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Possible Health Problems Caused by Bee Products and Uncontrolled Use

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Abstract: Traditional and alternative medicine practices are used in Turkey, as well as around the World, to protect health and treat various diseases. Among these applications, Apitherapy has come to the fore particularly in recent years. As the use of medicines causes serious side effects, especially on human health, people are increasingly turning to alternative medical treatments. Apitherapy is a treatment method involving bee products such as honey, pollen, Royal Jel, propolis, and bee venom. It is primarily used for the purpose of promoting a healthier lifestyle. While these products have been traditionally used in various treatments for many years, their systematic use has gained prominence in recent years. Studies have shown that these products strengthen the immune system, provide protection against various types of cancer, and exhibit antimicrobial and antioxidant properties. In addition, the high protein, vitamin, mineral and amino acid content in these products increases the treatment potential. However, in addition to the benefits of these supportive and therapeutic substances, there is also the possibility of various toxic effects when used irregularly and without medical supervision. Sometimes these conditions can lead to various organ failures. This review aims to reveal the adverse effects encountered in the use of bee products and apitherapy applications and emphasizes that all natural products, especially bee products, should not be used uncontrolled.

Arı Ürünleri ve Kontrolsüz Kullanımlarından Kaynaklanabilen Sağlık Sorunları

Anahtar Kelimeler
Apiterapi,
Bal,
Arı poleni,
Propolis,
Apilarnil
Arı zehri

Özet: Tüm Dünya'da olduğu gibi Türkiye'de de sağlığın korunması ve çeşitli hastalıkların tedavisinde geleneksel ve alternatif tıp uygulamaları kullanılmaktadır. Apiterapi bu uygulamalar arasında özellikle son yıllarda dikkat çekmektedir. İlaç kullanımının özellikle insan sağlığı açısında ciddi yan etkilere sebep olmasından dolayı insanlar yan etkileri az veya hiç olmayan alternatif tıbbi tedavi yöntemlerine yönelmektedir. Apiterapi, bal, polen, arısütü, propolis, arı zehiri gibi arı ürünleriyle yapılan bir tedavi yöntemi olup daha çok sağlılıklı yaşam amacıyla da kullanılmaktadır. Arı ürünleri her ne kadar uzun yıllardır geleneksel olarak çeşitli tedavilerde kullanılıyor ise de özellikle son yıllarda daha sistematik olarak kullanılmaya başlandı. Bu ürünlerin, immun sistemi

güçlendirdiği, çeşitli kanser türlerine karşı koruyucu olduğu, antimikrobiyal, antioksidan özellik gösterdiği yapılan çalışmalarda anlaşılmıştır. Ayrıca bu ürünlerin yüksek oranda protein, vitamin, mineral, aminoasitler içermesi de bu tedavi potansiyellerini yükseltmektedir. Bununla beraber, her destekleyici ve tedavi edici maddenin yararlarının yanında, düzenli ve doktor kontrolünde kullanılmadıklarında çeşitli toksik etki gösterme ihtimali vardır ve bazen bu durumlar çeşitli organ yetmezliğine de neden olabilmektedir. Bu derleme, arı ürünlerinin kullanımı ve apiterapi uygulamalarında karşılaşılan olumsuz etkileri ortaya koymayı amaçlamakta ve başta arı ürünleri olmak üzere tüm doğal ürünlerin kontrolsüz kullanılmaması gerektiğini vurgulamaktadır.

1. INTRODUCTION

Apitherapy has been increasingly utilized in recent years. However, as with any supportive or complementary product, the use of supplementary foods may have beneficial effects, they may also have harmful consequences for health. Therefore, the application of apitherapy under the medical supervision has gained importance. In this review, the benefits and potential risks of bee products will be discussed based on recent studies.

1.1. Honey

Honey is divided into two primary groups, flower honey and secretory honey, based on the origin of the collected nectar by bees. Flower honey originates from the nectar of various plant flowers, and notable varieties include lime, clover, citrus, cotton, thyme, and acacia honey. Secretory honey is sourced from plant secretions such as pine, oak, and leaf honey [1]. It is prohibited by law and regulation to add any external substance or to remove any substance from the natural structure of honey that contains many bioactive substances beneficial to health. According to the *Turkish* Food Codex Honey Regulation [2], honey should have a distinctive taste and odor, should be free of any additives, should not contain pollen and honey-specific substances that have not been removed, and should not contain pathogens, parasites and their eggs that are harmful to health such as *Clostridium botulinum.*

Honey contains on average 80% carbohydrate, 17% water and various minor compounds including organic acids, mineral salts, vitamins, proteins, phenolic compounds, fats, and free amino acids [3] The colour of honey can vary from a light yellow to a dark brown or even black colour. The colour of honey is determined by compounds such as the phenolic compounds of the pollen, carotene and anthocyanidins. Dark honey has higher mineral content and antioxidant properties than light honey [4].

