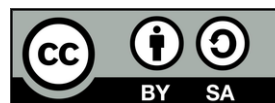




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Review Article

Royal jelly: chemical composition, health benefits and food applications: A review

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Abstract

Royal jelly (RJ) is a valuable bee product with complex chemical composition, high nutritional value and numerous health benefits. This article aims to review the general chemical composition, health promoting properties and food applications of RJ. RJ has been found to be a biological product that is characterized by a substantial protein content (approximately 50% of its dry matter), followed by other essential nutrients and bioactive compounds such as carbohydrates, lipids, fatty acids, minerals, vitamins, enzymes, hormones and phenolic compounds (mainly flavonoids). Particular attention is paid to the biological properties and therapeutic effects of RJ such as antimicrobial, antiviral, antioxidant, anti-inflammatory, antitumor, anti-aging and many others. The medical indications, dosage and health benefits of RJ consumption, (recently hailed as a “superfood”) are also discussed. It can be concluded that RJ has attracted extensive research attention in recent years due to its great potential for application in the food industry as a functional food ingredient and in the manufacture of probiotic dairy products.

Keywords

Royal jelly, bee products, functional foods, superfoods, healthy foods

Abbreviations

ACE – angiotensin 1-converting enzyme; Ala – alanine; Arg – arginine; Asn – asparagine; Asp – aspartic acid; DNA – Deoxyribonucleic acid; DPPH – 1,1-diphenyl-2-picrylhydrazyl; ERJ – enzyme-treated royal jelly; HBV – hepatitis B virus; HCV – hepatitis C virus; HSV-1 – herpes simplex virus type 1; 10-HDA – 10-hydroxydecanoic acid; 10-H2DA – trans-10-hydroxy-2-decenoic acid; IL – interleukin; Ile – isoleucine; Leu – leucine; LTA – lipoteichoic acid; Lys – lysine; MAPK – mitogen-activated protein kinase; MCP-1 – monocyte chemoattractant protein; MRJPs – major royal jelly proteins; MW – molecular weight; NF-κB – nuclear factor kappa-light-chain-enhancer of the activated B lymphocytes; Phe – phenylalanine; Pro – proline; RJ – royal jelly; RNA – Ribonucleic acid; ROS – reactive oxygen species; SA – sebacic acid; SARS-CoV-2 – human coronavirus type 2; SOD – superoxide dismutase; TNF-α – tumour necrosis factor-α; Tyr – tyrosine, VEGF – vascular endothelial growth factor

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Introduction

Royal jelly (RJ) is a secretion from the mandibular and hypopharyngeal glands of young worker honey bees (*Apis mellifera* L.) at the age of 5-15 days and known as nurses (El-Guendouz et al. 2020). It has a highly viscous consistency, white-yellowish color, sour taste, high acidity (pH=3.4-4.5) and is partially water-soluble (Sabatini et al. 2009). RJ is used as an essential food for all bee larvae during the first three days of their life. The larva chosen to develop into queen bee continue to be fed with RJ, thereafter it remains her only food source throughout the rest of her life. In addition, the RJ exerts a significant effect on bee longevity - the life of worker bees lasts on average 45 days, while that of the queen bee continues up to five years. During her life cycle, the queen can lay between 2000 and 3000 eggs per day, which is equivalent to her weight (Fratini et al. 2016a). The main bioactive compound in RJ that is responsible for the morphological transformation of larva into a queen bee is a major protein (MRJP1) known as royalactin. Its biological functions are related to increasing body size, stimulating ovary growth and reducing the time for development of honeybees (Kamakura 2011).

Chemical composition of RJ. RJ is a rich source of essential nutrients important for the honey bee development and differentiation as well as for the human nutrition. Recent studies revealed that the chemical composition of RJ includes water (60-70%), proteins (9-18%), carbo-hydrates (7-18%), lipids (3-8%), minerals and vitamins (Ahmad et al. 2020). Besides the main chemical components, RJ comprises other bioactive substances - amino acids, fatty acids such as 10-hydroxydecanoic acid (10-HDA) and trans-10-hydroxy-2-decenoic acid (10-H2DA), phenolic compounds and hormones (testosterone, progesterone, prolactin, estradiol), contributing to its wide range of pharmacological properties and health benefits (Pasupuleti et al. 2017). According to some scientific reports, the physicochemical characteristics of RJ are relatively constant irrespectively of the bee race and colony; however, they depend to a great extent on the bee feeding and supplementation, period and hygienic conditions in the hive during the harvesting as well as the environmental factors (Flanjak et al. 2019).

Unlike honey and wax, the standardization of royal jelly is considerably more difficult, but not

impossible. The quality and purity control of bee products uses organoleptic properties (appearance, colour, aroma, texture and consistency) and certain chemical and biological properties. The ranges, within which the values of the various parameters vary, linked to the origin and the method of storage and processing, have been established. Any deviation from the limits of certain parameters (defined in the established norms), indicates falsification (Balkanska et al. 2012).

Water. RJ is a biological mixture characterised by high water content (around 60%) and water activity (a_w) above 0.92 (El-Guendouz et al. 2020). The water content is a major criterion in determination of RJ quality (Sesta and Lusco 2008; Sabatini et al. 2009). This physicochemical parameter according to the International standard (ISO 12824:2016) should vary in the limits from 62.0 to 68.5% in the fresh product. The high water content of RJ is one of the prerequisites for its instability under normal storage conditions. Therefore, some researchers propose lyophilization (a freeze-drying process that reduce the moisture content to 3-4% and even less than 1%) and encapsulation of RJ as technological approaches, protecting the bioactive components and increasing its storage life (Kausar and More 2019; Spanidi et al. 2022; Ghadimi-Garjan et al. 2023).

