



*Cognitive Vitality Reports<sup>®</sup> are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.*

## Royal Jelly

### Evidence Summary

Royal jelly may decrease cholesterol, blood glucose, and cancer-related symptoms, but the clinical evidence is inconsistent. Royal jelly can cause anaphylaxis in people with bee allergies.

**Neuroprotective Benefit:** In preclinical studies, royal jelly showed pro-cognitive, neuroprotective, antioxidative, anti-inflammatory, and neurogenic effects. One clinical trial of a combination therapy that included royal jelly improved cognitive functions in MCI.

**Aging and related health concerns:** Royal jelly may reduce cholesterol, blood glucose, and menopausal symptoms, and possibly improve outcomes in cancer, but the evidence is inconsistent. Royal jelly increases lifespan in preclinical studies.

**Safety:** Royal jelly can cause anaphylaxis in people who are allergic to bee products. Otherwise, adverse events are typically mild. Royal jelly should not be taken with antihypertensive medications/supplements or warfarin.

<p><b>Availability:</b> available in specialty and supplement stores</p>	<p><b>Dose:</b> Clinical trials have typically tested daily oral doses of 500 mg to 3000 mg.</p>	<ul style="list-style-type: none"> <li>• <b>MRJP1-9</b> MW: 49-87 kDa</li> <li>• <b>10-HDA</b> Chemical formula: C<sub>10</sub>H<sub>18</sub>O<sub>3</sub> MW: 186.251</li> </ul>
<p><b>Half life:</b> varies depending on compound</p>	<p><b>BBB:</b> varies depending on compound; 10-HDA is penetrant</p>	
<p><b>Clinical trials:</b> Two meta-analyses, each including 205 and 270 subjects total, have evaluated the efficacy of royal jelly for metabolic indices.</p>	<p><b>Observational studies:</b> none available</p>	

**What is it?** Royal jelly is an acidic creamy substance excreted from the pharyngeal gland of worker bees (*Apis mellifera*). Royal jelly is fed to queen bees throughout their lives, and it contributes to their high physical fitness, excellent learning and memory performance, fertility, and significantly longer lifespan compared to worker bees. Royal jelly consists of water (50-60%), proteins (18%; representing 50% of dry weight), carbohydrates (15%; mainly glucose and fructose), fats (3-6%), and small amounts of polyphenols/flavonoids, vitamins (niacin, B5, B1, B2, B6, B8, B9, C, E, and A), minerals, trace elements, nucleotides, bioactive substances (e.g., acetylcholine), ketones, and alcohol ([Ali et al., 2020](#); [Ali and Kunugi, 2020](#)).

The most active components present in royal jelly are a group of 9 proteins weighing 49 to 87 kDa, known as major royal jelly proteins (MRJP1-9). Fats in royal jelly consist of a group of rare short hydroxyl fatty acids or dicarboxylic acids with 8-12 carbon atoms in the chain, including the bioactive trans-10-hydroxy-2-decenoic acid (10-HDA, also known as queen bee acid or royal jelly acid) and sebacic acid. 10-HDA exerts neurogenic effects. The antioxidant potency of royal jelly is attributed, in part, to its polyphenolic compounds and flavonoids. Flavonoids of royal jelly include flavanones (e.g., hesperetin, isosakuranetin, and naringenin), flavones (e.g., acacetin, apigenin and its glucoside, chrysin, and luteolin glucoside), flavonols (e.g., isorhamnetin and kaempferol glucosides), and isoflavonoids (e.g., coumestrol, formononetin, and genistein)([Kunugi and Ali, 2019](#)).

Levels of ADP, ATP, and AMP are higher in fresh royal jelly. Among all nucleotides, AMP N1-oxide is a unique active component that exists exclusively in royal jelly. AMP N1-oxide exerts neurogenic and neurotrophic activities ([Kunugi and Ali, 2019](#)).



Royal jelly has been extensively studied in preclinical studies based on the purported antioxidant, anti-inflammatory, neuroprotective, cardioprotective, anti-diabetic, anti-hypercholesterolemic, anti-rheumatic, anti-tumor, anti-fatigue, anti-microbial, nematocidal, and anti-aging effects ([Ali and Kunugi, 2020](#)). Some of the neuroprotective properties of royal jelly have been attributed to the increased expression of GDNF in the brain, the phytoestrogens exerting estrogenic effects leading to neuroprotective effects, and stimulation of ERK/MAPK signaling, leading to enhanced activation of the antioxidant transcription factor Nrf2 ([Ali et al., 2020](#)). Royal jelly is also used as an adjuvant therapy for the treatment of various diseases such as cancer, hypertension, hyperlipidemia, diabetes, and neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.

