Royal Jelly, Bee Brood: Composition, Health, Medicine: A Review

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For so work the honey-bees
Creatures that by a rule in nature teach
The Act of order to a peopled kingdom.
They have a king and officer of sorts.

Shakespeare, King Henry V

Alas, the poet did not know that the bees had a queen, the royal jelly being its marvellous food….

It is said that the ancient Egyptians knew royal jelly (RJ) and believed royal jelly will keep the pharao's body young and beautiful even after he passes away, using it also to prepare the mummy and that Cleopatra has used it for her cosmetics in order to keep herself beautiful…

The ancient Chinese used royal jelly as a aphrodisiac[207].

COMPOSITION

Royal jelly is a viscous jelly substance. It is partially soluble in water with a density of 1.1 g/mL. Its colour is whitish to yellow, the yellow colour increasing upon storage. Its odour is sour and pungent, the taste being sour and sweet. The sensory characteristics are important quality criteria. Old royal jelly, which has not been properly stored tends to be darker and a rancid taste can develop. For optimum quality it should be stored in frozen state. The viscosity varies according to water content and age - it slowly becomes more viscous when stored at room temperature or in a refrigerator at 50C. The increased viscosity appears to be related to an increase in water insoluble nitrogenous compounds, together with a reduction in soluble nitrogen and free amino acids [246]. These changes are apparently due to continued enzymatic activities and interaction between the lipid and protein fractions.
There are no royal jelly international standards. However, some countries like Brazil, Bulgaria, Japan and Switzerland have established national standards. A working group of the International Honey Commission, headed by Sabatini, is working on the elaboration of an international standard. A first work in view of establishment of a standard has been published[218]

Table 1: **Composition of royal jelly** after[218]

	fresh	lyophilized
Water %	60 - 70	< 5
Lipids %	3 - 8	8 - 19
10-hydroxy-2-decenoic acid %	> 1.4	> 3.5
Protein %	9 - 18	27 - 41
Fructose, glucose, sucrose %	7 - 18	-
Fructose %	3 -13	-
Glucose %	4 - 8	-
Sucrose %	0.5 – 2.0	-
Ash %	0.8 – 3.0	2 - 5
pH	3.4 - 4.5	3.4 – 4.5
Acidity in ml 0.1N NaOH/g	3.0 - 6.0	-

Humidity

The water content with 60-70 % is the main component of royal jelly. The dry substance is composed of carbohydrates, proteins, amino acids and fat. Smaller quantities of minerals and vitamins are also present (see table).

Proteins and peptides

with 17 to 45 % of the RJ dry weight are the main substance class of RJ [140]. They are the main nitrogenous substances, accounting for about 97-98 % of them [139]. About 60 % of them are water-soluble [139].

Free amino acids represent only 0.6-1.5 % , the majority of which belong to the L series. The most representative are proline and lysine [29, 223]. Upon storage at 4°C for 10 months no significant changes of amino acids were encountered, while after room temperature storage proline and lysine content increased [29]. This is due probably to proteolytic enzyme activity.

Lipids

The lipids with 3 to 19 % of the RJ dry weight [29, 142], are second in importance after the proteins. 80 to 90 % of the lipid fraction consists of free fatty acids, the rest being neutral lipids, sterols, hydrocarbons [121, 140, 142, 144, 145].

Most of the organic acids are free with rather unusual structure rarely encountered in nature, mono- and dihydroxy acids and dicarboxylic acids with 8 and 10 carbon atoms [141, 142]. The identification of this fraction – in particular as regards the pattern and quantitative analysis of free organic acids – is believed to represent the criteria of choice for defining the genuineness of RJ [28, 33]. The main acid 10-hydroxy-2-decenoic (HDA) is an unsaturated acid, which is determined for the evaluation of RJ genuinely.

The other fatty acids are all saturated mono- and dihydroxy-, mono- and dicarboxylic acids have not been quantified exactly can be roughly estimated to be around 0.5 to to 1 g/ 100 g [144]

HDA and also the other fatty acids of RJ have antibacterial properties [172, 226], thus contributing to the relatively low content of bacteria in this product.

Carbohydrates

They are third in importance, composed of mainly fructose, glucose and sucrose [143, 146, 225], with some traces of maltose, trehalose, melibiose, ribose and erlose also being found [143, 146].

Minerals

Ash content (minerals) represents 0.8 to 3 %% of RJ fresh matter.

The major elements are K, P, S, Na, Ca, Al, Mg, Zn, Fe, Cu and Mn but there are trace amounts (0.01-1 mg/100 g) of Ni, Cr, Sn, W, Sb, Ti and Bi. The sodium content of RJ varies between 11 and 14 mg/ 100 g. [239]

Vitamins

The concentrations of vitamins in RJ are distributed over a broad spectrum; vitamins showing fairly uniform values are riboflavin, thiamine, niacin and folic acid. Likewise present but with greater variations are pyridoxine, biotin, pantothenic acid and inositol. Only traces of vitamine C are present, while the tat soluble vitamins like vitamine A,D, E and K are absent [221].

Other minor components

Numerous minor compounds, belonging to diverse chemical categories, have been identified in royal jelly. Among these are two heterocyclic substances, biopterine and neopterine at 25 and 5 µg/g of fresh weight respectively [215]. These compounds are found in the food of worker bee larvae too, but at about one tenth of these concentration. Other substances identified include several nucleotides as free bases (adenosine, uridine, guanosine, iridin and cytidine) the phosphates AMP, ADP, and ATP [165], acetylcholine (1 mg/g dry weight, [85] and gluconic acid (1.4 % of fresh weight, [181]. Benzoic acid (8-15 mg/kg) has also been found [171]. Samall amounts of malic, lactic and citric acid have also been found [115].

ROYAL JELLY AS A NUTRIENT

Table 2 **Nutritional components of royal jelly and nutritional requirements,** after [218, 224, 264]

	g in 100 g	RDI (g/day)
Water	60-70	
Carbohydrates	11 - 23	320
Proteins	9 -18	50
Fat	3-8	80
Vitamins	**mg /100g**	**RDI* (mg/day)**
Niacin (B3)	4.5 – 19	15
Pyridoxin (B6)	0.2 – 5.5	1.4
Thiamin (B1)	0.1 – 1.7	1.1
Riboflavin (B2)	0.5 – 2.5	1.3
Pantothenic acid	3.6 – 23	6
Folic acid	0.01 – 0.06	0.4
Biotin (H)	0.15 – 0.55	0.045
Minerals	**mg /100g**	**RDI* (mg/day)**
Potassium (K)	200-1000	2000
Calcium (Ca)	25-85	1000
Magnesium (Mg)	20-100	350
Zink (Zn)	0.7-8	8.5
Iron (Fe)	1-11	12.5
Copper (Cu)	0.33-1.6	1.2

*- after the German Nutrition Society

The significance of royal jelly for human nutrition is relatively small. Assuming a daily intake of 2 g per day, the basic nutrients proteins, lipids and carbohydrates contained in RJ do not play a role for their RDI. The same is true for the minerals. From the vitamins there is a small contribution of pyridoxin (B6), thiamin (B1), riboflavin (B2) and biotin (H).