Proteins, peptides and amino acids. Proteins are presented in the composition of RJ with 9-18% forming the largest part of its dry substance (approx. 50%). The major RJ proteins (MRJPs), or apalbumins, accounting 83-90% of the total protein content, represent multifunctional glycoproteins with covalently linked oligosaccharides to their N-terminal residue. They have an important role in the queen bee growth and development (Uversky et al. 2021). The amino acid composition of MRJPs, which includes mainly lysine, arginine, valine, histidine, methionine, leucine, isoleucine, threonine, phenylalanine and tryptophan, is found to be similar to those of casein and ovalbumin. The MRJPs family includes nine proteins named as follows: MRJP1, MRJP2, MRJP3, MRJP4, MRJP5, MRJP6, MRJP7, MRJP8 and MRJP9 (Ramadan and Al-Ghamdi 2012), performing a variety of functions as RJ nutritional ingredients as well as in the honey bee organism. Proteins MRJP1 - MRJP5 have mainly nutritional functions; MRJP6 - MRJP8 possess non-nutritional properties, while MRJP9

unifies both groups of biological activities (Ramanathan et al. 2018). Besides the important physiological role of MRJPs in the larvae nutrition and immunity protection, it has been found that MRJP1 is a key factor in the brain functions

(learning, memory, task assignment and social behaviour) of the honey bees (Tian et al. 2018). Recent proteomic analyses revealed the presence of MRJP10, whose biological functions are not yet well studied (Table 1).

Table 1. MRJPs characteristics, main biological functions and health benefits

RJ proteins (synonyms)	Amino acid residues	Experimental MW*, kDa	Theoretical MW, kDa	Biological activities and health benefits	References
MRJP1 (royalactin, apalbumin 1, apalbumin α)	413	55	46.86	Anti-inflammatory, anti-aging, antimicrobial, wound healing, hypotensive, cell proliferative, antioxidant, antitumor, immunomodulatory, hypocholesterolaemic, growth-promoting, neuroprotective	(Han et al. 2011)
MRJP2 (RJ glycol-protein apalbumin 2, apalbumin β)	435	50-55	49.15	Antioxidant, antimicrobial, antitumor, cell proliferative, growth-promoting, wound healing, anti-inflammatory	(Ramadan and Al-Ghamdi 2012)
MRJP3 (apalbumin 3, apalbumin γ)	524	60-70	59.49	Immunomodulatory, anti-aging, anti-inflammatory, wound healing, growth-promoting, cell proliferative	(Yükünç 2019)
MRJP4	444	60	50.67	Antimicrobial	(Mureşan et al. 2022)
MRJP5	578	77-87	68.13	Wound healing	
MRJP6	417	n/a	47.58	Unknown	
MRJP7	426	n/a	48.66	Cell proliferative, growth-promoting, wound healing	
MRJP8	400	n/a	45.06	Antimicrobial agents in honey bee venom	(Carpena et al. 2020)
MRJP9	403	n/a	46.27	Antimicrobial agents in honey bee venom	
MRJP10	411	47	n/a	Unknown	(Uversky et al. 2021)

*MW - molecular weight; n/a - not available

Besides MRJPs, RJ contains a low variety of small proteins, or bioactive peptides, most of which are formed by proteolytic hidrolisis from MRJPs, or are their oligomeric forms. The monomeric form of MRJP1 is known as royalactin (Table 1). Apisin is an oligomeric form of MRJP1, which represents MRJP1 monomers associated with other RJ protein named apisimin (5.5 kDa) and 24-methylene-cholesterol. Apisin is a protein responsible for the

building of fibrillary network that gives the viscous consistency of RJ. Jelleins (classes I-IV) are short chain peptides with multiple functions, consisting of 8-9 amino acid residues, obtained by enzymatic cleavage from MRJP1. Jelleins I-III are known to exhibit significant antimicrobial activity (Tamura et al. 2009; Uversky et al. 2021; Mureşan et al. 2022).

Royalisin is also an antimicrobial peptide with a molecular weight of 5.5 kDa, which is pH- and

thermostable, and possess a wide spectrum of inhibitory activity expressed mainly against Gram-positive bacteria and some specific bee pathogens such as *Paenibacillus larvae* causing the American foulbrood - a fatal disease of the honey bee larvae (Yükünç 2019).

RJ also contains free amino acids, among which lysine is prevalent (62.43 mg.100 g⁻¹), followed by proline (58.76 mg.100 g⁻¹), cystine (21.76 mg.100 g⁻¹) and aspartic acid (17.33 mg.100 g⁻¹). The amino acids such as valine, glutamic acid, glycine, serine, threonine, cysteine, alanine, leucine, isoleucine, hydroxyproline, glutamine, phenylalanine and tyrosine are presented at concentrations below 5 mg.100 g⁻¹ (Guo et al. 2021).

Carbohydrates. The carbohydrates fraction of RJ is represented by 30% of the dry substance, whose components are in highly variable quantities. The monosaccharides glucose and fructose are constituted by 90% of the sugar content of RJ. The disaccharide sucrose is presented only by 0.6-3.6%. In RJ are also detected little amounts of other sugars - galactose, maltulose, mannitol, trehalose, turanose, melibiose, ribouse, erlose, isomaltose, palatinose, melezitose, trehalose, gentiobiose and others (Collazo et al. 2021). Although these sugars are presented in small concentrations, they can find practical application as indicators of the product authenticity (Sabatini et al. 2009; Barnutiu et al. 2011).

The sugar content of RJ varies in wide ranges depending on multiple factors as bee feeding, season, bee species, botanical source, geographical region and the exaction method. For example, the sucrose and erlose contents of French RJ were found to be lower (1.8% and 0.4%) in comparison with those produced by sugarcane-fed bees (7.7% and 1.7%, respectively) (Wytrychowski et al. 2013). According to another research on Italian RJ the sugar fraction was between 6.9 and 16.0% (average 11.4%), from which fructose 2.3-6.9% (average 4.6%), glucose 3.7-8.2%, (average 5.8%), sucrose 0.1-2.1% (average 1.0%). These values were similar to those reported for French RJ (Sesta 2006).

Lipids and fatty acids. The lipids are represented by 8-19% of the RJ dry substance. The lipid fraction contains mainly organic acids (80-90%), most of them are free and natively occur as mono- and

dihydroxy acids and dicarboxylic acids with 8-12 carbon atoms in the chain, which exhibit a specific arrangement (Sabatini et al. 2009; Kocot et al. 2018).

