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The Utilization of Bee Products in Therapy

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Abstract: The utilization of bee products for the treatment of various illnesses and promotion of a healthy lifestyle can broadly be termed as apitherapy. The bee products like honey, bee venom (BV) and royal jelly (RJ) among others, have numerous factors that show positive impact on the human body from wound healing to its antimicrobial and anticancer activities. The important bioactive compounds present in these bee products are studied to have a better understanding on their modes of action and how they work in treating several diseases. The use of bee products in therapyis an emerging field of integrative medicine, which provide natural and sustainable solutions for improving human health and wellbeing.

Keywords: Honey, Bee, Products, Antioxidant, Antimicrobial, Properties.

Introduction: Honey bees belonging to the Apisgenus are predominant insect pollinator of various agricultural crops. Bees are socially active insects, living in colonies or hives, with a sophisticated social structure that includes a queen bee, drones, and worker bees. Queen bee is considered the mother of the colony, leading every other member. The major duty of queen bee is to mate with the drone bees, lay eggs, feed the larvae, and maintain the integrity of the colony, while drones which are born from unfertilized eggs are responsible for mating with the queen. Worker honeybees are responsible for duties such as collecting nectar and pollen, tending to the young, and building and maintaining the hive. Furthermore, they are known for the provision of a variety of valuable products like honey, BV, beeswax, bee pollen, propolis and RJ. Natural products of bees are used in traditional medicine for thousands of years. These products can be made entirely of pollens, nectars, and other plant materials, or they can be made in combination with plant secretions and salivary gland secretions from bees [1]. They have antimicrobial, anti-inflammatory, antioxidant, and many other properties that helps in treatment of various illnesses. This review aims to summarize the healing properties shown by certain bee products.

Bee Products: It's Composition and Therapeutic Potential

The major bee products utilized for human needs both orally and externally include honey, BV, propolis, beeswax, bee pollen and RJ. These materials pose great medicinal value. All of these are significant natural compounds having a wide array of biologically active properties, including antioxidant, antibacterial, antiviral, anti-inflammatory, as well as antitumoral properties [2]. Bees chemically amalgamateBV, beeswax, and RJ on their own[3].

Honey: It is the original sweetener produced by the nature. It has been consumed as an edible item for a very long period, and it served as the only sweet supply for the entire world for much of that duration. Nectar, which is a commodity of phloem sap expressed by specialised cell groups called nectaries, is the source of almost all honey. Nectar, an aqueous solution, contains carbohydrates, lipids, minerals, amino acids, sugars, protein, and some other substances. Plant species and environmental conditions play an effective role on the accurate makeup of nectar [4]. According to the work done by Talha [5], ''moisture content of honey ranged from 27 to 31 g/100 g of honey and the ash level of honey samples that were analysed ranged from 0.15 to 0.90 g/100 g. Protein content was found to range from 0.2 to 0.8 g/100 g of honey. The carbohydrate level of honey samples was analysed and found between 67.58 and 72.25 g/100 g''. Both current and historical generations recognise honey as a nutritional supplement and medicinal agent. They applied it to treat eczema, inflammation, and dermatological ailments[6].

Antimicrobial Activity: Honey exhibits antimicrobial properties against a variety of pathogens in various surroundings. It possesses remarkable antibacterial properties against MRSA and multiple Pseudomonas strains, which are commonly associated with infections from burns and wounds[5]. The main factors influencing antimicrobial qualities of honey are its degree of acidity, osmolality, presence of glucose oxidase enzyme, and H_2O_2production. Itspotential to fight against bacteria is attributed to H_2O_2[7]. Four characteristics of honey are connected to its antimicrobialactions[6]: (1) Whilst honey has a high enough amount of sugar to stop microbes from growing, this is not the only factor influencing honey's antibacterial properties. Honey also dries out germs by eliminating moisture from the surrounding air [8]; (2) Honey has an acidity level that is sufficiently low to prevent the majority of bacteria from growing, ranging from 3.2 to 4.5; (3) The hydrogen peroxide that the glucose oxidase enzyme produces[9]; (4) Honey has a number of phytochemical components that have been linked to antimicrobial activity[10].