**Neuroprotective Benefit:** In preclinical studies, royal jelly showed pro-cognitive, neuroprotective, antioxidative, anti-inflammatory, and neurogenic effects. One clinical trial of a combination therapy that included royal jelly improved cognitive functions in MCI.

*Types of evidence:*

- 1 controlled clinical trial of a combination formulation that included royal jelly
- Numerous laboratory studies

***Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:***

In a clinical trial of 66 subjects with mild cognitive impairment, treatment with Memo<sup>®</sup> (dietary supplement combining 750 mg lyophilized royal jelly with 120 mg standardized extracts of ginkgo and 150 mg *Panax ginseng*) for 4 weeks significantly improved cognitive functions as measured by MMSE ([Yakoot et al., 2013](#)). Improvement in the Memo<sup>®</sup> group was significantly greater than in the placebo control group (+2.07 versus +0.13, respectively). This difference also held true after adjusting for age as a covariate and educational level as a factor. Larger-sized studies with longer treatment durations are needed to confirm these findings. Also, due to the combination formulation, it is not clear which ingredients underlie these improvements.

***Human research to suggest benefits to patients with dementia:***

None available.



***Mechanisms of action for neuroprotection identified from laboratory and clinical research:***

Compounds in royal jelly have been shown to exert neuroprotective effects by decreasing inflammation (IL-6, IL-1 $\beta$ , TNF- $\alpha$ , iNOS, and COX-2), oxidative stress, mitochondrial dysfunction, excitotoxicity, and A $\beta$  toxicity ([Ali and Kunugi, 2020](#)). Royal jelly also increases antioxidative defense (by increasing SOD, HO-1, GSH-Px, and catalase) and neurogenic/gliogenic activities.

Royal jelly also activates AMPK, a master energy sensing signaling pathway that promotes autophagy and antioxidant production, while suppressing microglial inflammation via inhibition of various oxidative, inflammatory, and apoptotic pathways (e.g., iNOS and NF- $\kappa$ B) ([Ali and Kunugi, 2020](#)). Royal jelly and its lipids bind to estrogen receptors  $\alpha$  and  $\beta$  to enhance the production of neurotrophins such as NGF and BDNF, which promote neurogenesis, synaptogenesis, and acetylcholine production.

*Cognitive impairment models:* In a rat model of cognitive impairment (intracerebroventricular injection of streptozotocin), royal jelly treatment (200 mg/kg, oral gavage; obtained from Estação do Mel, Brazil) for 14 consecutive days started on the seventh day after surgery improved cognitive functions (increased retention time for spatial working memory) and reduced oxidative stress levels and neurodegeneration in the hippocampal dentate gyrus ([de Souza e Silva et al., 2020](#)).

In aged rats, Greek royal jelly powder treatment (50 mg of powder/kg/day, gastric gavage) for 2 months significantly improved spatial memory as measured by the Morris water maze ([Pyrzanowska et al., 2014](#)). Memory-enhancing effects may be driven in part by MRJPs, as in aged rats, treatment with MRJPs for 14 weeks showed improved spatial memory by up to 48.5% compared to control aged rats given distilled water ([Chen et al., 2017](#)). Metabolomic analysis suggested that MRJPs may improve memory by altering cysteine and taurine metabolism.

*Neurodegenerative model:* In a mouse model of acute neurodegeneration (trimethyltin-intoxication), lyophilized royal jelly powder mixed with regular food (1% or 5%) significantly increased the number of dentate gyrus granule cells while improving cognitive functions ([Hattori et al., 2011](#)).

*Alzheimer's model:* In a mouse model of Alzheimer's disease (APP/PS1 mice), royal jelly treatment (300 mg/kg/day, orally) for 3 months substantially ameliorated behavioral deficits in the Morris Water Maze test and the step-down passive avoidance test ([You et al., 2019](#)). Royal jelly treatment significantly decreased amyloid plaque pathology, alleviated JNK phosphorylation-induced neuronal apoptosis by suppressing oxidative stress (decreased MDA), and increased hippocampal cAMP, phospho-PKA,



phospho-CREB, and BDNF levels, suggesting that the cAMP/PKA/CREB/BDNF pathway may, in part, underlie the neuroprotective benefits.