Among the most significant fatty acids of RJ are 10-hydroxydecanoic acid - 10-HDA (C₁₀H₂₀O₃) and trans-10-hydroxy-2-decenoic acid - 10-H2DA (C₁₀H₁₈O₃), which are hydroxy acids with 10 carbon atoms; and sebacic acid - SA (C₁₀H₁₈O₄), which is dicarboxylic acid with 10 carbon atoms (Kocot et al. 2018). 10-HDA is assumed to be specific to RJ as no other biological product has been reported to contain this unsaturated fatty acid. Similar to the sugar content, the 10-HDA content is accepted as a criterion for the RJ quality and authenticity (Sesta 2006). The lipid composition of RJ also includes 8-hydroxyoctanoic acid (8-HOC), 3,10-dihydroxydecanedioic acid (3,10-HDecDA), 9-hydroxy-2-decenoic acid (9-HDA), 3-hydroxydecanoic acid (3-HHDA), 2-decene-1,1-dioic acid (2-DecDA) and traces of sterols (Guo et al. 2021).

Apart from nutritional features and health benefits, the fatty acids in RJ perform various biological functions. For instance, 10-HDA, or so called queen acid, controls the epigenetic of honey bee caste differentiation (morphological, reproductive and behavioral phenotypes) (Polsinelli and Yu 2018).

It has been determined that 10-HDA possesses strong antimicrobial activity against Gram-positive bacteria as *Staphylococcus aureus* (Gao et al. 2022), *Micrococcus luteus* ATCC 9341, *Staphylococcus epidermidis* ATCC 12228, Gram-negative bacteria as *Salmonella enteritidis*, *Escherichia coli* ATCC 25922, yeasts *Candida albicans* ATCC 10351, *Candida parapsilosis* ATCC 22019 and fungi *Penicillium digitatum*, *Aspergillus flavus* (Ulubayram and Cinar 2023). 10-HDA has been found to be effective against *P. larvae*, which cause the American foulbrood disease and other virulent bacterial bee infections (Sediva et al. 2018).

Another important biological property of 10-HDA is its anti-inflammatory activity. Yang et al. (2018) found that 10-HDA exhibited *in vitro* anti-inflammatory activity in WiDR human adenocarcinoma cells, as well as antibacterial effect on different animal and human pathogens (*Staphylococcus aureus*, *Staphylococcus intermedius*, *Staphylococcus xylosus*, *Streptococcus alactolyticus*, *Salmonella cholearasuis*, *Vibrio*

parahaemolyticus and *Escherichia coli*). [Chen et al. \(2018\)](#) reported that 10-HDA exhibited *in vivo* inhibitory potential on the release of mediators of inflammation and nitric oxide, induced by the lipoteichoic acid (LTA) - a toxin produced by *S. aureus* that cause pulmonary damages in mice. The authors found that the intake of 10-HDA in dose of 100 mg.kg⁻¹ exhibited anti-inflammatory effect by attenuating the pathological changes in lungs.

Vitamins, minerals and hormones. One of the most common vitamins presented in RJ is B5, or pantothenic acid (3.6-23.0 mg.100 g⁻¹); followed by B3, or niacin (4.5-19.0 mg.100 g⁻¹); B6, or pyridoxin (0.2-5.5 mg.100 g⁻¹); B2, or riboflavin (0.5-2.5 mg.100 g⁻¹); B1, or thiamin (0.1-1.7 mg.100 g⁻¹); B7, or biotin (0.15-0.55 mg.100 g⁻¹); B9, or folic acid (0.01-0.06 mg.100 g⁻¹) ([Rizki et al. 2021](#)). Vitamins B8 (biotin), B12 (cobalamin) and C (ascorbic acid), are presented in limited quantities. It was found that RJ contains only water-soluble vitamins, while liposoluble vitamins (A, D, E and K) are not detected ([Fratini et al. 2016b](#)).

Minerals represent 2-5% of RJ dry substance ([El-Guendouz et al. 2020](#)). In contrast to honey and bee pollen, whose mineral composition varies to a great extent on the botanical source, soil type and other factors, the mineral content of RJ is relatively constant. This finding emphasizes the homeostatic regulation of mineral and trace elements amounts produced by the endocrine glands of nurse bees. It was also determined that RJ exhibits the same homeostatic regulation as mammalian and human breast milk ([Collazo et al. 2021](#)).

In addition to the most common macro- and microelements in RJ were detected also potassium (K) (200-1000 mg.100 g⁻¹); magnesium (Mg) (20-100 mg.100 g⁻¹); Iron (Fe) (1-11 mg.100 g⁻¹) ([Rizki et al. 2021](#)); calcium (Ca); sodium (Na); manganese (Mn) and trace elements such as aluminum (Al); barium (Ba); strontium (Sr); bismuth (Bi); cadmium (Cd); mercury (Hg); lead (Pb); tin (Sn); tellurium (Te); thallium (Tl); wolfram (W); antimony (Sb); chromium (Cr); nickel (Ni); titanium (Ti); cobalt (Co) and molybdenum (Mo) ([El-Guendouz et al. 2020](#)).

Different hormones such as testosterone, estradiol, gonadotropins, progesterone and prolactin have been identified as constituents of RJ ([Takaki-Doi et](#)

[al. 2009](#)), but detected in trace amounts ([Kumar et al. 2024](#)).

Phenolic compounds. Phenolic compounds are important class of biologically active substances in the plants and bee products. They represent organic compounds containing an aromatic ring, which is chemically bonded to one or more hydrogenated substituents in the presence of corresponding functional derivatives. In RJ phenolic compounds are presented mainly by flavonoids. Phenolic compounds in RJ are well known to exert various health benefits and therapeutic effects (antioxidant, antibacterial, antifungal, antiviral, wound-healing, and cardioprotective) ([Pasupuleti et al. 2017](#)).

