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Royal Jelly; Biochemical Properties, Activity and Medical Use

ABSTRACT

Royal jelly (RJ) has a rich nutrient content and valued natural bee product which has been mainly used in traditional medicines to protect and strengthen the health. It is a yellowish-white and acidic secretion of hypopharyngeal and mandibular glands of nurse bees used to feed young worker larvae during the first three days and the entire life of queen bees. Because of its functional properties, RJ is very effective in accelerating the protection of health and healing process in many diseases. The high quality and scientific standardization of RJ is very important for using it in prevention of health and medical use in treatment disease in complementary medicine. This review explains the effects of RJ on medical use for human health.

Keywords: Royal jelly, health, apitherapy, biochemical property, activity

Arı Sütü; Biyokimyasal Özellikleri, Aktivitesi ve Tıbbi Kullanımı

ÖZ

Arı sütü zengin bir besin içeriğine sahip olan ve geleneksel ilaçlarda sağlığı korumak ve güçlendirmek için kullanılan değerli bir doğal arı ürünüdür. Arı sütü, bakıcı işçi arıların hipofaringeal ve mandibular bezlerinden salgılanan, genç işçi larvalarını ilk üç gün boyunca ve ana arıyı tüm yaşamı boyunca beslemek için kullanılan sarımsı beyaz renge sahip asidik bir salgıdır. Sahip olduğu fonksiyonel özellikler nedeniyle arı sütü, birçok hastalıkta sağlığın korunması ve iyileşme sürecinin hızlandırılmasında oldukça etkilidir. Arı sütünün yüksek kalitesi ve bilimsel standardizasyonunun sağlanması, hem sağlığın korunmasında hem de tamamlayıcı tıp alanında hastalıkların tedavisinde kullanılabilmesi için çok önemlidir. Bu derlemede arı sütünün insan sağlığı için tıbbi kullanımdaki etkileri açıklanmaktadır.

Anahtar Kelimeler: Arı sütü, sağlık, Apiterapi, biyokimyasal özellikler, aktivite



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INTRODUCTION

Since royal jelly (RJ) contains a high concentration of nutrients from the beehive, which supports and protects health, it has a greater potential and impact than other bee products (Strant et al., 2019). Honeybees produce RJ, a nutritious material with antibacterial, antioxidant, and anti-inflammatory effects that is suitable for use as an ingredient in pharmaceutical and medical products (Uthaibutra et al., 2023). RJ, which feeds drone and young worker larvae and sustains queen bees throughout their lives, is secreted by nurse worker bees from their mandibular and hypopharyngeal glands (Ahmad et al., 2020). RJ is a sour, white-yellowish gelatinous fluid rich in vitamins, minerals, proteins, lipids, carbohydrates, and peptides (Uversky et al., 2021). The high biological value and nutritional value of RJ can be explained by the properties of the substances it contains. Proteins, fatty acids, phenols, and flavonoids are the primary active components of RJ. These substances have biological functions that both support and promote human health (Guo et al., 2021). In addition to these, there are all vitamins, very important minerals, enzymes and biologically active substances required for the development of larvae. The composition of RJ deteriorates rapidly at temperatures above 25°C and under light. Studies have reported that RJ can be stored at 4°C for up to one year without any change in its structure, although the best storage method for RJ is to freeze it at -18°C or lyophilize it as soon as it is harvested (Li et al., 2007; Sabatini et al., 2009). Fresh RJ is very rich in protein and its protein ratio varies between 9% and 18% (Ramanathan et al., 2018). Essential and non-essential amino acids such as arginine, cystine, histidine, lysine, valine, leucine, isoleucine, threonine, serine, methionine, glutamic acid, tryptophan, proline were determined in RJ. Its structure contains vitamins A, C, D and E, especially B vitamins, choline esterase, digestive system ferments, hormones and many biologically active substances as well as pollen and beeswax mixtures. Due to the healing and restorative properties of RJ, it is used in the treatment of numerous diseases. RJ has been consumed as human food for many years. Today, RJ is used in the pharmaceutical, cosmetic and food industry, especially for its beneficial effects on human health. RJ has strong cell regenerating properties. In addition, there are many scientific studies on the antibacterial, antifungal, antiviral, antidiabetic, nervous system supportive and musculoskeletal protective properties of RJ, so it has an important place especially in Apitherapy applications (Kolaylı and Keskin, 2020; Nazarzadeh et al., 2022; Botezan et al., 2023; Oršolić and Jembrek, 2024). Unlike other bee products, RJ contains Coenzyme Q-10 (Hryniewicka et al., 2016). Coenzyme Q-10 plays an important role in protecting cardiovascular health and regulating the circulatory system. In apitherapy applications, RJ provides beneficial results in reducing cholesterol, lipid, triglyceride levels, supporting the immune system and protecting the body against general disease factors, healing ulcerative diseases related to stomach and intestines, adjusting low and high blood pressure due to its blood pressure regulating effect, anaemia, sexual problems, reproductive problems, preventing weakness and many other ailments. In cosmetics, it is used for cell renewal and skin imperfections (Hryniewicka et al., 2016; Spanidi et al., 2020; Ahmad et al., 2020). RJ can be sold in different forms and packages such as powder, cream, injection, tablet and capsule. RJ is frequently used as a supplement for a variety of illnesses due to its antibacterial, antioxidant, anti-aging, immunomodulatory, and its diverse therapeutic properties.

