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Research

A Broad Overview of the Multifaceted Royal Jelly and Its Applicability in Health and Performance

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Royal Jelly (RJ) is a secretion of the hypopharyngeal and mandibular glands of worker bees, and is the exclusive food of the queen bee during her larval stage, so that she reaches almost twice the size of the worker bee. Over the years, the use of RJ has been associated with longevity and improved health quality during aging, post-menopausal hormonal modulation, as an adjuvant in the treatment of Chronic Non-Communicable Diseases, different types of cancer, in dermatology, as an antimicrobial treatment, to enhance fertility, as a nephroprotector, neuroprotector, hepatoprotector, immunometabolism modulator, and cognitive improvement. Only at the beginning of the 21st century did research with RJ and exercise emerge, identifying anti-fatigue effects, decreased serum lactate and ammonia, reduced muscle glycogen depletion, improved athletic performance, attenuating oxidative stress induced by High Intensity Interval Exercise (HIIE), to interrupt neurodegeneration in multiple sclerosis, in the positive modulation of cannabinoid-1 receptors as therapeutic targets for the treatment of autoimmune diseases such as multiple sclerosis, for reducing sarcopenia, skeletal muscle loss and weakness, and inducing mitochondrial adaptation with resistance training by activating AMPK in muscles.

Keywords: Nutraceuticals, oxidative stress, text mining, immunometabolism.

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INTRODUCTION

Perhaps the oldest known reference to human interest in bees is a cave painting from approximately 7,000 years ago in Arana Cave, Spain, depicting a man robbing a bee colony. Until the Middle Ages, honey remained the only and preferred source of sugar. Therefore, it is understandable why few creatures have received as much thought and writing as the honeybee. Only in recent decades have we gained some insight into the pattern of its social behavior and the chemical structures of the pheromones secreted by the queen, which are responsible for the expected behavior of a bee colony (Rembold, 1965). The nature of "royal jelly" (RJ) fascinated and perplexed writer Frederick Banting for many years. In 1930, the writer first published an enthusiastic account of facts and his fantasies about the bees' life history. While the social organization in the hive excited his admiration and amazement, it was the peculiar nutritional properties of the food given by the nurse bees to the developing queen bee that particularly intrigued him (Lucas, 1942).

Royal jelly (RG) is a secretion of the hypopharyngeal and mandibular glands of worker bees, being the exclusive food of the queen bee during her larval phase. This diet differs in its effects on bee development during the adult phase (Lewis et al., 2010). Female bee larvae develop as members of the queen or worker caste, depending on the nutrition and care received during larval development, so that the mature queen is almost twice as large as the worker (Melampy & Stanley, 1940). In the 1960s, three new compounds isolated from honeybee royal jelly (Apis mellifera, L.) were identified: 8-hydroxyoctanoic acid, 3-hydroxydecanoic acid, and a dextrorotatory isomer of 3,10-dihydroxydecanoic acid (Weaver et al., 1968). Subsequently, numerous studies characterized the components of royal jelly and their effects.

Townsend & Lucas (1940) separated royal jelly into four main fractions: (1) ether-soluble, (2) water-soluble and dialyzable, (3) water-soluble and non-dialyzable, and (4) water-insoluble. In this separation, the authors indicated that fraction 1 appeared to consist primarily of an organic acid (or mixture of acids), small amounts of phenolic material, and smaller amounts of beeswax, sterol, phospholipin, and a saponifiable substance. Fraction 2, the most significant fraction, was approximately 50% sugars, with glucose and fructose accounting for the majority of the reducing material. An unidentified acid, inorganic salts, and nitrogen compounds were also present. Fraction 3 is protein in nature, containing primarily aspartic acid, arginine, tyrosine phosphates, tryptophan, cystine, and histidine. Fraction 4 is a protein, soluble only in alkalis. It provides positive color tests for tyrosine, tryptophan, and arginine. They also indicated

some evidence that fraction 1 contains the physiologically active material responsible for the queen bee's sexual development.

As early as the late 1940s, chemical analyses of royal jelly showed that it is a complex mixture of substances with a protein content of 9 to 18% of the fresh material, indicating the presence of alanine, arginine, aspartic acid, cystine, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tyrosine, tryptophan, valine, beta-alanine, glutamine, and taurine (Pratt & House, 1949). More recently, it has been reported that royal jelly contains 12–15% protein, of which 82–90% are members of the prominent royal jelly protein family, the MRJPs. These proteins have critical pharmacological activities, including antifungal and bactericidal activities (Hojo et al., 2010; Tian et al., 2018).

In the 1990s, a new potent antibacterial protein, named Royalisin, was discovered in royal jelly, with a primary structure comprising 51 residues, three intramolecular disulfide bonds, and a calculated molecular mass of 5,523 Da. Royalisin is an amphipathic protein with the C-terminal half rich in charged amino acids, and it shows extensive sequence homology with two other antibacterial proteins: sapecin from Sarcophaga peregrina embryonic cells and formicins from Phormia larvae. terranovae. Royalisin exhibits potent antibacterial activity against Gram-positive bacteria at low concentrations. Royalisin may be involved in an active defense system against bacterial invasion of the honeybee (Fujiwara et al., 1990).

Royal jelly has additional properties, including evidence of therapeutic efficacy in transplantable mouse leukemia and antibiotic activity. Notably, royal jelly contains acetylcholine in an amount estimated to be about six times that found in insect brains. The occurrence of a neurohormone in royal jelly is of considerable interest, as it suggests that acetylcholine may have a function other than that associated with nerve transmission (Colhoun & Smith, 1960). 10-Hydroxy-delta (2)-decenoic acid, the main component of the lipid fraction of royal jelly, exhibits antibiotic activity against numerous bacteria and fungi, including Micrococcus. pyogenes, Escherichia coli, and Neurospora sitophila, as well as some unidentified fungi (Blum et al., 1959). Certain components of royal jelly can stimulate mitochondrial adaptation in skeletal muscle. In mice, GR supplementation increased the maximum activity of the enzymes citrate synthase and §-hydroxyacyl CoA dehydrogenase during a resistance exercise protocol (Takahashi et al., 2018).

In the case of physical exercise, royal jelly presents itself as a potential supplement in acute training, since, in addition to helping with antioxidant defense, it has anti-inflammatory (Chen et al., 2016) and hepatoprotective (Almeer et al., 2018), cardioprotective by decreasing the rate of cardiac lipid peroxidation and histopathological lesions such as myocardial necrosis (Malekinejad et al., 2016), improves insulin resistance, decreases glycated hemoglobin, and increases total antioxidant activity, being beneficial for diabetic individuals (Pourmoradian et al., 2014; Kusumawati et al., 2023). The biological activity of GR is associated with hydroxycarboxylic fatty acids with 8-12 carbon atoms and their derivatives; the main fatty acid is 10-hydroxydecanoic acid (10-HDA), found only in royal jelly (Kolayli et al., 2016; Kocot et al., 2018). Its composition also contains riboflavin, thiamine, niacin, folic acid, biotin, and pyridoxine, as well as smaller amounts of vitamins C, D, A, and E (Fujii et al., 1990; Oka et al., 2001); Aslan & Askoy (2015) showed that royal jelly is capable of preventing the production of ROS by affecting signalling pathways for the production of these species; its antioxidant composition was able to reduce inflammation associated with kidney damage. Liu et al. (2008) demonstrated that royal jelly exhibits DPPH radical-scavenging activity, inhibits linoleic acid peroxidation, and inhibits the formation of the superoxide and hydroxyl radicals (Kocot et al., 2018).

Kamakura et al. (2001) reported that administering royal jelly to mice improved endurance in forced-swimming tests, with reduced blood lactate accumulation and glycogen consumption. Furthermore, when the test was repeated after a brief rest, there was no significant difference in these parameters between the GR-supplemented group and the first phase of exercise, demonstrating the anti-fatigue potential of GR. The accumulation of ammonia generated during exercise may contribute to fatigue; however, when royal jelly was administered before exercise, the mice showed a significant decrease in serum ammonia concentration and achieved a longer maximum swimming time before fatigue than the control group (Kamakura et al., 2001).

The use of royal jelly has also been associated in scientific literature with longevity and improved health quality during aging (Kunugi. Ali, 2019), post-menopausal hormonal modulation (Balan et al., 2020), as an adjuvant in the treatment of Chronic Non-Communicable Diseases (Malek et al., 2019), of different types of cancers (Aavani et al., 2024), in dermatology (Kurek-Gorecka et al., 2020), as an antimicrobial treatment (Fratini et al., 2016), to enhance fertility (Abdelnour et al., 2020), as a nephroprotector (Almeer et al., 2019), neuroprotector (Ibrahim; Shahen, 2023), hepatoprotector (Mostafa et al., 2023), as a modulator of immunometabolism (Sugiyama et al., 2012), for cognitive improvement (Raoufi et al., 2023), among many others.

METHODS

This narrative review of the literature, conducted between March and May 2025, used PubMed (National Library of Medicine–National Center for Biotechnology Information) and the keyword “Royal jelly”.

