Volume:2 Issue:1
Year: 2021

International Journal of Traditional and Complementary Medicine Research

Publisher
Duzce University

REVIEW

Overview of Apitherapy Products: Anti-Cancer Effects of Bee Venom Used In Apitherapy

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Received: 16.12.2020 Accepted: 01.04.2021

Abstract
While Brazil and the United States of America are in the first place in world Apitherapy research, our country is in the fifth place after Japan and China. While the studies on apitherapy are continuing rapidly in the world, it has started to become widespread in our country especially in 2014 with the regulation of traditional and complementary medicine practices, and Apitherapy units and application centers have started to be established. Apitherapy is the use of bee products to protect and improve health, to strengthen the immune system and to complement the treatment process of some diseases. While bee products such as honey, propolis, bee pollen have been known and used for a long time, studies on apilarnil, royal jelly and bee venom have started to increase in recent years. These products have been used both as foodstuffs and as a source of healing from wound healing to anticancer effect for many years due to their rich content. With scientific studies, the interest in apitherapy products has increased even more.
Cancer is known as the leading cause of death in our country and all over the world. Side effects, costs, etc. Such adverse conditions have led researchers to research natural treatment methods. These natural treatments are used to increase the effectiveness of existing traditional treatments. In this review, literature information about Apitherapy, which is one of the traditional and complementary medicine applications, chemical content and physiological effects of bee products, is given and the therapeutic effect of bee venom on cancer is mentioned. Studies on the anticancer activity of bee venom in almost all types of cancer have been conducted and promising results have been obtained. This situation indicates that this apitherapeutic product will take place as a supplement in cancer treatment in the near future.
Keywords: Apitherapy, Bee Venom, Honey, Propolis, Neoplasms, Traditional Medicine

INTRODUCTION

What is apitherapy?

Apitherapy is one of the 15 therapies defined according to the Traditional and Complementary Medicine Practices Regulation that entered into force in the Official Gazette No. 29158 dated October 27, 2014. Other therapies that are legally permitted to be used; Acupuncture, Phytotherapy, Hypnosis, Leech Application, Homeopathy, Chiropractic, Cup Application (Cupping Application=Cupping), Larva Application, Mesotherapy, Prolotherapy, Osteopathy, Ozone Application, Reflexology, and Music Therapy.

It is the way of using bee and bee products (honey, propolis, bee pollen, bee bread, royal jelly, apilarnil, bee venom) as support and complementary application method in the treatment of some diseases in order to protect and improve health and strengthen the immune system[1].

Apitherapy applications are carried out by a certified Apitherapy Specialist in an Apitherapy Unit or Apitherapy Application Center approved by the Ministry of Health. It should be determined whether there is an allergy before the application. It should not be applied to those with allergies and hypersensitivity. For the application of bee venom to the skin, live bee stings or injections containing bee venom containing extracts or ointments

containing bee venom are used. Chemical analyzes should be made for oral bee products (honey, propolis, royal jelly, pollen, apilarnil, etc.) and these products should be in accordance with the Turkish Food Codex Regulation and the Turkish Standards Institute instructions, and their quality control should be done.

What are bee products?

Bee products; Honey, propolis, bee pollen, bee bread, royal jelly, apilarnil, and bee venom are examined under seven headings.

While honey, propolis, bee pollen, and bee bread are products created by adding their own secretions to plant products (such as pollen, resinous substances, nectar) collected by bees from plants, royal jelly, apilarnil, and bee venom are products secreted directly by the bee or produced from its own body [2].

Honey

Honey, which contains about 200 types of components in its structure, is defined according to the Turkish Standards Institute 3036 Honey Standard and the Codex as a sweet product that results from the collection of nectar secreted from the flowers or other living parts of plants by honey bees (Apis mellifera), changing their composition in their bodies and maturing after being stored in the honeycomb cells [3-5]. Honey, which has rich content, varies according to the vegetation and honey source, but it has an average of 80% carbohydrates (monosaccharides (55-85%), disaccharides (2-15%), and trisaccharides (1-7%), 0.5% proteic substances, 0.1-0.2% polyphenolic compounds, 0.01% lipids, very small amounts of vitamins and minerals [6-10]. In addition, about 500 different volatile compounds in honey [11]. Detailed information about the content is given in Table 1.