Flavonoids in RJ include various compounds such as flavones (apigenin and its glycosides, luteolin, chrysin and acacetin), flavanones (naringenin, hesperetin and isosakuranetin), flavonols (kaempferol and isorhamnetin glycosides), and isoflavonoids (genistein, formononetin and coumestrol) ([Ahmad et al. 2020](#)).

Health benefits

RJ is a valuable bee product known worldwide with its great therapeutic potential. As a biological product with complex chemical composition, RJ possess various health promoting properties - antimicrobial, antioxidant, anti-inflammatory, anticarcinogenic and cardio-protective activities ([Khalifa et al. 2024](#)), thus finding extensive application in the alternative medicine. The bioactive components in RJ have additional pharmacological properties expressed in the form of immunomodulatory, anti-aging, wound healing, anti-diabetic, anti-obesity, antihypertensive, anti-allergic, neuroprotective, estrogenic and other effects, which have been demonstrated in cell cultures, animals and human experimental models. In terms of healthy nutrition, RJ is recognized as a food with essential functional properties ([Oršolič and Jembrek 2024](#)).

Antimicrobial activity. Antimicrobial peptides of plant and animal origin are natural tools against different types of microorganisms. Due to the increasing resistance of a numerous bacterial strains to the conventional antibiotics, the interest in the application of new antimicrobial agents is growing with rapid temps ([Romanelli et al. 2011](#)). The antimicrobial activity of RJ is associated with the

presence of specific polypeptides (APMs) of variable length (10-50 amino acids) with defined antimicrobial functions. They interact with the negatively charged microbial surfaces and the penetration through the cell membrane by the bilayer phospholipids groups (Fratini et al. 2016b).

The antimicrobial potential of royalisin against Gram-positive bacteria was previously reported by Bilikova et al. (2001) who proved the inhibitory effect of this peptide on aetiological agent of American foulbrood (*Paenibacillus larvae*) and *Bacillus subtilis*.

The antibacterial activity of jelleines (I, II, III and IV), a group of RJ peptides with antimicrobial function, was reported by Romanelli et al. (2011). These authors stated that jelleins I and II were active against the Gram-positive bacteria *Staphylococcus aureus* ATCC 6535, *Staphylococcus saprophyticus* and *Bacillus subtilis* CCT 2471, and the Gram-negative bacteria *Escherichia coli* CCT 1371, *Escherichia cloacae* ATCC 23 355, *Klebsiella pneumoniae* ATCC 13 883 and *Pseudomonas aeruginosa* ATCC 27 853. It was found that jellein III exhibited limited antimicrobial potential, whereas jellein IV was not active against the tested microorganisms.

A study conducted by Coutinho et al. (2018) displayed that RJ possessed antimicrobial activity against various periodontal pathogens such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia* and *Fusobacterium nucleatum* (minimum bactericidal concentrations of 12.5-100 µg.mL⁻¹). These results revealed the effectiveness of RJ in the treatment of oral infections.

Antifungal potential of RJ has also been reported. Moselhy et al. (2013) observed inhibitory activity of Egyptian and Chinese RJ against *Aspergillus fumigatus*, *Aspergillus niger*, *Candida albicans* and *Syncephalastrum racemosum*.

Antiviral activity. Despite the numerous extensive publications on the biological properties of RJ, the information about its antiviral potential is still very limited. Like other bee products, RJ can exert its antiviral effect directly (through inhibition of the viral penetration or replication), or indirectly (by stimulating the immune response or enhancing the

effect of conventional antiviral drugs) (Asma et al. 2022).

Using Vero cell line, Hashemipour et al. (2014) observed that RJ in a dose of 250 µg.mL⁻¹ showed significant inhibitory effect on the replication of human herpes simplex virus type 1 (HSV-1). Two consecutive studies conducted by Habashy and Abu-Serie (2019 and 2020) revealed that purified MRJP2 and its isoform MRJP2 X1 were highly effective against the replication of some enveloped RNA-viruses such as hepatitis C virus (HCV) and human coronavirus type 2 (SARS-CoV-2) as well as DNA-viruses such as hepatitis B virus (HBV). The efficacy of RJ application in the treatment and prevention of SARS-CoV-2 respiratory syndrome and associated bacterial and fungal co-infections, especially in hospitalized patients was described by Lima et al. (2020).

Antioxidant activity. Oxidative stress is related to a disbalance between the production of reactive oxygen species (ROS) and the capability of antioxidants to scavenge them. Overproduction of ROS can damage membrane structures, proteins, enzymes and DNA molecule, thus causing aging and some diseases as atherosclerosis, hypertension, diabetes and cancer. However, the intake of dietary antioxidants by various foods and biological products can prevent the ROS-related diseases. Peptides in foods are potential natural antioxidants with limited adverse effects; therefore they are extensively used in the pharmaceutical and food industries (Guo et al. 2009).

The antioxidant activity of RJ is mediated from its protein components - MRJPs and peptides. The peptides derived from RJ by proteolysis are distinguished with the highest antioxidant activity towards the lipid peroxidation (Mureşan et al. 2017). Guo et al. (2009) examined the antioxidant activity of 29 peptides obtained from RJ hydrolysate. The authors stated that 12 small peptides consisting of 2-4 residues (Ala-Leu, Phe-Lys, Phe-Arg, Ile-Arg, Lys-Phe, Lys-Leu, Lys-Tyr, Arg-Tyr, Tyr-Asp, Tyr-Tyr, Leu-Asp-Arg, Lys-Asn-Tyr-Pro) had the highest antioxidant potential expressed as hydroxyl radical scavenging activity.

Gu et al. (2021) explored the protease treatment on the antioxidant capacity of RJ. The antioxidant activity of enzyme-treated RJ (ERJ) was assessed by the 1,1-diphenyl-2-picrylhydrazyl (DPPH)

method. The results revealed that ERJ had 20% higher DPPH free radical scavenging activity than untreated RJ. Moreover, the enzyme treatment did not affect the freshness and 10-HDA content of RJ, and led to a significant increase of free amino acids. The authors also concluded that enzyme-induced hydrolysis leads to degradation of two major protein allergens in RJ by converting into easy-to-absorb short chain monomers.

