







**Review**  
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## Use of Royal Jelly as Functional Food in Human and Animal Health

Arı Sütünün İnsan ve Hayvan Sağlığında Fonksiyonel Gıda Olarak Kullanımı

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### ABSTRACT

Bee products are used as supplements to provide nutrients in prevent or treatment of some health problems. Royal jelly has a rich nutrient contents in bee hive which protects and strengthens the health; compared to other bee products, it has a significant potential and effect. Because of its functional properties, royal jelly is very effective in accelerating the healing process in many diseases. The use of fresh royal jelly in our diets nowadays will help us to be healthy.

This review explains the effects of royal jelly on health, animal trials, and clinical studies for human health. Healthy doses are recommended by apitherapist medical doctors based on clinical observation and personal experience on the doses of use of royal jelly on human health. The review also mentions the positive effects of royal jelly consumption in our daily diet

### ÖZ

Arı ürünleri içerdiği besin maddeleri ile sağlık koruyucu ve destekleyici olarak kullanılmaktadır. Arı sütü; kovanın zengin besin içeriğine sahip, sağlık koruyucu ve güçlendirici üründür ve diğer arı ürünleriyle karşılaştırıldığında önemli bir potansiyele ve etkinliğe sahiptir. Arı sütü fonksiyonel özellikleri nedeniyle, pek çok hastalıkta başarıyla iyileştirici özelliindedir. Günümüzde beslenmemizde taze arı sütünün kullanımı, vücudumuzun sağlıklı kalmasına yardımcı olmaktadır.

Bu derlemede, arı sütünün hayvan deneylerinde ve insan sağlığında klinik çalışmalarda sağlık üzerine etkileri anlatılmıştır. İnsan sağlığında arı sütünün kullanımı ile ilgili doz önerileri özellikle apiterapist tıp hekimleri tarafından klinik gözlemlere ve kişisel deneyimlere dayalı olarak yapılmıştır. Günlük beslenmemizde arı sütü tüketiminin olumlu etkilerine de değinilmiştir.

### INTRODUCTION

Royal Jelly is a special nutrient used in the feeding of larvae and queen bee, which is secreted from hypopharyngeal and mandibular glands of 5 to 15 days old worker bees (Matsuoka et al., 2012; Märgäoan et al., 2017). Royal jelly is a bee product with a rather complex structure. In its composition, substances that target many different known and unknown biological

functions play an important role on the biomedical effect of the royal jelly (Stocker et al., 2005).

The composition of RJ is relatively constant at macro level and varies depending on bee nutrition, bee species, climate, season, harvesting method, and the age of the bee larvae (Liu et al., 2008). Royal Jelly is very rich in protein, fatty acids, sugars, hormones, vitamins, and minerals required for the development



of the larvae. It consists of: 60-70% of water, 18% protein, 9-18% carbohydrates, 3-6% lipids, 3-8% minerals, salt and vitamins containing numerous bioactive substances that have immune regulatory properties, antibacterial 10-hydroxy-2-decenoic acid (10-HDA) and peptides (Šimúth et al., 2003; Viuda-Martos et al., 2008; Sabatini et al., 2009; Bărnăuțiu et al., 2012; Premratanachai and Chanchao, 2014; Kolaylı et al., 2016; Mărgăoan et al., 2017). The sugars in the royal jelly are mostly composed of fructose and glucose, and are stable to the rate of honey. In many cases, fructose and glucose together constitute 90% of total sugars. Lipids consist of fatty acids with unusual structures with acidic, antibacterial, and fungicidal properties. Royal jelly, also contains neutral lipids, sterols, and candles. The main minerals are potassium, calcium, sodium, zinc, iron, copper, and manganese, with potassium dominance (Menkovska, 2013). It has been reported that the symbiotic effect of royal jelly and probiotic bacterial species provide important antioxidant activity (Nabas et al., 2014). The Royalisin, found in royal jelly is also an antibacterial peptide and has been reported to have antimicrobial effect against gram positive and negative bacteria (Bărnăuțiu et al., 2011; Biličkova et al., 2015).

Another compound found in royal jelly, royalactin is a glycoprotein essential for queen differentiation in honeybees. Royalactin plays a central role in this process by switching on the epidermal growth factor (EGF) receptor signalling pathway, which ultimately leads to epigenetic changes according to researcher (Kamakura, 2011).

The most important, major lipid component of the royal jelly is 10-hydroxy-2-decenoic acid (10-HDA) evaluated according to quality (Sesta, 2006; Bărnăuțiu et al., 2011; Honda et al., 2015). A quality royal jelly is expected to be in the range of 1.4% and 1.8% of 10-HDA. This value can vary according to the origin of the flora and fauna of the royal jelly and the technical procedures applied in the harvest of it. Unlike honey, the mineral substance composition in the royal jelly is not affected more than the geographical structure and vegetation (Kösoğlu et al., 2013). The harvest time of the royal jelly influences its quality and the content (Karlidağ and Genç, 2009; Zheng et al., 2011). In an analysis made of the local royal jelly produced in Romania, 10-HDA content was found to be ranging between 0.75-3.8% (Mărgăhițaș et al., 2013; Stangaciu et al., 2015; Mărgăoan et al., 2017). In the chemical composition of royal jelly produced in Bulgaria and Romania, low fructose levels were detected with high protein and sucrose from the Bulgarian royal jelly. It is

reported that climate differences between the two countries, the different equipment used for the analysis and even the methods used for the same purpose, the specific heterogeneity of the royal jelly can affect the composition of the product (Balkanska et al., 2013). Besides that, bee races also affect on royal jelly production (Şahinler and Kaftanoğlu, 2005; Karlidağ and Genç, 2009).

