Scientific Research Publishing

Advances in Biological Chemistry, 2023, 13, 1-16
https://www.scirp.org/journal/abc
ISSN Online: 2162-2191
ISSN Print: 2162-2183

The Application of Honeybee Products in the Health Sector

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How to cite this paper: Loukas, P. and Maria, T. (2023) The Application of Honeybee Products in the Health Sector. *Advances in Biological Chemistry*, **13**, 1-16.
https://doi.org/10.4236/abc.2023.131001

Received: November 22, 2022
Accepted: February 6, 2023
Published: February 9, 2023

Abstract

The chemical composition of each of the eight total products of beekeeping, which are honey, bee venom, propolis, royal jelly, drone brood, bee pollen, bee bread and beeswax, is analyzed. Each beekeeping product has its own chemical composition which varies from producer to producer. Some of these bee products have been used for centuries in traditional medicine, but to date research has demonstrated many other medicinal properties of these products that were not known. Therapeutic properties of bee products have been discovered even against various types of cancer and scientists are continuing their research to discover other secrets behind the therapeutic properties of bee products. In addition, therapeutic effects of bee products have also been discovered against COVID-19 disease which has significantly affected global health. Finally, it is concluded that bee products are proven to be one of the most valuable medicines that nature can offer showing the great value of the science of beekeeping.

Keywords

Honeybee Product, Health, Medicine, Propolis, Therapy

1. Introduction

This publication refers to scientific reviews on the application of bee products in human health issues. Their application concerning the treatment of diseases dates back to several years back, but many new applications concerning humans have been discovered today. Specifically, any positive effect that bee products offer in the treatment of various diseases including cancer and even the recently emerging COVID-19 disease that has affected human society worldwide will be referred.

Honey, as the most widely known product of beekeeping, contributes significantly not only to human nutrition but also to human health, due to its abundance of vitamins, sugars and enzymes. Bee venom is a source of many active molecules (peptides, enzymes and many others) that contribute to the treatment of inflammation and diseases of the central nervous system, with Parkinson's disease and Alzheimer's disease being the most important examples.

Propolis is a natural material produced by bees from various botanical sources. Its therapeutic effects, including antibacterial, antifungal and anti-inflammatory effects, have been known since ancient times. Royal jelly is one of the most important natural products that have been used mainly in traditional medicines, health foods and cosmetics since ancient times in different parts of the world. It is also the most studied product of the bee, with the aim of revealing its bioactivities in animal experiments, microbial organisms, farm animals and clinical trials.

Drone brood is the only one of the other bee products that are considered particularly rare as it ends up in the waste bin by most beekeepers. But most of them would be surprised at what this waste can offer to human health. Bee pollen and bee bread are two products that are linked because bee bread is the result of further processing of pollen by bees. They both have a rich therapeutic, chemical composition, to which many of their beneficial properties are due.

Finally, we have beeswax, which bees create for most of their work. Its use by man dates back many years ago and to this day a lot of useful properties have been found.

2. Honey and Its Role in Human Health

Honey has held an important place in traditional medicine for centuries. It is consumed for its high nutritional value and for its effects on human health, with antioxidant, bacteriostatic, anti-inflammatory, and antimicrobial properties, but it is also used to heal wounds and burns. It is particularly known for its use in wound healing. The importance of honey in this category has been known since ancient times. Its therapeutic property is related to the antioxidant and antibacterial action offered by honey, maintaining a fluid state of the wound, and with its high viscosity, it provides a protective barrier to the wound, preventing microbial contamination. Its immunological activity is also important for wound healing, simultaneously exerting pro-inflammatory and anti-inflammatory effects [1].

Honey is known to be able to inhibit the growth of various micro-organisms. This kind of effect was a strong motivation for the application of honey in clinical medicine. Research has shown that the main antimicrobial factors of honey are low water activity and low pH. Honey has been found to lower blood glucose in animals and in patients with impaired glucose tolerance or diabetes, although evidence from clinical studies has not been entirely conclusive [2]. However, apart from its contribution to the disease of diabetes, its effect on cancer cells has

also been researched, with the research evidence again lacking the necessary reliability. Remarkable research is the action of a unique tri-hydroxyketone from thyme honey, with antibacterial activity, which appeared to induce apoptosis in prostate cancer cells [3].

