains which adhere to the bee's body after it has visited a flower. The pollen collected on the head, and removed by the front legs, is mixed with a little nectar and passed to the back legs which have combed pollen from the abdomen. The rows of bristles on the legs assist this combing action. The pollen press, in the joint between the tibia and tarsus of the hind legs, squeezes the pollen which is passed to it from the pollen comb of the opposite hind leg. The pollen and nectar paste is thus pushed by the press into the pollen basket on the tibia, where it is retained by the fringe of setae. All this may be done while the bee hovers in the air or while hanging from the flower. The forager returns to the hive with the two packs of pollen and pushes them off into an empty cell or into one with some pollen already in it.

The younger house bees then break up the pollen masses and pack them down into the cell. When the cell is full it may be covered with a little nectar and sealed over. Both pollen and honey sealed in the store cells are eaten by the bees in the winter months when no other food is available. Water is collected and used to dilute the nectar with which the larvae are fed, but there is no evidence of water being stored. Propolis is a resinous substance that the bees collect from trees and sticky buds. They use it for sealing small cracks and gaps in the hive.

2-HoneyBeeProducts

2.1 Honey

Honey is a complex solution with three distinct “fractions”; a sugar fraction, water fraction, and a highly variable fraction that contains a range of amino acids, antioxidants, enzymes, flavonoids, phenolic acids, minerals, and vitamins. Both the sugar and water fractions are highly conserved between different honey types (Alvarez-Suarez *et al*., 2014). Honey has been highly prized for its flavor, as well as nutritional and medicinal values by the local communities. In areas deficient in other sugar sources, it is highly sought after for its sweetness and energy-giving properties.

2.2 Bees wax

Natural honey is not the only product associated with this activity. Beeswax, propolis, royal jelly and honey comb are all by products of bee keeping. Beeswax is used in the production of candles and cosmetics. Worker bees of a certain age secrete beeswax from a series of exocrine glands on their abdomens. They use the wax to form the walls and caps of the comb. As with honey, beeswax is gathered by humans for various purposes such as candle making, waterproofing, soap and cosmetics manufacturing, pharmaceuticals, art, furniture polish and more (Serda *et al.,* 2015).

2.3 Bee bread

Bees collect pollen in their pollen baskets and carry it back to the hive. Worker bees combine pollen, honey and glandular secretions and allow it to ferment in the comb to make bee bread. The fermentation process releases additional nutrients from the pollen and can produce antibiotics and fatty acids which inhibit spoilage. Bee bread is eaten by nurse bees (younger workers) which produce the protein-rich royal jelly needed by the queen and developing larvae in their hypopharyngeal glands. In the hive, pollen is used as a protein source necessary during brood-rearing. In certain environments, excess pollen can be collected from the hives of *A. mellifera*.

The product is used as a health supplement. It has been used with moderate success as a source of pollen for hand pollination (Tamrat, 2015)

2.4 Bee brood

Bee brood – the eggs, larvae or pupae of honeybees – is nutritious and seen as a delicacy in countries such as Indonesia, Mexico, Thailand, and many African countries; it has been consumed since ancient times by the Chinese and Egyptians.

2.5 Royal jelly

Royal jelly, a white and viscous jelly-like substance, is a form of hypopharyngeal and mandibular gland secretion from the worker bees. It is also known as a "superfood" that is solely consumed by the queen bee. Royal jelly is also fed to the honeybee larvae upon hatching and helps to nurture the brood. It is the exclusive nutriment offered to the immature young larvae in their first 2-3 days of maturation besides being used as a food specifically for the queen bee throughout her entire life cycle. Royalactin is the main compound in royal jelly that allows the morphological change of a larva into the queen bee. This superfood is the main reason for the longevity of the queen bee compared to the other bees. Royal jelly is widely used as a dietary nutritional complex to help combat various chronic health conditions. Furthermore, it is one of the profitable remedies for human beings in both traditional and modern medicine. Many pharmacological activities such as antibacterial, antitumor, antiallergy, anti-inflammatory, and immunomodulatory effects have also been attributed to it. (Pasupuleti *et al*., 2017).