Proteins found in the royal jelly play a very important role in the feeding of larvae, defense of immunity and task assignment, and have a wide range of pharmacological and health-promoting functions for humans (Han et al., 2014). The royal jelly contains eight of the nine important amino acids, only the compound lacks tryptophan. The total amount of the basic amino acids in royal jelly was 247.35 mg/100 g and the total FAA was 867.39 mg/100 g. The highest concentration in AA is lysine (LYS) (221.07 mg/100 g), proline (PRO) 234.10 mg/100 g, glutamine (GLN) 177.59 mg/100 g. Proline is a conditionally necessary amino acid and it is possible to limit the synthesis under specific pathophysiological conditions such as severe catabolic distress (Mărgăoan et al., 2017). The apicin is found as a heterooligomer consisting of major royal jelly protein 1 and apismine (Furusawa et al., 2016), which is composed of a large portion of the royal jelly's proteins. According to the study of the concentration of free amino acids (FAA) and total amino acids (Taas) in 13 different times to harvest between 24 and 72 hours of royal jelly. Total free amino acid concentration in royal jelly was determined as 4.30 mg/g in 24 hours and 9.48 mg/g in 72 hours as harvest time increased. The highest and lowest concentrations of total amino acids are 24h (197.96 mg/g) and 72h (121.32 mg/g) respectively (Jie et al., 2016).

The number of samples, analysis methods, and beekeeping techniques that can affect the chemical composition of the royal jelly are very important to evaluate its parameters (Kanelis et al., 2015). Because the proteins in the royal jelly are very sensitive to the storage temperature, it can therefore be a potential freshness marker and the best way to preserve the quality of the royal jelly is under freezing conditions (Li et al., 2007). The levels of lipids in royal jelly decrease in time due to lipid oxidation, meanwhile the protein content increases during storage (Mureșan et al., 2016).

There is a correlation between the measured refractive index and water content of the royal jelly. The presence of a simple linear relationship between refractive index and water content reveals the



suitability of the refractometric measurement for quality control purposes. This relationship provides similar estimates of water content originating from the Wedmore equation ( $R^2=0.9999$ ), which is used to predict the water content in honey. Refractometric evaluation of water content is fast and simple, which can provide adequate reliability in the routine quality control of the royal jelly (Sesta and Lusco, 2008).

The many benefits of the royal jelly are those of functional foods that have been on the agenda in recent years. Especially with the health awareness nowadays, the society is particularly interested in the quality of the food we consume. The study of royal jelly used in many health disorders has first started with animal trials (Topal ve ark., 2015), and subsequently in human studies too (Tolon, 1997).

### **The Use of Royal Jelly on Animal Health**

Many researches have been conducted to determining effects of royal jelly on animal health. According the results of these research, royal jelly increases the development of cartilage tissue in animals due to its high collagen content, strengthening bone and tooth structure because of its calcium and selenium amount, also protecting blood cells, heart and liver tissues as well as showing strengthening effects on the muscles and nervous system due to the presence of potassium (Stangaciu, 1999). After injuries, generally there is an inflammatory reaction and the cells under the dermis begin to increase collagen production. Then the epithelial tissue is regenerated. In the study conducted to determine the effect of different royal jelly ratio on the wound in mice; the results showed significantly increase in wound healing activity compared to royal jelly negative and positive control groups, and no significant difference was found between 200 mg / kg and 300 mg / kg royal jelly use ( $p > 0.05$ ). The results of this study indicate that daily application of royal jelly possesses better wound healing effects than *Nitrofurazon* and every two days usage of royal jelly (Shirzad et al., 2014).

According to a study performed by Çallı et al. (2008) it has been investigated the effectiveness of royal jelly in enhancing healing in tympanic membrane perforations. The study suggests that royal jelly is effective in increasing healing of tympanic membrane perforations in guinea pigs.

Royal jelly also effects the reproductivity in animals. It has been determined that the use of the royal jelly increases spermatozoa motility with the intensity of it reduces the rate of abnormal spermatozoa and positively affects sperm quality (Temamoğulları et al.,

2006). In another study, the loss of age-related testosterone function in old hamsters is reported to be inhibited by the use of royal jelly (Kohguchi et al., 2007). Other study has noted that with the use of royal jelly, the negative effect on stress on male rabbit fertility in hot summer conditions was reduced to a minimum, total sperm output, sperm motility, live sperm, and normal sperm showed a significant increase compared to untreated controls. Concentrations of plasma total protein, albumin, globulin, glucose, and HDL were statistically increased significantly when compared to controls in royal jelly groups, as opposed to the treatment of royal jelly therapy where plasma aggregate lipids, triglycerides, cholesterol, and low-density lipid (LDL) concentrations have been reported to cause a significant decrease (El-Hanoun et al., 2014).

Cisplatin is one of the most potent and effective chemotherapeutic agents. Antineoplastic use is limited due to cumulative nephrotoxic side effects. It has been reported that the royal jelly can be used as a preventive tool against subchronic cisplatin-induced kidney damage in studies conducted to investigate the nephroprotective potential of nutrition of royal jelly against subchronic cisplatin toxicity in rats (Ibrahim et al., 2016).

In the case of oxidative stress with serum biochemical changes in the liver and pancreas of diabetic rats induced by streptococcosis (*Streptozotocin*) (STZ), royal jelly improves the current oxidative damage (Ghanbari et al., 2016).