Flavonoids, such as quercetin and its derivatives (rutin, quercitrin and isoquercetin), are often found in propolis and honey samples, and have shown antiviral activity against various viruses including coronaviruses. Scientists claim that these compounds inhibit the function of the 3C-likepro enzyme. This enzyme is one of the most promising targets for drug discovery against coronaviruses because of its critical role in the virus' life cycle. However, the antiviral activity of honey against the novel coronavirus (SARS-CoV-2) has not yet been confirmed [4].

Despite the benefits that honey can have on humans, there are also cases where it can be toxic. And this can be mainly due to the origin of the nectar. Various occurrences of toxic compounds have been discovered and an important example is a honey from rhododendron plants such as *R. luteum* and *R. ponticum*. This type of honey is known as hallucinogenic honey, as it can cause severe nerve poisoning up to a fatal emergency, especially in the eastern Black Sea region of Turkey. The toxins responsible for the effect of this honey are called grayanotoxins (Grayanotoxins). Despite its toxicity, hallucinogenic honey is used as a traditional medicine for hypertension, sexual dysfunction, and other diseases [5] [6].

3. The Main Components of Bee Venom and Their Usefulness in Human Health

3.1. Melittin

Melittin is a peptide (**Figure 1**) consisting of 26 amino acids and is the main component of bee venom (40% - 50% of the venom). This is also the main substance that causes pain sensation [7]. The N- and C-terminal regions of melittin are predominantly hydrophobic and hydrophilic, respectively [2]. The mechanism of melittin toxicity is based on the disruption of phosphor-lipid bilayers, leading to cell lysis and release of damaging compounds, such as lysosomal enzymes, serotonin, and histamine, causing inflammation and pain [8]. Together with hyaluronidase and phospholipase A2 (PLA2), melittin is responsible for the allergenic properties of the venom [9].

Despite its toxicity, melittin is known as a traditional anti-inflammatory treatment for various diseases, such as dermatitis, neuritis, liver inflammation, atherosclerosis, and arthritis, but its mechanism of action at the cellular level has not yet been elucidated [10]. Antitumor effects of melittin have been reported from various sources, while attempts to elucidate the molecular mechanisms have been made with in vitro studies [11]. An important discovery is the contribution of melittin to the treatment of leukemia. Scientists showed that leukemia cells were more sensitive to melittin than normal cells in the spleen and bone

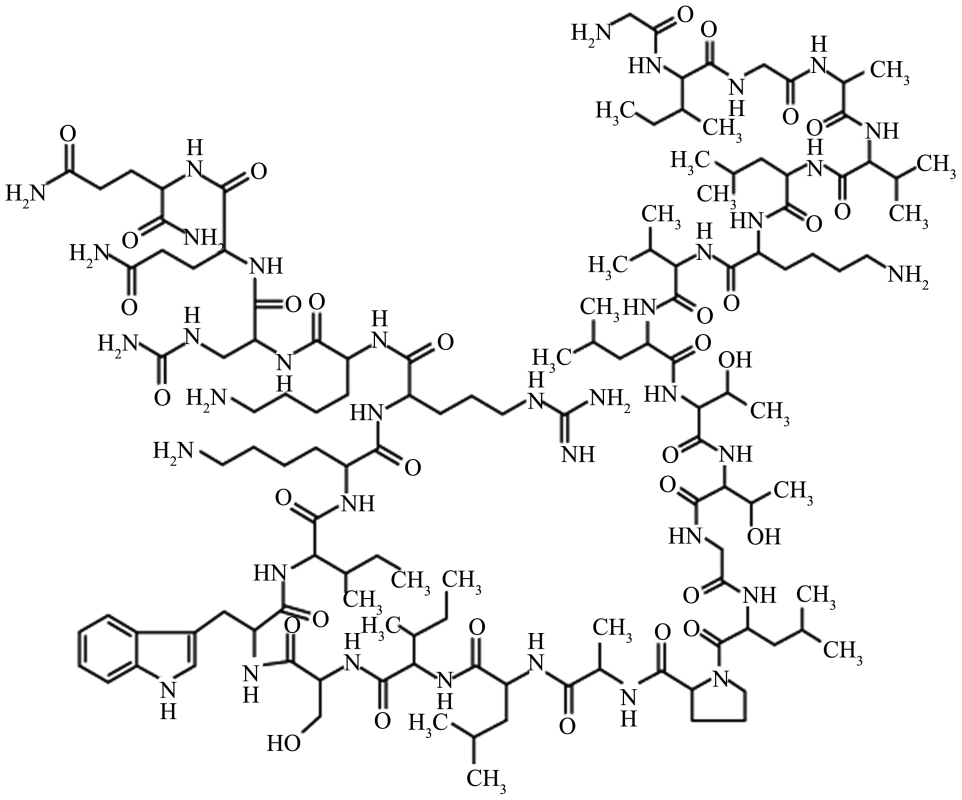

Figure 1. Melittin peptide.