2.6 Chemical Composition of Honey, Propolis, and Royal Jelly

Honey is also known as a supersaturated sugar solution. Natural honey is composed of 82.4% carbohydrates, 38.5% fructose, 31% glucose, 12.9% other sugars, 17.1% water, 0.5% protein, organic acids, multiminerals, amino acids, vitamins, phenols, and a myriad of other minor compounds. In addition, honey consists of minor amounts of bioactive components, including phenolic acid, flavonoid, and *α* tocopherol (Ferreres *et al.*, 1993). Honey constituents with health benefits include phenolic acids, flavonoids, ascorbic acid, proteins, carotenoids, and certain enzymes, such as glucose oxidase and catalase (Moniruzzaman *et al*., 2012).

Propolis is the third most important component of bee products. It is composed mainly of resin (50%), wax (30%), essential oils (10%), pollen (5%), and other organic compounds (5%) (Gómez-Caravaca *et al*., 2006). Phenolic compounds, esters, flavonoids, terpenes, beta-steroids, aromatic aldehydes, and alcohols are the important organic compounds present in propolis. Twelve different flavonoids, namely, pinocembrin, acacetin, chrysin, rutin, luteolin, kaempferol, apigenin, myricetin, catechin, naringenin, galangin, and quercetin; two phenolic acids, caffeic acid and cinnamic acid; and one stilbene derivative called resveratrol have been detected in propolis extracts by capillary zone electrophoresis. Propolis also contains important vitamins, such as vitamins B1, B2, B6, C, and E and useful minerals such as magnesium (Mg), calcium (Ca), potassium (K), sodium (Na), copper (Cu), zinc (Zn), manganese (Mn), and iron (Fe). A few enzymes, such as succinic dehydrogenase, glucose-6-phosphatase, adenosine triphosphatase, and acid phosphatase, are also present in propolis (Lotfy, 2006).

Royal jelly consists of water (50%–60%), proteins (18%), carbohydrates (15%), lipids (3%–6%), mineral salts (1.5%), and vitamins. Based on modern spectrometric analysis, approximately 185 organic compounds have been detected in royal jelly. Royalactin is the most important protein present in royal jelly. In addition, royal jelly is composed of a significant number of bioactive compounds, including 10hydroxy-2-decenoic acid (HAD), which has some immunomodulatory properties. Fatty acid, proteins, adenosine monophosphate (AMP) N1 oxide, adenosine, acetylcholine, polyphenols, and hormones such as testosterone, progesterone, prolactin, and estradiol are other useful bioactive components reported to be present in royal jelly (Ramadan and Al-Ghamdi, 2012)

2.7 Bioactive Compounds in Honey, Propolis, and Royal Jelly

Honey, propolis, and royal jelly are highly rich in bioactive compounds. Essential and nonessential compounds, such as polyphenols and vitamins occurringnaturally as part of food chains, are considered bioactive. These compounds are naturally present in food and confer useful health benefits. Phenolic compounds are bioactive compounds. Phenols are defined as organic compounds with an aromatic ring that is chemically bonded to one or additional hydrogenated substituents in the presence of corresponding functional derivatives (Marın *et al.*, 2002).

3-Health Benefits of Honey

3.1. Wound Management

Honey has traditionally been used to treat wounds, insect bites, burns, skin disorders, sores, and boils. Scientific documentation of the wound-healing capabilities of honey validates its efficacy as a promoter of wound repair and an antimicrobial agent. Honey promotes the activation of dormant plasminogen in the wound matrix, which results in the dynamic expression of the proteolytic enzyme. Plasmin causes blood clot retraction and fibrin destructions. It is an enzyme that breaks down fibrin clots with attached dead tissues in the wound bed (Esmon, 2004).