Bio-active ingredients

The bioactive compounds and health-promoting properties of royal jelly were reviewed in 2012[214]

HDA and other fatty acids

Most of the organic acids are free with rather unusual structure rarely encountered in nature, mono- and dihydroxy acids and dicarboxylic acids with 8 and 10 carbon atoms [141, 142], the man acid being 10-hydroxydecenoic acid (HDA, see chapter one). Numerous effects have being reported, most of them for HDA

- antibacterial and immuno activating [9, 14, 17, 159, 172, 226, 272, 277, 286],
- immuno-modulating, anti-cancer[47, 65, 241, 247, 258, 259, 270]
- anti-diabetes[192],
- collagen promoting and skin protecting[124],
- anti-ulcer[53],
- facilitates differentiation of brain cells[80],
- antidepressant in mice experiments[96, 97],
- promotes endothelial health, antihypertensive, antihyperlipoidemia[99, 170, 278],
- estrogenic[167, 178],
- anti-rheumatic[284]

- activation of TRPA1 and TRPV1 (induces thermogenesis and energy expenditure enhancement)[252]

Proteins and peptides

82 - 90 % of the RJ proteins belong to the Major Royal Jelly Protein type (RRJP) protein[222]. This protein belongs to the albumin protein class[232] and has immuno-modulating activity[190]. Different glycoproteins [117-120, 174, 265, 286] and peptides have been characterised: apisimin [13],one with antihypertensive activity [168, 169] and so called jeleines with antibacterial properties [58, 216].

Many effects have been encountered for different proteins and peptides:

- anti-oxidative[71, 72], immuno-modulating, monocyte-proliferation stimulating[116, 190], antibacterial[57, 216], anti-inflammatory[123, 160], vitalisation and anti-fatigue [108, 233, 234], anti-hypertensive[166, 170, 256], anti-allergic[190], anti-diabetes[125], collagen proliferating and skin fibroblast differentiating[261], lower the cholesterol levels[113]

AMP-N1 Oxide

Adenosine monophosphate N1 oxide is a compound found only in RJ. Its main effects are on the centrally nervous system:

- it stimulates neuronal differentiation, promots generation of all three types of cells composing the central nervous system: neurons, astrocytes and oligodendrocytes, against neuronal damage[82, 83]

Adenosine

Adenosine is an important biomolecule with many physiological effects. For example, adenosine has a predominantly hyperpolarising effect on the membrane potential of excitable cells, producing inhibition in vascular smooth muscle cells of coronary arteries and neurons in the brain. RJ contains 5.9 to 2057.4 mg/kg adenosine[279]

Acetylcholin[275]

The concentratons found is 1 mg/g dry weight [85]

- it is a nerve transmitter, having a number of hormone-like effects in the central and vegetative nervous system

The hormones testosterone, progesterone, prolactine, estradiol have been found in RJ [269] see table 11.

- They increase of male and female fertility, and also male power and endurance

Polyphenols have also been identified, having:

- Antioxidant effects[41, 154, 199]

Summarising the above it seems that the unique anti-fatigue and the brain activating properties of royal jelly are mediated by HDA, by a specific proteins by AMP-N1 oxide and by RJ hormones.

Dietology and prophylactics

Royal jelly is a functional food and thus an ideal additive for prophylactic purposes. Due to its ideal effects in newborn children it is an ideal additive to their food.

Hovanska examined the influence of infant nursing food containing also RJ and pollen in comparison with infant food without these ingredients. The infants fed on the food with the ingredients had a better adaptation to stress situations[91].

Krilov and Sokolski prepared a tablet containing 45 mg dry RJ, 30 mg ascorbic acid, the resting 265 mg containing lactose, sucrose, starch and calcium stearate. The authors tested the tablets, given to test students 3 times per day. While there was no influence on normal students, test persons with lowered immunity was beneficially influence, measured by normalised ratios between blood albumin and globulins ratios and the content of A,B, G immunoglobulin proteins and of other parameters[131].

In summary, RJ has a variety of biological properties which make it an ideal additive with rejuvenating, anti-aging. It can easily be combined with other compounds, vitamins, antioxidants and trace elements.

Royal jelly as a supplement for professional sportsmen for better performance

In a series of test in Russia a Russian preparation **Ap-iton 25** was tested in highly trained sportsmen. The tests were carried out at the beginning and after 21 days, the intake of RJ was 4 pills sublingually daily, each one containing 369 mg lactose-glucose absorbed RJ, in total corresponding to about 1.2 g dry RJ daily, a control group took placebo. In the tests the resilience of sportsmen was tested in a treadmill, until the sportsmen rejected a further load increase, the load being changed every minute. The endurance of the sportsmen who took the RJ supplement was significantly better than the controls after 10 and 21 day of the test and remained significant 5 days after the sportsmen stopped taking the supplement. It is known that in physical performance the endurance decreases because of an increase of blood lipid hydroperoxides. An antioxidant as RJ should theretically inhibit the building of the lipid peroxidaton. Indeed, there was a highly significant difference between the test and the control groups regarding this parameter, on the 10th and 21st day of training, this difference persisted 5 days after stopping supplementation. It is known that immunity decreases upon persistent physical strain. This results in a decrease of immunogloblines IgA, IgG and IgM. The humoral immunity was tested by measuring these parameters in the blood of the test persons. The IgA concentration in comparison with the initial values was higher than the controls after 21 days, while the change of the other two parameters was not significantly changed. The number of leucocytes, lymphocytes, T-lymphocytes, T-helpers and T-suppressers in the blood are a function of the cell immunity. All of these parameters were significantly higher in the test sportsmen after 21 days, when the values were compared to the initial ones, see page163-167 of [130]. This preparation is sold in Russia and is accepted as a sport supplement by the Russian Antidoping Agency, see **http://comilfo-api.com/**

A 45% ethanol solution containing 2.4 g native RJ in 100 ml was tested in a sport performance of 17-20 year old female students, who took 3 times 10 drops (approx. 100 mg RJ). Following tests were carried out: measurement of body mass, performance of Stange's breath holding test, measurement of the viso-motoric reaction, hanging on the bars, 30 m runs with maximal speed, measurement of heart rate afterwards, then a 5 minute step test with a step height of 30 cm, 30 climbs per minute followed by a 5 minute rest. There was a significant increase of the reaction of the organism to hypoxia, as measured by the Stange test and an improvement of the viso-motoric reaction[220].

Football players

In a test with young football players the effect of an intake of a RJ supplement on 13 morphological characteristics in initial and final measuring, tested against a control group (no intake). On the basis of the research results it could be concluded that football players from the experimental group who used royal jelly had statistically significant increase of body height and muscle components, and also a decrease of fat in the final measurement as compared to the initial ones. The results showed statistically significant increase in circumference above knee and circumference of lower leg in experimental group on the end of the experimental treatment. The examinees from experimental group had higher average values in body height, body mass, muscle and bone component, and lower average value of fat [103].

FUNCTIONAL PROPERTIES

The main significance of royal jelly lies in its health-promoting properties.

Chauvin reviews the biological and pharmacological effects of RJ and states that results are often controversial. He points out that RJ injection is very risky and thus ingestion should be used instead. Sublingual application by contact of RJ in order to achieve a direct transmission of RJ into blood is also recommended in order to avoid eventual decomposition of proteins in the digestion tract [36, 38]

Many East European studies are extensively reviewed in the Krylov and Sokolski's RJ monograph[131]. Prof. Krylov from the university of Nijni Novgorod has done many original contributions on this topic. The original Russian references will be often referred to as Krylov-Sokolski, as they are not accessible to non-Russian readers.

The different biological effects reported in the literature are compiled in table 3. For better clarity the different effects are summarised according to the type of effect.