Chemical Composition of Royal Jelly

The water content of RJ is an important criterion in assessing the quality of the fresh product. Various methods have been used to determine the water content of RJ. It has been found that the refractive index depends directly on the water content of RJ (Sesta, 2006). The major content of RJ is water (60–70%) which helps in dissolving and distributing the other bioactive components (Sabatini et al., 2009). The chemical composition of lyophilized RJ is presented in Table 1.



Table 1. Water content, dry matter, proteins, lipids, ash, fructose, glucose, sucrose, total sugars, pH, total acidity and electrical conductivity of lyophilized royal jelly samples (Balkanska and Kashamov, 2011).

Tablo 1. Liyofilize arı sütü örneklerinin su içeriği, kuru madde, proteinler, lipitler, kül, fruktoz, glikoz, sakkaroz, toplam şekerler, pH, toplam asitlik ve elektriksel iletkenlik (Balkanska ve Kashamov, 2011).

Contents	Means±S. E.	Min.	Max
Water content, %	3.99±0.18	3.49	4.76
Dry matter, %	96.02±0.18	95.24	96.51
Proteins, %	38.11±1.23	34.09	41.80
Lipids, %	6.22±0.72	3.09	8.56
Ash, %	2.75±0.08	2.50	3.03
Fructose, %	11.85±0.45	10.37	13.64
Glucose, %	9.9±0.94	6.82	12.78
Sucrose, %	7.65±1.11	4.19	11.62
Total Sugars, %	29.4±1.16	24.27	32.67
pH	3.87±0.03	3.80	4.00
Total acidity, ml 0,1 N NaOH/g	11.66±0.3	10.67	12.88
Electrical conductivity, µS/cm	451.33±9.03	421.00	481.00