Numerous preclinical studies have shown that royal jelly treatment alleviates A $\beta$  pathology by inhibition of BACE1 that cleaves APP into A $\beta$ , facilitating degradation (by increased A $\beta$ -degrading enzymes such as IDE and neprilysin), and increasing clearance of A $\beta$  (by upregulating the expression of LRP-1)(reviewed in [Ali and Kunugi, 2020](#)).

**APOE4 interactions:** Unknown.

**Aging and related health concerns:** Royal jelly may reduce cholesterol, blood glucose, and menopausal symptoms, and possibly improve outcomes in cancer, but the evidence is inconsistent. Royal jelly increases lifespan in preclinical studies.

*Types of evidence:*

- 2 meta-analyses or systematic reviews
- 13 controlled clinical trials
- 2 uncontrolled clinical trials
- Numerous laboratory studies

**Lifespan:** POTENTIAL BENEFIT IN PRECLINICAL STUDIES.

Numerous preclinical studies have shown that royal jelly treatment increases lifespan, but no epidemiological/observational studies exist for humans. The longevity effect in preclinical studies appear to be mediated by various mechanisms, such as downregulation of insulin-like growth factors and mTOR, upregulation of the epidermal growth factor signaling, dietary restriction signaling, and enhancement of antioxidative capacity ([Kunugi and Ali, 2019](#)). It is not clear which compounds of royal jelly are responsible for the longevity effect; MRJPs, 10-HDA, pantothenic acid, and royalactin appear to be probable candidates.

In mice (C3H/HeJ mice), royal jelly treatment (0.6, 6, or 60 mg/kg, orally) increased lifespan, but this effect depended on the dose ([Inoue et al., 2003](#)). The average survival times were 88 weeks for the control group, 79 weeks for the 0.6 mg/kg dose, 112 weeks for the 6 mg/kg dose, and 110 weeks for the 60 mg/kg dose. However, royal jelly did not extend the total life span. Average lifespan extension was speculated to be due to reduced oxidative damage, as measured by 8-hydroxy-deoxyguanosine.



In *C. elegans*, treatment with royal jelly (1, 10, and 100 ug/ml), protease-treated royal jelly (1, 10, and 100 ug/ml), and 10-HDA (10, 25, 50, and 100 uM) increased lifespan ([Honda et al., 2011](#)). Royal jelly increased lifespan in part by acting through the FOXO transcription factor DAF-16, the activation of which is known to promote longevity in *C. elegans* by reducing insulin/IGF-1 signaling. 10-HDA also increased lifespan; however, this increase was independent of DAF-16 activity. A subsequent study reported that 10-HDA increased lifespan in *C. elegans* through the dietary restriction signaling and TOR signaling ([Honda et al., 2015](#)). This study was partially funded by Api Company Limited, which manufactures and sells royal jelly products, where 3 of the authors are employees.

In contrast, studies in *Drosophila* flies have reported that royal jelly at high concentrations (40–70%) prolonged development time, shortened lifespan, increased mortality, and reduced productivity in both sexes ([Shorter et al., 2015](#)). In this study, excess nutrients in high royal jelly doses altered genes involved in amino acid metabolism and encoding glutathione S-transferase.

An *in vitro* study in human dermal fibroblasts reported that 10-HDA prevented ultraviolet A-induced damage, cytotoxicity, reactive oxygen species, and cellular senescence by inhibiting expression of MMP1 and MMP-3 and inhibiting activation of the JNK and p38 MAPK pathways ([Zheng et al., 2013](#)).

In another study, human embryonic lung fibroblast cells treated with MRJPs (0.1–0.3 mg/mL) showed increased proliferation, decreased senescence, and longer telomeres, which were associated with upregulation of the antioxidant SOD1 and downregulation of mTOR and p53 ([Jiang et al., 2018](#)).

**Menopausal symptoms:** POTENTIAL BENEFIT.

In a double-blind randomized controlled trial of 200 postmenopausal women, royal jelly treatment (1,000 mg/day; Nature Life Co., Canada) for 8 weeks significantly reduced the Menopause Rating Scale, whereas the reduction was not significant in the control group ([Sharif and Darsareh, 2019](#)). The authors of this study speculated that royal jelly's estrogenic activity may play an important role in the modulation of selective estrogen receptors, contributing to hormonal balance. Estrogenic compounds in royal jelly include 10-hydroxy-trans-2-decenoic acid, 10-hydroxydecanoic acid, and trans-2-decenoic acid.