It is known not only as food with delicious taste and nutritious qualities but also as a medicine that has been used in traditional medicine for centuries to protect health and treat some diseases [12]. As the most interesting product among apitherapy products, it has been known for many years that honey has a protective effect on the stomach against acute or chronic stomach injuries, has significant effects on the digestive system with its prebiotic properties, has a high healing potential in a wound and burn treatment, and its strong antimicrobial property is also supported by clinical studies [13-15]. The beneficial effects of honey are mainly due to its polyphenolic compound content [16] and have a high antioxidant capacity due to these compounds [17,18]. So much so that honey is considered to have higher antioxidant activity than antioxidant vitamins such as Vitamins C and E [19]. Thanks to this feature, it can reduce oxidative stress by eliminating the harmful effects of oxidizing molecules such as free radicals in the body [20]. It accelerates wound healing by providing tissue regeneration [21]. It has started to attract attention in recent years with its antiviral, antifungal, anti-inflammatory, antiallergic, anticancer, hepatoprotective, antiatherogenic, antinociceptive, and immunostimulant effects [22-24] and has been included in many studies. Compared to sweeteners such as sucrose and fructose in clinical studies, it has been found that honey consumption reduces postprandial glycemic response and provides a beneficial effect on diabetes by lowering serum glucose levels in patients with diabetes [25]. Honey, which has protective effects in addition to its therapeutic properties, has protective roles for many systems from the digestive system to the respiratory system, from the cardiovascular system to the nervous system [16].

Propolis

Although its content generally varies according to the vegetation, it is a product prepared by bees by collecting resinous substances and plant secretions from the leaves, buds, and branches of plants and adding some beeswax by subjecting them to enzymatic changes for the purposes of ensuring hygiene of the hive, preventing insects and other animals from entering the hive, and repairing cracks in the combs [26-28]. Recently, with the realization of its rich content, interest in propolis has increased and it has become popular with its positive effects on human health. It is known that propolis contains nearly 300 compounds as chemical content. The carbohydrate content of propolis, which has a high lipid content is

relatively low and it is only found in small amounts in resinous substances. The content of propolis; consists of 45-55% resinous substances, 25-35% wax and fatty acids, 10% essential oil, 10% polyphenolic compounds, 5% pollen, and 5% other organic compounds, vitamins, and minerals. In addition, it has been determined that there are 24 amino acids in its structure [22,29,30].

Due to the phenolic compounds, it contains, propolis is antimicrobial, antibacterial, antifungal, antiviral, antiallergic, antioxidant, anticancer, cytotoxic effect against tumor cells, hepatoprotective, cardioprotective, neuroprotective, renal protective, anti-aging, anti-ulcer, wound healing effect, anti-inflammatory effects against infections. Prominent with its immunomodulatory effect, propolis has been reported to reduce blood pressure and cholesterol levels [26,29,31-33].

Bee pollen

In flowering plants, the pollens that enable the fertilization of female cells are the structures that make up the plant's male reproductive cells. Bee pollen is defined as the product formed by the blending of pollen collected by bees from plants with their own body fluids (enzymes such as amylase and catalase secreted from salivary glands) [34,35]. This product is delivered to the hive by bees in pollen sacs on their hind legs and at all stages of development [36,37]. As with other bee products, the composition of bee pollen depends on a significant amount of plant source, climatic characteristics, and geographical conditions [38-40].