Proteins make up 1/3 to 1/2 of the dry matter of RJ. From a quantitative point of view, proteins represent the largest part of RJ dry matter (27-41%) (Sabatini et al., 2009). Major Royal Jelly Proteins (MRJPs) are a group of proteins, of which MRJP1 is the most abundant (Fang et al., 2023). MRJPs constitute 82% to 90% of the total amount of proteins in RJ and contain a relatively high amount of essential amino acids (Schmitzová et al., 1998). These proteins play important roles in growth, development and reproduction. MRJPs also have immunomodulatory and antimicrobial effects. RJ contains several enzymes, such as glucose oxidase and α -glucosidase, which contribute to its biological activities. MRJPs can modulate the immune response in a number of ways, helping to regulate the activity of immune cells, the production of cytokines and the pathways of inflammation (Wang et al., 2023). The study conducted by Bouamama et al. (2021) demonstrated that RJ significantly enhanced the proliferation of human peripheral blood mononuclear cells, accompanied by an increase in nitric oxide (NO) ($p=0.001$) and the release of interleukin 2 (IL-2), interleukin 4 (IL-4) and interleukin 6 (IL-6) cytokines. Additionally, RJ elevated the intracellular glutathione ($p=0.001$) and malondialdehyde ($p=0.001$). The water-soluble proteins of RJ were fractionated, resulting in the identification of a fraction that induced both proliferative and migratory effects on a human epidermal keratinocyte cell line. Lin et al. (2019) reported that a protein fraction, primarily comprising MRJP2, MRJP3 and MRJP7, elicited proliferative and migratory responses in human keratinocyte cell line (HaCaT) without evident cytotoxicity. The same authors postulated that major RJ proteins may possess potential wound-healing bioactivity. Glucose and fructose constitute over 90% of the total sugar content of RJ. Other sugars have been identified in minor quantities, including sucrose, maltose, trehalose, melibiose, ribose and erlose (Xue et al., 2017). These sugars provide a source of quick energy, but they also have roles in modulating immune responses. The lipid fraction constitutes around 7% to 18% of the total composition of RJ. Of these lipids, 90% are short hydroxy fatty acids with 8–12 carbon atoms in the chain and dicarboxylic acids. The most important fatty acid is 10-hydroxydecanoic acid (10-HDA) (Kunugi and Ali, 2019). The RJ contains eight of the nine important amino acids, only the compound lacks tryptophan (Strant et al., 2019). AMP-N1 Oxide stands for Adenosine monophosphate N1 oxide and is a unique compound, found only in RJ. It is connected with the effects on centrally nervous system. It stimulates differentiations, promotes generation of all 3 types of cells: neurons, astrocytes and oligodendrocytes, against neuronal damage. Adenosine is a biomolecule in RJ with many physiological effects. It produces inhibition in vascular smooth muscle cells of coronary arteries and neurons in the brain, by its hyperpolarising effect on the membrane potential of excitable cells. RJ contains 5.9 to 2057.4 mg/kg adenosine. Acetylcholine is a nerve transmitter, with a number of hormone-like effects in the central and vegetative nervous system. There is 1 mg of it at every gram of dry weight of RJ. Testosterone, progesterone, prolactine, estradiol hormones help increase the fertility of both male and female and also increase male power and endurance. The polyphenols present in RJ have been associated with its an oxidant effects (Mateescu, 2016). RJ also contains minor components, such as minerals (Fe, Na, Ca, K, Zn, Mg, Mn, and Cu), amino acids (eight essential amino acids Val, Leu, Ile, Thr, Met, Phe, Lys, and Trp), vitamins (A, B complex, C, and E), enzymes, hormones, polyphenols, nucleotides, and minor



heterocyclic compounds (Ahmad et al., 2020). The quality of the RJ is evaluated by 10-hydroxy-2-decenoic acid (10-HDA) level in its content and the level of the matter is expected to be found among 1.4% and 1.8 % levels. This value can differ due to the vegetation where RJ is obtained from and the implementation techniques in harvesting RJ (Yücel et al., 2017).

Medical Use of Royal Jelly

RJ is a unique natural bee product with a multitude of possible pharmaceutical properties and health-promoting benefits. With its anti-inflammatory and antioxidant qualities, as well as its function in boosting immunity, controlling cholesterol, and enhancing skin health, RJ has proven its worth as a natural health supplement. There are various scientific studies investigating the effects of RJ on human health.