Honeybees generally prefer flowers as a source of nectar and sometimes use secretions left by trees (oak honey) or secretions left by insects in trees (pine honey) [5]. Depending on the source of honey and the substances it contains, honey has antimicrobial, antitumour, antiparasitic, immunomodulatory, anti-inflammatory, antioxidant, gastroprotective (antiulcerative), cardioprotective, hepatoprotective, antianemic, prebiotic, antiosteoporotic, and wound healing properties [6].

Honey has been recognized for its effectiveness against both gram-negative and gram-positive bacteria [6]. In a study [3], a 10% concentration of honey applied to the *Echinococcus granulosus* parasite, which causes hydatid cyst (echinococcosis), exhibited a lethal effect from the third minute onwards. Aksoy et al. [7] evaluated the antimicrobial activity of honey samples collected from Bingöl region and reported that 0.1 mL honey inhibited the growth of bacterial species such as *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Bacillus brevis, Pseudomonas aeruginosa*, as well as fungal species like *Candida albicans and Rhodotorula rubra*. The antibacterial properties of honey are due to its osmotic structure and H_2O_2 formed by the glucose oxidase enzyme in its structure, in addition to phenolic compounds [8].

Viuda-Martos et al. [6] reported that flavonoids such as pinocembrin, galangin and caffeic acid phenethyl ester (CAPE) inhibit bacterial RNA polymerase. In addition, they reported that quercetin inhibited ATP synthesis of the bacterium by increasing the permeability of the cell membrane, leading to the loss of the ability to transport substances through the cell membrane and mobility.

The anti-cancer effects of honey has been noted across a range of tumour cells, including those associated with breast cancer, cervical cancer, leukaemia, renal cell cancer, bladder cancer, colon cancer, prostate cancer, oral cancer, bone cancer, and brain cancer [9]. Apart from honey's antimicrobial, antioxidant, and anticancer effects, researches indicate that the metabolites within its composition also exhibit positive influences on wound healing, as well as on the diseases of digestive system and cardiovascular system [9]. Ajibola et al. [10] reported that honey reduces the effect of gastritis and ulcer by inhibiting the development of *Helicobacter pylori* bacteria, the main causative agent of gastric ulcer. In addition to the many beneficial health effects of honey, it is emphasized that there are also some adverse effects. One of these situations is mad honey poisoning. Mad honey poisoning occurs when consuming honey produced from Rhododendron flowers containing grayanotoxin. Rhododendron is commonly found in the eastern Black Sea region and cities bordering the Black Sea in Turkiye. The flowers, particularly in spring, provide a rich source of nectar for honeybees. Grayanotoxins bind to sodium channels, resulting in their effects. The heart is the organ most rapidly affected by this toxin. Death with severe bradycardia can occur with consumption of this honey. Symptoms of poisoning in humans depend on the amount of honey consumed and may include increased salivary secretion, vomiting,

and paraesthesia around the mouth and extremities. The clinical signs are typical of grayanotoxin poisoning, as indicated by the patient's history of eating honey and clinical findings [11].

The consumption of honey is not recommended for infants under one year of age due to the possible presence of *Clostridium botulinum* bacteria spores. These spores can open in the stomach and intestines, producing toxins that cause poisoning. Symptoms typically include nervous system issues, weakness, decreased sucking, weak crying, constipation, and diminished muscle strength. If the symptoms untreated, respiratory muscle involvement can lead to death [12].

1.2. Propolis

Propolis is a collective term referring to a resinous substance that honeybees gather from various plants, along with pollens and waxes. Additionally, its quality is enhanced by incorporating assorted saliva and enzyme-containing secretions. Resin, primarily sourced from trees, is collected by bees, who enhance it with substances from their salivary glands and further process the mixture using their mandibles. Bees use propolis to disinfect honeycombs, as a building material and for mummification. The word, propolis, Pro"; front, entrance, and "police"; is Greek in origin, it means city and was used in relation to honeybees defending their hives [13].

The colour of propolis varies, appearing in shades of yellow, brown, or green, influenced by the region of collection and the diversity of the local plant flora. Structurally, it has a sticky and resinous form. It is known as bee glue due to its gummy feature. Propolis turns rigid and fragile when the temperature drops below 10 degrees, and it becomes smooth and resin-like at temperatures between 15 and 25 degrees. At 30-40 degrees, it becomes softer and has a pronounced sticky structure. It turns into the structure known as liquid propolis at temperatures above 40 degrees [14].

Propolis comes from several continents, locations, and plant species, which contribute to its unique composition. The composition and structure of propolis vary based on the diversity of plants accessible to bees. Propolis activities could consist of enhancing the stability of the structure and lowering vibration, enhancing the hive's thermal insulation, and minimizing water loss and offering defence against infections through antifungal and antibacterial qualities [15,16].

Propolis is primarily created by plants, compounds released by the metabolism of honeybees, and elements that arise during propolis synthesis (17). Propolis typically consists of approximately 50% plant resin, 30% wax, 10% essential oils, and 5% pollen. Its composition also contains small quantities of other chemicals (5%) including benzoic acid, lactones, quinones, steroids, sugars, vitamins (B1, B2, B3, and B6) and natural pigments (carotenoids and chlorophyll). Among the most significant chemical components of propolis are flavonoids, responsible for its antibacterial, antiviral, anti-fungal, and anti-inflammatory properties, along with aromatic acids, terpenoids (including diterpenoid acids and triterpenoids), fatty acids, esters, phenols, aldehydes, and ketones. [15, 18].