Cadmium (Cd) is a highly toxic heavy metal that causes genotoxic damage to the body. In addition, Cd changes the system of antioxidant defence enzymes, causing oxidative damage in various tissues. In the study, oral administration of two doses (100 and 250 mg / kg body weight) of royal jelly on Cd-induced genotoxicity and oxidative stress in rats had a protective role against Cd-induced genotoxicity and oxidative stress in mice due to the antioxidant effects (Çavuşoğlu et al., 2009). In another study, aluminum chloride ( $AlCl_3$ ) was administered to poisoned rats with follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), thyroxine ( $T_4$ ), triiodothyronine ( $T_3$ ), triiodothyronine/ $T_4$ ) and testosterone levels, and the use of royal jelly weakens these effects (Al-Eisa and Al-Nahari, 2017), while testicular oligospermine leads to the formation of hypoplasia, occluded blood vessels and exfoliation tubules, the use of royal weakens these effects. Royal jelly is a useful treatment for male adult rats receiving hydrogen peroxide (causing oxidative stress), especially on the number of spermatozoons, testosterone



hormone level, live spermatozoons percentage and glutathione and malondialdehyde tissue test (Al-Sanafi et al., 2007; Hassan, 2009). It has also been reported that royal jelly may be an alternative for reproductive management which has been found to increase the rate of ovulation until the start of estrus (Al-Eisa and Al-Nahari, 2017; Sosa-Pérez et al., 2017).

It has been reported that the performance of micronutrient components of bee pollen, honey, and royal jelly added to quail drinking water, propolis ethanolic extract and diets and the development of quail immunity system can be improved (Babaei et al., 2016). In another study, performance parameters and unsaturated fatty acid ratios in quail tissues were increased (Seven et al., 2014). Another study investigates the effect of royal jelly on fat tissue profiles in quails and it was determined that the ratio of unsaturated fatty acids in chest, kidney, leg, and liver tissues was improved (Seven et al., 2013).

The use of royal jelly has been found to increase hyperglycemia in obese/diabetic K.K.- mice and partially reduce body weight (Yoshida et al., 2017). It has been reported that royal jelly is preventing hyperlipidaemia in rats and improves blood clotting levels (Premratanachai and Chanchao, 2014). Royal Jelly supplementation has been again reported to reduce the development of epidural fibrosis after laminectomy in rats (Günaldı et al., 2014) and has been found to significantly reduce serum and hepatic lipids and cholesterol levels in rats and rabbits, and also delayed the formation of atheroma of the aorta in the rabbits fed with hyperlipidaemic diet (Vittekk, 1995).

In a study on rats, royal jelly demonstrated osteoinductive and anti-inflammatory effects in the treatment of periodontal diseases and prevention (Yanagita et al., 2011).

The consumption of royal jelly and bee pollen increased the calcium and phosphorus levels in the bone tissue and it was determined that osteoporosis-related bone loss was reduced in the oophorectomized rats model (Kafadar et al., 2012).

It has been reported that the administration of royal jelly at a level of 1% may improve premature mortality in mice through the restoration of immune system dysfunction caused by low micronutrient uptake (Kwon et al., 2017).

Feeding royal jelly major proteins (MRJP) to older rats has been reported to increase spatial memory up to 48.5% and it has got great potential for inhibiting cognitive impairment by catabolism of cysteine and

taurine metabolism in elderly rats (Pyrzanowska et al., 2014; Chen et al., 2017).

For the determination of the immunomodulative effect of royal jelly in the 4T1 breast cancer model in rats (0, 5g/kg) in mice bearing 4T1, tumour necrosis factor-alpha (TNF-a), immunoglobulin G (IgG), and kidney-upper cells are enlarged. It shows that royal jelly has an important immune modulator effect reflected in the serum. Thus, royal jelly has been reported to be associated with antitumor effects, which develops immunity in mice with 4T1 (Zhang et al., 2017a). In another study, using prophylactic-therapeutic (PTRJ) or therapeutic (trj) method, it has been shown to nourish the mice carrying 4T1 with royal jelly. It has been found that royal jelly treatment in mice reduces the development of breast tumour and also improves the antioxidant capacity of the serum, liver, and kidney, especially using prophylactic treatment method. These results have confirmed the efficacy of royal jelly supplementation in diets (Zhang et al., 2017b).

To investigate the effect of royal jelly on the growth of WEHI-164 fibrosarcoma cells in syngenic Balb/C mice, 100, 200, 300 mg / kg royal jelly were applied to groups 1-4, respectively and the tumour size in the case group was significantly lower than the control group ( $P < 0.05$ ). Metastasis was not observed in the test and control groups. It appears that royal jelly has an important role in the control and regression of fibrosarcoma cells. Since royal jelly has a delayed effect on fibrosarcoma control, it is recommended to use it at least 10 days before tumour inoculation (Shirzad et al., 2013).

It has been reported in rats that royal jelly has a protective effect on external cardiac muscle ischemia, increases contraction activity, develops intraventricular pressures and increases coronary blood flow (Krylov et al., 2006).

In a study showing the effect of fresh royal jelly on the mice fatigue: the mice in the group that consume the royal jelly, serum lactate and serum ammonia accumulation decreased significantly, while muscle glycogen has been decreased, therefore the consumption of royal jelly has been reported that it can heal physical fatigue (Kamakura et al., 2001). Royal jelly can modulate behavioural and histomorphometric disorders caused by Parkinson's disease in rats (Taherianfard et al., 2017).