The antioxidant capacity, protein and polyphenolic contents of RJ are not constant values. They can vary depending on different factors such as age of larvae and time of collection. [Liu et al. \(2008\)](#) reported that RJ collected during the first 24 h of the larval life, exhibited significantly higher scavenging activity (determined by the DPPH assay), higher reducing power and inhibitory effect on the linoleic acid peroxidation, but lower superoxide dismutase (SOD) activity, compared to the samples collected on the 48-th h and 72-th h from the beginning of the larval life. According to the same study, the decrease of antioxidant activity after the 24-th h of larval life could be associated with the decreasing levels of the total polyphenols and proteins.

Anti-inflammatory, immunomodulatory and anti-allergic activities. Inflammation is a defensive mechanism that is triggered by various pathogenic factors such as infectious agents, toxins, chemical substances and mechanical injuries. The biological response of the immune system at the tissue level appears with symptoms as redness, swelling, warming, pain and loss of tissue functions due to the release of pro-inflammatory cytokines by the host cells. The role of the inflammatory process is dedicated to regenerate the normal body functions. The macrophages are cells that modulate the immune response and have an essential role in the immune system ([Chen et al. 2017](#)).

The three most significant fatty acids in RJ - 10-HDA, 10-H2DA and SA have been examined for their anti-inflammatory activity and the effects on some inflammatory genes. Besides the inhibitory activity against the release of the major mediators of the inflammation - nitric oxide and interleukin-10 (IL-10), it has been found that the only SA showed ability to decrease the production of tumour necrosis factor- α (TNF- α) - a cytokine secreted by the macrophages/monocytes during acute inflammation process. The three RJ fatty acids

possess regulating effects on the proteins included in the mitogen-activated protein kinase (MAPK) as well as the signaling pathways of nuclear factor kappa-light-chain-enhancer of the activated B lymphocytes (NF- κ B) ([Chen et al. 2016](#); [Bagameri et al. 2023](#)). The research of [Chen et al. \(2018\)](#) demonstrated that a dose of 100 mg/kg of 10-HDA possess a significant protective effect on experimentally LTA-induced pulmonary damage in mice by limiting the production of inflammatory cytokines such as IL-10, monocyte chemoattractant protein-1 (MCP-1) and TNF- α , through a reduction in the expression of certain inflammatory genes.

The anti-inflammatory effect of RJ was confirmed also by [Arzi et al. \(2015\)](#), who used similar doses to treat formalin-induced paw edema in rats. The authors determined that RJ administered at a dose of 50-100 mg.kg⁻¹ was effective as the conventional anti-inflammatory drug aspirin at a dose of 300 mg.kg⁻¹ used to treat the positive control group.

[Maghsoudlou et al. \(2019\)](#) reported that due to its anti-inflammatory effect, RJ plays an essential role in improving the quality of life in patients with different autoimmune diseases such as rheumatoid arthritis by preventing joint destruction. [Karaca et al. \(2012\)](#) found that the anti-inflammatory activity of the RJ could improve health condition of rats with acetic acid-induced colitis and promote cell regeneration in the colon of the animals.

Anti-allergic properties of RJ have also been reported such as preventive effects against anaphylactic response in a murine model of cow's milk allergy ([Guendouz et al. 2017](#)) and suppression of allergic reactions in humans ([Oka et al. 2001](#); [Chansuwan et al. 2020](#)).

Antitumor activity. The term "cancer" unifies a broad range of diseases, which is associated with the rapid development of abnormal cells dividing in an uncontrollable manner and extending beyond their normal boundaries, thus forming cancerous tumors. The cancer cells can spread and enter adjacent tissues and organs in a process named metastasis, which can eventually cause death ([Williams et al. 2019](#)). The capability of tumor progress depends on the tumor microenvironment. The process of development of the new blood vessels from an existing vascular bed (angiogenesis) has significant role in tumor growth and metastasis. The key factor for cancer neovascularization is the vascular

endothelial growth factor (VEGF). In this regard, inhibition of tumor angiogenesis is targeted as one of the cancer treatment strategies (Pan et al. 2013).

The conventional methods used for cancer treatment (chemotherapy, radiotherapy and surgery) are effective, but often have serious complications; therefore the healthy lifestyle, in particular the nutritious diet, plays a crucial role in the treatment of various diseases, including cancer, and can significantly accelerate a patient's recovery. Admittedly, RJ cannot be used alone as an anticancer remedy, but it can be successfully combined with conventional chemotherapeutics, enhancing their healing effects in a synergistic manner, reducing their genotoxicity and DNA damages, or improving their entrance into the cells (Salama et al. 2022).

The antitumor potential of RJ has been demonstrated in many experimental models. It has been shown that the RJ has a notable *in vivo* antitumor activity tested in mice and humans. Whereas intraperitoneal and subcutaneous application of RJ on the 7-th and 14-th day before, or 2 and 9 days after tumor cell inoculation had no effect on the mammary metastasis formation, co-administration of RJ with tumor cells significantly suppressed metastasis formation in mice lungs (Khazaei et al. 2017). In another research carried out by Zhang et al. (2017), the application of RJ decreased the tumor mass and stimulated the antioxidant enzymatic activities of the liver and kidneys in mice with breast cancer.

In recent years, numerous studies have revealed the *in vitro* anticancer activity of RJ. Wang and Chen (2019) determined the ability of different types of RJ extracts to reduce the proliferation of the human leukemia cell line U937. The synergistic effects between the anticancer drugs and RJ have been revealed by Abandansari et al. (2018). The results showed that combined application of doxorubicin and RJ increased the antitumor effect on the prostate cancer cell line PC3, allowing to reduce the dose of the drug and mitigate its side effects.

Polyphenols (particularly flavonoids) and 10-HDA are among the major bioactive components that contribute to the RJ antitumor activity. This fact highlights a possible link between the antioxidant, anti-inflammatory and anticancer properties of RJ (Botezan et al. 2023).

Anti-aging activity. Aging is a physiological process, normally associated with a gradual weakening of the organism and progressive decline of cognitive, visual, hearing, muscular and sleep functions as well as overall deterioration of the quality of life (Ali and Kunugi 2020).

