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Reviews

Effect of Royal Jelly on serum lipids in experimental animals and humans with atherosclerosis

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Abstract. The primary objective of this review was to assess the size and consistency of Royal Jelly (RJ) effect on serum lipids in experimental animals and humans. The data from animal studies were pooled, where possible, and statistically evaluated by Student's t-test. Meta-analysis was used for the evaluation of human trials. It was found that RJ significantly decreased serum and liver total lipids and cholesterol levels in rats and rabbits and also retarded the formation of atheromas in the aorta of rabbits fed a hyperlipemic diet. Meta-analysis of the controlled human trials of RJ to reduce hyperlipidemia showed a significant reduction in total serum lipids and cholesterol levels and normalization of HDL and LDL as determined from decrease in β/α lipoproteins. The best available evidence suggests that RJ at approximately 50 to 100 mg per day, decreased total serum cholesterol levels by about 14%, and total serum lipids by about 10% in the group of patients studied.
Key words. Royal Jelly; serum lipids; serum cholesterol; atherosclerosis; humans; rat; rabbit.

Introduction

Hyperlipidemia results from an abnormality of plasma lipid metabolism and occurs as a consequence of genetic factors and/or various environmental factors such as diet[16,46,47,52,67]. Hyperlipidemia is considered to be one of the major risk factors for atherosclerosis[3,16,46,47,67], which is the most common of the human arteriopathies that cause intimal thickening[3]. It is, however, a polymorphic condition in both human and animals, whether naturally-occurring or in its experimentally-induced form[3]. Among other factors, an increased serum cholesterol has been implicated as an important risk factor for the development of human atherosclerosis[52]. There is a close relationship between coronary atherosclerosis and coronary artery disease, a major cause of morbidity and mortality[33,41].

The study of therapeutic intervention to prevent or to bring about the regression of atherosclerosis has been a major part of atherosclerosis research in the past half century. The evidence of regression and stabilization of atherosclerotic disease comes from both animal studies and clinical trials of various lipid-lowering therapies[3]. The initial regression study was done by Anitchnikov[1,2] 50 years ago in rabbits. Since then many studies have been done with a variety of experimental animals[3]. Cholesterol was again found to be a principal lipid accumulated in atherosclerosis and the principal lipid lost during regression of the lesion[3,13].

Within the spectrum of changes induced in cholesterol-fat arteriopathy in experimental animals, the most advanced and severe lesions may be similar or even identical to the lesions found in clinically significant human atherosclerosis. Furthermore, myocardial infarction, due to experimental coronary atherosclerosis induced by diet[59], and gangrene following peripheral atherosclerosis[60], have both been reported. As a rule, lesions in animals are less advanced than in humans and bear the special features noted in hyperlipidemic humans[3]. The human atherosclerotic lesions develop over decades of life, unlike the experimental lesions that are induced during the period of months or, in the most prolonged experimental investigations, a few years. The factors underlying the occurrence of atherosclerosis in humans are often multiple rather than single, unlike experimental atherosclerosis induced by marked hypercholesteremia[52].

Numerous studies[3,7,16,26,28,40,41,53] have shown that intensive lipid-lowering therapy reduced the frequency of progression of coronary lesions, increased the frequency of regression, and reduced the incidence of cardiovascular events. Reduction in cholesterol and systolic blood pressure correlated independently with less progression and more regression of coronary lesions and also improved vascular function and the stability of atheromatous vascular lesions[7].

Published reports in various medical journals during the past 30 years have suggested that Royal Jelly (RJ) may be effective in the prevention of experimental atherosclerosis[8,29] and be a useful medication in the treatment of atherosclerosis in humans[5,10,12,13,21,22,30,34,42,43,56,62,65,68].

RJ significantly influences lipid metabolism in rats[32] and prevents development of atherosclerosis in rabbits fed a cholesterol-rich diet[8,29]. Moreover, RJ significantly affects lipid metabolism in humans, decreasing serum cholesterol by as much as 25%, total serum lipids up to 15%, cholesterol/phospholipid quotient to 24% and lipoprotein beta/alpha quotient to 61%[10,13,14,45,64]. In addition, various beneficial effects of RJ have been shown, such as decrease in serum uric acid[56], euglobulin/lysis time[30], and decrease in blood pressure[35,42], normalization of ECG (increased T and normalization of ST segment in patients after MI)[4], and subsequent enhancement of physical well being of treated patients by diminution of stenocardia and other symptoms of atherosclerosis[4,12–14,30,35,39,42–45,49,56,65,66].

While all previous studies have suggested a beneficial effect of RJ no review has summarized the size and consistency of RJ effects on serum lipids and cholesterol levels in animals or human trials.