According to the study, the effects of RJ on the change of experimental colitis and mast cell distribution induced by acetic acid in the rat's colon,



ensuring that the royal jelly colon mucosa is protected against the harmful effects of acetic acid. It has also been reported that rats treated with royal jelly reduce the number of mast cells MC and the colonic erosion area in the colon (Karaca et al., 2010). As well, oral mucositis due to radiotherapy applied to the head and neck region in rats is effective in decreasing oral mucositis when administered at appropriate doses (100 mg/kg) (Cihan and Deniz, 2014).

Restraint and cold stress lead to the release of corticosterone from the adrenal gland of the hypothalamic-pituitary-adrenal (HPA) axis, which may worsen the antioxidant defence system in the central nervous system. Rats supplemented with RJ have been found to have reduced corticosterone in the brain, cerebellum, striatum, and hippocampus, as well as in the glutathione defence system of the cerebral cortex and striatum, as well as in hippocampus glycemia and fractions. This study reveals the anti-stress and neuroprotective effect of royal jelly in stress conditions (Teixeira et al., 2017).

It has been determined that royal jelly, propolis, and bee pollen have the greatest effect on *Aeromonas hydrophila* and *Vibrio cholerae* according to the study conducted to demonstrate the antibacterial effect against pathogenic bacterial isolates in the water. The results of current in vitro studies suggest strong natural products such as royal jelly, propolis, and pollen can control pathogenic bacteria (Salimi et al., 2013).

### **The Use of Royal Jelly on Human Health**

Royal Jelly is effective on the regeneration, production, and metabolism of cells in the body, resulting in vitality, health, energy, high immunity, and vigour in all tissues of the organism. Its structure is rich in natural hormones, vitamins, essential fatty acids, amino acids, sterols, phosphorous compounds, and acetylcholine. Acetylcholine is effective in the transmission of nerve messages and in the regular functioning of endocrine glands. Royal jelly, which is also rich in nucleic acids which are the basic substances of life, has anti-aging effects because it also contains gelatinous amino acid which is the basic component of collagen. Gammaglobulin in its structure is a factor in the fight against infection and strengthening of the immune system. 10-HDA content has strong antibiotic effect against many bacteria and fungi. It is well known that royal jelly has been successfully used in oncology, psychiatry and neurology, geriatrics, bone and cartilage tissue repair, vascular stiffness, urology, especially infertility treatment, skin protection, development and growth

due to its anti-tumour and metastatic counteracting effects (Eshraghi, and Seifollahi, 2003; Dođarođlu, 2007; Park et al., 2011; Pavel et al., 2011; Ramadan and Al-Ghamdi, 2012; Filipič and Potokar, 2013; Yang et al., 2015; Siavash et al., 2015; Ahmadnia et al., 2015). Royal jelly also contributes to the recovery of damage caused by 5-fluorouracil (Suemaru et al., 2008). It has been reported a variety of antitumor, antibiotic, immunomodulator, estrogenic and neurogenic pharmacological activities of 10-HDA in royal jelly (Eshraghi, and Seifollahi, 2003; Sugiyama et al., 2012; Stratev et al., 2015). Six-month intake of royal jelly has been noted to improve erythropoiesis, glucose tolerance, and mental health in humans (Morita et al., 2012).

It has been recorded that consumption of royal jelly has a significant impact on sperm count and motility and positive results are obtained in infertility treatment (Ahmadnia et al., 2015). Besides that royal jelly with honey is effective in early menopause formation and ovarian treatment caused by Adriamycin (Mahmoud and Anas, 2015). In chronic diseases such as menopausal osteoporosis and cardiovascular disorder, the intake of 150 mg royal jelly for three months has been determined to provide significant improvements in the lipid profile of postmenopausal women. It has also been investigated that royal jelly may be an alternative method for menopause-related dyslipidaemia control (Lambrinouadaki et al., 2016). Postmenopausal women may improve their quality of life in the treatment of sexual and urinary dysfunctions (Seyyedi et al., 2016). The oral consumption of 1000 mg capsule of royal jelly for 2 months is effective in reducing the premenstrual syndrome (PMS) (Taavoni et al., 2014).

Early foetal membrane rupture cases with high incidence of prematurity and foetal death are very critical and a study has reported that a mixture of Indian honey and Indian royal jelly has positive effects on the foetal membrane (Abdelhafiz et al., 2011).

Trans-10-hydroxy-2-decenoic acid (10-H2DA), 10-hydroxydecanoic acid (10-HDAA), and sebacic acid (SEA) are the three major fatty acids in royal jelly (RJ). Previous studies have revealed several pharmacological activities of 10-H2DA and 10-HDAA, although the anti-inflammatory effects. The results showed that 10-H2DA, 10-HDAA, and SEA had potent, dose-dependent inhibitory effects on the release of the major inflammatory-mediators, nitric oxide, and interleukin-10, and only SEA decreased TNF- $\alpha$  production. Several key inflammatory genes have also been modulated by these royal jelly fatty acids,



with 10-H2DA showing distinct modulating effects as compared to the other two FAs. Furthermore, it has been found that these three FAs regulated several proteins involved in mitogen-activated protein kinase (MAPK) and nuclear factor-kappa B (NF- $\kappa$ B) signaling pathways. Taken together, these findings provide additional references for using royal jelly against inflammatory diseases (Chen et al., 2016).