In a double-blind randomized controlled trial of 72 postmenopausal women, royal jelly treatment (capsules of dried royal jelly, equivalent to 3,000 mg/day of fresh royal jelly) for 6 months resulted in preservation of bone mineral density and hip structural analysis parameters, whereas the placebo group experienced a significant decline ([Matsushita et al., 2020](#)). The levels of total procollagen type 1 N-



terminal propeptide (P1NP), a marker of bone formation, and tartrate-resistant acid phosphatase decreased significantly in the placebo group, while these measures were preserved in the royal jelly group at postintervention compared with baseline. Royal jelly consumption may preserve femoral bone mineral density and strength in postmenopausal women.

In a randomized controlled trial in menopausal women, treatment with Melbrosia, which contains royal jelly, pollen, bee bread, vitamins, and other compounds, significantly decreased menopausal symptoms (headache, urinary incontinence, vaginal dryness, decreased vitality) compared to the placebo group ([Szanto et al., 1994](#)). This publication was in German, and therefore details of the study could not be evaluated.

***Cancer and chemo/radiotherapy-related conditions:*** IMPROVED OUTCOMES FOR SOME CONDITIONS.

In a double-blind randomized controlled trial of 33 patients with metastatic renal cell carcinoma, adding royal jelly treatment (800 mg, 3 times daily, oral; Yamada Agriculture Center Inc.) to molecular targeted therapies (tyrosine kinase inhibitors) for 3 months resulted in a larger decrease in tumor size compared to patients not supplemented with royal jelly ([Miyata et al., 2020](#)). One patient exhibited complete response after royal jelly supplementation. The frequency of patients with partial response in the royal jelly group (50.0%) was more than twice as high as that in the placebo group (17.6%). Compared to placebo-administered patients, no patient exhibited progressive disease in the royal jelly group. Royal jelly was also more effective than placebo in maintaining the relative dose intensity, though this was not statistically significant. At the end of the study period (3 months), the initial dose administered was maintained in 7 (43.8%) and 2 patients (11.8%) in the royal jelly and placebo groups, respectively. Post-to pre-treatment ratios of the TNF- $\alpha$  and TGF- $\beta$  serum levels were lower with royal jelly supplementation than those receiving placebo, and these ratios correlated with decreased tumor size and decreased frequency of anorexia or fatigue in patients. Patients receiving royal jelly experienced less anorexia and fatigue compared with the placebo group ([Araki et al., 2018](#)). In sunitinib-treated patients, a statistically significant correlation between royal jelly treatment and fatigue or anorexia was observed. In another double-blind randomized controlled trial of 52 cancer patients, patients who received honey plus royal jelly (5 ml, twice daily) for 4 weeks had less fatigue (Visual Analog Fatigue Scale and Fatigue Severity Scale) compared with the control group that received just honey (5 ml, twice daily) ([Mofid et al., 2016](#)).

Oral mucositis (erythema, atrophy, and/or ulceration of oral mucosa) is one of the main adverse events associated with chemotherapy or radiation therapy. It occurs in most patients who receive radiation therapy of the head and neck area and up to 80% of patients who receive chemotherapy ([Daugelaite et](#)



[al., 2019](#)). In a clinical study of 103 patients undergoing radiotherapy and chemotherapy, a mouthwash therapy (benzylamine hydrochloride and nystatin rinses) with or without royal jelly (twice daily, 1 g/day; Faculty of Agriculture, Ataturk University, Erzurum, Turkey) was tested ([Erdem and Gungormus, 2014](#)). The royal jelly-treated group had a significantly shorter mean resolution time of oral mucositis compared to the control group. The healing time of oral mucositis was 3 to 4 days in the royal jelly group, except for grade 2 mucositis in 1 case. In the control group, the time required for healing of the lesions was 3 to 5 days for grade 1 mucositis and 13-14 days for grade 2-3 mucositis. The mean healing time of grade 1 mucositis was 2.7 days for the control group and 1.1 days for the royal jelly group ( $p=0.0001$ ). The mean healing times of grade 2 mucositis for the control and royal jelly groups were 5.8 days and 3.0 days, respectively ( $p=0.0001$ ). The mean healing time of grade 3 mucositis in the royal jelly group was significantly shorter than that of the control group ( $p=0.005$ ). In a review on chemotherapy- and radiotherapy-induced oral mucositis, royal jelly, *Lactobacillus brevis* lotion, and zinc supplementation were discussed as treatments; however, it was not possible to compare the efficacy of these products as the study design and outcomes were different ([Daugelaite et al., 2019](#)).