It has been known since ancient times that bee pollen, known as the "life-giving dust" in ancient Egyptian civilization, is both a healing and nutritious food and has been used as traditional medicine for a long time. [40-42]. With the content analysis of bee products, its importance has increased even more in recent years and has been rapidly included in the human diet. Bee pollen has also been recognized as a valuable dietary supplement for humans [38]. It is also anti-inflammatory, antiosteoporosis, anti-neurodegenerative, antioxidant, antibacterial, antiviral, antifungal, hepatoprotective, radioprotective, cholesterol-lowering, immunostimulant, probiotic, antiallergic, due to its phytosterol content. It has been reported to have positive effects on anticancer, antinociceptive, antiulcer, and wound healing [35,37,41-45]. Its use as a support in the treatment of asthma is also beneficial [35]. Bee pollen, which is valuable for humans and has many benefits, has been standardized in our country as in some countries, and the features that should be included in it are specified in TS 10255 Pollen standard.

Although its content varies according to the plant source, it is known that there are about 200 substances in bee pollen. Bee pollen, rich in proteic substances and carbohydrates, is also a rich source of lipids, vitamins, minerals, and polyphenolic compounds. It contains 22 amino acids that people need. Due to its polyphenolic compounds, it has a high antioxidant capacity with its scavenging effect, without causing oxidative damage to free radicals that cause many diseases [34,43,46-48]. Detailed information about the content is given in Table 1.

Bee bread (Perga)

The product formed within two weeks after the honey bees deliver the pollen they collect to the hive and these pollens are mixed with honey and other bee secretions and exposed to lactic acid fermentation which is called bee bread [49]. Bee bread, which is an important source of protein, oil, and vitamins in the feeding of bees, also constitutes the raw material of royal jelly production [50]. It has also been used by humans for nutrition and treatment since ancient times [51]. Recently, it has become a preferred product to treat many diseases with its rich bioactive substance content.

Although its content varies according to plant origin, it consists mainly of carbohydrates, proteins, and lipids, as well as phenolic compounds such as anthocyanins and flavonoids, lactic acid, volatile compounds, various vitamins, and minerals [52-54]. Although it is mainly composed of pollen, it is different in the content; while it contains richer carbohydrates and lactic acid than pollen, it contains less protein and fat [55].

Although the studies on bee bread are limited, more literature information will be obtained as its importance is understood. According to current information, it has been reported to have in vitro antibacterial, antiviral, antimicrobial, anti-inflammatory, antioxidant, hepatoprotective, radioprotective, immunomodulatory, anti-tumor, and adaptogenic properties [8,56-59]. It has positive effects on the liver, endocrine, and nervous system functions. Crisin and kaempferol isolated from bee bread have neuroprotective, anxiolytic, and anticonvulsant effects. It increases the regeneration of tissues and is important for physical and mental health [51,55].

Royal jelly

Royal jelly secreted from the upper pharynx and jaw glands of young worker bees is a product used for feeding the larvae [60]. Its nutritional value is quite high and it has a special nutritious environment that enables the queen bee to differentiate. While worker bees can only benefit from this food store in the first three days of their larval stages, it is the only nutritional product for the queen bee [61]. The chemical content analysis of royal jelly started in the mid-19th century and continues today [62]. Royal jelly, which has a highly mixed content, contains carbohydrates, proteins, amino acids, lipids, organic acids, steroids, esters, phenolic compounds, minerals, and trace elements. Fresh royal jelly contains 50-70% water, 7-18% carbohydrates, 9-18% proteins, 3-8% lipids, 0.8-3% minerals, and low amounts of vitamins and polyphenolic compounds. Lyophilized royal jelly contains <5% water, 22-31% carbohydrates, 27-41% proteins, and 15-30% lipids. Royal jelly, which contains all the amino acids required for humans, has 29 defined amino acids and derivatives, mainly glutamic acid and aspartic acid. This product, which is different from other products in terms of lipid content, has short-chain and long-chain fatty acids, which are also responsible for their biological activities [63-67]. Detailed information about the content is given in Table 1. With its rich content, this product, which provides food for worker bees for a short time and the queen bee for a lifetime, has also attracted the attention of humans. Studies increasing day by day include anti-aging, anti-inflammatory, antioxidant, antibacterial, antifungal, antiviral, antihypertensive, immunomodulatory, preventing osteoporosis risk, hepatoprotective, cardioprotective, antiulcer, neuroprotective, anticancer, growth promoting, wound healing, stated that it has antirheumatic, antidepressant, antiallergic, and balancing effects of high cholesterol levels [68-75]. Since it has estrogen-like activity, current studies are investigating that it can be a traditional solution for postmenopausal symptoms and reduce complaints [76].