The jelly, cancer, and antioxidant triad

Reports and publications on royal jelly, its composition, and effects have been available since the 1930s. However, in the early 2000s, researchers worldwide expanded their investigations, examining this supplement as an antioxidant across various experimental models. Silici et al. (2009) examined the antioxidant effect of royal jelly on cisplatin (CP)-induced spermiotoxicity using quantitative, biochemical, and histopathological approaches. They concluded that CP-induced changes in testicular histopathological findings were partially reversed by royal jelly treatment. Their results provide further insight into the mechanisms of CP-induced sperm toxicity and confirm the antioxidant potential of royal jelly.

Inoue et al. (2003) investigated the effect of dietary royal jelly on oxidative tissue DNA damage and lifespan in C3H/HeJ mice. Their results indicated that this supplementation increased the average lifespan of C3H/HeJ mice, possibly by reducing oxidative damage. Royal jelly peptides (RJPx) exhibited hydroxyl radical scavenging activity and antioxidant activity against lipid peroxidation, suggesting that RJPx can inhibit lipid peroxidation both in vitro and in vivo (Guo et al., 2008). Nagai et al. (2006) prepared enzymatic hydrolysates of royal jelly using three enzymes (pepsin, trypsin, and papain) and evaluated the antioxidant properties of the hydrolysates. The yield of these hydrolysates was very high, about 20–26% on a gross weight basis. Compared with the antioxidant activities of the aqueous and alkaline extracts of royal jelly, the antioxidant and

scavenging activities against active oxygen species, such as the superoxide anion radical and hydroxyl radical, of each hydrolysate were higher in the sample with a low protein concentration. These results suggest that, once royal jelly is hydrolyzed with an enzyme, the hydrolysate exhibits much greater antioxidant and scavenging activities against active oxygen species. Royal jelly may act as a medicinal food in the human body.

To investigate the antioxidant action of royal jelly on the yeast Saccharomyces cerevisiae as a model organism, Jamnik, Goranovic, and Raspor (2007) cultivated the yeast in YEPD medium enriched with different concentrations of royal jelly, such as 1, 2, and 5 g/L. The results showed that royal jelly reduced intracellular oxidative stress in a dose-dependent manner. Furthermore, it affected growth and cellular energy metabolism in a growth-phase-dependent manner. Protein profiling revealed that royal jelly in the cell serves not only as a scavenger of reactive oxygen species but also influences protein expression. Differentially expressed proteins were identified.

In cancer research, Nakaya et al. (2007) found that royal jelly exhibits environmental antiestrogenic activity. Bisphenol A (BPA) is an environmental estrogen that stimulates the proliferation of human breast cancer MCF-7 cells. Royal jelly inhibited the growth-promoting effect of BPA on MCF-7 cells, although it did not affect cell proliferation in the absence of BPA. Furthermore, this inhibitory effect of royal jelly was heat-stable. Fumonisins (FB) are mycotoxins produced by Fusarium verticillioides, often associated with corn. It produces toxicity, including teratogenicity, equine leukoencephalomalacia, porcine pulmonary edema, liver or kidney damage in most animal species, and disrupts sphingolipid metabolism. El-Nekeety et al. (2007) evaluated the protective effects of royal jelly against FB toxicity. It can be concluded that RJ has protective effects against FB toxicity, with protection dose-dependent.

Knowing that cadmium (Cd) is a highly toxic heavy metal that induces genotoxic damage in the body and oxidative damage in various tissues by altering the antioxidant defense enzyme system, Cavusoglu, Yapar, and Yalçin (2009) investigated the protective role of RJ on Cd-induced genotoxicity and oxidative stress in mice. In this study, treatment with two doses of RJ resulted in a significant increase in GSH levels and a significant reduction in MDA production. It can be concluded that RJ exerts a protective role against Cd-induced genotoxicity and oxidative stress in mice, attributable to its antioxidant effects. Furthermore, in vitro studies and animal experiments have shown that RJ inhibits cell proliferation and stimulates apoptosis in various types of malignant cells, and affects the production of several chemokines, antioxidants, and growth factors, as well as the expression of cancer-related molecules in patients with malignancies, especially in patients treated with anticancer agents. RJ has also been shown to help suppress adverse events, maintain quality of life during treatment, and improve prognosis in animal models and in patients with malignancies (Miyata & Sakai, 2018).

Royal jelly as an adjuvant in the treatment of chronic non-communicable diseases (NCDs)

In the early decades of research on royal jelly supplementation, authors focused on characterizing its components and testing its antibacterial, antifungal, and growth-promoting effects. However, in the early 2000s, other effects came to the forefront of investigation. Zamami et al. (2008) investigated the effects of royal jelly on insulin resistance in fructose-fed rats (an animal model of insulin resistance). In this study, the authors suggested that royal jelly may be an effective functional food for preventing insulin resistance associated with hypertension. Münstedt et al. (2009) found that serum glucose levels at 2 hours and the glucose area under the curve were significantly lower ($p = 0.041$) after royal jelly administration. Substances originating from the bee's pharyngeal glands with insulin-like activity likely caused this effect. They may therefore be at least partially responsible for reducing the impact of honey on blood glucose levels. In addition to this activity, Kim et al. (2010) found that oral administration of royal jelly promotes wound healing in diabetic mice by increasing fibroblast migration and altering the levels of several lipids involved in the wound healing process.

In addition to NCD diabetes, the angiotensin I-converting enzyme (ACE) inhibitory and hypotensive effects of 7 peptide fractions (Frs) from royal jelly protein hydrolysate (RJPH) were compared with those of RJPH alone. Fr 4 and Fr 5 were the highest in ACE inhibitory activity and yield, respectively. The molecular

weights (MWs) of RJPH and Fr 1-Fr 7 were distributed from 100 to 5000, and those of Fr 1-Fr 7 increased in order from Fr 1 to Fr 7. RJPH, Fr 3, and Fr 4 at doses of 10, 30, and 100 mg/kg i.v. And Fr 5 and Fr 6 at doses of 30 and 100 mg/ kg i.v. Caused transiently significant hypotensive effects in spontaneously hypertensive rats (SHR). Fr 3, Fr 4, Fr 5, and Fr 6, at a dose of 1,000 mg/kg, also caused significant hypotensive effects at 3, 4-5, 7-8, and 8 hours after oral administration in SHR, respectively. RJPH produced a long-lasting hypotensive impact, proportional to the MWs of the RJPH fractions. The hypotensive pattern of RJPH was similar to the combined pattern of Fr 3-Fr 6. From these results, it can be concluded that the long-lasting hypotensive effect of oral RJPH administration depends on the MWs of its ACE-inhibitory peptides and the time required to digest them (Takaki-Doi et al., 2009).

In the same sense, Tokunaga et al. (2004) demonstrated that Protease N treated with Royal Jelly (ProRJ) and ProRJ peptides (Ile-Tyr (IY), Val-Tyr (VY), Ile-Val-Tyr (IVY)) inhibited angiotensin I-converting enzyme (ACE) activity. They have an antihypertensive effect in repeated oral administration for 28 days in spontaneously hypertensive rats (SHR). Therefore, it is reasonable to consider that the consumption of peptides as a functional food may benefit blood pressure in individuals with hypertension.

Another NCD that has gained attention in recent decades is dyslipidemia. In this regard, RJ has demonstrated several pharmacological actions, including hypolipidemic, hypocholesterolemic, and antiatherosclerotic effects, in experimental animals. Kamakura et al. (2006) investigated changes in the expression of genes associated with lipid metabolism in the liver of RJ-treated mice to obtain clues about the mechanism of RJ's hypocholesterolemic action. RJ decreased gene expression of squalene epoxidase (SQLE), a key enzyme in cholesterol biosynthesis, and sterol regulatory element-binding protein (SREB)-1, which may be a transcriptional factor of SQLE. It increased gene expression of the low-density lipoprotein receptor (LDLR), which mediates hepatic cholesterol uptake. Thus, the hypocholesterolemic action of RJ appears to be associated with decreased SQLE and increased LDLR in mice.

Royal jelly in the field of dermatology

RJ contains a unique combination of proteins (12-15%), sugars (10-12%), lipids (3-7%), amino acids, vitamins, and minerals. In dermatology, skin inflammation and skin barrier dysfunction are the leading causes of atopic dermatitis (AD). Oral administration of RJ inhibited the development of AD in mice, being associated with a

significant reduction in cytokine production and total skin severity scores. To assess the effect of RJ on human skin barrier function in the absence of inflammation, stratum corneum (SC) conductance and transepidermal water loss (TEWL) were used as noninvasive measures. The electrical properties of SC can be used to determine its hydration status. An increase in TEWL suggests deterioration of SC barrier function, as is typically observed in dry skin. SC conductance was significantly higher in the RJ group than in the control group. The findings suggest that oral intake of RJ may increase SC hydration without affecting TEWL. In conclusion, RJ may help maintain SC hydration (Nakashima et al, 2018).