Anti-inflammatory Activity: While inflammation is an essential part of the body's natural reaction to an illness or wound, excessive or protracted inflammation can hinder recovery or even worsen the situation [11]. Low-grade chronic inflammation, which leads to the development of numerous chronic diseases, is caused by non-resolving inflammation brought on by a persistent bacterial infection, obesity, or ageing. Honey has been proposed as a dual-purpose immune-modulatory agent. First, it has inflammation reducing propertieswhich work by minimizing the yield of signalling proteins (that originate mainly from activated macrophages) also while reducing inflammatory transcription factors; second, stimulating the making of inflammatory mediators such PGE2 and COX-2[12].

Antioxidant Activity: Substances that prevent the damage done by oxidants are referred to as antioxidants, which include lipid peroxyl radicals, O2, OH-, superoxide, and other oxidants. Oxidative stress is linked to several chronic and degenerative lingering diseases, ageing, cancer, mutagen production, and atherosclerosis[13]. Cells have an antioxidant defence mechanism. Free radicals and other oxidative protection catalysts including peroxidase, polyphenols, ascorbic acid, catalase, tocopherol and superoxide dismutase make up this defence system[14]. These antioxidants activate biomolecules, including nucleic acids, proteins, lipids, and carbohydrates. This stimulation modifies cells and eventually triggers an antioxidant response[15]. Strong antioxidant action is shown by honey[16]. Honey's antioxidant properties help to prevent a number of acute and long-term illnesses, including cancer, diabetes, thrombotic, inflammatory, and allergy diseases [17].Flavonoids and phenolic acids present in honey is a hallmark of its well-known antioxidant properties. In addition, the generation of ROS, amino acids, proteins, carotenes, sugars, organic acids, and Maillard reaction products along with a small number of other substances all serve the antioxidant impact [14,18].

Wound Healing Properties: One of the most well-studied and effective uses of honey is wound healing [19]. Normally, healing of a wound is a complex process that involves a number of co-occurring processes, such as inflammation, coagulation, proliferation of cells, remodelling of the injured tissue, and substitution of thismaimed tissue. A wide range of chronic wounds have been successfully treated with honey [20,21,22]. Using honey for wound treatment promotes the healing process and quickly gets rid of infection. Honey contains anti-inflammatory, pro-tissue-regeneration, and cleaning properties for wounds. Pads infused with honey function as a non-adhesive tissue dressing [23,24,25].

Antidiabetic Effect: In a randomised crossover trial, the effects of honey intake on people affected by type 1 diabetes were investigated. Twenty individuals, aged 4 to

18, were included in the study and each received a 12-week dietary intervention consisting of 0.5 ml of honey per kilogram of body weight each day. It was deduced that the continued intake of honey may significantly diminish the risk of type 1 diabetes, as it was observed by the researcher that there was a considerable deterioration in total cholesterol skinfold thickness, fasting serum glucose, LDL, serum triglycerides and C-peptide increase[26].

Anticancer Activities: Studies on the utilisation of organic products for cancer therapy and prevention have increased recently. Honey being a natural product has been explored a lot. Honey's apoptotic, antitumor necrosis factor, antiproliferative, anti-inflammatory, estrogenic, antioxidant and immunomodulatory properties may be the reason behind its anti-cancer effectiveness as a chemo-preventive and therapeutic drug [16]. It has been shown that the phenolic component of honey exhibits antileukemic action against various leukemic cell lines [27]. Its anticancer properties have been demonstrated against a range of cancer cell lines and tissues, including those from the breast, colon, prostate, kidney, endometrial, cervical, and oral regions [28,29,30,31]. Anticancer effectiveness of chemotherapy medications, such as cyclophosphamide and 5-fluorouracil, is escalated by honey [32].Honey causes the mitochondrial membrane to depolarize, which causes apoptosis in a variety of cancer cell types [30]. Manuka honey causes cancer cells to undergo apoptosis by inducing caspase 9, which then triggers the executor protein caspase 3. Manuka-induced apoptosis also includes loss of Bcl-2 expression, activation of PARP, and induction of DNA fragmentation [33]. Due to its disruption of the cell cycle, honey or its constituents mediate the suppression of cell growth [34]. Since many currently used chemotherapeutics promote apoptosis, honey's apoptotic capability makes it a potential natural anti-cancer drug. There is evidence that honey influences cell cycle arrest [16].