Antioxidant, Antimicrobial and Anti-Inflammatory Effects

RJ is renowned for its potent antioxidant properties. In order to prevent cellular damage and chronic diseases like cancer and cardiovascular disorders, antioxidants are essential in combating free radicals. Studies have shown that the antioxidant compounds in RJ can help reduce oxidative stress, thereby protecting the body against various health issues. RJ is known for its potent antimicrobial and antioxidant activities. Studies have shown that RJ can effectively inhibit the growth of various bacterial strains and reduce oxidative stress, making it beneficial for preventing infections and maintaining cellular health (Bagameri et al., 2022). While inflammation is the body's normal reaction to damage or infection, prolonged inflammation can cause a number of health issues, such as autoimmune disorders, arthritis, and heart disease. RJ has demonstrated significant anti-inflammatory properties in various studies. These properties help reduce inflammation and may alleviate symptoms of conditions such as rheumatoid arthritis. Studies have demonstrated that components like royalisin and 10-hydroxy-2-decenoic acid (10-HDA) contribute to its potent antimicrobial activity (Fratini et al., 2016). The mixture of RJ and honey showed enhanced antimicrobial effects, particularly against Gram-positive bacteria. The combination was effective in inhibiting the growth of pathogens like *Staphylococcus epidermidis* and *Enterococcus faecalis* (Maželienė et al., 2022).

Effects on Cardiovascular Diseases

RJ has been shown to positively influence cardiovascular health. It lowers serum levels of low-density lipoprotein and total cholesterol, which lowers the risk of cardiovascular diseases. The hypocholesterolemic effects are primarily due to its ability to decrease small very-low-density lipoprotein (VLDL) levels (Guo et al., 2007). Meta-analysis of RJ 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 β / α 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 (Strant et al., 2019). Recent research suggests that RJ can improve cardiovascular health by augmenting vascular endothelial function and reducing markers of liver damage. This has been shown in clinical trials where RJ supplementation led to significant improvements in vascular function and reductions in liver enzyme levels (Fujisue et al., 2022). RJ's possible insulin-like action was demonstrated in a different study where it dramatically lowered serum glucose levels in healthy participants following an oral glucose tolerance test (Münstedt et al., 2009).

Effects on Immune System

The immune-boosting effects of RJ have been a subject of interest in recent research. It has been found to enhance the body's immune response, making it more effective in fighting off infections and diseases. The presence of specific proteins and fatty acids in RJ helps modulate the immune system, potentially offering protection against various pathogens. Additionally, RJ improves immunological function by encouraging immune cell proliferation and raising cytokine production. This immunomodulatory effect helps in maintaining a robust immune system, particularly in aging populations (Bouamama et al., 2021). RJ and its enzyme-treated variant showed anti-inflammatory and immune-enhancing properties in mice (Gu et al., 2018). Besides, by modifying immune response-related gene expression, RJ prevented tumor growth in mice, indicating its potential for use in cancer immunotherapy (Zhang et al., 2017). RJ has immunomodulatory properties, stimulating antibody production and immunocompetent cell proliferation in mice (Sver et al., 1996).



Effects on Gut Microbiota

RJ has been observed to modulate gut microbiota composition, enhancing overall health. It increases beneficial bacteria and improves antioxidant activities in the liver and kidneys, indicating a positive correlation between gut health and systemic health benefits (Chi et al., 2021). RJ additionally fosters the growth of advantageous gut flora like *Bacteroides fragilis* and *Bacteroides thetaiotaomicron*, improving gut health and possibly providing therapeutic advantages for disorders related to the gut (Kazemi et al., 2019). Additionally, RJ prevents colitis by modifying the gut microbiota and strengthening the colonic mucosal barrier (Guo et al., 2022).

Anti-Tumor and Anti-Cancer Effects

Research indicates that RJ possesses anti-tumor properties, which can inhibit the growth of cancer cells. This effect is attributed to its bioactive compounds that modulate cell proliferation and apoptosis (Viuda-Martos et al., 2008). In a study on dimethylhydrazine-induced colorectal cancer in rats, RJ significantly reduced oxidative stress and tumor markers, demonstrating its potential as an anticancer agent. Royal jelly-treated rats showed less necrosis, inflammation, and cell proliferation compared to untreated rats (Khoob et al., 2022). RJ stimulated human mononuclear cells to secrete cytokines that inhibited the growth of leukemic U937 cells and induced their differentiation. This indicates its potential in treating leukemia by modulating immune responses (Wang et al., 2019).