According to the researches propolis and its extracts in particular, have been shown to possess antibacterial, antiviral, antifungal, antioxidant anti-inflammatory, anti-allergic, anticarcinogenic, anti-diabetic, cytostatic, hepatoprotective, photoprotective, immunogenic, and because of its wide range of biological actions, including anaesthetic, it has been used for a very long time for both illness prevention and therapy [19, 20, 21, 22, 23]. Propolis is beneficial in treatments of tumours, some types of cancer, some neurological diseases, mouth sores, wound, burn and respiratory system diseases (flu, pneumonia, bronchitis), some digestive system diseases, and infections affecting the urinary tract. [17, 24, 25]

Propolis and its constituents play a crucial role in promoting good health and preventing and treating minor illnesses. It has many positive qualities, however researches have shown that in those who are allergic to any of its constituents, it can trigger allergic reactions. The following adverse reactions were observed: dyspnea, oral pain, perioral dermatitis, labial edema, peeling of the lips, and contact cheilitis [26, 27]. Propolis has been found to contain a few allergens, including phenylethyl caffeate, ferulic acid, benzyl caffeate, 3-methyl-2-butenyl caffeate, geranyl caffeate, methyl cinnamate, benzyl alcohol, and tectochrysin. Propolis should also be routinely tested in children and adolescents prior to prescription, as it appears to be one of the most common allergens [26].

Moreover, heavy metals and other environmental contaminants may be present in propolis as a natural product. According to the analysis, six harmful metals were detected in 106 samples of raw propolis from Brazil [20], Harmful metals, as they do not break down naturally, can build up in organisms throughout the food chain and ultimately reach humans primarily through food (up to 90%). It's noteworthy to note that heavy metal concentrations are decreased by 24.24% to 100.00% during the filtration and separation of crude propolis [26].

A study assessing the effects of propolis extracts on health revealed that propylene glycol extract led to blood vessel dilation and neuron apoptosis in brain tissue. Furthermore, it was observed that propylene glycol extracts of propolis exhibited higher toxicity levels compared to olive oil and water extracts. Consequently, olive oil and water extracts of propolis are regarded as safer alternatives for pregnant and infant rats in comparison to propylene glycol extract [28].

Propolis and products derived from it have the potential to become contaminated with in-hive acaricides such as coumaphos and tau-fluvalinate. Moreover, since honeybees utilize propolis in the hive as a protective substance and building material, they are consistently

exposed to pesticide residues present in the product [29]. The available data suggests that various pesticide residues, particularly acaricides, may accumulate in perge, propolis, and beeswax, reaching concentration levels exceeding a thousand µg/kg [30].
Diagnosing medication-induced liver injury can pose a challenge for many potential causes, including both prescription and over-the-counter medications, as well as herbs and other medicines. Propolis is not currently listed as a cause, and there is no recommended dosage as the product is considered safe. But a case report describes a young man who experienced elevated liver enzymes because of chronic consumption of high doses of propolis [31].

Propolis finds extensive use in traditional medicine, so more research in this area is necessary. Additional data collection is needed to assess the potential harmful impact of this bee product when consumed in large amounts over an extended period. Despite the numerous advantages, widespread accessibility, and economic viability, it is crucial to reconsider the potential applications of propolis and its flavonoids as medicinal treatments.

1.3. Bee Pollens

Basically, Pollen, the reproductive cell of flowering plants, is a microscopic structure resembling grains that is discovered in the anthers of stamen within closed-seeded plants. Honeybees collect and process this pollen into bee pollen.

Thanks to its high protein content, it plays a crucial role in sustaining the nutrition of bees royal jell production, the development of the muscular and digestive systems of young bees, the development of offspring, in short, in ensuring the continuity of the colony [32].

Different plant sources are the reason to produce different colours, such as red, yellow, green, purple and orange. The size (6-300 µm), colour and shape of pollen grains varies according to its plant origin [32; 33].

The physical, biological, or chemical properties of pollen may vary depending on the geographical location of the region from which it is collected, climatic characteristics, storage and packaging [33]. Typically, bee pollen constitutes a multicomponent colloidal system consisting of biopolymers and diverse particles, including oil droplets, gas bubbles, lipid crystals, and more.

According to plant sources, pollen has approximately 200 components. Although the carbohydrate ratio of bee pollen varies between 13-55%, it is around 30.8% on average. Of the total 30.8%, 25.7% comprises glucose and fructose sugars, while the protein content of bee pollen ranges from 10% to 40% depending on the plant source, with an average of 22.7%. [34]

Recently, there has been significant interest in refining snacks using honey-making irritant, as it serves as an excellent model for healthy minerals [35)]. It holds lipids, proteins and micronutrients essential principally for honeybees, while presenting nutraceutical potential for human countering many afflictions [36].