marrow of mice. The reason is that bone marrow cells have several binding sites for carbohydrates in their membrane. These sites tend to disappear in adult spleen cells, while they almost disappear after neoplastic changes, which could make cancer cells more sensitive to melittin [12].

3.2. Phospholipase A2 (PLA2)

Phospholipase A2 (PLA2) is a polypeptide chain of 128 amino acids and contains 4 disulfide bonds. There are more than 30 known PLA2s and each of them has its own characteristics and functions. This specific phospholipase, however, belongs to enzyme group III sPLA2 and is the main allergen in bee venom. It is found at 10% - 12% in dry venom and is an extremely alkaline enzyme. It destroys phospholipids, disrupting the integrity of lipid bilayers, thus making cells vulnerable to further degradation. In fact, PLA2 reaction products, such as lyso-phosphatidyl-choline, lysophosphatidic acid and sphingosine 1-phosphate, can have cytotoxic or immunostimulatory effects on various cell types, causing inflammation and immune responses [13] [14]. Although severely allergenic, research has shown that PLA2 has protective immune responses against a wide range of diseases, including asthma, Parkinson's, and Alzheimer's disease [9].

3.3. Apamin

Apamin (Figure 2) is an 18 amino acid peptide containing two disulfide bonds.

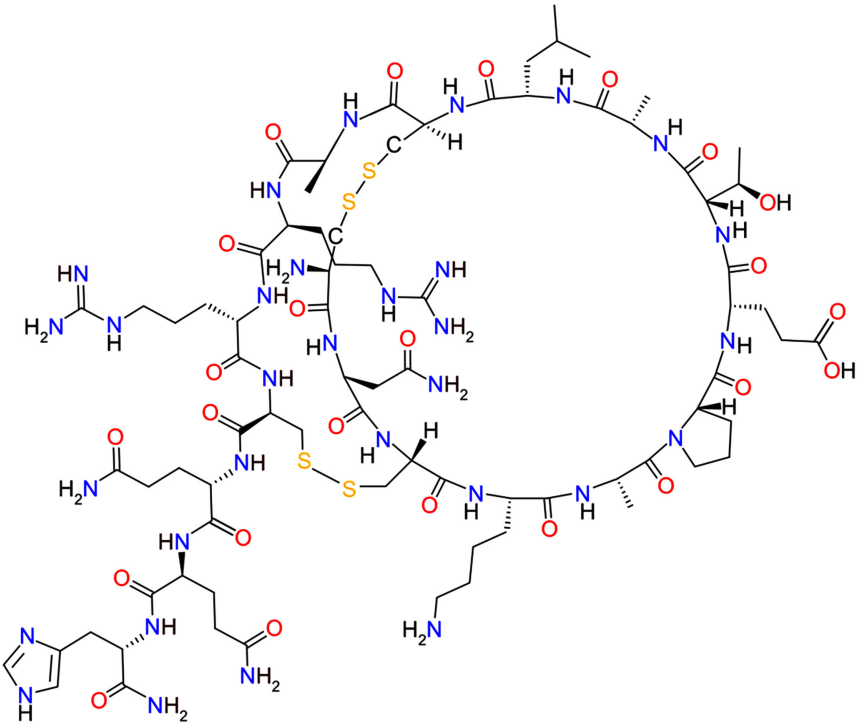

Figure 2. Apamin peptide.

It is the smallest neurotoxin in bee venom (2% - 3% in dry venom) and can affect the central nervous system [9]. Apamin has long been known as a specifically selective blocker of Ca^{2+}-activated small conductance K^+ channels (SK channels). In essence, apamin acts as an allosteric inhibitor. These channels play a key role in various pathophysiological responses, such as atherosclerosis and Parkinson's disease [15]. Because of its ability to selectively target SK channels, apamin has been used as a tool for physiological characterizations of this type of K^+ conductance. Pharmacologically, such a property has been taken as an illustrative example of the accumulating evidence that apamin facilitates learning and memory. Apamin can cross the blood-brain barrier and its administration to animals ameliorates their cognitive deficits, suggesting that SK channels would be suitable targets of apamin to treat these neural disorders [16] [17].