Neuroprotective Effects

The anti-inflammatory and antioxidant qualities of RJ are vital in preventing damage to neuronal cells (Siğ et al., 2019). RJ has shown promise in improving memory and exhibiting neuroprotective effects in a rodent model of sporadic Alzheimer's disease. It reduced neurodegeneration and oxidative stress while enhancing the proliferation of new neurons (Silva et al., 2020). Additionally, when given for two weeks, RJ increased consciousness in traumatic brain injury patients (Shafiee et al., 2022). RJ was shown to protect cortical neurons from cadmium-induced damage in mice by reducing oxidative stress and inflammation (Almeer et al., 2018).

Effects on Diabetes

RJ has shown potential in managing diabetes by improving glucose tolerance and lowering serum glucose levels. Its insulin-like activity helps in reducing blood sugar levels, making it beneficial for diabetic patients (Münstedt et al., 2009). A systematic review confirmed that RJ could improve glycemic status and reduce fasting blood sugar levels in diabetes mellitus patients (Maleki et al., 2019). In type 2 diabetic females, RJ supplementation significantly lowered fasting blood glucose levels and HbA1c, indicating improved glycemic control (Pourmoradian et al., 2014).

Anti-Aging Effects

RJ promotes healthy aging and longevity, potentially leading to the development of anti-aging drugs. Components like royalactin and 10-HDA enhance antioxidative capacity and signalling pathways (Bagameri et al., 2022). Human dermal microvascular endothelial cells are preserved by RJ, which also lessens the effects of UV exposure on vessel aging, thereby preventing skin aging (Kawano et al., 2019).

Effects on Hormonal Balance and Reproductive Health

RJ has demonstrated effectiveness in relieving menopausal symptoms and aging-related pathologies. It exhibits estrogen-like effects, which help mitigate symptoms such as hot flashes and mood swings. Additionally, RJ's antibacterial, anti-inflammatory, and antioxidant properties support overall health in postmenopausal women (Bălan et al., 2020). RJ has been recommended for alleviating menopausal symptoms due to its estrogen-like effects. Studies suggest that it can improve overall menopausal symptoms and promote healthy aging (Bălan et al., 2020; Münstedt and Männle, 2020). It activates estrogen receptors and enhances gene expression related to estrogen response (Mishima et al., 2005). Oral consumption of RJ was found to significantly reduce premenstrual syndrome (PMS) symptoms in a randomized controlled trial among Iranian medical students. This suggests its potential as a non-pharmacological treatment for PMS (Taavoni et al., 2014). RJ has been observed to have estrogenic effects in both in vitro and in vivo studies. It stimulates the expression of genes that are responsive to estrogen by binding to estrogen receptors, suggesting its potential in managing menopausal symptoms and other estrogen-deficient conditions (Mishima et al., 2005). RJ in treatment of sexual and urinary



problems of postmenopausal women is related to its estrogenic properties and could be suitable in promotion of life quality in postmenopausal women (Seyyedi et al., 2016). In addition, RJ has been shown to improve male fertility in various animal studies. Oral administration of RJ enhanced sperm quality and sexual behavior in male rabbits, and it protected against heat-induced infertility (Abdelnour et al., 2020). RJ-based apitherapy can mitigate nicotine-induced testicular damage by acting as an antioxidant and scavenger of reactive oxygen species (Nazarzadeh et al., 2022).