Clinical evidence supporting the effectiveness, specificity, and sensitivity of honey in wound care indicates that the performance of conventional and modern wound care dressing is inferior to that using honey. Certain cases have shown that honey stimulates wound-healing properties even in infected wounds that do not respond to antiseptics or antibiotics and wounds that have been infected with antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus*(MRSA) (Natarajan *et al.*, 2001). Honey also aids autolytic debridement and accelerates the growth of healthy granulated wound bed (Subrahmanyam, 1998).

3.2. Pediatric Care

Honey also controls skin damage near stomas, such as ileostomy and colostomy, by enhancing epithelialization of the afflicted skin surface. Honey has a beneficial effect on pediatric dermatitis caused by excessive use of napkins and diapers, eczema, and psoriasis. The effect of honey mixed with beeswax and olive oil was investigated on patients with psoriasis or atopic dermatitis condition. A clinical trial showed that a mixture containing honey was extremely well tolerated and caused significant improvements. Honey consists of various nitric oxide metabolites, which reduce the incidence of skin infection in psoriasis (Aminu *et al.*, 2000).

3.3. Diabetic Foot Ulcer (DFU)

Consumption of honey is a low-cost and effective therapy for the treatment of DFU. DFU is often complicated by microbial infections and slows the healing process. Apart from the infection, symptoms such as pain, swelling, and redness might not be present for diabetic peripheral neuropathy patients due to their reduced immune response, which further complicates the diagnosis. A review indicated that using honey for the treatment of venous ulcers yielded positive outcomes with good acceptance rates from the patients (Dunford and Hanano, 2004).

3.4. Gastrointestinal (GI) Disorder

Natural honey is composed of enzymes that facilitate the absorption of molecules, such as sugars and starch. The sugar molecules in honey are in a form that can be easily absorbed by the body. Honey also provides some nutrients, such as minerals, phytochemicals, and flavonoids that aid digestive processes in the body. Pure honey has bactericidal properties against pathogenic bacteria and enteropathogens, including *Salmonella* spp., *Escherichia coli*, *Shigella* spp., and many other Gram-negative species (Adebolu, 2005).

The gastrointestinal tract (GIT) contains many important beneficial microbes. For example, Bifidobacteria is one of the microorganisms present primarily for the sustenance of a healthy GI system. It has been suggested that consuming foods rich in probiotics can increase the population of Bifidobacteria in the GIT. The biological activities and development of these bacteria are further enhanced in the presence of prebiotics. Studies have shown that natural honey contains high amount of prebiotics. Some in vitro and in vivo experimental trials on honey have reported it as a prominent dietary supplement that hastens the growth of *Lacto bacillus* and Bifidobacteria and catalyzes their probiotic potency in the GIT (Abeshu and Geleta, 2016). Under in vitro conditions, prebiotic ingredients in honey such as inulin, oligofructose, and oligosaccharides promoted the increase in the numbers of *Lactobacillus acidophilus* and *L. plantarum*by 10–100 folds, which was beneficial for the intestinal microbiota (Kajiwara *et al*., 2002).

3.5. Oral Health

Honey is useful for the treatment of many oral diseases, including periodontal disease, stomatitis, and halitosis. In addition, it has also been applied for the prevention of dental plaque, gingivitis, mouth ulcers, and periodontitis. The antibacterial and antiinflammatory properties of honey can stimulate the growth of granulation tissue, leading to the repair of damaged cells. *Porphyromonas gingivalis* is a Gram-negative bacteria that causes periodontitis. Honey exerts antimicrobial activity against these anaerobic bacteria and prevents periodontal disease (Eick *et al*., 2014). Inflammation of mucous membranes in the mouth (stomatitis) may induce redness and swelling of oral tissues and cause distinct and painful ulcers. Honey penetrates into the tissues very quickly and is effective against stomatitis (Song *et al*., 2012). Halitosis is an oral health condition that causes malodorous breath. Most of the odor in the oral cavity is caused by the activity of degrading microbes. A recent study has reported that honey consumption ameliorates halitosis due to its strong antibacterial activity resulting from its methylglyoxal component (Shiga *et al.*, 2010).