In a pilot open-label clinical study of 40 men with benign prostatic hyperplasia, royal jelly treatment (38 mg fresh frozen; Bee Farm JTM, Duke butter 30, Uzice, Serbia) for 3 months did not lead to any significant reduction in post-void residual volume, prostate volume, or to any involution of the transitory zone, but it reduced prostatic-specific antigen (PSA) levels ([Pajovic et al., 2016](#)). Royal jelly treatment also improved quality of life. Since royal jelly decreased PSA levels without changing other measures of prostate health, it is important to rule out the presence of prostate cancer before long-term royal jelly treatment to avoid the risk of masking the results of PSA screening for cancer. This study had some limitations including the small sample size, absence of a placebo control group, and the lack of long-term follow-up after treatment.

***Type 2 diabetes and metabolic profiles:*** POTENTIAL BENEFIT BUT MIXED/INCONCLUSIVE.

In a meta-analysis of 5 randomized controlled trials including a total of 205 subjects, royal jelly treatment (500-6,000 mg, daily) for 4-8 weeks did not significantly reduce fasting plasma glucose or HbA1c ([Mahboobi et al., 2019](#)). However, in a systematic review of 6 randomized controlled trials including a total of 270 patients with type 2 diabetes mellitus, royal jelly treatment (1-3 g/day) for 8 weeks reduced fasting blood sugar in several studies and reduced HbA1c in one study ([Maleki et al., 2019](#)). Although royal jelly supplementation resulted in significant reductions in HOMA-IR in 3 studies, the findings on insulin levels were mixed.





In a double-blind randomized controlled trial of 50 women with type 2 diabetes mellitus, royal jelly treatment (1,000 mg lyophilized royal jelly/day) for 8 weeks decreased mean body weight (before, 72.45±4.42 kg; after, 71.00±6.44 kg) while it increased insignificantly in the placebo group (before, 73.02±6.44 kg; after, 73.52±6.80 kg)([Pourmoradian et al., 2012](#)). Royal jelly supplementation also resulted in significantly decreased mean daily total energy ( $p<0.01$ ) and carbohydrate ( $p<0.01$ ) intakes, while in the placebo group the mean daily total energy and fat intakes were increased significantly ( $p<0.05$ ). P-values indicate differences between before and after intervention, not between royal jelly vs control groups.

In a double-blind randomized controlled trial of 61 healthy adults, royal jelly treatment (3 g in 100 ml liquid/day) for 6 months improved glucose tolerance (fasting plasma glucose and insulinogenic index)([Morita et al., 2012](#)). However, there were no treatment effects on BMI, waist circumference, lipids, hepatic and renal functions, atherosclerotic measures (blood pressure, homocysteine, and high molecular weight-adiponectin), other glycemic metrics (HbA1c, HOMA-IR, HOMA-B, and leptin), and bone metabolic variables.

In a single-blind randomized controlled trial of 40 people with mild hypercholesterolemia (180-200 mg/dL), royal jelly treatment (9 capsules/day, 350 mg/capsule; Bee Touched, Yunlin Country, Taiwan) for 3 months did not alter anthropometric parameters like body weight, waist circumference, or body fat ([Chiu et al, 2017](#)).

Based on the existing literature, royal jelly may increase glucose uptake by reducing oxidative stress and inflammation, enhancing insulin signaling, and activating the AMPK pathway ([Maleki et al., 2019](#)). However, in human clinical trials, the results are not consistent.

**Blood pressure:** INCONCLUSIVE.

In a double-blind randomized controlled trial of 100 postmenopausal women, the effects of honey cocktail (mixture of 95% honey, 4% bee bread, and 1% royal jelly; 20 g/day) versus honey treatment (Tualang honey; 20 g/day) for 12 months were compared ([Wahab et al., 2018](#)). The regular honey group showed a significant decrease in diastolic blood pressure (from 77.92 mmHg at baseline to 73.45 mmHg at 12 months) and fasting blood sugar (from 6.11 mmol/L at baseline to 5.71 mmol/L at 12 months), which was not seen in the honey cocktail group. Independent t-tests were used for numerous anthropometric variables without corrections for multiple comparisons; thus, observed treatment effects could be products of type I error.