Bee pollen has a wide range of therapeutic properties, including antioxidant, antimicrobial, fungicidal, anti-radiation, hepatoprotective, chemoprotective, and/or chemotherapeutic It has preventive, anti-inflammatory and intestinal function regulating activities. Additionally, it improves cardiovascular health and acts as an antibiotic, anticancer, and antidiarrheal agent. It also strengthens the digestive and immune systems, consequently delaying aging, and improving issues such as gastroenteritis, arteriosclerosis, respiratory diseases, and prostate problems [37]. In addition to the therapeutic effects of pollen, many side effects including allergic reactions such as anaphylactic shock have been reported.

1.3.1. Pollen Allergy

In addition to the therapeutic effects of pollen, anti-therapeutic properties have also been revealed by various studies. Pollen allergy, anaphylactic shock and many side effects are examples. Pollen allergy is the result of a distinguishing reaction invulnerable structure to an irritant. Antigen-presenting cells (APCs) introduce the invulnerable response by communicating incidental signals to added containers. T cells are triggered by aeroallergens [38]

1.3.2. Bee Pollen-Induced Anaphylaxis:

There are various reports of acute susceptible reactions induced by honey-making pollen, containing anaphylaxis [39, 40, 41]. The literature reports cases of anaphylaxis linked to bee pollen consumption, yet many individuals are unaware of this potential danger. Evidence supporting this association mainly stems from case reports and a single small case-control study. For example, Cohen and others reported three cases of allergic rhinitis, one of them developed severe allergic reactions after consuming honey containing dandelion pollen, indicating cross-allergenicity between wind-pollinated ragweed and insect-pollinated dandelion [40, 42].

They have also documented hypersensitive reactions triggered by honey-making pollen [42]. In 50% of these cases, individuals sensitized to wind-pollinated irritant pollen experienced intrinsic allergic responses after consuming honey-made pollen containing bug-pollinated Compositae family appendages like dandelion and goldenrod. Common syndromes observed include facial edema, urticaria, and transient allergic rhinitis.

1.3.3. Other Side Effects of Bee Pollen

Despite honey-making irritant appearing to be generally safe and effective, approvals for using honey-making pollen for hypersensitivity, immunological, and other conditions, as well as emphasizing the healthful compounds it contains, it is essential to consult a

physician before utilizing any unrefined product for any medical condition. Some irritant contains poisonous wealth such as mannose sugars, miscellaneous alkaloids, heavy metals, pesticides, herbicides, mycotoxins, microorganisms, medicines and polyphenolic compounds [42, 43]

Due to the aforementioned anti-therapeutic effects, pollen and pollen products need to be thoroughly characterized for allergens and other components with potentially harmful effects.

In conclusion, there are many mechanisms and much to be investigated on the anti-therapeutic effects of pollen.

1.4. Royal Jelly

Royal Jelly (RJ) which is also known as Apilak has creamy composition and displays colour range between white to yellow. This substance is produced by worker honeybees locally in their hypopharyngeal and mandibular glands. In their life circle, specifically, during the beginning of their larvae stages, bees are fed by this unique food for first three days. Subsequently, the worker bees' diet substitutes to different food choice which is named as perge that includes dominantly honey and pollen while the bees that is selected as the future queen bee proceed to consume RJ for rest of its lifetime [44].

RJ has traditionally been favored in alternative medicine, particularly since ancient times in Egypt, and throughout Asian apitherapy practices, it has been utilized extensively. Today, RJ is favored in the pharmaceutical and alimentary industries and is available over-the-counter as a dietary supplement [45].

RJ contains approximately 67% water, 16% carbohydrates, 12.5% protein and amino acids, and 5% lipids, with notable variations observed among different sources [46]. The distinct and abundant nutritional content of carbohydrates, proteins, lipids, vitamins, minerals, polyphenols, flavonoids, and several biologically active substances is attributed to the many pharmacological properties of RJ [47]. The primary constituent of RJ is protein, accounting for 50% of its dry matter [48]. Sugars, mainly glucose and fructose, compromise 90% of the overall carbohydrates content of RJ, while sucrose 0.8-3.6%. [49]. Minor components of RJ are enzymes, minerals, vitamins and phenolics [46].

RJ contains royalisin peptides and antimicrobial jelleins, MRJPs, 10-hydroxy-2-decenoic acid (10-HDA), which have anti-inflammatory, immunomodulatory, antimicrobial, metabolic syndrome-protecting, neuromodulatory and anti-aging properties [45].

Several research have documented antimicrobial effects of RJ on bacterial, fungal and viral pathogens, while hypotensive, antihypercholesterolemic, antitumor, and anti-inflammatory effects have been reported in model animals [50].

Furthermore, clinical studies have demonstrated antidiabetic effects, benefits for non-malignant prostatic hyperplasia, and assistance in wound repair for diabetic foot ulcers [51].