Because the literature already indicated that Th1 and Th2 cytokines play pathogenic roles in the development of atopic dermatitis (AD), Taniguchi et al. (2003) examined whether RJ suppresses the development of AD-like skin lesions in mice. Oral administration of RJ to mice inhibited the development of AD-like skin lesions, hyperkeratosis, and inflammatory cell infiltration of the epidermis and corium. Because NO derived from inducible nitric oxide (NO) synthase (iNOS) has been suggested as an essential immunoregulatory mediator in inflammatory autoimmune diseases, they also examined iNOS expression in dorsal skin lesions. Interestingly, iNOS expression was significantly increased in the skin lesions of mice treated with RJ compared with controls. These results suggest that RJ suppresses the development of AD-like skin lesions in mice, possibly by downregulating TNP-specific IFN-gamma production and upregulating iNOS expression.

Royal jelly as a natural antimicrobial

Honey and other bee products have been the subject of laboratory and clinical investigations over the past few decades, and the most notable discovery has been their antibacterial activity. Honey has been used since ancient times to treat certain diseases and to heal wounds, but modern dressings and antibiotic therapy have supplanted its use as an anti-infective agent. However, the emergence of antibiotic-resistant bacteria has complicated antibiotic use, prompting a reexamination of prior treatments. Honey, propolis, royal jelly, and bee venom have potent antibacterial activity. Even antibiotic-resistant strains, such as epidemic strains of methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE), are as sensitive to honey as antibiotic-sensitive strains of the same species (Boukraa & Sulaiman, 2009).

RJ is one of the most valued natural products, known for its health-promoting properties. Due to its therapeutic effects, it has been used in medicine since ancient times. Several studies indicate that RJ is a potent antimicrobial agent. RJ's biological properties are associated with its bioactive compounds, including proteins, peptides, phenolic acids, and fatty acids (Bagameri et al., 2022).

In recent years, silver nanoparticles (Ag NPs) have gained widespread applications across industry, technology, and medicine. Gevorgyan et al. (2022) reported the green synthesis of silver nanoparticles (Ag NPs) using a low-molecular-weight fraction (LMF) of royal jelly, their characterization, and, in particular, their antibacterial activity. The antibacterial activities were evaluated against Gram-negative and Gram-positive bacteria using colony-counting assays. The growth inhibition curve method was used to determine the minimum inhibitory

concentrations (MICs) and minimum bactericidal concentrations (MBCs). The results obtained showed that (i) the sizes of Ag NPs increase with increasing silver ion precursor concentration, (ii) DLS, in agreement with NTA, showed that most particles have dimensions in the range of 50–100 nm, and (iii) the presence of a spherical ion-binding agent (SLA) in the spherical ion-binding agent (SLA) is a spherical ion-binding agent. (iii) E. coli was more susceptible to all Ag NP samples compared to B. subtilis.

Despite its well-known broad-spectrum antibacterial activity, the precise molecular mechanism underlying this activity remains unclear. Xia et al. (2024) investigated the impact of RJ on the bacterial model MG1655 at its half-maximal inhibitory concentration, using LC-MS/MS to analyze proteomic changes. Notably, RJ treatment markedly inhibited superoxide dismutase and catalase activities, leading to increased oxidative damage and lipid peroxidation. Furthermore, through a protein-protein interaction network analysis using the STRING database, we identified CRP and IHF as crucial host regulators responsive to RJ. These findings significantly advance understanding of RJ's antibacterial mechanism, highlighting its potential as a natural alternative to conventional antibiotics. The identification of CRP and IHF as central players underscores the intricate regulatory networks underlying RJ action, thereby offering new targets for developing innovative antimicrobial strategies.

Royal jelly as a nephroprotector

Administration of cisplatin (CP) to rats induced marked renal failure, characterized by significant increases in serum blood urea nitrogen and uric acid concentrations, and they exhibited higher renal malondialdehyde (MDA) activity and lower glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), and catalase (CAT) activities. CP-induced changes in kidney histopathological findings were partially reversed by royal jelly treatment. The results provide further insight into the mechanisms of CP-induced nephrotoxicity and confirm the antioxidant potential of royal jelly (Silici et al., 2011).

Cisplatin-induced subchronic toxicity (1 mg/kg bw, i.p.) was evaluated twice weekly for 10 weeks. Cisplatin-treated animals showed a significant increase in serum levels of kidney injury products (urea, creatinine, and uric acid). Histopathologically, cisplatin produced pronounced tubulointerstitial lesions, increased expression of fibrogenic factors, α-smooth muscle actin (α-SMA), and transforming growth factor-β1 (TGF-β1), and decreased the cell proliferation marker bromodeoxyuridine (BrdU). RJ normalized serum kidney injury biomarkers, improved histopathological changes, reduced α-SMA and TGF-β1 expression, and increased Brdu expression. Therefore, it can be concluded that royal jelly can be used as a preventive natural product against cisplatin-induced subchronic kidney injury (Ibrahim et al., 2016).

In addition to cisplatin, gentamicin (GM), one of the most effective antibiotics for Gram-negative infections, has been restricted due to its nephrotoxic potential. RJ may individually prevent such toxic effects (Alaraj, 2020). Knowledge of RJ's nephroprotective effects remains incipient.

Royal jelly as a hepatoprotector

Liver diseases are severe, life-threatening conditions that must be controlled. In this regard, Abu-Serie & Habashy (2019) identified an RJ protein fraction that represents the most effective compound against CCl4-induced hepatotoxicity and HepG2 cell growth. Two closely related proteins were purified from this fraction by a novel, simple method and identified by MALDI-TOF MS as major RJ protein 2 (MRJP2) and its predicted X1 isoform. These two purified proteins were able to alleviate necrotic hepatocytes (by 60.4%) by reducing tumor necrosis factor (TNF)-α, mixed lineage kinase domain-like protein (MLKL), and intracellular reactive species.

Furthermore, they demonstrated a potent anticancer effect by inducing caspase-dependent apoptosis and regulating Bcl-2 and p53 expression in HepG2 cells. Thus, MRJP2 and its X1 isoform may be a promising dual strategy to combat liver injury and cancer in future animal and human studies.

Kanbur et al. (2009) investigated the protective effect of royal jelly against paracetamol-induced liver damage. The study was conducted on 90 female Swiss Albino mice, and six groups were established. While Group 1 served as the control, Groups 2–6 received different doses of RJ per kg of body weight. In conclusion, administration of royal jelly as a hepatoprotective agent for 7 days against paracetamol-induced liver damage was found to exhibit a marked protective effect on liver tissue.

Aiming to elucidate the underlying molecular mechanism, as well as the potential hepatoprotective effects of RJ against hepatic ischemia/reperfusion (IR) injury, Ali et al. (2021) divided rats into four groups: sham (received vehicle), IR (30 minutes of ischemia and 45 minutes of reperfusion), sham pretreated with RJ (200 mg/kg PO) and IR pretreated with RJ (200 mg/kg PO). Hepatic IR significantly induced liver dysfunction, as evidenced by elevated serum transaminase, ALP, and LDH levels. Furthermore, hepatic IR caused significant upregulation of p38 MAPK, NF-κB p65, TNF-α, and MDA levels, along with marked downregulation of Nrf2, HO-1, COX-4, cytoglobin, IκBα, IL-10, GSH, GST, and SOD levels. Furthermore, marked histopathological changes were observed after hepatic IR injury. In contrast, pretreatment with RJ significantly improved liver function and alleviated histopathological changes. Moreover, RJ restored the oxidant/antioxidant balance and hepatic expression of Nrf-2, HO-1, COX-4, and cytoglobin. Simultaneously, RJ significantly attenuated the inflammatory response by downregulating the expression of p38 MAPK, NF-κB p65, and TNF-α. The current results revealed that RJ successfully protected the liver against hepatic IR injury through modulating the cytoglobin, Nrf-2/HO-1/COX-4, and P38-MAPK/NF-κB-p65/TNF-α signaling pathways.

Royal jelly as a neuroprotector

Nazarinia et al. (2013) evaluated the neuroprotective effects of different doses of RJ (100 and 200 mg/kg) against pentylenetetrazol (PTZ)-induced seizures. Elevated plus maze, Y-maze, and shuttle box tests were performed to assess anxiety-like behavior, short-term memory, and passive avoidance memory, respectively. The findings showed that PTZ-treated rats had increased seizure intensity, anxiety-like behavior, memory dysfunction, and higher levels of TNF-α, IL-1β, and oxidative markers. RJ could alleviate seizure severity and duration. It also improved memory function and anxiety level. In biochemical evaluation, RJ resulted in a significant decrease in IL-1β, TNF-α, and MDA levels and restored GPX and SOD activities.