Bee Venom: Honeybees produce BV or apitoxin, in poison glands in their abdominal cavity, which is a key defensive tool [2]. Specifically, the female worker bees produce it. BV is bitter liquid with no colour. It is a convoluted protein ensemble [35]. It is found that it comprises enzymes, amino acids, peptides, and some volatile compounds [36]. A combination of proteins in its active component generates localised inflammation and function as anticoagulants [35].Some of the main compounds of BV include, apamin, adolapin, mast cell degranulating peptide, hyaluronidase,melittin and Phospholipase A_2.

Antimicrobial Activities: Extensive research has delved into the natural antibacterial qualities of BV, suggesting it as a prospective substitute to conventional antibiotic treatments [37]. These studies have unveiled the potent antibacterial

properties of BV against a broad range of microorganisms, including both Gram + and Gram - types [38]. Nakatsuji[39] reported that it has proven effective in inhibiting the proliferation of bacteria such as Staphylococcus aureus. Furthermore, BV has demonstrated its ability to effectively combat bacteria commonly found on the skin, including Propionibacterium acnes, Staphylococcus epidermidis, and Streptococcus pyogenes[40].During researchcarried out by Yu [41], it was discovered that BV has strong antifungal properties against Trichophyton rubrumand T. mentagrophytes, far stronger than those of fluconazole, a commercial antifungal medication used to treat and prevent fungal infections.

Anti-inflammatory Activities: BV compound has broad anti-inflammatory properties that can be induced at low dosages. Numerous studies examined the ways that melittin reduces inflammation in a variety of illnesses, including Amyotrophic Lateral Sclerosis and Rheumatoid Arthritis. It works by blocking inflammatory cytokines such as TNF-α, IFN-γ, and interleukin-6 and -8. Furthermore, melittin inhibits signalling pathways that trigger inflammatory cytokines. These results suggest that melittin suppresses inflammatory cytokines by inhibiting their primary signalling pathways, which reduces inflammation in the skin, liver, joints, and neural tissue[36]. In reference to a recent study by Kim [42], BV lowers the incidence of Atopic Dermatitis, the most prevalent chronic inflammatory allergic skin conditions.

Antioxidant Activities: Compounds with strong antioxidative properties are found in BV. This reaction can be attributed to PLA2, apamin, and melittin. The potential of these substances to suppress lipid peroxidation and heighten superoxide dismutase activity may be the cause of the antioxidant action. By immediately shielding the cell from oxidative stress and giving the celldefence opposed toROS, vitellogenin present in BV exhibits antioxidant function in mammalian cells [43].

Wound Healing Properties: BV is widely used in treating inflammatory conditions like rheumatoid arthritis and multiple sclerosis. It's known to enhance wound healing, particularly crucial for diabetic patients facing impaired healing due to hypoxia. BV expedites wound repair by influencing caspase activity, promoting growth factors, as well as boosting collagen production. Combining BV with substances like polyvinyl alcohol and chitosan speeds up wound healing while minimizing inflammatory markers. However, potential allergic reactions necessitate assessing patient hypersensitivity to apitoxin before initiating treatment [44].

Anticancer Activities: BV is also widely used in the therapy of tumors. It has been established that BV and melittin are effective therapies for prostate cancer, ovarian cancer, and malignant hepatocellular carcinoma in humans. In addition, studieshave

demonstrated that melittin and BV may mitigate breast cancer. It was established through research done by Kwon [45] that BV reduces cell feasibility with respect to dose and duration and regulates the spread of breast cancer cells. Moreover, they discovered that mechanisms of breast cancer cell inhibition include toxicity to cells, cell death, targeting, gene expression modulation, and cell disintegration. The most concerning negative impact of BV is hemolysis, which can be minimized by boosting selectivity, limiting the dosage to a suitable level, or making use of inhibitory characteristics of moDCs.

Royal Jelly: The growth and development of queen honeybees are aided by RJ, a material processed and releasedfrom the hypopharyngeal glands of worker bees. It is one of the most challenging foods to harvest since it is exceedingly perishable [46]. Being a complex mixture, RJ contains free amino acids, trace minerals, water-soluble vitamins, 18% proteins, 15% carbohydrates, 3%–6% lipids, and many other substances in smaller quantities [47]. Among these, proteins cover a major part [48].