3.4. The MCD (Mast Cell Degranulating) Peptide

The MCD peptide, also known as the 401 peptides, is a polypeptide containing 22 amino acids with a similar structure to that of apamin, both containing two disulfide bonds. It represents 2% - 3% of the dry weight of bee venom [9]. The name MCD echoes the biological activity of the peptide in the release of histamine from mast cells. Studies describe the MCD peptide as a potent anti-inflammatory agent and may serve as a potential candidate for studying the secretory mechanisms of inflammatory cells, such as mast cells, basophils, and leukocytes, leading to the design of compounds with therapeutic applications [18].

3.5. Hyaluronidase

Hyaluronidase accounts for 1% - 2% of the dry weight of bee venom and is known to break down hyaluronic acid in tissues such as the joint capsule in rheumatoid arthritis. Bee venom hyaluronidase helps diffuse the venom's active substances into the bee victim's tissue, affecting its structural integrity and increasing blood flow to the area. These two actions combine to enhance the widespread distribution of the venom [19] [20].

4. Bee Venom Therapy

Bee venom therapy (BVT) is the medicinal application of bee venom to the human body to treat certain diseases, such as rheumatoid arthritis [21]. It has been proven that bee venom can protect dopaminergic neurons from degeneration in experimental models of Parkinson's disease [22]. Through bee venom treatment, phospholipase A2 (PLA2) can be used as a therapy to block the progression of Alzheimer's disease in transgenic mice. In the same research, it was discovered that PLA2 can increase brain glucose metabolism and reduce neuroinflammatory responses in the hippocampus of the brain, which may limit the pathogenesis of Alzheimer's disease [23]. Study showed that bee venom and especially melittin have significant antiviral effects against numerous enveloped viruses (vesicular stomatitis virus, influenza A virus, herpes simplex virus, etc.) and non-enveloped viruses (enterovirus-71 and Coxsackievirus) *in vitro*. The study also showed that melittin pre-immunized mice were exposed to lethal doses of influenza A and H1N1 (swine flu) viruses [24].

A survey of 5115 beekeepers (who due to their work will certainly be stung several times by bees) and 121 patients who have undergone treatment with bee venom (for two months without any other treatment) conducted by a clinic in the provinces of China, showed that none of the beekeepers and patients had symptoms related to the disease COVID-19. None of these people were infected with SARS-CoV-2 although they had close contact with immediate family members with a confirmed case of SARS-CoV-2. These people had one thing in common which was essential tolerance to bee stings. Therefore, bee venom can enhance the immune system and reduce susceptibility to SARS-CoV-2 infection [25].

5. Propolis and Its Role in Human Health

Propolis, generally known as "bee glue", is a resinous mixture produced by bees by mixing their saliva, which contains certain enzymes and beeswax, with secretions they collect mainly from the buds of leaves and flowers, the stems and bark cracks of numerous tree species [26].

The antimicrobial activity of propolis has been demonstrated in clinical, *in vivo* and *in vitro* studies. Propolis has antibacterial properties against Gram-positive and Gram-negative bacteria, with streptococcus species as an important example and according to research, its antibacterial properties are probably due

to some flavonoids due to their ability to increase the permeability of the bacterial membrane. In addition to antibacterial properties, propolis has been shown to act as an antifungal agent against pathogenic yeasts such as *C. albicans*, *C. parapsilosis*, *C. tropicalis* and *C. glabrata* [2]. Propolis is also known for its antiviral activity, which in some cases can exceed that of drugs commonly used to treat various diseases. An important example is a study comparing results between an ointment containing Canadian propolis and Acyclovir (an antiviral drug) in the clinical treatment of genital herpes simplex. The results showed that propolis ointment had a better response to treatment [27].

Many studies have also reported anti-inflammatory properties of propolis, possibly linked to the presence of phenolic acids. These properties are widely used in oral solution products but also as sun protection, probably due to the polyphenols and their immunity to ultraviolet radiation, which some types of propolis possess [2]. Research has shown that propolis can also help fight the COVID-19 disease. Propolis is rich in phenolic compounds and flavonoids and several studies have confirmed the activity of propolis flavonoids against coronaviruses, such as chrysin and kaempferol which were found to inhibit the proliferation of coronaviruses *in vitro* [24].