In preclinical models, royal jelly and protease-treated royal jelly exhibit antihypertensive effects, including aortic relaxation, improving heart rate variability and baroreceptor sensitivity, and reducing blood pressure (reviewed in: [Ali and Kunugi, 2020](#)). The suggested mechanism of action involves acetylcholine activation of muscarinic receptors, leading to increased nitric oxide.

***Cholesterol and lipid profiles:*** POTENTIAL BENEFIT BUT MIXED/INCONCLUSIVE.

In a systematic review of 6 randomized controlled trials including a total of 270 patients with type 2 diabetes mellitus, royal jelly treatment (1-3 g/day) for 8 weeks improved serum levels of triglycerides, cholesterol, HDL, LDL, VLDL and Apo-A1 ([Maleki et al., 2019](#)). However, results were not consistent across included trials.

In a randomized controlled trial in 15 healthy volunteers, royal jelly treatment (6 g/day, Maruwa Co. Ltd, Tokyo, Japan) for 4 weeks resulted in significantly decreased total cholesterol (from  $194.0 \pm 11.4$  mg/dL to  $182.4 \pm 12.7$  mg/dL) and LDL cholesterol levels (from  $120.3 \pm 11.1$  mg/dL to  $109.3 \pm 12.1$  mg/dL) compared to the control group ( $p < 0.05$ ) ([Guo et al., 2007](#)). Among the lipoprotein fractions, small very-low-density lipoprotein was significantly decreased with royal jelly ( $p < 0.05$ ). There were no significant differences in serum HDL or triglyceride levels. One limitation of this study is that the control group received no treatment, so it was not placebo-controlled. It is also worth noting that one of the co-authors was employed at Maruwa Co., the company that provided the royal jelly intervention.

In a single-blind randomized controlled trial of 40 people with mild hypercholesterolemia (180-200 mg/dL), royal jelly treatment (9 capsules/day, 350 mg/capsule; Bee Touched, Yunlin Country, Taiwan) for 3 months significantly reduced total cholesterol (by 11.5%, from 207.05 mg/dL to 183.15 mg/dL) and LDL cholesterol (by 4.8%, from 126.44 mg/dL to 120.31 mg/dL) ( $p < 0.05$ ) ([Chiu et al., 2017](#)). However, total cholesterol and LDL levels increased after the follow-up period post-treatment. Royal jelly treatment also significantly increased the concentration of DHEA-S (from 1788.09 ng/mL to 1992.31 ng/mL;  $p < 0.05$ ). However, triglyceride and HDL cholesterol levels were not significantly altered.

In a prospective follow-up study of 36 postmenopausal healthy women, royal jelly treatment (150 mg/day) for 3 months significantly decreased total cholesterol (by 3.09%; from  $224.4 \pm 38.6$  mg/dL to  $216.1 \pm 36.5$  mg/dL;  $p = 0.018$ ) and LDL cholesterol (by 4.1%; from  $143.9 \pm 37.5$  mg/dL to  $136.2 \pm 32$  mg/dL;  $p = 0.011$ ) and increased HDL cholesterol (by 7.7%; from  $60.2$  mg/dL  $\pm 12.3$  to  $64.7$  mg/dL  $\pm 13.9$ ;  $p = 0.0003$ ) ([Lambrinoudaki et al., 2016](#)).



In a double-blind randomized controlled trial of 100 postmenopausal women, the effects of honey cocktail (mixture of 95% honey, 4% bee bread, and 1% royal jelly; 20 g/day) and honey treatment (Tualang honey; 20 g/day) for 12 months were compared ([Wahab et al., 2018](#)). Neither honey cocktail nor honey group showed significant effects on lipid profiles. However, because the cocktail included components other than royal jelly (which constituted just 1%), this study does not rule out the potential effects of royal jelly on lipid profiles.

**Muscle strength:** INCONCLUSIVE.

In a double-blind randomized controlled trial of 194 elderly nursing home residents, protease-treated royal jelly (1.2 or 4.8 g/day) for 1 year did not result in significant effects on handgrip strength or other measures of physical performances ([Meng et al., 2017](#)). The mean changes in handgrip strength for placebo, low-dose, and high-dose royal jelly groups were -0.98 kg (95% CI, -2.04 to 0.08), 0.50 kg (95% CI, -0.65 to 1.65) and 1.03 kg (95% CI, -0.37 to 2.44), respectively ( $p=0.06$ ). Thus, protease-treated royal jelly treatment did not significantly improve muscle strength, but there was possibly a trend for attenuation of muscle strength decline.