Antibacterial, antiviral and fungicidal effects

Many studies have shown that royal jelly has antibacterial activity. These properties have been reviewed. RJ inhibits both gram-positive and gram-negative bacteria, but the first group is stronger inhibited: Antibacterial activity towards different bacteria, many of them pathogenic, has been registered: [238]

The antibacterial activity is due to: *HDA* [17, 226] and to *different proteins and peptides* [58, 62, 238, 276]

Antibiotic resistance increasingly encountered *today, e.g against Pseudomonas aeruginosa* could be overcome *by RJ* [147]

Bio-stimulating and antiaging activity

The role of RJ in the bee colony is to stimulate and increase the growth of larvae, increasing metabolic processes. The most evident effect is the increase of weight of many animals, reported after ingestion of RJ (see table 3). In an early work it was found in an animal experiments that RJ increases oxygen metabolism of tissues and causes increased activity in mice, due to increased concentration and use of blood glucose [68] RJ increases also tissue oxygen consumption and thus increases performance and endurance. These effect are due to RJ induced increase of respiration and oxidative phosphorylation [131]. The anti hypoxic, i.e. oxidative effect of royal jelly in animal experiments can be also mentioned here [131]. It was also found that RJ increases the metabolism of humans (especially increased were breathing frequency and basal metabolism [38].

RJ and its related substances extend lifespan in C. elegans, suggesting that RJ may contain longevity-promoting factors. Further analysis and characterization of the lifespan-extending agents in RJ broaden our understanding of the gene network involved in longevity regulation in diverse species and may lead to the development of nutraceutical interventions in the aging process[90]

Immuno-modulating effects

Immunomodulating effects lay an important effect in cancer, allergy,and inflammation. They can be activating and deactivating. In the case of RJ the activating effects predominate as they have been reported by many workers (see table 1).

Krylov reports on the increase of all blood cells and the α-1 and α-2 globulins fraction after RJ ingestion [131] The effect on the alpha globulin fraction is probably connected to the reported immunomodulating activity of RJ. RJ induces the formation T-lymphocytes, responsible for the immune response for the immune response against viruses and cancer cells and play an important role in inflammation processes[270]. This activity seems to be due to 10-HDA. Tamura et al. [247] showed in experiments with rats that inhibition of tumor growth of slow growing tumors (Ehrlich and Sarcoma strains) is better than that of fast growing ones (leukaemia).

Recently the effect of RJ was tested on tumour development and metastasis in murine tumour models. RJ did not affect the formation of metastases when given intraperitoneally or subcutaneously. However, synchronous application of tumour cells and royal jelly intravenously significantly ($p < 0.001$) inhibited the formation of metastases [195]

The immuno-activating effects or RJ are due to its main protein apalbumin1[159]. In one case it has been reported that RJ has also immuno-inhibitory anti-allergic effects in mice [190].

Anti-inflammatory effects, reported for RJ, are hormone-like effects reducing inflammation. Tissue inflammation is generally thought to be a major cause for body degeneration and ultimate death.

Effects on the nervous system

RJ has also a stimulating, activating effects on the central nervous system, CNS [68] and also on the vegetative NS [131]**.** Krylov reports on acetyl-choline like effects on the intestine and on the innervation of the smooth respiration muscle. These effects result in an improved muscle tonus and activity. Intake of Apilac, a Russian preparation based on RJ, leads to an increased phosphorilation of the CNS, to increase of rat brain cholinesterase activity. High doses of 100 mg/kg to mice lead to structural changes of nerve neurons [131].

RJ shows neurotrophic effects on the mature brain via stimulation of Glial Cell-Derived Neurotrophic Factor, GDNF production. The enhanced expression of neurofilament H mRNA is involved in events subsequently caused GDNF. RJ may play neurotrophic and/or neuroprotective roles in the adult brain through GDNF[77]

Recent brain research has elucidated the mechanism of action for the RJ effects on the CNS. A unique RJ component, cAMP-N_1 oxide, not found in any other materials, acts directly on neuronal differentiation and stimulates the formation of different brain cells [79]. RJ facilitates also the differentiation of all types of brain cells: neurons, astrocytes, and oligodendrocytes [80]. It also RJ ameliorates neuronal function by regenerating hippocampal granule cells that function in the cognition process [84]

Royal jelly may be a promising agent for the activation of neural stem cells in a mature brain expected to differentiate into neurons or glial cells. Recent investigations clarified a relationship between the neurogenesis in the dentate gyrus of the hippocampus and the symptoms of depression, expecting efficient use of royal jelly to

activate neurogenesis. Reduction of neuronal death and an increase of neurogenesis in Alzheimer's disease and Parkinson's diseases may be also supported by royal jelly, although a detailed animal experiment is necessary[63].

To prove the pharmacological actions of honeybee royal jelly (RJ) on the nervous system, the effects of RJ on CRE-mediated transcription.RJ increased CRE-mediated transcription in PC12D cells were examined. Moreover, CRE-mediated transcriptional activity by RJ was enhanced by nobiletin. U0126, a MEK inhibitor, inhibited CRE-mediated transcription by combining RJ plus nobiletin without affecting transcription by RJ alone. These results suggest that RJ stimulates CRE-mediated transcription via an ERK-independent cascade, whereas the increasing CRE-mediated transcriptional effect by nobiletin is dependent on ERK phosphorylation[61]

Table 3: **Biological and pharmacological effects of royal jelly in animal and cell culture experiments**

Effect	**References**
Antibacterial, fungicidal, antiviral, antiparasitic effects	
Antibacterial	1, 9, 62, 88, 89, 137, 238, 276, 285
Fungicide	238 ,
Antiviral	43, 238
Active against various parasitic *Trypanosomidae*	153
Bio stimulatory effects, anti-aging	
Estrogenic and gonadotropic effects in cells and in rats	87, 173, 242
Increases growth and weight of chickens, turkeys, ducks, rabbits, guinea-fowls, pigs, calves, guinea pigs, mice and rats	18-27, 36, 40
Anti-fatigue, increases activity improves its resistance to stress	87, 108, 131
Increases reproduction capacity of rats and sheep	92, 93, 127-129
Increases oxygen consumption in tissues in vitro, antihypoxia	68, 131, 205
Against infertility of male rabbits, improves sexual efficiency in rats and hamsters	49, 78, 122
Life-prolonging in mice and other organisms	90, 95
RJ fed mice have higher sperm motility, higher sperm concentration and lesser sperm abnormality	111
Prevents the progression of Sarcopenia in aged mice	187
Testis protective effects in rats	41
Immuno-modulating effects: anti-cancer, anti-allergy and anti-inflammatary	
Immuno-stimulating activity in animals or in cell cultures, increase of leucocytes count	5, 50, 65, 131, 133, 163, 189-191, 231, 243, 270, 272, 280, 281
Anti-tumor effects in cell culture and animal experiments (ingestion or injection)	15, 42, 45, 184, 194, 195, 247, 257, 260
Inhibits autoimmunity in mice	162
Anti-inflammatory in cell culture tests	123
Increases antiapoptotic activity of hepatocytes and tubular epithelium	112
Cardiovascular effects	
Anti-hypertenisive, hypotensive, vasodilatative effects in animals	6, 134, 166, 228, 254, 255
Anti-atherosclerosis: reduces serum cholesterol and triglycerides levels, increases HDL levels, lowers plasma fibrinogen levels and thrombosis	131, 135 39, 213, 227
Cardio-protective in animal experiments, prevents myocarditis	131
Increases blood levels of thyroxine, cortison albumin/globulin ratio and decreases serum proteins after oral administration in rats	36, 38
Increases number of blood cells	131 .
Effects on the central and vegetative nervous system	
Acts on central nervous activity, activates and protects it. Facilitates the differentiation of brain cells.	68, 79-81, 131
Increases phosphorilation of the CNS to increase of rat brain cholisterase activity	131
Acetyl-choline like effects on the intestine and on the innervation of the respiration smooth muscle	131
Tranquillisation of rats	36, 38
Diminishes secondary neuronal damage in rats	8
Improves the spatial memory in rats	211