RJ is considered a significant contributor to healthy aging and longevity. This is because it promotes the overall health and reproductive capabilities of queen bees. Queen bees, which can produce up to 3,000 eggs in a day and live for up to five years, owe their longevity to RJ, while sterile worker bees typically survive for only 45 days 45 days [52]. The beneficial effects of RJ in humans extend beyond physical health improvements to encompass enhancements in general mental health, including reductions in anxiety levels and improvements in mood and mild cognitive decline among the elderly (>60 years) [53, 54].

The neurological psychological benefits of RJ are shown by changes in biomarkers of physical health; cholesterol and apolipoproteins can be given as examples. Hypercholesterolaemia has been shown to favour the accumulation of β-amyloid, leading to neuronal loss - a signature finding of Alzheimer's disease. On the other hand, the decrease in plasma lipids caused by RJ has been related with an increase in antioxidant effect, a decline in β-amyloid accumulation and the protection against neuronal damage [55].

In terms of appropriate RJ usage dose, research has shown that 100 mg/kg is typically the most efficient dose, and greater doses are rarely needed. 0.5g/day is suggested and can be continued for 2 to 12 months for infants. For adults, doses ranging from 1 to 5 grams per day can be taken based on the underlying medical condition. To achieve more potent and rapid results, a higher dosage of 10 grams per day can be administered for a shorter duration, such as 3 months with 10 days per month [56].

Ensuring the effectiveness of RJ is essential for its successful application in promoting health. Exposure to heat and certain handling methods can compromise the constituents and efficacy of RJ. Most of RJ's biological properties diminish after being exposed to 40°C for 30 days [57].

Royal jelly is utilized in various products globally, including dietary supplements, beverages, beauty items, and numerous other goods. While it is regarded as relatively harmless and non-toxic adverse reactions of RJ have been reported, the most common of which are allergic reactions, with symptoms ranging from slight to serious [58]. These reactions range from mild to serious, mild gastrointestinal upset, haemorrhagic colitis, and typically include rash, allergic rhinitis, contact dermatitis eczema, conjunctivitis acute asthma, anaphylactic shock, bronchospasm and in a few cases fatality [58, 59].

As with honey, environmental pollutants may exist in RJ. The most prevalent are organochlorine, organophosphorus and carbamate pesticides, which are generally under the minimum hazard grade.

Nevertheless, there have been instances where the highly toxic chloramphenicol has been detected [60].

Bee products like pollen, honey, and venom may lead to allergic reactions that are less severe when compared to those caused by royal jelly. People allergic to these products should not take RJ orally. In addition, caution should be taken when advising RJ to pregnant or breastfeeding women, children [59] and patients with a medical background of allergic conditions such as asthma, rhinitis or atopic dermatitis. If allergic reactions occur following the initial consumption of RJ, this could be attributed to the presence of allergens that cross-react with RJ. [58]. Intake of RJ can incidentally cause contact dermatitis, anaphylaxis, and asthma while MRJP-1 and MRJP-2 are reported as potent allergens [61].

In conclusion, to ensure the efficient and harmless use of RJ as a dietary supplement allergy test should be carried out prior to RJ consumption [58, 59].

1.5. Bee Venom

Bee venom, also known as apitoxin, has a significant role in the defence of the bee colony and is produced in the venom glands located in the abdominal cavity of the bee and stored in the venom sac. The amount of this venom collected in the sac is approximately 0.3 mg. Bee venom is a clear and acidic (pH 4.5-5.5), odorless and watery liquid with a bitter and pungent taste and yellowish-white crystalline structure when dried [62].

The arrangement of bee venom changes depending on many factors to a degree the race of the bee, feeding environments, collection time, and the encircling flora. In general, bee venom consists of various bioactive molecules such as peptides such as melittin, apamin, mast cell degranulation peptide (MCD peptide); minerals such as P, Ca and Mg; enzymes such as phospholipase A2, hyaluronidase, lysophospholipase; biological amines such as dopamine and histamine; and phospholipids [63, 64].

The therapeutic effect of bee venom has been examined by in vivo and in vitro studies, such as its anti-inflammatory, analgesic, anti-hepatotoxic, cytoprotective, antioxidant, antimicrobial, antiviral, radioprotective, antimutagenic, anti-arthritic and anticancer effects [19, 45, 65, 66]. Furthermore, it has been shown that bee venom halts the progression of Alzheimer's disease by protecting the nervous system [67].

The various and complex arrangements of bee venom and the synergistic effects between these components have been stated to aggravate multiple organ damage. Therefore, the mechanisms of toxic reactions caused by bee stings should be thoroughly investigated before treatment with bee venom [68]. The components of bee venom that cause these effects are mainly melittin and phospholipase A2. Melittin has been stated to have analgesic, anticancer, and anti-inflammatory effects. However, it has inflammatory, cytolytic, and hemolytic effects at high doses. Phospholipase A triggers inflammation is a strong allergen and is the most harmful bee venom component. In the body, it can cause hemolysis and damage the lipid structure of the cell membrane, leading to cell damage and lysis [69] Hyaluronidase has an allergic effect, while apamin has a neurotoxic effect at high doses. Histamine is another component of bee venom with allergic effects [70].