Regarding cancer, there have been many in vitro and preclinical studies on the anticancer effects of propolis, but only a few clinical studies have been conducted and their results are controversial [2]. One study reported that propolis has the potential for treating breast cancer due to its anti-cancer property of inducing apoptosis in breast cancer cells. It also exhibits little to no toxicity to normal cells due to its selective toxic properties against cancer cells, and it is believed that propolis may become an important agent in the treatment of breast cancer [28]. In another in vitro study in mice, the effect of the ethanolic extract of Algerian propolis on the development of melanoma tumors was investigated. This study showed that galangin, a common flavonoid in propolis, induced apoptosis and inhibited melanoma cells [29].

6. Royal Jelly and Its Role in Human Health

Royal jelly (or "royal milk") is known as a "superfood" produced by worker bees to feed the young workers, larval bees, and queen bees. For queens, their royal jelly feeding lasts as long as their life cycle [30]. The main components of royal jelly are (60% - 70%) water, (9% - 18%) proteins, (7% - 18%) sugars and (3% - 8%) lipids. It also contains secondary components such as metallic elements (Fe, Na, Ca, K, Zn, Mg, Mn and Cu), amino acids (eight essential amino acids which are valine, leucine, isoleucine, threonine, methionine, phenylalanine, lysine and tryptophan), vitamins (A, B, C and E), enzymes, hormones, polyphenols, nucleotides and secondary heterocyclic compounds [31].

It has been confirmed that proteins, peptides, lipids, phenolics and flavonoids are the main bioactive compounds responsible for the various medicinal properties of royal jelly [32]. Recently, much has been reported about the origin and function of basil pulp, such as its 9 major proteins (MRJPs) for the development

of pro-nymphs, its antimicrobial properties, its medicinal value, its possible applications in cancer treatment and longevity. Royal jelly has antioxidant activity, and it was discovered that this activity came from its major proteins (MRJP 1 - 9) and its peptides. Recently, the hepatoprotective effect of royal jelly against non-alcoholic fatty liver disease (NAFLD), the most common liver disease in the world, was examined *in vivo* [33]. Also, a clinical trial study reported the effectiveness of royal jelly in treating urinary tract problems and promoting the quality of life in postmenopausal women [34].

The use of royal jelly alone or in combination with propolis reduced the viral load of cells infected with influenza A2 virus *in vitro*. Additionally, clinical evidence has shown that combining royal jelly with other bee products prevents infection during flu epidemics [4]. Potential antitumor properties of royal jelly have been discovered, such as inhibition of tumor growth and/or metastasis to the liver or lung, through inhibition of tumor-induced angiogenesis and/or activation of immune function [35]. Raw royal jelly was also found to stop bisphenol A damage, which causes human breast cancer cells to swell [36]. Finally, the discovery of treatment for three months with royal jelly that has better results in reducing prostate specific antigen and improves the quality of life in patients with benign prostatic hyperplasia is considered important [37].

7. Drone Brood and Its Role in Human Health

Bee brood or drone brood is not widely known in Europe, but it is a recognized and frequently used medicine in certain countries of the world, such as Romania and China. It is obtained by collecting drone larvae from drone cells (3 - 11 days after hatching) [38]. In the field of beekeeping, drone brood is sometimes treated as waste, when it should be used for its wealth of valuable nutrients and bioactive components. The chemical composition of fresh drone brood is similar to that of royal jelly. Due to its high content of proteins, vitamins and hormones, the spawn effectively prevents cellular aging and many diseases. This therapeutic effect is widely described by scientists in Romania, Slovakia, Ukraine, and Russia [38].

Animal studies have shown that the administration of drone brood, results in a reduction of cholesterol and triglyceride levels. It also exhibits hepatoprotective activities and stimulates the immune system [39] [40]. DNA obtained from drone brood has been shown to protect liver tissue from the toxic effects of acetylsalicylic acid (aspirin), buserelin (given to treat prostate cancer and endometriosis) and carbon tetrachloride [39] [41]. It has been proven that the brood of drones has a therapeutic effect on diseases of the nervous system and on mental illnesses. Including:

- Improving the mental state of patients with depression, fatigue, anorexia, and a feeling of weakness [38].
- Improving memory and reducing psychomotor instability [38].
- Improving neurological and sexual functions of the elderly [42].