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive decline in cognitive function. Intracerebroventricular injection of streptozotocin (icv-STZ) has been used as an experimental model of sporadic AD (SAD) in rodents. It represents a promising tool for etiopathogenic analysis and evaluation of new therapeutic approaches for AD. Research indicates that RJ exhibits several pharmacological activities, including neuroprotection and cognitive function improvement. This study aimed to investigate the effects of a 2-week oral royal jelly treatment in Wistar rats subjected to icv-STZ on working memory and neuroprotection, as assessed by neurogenesis, neurodegeneration, and oxidative stress. Silva et al. (2020) applied icv-STZ injections in a murine model, which induced deleterious effects in the hippocampus, associated with cognitive impairment. They developed marked neurodegeneration, in addition to reduced neurogenesis and increased oxidative stress. Prolonged oral administration of RJ induced beneficial effects in animals injured by icv injection of -STZ, increasing the retention time of spatial working memory, reducing neurodegeneration and oxidative stress, and increasing the proliferation of new neurons in the hippocampus.

Royal jelly, immunometabolism, and its anti-inflammatory potential

In the 1990s, a study investigating whether royal jelly has a hypoglycemic effect showed no insulin-like activity when administered orally at doses of 10, 100, and 1000 mg/kg/day. However, it exhibited some anti-inflammatory activity, as evidenced by reduced exudation and collagen deposition during granulation tissue formation using the cotton-wool pellet method. It also shortened the healing time of scaly skin lesions, indicating that royal jelly has anti-inflammatory action and can enhance wound healing (Fujii et al., 1990). In the same decade, a meta-analysis found that royal jelly significantly reduced serum and hepatic total cholesterol and lipid levels in rats and rabbits, and delayed atheroma formation in the aorta of rabbits fed a hyperlipemic diet. It also showed a significant reduction in total cholesterol and serum lipid levels and normalization of HDL and LDL. In this regard, the best available evidence suggests that royal jelly at approximately 50-100 mg per day decreased total serum cholesterol by about 14% and total serum lipids by about 10% in the patients studied (Vittek, 1995).

Furthermore, in murine models of experimental hyperlipidemia, animals were fed 700 mg/kg of body weight of freeze-dried royal jelly daily for six weeks. The results showed that freeze-dried royal jelly, in addition to reducing serum cholesterol and increasing HDL, increased red blood cell deformability and decreased plasma fibrinogen levels. Thrombus formation was lower in test animals than in controls, suggesting that freeze-dried royal jelly can be used to prevent and treat hyperlipidemia and to improve the hypercoagulable state of the blood (Shen et al., 1995). Guo et al. (2007) corroborated these previous findings by examining the effects of royal jelly supplementation on serum lipoprotein metabolism in humans. Their results suggest that dietary royal jelly lowers total and LDL cholesterol by decreasing VLDL levels.

To study a possible immunomodulatory effect of royal jelly, Sver et al. (1996) used a rodent model in which CBA mice received 0.1 ml of RJ sc 7 days before or immediately after immunization with sheep red blood cells (SRBC). Serum levels of total proteins and immunoglobulins in mice that received royal jelly once or twice in 2 weeks were significantly lower ($P < or = 0.05$) compared with untreated animals. In mice that were immunized with $4 \times 10(8)$ of SRBC 7 days after royal jelly application, the number of plaque-forming splenocytes was significantly higher ($P < or = 0.05$) than in controls. Both the weight of the inguinal lymph node and the number of peripheral blood lymphocytes increased ($P < 0.05$) in mice treated with RJ 3 or 5 days after immunization, respectively. Neutrophils decreased ($P < or = 0.05$) in mice that were sacrificed 5 or 10 days after RJ treatment. The results indicated that royal jelly exhibited immunomodulatory properties, either by stimulating antibody production and the proliferation of immunocompetent cells in mice or by depressing humoral immune functions in rats.

Also, to investigate its immunomodulatory potential in humans, Manoor et al. (2009) conducted a study to determine whether oral administration of royal jelly could alter the development of systemic autoimmunity in F1 New Zealand Black (NZB) x New Zealand

White (NZW) mice, which genetically exhibit many manifestations similar to human systemic lupus erythematosus (SLE). Mice treated with royal jelly showed a significant delay in disease onset, as evidenced by decreased proteinuria and a prolonged lifespan. Furthermore, administration of RJ after disease onset significantly improved renal symptoms, thereby extending lifespan. Administration of RJ to mice caused a significant decrease in serum IL-10 levels and autoantibodies against ssDNA, dsDNA, and erythrocytes, as well as a reduction in the number of splenic autoreactive B cells. Erem et al. (2006) also observed that royal jelly has an immunomodulatory effect on another autoimmune disease, Graves' disease, by modulating the quantity of immune cells and the cytokines they produce.

Kohno et al. (2004) suggested that royal jelly has anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines, including TNF-alpha, IL-6, and IL-1, by activated macrophages. Okamoto et al. (2003) screened for anti-allergic factors in royal jelly based on the inhibition of IL-4 production by anti-CD3-stimulated spleen cells derived from OVA/alum-immunized mice. Using a series of column chromatographic steps, we purified a 70-kDa glycoprotein, major royal jelly protein 3 (MRJP3), which suppresses IL-4 production. The results indicate that MRJP3 may exhibit potent immunoregulatory effects in vitro and in vivo. Furthermore, given the intriguing immunomodulatory effects of MRJP3, it may be clinically significant to design anti-allergic peptides derived from MRJP3 by identifying the regions of the polypeptide that are associated with these effects.

Vucevic et al. (2007) studied the effect of 10-hydroxy-2-decanoic acid (10-HDA) and 3,10-dihydroxy-decanoic acid (3,10-DDA), isolated from RJ, on the immune response using a rat dendritic cell (DC)-T cell coculture model. Both fatty acids inhibited allogeneic T cell proliferation at higher concentrations. The effect of 10-HDA was more potent, accompanied by decreased interleukin-2 (IL-2) production and downregulation of IL-2 receptor expression. Spleen DC, cultured with 10 microg /ml of fatty acids, downregulated CD86 expression and IL-12 production, but upregulated IL-10 production. In contrast, DC pretreated with 100 µg/ml 3,10-DDA increased CD86 expression and allogeneic T-cell proliferation. The highest dose (200 microg/ml) of both fatty acids, which was non-apoptotic for T cells and DC, decreased MHC class II and CD86 expression, decreased IL-12 production, and rendered these DC less allostimulatory. These results demonstrated the immunomodulatory activity of RJ fatty acids and suggest that DC are a significant target of their action. It was also found that the main RJ proteins, apalbumin-1 and apalbumin-2, stimulate mouse macrophages to release TNF-alpha, demonstrating that physiologically active honey proteins can be used for biological evaluation (Simuth et al., 2004).

Royal jelly and cognitive activity

Despite hundreds of studies on royal jelly since the 1930s, it was only in the 21st century that researchers began investigating its potential effects on cognitive function. Hattori et al. (2011), recognizing that trimethyltin (TMT) is a toxic organotin compound that selectively induces acute neuronal death in the dentate gyrus (DG) of the hippocampus, followed by cognitive impairment, tested whether royal jelly stimulates the regeneration of the DG injured by TMT. They found that orally administered TMT significantly increased the number of DG granule cells and simultaneously improved cognitive impairment.

Neural stem/progenitor cells (NSCs) proliferate vigorously as neurospheres in medium containing basic fibroblast growth factor (FGF-2) but begin to differentiate into neurons, astrocytes, or oligodendrocytes in FGF-2-free medium. A royal jelly extract significantly increased the percentage in the total cell population not only of neurons immunoreactive for class III beta-tubulin (Tuj1), but also of astrocytes immunoreactive for glial fibrillary acidic protein (GFAP) and oligodendrocytes immunoreactive for 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase) generated from NSCs, but decreased that of NSCs nestin-positive cells. These observations suggest that royal jelly contains multiple components that differentially influence neuronal and/or glial lineages, thereby facilitating NSC-mediated neurogenesis (Hattori et al., 2007).

Royal jelly for longevity and quality of life

Gardner (1948) had already identified royal jelly and its chemical components as longevity factors, using Drosophila melanogaster as a test organism. In this study, pantothenic acid was recognized as the main anti-aging factor in royal jelly. Inoue et al. (2003) investigated the effect of dietary royal jelly (RJ) on oxidative tissue DNA damage and lifespan in C3H/HeJ mice. Their results indicated that dietary royal jelly increased the average lifespan of C3H/HeJ mice, possibly by reducing oxidative damage.

Regarding longevity, we cannot overlook a serious problem associated with aging: osteopenia and osteoporosis. Narita et al. (2006) demonstrated that RJ stimulated the proliferation of mouse osteoblast-like MC3T3-E1 cells at 0.1 mg/ml, and this effect was blocked by the specific estrogen receptor antagonist ICI 182,780. The addition of 0.1–1.0 mg/ml of RJ increased collagen production in culture medium. Oral administration of RJ to normal female mice for 9 weeks increased the ash content of their tibiae. DNA microarray analysis revealed significant changes in gene expression associated with extracellular matrix formation in the femurs of mice fed RJ. Quantitative reverse-transcriptase PCR (RT-PCR) confirmed upregulation of procollagen I alpha1 gene expression. These data suggest that RJ, as a whole or in its individual components, stimulates type I collagen production and other bone-forming activities by acting on osteoblasts.