Royal jelly has also a stimulating, activating effects on the central nervous system, Acetyl-choline like effects on the intestine and the innervation of the smooth respiration muscle. These effects result in an improved muscle tonus and activity. Royal jelly shows neurotrophic effects on the mature brain via stimulation of Glial Cell-Derived Neurotrophic Factor, GDNF production. The enhanced expression of neurofilament H mRNA is involved in events subsequently caused GDNF. Royal jelly may play neurotrophic and/or neuroprotective roles in the adult brain through GDNF. Recent brain research has elucidated the mechanism of action for the Royal jelly effects on the CNS. A unique royal jelly component, cAMP-N1 oxide, not found in any other materials, acts directly on neuronal differentiation and stimulates the formation of different brain cells. Royal jelly facilitates also the differentiation of all types of brain cells: neurons, astrocytes, and oligodendrocytes. It also royal jelly ameliorates neuronal function by regenerating hippocampal granule cells that function in the cognition process (Bogdanov, 2015).

There are also studies proving that the royal jelly has positive effects for diabetes patients (Pourmoradian et al., 2014; Khoshpey et al., 2016). In addition, the intake of royal jelly has reported positive effects on serum total antioxidant capacity and insulin resistance (Homa-IR) in diabetics (Shidfar et al., 2015). Other than that, Mobasseri et al, (2015) noted a significant effect on the glycemic factor in the Type 2 diabetic patients on consumption of royal jelly. It has been reported that royal jelly intake might be beneficial in weight management for type-2 diabetes in women (Pourmoradian et al., 2012).

The use of royal jelly and honey supports the improvement of the fatigue period in cancer patients (Mofid et al., 2016). It has also been recorded that royal jelly improves the symptoms of oral mucosa in patients undergoing radiotherapy and chemotherapy and significantly shortens the healing time (Erdem and Güngörmüş, 2014). Rafat et al, (2016) reported that royal jelly would have a protective role for 14 days of its consumption versus radiation-induced apoptosis in human peripheral blood leukocytes. It

has been reported that the use of honey and royal jelly for the antioxidant effects for the protection of acute renal damage induced by Cisplatin (the most potent antineoplastic drug) in cancer patients is effective in reducing Cisplatin nephrotoxicity and potentially important for the treatment of Cisplatin kidney side effects (Osama et al., 2017).

It is reported that the use of royal jelly cannot prevent the weakening of physical performance in elderly people, but may slow down muscle strength (Meng et al., 2017). In the aging process of human populations, it has been noted that a non-toxic, natural food product can contribute to the preservation of memory in the development of a better quality of life in the elderly (Pyrzanowska et al., 2014). Royal jelly can protect the skin by increasing collagen production in the UVB-induced photoaging (Park et al., 2011).

*Pseudomonas aeruginosa* is a gram-negative bacterium that causes respiratory tract infection, especially in elderly patients. The royal jelly inhibited *P. aeruginosa* adhesion and showed that it protects epithelial cells from extreme inflammatory responses to *P. aeruginosa* infection (Susilowati et al., 2017). It has also been noted that royal jelly plays an important, protective role against Fumacein toxicity (El-Nekeety et al., 2007).

Antibiotic resistance of pathogenic bacteria is an increasing public health problem. Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important burden for healthcare services, as it causes difficulty in treating people with infections. Honey and royal jelly have been reported to have the potential as alternative therapeutic substances against MRSA infections, in the case of individual or as a combination, but the clinical trials are needed for confirmation (Dinkov et al., 2016).

Dry eye; It is a multi-factor disorder characterized by visual impairment and eye discomfort. The lacrimal gland function is known to be a strong risk factor for eye drying and decreases with aging. With the introduction of technology into our lives, symptoms such as eye drying and tear deficiency are reported to occur more frequently. It has been reported that the use of RJ in this situation is a promising basic alternative to increase tear secretion within 8 weeks and to preserve lacrimal gland function (LG), and topical application of royal jelly is a safe and effective intervention to increase tear volume in dry-eyed patients (Imada et al., 2014; Inoue et al., 2017).

The two major bee products, propolis and royal jelly, have been widely used throughout the world as



traditional and ethnopharmacological nutrients since ancient times. Both have a number of factors known to be effective for various medical conditions. The use of royal jelly and propolis in upper respiratory tract infections (URTI) is thought to be given together as a dietary supplement and can be separately. 10-HDA is the most prominent active compound in the RJ. The acid phenethyl Ester is the most effective ingredient in propolis showing antimicrobial and anti-inflammatory effects. Compared with propolis, royal jelly is known to have a rich content for all three main nutrients in proteins, carbohydrates, and lipids. In addition to other secondary compounds with health beneficial effects, more clinical, experimental and fundamental research is needed to find the best standardized mixture to cope with URTI, which will be the main components of royal jelly and propolis. In addition to classical treatment methods, it is an urgent need to find the most reliable and standardized best mix approved for healthy beneficial effects such as propolis, royal jelly, Echinacea as healing agents for children to cope with seasonal UTI as an alternative option (Yüksel and Akyol, 2016).

No significant change in any of the anthropometric parameters such as body weight, waist, and body fat could be determined by studying the effects of royal jelly (350 mg / capsule) on mild hypercholesterolemic participants. Serum total cholesterol and low density lipoprotein cholesterol levels decreased significantly ( $p < 0.05$ ) after application of royal jelly, but triglyceride (TG) and high density lipoprotein cholesterol (HDL-c) levels did not change significantly. It has also been reported that the consumption of royal jelly significantly reduces the risk of cardiovascular disease and improves the concentration of sex hormones such as dehydroepiandrosterone sulphate (DHEA-S) and reduces the risk of cardiovascular disease according to (KVH) (Chiu et al., 2017).