As mentioned above, in the honey bee population RJ plays an important biological role as it mediates the transformation of larva into a queen bee and ensures her fertility and longevity (queen bee can live up to 5 years, while worker bees live only 45 days). It is believed that RJ bioactive components (MRJPs, peptides, amino acids, 10-HDA, vitamin B5 and hormones) can modulate the mechanisms of aging; however the exact mechanisms by which RJ may enhance longevity are still not well-studied (Kunugi and Ali 2019).

At present, numerous studies have investigated the lifespan extending effects of RJ in different animal species; however, the information about delay of aging and longevity enhancing in humans is still very limited. In a study conducted with mice, prolonged administration of RJ was shown to enhance memory and age-related weight loss. Moreover, the physical performance of RJ-treated animals was found to be improved compared to the control group. In the same study, it was found that after treatment, animals had enhanced muscle stem cells and had a lower degree of muscle atrophy (Bălan et al. 2020). A research performed by Okumura et al. (2018) showed that age-associated disruption of motor functions in mice was significantly delayed after treatment with RJ.

Nowadays, RJ is evaluated as a highly protective agent against skin aging. In an *in vitro* experiment, normal human dermal fibroblasts (HDFs) were exposed to ultraviolet-A (UV-A) irradiation (as a model of skin photoaging) and subsequently treated with 10-HDA. The results showed that 10-HDA application protected HDF cells from UV-A-induced cytotoxicity, ROS-related oxidative damage, delayed cellular senescence and significantly stimulated the production of collagen (Zheng et al. 2013).

Antihypercholesterolemic, antihypertensive and antidiabetic activities. Cholesterol is an essential compound in the human body, but can lead to hypercholesterolaemia when its level in the blood stream rises significantly, causing various harmful

conditions such as atherosclerosis and associated cardiovascular diseases (Roman et al. 2015).

Recent experimental data showed that MRJP1 reduced the cholesterol absorption in Caco-2 cell line by inhibition of the micellar cholesterol solubility. It was also found that MRJP1 possessed high bile acid-binding ability in the small intestine, thus increased the fecal cholesterol excretion and cholesterol catabolism in the liver (Kashima et al. 2014). Apart from MRJPs, the RJ substances with estrogenic activity can also exert cholesterol-lowering effects. Regular consumption of RJ may modulate the levels of cholesterol 7- α -hydroxylase, which is one of the main enzymes for the bile-acid synthesis from cholesterol in the hepatic cells. It was also proved that a daily intake of RJ for more than 90 days can regulate the cholesterol rates and improve the blood lipid parameters (Hadi et al. 2018), thus decreasing the risk of cardiovascular diseases in the long term (Bahari et al. 2023).

Hypertension represents a serious health problem, which is among the risk factors for development of heart insufficiency, cerebral stroke and acute myocardial infarction. It is well known that there is a close relationship between the hypertension and the metabolic syndrome (obesity, dyslipidemia and insulin resistance). According to some authors, 10-H2DA and 10-HDA significantly contribute to the blood pressure control (Tahir et al. 2020). Other researchers concluded that enzymatic hydrolysis of MRJP1 increased its antihypertensive effect and reduced the high blood pressure in spontaneously hypertensive rats. In the gastrointestinal system, glycosylated MRJP1 can act as an ACE inhibitor. Generally, blood pressure is regulated by the renin-angiotensin system, which plays an important physiological role in the circulatory system. The ACE inhibitor peptides, obtained from RJ after protease treatment, are resistant to the digestive proteases, which is important in oral administration of RJ (Matsui et al. 2002).

Diabetes mellitus is one of the most prevalent endocrine diseases in the world, characterized by hyperglycemia as a main disorder due to impaired insulin secretion, insulin function or both (Maleki et al. 2019). RJ contains biologically active compounds that are structurally and functionally similar to insulin. Moreover, RJ can effectively regenerate damaged pancreatic cells, thus

preventing the development of diabetes. The regeneration of pancreatic cells and regulation of insulin levels are the crucial factors in lowering blood glucose levels (Oršolič and Jembrek 2024).

It was found that RJ significantly reduced serum glucose levels in healthy volunteers and in diabetic patients 2 h after ingestion. Experiments conducted on animal models of diabetes (rats) showed that RJ intake led to additional positive effects expressed in improving the plasma antioxidant properties, reduction of some biochemical parameters (lowering liver enzyme levels) and fasting blood glucose, and even recovery of the reproductive tissues (Oršolič and Jembrek 2024).

Neuroprotective effects. Recently, numerous clinical studies as well as *in vivo* experiments on laboratory animals revealed that RJ plays an important role in the brain cells differentiation and induces neurogenesis in the hippocampal dentate gyrus. It was found that oral administration of RJ can significantly improve the neural functions due to the regeneration of hippocampal granule cells, which is critical for the cognition process and can prevent the oxidative injury of the brain (Ahmad et al. 2020). Clinical trials have shown that the RJ intake has a positive impact on the central nervous system by reducing the degree of brain tissue damage and death. 10-HDA has neuroprotective properties, potentially enhancing the survival of nerve cells (Mohamed et al. 2015). The intake of 3 g of RJ for a period of six months improves the glucose tolerance, erythropoiesis and mental health in humans (Morita et al. 2012). Aslan et al. (2012) observed that oral treatment with RJ in a dose of 100 mg.kg⁻¹ reduces the apoptotic cell number after experimental injury of the spinal cord in rabbits by increasing the endogenous enzymatic and non-enzymatic antioxidant protection system and decreasing the lipid peroxidation. RJ is also highly effective mean for treatment of neurodegenerative disorders such as Alzheimer's disease in aged patients (Pan et al. 2019).

Effects on sexual dysfunctions and infertility. Infertility is a common problem among men and women, as well as among many animal species, which is polyethologic and difficult to treat. RJ possesses many benefits for human fertility such as improving hormonal balance, and increasing sperm and ovule quality. RJ contains hormones and

hormone-like substances such as royalactin, which can enhance reproductive health through regulating hormonal balance, supporting fertility, menstrual cycle regularity and relieving symptoms of some hormonal imbalances such as postmenstrual syndrome and menopause (Kumar et al. 2024).