Bee venom injection, like many different alternative medicine approaches, has been used for thousands of years to relieve pain and various symptoms of inflammatory and painful diseases. Bee venom may be applied in various ways, such as direct bee sting, bee venom injection, or bee venom acupuncture [71]. Clinically, injection of bee venom into acupuncture points has been reported to be successful in the treatment of diseases such as arthritis, Parkinson's disease, multiple sclerosis neuropathic pain, and Alzheimer's disease. In the treatment of rheumatoid arthritis, bee venom treatment in combination with other medications has been reported to be more efficient than treatment with medication alone. In addition, the relapse rate was significantly reduced in patients treated with bee venom [72]. Bee venom has also been reported to have many beneficial effects in vivo and in vitro in Amyotrophic Lateral Sclerosis (ALS), a central nervous system disease defined by degeneration of upper and lower large motor neurons resulting in muscle weakness, including anti-neuroinflammation, reduced neuronal mortality, and decreased glutamate toxicity. A recent study proved that treatment with bee venom showed bright results as a safe adjunctive treatment for Parkinson's disease, providing significant clinical improvement compared to conventional treatment. In Parkinson's Disease in vivo and in vitro, bee venom improved motor symptoms through anti-neurodegenerative effects [71].

Studies have been conducted to examine the anti-cancer activity of bee venom in lung cancer, colon cancer, prostate cancer, melanoma, pancreatic cancer, and many different cancer cell lines. The mechanism of anti-cancer action of bee venom depends on the inhibition of cell proliferation, induction of cell death and apoptosis, inhibition of metastasis, and cytotoxicity. It has been reported that beekeepers have a lower incidence of cancer compared to others, especially a significantly lower incidence of lung cancer [73].

Treatment with bee venom can be therapeutically beneficial or harmful in some patients. Although bee venom therapy is studied as a hopeful therapeutic alternative for the treatment of chronic pain and various diseases, it has not been accepted by food and drug authorities globally. The first reason is that bee venom can cause various allergic reactions in susceptible individuals, which include systemic and anaphylactic reactions. Allergy to bee venom is hazardous and can be lethal [74]. In the study investigating the organismal response following injection of melittin and phospholipase A2, rats were injected with the potential stressors melittin and phospholipase A2. As a result, it was reported that these compounds are extremely potent

stress factors, toxic at the doses tested, and cause degenerative changes in various cell compartments, especially mitochondria [75].

Systemic allergic bee sting reactions have been notified in 3,4% of children and 7,5% of adults. These allergic responses can be mild with skin symptoms such as flushing and angioedema, or categorized as moderate to severe with the risk of lethal anaphylaxis. For this reason, allergy testing should be performed before bee venom treatment [76].

Besides all this, bee venom is a neurotoxin, and apamin in its composition has been shown to trigger depression and drowsiness in rats by blocking Ca+2-dependent K+ channels (Ludman and Boyle, 2015). Additionally, histamine, acetylcholine, and norepinephrine, which also exist in bee venom, have been shown to affect neuronal responses in rats [77].

Bee venom increased ion permeability and haemoglobin release in human erythrocytes and had a significant lysis activity on human erythrocytes [78].

Several research studies have shown that the therapeutic use of bee venom is contraindicated in children under 5 years of age, pregnant and lactating women, Type 1 diabetes, infections, kidney and liver failure, hepatitis, heart and lung problems, and chronic tuberculosis [79].

In conclusion, despite the therapeutic effects of bee venom therapy that have been concluded in many diseases, its safety is still a limitation and an obstacle to its use as the main treatment. In a systematic review and meta-analysis, 58 out of 145 studies reported mild to severe adverse outcomes following administration [80]. Therefore, more studies are needed to evaluate the safe use and efficacy of bee venom therapy.

1.6. Apilarnil

Apilarnil, which is obtained by collecting and homogenizing Drone larvae in 3-7 days, contains a small amount of RJ, perge, honey and propolis. Although it is not usually used, the honeycomb with apilarnis is cut by beekeepers and thrown away. Apilarnil is a highly concentrated nutritious bee product which ingredients are known to have antiviral, immune-boosting, regenerative power and vitality of the body [81]. It is contained proteins, carbohydrates, fats, polyphenols, amino acids, vitamins (vitamin A, betacarotene, B1, B6, and choline), minerals (calcium, phosphorus, sodium, zinc, manganese, iron, copper, and potassium), hormones, unsaturated compounds (desenoic acids and sulfhydryl compounds), antiviral substances [82]. Apilarnil contains all the essential amino acids of the basic building block of bee larvae so that it is considered a complete food and is widely used in human and animal diets [14].
It has been established by studies that apilarnil stimulates spermatogenesis in men, since it comes mainly from the structure of the male bee larva and is very rich in androgenic hormones. Therefore, both the androgenic and anabolic effect of apilarnil is considered a natural alternative to medicines and chemicals to stimulate sexual development [83, 84]. Bee larvae in honeycomb cells are consumed as food in many countries [85]. Most of the economically important and edible insects are obtained through production in existing agricultural systems. Apilarnil was first used in Romania in 1980. It was applied by Nicola Iliesu for the treatment of the elderly with neurodegenerative, psychotic or sexual disorders [84].