Hikada et al. (2006), based on evidence that RJ contains testosterone and exhibits steroid hormone-like activities, tested the hypothesis that it may have beneficial effects on osteoporosis using an ovariectomized rat model and a tissue culture model. In tissue culture models, RJ increased calcium content in cultures of femoral-diaphyseal and femoral-metaphyseal tissues obtained from normal male rats. The results suggest that RJ may prevent osteoporosis by increasing intestinal calcium absorption, rather than by directly antagonizing PTH.

Royal jelly, hormonal modulation, and fertility

Heyl (1939) had already demonstrated that subcutaneous injection of royal jelly extract into immature female rats produced precocious ovarian development, indicating that 5 days of administration were sufficient for the early development of Graafian follicles. He suggested the presence of gonadotropic hormones in royal jelly. Some researchers have been unable to reproduce these findings, primarily because they used royal jelly dried with acetone. Using such a solvent to remove water would also remove sterols, phenols, acids, esters, glycerides, and other compounds, some of which are among the most likely to possess gonadotropic activity (Townsend & Lucas, 1940). Royal jelly contains a unique combination of proteins (12–15%), sugars (10–12%), lipids (3–7%), amino acids, vitamins,

and minerals. Compared with short-lived, infertile worker bees, the queen bee, which is fed exclusively on RJ, has a prolonged lifespan and well-developed gonads (Nakashima et al., 2018).

RJ excreted by honeybees has estrogen-like effects; the possible effects of three RJ fatty acids (FAs) (10-hydroxy-2-decenoic-10H2DA, 3,10-dihydroxydecanoic-3,10DDA, sebacic acid -SA) on estrogen signaling were investigated in several cell systems. In the absence of estradiol (E(2)), RJ modulated estrogen receptor (ER) recruitment to the pS2 promoter and pS2 mRNA levels via only ERβ, whereas in the presence of E(2), it modulated both ERβ and ERα. Furthermore, E(2)-induced recruitment of the coactivator peptide EAB1 to ERα is masked, and E(2)-induced estrogen response element (ERE)-mediated transactivation is inhibited. In HeLa cells, in the absence of E(2), ERβ inhibited ERE-mediated transactivation, but ERα did not. In contrast, in the presence of E(2), they also inhibited ERE activity by ERβ and ERα. Thus, the data suggest a molecular mechanism for the estrogenic activities of RJ components, which, although structurally distinct from E(2), mediate estrogen signaling by modulating the recruitment of ERα, ERβ, and coactivators to target genes (Moutsatsou et al., 2010).

Elnagar (2010), aiming to address the problem of heat-induced infertility in rabbits during the summer, tested the influence of royal jelly on this phenomenon and concluded that administering royal jelly to heat-stressed male rabbits can counteract their "summer infertility" and improve their physiological status. In female rabbits, Mishima et al. (2005) tested the effects of royal jelly on menopausal symptoms. They found evidence of estrogenic activity through interaction with estrogen receptors, resulting in altered endogenous gene expression.

Husein & Kridli (2002) sought to determine whether RJ jelly paste, administered orally or intramuscularly (i.m.), in combination with exogenous progesterone, is associated with improved reproductive responses in ewes. RJ treatment resulted in a higher incidence of estrus and shorter intervals to estrus onset. Progesterone increased on day 3 in RJ-treated ewes. Progesterone remained elevated until day 18 in 8 of 20 RJ-treated ewes. All pregnant ewes presented estrus 14 h earlier, ovulated approximately 1 day earlier, and had higher luteal phase progesterone levels than non-pregnant ewes. Non-pregnant ewes had higher body weights than pregnant ewes. In conclusion, the results demonstrate that both RJ treatments, in conjunction with exogenous progesterone, were equally effective in improving estrus response and pregnancy rate.

Royal jelly as a nutritional resource for exercisers

Despite the large number of studies on RJ since the 1930s, research combining RJ supplementation with physical exercise emerged only at the beginning of the 21st century. Nakamura et al. (2001) investigated the anti-fatigue effect of RJ in male Std mice. ddY. Mice were acclimated to swimming in an adjustable-current pool, then subjected to forced swimming 5 times over 2 weeks; the total swimming time to exhaustion was measured. All mice were forced to swim for 15 minutes once, after which the maximum swimming time to fatigue was measured following a rest period. The swimming endurance of the RJ group increased significantly compared to the other groups. Mice in the RJ group showed a considerable reduction in the accumulation of serum lactate and serum ammonia and decreased muscle glycogen depletion after swimming compared to the other groups. These findings suggest that RJ may reduce post-exercise fatigue.

Recently, there has been growing interest in exploring the effects of royal jelly on athletic performance. A systematic review examined the existing literature on the effects of royal jelly on athletic performance. This review highlighted the beneficial effects of royal jelly in reducing blood lactate levels and improving athletic performance. However, the influence of royal jelly on athletes' body composition measures remains inconclusive, highlighting the need for further research (Pasdar et al., 2024).

It is well known that excessive free radical production during many types of exercise leads to oxidative stress, which in turn causes muscle damage, fatigue, and impaired performance. RJ supplementation has been shown to mitigate exercise-induced oxidative stress and improve several aspects of exercise performance. Improvements in High-Intensity Interval Exercise (HIIE) performance in swimmers were due to RJ-induced reductions in lipid peroxidation and muscle damage in response to exercise. These findings suggest that 10-day RJ supplementation, particularly when combined with coenzyme Q10, may improve HIIE performance and alleviate oxidative stress. This RJ supplementation with coenzyme Q10 also showed marked effects on HIIE in runners after 10 days (Ovchinnikov et al., 2022).

Natural nutrition and exercise training have been defined as non-pharmacological complementary and alternative medicine for the prevention and treatment of various pathologies. Royal jelly possesses several pharmacological properties and is an effective therapeutic supplement for halting neurodegeneration. Multiple sclerosis is a prevalent neurodegenerative disorder that manifests as a progressive neurological condition. Inflammation, hypoxia, and oxidative stress have been identified as significant hallmarks of multiple sclerosis pathology. The interaction between exercise training and 100 mg/kg royal jelly has been shown to have a greater effect on the regulation of microRNA profiles and core genes in mice with multiple sclerosis (Lohrasbi et al., 2022).

Based on the knowledge that cannabinoid-1 receptors (CB1R) are therapeutic targets for both the treatment of autoimmune diseases, such as multiple sclerosis (MS), and for some related symptoms, such as pain, Kheirdeh et al. (2022) sought to evaluate the effect of aerobic training and two dosages of royal jelly (RJ) on hippocampal CB1R and pain threshold (PT) in an experimental model of autoimmune encephalomyelitis (EAE). The overall results suggested that the combination of ET and increasing doses of RJ improved the pain threshold, likely via CB1R, in an EAE model. At the same time, this was not observed for ET or RJ alone.

The global pandemic of sarcopenia—skeletal muscle loss and weakness—which affects up to 50% of older adults—is increasing worldwide due to the expanding aging population. It is now also affecting young and middle-aged adults due to sedentary lifestyles and increased consumption of unhealthy foods. Following the Coronavirus Disease 2019 (COVID-19) pandemic, the prevalence of sarcopenia increased. In this regard, Ali & Kunigi (2020) highlighted the nutraceutical effect of RJ as a safe treatment for preventing and/or treating sarcopenia. Thanks to its versatile pharmacological activities (e.g., anti-aging, anti-inflammatory, anticarcinogenic, antimicrobial), it has also been used in ongoing studies to treat sarcopenia in laboratory animals and humans.

Takahashi et al. (2018) investigated the effect of RJ on mitochondrial adaptations induced by resistance training in skeletal muscles of ICR mice. The mice received RJ (1.0 mg/g body weight) or distilled water for three weeks. Mice in the training group underwent resistance training (20 m/min; 60 min; 5 times/week). There was a main effect of resistance training on the maximal activities of the mitochondrial enzymes, citrate synthase (CS) and β-hydroxyacyl coenzyme A

dehydrogenase (β-HAD), in the plantaris and tibialis anterior (TA) muscles. In contrast, no effect of RJ treatment was observed. In the soleus muscle, the maximal CS and β-HAD activities were significantly increased by resistance training in the RJ-treated group. At the same time, training did not affect the control group. Furthermore, we investigated the effects of acute RJ treatment on the signaling cascade involved in mitochondrial biogenesis. In the soleus, phosphorylation of 5'-AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) was additively increased by a single RJ treatment and resistance exercise. In contrast, only an exercise effect was found in the plantaris and TA muscles. These results indicate that RJ treatment induced mitochondrial adaptation to resistance training by activating AMPK in the soleus muscles of ICR mice.

Discovering the biological effects of various micronutrients and macronutrients has been a focus of modern science (Alqahtani, 2025; He, Dong, and Xiang, 2025; Luo et al., 2025; Monda et al., 2025; Sasiarini et al., 2025). Despite growing worldwide interest in the effects of royal jelly on performance and in the combination of this supplementation with regular exercise for public health, many gaps remain to be filled in the coming years.