**Safety:** Royal jelly can cause anaphylaxis in people who are allergic to bee products. Otherwise, adverse events are typically mild. Royal jelly should not be taken with antihypertensive medications/supplements or warfarin.

*Types of evidence:*

- 5 controlled clinical trials
- 2 clinical studies of allergenicity
- 3 reviews

**Allergies/anaphylaxis:** Allergic reactions to bee products have been documented, including contact dermatitis, acute asthma, and in some cases, anaphylaxis leading to death ([Ali and Kunugi, 2020](#)). An allergenicity study in 4 people with royal jelly allergy reported that an alkaline protease-treated royal jelly did not induce any allergenic response in 3 out of 4 subjects based on an *in vivo* skin-prick test ([Moriyama et al., 2013](#)). Also, *in vitro* assays of the blood from royal jelly allergy patients showed that IgE-binding capacity of the protease-treated royal jelly was very significantly reduced. In contrast, sera from the patients recognized a molecular mass of 55 kDa in the untreated royal jelly sample. Histamine-release test in basophil cells and leukocytes obtained from the royal jelly allergy patients showed that the untreated royal jelly induced histamine release that was 5-10-fold that induced by enzyme-treated



royal jelly. IgE-binding allergenic proteins in royal jelly were determined to be MRJP1 and MRJP2. An older study of 53 people with royal jelly allergy had also reported that the major IgE-binding proteins for royal jelly were proteins weighing 32-67 kDa and corresponded to MRJP1 and MRJP2 ([Rosmilah et al., 2008](#)). Protease treatment of royal jelly effectively degraded these two proteins ([Moriyama et al., 2013](#)).

***Adverse events from clinical trials:*** In a placebo-controlled clinical trial of 66 subjects with mild cognitive impairment, treatment with Memo<sup>®</sup> (dietary supplement combining 750 mg lyophilized royal jelly, 120 mg standardized extracts of ginkgo, and 150 mg *Panax ginseng*) for 4 weeks did not result in any serious adverse events ([Yakoot et al., 2013](#)). Only mild nausea and dyspeptic symptoms were reported in 3 subjects each in Memo<sup>®</sup> and control groups, and mild transient headache in 3 subjects in the Memo<sup>®</sup> group and 2 subjects in the control group. A mild subjective sense of flushing and palpitation during the first 3 days of treatment was reported by 5 patients in the Memo<sup>®</sup> group and 3 patients in the control group. In this clinical trial, Memo<sup>®</sup> capsules and placebo capsules were supplied by Pharco Pharmaceutical Industries free of charge. The last author of the manuscript was affiliated with Pharco Pharmaceutical Industries.

In a double-blind randomized controlled trial of 200 postmenopausal women, royal jelly treatment (1000 mg/day; Nature Life Co., Canada) for 8 weeks did not result in any serious adverse effects ([Sharif and Darsareh, 2019](#)).

In a double-blind randomized controlled trial of 33 patients with metastatic renal cell carcinoma, adding royal jelly treatment (800 mg, 3 times daily, oral; Yamada Agriculture Center Inc.) to molecular targeted therapies (tyrosine kinase inhibitors) for 3 months resulted in several adverse events including hypertension (23/33; 67.9%), fatigue (20/33; 60.6%), anorexia (18/33; 60%), and hand-foot syndrome (18/33; 60%) ([Miyata et al., 2020](#); [Araki et al., 2018](#)). Blood tests revealed leukopenia, anemia, renal dysfunction, liver dysfunction, and thyroid abnormality in 11 (36.7%), 9 (27.3%), 15 (45.5%), 7 (21.2%), and 14 patients (42.4%), respectively. Of these adverse events, anorexia and fatigue in patients treated with royal jelly occurred at significantly lower incidences compared to those in the placebo group ( $p=0.009$  and  $p<0.001$ , respectively). None of the laboratory blood test results differed significantly between royal jelly and placebo groups ([Araki et al., 2018](#)).

In a clinical study of 103 patients undergoing radiotherapy and chemotherapy, a mouthwash therapy (benzydamine hydrochloride and nystatin rinses) with or without royal jelly (twice daily, 1 g/day; Faculty of Agriculture, Ataturk University, Erzurum, Turkey) was tested ([Erdem and Gungormus, 2014](#)). There

was no differential incidence of nausea, vomiting, anorexia, dysphagia, diarrhea, or constipation between the royal jelly group versus the control.