Male bee larvae are mostly considered a byproduct of beekeeping but have recently been advocated as a high-protein food source. There are some cases related to their allergenic potential [86]. An instance involves a 29-year-old beekeeper who encountered an anaphylactic reaction after consuming a freshly prepared beverage made from male bee larvae. Larval specific susceptibility has been tested and confirmed by basophil activation tests [87]. It has been established that there is an IgE-mediated allergy to drone larvae. There are not enough case reports to develop a specific awareness of the allergenicity of bee larvae, but allergen awareness against the use of apilarnil may be recommended if cases of allergy to other bee products are considered.
It has been described that in some cases of overdose, gastric pain, nausea, diarrhoea. In addition, toxicity, hyperandrogenism, hyperspermatogenesis and a strong antibacterial effect against gram-positive bacteria (Bacillus aureus) may occur if the dosage exceed normal usage [88].

The primary function of Apilarnil is to contribute to the battle against disease progression and potentially offer remedies. The diseases that Apilarnil may alleviate include; hypoproteinemia, metabolic diseases, decrease in muscle body weight, chronic fatigue syndrome, physical fatigue, convalescence, premature aging, depression in the elderly, diseases of the nervous system (mental disorders, neuro-psychomotivational diseases), respiratory apparatus diseases, skin deficiencies [89].

Especially, owing to its sexual development properties, Apilarnil offers notable benefits in treating conditions originating from the genital areas, deficiencies in hormones, vitamins, and minerals essential for the optimal development and function of these organs. It is particularly effective against sexual impotence, including issues like low spermatogenesis, erectile dysfunction, and shortened sexual activity duration in men. Moreover, it proves beneficial in addressing endocrine system disorders such as weakened pituitary and adrenal glands, along with alleviating premenstrual syndrome [83, 89].

Several factors may diminish the efficacy of Apilarnil. In cases of diathesis, the body may struggle to digest or absorb Apilarnil efficiently, leading to inadequate processing of its components. Another factor relates to genetic issues; when the "target" organs, such as the endocrine glands, exhibit significant structural or genetic problems, they may not effectively utilize the active compounds present in Apilarnil. It can be inferred that Apilarnil, like other bee products, cannot cure every

disease or bodily issue in instances of diathesis or genetic problems [89].

Performing apitherapy applications by unqualified people, using products that are not medical products, uncontrolled use of products that do not have dose studies, or epigenetic problems specific to the person to whom the application is made may cause negative results in treatment with bee products.

The use of bee products both as food and for apitherapy purposes is very important. However, some allergic reactions may occur in users after the consumption of bee products, incorrect apitherapy applications may be made by non-experts, or some undesirable effects may occur after apitherapy applications in patients.

Although the right applications have been made, the fact that the product used is exposed to environmental contaminants and heavy metals such as pesticide-derived organochlorines, organophosphates, carbamates, and chloramphenicol during the production phase causes the production of unhealthy raw materials [90]. Synthetic acaricides are mostly fat-soluble and persistent in wax [91] These drug residues accumulated in apitherapy products adversely affect human health and are not suitable for apitherapy. In nature, toxic substances absorbed and stored by plants, as well as pesticides, poison honeybees and their products. All kinds of fat-soluble toxins can be absorbed, and even after a long time, when consumed as food or used in cosmetics, it shows its harmful effect. However, bee products are preferred over drugs due to resistance to antibiotics. Therefore, these products must be natural, antibiotic residue-free products with known quality standards.

1.7. Beeswax

Beeswax is a natural product synthesized from eight wax glands located in the abdomen of the female worker bee and used in the construction of honeycombs [92]. It is mostly produced by *Apis mellifera* and *Apis cerena*, the two most commonly bred species by human.

The amount of beeswax secreted is mostly determined by the needs of the colony. *A.mellifera* can produce approximately half of its body weight in beeswax throughout its life [93]. Beeswax is secreted in liquid form by 12-18 days old young worker bees, and solidifies into flakes as a result of contact with air [94]. The secreted beeswax appears thin and almost white, but later, when it comes to in contact with honey and pollen, it becomes intensely yellowish and solidifies due to the effect of the carotenoid pigment passing through the pollen. After four years, its color turns brown because it includes a cocoon [94, 95].

Bees consume 6-10 kg of honey to secrete one kilogram of beeswax and produce the beeswax by forming clusters from their wax glands [96]. The content of the beeswax varies depending on the location of production, the type of honeybee and the age of the beeswax. However, unhydrolyzed beeswax generally contains 71% of esters, 15% of hydrocarbons, 8% of free acids and 6% of the other compounds.

Beeswax is resistant to acids and also gastric juices of honeybees. Water and cold alcohol can not dissolve them, but they are partially soluble in boiling alcohol and completely soluble in chloroform, carbon disulfide and hot turpentine essence. The density of beeswax at 15℃ varies between approximately 0.960-0.970 kg/m^3 and it melts in the temperature range 63.5-64.5℃ [94].