3.6. Pharyngitis and Coughs

Pharyngitis, commonly known as sore throat, is an acute infection induced by *Streptococcus* spp. in the oropharynx and nasopharynx . In addition to streptococci, viruses, nonstreptococcal bacteria, fungi, and irritants such as chemical pollutants may also cause sore throat. Manuka honey is effective for treating sore throat with its anti-inflammatory, antiviral, and antifungal properties. Honey coats the inner lining of the throat and destroys the harmful microbes while simultaneously soothing the throat (Gupta and Stangaciu, 2014).

3.7. Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is a mucosal infection caused by contents of abnormal gastric reflux into the esophagus and even the lungs. Symptoms of GERD include heartburn, inflammation, and acid regurgitation. Consumption ofhoney helps this condition by coating the esophagus and stomach lining, thus preventing the upward flow of food and gastric juice. Honey can further stimulate the tissues on the sphincter to assist in their regrowth and finally reduce the chances of acid reflux (Abdellah and Abderrahim, 2013).

3.8. Gastroenteritis

Gastroenteritis known as stomach or gastric flu, causes inflammation of the digestive tract. This condition may be due to foodborne, waterborne, and person-to-person spread of infectious agents. The symptoms of gastroenteritis include dehydration, watery diarrhea, bloating, abdominal cramps, and nausea. There are many infectious agents, such as *Salmonella*, *Shigella*, and *Clostridium*, that can cause this condition. A clinical study by Abdulrahman (2010) has reported the treatment of infantile gastroenteritis using honey. The study found that replacing the glucose in standard electrolyte oral rehydration solution (ORS) with honey reduced the recovery time of patients with gastroenteritis because the high sugar content in honey boosts electrolyte and water reabsorption in the gut (Abdulrhman *et al.*, 2010).

3.9. Constipation and Diarrhea

Chronic constipation is a common and multifarious illness characterized by intolerable defecation (irregular stools and difficult stool passage). Difficult stool passage includes symptoms such as straining, hard to expel stool, a sense of incomplete evacuation, hard or lumpy stools, and prolonged time to pass stool (Piccirillo et al., 1995). Diarrhea is defined as a high frequency of bowel movements with watery stool. Honey has minimized the pathogenesis and duration of viral diarrhea compared to conventional antiviral therapy. In another case, people diagnosed with inflammatory bowel syndrome (IBS) experiencing severe diarrhea or constipation, bloating, and stomach discomfort was successfully treated with raw Manuka honey on an empty stomach (Zhang *et al*., 2014).

3.10. Liver and Pancreatic Diseases

Honey helps to soothe pain, balance liver systems, and neutralize toxins. Complications in the liver system can be attributed to oxidative damage. Honey exhibits antioxidant activities that have a potential protective effect on the damaged liver. A study on paracetamol-induced liver damage rats showed that the antioxidant and hepatoprotective activity of honey minimized liver damage. Honey, which has a1 : 1 ratio of fructose to glucose, may help to promote better blood sugar level, which is useful for those suffering from fatty liver disease since it provides adequate glycogen storage in liver cells. Insufficient glycogen storage in the liver releases stress hormones that impair glucose metabolism over time. Impaired glucose metabolism leads to insulin resistance and is the main factor of fatty liver disease (Erejuwa *et al.,* 2010).

3.11. Cancer and Oncogenesis

Breast Cancer

Imbalance in estrogen signaling pathways and propagating levels of estrogens have important roles in breast cancer growth and propagation. Treatments for breast cancer are associated with targeting the estrogen receptor (ER) signaling pathway. Phytoestrogens are a subclass of phytochemicals with a common structure to the mammalian estrogen that enables them to bind to estrogen receptors. Several experimental studies have investigated the efficiency of honey in modulating the ER signaling pathway (Erejuwa *et al.*, 2014). On the other hand, cytotoxic activities of Tualang honey in human breast cancer cells were demonstrated by elevated secretion of lactate dehydrogenase (LDH) and further illustrated the cytotoxic properties of honey. The study also showed that honey only exerts cytotoxic effects on breast cancer line and not on nonmalignant breast cells. Therefore, this indicates that Tualang honey shows highly specific and selective cytotoxic effects towards breast cancer cell lines and has a good potential as a chemotherapeutic agent (Fauzi *et al*., 2011).