Methods

The literature was searched to find all animal and human studies that examined the effect of RJ on the cardiovascular system with special emphasis on lipid metabolism and atherosclerosis. This was done for the years from 1950 to 1994 inclusive, using a computerized literature search (MEDLINE) and by an assessment of the bibliographies of published studies and reviews[49,64–66]. Of the initial 41 articles identified, 17 experimental animal studies and 24 human studies dealt with RJ effects on the cardiovascular system and/or lipid metabolism. From the experimental animal research five studies were included in the evaluation of lipid metabolism and experimental atherosclerosis under RJ treatment. All human studies, which did not provide enough data to calculate effect size, were excluded. From 24 studies only nine were used for evaluation of effect sizes, and only five for meta-analysis of serum lipids and cholesterol.

The data from animal studies were pooled, where possible, and statistically evaluated by using Student's t-test. The statistical technique used to estimate the magnitude and direction of RJ effect on serum cholesterol and lipids was computation of effect size by meta-analysis[19,37]. The effect size was computed as the difference between the RJ treatment and placebo groups. For each study, a treatment effect size and 95% confidence interval (CIs) were calculated. Each study contributed to the pooled estimate a weight that was inversely proportional to its variance. Variance was defined as the square of the standard errors (SE) of the difference in cholesterol changes between the RJ and placebo groups. The standard deviation (SD) terms for the change in cholesterol in trials[42,64] were estimated from the initial and final mean cholesterol SD reported in each trial, and from the computed correlation coefficient between initial and final cholesterol values obtained from the raw data provided.

A sensitivity analysis was done by relaxing our inclusion criteria to include studies without adequate control groups. Nine trials[12,13,21,30,42,43,56,64] were included in the pooled sensitivity analysis. Effect size estimates were calculated for these nine studies. Effect size estimates were also calculated for the RJ treatment arms of each study included in the primary analysis. To compute the pooled estimate of treatment effect t-values from the original data were also used. Test of homogeneity and visual display were done.

Other data, i.e. phospholipids, cholesterol/phospholipid quotient and lipoproteins were calculated from the difference between the RJ and placebo groups and expressed as % increase or decrease.

Results and discussion

Hypolipidemic effect of Royal Jelly and its role in prevention of experimental atherosclerosis

Several authors have studied the effect of RJ on lipid metabolism and experimental atherosclerosis[9,29,32,36,38]. In an experiment with 296 male rats Makarova[32] found that intradermal injection of RJ (Apilak) in concentrations of 0.1, 1.0 and 25 mg/kg significantly decreased serum and liver cholesterol ($p < 0.001$) with the simultaneous rise in serum phospholipids over a period of 20 days (fig. 1). In addition, RJ decreased cholesterol lecithin quotient from 0.8 to 0.5. These effects of RJ were proportional to dose and the period of its use. Moreover, the author concluded that 1 mg of RJ/kg body weight given for 10 to 15 days is optimal and sufficient to cause these changes in the rats.

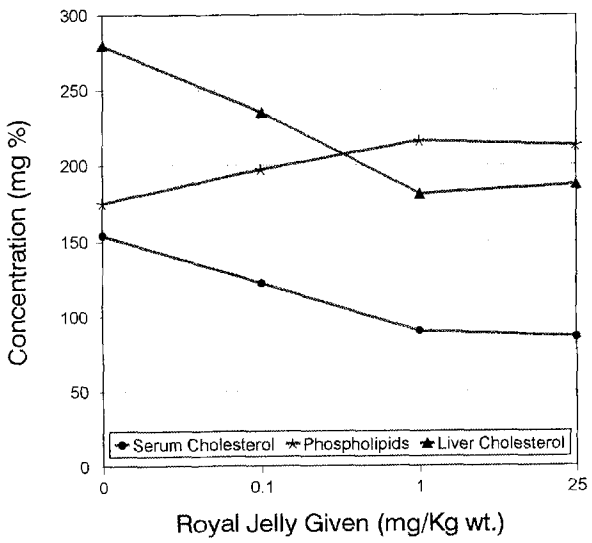

Figure 1. Relationship between the dose of Royal Jelly used and serum and liver concentrations of cholesterol and phospholipids in rats. All results are statistically significant ($p < 0.001$) when compared to controls. Compiled from Makarova[32].

Table 1. Effect of Royal Jelly on serum cholesterol in rabbits fed hyperlipemic diet.

Diet/treatment dose and duration	N	Serum cholesterol		Authors
		mg/dL	% difference	
Hyperlipemic only	4	$1.780 \pm 87^{+}$	0	Nakajin et al. [38]
+ RJ				
100 mg/kg inj. 7 weeks	4	1.350 ± 120*	−24	Nakajin et al.[38]
200 mg/kg inj. 7 weeks	4	1.025 ± 151**	−42	Nakajin et al.[38]
Hyperlipemic only	7	2.386 ± 253	0	DeCarli et al.[9]
+ RJ				
5 mg/kg inj. 11 weeks	7	2.607 ± 273	+9	DeCarli et al.[9]
10-15 mg/kg oral 11 weeks	11	1.550 ± 165***	−35	DeCarli et al.[9]

* = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.0025$; $^{+}$ = mean + SEM (Standard error of the mean); N = number of animals used.