Effects on Skin diseases

The anti-aging qualities of RJ can lessen the visibility of wrinkles and fine lines while also improving wound healing and hydrating the skin. Its antimicrobial properties also contribute to its effectiveness in treating acne and other skin conditions. It has been demonstrated that applying RJ topically reduces pruritus in a mouse model of allergic contact dermatitis (Yamaura et al., 2013). RJ reduces melanin synthesis by downregulating tyrosinase expression, suggesting its potential use as a skin-whitening agent (Han et al., 2011). The wound-healing capabilities of RJ are attributed to its anti-inflammatory and antimicrobial properties. Studies have shown that RJ can accelerate the healing process by promoting tissue regeneration and reducing infection risks. This makes it a valuable natural remedy for cuts, burns, and other skin injuries. A study highlighted the distinct wound-healing properties of RJ derived from different floral sources, demonstrating its potential in accelerating wound closure and promoting skin repair (Lin et al., 2020). RJ protects the skin against oxidative stress and promotes healthy skin by upregulating the expression of NAD(P)H quinone dehydrogenase 1 (NQO1), which plays a role in antioxidation and detoxification (Okumura et al., 2021).

Effects on Memory and Mental health

Emerging research suggests that RJ may have a positive impact on cognitive function and memory. Its antioxidant properties, combined with its ability to reduce inflammation, can protect the brain from oxidative stress and improve neural function. Some studies have indicated that regular consumption of RJ may enhance learning abilities and memory retention, although more research is needed to confirm these effects. Major royal jelly proteins (MRJPs) have been shown to improve spatial memory in aged rats by 48.5% compared to controls. This improvement is linked to alterations in metabolism pathways like nicotinate and nicotinamide metabolism (Chen et al., 2017). A study conducted by Morita et al. (2021) demonstrated that long-term ingestion of RJ significantly improved mental health scores in healthy volunteers. The study found that after six months, participants who consumed RJ showed a notable improvement in their mental health as measured by the The Short-Form 36 (SF-36) Health Survey subscale score. Research by Ilegaki et al. (2019) on a murine model indicated that RJ could reduce depression-like behaviour through its effects on adrenal steroidogenesis. The study found that RJ suppressed stress-induced depression-like behaviour by regulating the synthesis and transport of cholesterol, which is crucial for adrenal steroidogenesis. Asama et al. (2018) conducted a placebo-controlled study on postmenopausal Japanese women and found that RJ supplementation significantly alleviated anxiety and back pain which highlights the potential of RJ in managing anxiety symptoms in specific populations.

Effects on Stem Cell Function and Regeneration

RJ has shown promise in influencing stem cell functions. A recent randomized trial demonstrated that RJ administration increased the count of hematopoietic stem cells in the peripheral blood of healthy subjects, indicating its potential role in promoting regenerative processes (Okamoto et al., 2023). It also enhances the oxidants superoxide and glutathione and is rich in nucleic acids, RNA, and DNA (Mateescu, 2016).

Recommended Royal Jelly for Human Diet

A common dosage for general health benefits is about 1000 mg of RJ daily. The use of RJ above the specified dose must be under the supervision of a physician. RJ is generally considered safe for most people when used appropriately. Nonetheless, some people may experience allergic reactions to it, especially those who have asthma or allergies to bee products. High doses might lead to gastrointestinal discomfort or other mild side effects. When adjusting to the recommended dosage, it is advisable to begin with a lower dose to determine tolerance (Strant et al., 2019).



CONCLUSION

RJ's importance in apitherapy applications lies in its rich nutritional composition and its wide range of potential health benefits. Its anti-inflammatory, antioxidant, immune-boosting, and antimicrobial properties make it a valuable natural remedy for various health conditions. Additionally, RJ's ability to support skin health, balance hormones, improve neurological function, and enhance cardiovascular health underscores its therapeutic potential. The impact of bee products on health protection is much more important than treatment. Bee products, which can prevent and cure such a large number and variety of health problems, can be used as complementary applications in both preventive medicine and modern medicine, if they are Used under the supervision of a doctor at the appropriate dose and period. RJ appears to be a good and useful agent that can be used in these applications. It is important to consult a professional doctor or Apitherapist for advice on the use of RJ, especially regarding product validation, specific and appropriate dosage and method of administration for each disease. RJ can be used as a preventive treatment in the form of a cure as well as in treatment, depending on the health status of the person and the progress of the disease, it must be applied under professional evaluation. While more detailed in vitro and in vivo scientific research is needed to fully validate and understand these benefits, RJ remains a promising component of apitherapy and human health.

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