PHASE II: ARTICLE TEXT MINING

The analysis was performed in a sandboxed environment using the following tools and Python libraries: (Python [python-docx 1.2.0; nltk 3.9.2; scikitlearn 1.7.2; wordcloud 1.9.4; matplotlib 3.7.1; textstat 0.7.10]).

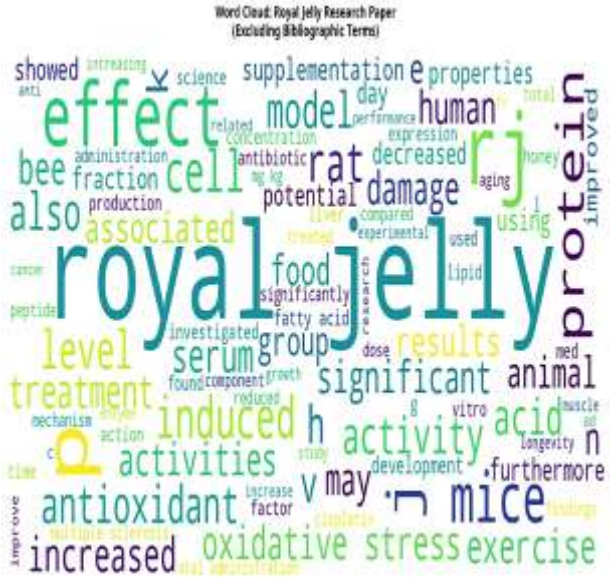

Figure 2. A word cloud highlighting the most frequent terms in the paper. "Royal jelly" is clearly the most dominant theme, followed by terms related to effects, treatment, and biological activity.

Thematic Insights

Based on the frequency analysis, several key themes emerge from the paper:

1. Composition and Biochemistry: The high frequency of "acid," "protein," and "acids" indicates a strong focus on the chemical composition of royal jelly, particularly its bioactive compounds.
2. Biological Effects: Terms like "effects," "effect," "activity," "oxidative," and "antioxidant" suggest extensive discussion of the biological and pharmacological activities of royal jelly.
3. Animal Research: The prominence of "mice" and "rats" confirms that much of the reviewed literature is based on animal model studies.
4. Health Applications: Words such as "exercise," "performance," "treatment," and "health" highlight the paper's emphasis on therapeutic and performance-enhancing applications.
5. Experimental Context: The frequent use of "increased," "levels," and "treatment" points to experimental studies measuring physiological changes and treatment outcomes.

Text mining highlights

Based on the text mining analysis, here are the four main highlights of the paper:

1. Central Focus on Royal Jelly: The terms "royal" and "jelly" are by far the most frequent (198 occurrences each), confirming the paper's unwavering focus on this single bioactive substance as the primary subject of investigation.
2. Emphasis on Biological Effects and Treatment: With "effects" (52), "effect" (41), "treatment" (26), and "activity" (31) among the top terms, the paper clearly prioritizes understanding the therapeutic and biological impacts of royal jelly across various health domains.
3. Animal Model Research Dominance: The high frequency of "mice" (50) and "rats" (28) indicates that the reviewed literature heavily relies on animal studies, suggesting that much of the evidence base for royal jelly's effects comes from preclinical research.
4. Focus on Exercise, Performance, and Antioxidant Properties: Key application areas include "exercise" (26), "performance" (14), "oxidative" (26), and "antioxidant" (22), highlighting the paper's particular interest in royal jelly's role in physical performance enhancement and oxidative stress management

FINAL CONSIDERATIONS

The use of RJ has been associated with longevity and improved health quality during aging, post-menopausal hormonal modulation, as an adjuvant in the treatment of Chronic Non-Communicable Diseases, different types of cancer, in dermatology, as an antimicrobial treatment, to enhance fertility, as a nephroprotector, neuroprotector, hepatoprotector, immunometabolism modulator, and cognitive improvement. Only at the beginning of the 21st century did research with RJ and exercise emerge, identifying anti-fatigue effects, decreased serum lactate and ammonia, reduced muscle glycogen depletion, improved athletic performance, attenuating oxidative stress induced by High Intensity Interval Exercise (HIIE), to interrupt neurodegeneration in multiple sclerosis, in the positive modulation of cannabinoid-1 receptors as therapeutic targets for the treatment of autoimmune diseases such as multiple sclerosis, for reducing sarcopenia, skeletal muscle loss and weakness, and inducing mitochondrial adaptation with resistance training by activating AMPK in muscles.

REFERENCES

Aavani F, et al. Royal jelly and its hormonal effects in breast cancer: a literature review. Daru. 2024;32:745-760. https://doi.org/10.1007/s40199-024-00513-2.

Abdelnour SA, et al. Useful impacts of royal jelly on reproductive organs, fertility rate, and sperm traits of animals. J Anim Physiol Anim Nutr (Berl). 2020;104:1798-1808. https://doi.org/10.1111/jpn.13303.

Abu-Serie MM, Habashy NH. Two purified proteins from royal jelly with in vitro dual anti-hepatic damage potency: Major royal jelly protein two and its novel isoform X1. Int J Biol Macromol. 2019;128:782-795. https://doi.org/10.1016/j.ijbiomac.2019.01.210.

Alaraj M. Royal Jelly and Aliskiren mutually annul their protective effects against gentamicin-induced nephrotoxicity in rats. Vet World. 2020;13:2658-2662. https://doi.org/10.14202/vetworld.2020.2658-2662.

Alqahtani SAM. Effect of Vitamin D on Thyroid Function Among Diabetic Patients. Current Topics In Nutraceutical Research. 2025;23:1-7. https://doi.org/10.37290/ctnr2641-452X.23:1-7.

Ali AM, Kunugi H. Apitherapy for Age-Related Skeletal Muscle Dysfunction (Sarcopenia): A Review on the Effects of Royal Jelly, Propolis, and Bee Pollen. Foods. 2020;9:1362. https://doi.org/10.3390/foods9101362.

Ali FEM, et al. The Impact of Royal Jelly against Hepatic Ischemia/Reperfusion-Induced Hepatocyte Damage in Rats: The Role of Cytoglobin, Nrf-2/HO-1/COX-4, and P38-MAPK/NF-κB-p65/TNF-α Signaling Pathways. Curr Mol Pharmacol. 2021;14:88-100. https://doi.org/10.2174/1874467213666200514223829.

Almeer RS, et al. The potential hepatoprotective effect of royal jelly against cadmium chloride-induced hepatotoxicity in mice is mediated by suppression of oxidative stress and upregulation of Nrf2 expression. Biomed Pharmacother. 2018;106:1490-1498. https://doi.org/10.1016/j.biopha.2018.07.089

Almeer RS, et al. Royal jelly attenuates cadmium-induced nephrotoxicity in male mice. Sci Rep. 2019:9:5825. https://doi.org/10.1038/s41598-019-42368-7.

Aslan Z, Aksoy L. Anti-inflammatory effects of royal jelly on ethylene glycol-induced renal inflammation in rats. Int. Braz jurol. 2015;41:1008-1013. https://doi.org/10.1590/s1677-5538.ibju.2014.0470

Bagameri, et al. Royal Jelly as a Nutraceutical Natural Product with a Focus on Its Antibacterial Activity. Pharmaceutics. 2022;14:1142. https://doi.org/10.3390/pharmaceutics14061142.

Bălan A, et al. Royal Jelly: A Traditional and Natural Remedy for Postmenopausal Symptoms and Aging-Related Pathologies. Molecules. 2020;25:3291. https://doi.org/10.3390/molecules25143291.

Blum MS, et al. 10-Hydroxy-delta 2-decenoic acid, an antibiotic found in royal jelly. Science. 1959:130:452-39. https://doi.org/10.1126/science.130.3373.452.

Boukaa L, Sulaiman SA Rediscovering the antibiotics of the hive. Recent Pat Antiinfect Drug Discov. 2009;4:206-13. https://doi.org/10.2174/157489109789318505.

Cavusoglu K, et al. Royal jelly (honey bee) is a potential antioxidant against cadmium-induced genotoxicity and oxidative stress in albino mice. J Med Food. 2009;12:1286-92. https://doi.org/10.1089/jmf.2008.0203.

Chen YF, et al. In Vitro Anti-inflammatory Effects of Three Fatty Acids from Royal Jelly. Mediators lnflamm. 2016. https://doi.org/10.1155/2016/3583684

Colhoun EH, Smith MV. Neurohormonal properties of royal jelly. Nature. 1960:188:854-5. https://doi.org/10.1038/188854a0.

Elnagar SA. Royal jelly counteracts bucks' "summer infertility". Anim Reprod Sci. 2010;121:174-80. https://doi.org/10.1016/j.anireprosci.2010.05.008.

El-Nekeety AA, et al. Efficacy of royal jelly against the oxidative stress of fumonisin in rats. Toxicon. 2007;50:256-69. https://doi.org/10.1016/j.toxicon.2007.03.017.