Anti-oxidation, hepatoprotective, radioation-protective	
Anti-oxidative	37, 95, 100, 101, 182, 183
Hepato-protective in animal experiments	131
Reduces stress and terratogenicity, pulmonary oedema, hepatic or renal damage in rats due to intoxication with mycotoxins	48, 132
Activates stimulation of hepatocyte DNA synthesis and protects cells from apoptosis, mitogenic effect, prolongs cell proliferation, enhances albumin production.	106, 109, 189
Radiation-protective	67, 197, 198, 204, 271

Skin protection, antidiabetic, gastroprotection, osteoprotection and others	
Skin protection: promotes building of collagen in cell cultures and in rat model	124, 198
Suppresses the development of atopic dermatitis-like skin lesions in rats	248
Against skin itching in a mice model	282
Hyperglycaemic action, prevents insulin resistance, antidiabetic	34-36, 188, 192
Decreases experimental colitis in rats	110
Gastroprotective in a rat model	55
Prevents osteoporosis in rats and stimulates bone formation	86, 185, 267
Osteoinductive and anti-inflammatory effects in periodontal disease model	283
RJ topical application has a healing effect on oral mucositis in hamsters	240, 273
Restores the function of alcoholic liver diseases in a rat model	151
Against experimental oral mucositis in hamsters	274

Cardiovascular effects

RJ influences different blood parameters: reduction of serum cholesterol and triglycerides levels, increase of high-density lipoprotein-cholesterol levels, lowering of plasma fibrinogen levels and thrombosis (table 1). Due to these effects RJ caused cardioprotective effects in physiological and biochemical experiments with mice [131].

Experiments on the isolated heart showed that RJ increased the blood pressure of the heart chamber by 60 %, the maximum velocity of the myocard contraction by 22 and the maximum velocity of the myocard relaxation by 87 %. The coronary blood stream was increased by 42 % and the diastolic blood pressure was reduced by 20 %. These effects are explained by an increased synthesis of bio-energy, ATP in the heart muscle. On the basis of these experiments RJ can be recommended as a cardio-protectant. Krylov reports also on experiments in rats of positive effects of RJ in adrenaline-induced myocarditis [131].

Anti-hypertenisive, hypotensive, vasodilatative effects in animals has been reported by different authors (table 3).

RJ peptides have been found to have an anti-hypertensive activity[170]

Other effects

Different other biological effects have been also reported (table 3)

- Anti-oxidative and radiation-protective and hepatoprotective (liver-protecting
- Hyperglycaemic, preventing insulin resistance
- Stimulating bone formation and promoting bone healing in rabbits, preventing osteoporosis in rats
- Promoting building of collagen in cell cultures
- Suppressing the development of atopic dermatitis-like skin lesions in rats

ROYAL JELLY IN MEDICINE

Table 4: **Medicinal effects of royal jelly in humans**

Use	References
Pediatry: in premature babies or with nutritional deficiencies: improvement of general conditions, increase in weight, appetite, red blood cells and haemoglobin	39, 131, 161, 177, 210, 212, 219, 229
Geriatry: improves general condition and weakness of old people relief of menopausal problems,	44, 131, 155, 229, 244, 268
Against stenocardia and after heart infarct; arteriosclerosis and atherosclerosis; hypertension, hypotension	59, 73, 131, 200, 229, 268
Against respiratory diseases, asthma	131, 136, 229, 237
Against eye diseases, e.g. blepharitis, conjuctivitis and corneal burn, disturbed eye blood circulation;	131, 206, 250
Bio-stimulatory, improves physical performance of humans and resistance to hypoxia	131, 229
Improvement of memory, neuro- vegatative activation	131, 229
Against diabetes	131, 179, 217
Against cancer	105, 281
Against gastric, gastric and duodenal ulcer	98, 131
Improves regeneration of skin in wounds	66
Against degenerative rheumatism	64
Against warts, acne, ulcers, seborhoe, neurodermitis	136
Against renal disfunction	7

Royal jelly is especially popular in Asia, see Krell [126]. An important part of the clinical research comes also from Asia. However, most of the original Chinese literature, the biggest producer of RJ of the world, is not accessible to non-Chinese.

Having in mind the many different biological effects of RJ it is difficult to imagine specific medical effects. In the Western World there are only very few clinical studies with RJ. In more recent Eastern European monographs there are extensive descriptions of the clinical uses of RJ: Shkenderov and Ivanov, 1983[229] Ludyanski, 1994[155], Krylov and Sokolski, 2000[131], Asafova et al. 2001[7] and Krylov et al. 2007[130]. Many of the clinical applications described here are taken from these monographs, the original citations could not consulted as they are not accessible to the author. The majority of the cited studies are old and do not stand the criteria for modern clinical tests, i.e. double blind studies or with necessary controls. However they are carried out with a considerable number of patients and in some of the studies control treatments have been carried out.

Pediatry, nursing and geriatry

RJ activates a number of physiological processes and has a stimulating effect on biological growth. Thus its main medicinal use is in pediatry, nursing and geriatry (see tables below). It has a proven effect on the increase of weight of different animals supposes its use in young infants for the same purpose. In the references cited in the table, beneficial effects have been observed in infants with nutritional deficiencies and premature babies or: improvement of general conditions, increase in weight, appetite, red blood cells and haemoglobin.

Table 5 : **Royal jelly in pediatry and nursing**

Author, clinical test, disease	RJ intake, recommendation, results
Lebedeva, 1959, increase of weight and apetite of 1 year old children [138]	Intrarectal intake of 5 mg lyophylized RJ, 3 times a day
Fateeva and Rochal, [54] hypertrophy and lacking appetite of 4 month to 3 years old children	Intrarectal intake of 5 mg lyophylized RJ by smaller children and twice 10 mg sublingual intake by the older ones. 35 children were treated successfully: After 2-3rd day the children began eating, after 15 days the average weight increase was 200 g per day
Iliash[94], Vasileva[263]	Similar results for similar symptoms as above
Zweer[289]	Similar experiments but with a control group. 25 premature-born children, 30-60 mg RJ was given to the nursing mothers. 76 % of the children recovered, while in the control group the recovery was 46%. The lactation of the 61 % of the nursing mothers (n=93) was improved, while in the control group (n=100) the success rate was 16 %.
Zweer[290]	30 mg of dry RJ per day was given sublingually to nursing mothers having big blood losses during the birth. Within 8-9 days their blood haemoglobin was normalized.
Magdalena, 1965[157]. treatment of maldevelopment of breast infants	Comparing the effectivity of different RJ preparations to treat (fresh, lyophilised, RJ in honey) it was concluded that best results were achieved with fresh RJ
Popova, 1960[208]	RJ was also successfully used in the treatment of Herters intestinal infantilism (disturbance of nutrition in infants)
Destekina, Iliash 1974, after [130]	Successful use of Apilac in new born children with brain trauma
Dmitrieva et al. 1994 after [130]	Use of royal jelly in new born; positive development of the bactericide properties of the skin and elimination of bacterial infections
Gyuzikina 1993, 1998 [74, 75]	In a trial with premature born children with *Candidas* infections Apilac (contains 10 mg dry RJ) was given for 3 weeks the infections decreased, together with a good weight increase.
Mahmoud 1997[158]	RJ was given to premature babies in doses of 1 gr per day for 5 days. The babies had a higher weight gain and a higher blood glucose concentration (within limits) than the controls. The authors presume that RJ, and also honey, cause an increased appetite, and thus a higher assimilation of food.