The benefits of RJ on reproductive functions have been proven through numerous experiments on different animal models. Administered orally or intramuscularly, RJ ration containing exogenous progesterone improves the estrus and pregnancy in Awassi breed ewes (Husein and Kridli 2002). Ghanbari et al. (2018) observed that intraperitoneal $\alpha\pi\pi\lambda\iota\chi\alpha\tau\iota\omicron\nu$ of RJ (doses of 100-400 mg.kg⁻¹ per day) stimulates follicular growth and ovarian hormone secretion in immature female rats through its estrogenic effects on the reproductive system, thus improving their fertility.

Long-term RJ intake also increases the testosterone levels, ejaculate volume, sperm motility, sperm count and seminal plasma fructose in infertile men and male animals. In this regard, Kohguchi et al. (2007) reported that RJ supplementation (50-500 $\mu\text{g.g}^{-1}$ diet for 12 weeks) increases the levels of intra-testicular free testosterone and improves the process of spermatogenesis, halting the age-related decline in testicular functions of male golden hamsters. Similarly, the application of RJ in doses between 50 and 150 mg.kg⁻¹ twice per week, for a 20-week period, led to significant increase in the total sperm output, sperm concentration, sperm motility and sperm viability in male rabbits (El-Hanoun et al. 2014).

Application of RJ in foods. As multicomponent biological mixtures possessing diverse health effects, in recent years, beekeeping products (honey, pollen, bee bread, propolis and RJ) have received extensive research attention for their potential pharmaceutical and functional food applications. In recent years, RJ is considered as an appealing ingredient in functional food products and has even gained a reputation as a “superfood” due to its high nutritional value and numerous health benefits.

Regarding the basic nutrition, the contribution of RJ is relatively small. The average recommended daily intake of RJ (2 g) does not meet the daily nutritional needs of proteins, carbohydrates, lipids and minerals, but supplies the necessary bioactive

substances, which have various health benefits. RJ is among the best sources of vitamin B5 and vitamin B3. Deficiency of vitamin B5 increases the risk of infections and gastrointestinal disorders. All B group vitamins are involved in transformation of proteins, carbohydrates and fats into energy, thus helping to release energy from food. B vitamins possess many health effects – they are essential for maintaining healthy eyes, skin and hair; improve the functions of the nervous system, liver and gastrointestinal tract; stimulate the proliferation of the red blood cells as well as the secretion of steroid hormones by the adrenal glands (Oršolič and Jembrek 2024).

RJ is a bee product widely used for a variety of medical and food purposes. The dosage, scheme and treatment period with RJ depend to a great extent on the individual needs, age and health status of the patients (Table 2). According to some studies, a dose of 100 mg.kg⁻¹ of RJ provides the best healing effect even in severe conditions, and a higher dose is very rarely required (Strant et al. 2019). Although rare, some side effects of RJ application are reported, such as allergic reactions, asthma, skin disorders (dermatitis, eczema), bronchospasm, anaphylaxis, haemorrhagic colitis and anaphylactic shock. In these cases, the main role of allergens is played by the RJ proteins MRPJ1 and MRPJ2, which are common with bee venom allergens (Bălan et al. 2020).

Application in functional foods. Functional foods are one of the most dynamically developing sectors of the food industry. According to the generally accepted definition, functional foods are those that positively affect one or more physiological functions beyond the capability of basic nutrition, thus exerting their health benefits. The improvement of health-promoting effects of functional foods can be achieved through different technological approaches such as fortification (addition of one or more nutrients), modification and removing a specific component in order to enhance a certain physiological function, or to reduce some negative effects (Granato et al. 2010).

In recent years, hydrolysis of proteins has noted a growing scientific interest in the pharmaceutical industry and food production sector. Proteases are enzymes secreted by different parts of the digestive system. Their proteolytic action leads to a change in

molecular conformation of the native proteins, thus obtaining bioactive products, which are applied as additives in various food systems. These bioactive peptides can enhance the nutritional and functional features of the proteins, and even to reduce the level of milk allergens in dairy products. Moreover, several studies have revealed that some dietary proteins hydrolyzed by the proteases demonstrated higher biological potential and more health benefits. At present, it is still unresolved whether the proteases in RJ are secreted by the honey bees, or they are of plant origin, which stimulates the research efforts in this area (Darwish et al. 2023).

Hydrolysis of proteins in the manufacture of functional foods can be performed by application of

different methods. Fermentation of foods by probiotic bacteria (lactic acid bacteria and bifidobacteria) is the main technological approach that can induce the production of bioactive compounds in the food matrix in order to achieve certain health benefits. Probiotics possess many physiological and health effects such as stimulating the secretion of digestive enzymes and vitamins, reducing gastrointestinal pH, producing antimicrobial substances (bacteriocins, organic acids, diacetyl, H₂O₂), stimulation of immunity, removing carcinogenic agents and reducing fecal enzyme activity (Alu'datt et al. 2015). From this point of view, the use of RJ proteases could be considered as a mean for food functionality improvement.

Table 2. Medical indications and dosage of RJ (oral administration)

Age group	Indications	Dosage, g per day	Reference
Premature infants	Stimulation of growth and development, strengthening of immune and nervous systems	0.25	(Strant et al. 2019)
Infants		0.5	
Children 1-5 years old 5-12 years old	Low immunity, acute infections, colds, nervous system impairment, anorexia, weakness, loss of appetite, anaemia	0.5 0.5-1	(Strant et al. 2019)
Adults	- Low immunity, insomnia, skin disorders, wounds, anaemia, low libido, hormonal imbalances, infertility, premenstrual syndrome, menopause, osteoporosis, cancer, autoimmune diseases;	1-2	(Morita et al. 2012) (Taavoni et al. 2014) (Ahmadnia et al. 2015) (Osama et al. 2017) (Strant et al. 2019)
	- Diabetes, depression, Hashimoto's disease, arthritis;	3-5	(Sharif and Darsareh 2019)
	- Acute infections, colds, heavy working conditions	up to 10	

Probiotic fermented milk products (in particular yogurt) are important part of daily human diet and represent a suitable matrix for incorporation of RJ as a functional component. The manufacture of probiotic yogurts with RJ is a promising approach to obtain innovative functional products with enhanced nutritional value and health-promoting properties (Darwish et al. 2023).