Erem C, et al. The effects of royal jelly on autoimmunity in Graves' disease. Endocrine. 2006;30:175-83. https://doi.org/10.1385/ENDO:30:2:175.

Fratini F, et al. Royal Jelly: An ancient remedy with remarkable antibacterial properties. Microbiol Res. 2016;192:130-141. https://doi.org/10.1016/j.micres.2016.06.007.

Fujii A, et al. Augmentation of wound healing by royal jelly (RJ) in streptozotocin-diabetic rats. Jpn J Pharmacol. 1990;53:331-7. https://doi.org/10.1254/jjp.53.331

Fujiwara S, et al. potent antibacterial protein in royal jelly. Purification and determination of the primary structure of royalisin. J Biol Chem. 1990:265:11333-7.

Gardner TS. The use of Drosophila melanogaster as a screening agent for longevity factors; pantothenic acid as a longevity factor in royal jelly. J Gerontol. 1948;3:1-8. https://doi.org/10.1093/geronj/3.1.1.

Gevorgyan S, et al. Structural characterization and antibacterial activity of silver nanoparticles synthesized using a low-molecular-weight Royal Jelly extract. Sci Rep. 2022;12:14077. https://doi.org/10.1038/s41598-022-17929-y.

Guo H, et al. Royal jelly supplementation improves lipoprotein metabolism in humans. J Nutr Sci Vitaminol (Tokyo). 2007;53:345-8. https://doi.org/10.3177/jnsv.53.345.

Guo H, et al. Royal jelly peptides inhibit lipid peroxidation in vitro and in vivo. J Nutr Sci Vitaminol (Tokyo). 2008;54:191-5. https://doi.org/10.3177/jnsv.54.191.

Hattori N, et al. Royal jelly and its unique fatty acid, 10-hydroxy-trans-2-decenoic acid, promote neurogenesis by neural stem/progenitor cells in vitro. Biomed Res. 2007;28:261-6. https://doi.org/10.2220/biomedres.28.261.

Hattori N, et al. Royal jelly facilitates the restoration of cognitive ability in trimethyltin-intoxicated mice. Evid Based Complement Alternat Med. 2011;2011:165968. https://doi.org/10.1093/ecam/nep029.

He M, Dong C, and Xiang S. Magnolol plays a protective role in the kidney of rats with diabetic nephropathy. Current Topics In Nutraceutical Research. 2025;23:8-13. https://doi.org/10.37290/ctnr2641-452X.22:8-13.

Heyl HL. An observation suggesting the presence of a gonadotropic hormone in royal jelly. Science. 1939;89:540-1. https://doi.org/10.1126/science.89.2319.540.

Kheirdeh M, et al. The Effect of Exercise Training and Royal Jelly on Hippocampal Cannabinoid-1-Receptors and Pain Threshold in Experimental Autoimmune Encephalomyelitis in Rats as Animal Model of Multiple Sclerosis. Nutrients. 2022;14:4119. https://doi.org/10.3390/nu14194119.

Hidaka S, et al. Royal jelly prevents osteoporosis in rats: beneficial effects in ovariectomy model and in bone tissue culture model. Evid Based Complement Alternat Med. 2006;3:339-48. https://doi.org/10.1093/ecam/nel019.

Hojo M, et al. Reduced expression of major royal jelly protein 1gene in the mushroom bodies of worker honeybees with reduced learning ability. Apidologie. 2010;41:194-202. https://doi.org/10.1051/apido/2009075

Husein MQ, Kridli RT. Reproductive responses following royal jelly treatment administered orally or intramuscularly into progesterone-treated Awassi ewes. Anim Reprod Sci. 2002;74:45-53. https://doi.org/ 10.1016/s0378-4320(02)00165-3.

Ibrahim A, et al. Nephroprotective effect of bee honey and royal jelly against subchronic cisplatin toxicity in rats. Cytotechnology. 2016;68:1039-48. https://doi.org/10.1007/s10616-015-9860-2.

Ibrahim DS, Shahen EMS. Effect of royal jelly on acrylamide-induced neurotoxicity in rats. J Chem Neuroanat. 2023;134:102358. https://doi.org/10.1016/j.jchemneu.2023.102358.

Inoue S, et al. Royal Jelly prolongs the life span of C3H/ HeJ mice: correlation with reduced DNA damage. Exp Gerontol. 2003;38:965-9. https://doi.org/10.1016/s0531-5565(03)00165-7

Jamnik P, et al. Antioxidative action of royal jelly in the yeast cell. Exp Gerontol. 2007;42:594-600. https://doi.org/10.1016/j.exger.2007.02.002.

Kamakura M, et al. Changes in hepatic gene expression associated with the hypocholesterolaemic activity of royal jelly. J Pharm Pharmacol. 2006;58:1683-9. https://doi.org/10.1211/jpp.58.12.0017.

Kanbur M, et al. The effects of royal jelly on liver damage induced by paracetamol in mice. Exp Toxicol Pathol. 2009;61:123-32. https://doi.org/10.1016/j.etp.2008.06.003.

Kim J, et al. Royal jelly enhances migration of human dermal fibroblasts and alters the levels of cholesterol and sphinganine in an in vitro wound healing model. Nutr Res Pract. 2010;4:362-8. https://doi.org/10.4162/nrp.2010.4.5.362.

Kocot J, et al. Antioxidant Potential of Propolis, Bee Pollen, and Royal Jelly: Possible Medical Application. Oxid Med Cell Longev. 2018:1-29. https://doi.org/10.1155/2018/7074209

Kolayli S, et al. A Member of Complementary Medicinal Food: Anatolian Royal Jellies, Their Chemical Compositions, and Antioxidant Properties. J Evid Based

Complementary Altern Med. 2016;21:43-48. https://doi.org/10.1177/2156587215618832

Kohno K, et al. Royal jelly inhibits the production of proinflammatory cytokines by activated macrophages. Biosci Biotechnol Biochem. 2004;68:138-45. https://doi.org/10.1271/bbb.68.138.

Kunugi H, Ali MA. Royal Jelly and Its Components Promote Healthy Aging and Longevity: From Animal Models to Humans. Int J Mol Sci. 2019;19:4662. https://doi.org/10.3390/ijms20194662.

Kusumawati, N. R. D., Ulfah, M. M., Panunggal, D. G., Sudarmo, S. M., Mexitalia, M., Utari, A., & Sidhartani, M. (2023). Hepatoprotective effects of probiotic administration on high fat–high fructose diet induced nonalcoholic steatohepatitis in Sprague-Dawley rats. International Journal of Probiotics and Prebiotics, 18, 1–6. https://doi.org/10.37290/ijpp2641-7197.18:1-6

Kurek-Górecka A, et al. Bee Products in Dermatology and Skin Care. Molecules. 2020;25:556. https://doi.org/10.3390/molecules25030556.

Lewis GD, et al. Metabolic signatures of exercise in human plasma. Sci Transl Med. 2010;2:33-37. https://doi.org/10.1126/scitranslmed.3001006

Liu JR, et al. Antioxidant properties of royal jelly associated with larval age and time of harvest. J Agr Food Chem. 2008;56:11447-11452. https://doi.org/10.1021/jf802494e

Lohrasbi M, et al. The functional mechanisms of synchronizing royal jelly consumption and physical activity on rat with multiple sclerosis -like behaviors hallmarks based on bioinformatics analysis, and experimental survey. BMC Neurosci. 2022;23:34. https://doi.org/10.1186/s12868-022-00720-0.

Luo L, et al.(2025) Participant Experiences from Chronic Administration of Irvingia Gabonensis Seed Extract and Inulin on the Body's Satiety: An Exploratory Analysis of a Single-Blind Clinical Trial. Current Topics in Nutraceutical Research. 23(1),56-63. https://doi.org/10.37290/ctnr2641-452X.22:56-63.

Maleki V, et al. Effects of Royal Jelly on metabolic variables in diabetes mellitus: A systematic review. Complement Ther Med. 2019;43:20-27. https://doi.org/10.1016/j.ctim.2018.12.022.

Malekinejad H, et al. Cardioprotective effect of royal jelly on paclitaxel-induced cardio-toxicity in rats. Iran J Basic Med Sci. 2016;19:221-227. http://www.ncbi.nlm.nih.gov/pmc/articles/pmc4818372/.

Mannoor MK, et al. Honeybee royal jelly inhibits autoimmunity in SLE-prone NZB x NZW F1 mice. Lupus. 2009;18:44-52. https://doi.org/10.1177/0961203308094765.

Melampy RM, Stanley AJ. Alleged gonadotropic effect of royal jelly. Science. 1940;91:457-8. https://doi.org/10.1126/science.91.2367.457.

Mishima S, et al. Royal jelly has estrogenic effects in vitro and in vivo. J Ethnopharmacol. 2005;101:215-20. https://doi.org/10.1016/j.jep.2005.04.012

Miyata Y, Sakai H. Anti-Cancer and Protective Effects of Royal Jelly for Therapy-Induced Toxicities in Malignancies. Int J Mol Sci. 2018;19:3270. https://doi.org/10.3390/ijms19103270.