Liver Cancer

The most common type of liver cancer is hepatocellular carcinoma (HCC). The antitumor effects of honey on liver cancer cells have been investigated in various experimental studies. Treatment of HepG2 cells with honey minimized the amount of nitric oxide (NO) levels in the cells and decreased the HepG2 cell number greatly. This increased the overall antioxidant profile of the cells. The survival of HepG2 cells is promoted by reactive oxygen species (ROS), and adequate levels of ROS trigger cell proliferation and differentiation. Decreasing the amount of NO resulting from honey treatment supported this study. Thus, reduced ROS and enhanced antioxidant efficacy inhibit cancerous cell proliferation and lowered the number of HepG2 cells (Abdel Aziz *et al*., 2009).

Colorectal Cancer

Most colorectal cancers begin as a polyp, which generally starts on the inner lining of the colon or rectum and grows towards the center. Some polyps are not dangerous but some will eventually grow into adenomas and can eventually result in cancer. A study [88] that investigated the chemopreventive effects of Gelam and Nenasmonofloral honeys against colon cancer cell lines found that the honey inhibited proliferation of colon cancer cells. Hydrogen peroxide-induced inflammation in the colon cancer cells was used to examine the effect of honey. The results showed that honey curbed inflammation in the cancerous cells (Wen *et al.*, 2012). Another study was done to investigate the apoptotic effects of crude honey on colon cancer cell lines. The study confirmed the antiproliferative effect of honey in these cells. In addition, at high phenolic concentrations (such as those of quercetin and flavonoids), significant antiproliferative action against colon cancer cells was observed (Jaganathan and Mandal, 2009).

4-Therapeutic Effect of Honey Bee

4.1 Venom

Honeybee venom is produced by two gland associated with the sting apparatus of worker and queen bees. Its production increases during the first two weeks of their life and reaches a maximum when they become involved in hive defense and foraging. It diminishes as the bee gets older. The queen bee’s production of venom is highest on emergence, which allows her to be prepared for immediate battles with other queens. When a honey bee stings, it does not normally inject all of the 0.15 to 0.3 mg of venom held in a full venom sac. Only when it stings an animal with skin as tough as ours will it lose its sting and the whole sting apparatus, including the venom sac, muscles and the nerve center. These nerves and muscles keep injecting venom for a while until the venom sac is empty. The loss of such a considerable portion of its body is always fatal to the bees (Schumacher, 1989).

4.1.1 Physical and chemical properties of bee venom

Honeybee venom is a transparent liquid which dries up easily at room temperature. It is characterized by its odourless nature ornamental pungent smell, a bitter taste, hydrolytic blend of proteins with pH 5.0 to 5.5 that is used by bees for defense. Bee venom is soluble in water and insoluble in alcohol and ammonium sulphate. Its contact with air forms grayish-white crystals. Dried venom has a light yellow colour and some commercial preparations are brown, may be due to oxidation of some of the venom proteins. Bee venom contains a number of very volatile compounds which might lost during collection, it is a rich source of enzymes, peptides and biogenic amines. Bee venom contains at least 18 active substances (Feraboli, 1997).

Mellitin is the most prevalent substance which is one of the most potent anti-inflammatory agents known and it is 100 more potent than hydrocortisol. Adolapin is a strong antiinflammatory that inhibits cyclooxygenase. Phospholipase A 2 degrade phospholipids of cellular membranes. It also decrease blood presure and inhibits blood coagulation. Hyaluronidase dilates the capillaries causing the spread of inflammtion. Histamine is responsible for allergic response. Protease inhibitors act as anti-inflammatory agent and stop bleeding. Other biochemicals like Apamin, Compound X, and Mast Cell Degranulating Protein (MCDP) etc work to soften tissues and facilitate the flow of fluids. Also, there are measurable amounts of the neurotransmitters; Dopamine, Noradrenaline, and Seratonin (Alvarez-Fischer *et al*., 2013).