Table 6 : **Royal jelly in geriatry**

Author, clinical test, disease	RJ intake, recommendation, results
Different authors, treatment of different geriatric diseases [44, 155, 268]	Effective in the treatment of arteriosclerosis, weakness and menopause
Vitek and Janci, 1968[229] treatment of poor blood circulation in the brain, local brain damages, Parkinson, astenic and chronic neurosis.	Summary of the experience of several authors treating with RJ different diseases typical for aged persons: 113 patients were examined. 71% of the cases had an improved condition while 13 % experienced complete healing. Best results were achieved in treating weakness while Parkinson was at least influenced.
Valiukiene et al. 1997[262], weakness	Intake by 23 volunteers 45 to 89 years old of Apilac tablets containing 70 mg lyophilised RJ, 2 times a day for 25 days: disappearance of dizziness and weakness, improvement of sleep etc. 74 % of the persons had a decreased cholesterol and triglyceride content, increased blood counts of immunoreactivity factors

RJ has been successfully used to improve the general condition and weakness due to old age. As sclerosis, weakness, menopause etc. In these treatments, the cardio-protective, anti- atherosclerosis and anti-arteriosclerosis

effects of RJ should also play a role. Fujii hypnotises that RJ gamma globulin and gelatine collagen are responsible for the anti-geriatric skin activating action of RJ[60]

Heart and blood circulation diseases

According to Krylov and Sokolsky and Krylov et al.[130, 131]*:*

Nemanov (1959) and Mistenko (1960) used RJ for a successfull treatment of stenocardia by sublingual ingestion of 10 mg dry RJ, 3 times a day for 2-4 weeks. The effect of RJ was gradual, complete healing was after 4 week, the effects are not immediate like that of nitroglycerine.

Nisov and Lupachev (1962) treat successfully stenocardia by treatment with Apilac, the effects are not immediate like nitroglycerine, they are explained the effect by the normalisation of the blood protein pattern.

Kadiseva (1962) report on a successful treatment of arteriosclerosis by treatments of 20-30 mg RJ daily for 40 days.
Zaitzeva and Poryadina (1962) report on the use of Apilac (10 mg dry RJ) twice a day for one month in arteriosclerosis patients. Best results were achieved in patients with initial forms of the disease. Kadiseva (1962) treated successfully arteriosclerosis patients by using 10 day Apilac treatments: initially increasing from 10-20mg, then from 20 to 30 mg, the final two periods decreasing 30-20 and 20-10.

Lupachev (1965) used 3 to 6 pills of Apilac per day to treat 80 persons more than 40 year old myocardial infarct patients, some of them with hypertension. Contrary to the action of nitroglycerine the heart pain was not extinguished, but its duration and intensity decreased. The author presumes an anti-spasmolytic action , increase of coronary blood flow and the positive neuro-vegetative effects of RJ to be the cause of the RJ action. The blood tension normalized and the blood parameters improved[156].

Okorokova and Fomina (1993) was used sublingually 200 dry RJ for 20 days, alone or in combination with anti-stenocardia agents like nitroglycerine. After 2-3 weeks the intake of nitroglycerine could be interrupted or the dose decreased by a factor of 2. The heart dynamic factors as arterial blood pressure and normalisation of EKG improved too.

Okorkov et al. (1993) report in two clinical studies: a) on stenocardia patients and b) of 42-55 years old women with neuro-vegetative-hormonal based myocardial dystrophy using RJ in combination with bee venom. The authors from the cardiology department of the university of Ryazan, Russia, explain the positive effects by the positive hormone-like effects and by the improved nutritional and functional supply of the myocard.

Lyusov and Meshteryakov (1994) compared the effect of RJ with other anti-stenocardia agents. 300 mg RJ per day was given to all patients with ischemic heart disease (first group) and stenocardia (second grop. As whole 76 % of the RJ treated patients had an improvement of the symptoms, best results with 86% success rate was in the group with stenocardia of the second functional class.

Fomina et al. (1998) report on a positive effect of RJ in the treatment of hypotony. 60 patients with blood pressures of 100/60 or less all improved their readings to values of 110/70 to 120/75.

According to Asafova et al.[7]:

Margavichene et al. 1988 tested the use of RJ (Apilac, 0.07 g) against ischemic heart disease (including angina pectoris) in 25 men, decrease of cholesterol was achieved only after 5 months.

Dudaev, Ljusov (1988) used RJ against the same disease (0.5 g RJ per day sublingually), resulted in decrease of cholesterol.

Ohotskyi and Kovrigonoi (1984) tested RJ (1-2 tablets of Apilac) in 2141 patients, 412 p. with coronary sclerosis 243 p with stenocardia, 49 p. after myocardial infarct, 384 p. with vegetative vascular dystonia and 384 p. with hypertension climacterium syndrome (men and women). The conclusion of the authors: the general conditions of patients with athero- and coronary cardial sclerosis with tendency towards vascular spasms improved, stenocardia attacks disappeared, the blood circulation in the limbs improved.

Ogorkov and Fomina (1994) used 10 g honey-royal jelly (2%) for 25 days to treat 20 women with vegetative myocardial distrophy of women in climacterium. Results: improvement of general condition, blood pressure stabilized.

Positive results on the blood arteriosclerosis and atherosclerosis parameters , cholesterol and triglycerides, were found by Kaczor et al. (1962)[104] and Vittek (1995)[266], in the latter studies cholesterol was lowered by 14 % in people with moderately high cholesterol levels.

A trial by Muenstedt et al. in 2009 failed to detect immediate changes of blood lipids after RJ intake[180].

Other diseases

Respiration diseases

According to Shkenderov and Ivanov[229]:
Vitek and Janci (1968) have reviewed 10 publications on the use of RJ against bronchial asthma: RJ was used sublingually in doses of 50 to 500 mg per day. Out of 311 patients 75 % showed improvement and the symptoms stopped for a longer time.

Matushevski et al. (1972) treated patients with bronchial asthma with 3 times a day 100-150 mg dry RJ sublingually, for one month. The condition of the patients improved, the eosinophil cell values were back to normal.

Petrov (1971) treated successfully 170 children with spastic bronchitis by aerosol inhalations with honey and RJ.

Diabetes

In 1956 a work on the antidiabetic effect of RJ was published[217]

RJ contains substances with anti-diabetes activity like 10 HDA and other fatty acids[192] and improves insulin resistence in fructose drinking rats[287]

Muenstedt et al. (2009) confirmed the RJ antidiabetic effects: twenty volunteers underwent the standardized oral glucose tolerance test (OGTT) and afterwards a second OGTT after ingestion of 20 g of native royal jelly. Serum glucose levels after 2 hours and the area under the curve for glucose were significantly lower (P = .041) after royal jelly administration. Substances originating from the pharyngeal glands of the honey bee with insulin-like activity are likely to have caused this effect and may thus be, at least partially, responsible for the lowering impact of honey on blood glucose levels [179]

Cancer

The anti-tumor effect being tested in children with accute leukaemia, lypmpoma and hepablastoma. RJ showed some positive results: gain of weight and improvement of the general condition of the chidren, together with increase of white blood cells, neutrophils and leukocytes. The authors concludes that although RJ can influence positevely cancer growth, it is not a drug and patients should not rely on RJ only for treatment of cancers [105]

In another test RJ stimulated the immunoglobuline production by lymphocytes and increased the anti-cancer factors IgM and IgG in patients with breast cancer [281].

A Russian study by Oveckin in 2004 reported on the successful palliative use of the preparation Apitonus (3 times a 100 mg RJ dose), alone or in combination with chemotherapy and radiation in patients with malignant duodenal ulcers, kidney and glandular cancers. RJ improved the life quality of the patients: their appetite improved and the pains decreased, reported in[130]

Gastroentorology

Mishtenko (1974) treated patients with gastric and duodenal ulcers and gastritis by 20-25 mg dry RJ 3 times per day for one month, patients being on a diet, a 1. control group on diet only 2. group with a diet and RJ 3. traditional medication and RJ. In group 1 (diet only) 41 % (40 patients) improved, 66 % of the group 2 patients (n=40) improved while in group three 88 % (130 patients) improved, cited by[131].