Another study examined the effects of royal jelly supplementation on serum lipoprotein metabolism in humans. Fifteen volunteers were divided into a royal jelly intake group ( $n=7$ ) and a control group ( $n=8$ ). The royal jelly group took 6 g per day for 4 weeks. Their serum total cholesterol (TC) and serum low-density lipoprotein (LDL) decreased significantly compared with those of the control group ( $p < 0.05$ ). There were no significant differences in serum high-density lipoprotein (HDL) or triglyceride concentrations. Moreover, the relationship between the serum cholesterol and lipoprotein levels was investigated. Among the lipoprotein fractions, small very-low-density lipoprotein was decreased ( $p < 0.05$ ) after RJ

intake. The results suggest that dietary royal jelly decreases TC and LDL by lowering small VLDL levels (Guo et al., 2007).

Meta-analysis of royal jelly human studies to reduce hyperlipidaemia has shown that there is a significant reduction in total serum lipids and cholesterol levels and that normalization of HDL and LDL is determined without decreasing  $\beta / \alpha$  lipoproteins. The best dose obtained shows that about 50 to 100 mg of RJ per day reduced total serum cholesterol levels by about 14% and total serum lipids by about 10% in the studied group of patients (Vittekk, 1995).

Twenty volunteers underwent the standardized oral glucose tolerance test (OGTT) and afterwards a second OGTT after ingestion of 20 g of royal jelly. Serum glucose levels after 2 hours and the area under the curve for glucose were significantly lower after royal jelly administration (Münstedt et al., 2009).

It has been determined in children that the clinical severity score for royal jelly on systemic lupus erythematosus (SLE) is improved by 3 months of royal jelly treatment in terms of laboratory markers, and apoptotic CD4 T lymphocytes that significantly reduced after royal jelly therapy compared with baseline values and control group (Zahran et al., 2016).

Another study evaluates the antibacterial effect of 0.2% of royal jelly and chlorhexidine in dental practice. As a conclusion of the study, the royal jelly contains important elements with antibacterial action compared to the chlorhexidine one (Meto et al., 2017). Clarification of the components of royal jelly which possess this effect along with other behavior cell adhesion, migration, collagen production would lead to a more complete picture of the effect of royal jelly on cells. Considering its availability and possibly positive effect on the periodontium, royal jelly seems to be an interesting agent in dentistry (Dhanesuan et al., 2011).

Serum anti- $\beta$ -IG IgE and IgG have inhibited the plasma levels of histamine as a result of giving royal jelly to rats orally and reduced the intestinal anaphylactic response and histological lesions caused by  $\beta$ -Lg sensitivity. These results have been reported that royal jelly can have a beneficial effect by reducing symptoms in your allergies to cow's milk protein (Guendouz et al., 2017).

Graves' disease is an organ-specific autoimmune disease with unknown etiology. It is reported that royal jelly may be effective as anti-thyroid drug



therapy in the treatment of this disease (Erem et al., 2006).

The validation data showed the potential of 10-HDA for use in suppressing skin pigmentation. The 10-HDA has been shown to inhibit melanogenesis, thus it could be developed as cosmetics skin care products (Peng et al., 2017).

Long-term overeating or alcohol consumption causes a viral hepatitis and/or fatty liver intensification resulting in eventual liver failure. Prolonged intake of alcohol not only leads to a reduction in immune function, but also promotes the production of inflammatory cytokines by Kupffer cells activated by enterobacterial endotoxins. The use of royal jelly demonstrates a pro-active effect on alcohol-induced hepatomegaly and indicates that it may function in the restoration of transaminase levels caused by impaired hepatocytes, ie, the ability of the immune system to function in individuals with alcoholic liver diseases (Li et al., 2011).

It has been reported that hepatoprotective effects of royal jelly on paclitaxelin (TXL) -induced toxicity, which may lead to a clear cross between E2f1 and c-Myc as two regulators of liver growth (Malekinejad et al., 2016).

Dietary, freeze-dried royal jelly improves epidermal hydration with increased ceramide levels in the epidermis of middle-aged healthy people at a dose of 520 mg / day for 10 weeks. Topical application of royal jelly has been reported to have beneficial effects on dry skin protection (reduced epidermal hydration) according to (Cho et al., 2016).

Foot ulcers and infections in diabetic patients are the main sources of morbidity. Studies shows that topical royal jelly application helps in recovering diabetic foot ulcers and it might be an effective method for the treatment of diabetic foot ulcers as well as standard treatment for an average of 41 days of complete healing over 8% of patients (Siavash et al., 2011).

Several studies have shown that oxidative stress occurs in patients with kidney stones. Exposure to Ca oxalate is caused by oxidative damage with reactive oxygen species such as superoxide and H<sub>2</sub>O<sub>2</sub>. The produced ROS activate a variety of signal paths. It is reported that the antioxidants in royal jelly have positive impact on renal damage caused by inflammation, inhibits ROS production and supports the overall antioxidant system (Aslan and Aksoy, 2015).

Royal jelly used as a supplement is applied as a criterion of positive change in the phase of adaptation

and exhaustion of young football players' bodies. Research carried out with 12 years old football players. It was observed 13 morphological characteristics in initial and final measuring. It could be concluded that football players who used royal jelly had statistically significant increase of body height and muscle component, and decrease of fat component in final measurement compared to the initial. Also, the results show statistically significant increase in circumference above knee and circumference of lower leg in experimental group at the end of the treatment. The results also showed higher average values in body height, body mass, muscle and bone component, and lower average value in fat component as well (Joksimović et al., 2009).