Another important discovery is the contribution of the drone brood to the

treatment of thyroid disorders. A study in dogs demonstrated that thyroxine (T4) and triiodothyronine (T3) concentrations increased by 40%, while thyroid-stimulating hormone (TSH) decreased by 37% after 30 days of providing brood [43]. Research done on mutant mice with hereditary hemolytic anemia showed how giving freeze-dried drone brood increased their survival rate. Specifically, the survival of the mice increased from 2 weeks to 7 months in 50% of the experimental animals. This discovery, like all the others, shows that the offspring of drones can be just as beneficial for humans [44].

8. Bee Pollen and Its Role in Human Health

Many of the compounds contained in bee pollen, especially polyphenols, have promising activity against coronaviruses such as SARS-CoV-2. The phenolic elements with the highest concentrations in bee pollen are quercetin and kaempferol. Research has concluded that the main protease of the coronavirus, 3C-likepro, may also be sensitive to the inhibitory effect of quercetin and its derivatives. Kaempferol and its glycoside analogs have been found to inhibit the 3a protein of the coronavirus. Protein 3a forms a cation channel, which is expressed in the infected cell and is involved in the virus release mechanism. Ion channel-blocking drugs can, therefore, inhibit virus release, providing a source for the development of new therapeutic antiviral agents against SARS-CoV-2 [4].

An important category in which bee pollen has a large effect are the metabolic syndrome disorders. Metabolic syndrome disorders are a group of conditions that increase the risk of cardiovascular disease, stroke, and diabetes. These problems lead to increased blood pressure, hyperglycemia, extra visceral fat, and abnormal cholesterol and triglyceride levels [45]. Due to its components, bee pollen can help to deal with these disorders. A research has shown that bee pollen can improve blood sugar levels. Intestinal enzymes (α-amylase and α-glucosidase) break down polysaccharides into glucose which is transported to the cells of the body. Glucose levels could be altered by attenuating the activity of these enzymes [46]. Bee pollen could act as a natural α-glucosidase inhibitor to improve blood sugar levels [47].

Another case in which pollen has been proven to be beneficial is obesity. The latest data from research in mice have shown that phenolic compounds can enhance nutrient absorption, lipid metabolism and weight loss, and bee pollen is rich in phenolic compounds that could play a key role in preventing obesity and other secondary health complications [7] [48].

Bee pollen has shown antiatherosclerotic and cardioprotective activity and has been successfully applied to patients who have not responded to classical drugs [2]. In addition, scientists found the presence of antidiabetic compounds in the pollen grains, such as steroids and alkaloids in the pollen of the *C. roseus* plant, saponins, flavonoids, sugars, and tannins in the *M. charantia* plant, sugars, flavonoids, and sterols in the *B. monosperma* plant, and alkaloids and tannins in *S. cuminii*, which suggests therapeutic potential for bee pollen as a hypoglycemic agent [49].

Compared to other bee products, bee pollen appears to yield a relatively weaker anticancer activity [50]. Nevertheless, scientists discovered the important role of bee pollen in mitigating the side effects of chemotherapy. Bee pollen has been found to alleviate the deterioration of the antioxidant barrier and inhibit the process of lipid peroxidation after chemotherapy [26]. It was also discovered that the enzymatically broken proteins of bee pollen, known as hydrolysates, exhibited strong anti-cancer properties. Hydrolytic peptides with sufficiently low molecular weight were reported to be able to inhibit ChaGo-K1 cells, a human model of bronchogenic carcinoma [51].

9. Bee Bread and Its Role in Human Health

Bee bread has been proven to have significant beneficial properties against various conditions. A notable case is its antimicrobial property. Bee bread extract contains phenolic compounds, which can be attributed to its antimicrobial properties. Therefore, its importance as an antimicrobial agent should be recognized not only against bacteria but also against yeasts and parasites. Scientists demonstrated that bread extracts of the bee *M. compressipes manaosensis* effectively inhibited the bacteria *P. aeruginosa* and *M. smegmatis* and the fungus *Candida albicans*, as well as the larvae of the mosquito *C. quinquefasciatus*, carrier of the human parasitic worm *Wuchereria Bancroft* [52]. Scientists used an extract of the bread of the bee *Heterotrigona itama* against *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli* and *Salmonella spp*. Gram-positive bacteria (*Bacillus cereus* and *Staphylococcus aureus*) were more sensitive to the extracts of this bee bread [53].