Royal jelly, a natural product that is frequently used and preferred in the fields of traditional medicine and cosmetics, is being used as a supportive treatment for Alzheimer's, cancer, diabetes, and cardiovascular diseases, It is inevitable that the anti-aging effect will cause royal jelly to increase its popularity and even to remain in the for a long time [77].

Apilarnil

Apilarnil in Turkey is unknown yet, however, while the male bee larvae pupae collected during the period of 3-7 days the larvae before they found the result is a lyophilized product consisting of bees. It has high biological activity due to the sum of nutrient compounds found in both the egg and larval body [78,79].

Its chemical composition changes with the effect of many factors such as the production period, the age of the larva, and the flora in which the colony is located. Although it is similar to royal jelly in content, it has less protein and carbohydrate and more water content. In the studies, moisture content was determined between 65-80%, total protein ratio 9-12%, total lipids 5-8%, phenolic substance 0.8%, and total sugar between 6-10%. From sugar profiles; fructose 0.11-0.60%, glucose 3.40-6.74%, sucrose 0.00- 0.14% [78-82]. It can be considered as a good source of amino acids due to the essential and non-essential amino acids in its composition. In apilarnil, calcium, magnesium, phosphorus, iron, manganese, copper, zinc, sodium, potassium minerals have been determined [83] vitamin A, vitamin B1, vitamin B2, niacin,

Table 1. Chemical contents of apitherapy products.

	Honey	Propolis	Bee pollen	Bee bread	Royal jelly (fresh)	Apilarnil	Bee venom (dry venom)
Carbohydrates	80% Monosaccharides (55-85%): fructose, glucose Disaccharides (2-15%): sucrose, maltose, turanose. Trisaccharides (1-7%):erlose, maltotriose …	It contains 45-55% resin.	15-60% Reduced sugars (glucose, fructose), sucrose	24-35% Monosaccharides (93-94%): Fructose, glucose. Disaccharides: turanose, maltose, trehalose and erlose	7-18% (More than 90% of total sugar content glucose and fructose). Other sugars; sucrose, maltose, trehalose, melibiose, ribose, and erlose	6-10% (0.11-0.60% Fructose, 3.40-6.74% glucose, 0.00-0.14% sucrose, maltose, trehalose)	2-4% (Glucose, fructose)
Proteic substances	0.5% 26 amino acids, enzymes (glucose oxidase, invertase, amylase ...) Choline, acetylcholine Approximately 50% of the amino acid content is proline	24 amino acids	7.5-35% Proteins Amino acids (including essential) Enzymes	14-24% Peptides and amino acids Enzymes (Saccharose, amylase, phosphatases)	9-18% Proteins Amino acids (proline, lysine, glutamic acid, phenylalanine, aspartate serine)	9-12% Proteins Amino acids (glycine, proline, lysine, glutamic acid, aspartic acid, valine, isoleucine) Enzymes Hormones (testosterone, estradiol, progesterone, prolactin)	48-58% Small proteins and peptides (Melittin, apamin, MCD et al.) 15-17% Enzymes (Phospholipase A2 and B, hyaluronidase et al.) 0.13-1% Amino acids
Lipids	0,01%	Contains 10% essential oil. It contains 25-35% Beeswax and fatty acids.	4-7% Essential fatty acids, phospholipids, phytosterols, cholesterol	5-11% Medium and long chain saturated fatty acids, polyunsaturated fatty acids (oleic, palmitic and stearic acid)	3-8% 80--85% fatty acids, 3-4% steroid and 0.4--0.8% phospholipids	5-8% Saturated fatty acids (palmitic acid, stearic acid, myristic acid etc.) Mono and polyunsaturated fatty acids (oleic acid et al.)	4-5% Phospholipids (6-phospholipids)
Polyphenolic compounds	0.1-0.2% Flavonoids (crisis, luteolin, quercetin, kaempferol, apigenin, galangin…) Phenolic acids (caffeic acid, gallic acid, chlorogenic acid ... Procyanidins Coumarins	10% Polyphenols Flavonoids KAFE-caffeic acid phenylethylester; pinosembrine, gakangin, pinobanksin, seizure, quercetin, kaempferol	1.6% Flavonoids (rutin, quercetin, kaempferol, naringin…) Phenolic acids (gallic acid, vanillic acid…)	12-25% Flavonoids (quercetin, rhamnoside, rutin, luteolin, apigenin, kaempferol, isorhamnetin…) Phenolic acids (gallic acid, vanillic acid…)	Flavonoids (quercetin, luteolin, apigenin, kaempferol, galangin, fisetin, naringin, hesperidin, crisisin)	0,8 %	