Another study conducted showed the analgesic effect of royal jelly on acute pain in a dose of 200 mg/kg was found to be equal to aspirin and lower than morphine. However, RJ and aspirin have been found to be more effective on chronic pain. Given its analgesic, antioxidant, and anti-inflammatory properties, royal jelly could be recommended for reduce the pain accordingly (Arzi et al., 2015).

Royal jelly is known as a functional food containing many useful minerals. This study, shows an anti-environmental oestrogen activity of royal jelly. Bisphenol A (BPA) is an environmental oestrogen that stimulates proliferation of human breast cancer MCF-7 cells. Royal jelly inhibited the growth-promoting effect of BPA on MCF-7 cells, even though it did not affect the proliferation of cells in the absence of BPA. In addition, this inhibiting effect of royal jelly was heat-stable (Nakaya et al., 2007).

#### **Dosage of Royal Jelly for Human Use**

Bee products may trigger an allergic effect for some people (Paola et al., 2014; Abdulla and Abdulla, 2016). For example, the use of RJ in cases of asthma and anaphylaxis conditions may cause an allergic reaction to occur (Thien et al., 1996). People with allergies should perform allergy tests before starting to use them, or start using low doses. If they have allergic symptoms bee products must not be used. Since each person's immune system is different, checking a doctor's advice is an important key to success.

Recommending royal jelly to the patients is related very much to their specific needs, their health conditions, age but also with the results that was observed in laboratory by the researchers. Sometimes, very low doses can be very effective, but other times large doses might be needed. Studies shows that a dose of 100 mg/kg give the best effect in severe conditions, higher doses very rarely being needed.





**Infants:** Growth and development, strengthen immunity and nervous system: 0,5 g/day for 2-12 months. For premature babies we found in literature various dosages to treat the complications of this condition, starting with 50 mg to 1 gram per day. As a general observation, in the beginning, practitioners used very small does of royal jelly, but in time they increased dosages (sometimes significantly) with great results and no sides effects. For premature infants we used a medium doze of 0.25 g/day raw royal jelly (Gyuzukina and Dimitrieva, 1993; Mahmoud et al., 1997; Gyuzukina and Dimitrieva, 1998; Magdalena, 2010; Strant and Grosu, 2016; Strant, 2017a; Strant, 2017b).

**Children:** low immune system, nervous system impairment (foetal suffering, delivery complication when born), weakness, loss of appetite, anorexia, anaemia, etc. for children aged 1-5 yrs 0.5 g/day and for children between the age of 5-12 yrs old 0.5-1 g/day royal jelly only or used in combination with other bee products, it is used in a lower dose due to synergistic effect. For children aged 1-5 yrs old, 1-3 days 2.5 g/day RJ and 5-12 years for children with acute infection and colds, 5 g/day royal jelly in the 1-3 daily period (Strant, 2017a; Strant, 2017b).

**Adults:** Immunity, insomnia, skin disorders, anaemia, low libido, hormonal imbalance, wounds, premenstrual syndrome, menopause, osteoporosis, etc. In such cases, 1 to 2 g / day can be used, diabetes, depression, Hashimoto's disease, in cases of arthritis with 3-5 g / day may be used. In cases of recent depression, different doses are applied to the royal jelly in our practice. In some cases, larger doses such as 10g/day are available for a faster, more powerful response for a shorter period of time (10 days/month for 3 months). In combinations with other bee products and plants-1 gr/day royal jelly (immunity, convalescence, preparation for surgery, autoimmune diseases, cancer, hormonal imbalances, infertility, ovarian cyst, uterine fibroma, thyroid problems etc.) Up to 10 g/day for 1-3 days in the beginning of colds, 10 g/day for 1-3 days in other acute infections, up to 3-5 days to accelerate post-operative healing, 5-10 g/day. For individuals under heavy working conditions, 10g/day royal jelly. For early onset of colds for 1-3 days, 10 g / day cough until it stops, 10 g for 1-3 days in other acute infectious to accelerate healing after surgery 5-10 g for 3-5 days. The side effects of chemotherapy such as paresthesia, pain or burning sensation of fingers, imbalance during walking, the sensation of weakness in the legs 3 g/day royal jelly can be used for 6-8 weeks (Strant, 2014; Strant, 2016;

Strant and Varadi, 2016; Strant and Grosu, 2016; Strant, 2017a; Strant, 2017b). Neurodegenerative diseases, multiple sclerosis, long-term 10-15 g/day in Parkinson's (according to the condition of symptoms). It is known that royal jelly has good effects for skin problems (Kohno et al., 2004; Tatsuhiko et al., 2011). Combination of royal jelly with essential oils can be used to treat various conditions of skin. One of the most common condition is the acne, which can be severe sometimes, affecting not only the good looking of the patient, but also giving disturbing symptoms due to the inflammation and also psychological discomfort. One of the best essential oils is frankincense (*Boswellia spp*). Studies showed that frankincense essential oil applied topically reduce inflammation, determine significant improvements of fine lines, elasticity of the skin, reduction of sebum excretion, as well as overall echographic parameters of skin photoaging (Calzavara-Pinton et al., 2010; Hamidpour et al., 2013). Using a mask with raw royal jelly combined with *Boswellia* essential oil in treatment of severe acne combined with oral treatment with propolis and healed the acne completely and reduced the scars.