4.1.2 Mechanism of Action

Honey bee venom therapy is not a single mechanism; it explains a wide range of treatment applications. Several mechanisms have been proposed. Components of bee venom describe the effectiveness of it for the treatment of different types of diseases. The immune system is a complicated web of communication between the “brain and bone marrow”. Bee venom stimulates key centers in the immune system by stimulating a nonspecific response. It appears to stimulate cortisone secretion, enhances antibody production, and affects cytokine production. It is also a powerful inhibitor of prostaglandin formation and antioxidant membrane (Son *et al.,* 2007). The pharmacological effects of bee venom are based on its components. It has been found that phospholipase A2 acts in a synergistic way with melittin to lyse erythrocytes. Phospholipase A2 (PLA 2) has been implicated in the management of arthritis. It is the most destructive component of apitoxin. It is an enzyme that degrades the phospho-lipids which are made of cellular membranes. Prostaglandins which are form from cyclooxynase cycle regulate the body's inflammatory response (Jeong, 2011). Apamin has a high affinity for the central nervous system and is responsible for the beneficial results in treating Multiple Sclerosis patients (Wesselius *et al.,* 2005). It increases cortisol production in the adrenal gland, a mild neurotoxin. Melittin interferes with the cellular membrane enzyme phospholipase A2 and is responsible for the beneficial result in treating arthritic patients and other disease.

MCD-peptide is a powerful anti-inflammatory agent (Meier and White, 2011). Adolapin acts as an anti-inflammatory and analgesic because it blocks cyclooxygenase. Hyaluronidase dilates the capillaries causing the spread of inflammation. Histamine involved in the allergic response. Dopamine and noradrenaline increase pulse rate.

Protease-inhibitors act as anti-inflammatory agents and stop bleeding (Jeong, 2011).

4.1.3 Novel Therapeutic Use of Bee Venom

When use in a normal doses, bee venom can be of benefit in treating many number of ailments. Its therapeutic value was already known to many ancient civilizations. Based on recent researchers, bee venom destroys HIV and spare surrounding cells. Nanoparticles containing bee venom toxin which is melittin can destroy human immunodeficiency virus (HIV) without harming surrounding cells (Hood *et al.*, 2013).

Melittin is a powerful toxin found in bee venom can poke holes in the protective viral envelope that surrounds the human immunodeficiency virus and other viruses. Free melittin can cause considerable damage. The scientists showed that nanoparticles loaded with melittin do not harm normal healthy cells. When Protective bumpers added to the nanoparticles surface, they come in contact with normal cells which tends to be much larger, the nanoparticles bounce off rather than attach themselves. HIV is much smaller than the nanoparticles and fits in between the bumpers. When HIV comes across a nanoparticle it goes in between the bumpers and comes into direct contact with its surface, which is coated with the bee toxin and then destroys it. "Melittin on the nanoparticles fuses with the viral envelope. The melittin forms little porelike attack complexes and ruptures the envelope, stripping it off the virus. "While most anti-HIV medications work on inhibiting the virus' ability to replicate, this one attacks a vital part of its structure and kill it off Said Hood *et al.* (2013).

4.1.5 Toxicity of Honey Bee Venom

Bee stings may cause medical emergencies by two distinct types of mechanisms: type I hypersensitivity allergic) reactions, and envenoming. In the first, an individual becomes sensitized to bee venom components by producing IgE antibodies to them. If re-exposed to venom, an acute reaction may follow within minutes, whereby IgE sensitized mast cells degranulate and release their potent vasoactive mediators. Such reactions may range from a mild, local inflammation, to a life-threatening systemic anaphylaxis involving dyspnoea, asphyxia, hypotension, and cardiovascular shock (Riches *et al*., 2002). Importantly, an allergic reaction may be triggered in a susceptible individual after exposure to minute amounts of venom, even after a single bee sting. This is in sharp contrast with the case of envenoming due to massive bee attacks, which may involve hundreds or even thousands of stings, leading to systemic toxicity.