Moreover, the application of RJ in dairy products can lead to prebiotic effect by stimulating the growth of lactic acid bacteria. In this context, Haddadin et al. (2012) reported that the addition of RJ to milk improved the growth of *Lactobacillus acidophilus* and *Bifidobacterium bifidum*. The authors stated that highest count of *L. acidophilus* (9.01 log cfu.mL⁻¹) was determined when RJ was added in concentration of 2%, while the highest count of *B. bifidum* (9.07 log cfu.mL⁻¹) was

observed when RJ was added in concentration of 5%. The obtained results showed that RJ had prebiotic potential by increasing the number of viable cells of *Lactobacillus acidophilus* and *B. bifidum*, and stimulated the production of short chain fatty acids. The stimulating effect of RJ application on the growth of probiotic bacteria was also confirmed by [Guldas \(2016\)](#). The author reported that the viable cell count of probiotic strains *Bifidobacterium animalis* spp. *lactis* BB12, *Lactobacillus casei* ATCC 55544 and *Lactobacillus acidophilus* LA-5 increased in a parallel to the concentration of RJ added to the growth medium. The observed increase in bacterial count was most significant at concentration of RJ up to 75 mg during the first 24 h of the cultivation.

The fortification of dairy products with RJ can improve not only their functional properties, but can also positively influence the fermentation process and technological properties of the products. [Alu'datt et al. \(2015\)](#) investigated the physico-chemical and biological properties of skimmed milk enriched with *Lactobacillus acidophilus* and RJ (2.5, 5 and 7.5%) and fermented for 24 h. The authors stated that the number of viable cells in skimmed milk increased with fermentation time regardless of the increasing concentrations of RJ. The antioxidant activity of skimmed milk fortified with 2.5% of RJ increased most significantly after the 4-th hour of fermentation process, compared to the control sample and other experimental groups. The results demonstrated that the fermentation in the presence of RJ has led to higher ACE inhibitory and α -amylase inhibitory activities in the treated samples compared to those without fortification. This study revealed the potential application of the fermented milk product in the therapy of hypertension and hyperglycemia (type 2 diabetes).

[Atallah \(2016\)](#) designed a bio-yogurt with addition of probiotic bacteria (*Lactobacillus gasseri* ATCC 33323, *Lactobacillus rhamnosus* DSM 20245 and *Bifidobacterium angulatum* DSM 20098) and RJ. The supplementation of yogurt with probiotic strains and RJ increased the coagulation time, the total solids, ash, fat, protein and acidity contents as compared to the control sample during refrigerated storage for 21 days. The obtained bioyogurt exhibited improved rheological properties and sensory characteristics.

[Cinar et al. \(2021\)](#) produced a probiotic variant of the Turkish traditional dairy dessert (keskul) with addition of RJ. The authors found that among the three investigated probiotic strains (*Lactobacillus rhamnosus*, *Lactobacillus plantarum* and *Bifidobacterium animalis* subsp. *lactis*), *Lactobacillus plantarum* was the most suitable for the production of dairy dessert with RJ. *Lactobacillus plantarum* displayed high rate of survival in the dessert during its storage at 4°C for 15 days. With regard to the sensory evaluation, the combination of *Lactobacillus plantarum* + 1 mg.mL⁻¹ of RJ received higher scores from the consumers, compared to the dessert with *Lactobacillus plantarum* + 5 mg.mL⁻¹ of RJ and the control.

[Kavas \(2022\)](#) developed a probiotic yogurt with enhanced functionality by adding 2% of fresh RJ. The author determined that yogurt with addition of RJ was more acceptable than the samples without RJ in terms of some parameters such as rheological properties, viability of probiotic cultures and fatty acid content. It was found that the 10-HDA concentration (one of the most important bioactive components of RJ) was above the minimum level specified in the standards in yogurt samples.

[Hassan et al. \(2022\)](#) evaluated the effects of RJ application (0.5%, 1% and 1.5%) on the physico-chemical characteristics, sensory properties, viable cell count and biological activities of fermented milk. The obtained results exhibited that the addition of RJ reduced the fermentation time, and improved the rheological properties and antioxidant activity of the fermented milk. In comparison with the control (without RJ), fermented milk with addition of 1% RJ maintained higher count of the probiotic strain *Lactobacillus helveticus* Lh-B02, (9.73 log cfu.g⁻¹) during the refrigerated storage for 21 days. Furthermore, the application of RJ improved some biological activities of fermented milk. Fermented milk supplemented with 1.5% RJ showed the highest antibacterial and anticancer activities, while the milk with 1% RJ had the highest sensory score.

Based on the estimations from the above studies, it can be concluded that RJ is a prospective bee product with high nutritional value and therapeutic potential, which can be successfully applied as an ingredient of novel functional products.

Beekeeping is an economic activity in the agricultural sector and an ecologically sustainable production model that is crucial for biodiversity and agriculture. Given the fact that RJ is a valuable raw material for the pharmaceutical, cosmetic and food industries, its production can have a significant economic impact on rural regions and contribute to the well-being of many producers of bee products (Lyubenov et al. 2021; Nikolova et al. 2023).

Conclusions

RJ is a valuable bee product used by humans since ancient times for its rich nutrient content and health promoting effects. In recent decades RJ has become increasingly popular as an attractive dietary supplement and functional component. Due to its important health benefits, it has been widely used in the manufacture of medical products, cosmetic products and functional foods in many countries worldwide. However, more collaborative studies by researchers from different scientific fields (chemistry, biochemistry, biotechnology, biology, physiology, nutrition and medicine) are needed to expand the knowledge about RJ food applications in the future.

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