Royal jelly is an expensive product, so it will be economically correct to use the dose that will give the maximum effect.

### Royal Jelly and Diet

In general, bee products are a rich source of intelligent essential nutrients to keep your body healthy. As a result of environmental pollution and overuse of chemicals, increasing the load of toxic environment becomes difficult for us to maintain health. Both our food supply and diet are often inadequate in terms of important nutrients. In recent years we are going to turn this situation off with functional foods. Royal jelly and other bee products, have a lot of features of functional products/foods, that are very important in our diets.

The addition of royal jelly to our diet and using bee products as food, the composition found works predominantly in preventive treatment and comes with valuable nutrients that are found in very little food. Nutrients such as 10 HDA, B5, B12, folate (valuable micronutrients), which are found in large quantities in the royal jelly, provide a high level of nutrition in the diet of humankind (Lab Reference: CS20133271, Food Intertek, test report, for the Romanian royal jelly, 27.02.2017).

Folate is a generic term for a naturally occurring family of B-group vitamins. It is found naturally in foods, including royal jelly (folate=40.22 ug/100 g,



Intertek Laboratory, United Kingdom test report, for the Romanian royal jelly, 27.02.2017). Folic acid is a synthetic form of folate which is widely used in supplements and for food fortification and supplementation of folic acid has been associated with an increased risk for autism during gestation (Desoto and Hitlan, 2012).

The basic action of royal jelly, which contributes to our diet more than a meal, is the preventive effect of a faster recovery by acting on a cell and at the level of the disease. Two of the most important functions of royal jelly is balancing and normalizing cell life functions that are based on detoxification and renewal (Menkovska, 2013).

Apinutrition refers to the addition of the beehive products such as honey, fresh bee pollen, royal jelly, bee bread, queen bee larvae, apilarnil (drone larvae), propolis to our daily diet to support, nourish and revitalise our health. These natural foods have historically played an enormous part in offering an exceptional quality of nourishment and energy, immensely supporting all the body functions, to promote harmony among all the systems due to their synergistic effect.

The nutritional complexity of the beehive is vast and bee products are remarkable for their potential to transform the human body in a number of ways. Medical trials around the world have shown that bee products are a great support in keeping and improving our health, not only through their nutritional content which is a true fuel for our wellbeing, but also for their ability to be totally assimilated by our body without any effort.

Due to the various pharmacological properties, including antioxidative, anti-inflammatory and antibiotic properties, RJ is extensively consumed in daily diets in many countries (Eshraghi and Seifollahi, 2003; Bărnutiu et al., 2012; Stangaciu et al., 2015; Stratev et al., 2015; Zhang et al., 2017b).

When the results of the scientific studies are examined, the consumption of RJ eliminates factors of many diseases and/or helps heal the disease and will provide support in maintaining our health.

Royal jelly is also used to help reduce allergic symptoms, to control cholesterol levels, muscle dystrophy, MS and Parkinson's disease. Especially in patients receiving radiotherapy and chemotherapy, the immune system weakens. In such cases, royal jelly with its high amino acid content can help the immune system and provide a basic defence against external elements that normally attack the immunity and

reduce the ability to defend our body. Supporting our diet with royal jelly helps to reconstruct the good cells that are destroyed by chemotherapy and help strengthen the immunity. Royal jelly also contains amino and gamma globulin, which helps the immune system to fight viral infections. It also contains sterols, phosphorous compounds, and acetylcholine, which are required to transmit nerve messages from cell to cell. The high concentration of essential amino acids in royal jelly is very important supporting chronic fatigue, skin, hair, nails, bones, joints, hormonal regulator, asthma, sexual vitality, impotence, weight control, rejuvenation, disease recovery, immune system stimulation, cardiovascular health/cholesterol regulator, anti-depressive, anti-anxiety, high blood pressure, mental condition, memory, depression, arthritis, liver disorders, eczema, impetigo, skin disorders, diabetes, wounds (Fujii et al., 1990; Joksimović et al., 2009; Saritaş et al., 2011; Min et al., 2013; Menkovska, 2013; Raja, 2016; Meto and Meto, 2017). In addition, RJ is known as an adaptogen substance, with maximal fertility boosting properties, providing the maximum life span without diseases (Menkovska, 2013).

#### **Contraindications and Adverse Reactions of Royal Jelly**

Even of reliable many positive effects of royal jelly, it can be contraindicated in bronchial asthma in crisis, possible allergy to any of its components, Addison disease and cancers in acute phase. Digestive tract disorders may occur through overdose: stomachaches, vomiting, diarrhoea, and insomnia (especially in women). Decreasing the dose, or stopping the royal jelly administration will eliminate these adverse reactions. Toxicity may appear in major overdose cases. Several factors can diminish the effectiveness of royal jelly. If body is too weak or unable to digest and/or absorb, or people have major structural or genetic problems, they can not use the active compounds from royal jelly properly. In these cases, more attention pay and many details should be evaluated before using.

#### **CONCLUSION**

In last decades, healthy eating habits for natural nutrition and non-sickness are increasing demand in the world. Royal jelly is one of the most important products in the bee products. Royal jelly, which has great positive effects on health, will make a big contribution in the right place at the right time and at the right dose and doctor's recommendation to use it. It can be recommended for people without allergy risk.



In particular, royal jelly is an excellent food and its content is very important for the development and renewal of children and the elderly, and encouraging

consumption by people can be considered as a measure to meet the substances our bodies need and as a pre-sickness measure.

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