Vitamins	C, K, B1, B2, B3, B5, B6	B1, B2, B3, B5, B6, C, E	C, β-carotene, E, B1, B2, B3, B5, B6, B9	C, B1, B2, B3, B5, B6, folic acid, biotin, inositol, choline	B1, B2, B3, B5, B6, folic acid, biotin, inositol, vitamin C (in trace amounts)	A, C, B1, B2, B3, B5, B6 (trace amounts), folic acid, choline, inositol	
Minerals	P, S, Ca, Mg, K, Na, Zn, Fe, Cu, Mn, Se	Na, K, Mg, Ca, Ba, Bo (eser), Sr, Zn, Cd, Al, Si, Se (trace), Fe, Ni, Cr, Mn, Ti), Ag, Co, V	Fe, Ca, Mg, Zn, Cu, K, Na,	Na, K, Mg, Ca,Mn, Zn, P, Cu, Fe, Se	0,8-3% K, Ca, Na, Mg, Zn, Fe, Cu, Mn	K, Ca, Na, Mg, Zn, Fe, Cu, Mn, P	3-4% P, Ca, Mg
Water	15-20%	2-4%	6-18%	5-6%	50-70%	65-80%	-

Table 2. Comparison of biological activities of apitherapy products

Effect / Apitherapy products	Honey	Propolis	Bee pollen	Bee bread	Royal jelly	Apilarnil	Bee venom
Antibacterial	✓	✓	✓	✓	✓		✓
Antiviral	✓	✓	✓	✓	✓		✓
Antifungal	✓	✓	✓		✓		✓
Antioxidant	✓	✓	✓	✓	✓	✓	✓
Hepatoprotective	✓	✓	✓	✓	✓	✓	✓
Anti-inflammatory	✓	✓	✓	✓	✓		✓
Radioprotective		✓	✓	✓			✓
Anti-cancer	✓	✓	✓	✓	✓	✓	✓
Imunstimulant	✓	✓	✓	✓	✓	✓	✓
Antiallergic	✓	✓	✓		✓		✓
Wound healing effect	✓	✓	✓	✓	✓		✓
Antiatherogenic	✓	✓	✓		✓		✓
Antinociceptive	✓	✓	✓				✓
Anti-Neurodegenerative	✓	✓	✓	✓	✓		✓
Anti-osteoporosis			✓		✓		
Antirheumatic		✓			✓		✓
Anti-ulcer	✓	✓	✓		✓		
Anti-aging		✓			✓	✓	✓

pantothenic acid, vitamin B6, vitamin C, folic acid, inositol, and choline was found [84].

It shows androgenic and anabolic activity because it contains testosterone, estradiol, progesterone hormones. For this reason, it has been a preferred product to treat infertility. It has been reported that it has immunomodulatory, hepatoprotective, antioxidant, anti-aging, anticancer, hypolipidemic effects and contributes to body development [85]. Although information about Apilarnil is limited, more data will be obtained with the increase of studies on this product whose value has been understood.