Monda A, et al.(2025) The Effects of the Combination of Hyaluronic Acid, Malva sylvestris, and Sodium Alginate on the Pharyngolaryngeal Reflux: A Randomized Case-Control Study. Current Topics in Nutraceutical Research. 23(1),43-49. https://doi.org/10.37290/ctnr2641-452X.23:43-49

Mostafa RE, et al. Protective effects of royal jelly and Echinacea against moxifloxacin-induced renal and hepatic injury in rats. Drug Chem Toxicol. 2023;46:1193-1202. https://doi.org/10.1080/01480545.2022.2141773

Moutsatsou P, et al. Fatty acids derived from royal jelly are modulators of estrogen receptor functions. PLoS One. 2010;5:e15594. https://doi.org/10.1371/journal.pone.0015594.

Münstedt K, et al. Royal jelly reduces the serum glucose levels in healthy subjects. J Med Food. 2009;12:1170-2. https://doi.org/10.1089/jmf.2008.0289.

Nagai T, et al. Antioxidant properties of enzymatic hydrolysates from royal jelly. J Med Food. 2006;9:363-7. https://doi.org/10.1089/jmf.2006.9.363.

Kamakura M, et al. Antifatigue effect of fresh royal Jelly in mice. J Nutr Sci Vitaminol (Tokyo). 2001;47:394-401. https://doi.org/10.3177/jnsv.47.394.

Nakashima C, et al. The effect of oral royal jelly administration on skin barrier function: a double-blind randomized placebo-controlled trial. Eur J Dermatol. 2018;28:563-564. https://doi.org/10.1684/ejd.2018.3352.

Nakaya M, et al. Effect of royal jelly on bisphenol A-induced proliferation of human breast Cancer cells. Biosci Biotechnol Biochem. 2007;71:253-5. https://doi.org/10.1271/bbb.60453.

Narita Y, et al. Royal jelly stimulates cap formation: physiologic and nutrigenomic studies with mice and cell lines. Biosci Biotechnol Biochem. 2006;70:2508-14. https://doi.org/10.1271/bbb.60240.

Oka H, et al. Suppression of allergic reactions by royal Jelly in association with the restoration of macrophage function and the improvement of Th1/Th2 cell responses. Int lmmunopharmacol. 2001;1:521-32. https://doi.org/10.1016/s1567-5769(00)00007-2

Okamoto I, et al. Major royal jelly protein 3 modulates immune responses in vitro and in vivo. Life Sci. 2003;73:2029-45. https://doi.org/10.1016/s0024-3205(03)00562-9.

Ovchinnikov AN, et al. Royal Jelly Plus Coenzyme Q10 Supplementation Enhances High- Intensity Interval Exercise Performance via Changes in Cardiac Autonomic Regulation and Blood Lactate Concentration in Runners. Front Nutr. 2022;9:893515. https://doi.org/10.3389/fnut.2022.893515.

Ovchinnikov AN, et al. Royal jelly plus coenzyme Q10 supplementation improves high- intensity interval exercise performance via changes in plasma and salivary biomarkers of oxidative stress and muscle damage in swimmers: a randomized, double-blind, placebo-controlled pilot trial. J Int Soc Sports Nutr. 2022;19:239-257. https://doi.org/10.1080/15502783.2022.2086015.

Pasdar Y, et al. The Impact of Royal Jelly on Athletic Performance, Lactate Levels, Anthropometric Parameters, and Muscle Damage: A Systematic Review. Prev Nutr Food Sci. 2024;29:385-393. https://doi.org/10.3746/pnf.2024.29.4.385.

Pourmoradian S, et al. Effects of royal jelly supplementation on glycemic control and oxidative stress factors in type 2 diabetes female: A randomized clinical trial. Chin J lntegr Med. 2014;20:347-352. https://doi.org/10.1007/s11655-014-1804-8

Pratt JJ Jr, House HL. A Qualitative Analysis of the Amino Acids in Royal Jelly. Science. 1949;110:9-10. https://doi.org/10.1126/science.110.2844.9.

Raoufi S, et al. Royal jelly improves learning and memory deficits in an amyloid β-induced model of Alzheimer's disease in male rats: Involvement of oxidative stress. Metab Brain Dis. 2023;38:1239-1248. https://doi.org/10.1007/s11011-023-01168-9.

Rebold H. Biologically active substances in royal jelly. Vitam Horm. 1965;23:359-82. https://doi.org/10.1016/s0083-6729(08)60385-4.

Sasiarini L, et al. (2025) Effect of Brown Rice on Insulin Resistance and Insulin-Sensitive Glucose Transporters Expression in Adipose Tissue of Diet-Induced Obese Rats. Current Topics in Nutraceutical Research. ;23(1), 75-81. https://doi.org/10.37290/ctnr2641-452X.23:75-81.

Shen X, et al. Effects of lyophilized royal jelly on experimental hyperlipidemia and thrombosis. Zhonghua Yu Fang Yi Xue Za Zhi. 1995;29:27-9.

Silici S, et al. Antioxidative effect of royal jelly in cisplatin-induced test damage. Urology. 2009;74:45-51. https://doi.org/10.1016/j.urology.2009.05.024.

Silici S, et al. The protective effect of royal jelly against cisplatin-induced renal oxidative stress in rats. World J Urol. 2011;29:127-32. https://doi.org/10.1007/s00345-010-0543-5.

Silva TGS, et al. Oral treatment with royal Jelly improves memory and presents neuroprotective effects on icv-STZ rat model of sporadic Alzheimer's disease. Heliyon. 2020;6:e03281. https://doi.org/10.1016/j.heliyon.2020.e03281.

Simúth J, et al. Immunochemical approach to detection of adulteration in honey: physiologically active royal jelly protein stimulating TNF-alpha release is a regular component of honey. J Agric Food Chem. 2004;52:2154-8. https://doi.org/10.1021/jf034777y.

Sugiyama T, et al. Royal jelly acid, 10-hydroxy-trans-2-decenoic acid, as a modulator of the innate immune responses. Endocr Metab Immune Disord Drug Targets. 2012;12:368-76. https://doi.org/10.2174/187153012803832530.

Sver L, et al. A royal Jelly as a new potential immunomodulator in rats and mice. Comp Immunol Microbiol Infect Dis. 1996;19:31-8. https://doi.org/10.1016/0147-9571(95)00020-8.

Taniguchi Y, et al. Oral administration of royal jelly inhibits the development of atopic dermatitis-like skin lesions in NC/NGA mice. Int Immunopharmacol. 2003;3:1313-24. https://doi.org/10.1016/s1567-5769(03)00132-2.

Takahashi Y, et al. Effects of Royal Jelly Administration on Endurance Training-Induced Mitochondrial Skeletal Adaptations Muscle. Nutrients. 2018;10:1735. https://doi.org/10.3390/nu10111735.

Takaki-Doi, et al. Antihypertensive activities of royal jelly protein hydrolysate and its fractions in spontaneously hypertensive rats. Acta Med Okayama. 2009;63:57-64. https://doi.org/10.18926/AMO/31859.

Tokunaga KH, et al. Antihypertensive effect of peptides from royal Jelly in spontaneously hypertensive rats. Biol Pharm Bull. 2004;27:189-92. https://doi.org/10.1248/bpb.27.189.

Townsend GF, Lucas CC. The chemical nature of royal jelly. Biochem J. 1940;34:1155-62. https://doi.org/10.1042/bj0341155.

Townsend GF, Lucas CC. Chemical examination of the lipid fraction of royal jelly. Science. 1940;92:43. https://doi.org/10.1126/science.92.2376.43.

Tian W, et al. Architecture of the native major royal jelly protein 1 oligomer. Nat Commun. 2018;9:3373. https://doi.org/10.1038%2Fs41467-018-05619-1.

Vittek J. Effect of royal jelly on serum lipids in experimental animals and humans with atherosclerosis. Experience. 1995;51:927-35. https://doi.org/10.1007/BF01921742.

Vucevic D, et al. Fatty acids isolated from royal jelly modulate dendritic cell-mediated immune response in vitro. Int Immunopharmacol. 2007;7:1211-20. https://doi.org/10.1016/j.intimp.2007.05.005.

Weaver N, et al. Novel fatty acids from the royal jelly of honeybees (Apis mellifera, L.). Lipids. 1968;3:535-8. https://doi.org/10.1007/BF02530898.

Xia Z, et al. CRP and IHF act as host regulators in Royal Jelly's antibacterial activity. Sci Rep. 2014;14:19350. https://doi.org/10.1038/s41598-024-70164-5.

Zamami Y, et al. Royal jelly ameliorates insulin resistance in fructose-drinking rats. Biol Pharm Bull. 2008;31:2103-7. https://doi.org/10.1248/bpb.31.2103.

Figure 1. Graphical abstract.

Source: Author.

Abbreviations Used: None