Beeswax has a much larger range of uses compared to other bee products. In the past, beeswax candles were valued more because they had a higher melting point temperature value than other candles and could stay upright in hot weather [93]. In ancient Rome, a cream containing beeswax, olive oil and rose water, known as cold cream, was used to treat burns, cuts, bruises and fractures. Beeswax is included in the first cosmetic cream, together with olive oil and water/rose water emulsion, obtained by the Greek physician Galen in 150 B.C.

Beeswax has also been used in modeling and casting processes, there are sculptures made of beeswax [93, 97]. According to researchs beeswax and various combinations of beeswax show antimicrobial properties [97]. Kačániová et al. [98], collected propolis, bee pollen and beeswax samples from two different places in Slovakia and evaluated their antimicrobial activity against various bacteria, molds and yeasts. Beeswax extracts showed antimicrobial effects.

The approach to treatment of non-alcoholic fatty liver disease, which is a disease that can progress to liver fibrosis and cirrhosis, is nutritional change and weight loss. There is no completely successful pharmacological approach, but alternative treatments are being tried to be applied. Studies have shown that a mixture of beeswax alcohols with antioxidant effects, called D-002, help protect the liver [99]. In this research the effectiveness of D-002 was investigated and has been determined that 100 mg D-002 per day improves ultrasonographic findings and insulin resistance indicators in patients, but it has been reported that further studies are needed for confirmation.

Puente et al. [100] determined that administration of D-002, a mixture of beeswax alcohols, administered at 50-100 mg/day for 6 weeks positively affected osteoarthritis symptoms. There was amelioration in pain and stiffness and improvement in physical functionality were observed.

In the study of Perugini et al. [101], 178 beeswax samples collected from Italian hives between 2013 and 2018 were tested for 247 pesticides and the existence of one or more pesticides was determined in 73.6% of the samples. On average, each beeswax sample was reported to contain an average of three different pesticides, each containing up to 14 compounds, some of which are banned in Europe or not permitted in Italy.

It has been determined that more lipophilic pesticides are predominantly found in beeswax. While chromium and zinc were at the highest average concentration values in honey samples, lead and molybdenum were detected only in beeswax. It has been reported that the results obtained show that daily consumption of honey and beeswax may endanger the health of children [102].

1.8. Api-Air

Api-air is an area where the air from beehives is used. The hive contains many flavonoids, including RJ, propolis, honey and pollen. The api-air system was introduced by the German beekeeper Hans Munsch. The basic principle of the api-air system is based on the inhalation of the volatile active components in the bee products in the hive [96].

Heinrich Huttner developed a technique that uses beehive air for treating respiratory diseases. The method involves a hole in the top of the hive equipped with a ventilator and air, a hose through which the patient breathes, and a mask [103]. This therapy is used to treat asthma, bronchitis, pulmonary fibrosis, and respiratory infections [104].

A study identified 56 volatile components in beehive air originating from honey, propolis, perge, RJ, and beeswax. These components include fatty acids, alcohols, aldehydes, esters, ethers, hydrocarbons, phenol, ketones, nitrogenous compounds, and terpenes [105]. In terms of antibacterial activity, beehive air has only been shown to be effective against saureus. However, individuals using beehive air have reported experiencing relaxation, uninterrupted and restful sleep, increased lung capacity, and improved breathing comfort. Beehive air has also been claimed to be effective in treating various diseases, including bronchitis, asthma, allergies, chronic obstructive pulmonary disease (COPD), emphysema, immune system deficiencies, migraines, and depression. The patients underwent several medical evaluations, including observation of attacks, lung capacity tests, blood tests, and isotope measurements, which showed a rapid and effective recovery process. A beehive air condensation device has been developed for Hiveair in Ukraine.

Currently, in some European countries, such as Germany and Slovenia, this treatment is administered to humans by inhalation of beehive air in well-structured rooms. The aroma produced and inhaled in beehives has been suggested to be beneficial to human health. Air saturated with essential odours treats people with respiratory diseases. This alternative medicine is still a new field of study.

Some cases encountered after the use of other bee products or during their application are not known because they have not been written up. Api-air is one of the popular applications today. Although this application seems to be an innocent application, there are oral reports that the patient died during api-air application due to mycoplasma formation in the hive [106].

2. CONCLUSION

Bee products exhibit numerous pharmacological activities. It is a well-known fact that bee products are used in the treatment of many diseases. However, it is also known that this usage area lacks any control mechanism and is not subject to regulation. Therefore, as observed in many instances, it has been noted that bee products exhibit side effects ranging from mild to potentially fatal levels. To prevent unexpected side effects and potential harms, it is essential that the products obtained after production undergo quality tests and are prepared according to appropriate standards through various processes. Furthermore, routine monitoring of the quality and residue of these products should be conducted through analyses. Based on the detailed information provided, we strongly advise that apitherapy should be carried out under the supervision of a medical professional, considering the potential health issues it may pose.

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