Bee venom

Bee venom, also called apitoxin, is a substance that can be obtained from all honey bee species (such as Apis mellifera, Apis cerena, Apis florea, and Apis dorsata) and produced in venom sacs in the abdominal cavity of bees. Approximately 0.3mg of bee venom can be produced in this venom sac [86,87]. It is mainly composed of peptides such as melittin, apamin, mast cell degranulating peptide (MCD), enzymes such as hyaluronidase and phospholipase A_2, and biologically active amines such as histamine and dopamine. It has a very complex chemical content. The protein content consists of 48-58% small proteins and peptides, 15-17% enzymes, 0.13-1% amino acids, and a small amount of biologically active amines, while the carbohydrate content is 2-4%, the lipid content is 4-5%, the volatile component (pheromone) content is 4-8% and the mineral content is 3-4% [88,89].

Bee venom rich in peptides is an apitherapeutic agent used in degenerative diseases such as autoimmune and osteoarthritis such as rheumatoid arthritis, some neurodegenerative diseases such as Alzheimer's and Parkinson's, and skin diseases. Since it has an antinociceptive effect, it has traditional use to reduce pain and treat chronic pain. Positive effects on the nervous system have been found due to biologically active amines (apamin et al.) [90,91]. It also has a radioprotective feature [92]. Bee venom, which has increased its popularity as a natural treatment method, has been examined in detail in terms of content, and it has been revealed as a result of research from which material the biological effects originate. For example, the highest amount of melittin is responsible for anti-inflammatory, antiarthritic, antibacterial, antiviral, antifungal, antinociceptive, and cytotoxic effects against cancer cells [93,94]. Apamine is anti-inflammatory, antinociceptive, and cytotoxic effects [95]. MCD peptide is anti-inflammatory, antinociceptive and causes low-dose histamine release while inhibiting high-dose histamine release [96]. Adolapine peptide also has anti-inflammatory and analgesic effect [97]. Phospholipase A_2, one of the enzymes, has anti-inflammatory and cytotoxic activity, while hyaluronidase enzyme has a role in the immune system response [95,98].

Cancer development and progression is a multifactorial process accompanied by external factors such as smoking, infectious agents, environmental pollutants, and unhealthy diet, or internal factors such as inherited genetic mutations, hormones, and immune conditions [99]. It continues to be a disease group that affects a large mass in the world and death rates due to cancer are gradually increasing. According to the data of the World Health Organization (WHO), lung, breast, and colorectal cancers were the most frequently diagnosed cancers for both sexes in 2018, while the most deaths were seen in the lung, colorectal, stomach, and liver cancer cases. When we look at the cancer profile of our country, we encounter a similar picture in the world [100,101]. The number of cases, which is 18 million today, will increase to 29 million by 2040, according to the estimates of WHO. This increasing cancer incidence reveals other treatment needs in addition to existing treatment methods such as surgical treatment, radiotherapy, chemotherapy, gene therapy, and hormonal therapy. In addition, the drugs used in current treatments treat the disease, but are not specific to cancer cells, but also damage the normal cells of the body and cause many side effects [102]. For these reasons, the use of biotoxins such as animal poisons as therapeutic agents in cancer treatment has become an important approach. It has also been stated with

current data that bee venom is a potential agent with anti-cancer activity and this activity is due to the peptide called melittin. Melittin, the main biologically active component, is a basic polypeptide consisting of 26 amino acids [94,103]. Anticancer activity mechanisms of Melittin; cell cycle changes, its effect on proliferation and / or growth inhibition, and stimulation of the activation of caspase and matrix metalloproteinases that cause apoptotic or necrotic cell death [104,105]. Various enzymes such as G protein, protein kinase C, adenylate cyclase, phospholipase C, and D shows their effect by stimulating. The lytic effect on the phospholipid layer of the cell membrane by activating the phospholipase A_2 is also one of the important mechanisms [103-107].