In a single-blind randomized controlled trial of 40 people with mild hypercholesterolemia (180-200 mg/dL), royal jelly treatment (9 capsules/day, 350 mg/capsule; Bee Touched, Yunlin Country, Taiwan) for 3 months did not result in any changes in liver or kidney functions ([Chiu et al, 2017](#)). No considerable changes were noted in liver enzymes (levels of glutamic oxaloacetic transaminase, glutamic pyruvic transaminase) or kidney function biomarker (creatinine levels) in the royal jelly or placebo group.

The highest single dose of royal jelly tested in humans was a dose of 20 g of royal jelly in 20 healthy subjects. Two hours after ingestion of royal jelly, serum glucose levels were significantly decreased, while no adverse events were reported ([Munstedt et al., 2009](#)).

**Preclinical studies:** Numerous preclinical studies have also investigated the safety of long-term use of royal jelly and found no negative effects on liver or kidney functions ([Ali and Kunugi, 2020](#)). Magnitudes of benefit conferred by royal jelly in preclinical models varied, with some dose-dependent effects, while extremely high doses were associated with unfavorable outcomes in some studies. Authors of a review on royal jelly and its anti-aging properties speculated that the adverse events associated with high doses of royal jelly may be the result of reductive stress (shift of redox balance into an excessively reduced state) induced by antioxidants in royal jelly (e.g., phenols, vitamins, fatty acids, etc.)([Kunugi and Ali, 2019](#)).

**Pesticides:** Some concerns have been raised for bee products due to contamination with pesticides such as neonicotinoids, which are used worldwide. Pesticide exposure can also affect the quantity and the nutritional composition of the royal jelly produced ([Milone et al., 2021](#)). However, compared with pollen and honey, royal jelly contamination with neonicotinoids is very limited (1 to 9.5 µg/kg), equivalent to 0.016% of the original concentrations of pesticides ingested by worker bees ([Kunugi and Ali, 2019](#)). Therefore, royal jelly is significantly less contaminated compared with other bee products.

**Drug interactions:** Royal jelly should not be ingested if you are allergic to bees or bee pollen. Royal jelly should be avoided if taking other drugs or supplements that lower blood pressure ([Drugs.com](#)). These include antihypertensive medications, warfarin (Coumadin, Jantoven), Andrographis, casein protein, cat's claw, coenzyme Q-10, fish oil, L-arginine, lyceum, stinging nettle, and theanine.



**Sources and dosing:** Royal jelly is harvested from queen bee honeycomb, where large amounts of royal jelly is deposited by worker bees. Royal jelly can come in fresh pure forms, mixed with other bee products (e.g., pollen, propolis), enzyme/protease-treated forms, and in capsules (typically freeze-dried). The pH of fresh royal jelly ranges from 3.6 to 4.2 ([Kunugi and Ali, 2019](#)).

There are no universally accepted quality standards for the production of royal jelly ([Ali and Kunugi, 2020](#)). The composition of royal jelly varies considerably depending on bee species, geographical location, botanical origin, season, timing of harvesting (e.g., harvesting within 24 hours from larvae maximizes phenol content), and method of processing (e.g., protease-treatment) ([Ali et al., 2020](#)). Royal jelly is heat-sensitive, and it should be kept frozen in order to protect its bioactive ingredients from degradation. Storage of royal jelly at a temperature of 5°C or above promotes enzymatic degradation. All MRJPs except for MRJP2 get rapidly degraded in the stomach and small intestine ([Muresan et al., 2018](#)). Royal jelly is typically consumed orally, but the absorption of capsulated royal jelly might resist proteolytic digestion better than direct oral consumption. 10-HDA is used as an indicator of the freshness of royal jelly ([Ali and Kunugi, 2020](#)).

**Research underway:** No clinical studies are ongoing to test royal jelly; however, there are 8 active clinical trials testing beeswax, propolis, or other honey products in clinical studies, based on [ClinicalTrials.gov](#). Several of these trials are in cancer patients while others are for oral health, kidney disease, skin issues, and burn healing.

#### Search terms:

Pubmed, Google: royal jelly

- + cognitive, + ApoE, + clinical trial, + meta-analysis, + observational, + epidemiological, + lifespan, + mortality

Websites visited for royal jelly:

- [Clinicaltrials.gov](#)
- NIH RePORTER (0)
- [Examine.com](#)
- [DrugAge](#)
- [Drugs.com](#)
- WebMD.com (0)
- Labdoor.com (0)
- ConsumerLab.com (0)



- Cafepharma (0)
- Pharmapro.com (0)

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