Wounds and cosmetics

Wounds and cosmetics

RJ has wound healing properties. Its major protein activates keratinocytes, involved in wound healing[160]. It inhibits the production of proinflammatory cytokinines, thought to play a role in skin inflammation[123], promotes the wound healing in diabetic mice[114] and heals foot ulcers of diabetic patients[230].

The antimicrobial properties, together with the proteins and fatty acids makes it appropriate for skin applications. In cosmetic preparations RJ prevents spots and wrinkles and moisturises the skin[251] A RJ extract increases the natural

moisturizing factor (NMF) by promoting the expression of profilaggrin in the skin, as well as by having a moisturizing effect on the stratum corneum[193]. RJ reduces melanine synthesis and is a good candidate for skin-whitening in cosmetics[76]

According to Krylov et al. [130] :

Somov and Abramova (1962) used a 5 % RJ aerosol, 2-3 times a day, against seborrhoea and other eczema-like skin inflammations. Many skin creams and lotions contain RJ. Malay et al. (1965) have used of GR against: warts (cream containing 1 % RJ). Smirnova (1960) has used 0.6 % RJ emulsion to counteract face dryness, to improve elasticity of the skin and to diminish pigmentation, to diminish fatty seborrhoea, to clean the oil glands. Omarov (1990) uses creams with RJ to tonify the face skin, to moisture its dry skin and to make it fresher.

Ophthalmology

According to Krylov et al. [130]:

RJ has been applied also: in ophthalmology: Maximenko (1975) has used a RJ preparation for the treatment of retina diseases connected with the disturbance of the eye microcirculation.

Nedelka et al. (1987-1990) used RJ, 1 % in methylcellulose glycerol) successfully against traumatic keratitis and lesions of the conjunctiva and the cornea. Nedelka et al. developed different preparations: drops, creams and soluble films. These results were confirmed by Takrovski (1974) and Tanev and Peitshev (1974).

The experience in Ludyanski's hospital:

The table below table summarises the different medical uses of RJ while in table the results of treatments with RJ against different diseases in Ludyanski's hospital[155]

Table 7: **Uses of royal jelly in a Russian hospital**

Treated disease	Cases Very good and good improvement	Cases with no improvement
Arteriosclerosis	27	6
Cerebral insufficiency	46	12
Climacterium	39	5
Hypertonia	21	8
Hypotony	16	5
Pediatric diseases	12	3
Poor blood circulation	35	11
Sexual disfunction (men)	26	5

Royal jelly for sexual disfunctions and good fertility?

RJ makes fertile queens out of infertile worker bees. Are there similar effects in vertebrates?
In Russian apitherapy RJ has been successfully used in women with climacterium and sexual disfunction, as mentioned by Ludyanski (see table above).

Zweer (1974) reported also on the the successful treatment of 100 women from 40 to 62 years with climacterium problems. After an intake of twice 20 mg RJ for 2 to 4 weeks the symptoms disappeared in the majority of the patients: hot flashes, sleeplessness and irritability disappeared, work capacity improved [291].

In a study on the use of RJ against sheep infertility [128] a study was cited, that RJ is used to increase the fertility of men and women[4]. In a book about infertility by R. Lewis, it is claimed that said to improve fertility in both men and women, in men by increasing the quality of their sperm, and in women by increasing the quality of their eggs[150].

An intravaginal application of mixture of honey and royal jelly was successful for treating male factor infertility (asthenozoospermia)[3], and also of treating female infertility by a collagen-like promoting action on fetal membranes[2].

As RJ has estrogenic and proven effects to increase animal fertility (see table 3) it could also influence positively human fertility.

TOXICITY, COUNTER-INDICATIONS AND PRECAUTIONS

Chronic toxicity

Krylov et al. [130] describes experiments of Vassiliva (1962) and Lupachev (1962, 1976) with animals: doses from 1 to 10 mg/kg per day cause a progressive weight increase stimulation, in a dose of 100 mg/kg the weight increase begins to become smaller and at doses of 1000 mg/kg there is a weight decrease in comparison to controls. The toxic effect at higher dose is abnormal morphology of the brain tissue of the animals. Spiridonov et al. found no cytotoxic effects for RJ on rat lymphoblast cells[236].

An injection of 1ml RJ per mice (about 50 g/kg) seem to be toxic, while a dose of 5 g/kg was not toxic and induced an increase of the weight of the lymphatic tissue[70].

The chronic toxicity of RJ upon ingestion should be further studied, while it seems that RJ ingestion might be toxic in relatively low doses

A good therapeutic index means that the safety factor between the therapeutical and the toxic dose is at least 500 (for most synthetic drugs the TD lies between 3 and 100). In humans a safe dose with a therapeutic index of 500 corresponds to 2 mg RJ per kg, and a therapeutic index for a 75 kg individual this being 150 mg RJ per day. Increasing of this dose to 750 mg per day, RJ will still have an acceptable therapeutical index of 100.

Allergy

During the last 10 years there are several publications, reporting cases of allergy following the applications of RJ. Asthma and anaphylaxis have been reported in rare cases [46, 69, 201-203, 253], as well as one case of skin contact dermatitis [245]. These reports are mostly from East Asia, where RJ is consumed more often, while allergy cases in Europe are much less frequently reported. According to an epidemiological study in Hong Kong with 1471 normal persons the allergy prevalence is 6.1 per 1000[148]. Patients with a risk of RJ allergy have often an allergy towards bee venom and are atopic (show immediate allergy reactions)[149]. On the other hand, an epidemiological study in Russia with 640 no cases of RJ were encountered[235].

RJ should be used as a food-ingredient or medicine only after an allergy test. In persons with a history of allergies or with asthma, taking royal jelly has caused bronchial spasms, acute asthma and anaphylactic shock. It is therefore imperative that anyone who is considering supplementing with royal jelly consults with a physician before its use, especially those who are allergic to bee stings, honey, or who have asthma. People with bee venom allergy, asthma and with a high incidence of allergy should avoid RJ intake. A special caution should be noted for pregnant and/or lactating women as well as for pregnant and/or lactating women as well as for small children.

The major royal jelly proteins 8 and 9 are glycosylated components of Apis mellifera venom with allergenic potential beyond carbohydrate-based reactivity. They have IgE-sensitizing potential in BV-allergic patients beyond are allergens, which might be potentially important for a fraction of venom allergic patients[16]

The hypoallergenicity of alkaline protease-treated RJ in vitro and in vivo was tested: the treated RJ contained the same levels of vitamins, minerals and specific fatty acid as in untreated RJ. Also the IgE-binding capacity of the treated RJ was very significantly reduced by conducting in vitro assays of the blood from RI-sensitive patients. An in vivo skin-prick test on the RJ-sensitive patients also showed that, in the majority of the patients (3 out of 4 tested), the treated RJ did not evoke any allergenic response. It is thus advantageous to prepare hypoallergenic RJ by a protease enzyme treatment for its safe consumption[176]

HEALTH CLAIMS FOR ROYAL JELLY

According to the EU Regulation 1924/2006 [52] different health claims can be made.

1. Diet-related cardiovascular disease

Long term ingestion of royal jelly can improve cardiovascular health, concerning the drop of the blood cardiovasuclar disease risk factors blood lipids and cholesterol

2. Physical performance and fitness

Intake of royal jelly can improve the performance and fitness, especially of elderly people (anti-aging)

3. Diet-related cancer

Intake of royal jelly can reduce the risk for cancer

4. Mental state and performance

Intake of royal jelly can improve the mental state and physical performance. These effects are especially significant in older people (anti-aging effect).