Studies on anti-cancer effects of bee venom

With the positive results obtained in studies on the anticancer activity of bee venom, interest in the subject has increased and it has been tried in many types of cancer. In studies on ovarian cancer cells, bee venom caused apoptotic cell death by increasing the expression of death receptors and inhibiting the JAK-STAT (The Janus kinase / Signal transducers and activators of transcription) pathway [108]. JAK-STAT pathway cell proliferation, differentiation, It is a pathway that plays a central role in the survival and embryological processes and may show abnormal activity due to some genetic mutations, polymorphisms, and alter the functioning of the pathway, leading to the development of cancer [109]. In a study conducted in 2017, it was given in combination with cisplatin, which is mostly the first treatment option in ovarian cancer, and a synergistic effect was observed, different results were obtained from the effect of both agents alone. Whether the growth of human cervical tumors was inhibited by bee venom on mice was investigated and it was found that tumor growth was inhibited as a result of the inhibition of nuclear factor kappa B (NF-κB) by increasing death receptors [110]. It has revealed the effect of bee venom by inhibiting the NF-κB pathway in prostate cancer cells as well as apoptotic cell death [111]. In a study conducted on human leukemia cells in 2020, it was stated that melittin induced apoptosis in leukemia cells and could be a therapeutic agent in the treatment of leukemia [112]. The anticancer activity has been demonstrated in the human lung cancer cell line by inducing apoptosis and inhibiting the expression of cyclooxygenase-2 [113]. In a study conducted in 2018 to examine the effects of bee venom on colon cancer, it was shown that apoptosis was induced and colon cancer cell growth was inhibited by activation of death receptors and inhibition of NF-κB [114].

As seen from studies, lung, liver, colon, prostate, ovarian cancer cells are targets for the anti-cancer activity of bee venom and Melittin. For each cancer whose incidence is increasing, bee venom will continue to attract the attention of scientists and be the subject of studies as a more preferred and future preferred product compared to other apitherapy products. More clinical studies are needed for the development of this field and the increase of the applications in this field in our country.

CONCLUSION

Interest in apitherapy, one of the traditional and Complementary Medicine practices, is increasing day by day. In this context, it has become one of the popular products of recent times, as it has been known since ancient times and is used by the public as a healing source and with the support of scientific research on bees and their products [115]. In addition, patients are not satisfied with the applications made with synthetic drugs in the treatment of chronic, difficult to heal, and time-consuming diseases, especially cancer, they want to stay away because of their side effects and the promising results in the researches have led to an increase in the demand for the use of these products. In order to strengthen this area in our country, the production of quality, effective and reliable products must be ensured.

In this review, the effects mentioned for bee products vary according to the content of the product. It should not be forgotten that the content

of the product varies according to the plant source and geographical conditions. Organic bee products produced naturally have therapeutic efficacy for humans and should be supported by scientific research in order to reveal their functions. The biological activities of apitherapy products are very diverse as shown collectively in Table 2, and there are cases that can be treated without encountering adverse situations such as side effects, non-drug effects, or situations that strengthen the effect of existing treatments in the treatment of diseases. Although interest in apitherapy products has increased in our country since 2014, it is not at the desired level. More studies should be conducted on this subject, and our country, which is a natural rich source of bee and bee products, should take its place in the literature in this field.

Although honey, propolis, pollen, bee bread, apilarnil and bee venom are all valuable products, recently scientific studies have focused on bee venom. With its anti-cancer activity coming to the fore, it is the most important agent that has been more involved in studies compared to other apitherapeutic products. It attracts the attention of people as it is a natural product. As mentioned, its effects on many cancer cells have been investigated and will continue to be investigated. The results of the studies are promising for cancer, which is the most common disease group globally. Bee venom can be applied on its own as a chemotherapeutic agent or it can be used together with other available chemotherapeutic agents to create a synergistic effect. Thus, by ensuring the use of each agent in lesser amounts, the negative effects of the agents on the body are reduced. By increasing the number of clinical studies, the application dose, route, and side effects will be determined and it will be inevitable to be used in treatments as an anti-cancer agent in the future. The issue to be considered is that the application of bee venom is done by the doctor who has the Apitherapy Expertise certificate. It should be determined whether there is an allergy before the application. It should not be applied to those with allergies and hypersensitivity.

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