Another important effect of bee bread is its antioxidant effect. Phenolic compounds are one of the most important natural antioxidants, which can be found in bee bread.

Bee bread contains antioxidant compounds such as phenolic compounds and vitamin C. Therefore, its ability to scavenge free radicals has been investigated. But in addition to phenolic compounds, the antioxidant activities of bee bread also depend on the time of the year of pollen collection, the botanical origin, and the storage time of the pollen as bread [54]. Some studies also show the ability of bee bread extract to reduce inflammation. Ethanol extracts of the honeybees *Melipona fasciculata* and *Scaptotrigona affinis postica* were administered to a mouse model of induced edema in two separate studies. Anti-inflammatory responses were time and dose independent. After 5 hours, bee bread treatments were able to reduce leg volume equivalent to indomethacin (anti-inflammatory) and cyproheptadine (antihistamine) medication. Further analysis identified the potential mechanism of bread phenolic compounds inhibiting histamine release and reducing prostaglandin synthesis [55].

In one study five samples of bee bread were tested, using in vitro assays, against different human cancer cell lines: HeLa (cervical cancer cell line), HepG2 (liver cancer cell line), MCF-7 (breast cancer cell line), NCI-H460 (lung cancer cell line), as well as against non-cancerous liver cells (porcine liver cells). Of all

the tested samples, the 3rd sample was the only one that inhibited the growth of all the tested cell lines, with the greatest activity against the growth of the HepG2 cell line. The 1st and 2nd samples were active against MCF-7 cells, the 4th and 5th samples against NCI-H460 cells, and especially the 4th sample together with the 1st and 5th against the HeLa cell line. It is important to note that none of the bread samples showed toxicity to normal cells [56].

10. Beeswax and Its Role in Human Health

Beeswax has been used since ancient times for its antimicrobial properties in European and Asian traditional medicines [2].

Regarding its antimicrobial activities, a crude extract of beeswax has shown inhibitory effects against *S. aureus*, *Salmonella enterica*, *C. albicans* and *Aspergillus niger*. Such effects could be at least partially dependent on the plant-derived compounds of beeswax [2] [57].

A mixture of beeswax, honey and olive oil can be used successfully against dermatitis, psoriasis, against fissures variegated, against fissures of the anus and hemorrhoids and against burns. This mixture also containing propolis has been used successfully against oral mucositis [58] [59] [60].

Oral administration of a mixture of six beeswax alcohols called D-002 (50 to 100 mg/day) for 6 weeks can improve arthritic symptoms and improve clinical progression in patients with osteoarthritis. The blend has also been reported to have effects on both joint health and gastrointestinal health, tested in both animal and human clinical trials. These activities are due to the antioxidant and anti-inflammatory effects of this mixture. The addition of D-003, a blend of sugarcane fatty acids, to D-002 is even more successful in treating human osteoarthritis [61] [62].

11. Conclusions

This review focused on the potential benefits of bee products for human health. These products are particularly rich in active ingredients such as flavonoids, phenolic acids, phenolic compounds, and enzymes, which have bioactive functions in preventing certain diseases and promoting good health. Bee products (honey, propolis, bee pollen, drone brood, royal jelly, bee bread, bee wax and bee venom) have been widely used in traditional healing practices. With their potential medicinal and pharmaceutical properties, this last century there has been an increased interest and research of bee products. With the prodigious technological development in research tools and the enormous progress in human understanding of biological processes, the main active ingredients responsible for the anticancer, antimicrobial, and other properties of bee products need to be clearly specified in a standardized manner to improve the application of bee products in disease management. Each bee product has a distinct efficacy with important nutritional properties and functional values. Thus, bee products can be developed into powerful therapeutic agents.

It is important to mention that numerous animal studies were reviewed. Therefore, it is imperative that further studies be conducted on humans for the determination of the critical mechanisms associated with the pharmacological activities of these products, in order for the confirmation of the benefits on human health. However, it is very important to emphasize the fact that so far, bee products have been proven to be perhaps the most important drugs that nature has offered to humans.

Agree to Conditions

1) All authors of the manuscript have read and agreed to its content and are accountable for all aspects of the accuracy and integrity of the manuscript;

2) The submitted article must be the one presenting original work that is not being considered or reviewed by any other publication, and has not been published elsewhere in the same or a similar form.

Acknowledgements

The publication of this article was financially supported by the Special Accounts for Research Grants, University of West Attica.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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