APPLICATION FORMS AND INTAKE

Storage and shelf life of the product

Freshness has been attributed a great importance for RJ quality. Royal jelly can be spoiled easily if not properly stored. Immediately after harvest it should be placed in dark vessel and stored 0 - 5°C. Stored under these conditions its quality remains OK for half an year. Deterioration of royal jelly can be prevented by storing RJ in Argon after harvesting[102]. After longer storage it will turn rancid. Frozen royal jelly can be lyophilised as it can be transported more easily in the dry state. If frozen, it can be stored for 2-3 years without loosing of its quality. Chauvin states that the physical properties of RJ change after 20 hours after harvest, if left at ambient temperature [38]. That means that RJ should be stored in the cold immediately after harvest. According to Chauvin RJ the biological properties of RJ in what regards its capability to induce hyperglycaemia, remain intact only for 1 month, if stored at about 4°C. On the other hand Krylov tested whole RJ, stored for one year at 5 °C and found out that its antimyocard activity, measure was not different, in comparison to fresh RJ[131]. Recently it was also shown that only storage of RJ in frozen state prevents decomposition of biologically active RJ proteins[152].

On the other hand, storage experiments of fresh RJ and FTIR measurements of protein degradation showed that after 21 months of storage at -20°C the protein begins to decompose. When RJ is stored at 4 °C RJ should be stored for a maximum of 7 weeks[249]

Experiments have shown that the enzyme glucose oxidase enzyme contained in RJ is influenced both by storage temperature and time[10, 28]. At 4°C there was small reduction of enzyme activity, while at 20°C it decreases significantly after one month and degrades completely after one year[28]. At 37 and 50°C this decrease is faster[11]. The determination of glucose oxidase is analytically very simple and thus within the capabilities of all laboratories. This method could be used to evaluate the product's freshness; however, further investigation must first be conducted into the natural variability of this component in the fresh product.

Recently it was proposed that furosine content can be used as a marker for RJ freshness[164]. The initial content of this compound is very low in fresh royal jelly. Specifically, the content rose to as high as 500 mg/100g of protein after 18 months' storage at room temperature and 50 mg/100g at 4°C. Samples taken from store shelves showed values ranging from 40 to 100 mg/100g protein. The value of furosine, a product of Maillard's reaction, proved very low (from 0 to 10 mg/100g of protein) in freshly produced RJ samples but increases over time and in relation to temperature. A limit of 50 mg furosine / 100g protein could be used for fresh RJ. A specific RJ protein, decomposing upon storage can also be used as a freshness marker[107]. A cheap and fast method based on a chromogenic reaction of RJ and HCl has been proposed[288].

Improvement of storability

From the above findings it is clear that RJ is an unstable product. Freeze drying is the most important technological method in order to improve the storability of RJ. However, there is a loss of volatile substances, as reported by Vahonina, 1995 in [32]. Stabilisation can be achieved by mixing 1 to 2 % of RJ into honey, where all enzymatic activity is stopped.

As reported in[32] the Russian Braines found out in 1968, that RJ can be bound to a mixture of lactose and glucose, which improves its durability. In Russia RJ is often offered in such lactose-glucose pills under the name of Apilac. The method of Braines was improved as follows: Six part of frozen RJ are added to one part of dried glucose-lactose (1:1), then the mixture containing 50 mg/kg L-ascorbic acid as an antixodant is dried until 4 % humidity. This product is stable at 4 to 8 ^{0}C for 2 years[31, 32].

Shelf life

Fresh royal jelly:

- 6 months, if stored in the refrigerator (3 to 5 ºC)
- 2 years if stored in the freezer (< - 18 ºC)

Lyophylised royal jelly

- One year if stored in the refrigerator (3 to 5 ºC)
- At least 2 years if stored in the freezer (< - 18 ºC)

Fresh or lyophylised royal jelly in honey

- Two years at room temperature, if honey-RJ total humidity is less than 18 %.

Application forms

Royal jelly is used in different forms: as raw royal jelly (alone or in combination with honey and other bee products, as alcohol extracts in ampules), in lyophylised form or as pills. Most of the natural RJ is stored in frozen state before selling. Whole fresh royal jelly loses its biological activity upon storage at 40 ^{o}C for seven days[108] It is packed often in small, closed, dark coloured bottles, containing 10, 15 or 20 g. Spoilage due to sun light and oxidation is thus prevented. Royal jelly is consumed together with honey or as pills. RJ can be ingested sublingually or directly ingested. Injections are no longer used because of allergy problems.

The daily ingestions dose for adults used in the different studies varies between 10 and 500 mg of fresh royal jelly per day, most human studies are carried out with doses of 20 to 200 mg daily

For apitherapy higher doses are recommended: children 20-100 mg/day; adults: 200-500 mg/day

All apitherapy applications of royal jelly should be carried only after consulting a doctor and testing for an eventual allergy People with bee venom allergy, asthma or with a high incidence of allergy should avoid RJ intake. A special caution should be noted for pregnant and/or lactating women as well as for pregnant and/or lactating women as well as for small children.

Royal jelly in honey

For mixing fresh RJ consider honey with a low humidity, lower than 16 % water, in order to prevent spoilage by fermentation. If freeze-dried RJ is added to honey to achieve a higher RJ concentration, crystallised honey with low water content should be used, in order to prevent rising of RJ to the surface. The RJ honey should be stored at lower temperature. One table spoon of about 20 g 1 % RJ in honey of it will contain 200 mg fresh RJ, which equals the recommended dosage per day. It has been reported that HDA content of RJ-honey products decreases upon storage [51]. Thus these products should be stored also at cool temperatures or frozen for optimum activity. In Asia RJ is often an ingredient of beverages.

Higher doses can be achieved my mixing directly freeze dried RJ in honey. Until 5 % of FDRJ in honey can be achieved with an acceptable sour taste of the mixture.

Royal jelly bound in lactose-glucose pills

According to Burimistrova, the storability of fresh RJ can be improved, similarly to the one of FDB by binding RJ to a glucose-lactose adsorbent according to the following manner: 6 parts of FRJ are added to one part of dried glucose-lactose (1:1), the mixture containing 50 mg/kg L-ascorbic acid as an antixodant, the mixture is dried until 4 % humidity. This product is stable at 4 to 8 ^{0}C for 2 years[31, 32].

Cosmetics

RJ is often used as an ingredient of cosmetics or for skin application for treatment of burns and other wounds. It is usually included in small dosages (up to 1 %) but it deteriorates quickly. The freeze-dried form should be used because it is easier to handle and is more stable.

Facelifting cream with RJ (found in www.royalbeejelly.net):

- 80 grams of blended oil; 45 grams of cocoa butter; 15 grams of beeswax; 1,5 dcl of water; 10 grams of fresh royal jelly
- Melt the oils and wax at low heat, stir for 12 minutes, remove the melted liquid from the stove and add water, mix with a mixer (handy one) until it gets creamy like – smooth, poar into a glass, cover and store on a dark place. See recipes for other RJ cosmetic products in Krell[126]

BEE BROOD FOR NUTRITION AND HEALTH

Composition and nutritional requirements

The composition of fresh bee larvae has been studied only by Finke[56], while the composition of powedered bee larvae is studied by Narumi[186]. There is quite a good agreement for the bee larvae composition between these two studies excepting for biotin content. Bee larvae could be used in bigger quantities as a part of the food diet, especially as a protein source, especially rich in essential amino acids (tables 7 and 8). The fatty acids are mostly saturated (52 %), monoansatturated acids being 46 % and poly-unsatturated acids only 2 % three primary fatty acids are oleic, palmitic and stearic acids. Indeed, the greater part of the protein is composed of amino acids. Of all amino acids only sulphur amino acids methionine and cysteine are lacking. If consumed in a quantitiy of 50 to 100 g daily, it can be a good source of vitamine C, choline, inositol, and most of the B vitamins, while it contains no detectable levels of fat-soluble vitamins. It is also a good source of minerals, from all trace elements the content of Selenium being most noteworthy.