Antimicrobial Activities: By directly inactivating the microorganisms present in honeybee products, proteins and peptides from RJ support thedefense mechanism shown by honeybees against microbial infections. It was discovered that the antibiotic polypeptide- royalisin exhibited strong antibacterial action at low concentrations only against Gram-positive bacteria. Royalisin might be a part of the honeybee's active defense mechanism against infection by bacteria. It demonstrates the antibacterial activity, namely against the pathogen that infects honeybees, Paenibacillus larvae, which results in American foulbrood, a dangerous illness that affects honeybee larvae. Jelleines, exhibiting antimicrobial activity, are also peptides. Four antimicrobial peptides, Jelleine I–IV, were isolated from the RJ of honeybees. Jelleine-IV was found to be dormant in any of the tests, while Jelleines-I–III showed only antibacterial activity against yeast and Gram + and Gram - bacteria [49].

Antioxidant Activities: Antioxidant properties of RJ can be attributed to the presence of phenolic chemicals and short peptides found in its structures, as well as the different antioxidant-type vitamins A and E, and the short-chain hydroxyl and carboxylic fatty acids. It has been demonstrated that these peptides had substantial hydroxyl radical scavenging action.

Anticancer Activities: By inhibiting tumor-induced angiogenesis and stimulating the immune system, RJ may have anti-cancer effects on tumor growth, metastasis, and/or liver or lung metastases. Crude RJ inhibits bisphenol A's damaging effects, which lead to the growth of human breast cancer cells. For individuals with benign prostatic hyperplasia, a three-month course of RJ therapy improves quality of life and

has greater results on lowering prostatic-specific antigen. RJ may be able to lessen doxorubicin's cytotoxic effects on the prostate cancer cell line[50].

Wound Healing Properties: RJ increases the number of sphingolipids, which aid in wound healing, and changes the levels of various lipids to encourage the migration of fibroblasts in humans at a dose of 5 μg/mL. In addition, RJ dressing works well in conjunction with other conventional techniques to treat patients with diabetic foot ulcers. Moreover, this technique produces vasodilation effects surrounding the area, which may widen blood vessels to improve blood flow and shield this region from microbial invasion. Moreover, RJ stimulates the wound-repairmechanism to manage MRSA-induced cutaneous infection[50].

Antidiabetic Effects: Following the delivery of RJ, blood glucose levels in healthy individuals significantly lowered in a clinical investigation. By raising insulin concentration, RJ supplementation demonstrated notable reductions in fasting blood glucose and serum glycosylated hemoglobin levels, which may aid in the management of diabetes. When given to individuals affected by type-2 diabetes, RJ treatment lowers the measurement of resistance by insulin and increases total antioxidant capacity. In diabetic settings, RJ may also lessen the erratic state of 30 mM glucose conditions in human endothelial cells. In addition, RJ significantly lowers blood levels of triglycerides, cholesterol, low-densityand high-density lipoprotein, and ApoA-1 in people affected by diabetes, improving oxidative stress, lipid profiles, and glycemic status [50].

Conclusions

From various previous works done, it has been understood that in apitherapy, usage of high-quality bee products containing high amounts of bioactive compounds is necessary for itsmaximum utilization and effectiveness while applying in different kinds of treatment. Bee products like honey, propolis, BV, etc. have shown effectiveness in treating burns, several types of ulcers, gastrointestinal conditions, headaches, fungal infections, conjunctivitis, and many others. The beneficial effect obtained by the usage of these products has gained worldwide attention, especially in an era when people are turning towards consumption of organic products. Furthermore, attempts have been made to incorporate these products into clinical practice; however, these endeavors have nearly failed due to the high levels of chemical, nutritional, and phytochemical variability that depend on many factors, such as types of honeybees, plant, region, and the seasons, making the process of medicinal standardization challenging. A more thorough understanding of these products may be essential to promoting their use in the public for the prevention of prevalent conditions as well as the exploration of novel pharmaceutical

organic alternatives which can be used when paired along withconventional therapies to treat different diseases [1].

Authors' Contribution

Fathima Abdul Salam: Data curation, Formal analysis, Investigation, Writing – original draft.

Dr. Lovleen Marwaha: Editing, Conceptualization, Supervision, Validation, Writing – review & editing.

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