Massive bee attacks have been related to the emergence and successful expansion of "Africanized" bees in the Americas, known to display a more vigorous and persistent colony defensive behavior than their parent species (Rinderer *et al*., 1993). Africanized honeybees produce lower amounts of venom than their European counterparts (Schumacher et al., 1990), although the general biochemical composition does not differ (Schumacher *et al*., 1990). Nevertheless, due to the large number of stings that may occur during an attack by Africanized honeybees, a systemic envenoming may ensue, with a potentially fatal outcome. Bee stings have become a public health concern in the American continent, where severe envenomings in humans and animals have been documented (Betten *et al*., 2006; Mitchell, 2006).

Bee venom pharmacopuncture (BVP) is a new type of treatment combining the efficacy of acupuncture and the pharmacological actions of the venom that is artificially extracted and refined from live honey bees (*Apismellifera*). BVP has been used to treat degenerative and rheumatoid arthritis and spine disorders (Lee *et al.*, 2006). However, several types of allergic responses can occur during the treatment period; especially, anaphylactic shock, which is fatal to people who are hypersensitive to bee venom, is an obstacle faced by Korean doctors who use BVP. Thus, sweet bee venom (SBV) was developed to reduce these allergic responses. Enzymes, known as allergens, are eliminated through a protein separation technique, so only melittin is left in SB. Melittin is the dominant component of bee venom; melittin constitutes 40% ─ 50% of bee venom's dried weight and has strong anti-inflammatory and analgesic actions. SBV has been reported to have fewer allergic responses than BVP; for that reason, SBV treatment is considered to be as effective, or better, than BVP treatment. Also studies using several toxicity tests have shown SBV to be safe (Kang *et al.*, 2014).

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العلاج بالنحل كبديل طبيى: مقالة مرجعية

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المستخلص

نحل العسل هو "الحشرات الذهبية" التي تنتج العسل ومنتجات نحل العسل الحيوية الأخرى. ومع ذلك ، فإن أفضل المنتجات الأولية المعروفة لنحل العسل هي العسل وشمع النحل ، ولكن حبوب اللقاح ، البروبوليس ، غذاء ملكات النحل ، سم النحل ، ملكة النحل ويرقاتها هي أيضًا منتجات نحل أولية قابلة للتسويق. زاد استخدام المنتجات الأولية في جميع أنحاء العالم مثل البروبوليس والغذاء الملكي وسم النحل في الغالب بسبب إدراجها في مستحضرات التجميل. سيزداد الاستخدام الطبي بمجرد الانتهاء من الدراسات الأكثر تفصيلاً ، والتي قد لا تكون في المستقبل القريب جدًا. للعسل استخدامات طبية مثل المطهرات وخصائص التئام الجروح ، بينما يستخدم البروبوليس لعلاج مرضى السكري. بالإضافة إلى ذلك ، حبوب اللقاح لها خصائص مضادة للأكسدة وخصائص مضادة للتخثر ومضادة للالتهابات لسم النحل تعمل على علاج التهاب المفاصل وحالات الالتهابات الأخرى. أكثر منتجات الخلية استخدامًا في جميع أنحاء العالم هي العسل وشمع النحل الذي يخدم العديد من الوظائف ، بدءًا من المشروبات المحلية إلى الاستخدامات الطبية المختلفة. وبالتالي ، فإن هذه المقالة سوف تلخص في موجز حياة نحل العسل ، أهم المنتجات وخاصة سم النحل واستخداماته كعوامل علاجية.

الكلمات المفتاحية: مضاد للتخثر - علاج - عسل النحل - سم النحل - حبوب اللقاح - التهاب المفاصل.