Budnikova (2009) found that fresh drone brood contains 2.73 % 10-HDA 8 nMoles/l testosterone and 2745 nMoles/l estradiol[30].

Table 8: **Composition of bee brood compare to that of beef and soybean**, after [126]

Component	larvae	pupae	beef	soybean
Water	77	70.2	74.1	70.0
Protein	15.4	18.2	17.7	12.9
Fat	3.7	2.4	2.8	5.9
Glycogen*	0.4	0.8	0.1-0.7	2.4

*- glycogen (a carbohydrate polymer) was determined instead of sugar, contained as 9 % of total, which originates from honey rests.

Besides a possibility to be used as food for its protein content, it could also have similar effects as RJ. However, there are very few published works. Italian psychiatrists observed improvements in respect to the appetite, body weight, hepatic activity, digestion and haemopholetic functions of 15 female psychiatric patients who were suffering from loss of weight and appetite [175].

Drone brood, after addition of a little propolis, was desiccated under vacuum until 99 % dry matter concentration. The product kept the original biological properties, measured by its immunomodulating, spleen and T-cell stimulating properties[209].

Table 9**: Main components of fresh** [32, 56] **and powedered bee brood**[186]

Component	Fresh g/100 g	Powedered g/100 g	RDI g
Water	76.8	4.5	
Proteins total	9.4	52.3	48-56
(Amino acids)	7.9	57.7	
Lipids	4.7	21.9	
Fatty acids	4.0		
10-HDA	3.3		
Carbohydrates	8	17.8	300-340
Fiber content	0.5		
Ash content	0.8	3.5	

Table 10: **Secondary components of fresh [32, 56] and powedered bee brood**[186]

Component	Fresh	Powedered	RDI
Vitamins	mg/kg	mg/kg	mg
Vitamin A (IU/kg)	< 1000		
β-Carotene	< 0.2		
Vitamine E (IU/kg)	< 5		
Vitamine C	38		
Vitamine B_1 Thiamine	4.1	16.9	1.4
B_2; Riboflavin	9.1	31.2	1.6
B_3; Niacin	36.7		18
Folic acid		0.93	0.4
B_5; Pantothenic acid	11.9	51.5	6
B_6; Pyridoxin	1.2	1.8	2
B_{12};Cobalamine	< 1.2	0.31	6 µg
H; Biotin (µg/kg)	0.23	776	30 µg
Choline (g/kg)	1.68	6.9	0.5
Inositol (g/kg)		10.5	30 mg
Minerals	**mg/kg**	**mg/kg**	
Sodium	128	423	2400
Potassium	2690	10400	3500
Magnesium	211	816	350
Calcium	138	446	1000
Phosphorus	1790	8040	1000
Iron	16	63.2	15
Manganese	0.6	3.3	5
Copper	4	16.9	2
Selenium	0.06	0.12	35 µg

Table 11: **Hormones in fresh royal jelly and fresh drone brood**[32]

	Fresh royal jelly	**Fresh drone brood**
	nmoles /100 g	nmoles /100 g
Testosterone	0.20 ± 0.03	0.31 ±0,015
Progesterone	4.61 ± 0.26	51.32 ± 8.69
Prolactine	70.8 ± 20,0	410.0 ± 65,4
Estradiol	52.0 ± 6,0	677.6 ± 170,3

Besides these hormones Burismistrova reports on Chinese studies by Li et al. (1982) and Pan Jian-Guo (1995) that DB contains also the typical bee hormones prothoracicotropic hormone (PTTH), juvenile hormone and ecdyson.

Osintzeva et al. (2009) tested a drone brood (DB) homogenate by feeding 15 mg per kg to 2 years old dogs 20 min. before the regular feeding. The dogs ate voluntarily the DB. Blood was tested before and 30 days after intake. : Thyroxin and Tri-iodothyronine concentrations increased by 40 %, while thyreotropic hormone (Th) concentration decreased by 37 %, increase was measured in total blood proteins increased by 12 %, triglycerides by 99 %, high density lipoproteins by 12 % and low density lipoproteins by 94 %. The weight increase was 92 % higher than that of the controls[196].

Bee brood for human consumption after Krell[126]

Gather larvae by cutting them out from the combs. Refrigerate or freeze or eat immediately. If larvae are refrigerated immediately, freezing, drying, boiling or frying should be completed less than 24 hours after collection of larvae to avoid any spoilage since insect proteins decay much faster than those of beef, chicken, lamb or pork.

Where no refrigeration is available, processing will have to be started immediately after collection. If there is no freezer or refrigerator, the boiled larvae should be consumed within a day. Fried larvae will keep a little longer.

See more information on bee brood in Krell[126]

Bee brood in lactose-glucose pills

According to Burimistrova, the storability of fresh bee brood can be improved, by binding fresh BB to a glucose-lactose adsorbent according to the following manner: 6 parts of BB are added to one part of dried glucose-lactose (1:1), the mixture containing 50 mg/kg L-ascorbic acid as an antixodant, the mixture is dried until 4 % humidity. This product is stable at 4 to 8 ^{0}C for 2 years[32].

Biological action

Burimistrova carried a series of biological experiments. DB shows antibacterial activity, but it is weaker than that of RJ. Mice were fed with: normal feeding without additives (control), with and 10 and 20 mg/kg DB or RJ and were subjected to daily swimming. The animal size of the DB fed mice and the swimming capabilities were less pronounced than after the feeding of the same quantities of RJ, but bigger than the controls. The author concludes that DB has a less pronounced activating and autoprotective activity than RJ, but these activities are more pronounced than the control non treated animals. On the other DB has a more pronounced gonadotropic activity than RJ, allowing the rehabilitation of blood concentration of testosterone and fructose[32].

Belyaev and Sofonkaya (2009) tested a liquid drone brood by feeding rabbits by intraoral intake of 0.6 ml/kg every 48 hours (controls treated with gelatine). The thiobarbituric reactive substances (a mass for lipid peroxidation and oxidative stress) decreased by 26 %, while that of the controls increased by 25 %, serum sialic acid concentration (a mass of the cardiovascular mortality risk) decreased in the treated groups decreased by 20 % while the controls it increased by 24 %. The experiments showed a decrease of oxidated reaction products in blood and increase of the cell resistance of the DB treated rabbits. In a second series of experience the endurance of the animals under stress condition was tested by giving 0.015 ml per mouse (controls fed with gelatine) and testing the animals for active swimming after 10 days intake. The endurance of the controls increased by 9 %, that of the DB treated group by 35 % in comparison with the beginning of the test[12].

Apitherapy

In Romania a drone brood preparation Apilarnil based on drone brood has been developed and used. It is based on freeze dried drone brood. A Romanian book by N. Iliesu: “Apilarnil – health, power and long life” was published in 1990. Apilarnil is used as a biostimulator for similar conditions as royal jelly: for rehabilitation and activation of the aged people, against neuro-vegetative and sexual problems.

In the Russian book “Theory and agents in apitherapy”, written by a group of Russian scientists, applications against chronic gastric ulcers and liver insufficiency are mentioned, mainly Apilarnil use in Romania. Also Romanian studies of the use of Apilarnil are cited: Ardelianu et al. 1983, reporting on successful use in elderly people with psycho-neurotic sympoms and climacterium related symptoms [130].

Allergy

In a study in Russia the incidence of allergy towards DB application was 2.4 % (n=41)[235]

You can find more information on the production, collection and quality and applications forms of RJ in the Royal Jelly Chapter One on **www.bee-hexagon.net**.

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