Results from two independent trials[9,38] with rabbits fed hyperlipidemic diet for 90 to 100 days showed a significant decrease in serum cholesterol of up to 42% (table 1). While serum phospholipids, triglycerides, free fatty acids, β-lipoproteins and serum and liver total lipids also decreased in RJ-treated animals, these differences were not statistically significant[38]. It is of particular interest, that 10 to 15 mg of RJ/kg body weight given orally had a similar effect as that of 100 and 200 mg of RJ/kg body weight given by injection. This finding is similar to that obtained in rats by Makarova[32], when the effect of RJ did not differ significantly when 1 or 25 mg of RJ were given. In the present trials, however, the different response to various doses was probably due to a different preparation, and/or different diet used.

Liver cholesterol also decreased significantly in RJ-treated animals when compared with controls (from 41.1 ± 8.3 to 15.0 ± 3.9 mg/g or 64% ($p < 0.05$)[38] Moreover, fatty changes in the liver of rabbits fed a hyperlipemic diet together with RJ were negligible when compared to rabbits fed a hyperlipemic diet without RJ (8.3% and 67.5% respectively)[9]. These results suggest that RJ influences metabolism of fat in the liver and its excretion.

Rabbits fed a high cholesterol diet (1 g cholesterol/kg body weight) for 92 day with 50 mg of RJ/day, or with 15 mg/kg in the diet, had lower deposition of lipids in the aorta when compared to controls without RJ in the diet (5.39 ± 0.32 and 7.47 ± 1.15 mg/100 mg of aortal tissue respectively, $p < 0.05$)[29]. As shown in figure 2, the content of lipids in the tissue was in good correlation with the development of atheromatous lesions in the aorta[29]. The microscopic evaluation of the aorta revealed that RJ retarded lipid deposition mainly in the intimal region and to a lesser degree in the median region of the aortal wall[29].

A summary of the data on the effect of various concentrations and forms of RJ on development of atheromas in the rabbit aorta (table 2) from two independent studies[9,29] indicates that RJ significantly ($p < 0.0005$) retarded the development of atheromas in the aorta of rabbits fed a hyperlipidemic diet over 90 to 100 days of trial. Both injectable (5 mg RJ/kg wt) and oral (10 to 15 mg/kg of RJ/day) forms of RJ were equally effective. According to DeCarli et al.[29] rabbits fed hyperlipemic diet alone developed significantly more atheromas. The process was not substantially influenced by the use of Clofibrate (20 mg/kg) in the diet. Herapin (3 mg/kg i.m. injection) had some beneficial effect in retarding this atheromatous process. In contrast, RJ by all forms of application significantly retarded the development of atheromas in the aorta when compared to controls (45.5% and 91.6% respectively). Moreover, retardation of the atheromatous changes in the arteries of RJ groups corresponded well with the retardation of narrowing of the ocular arteries (37.5% in RJ and 67.5% in the controls).

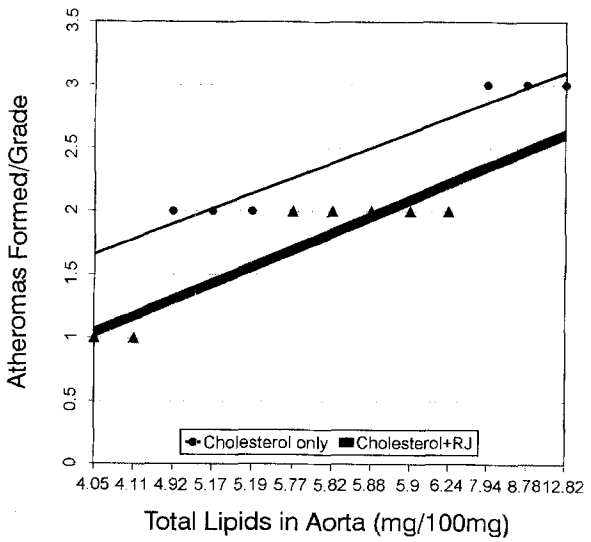

Figure 2. Relationship between total lipid in the aortal tissues and the incidence of atheroma in rabbits fed high cholesterol diet with Royal Jelly (triangles and thicker line) and without (closed circles and thinner line). Compiled from Madar et al.[29]

Table 2. The effect of Royal Jelly on atheroma formation in rabbits fed hyperlipemic diet.

Diet/treatment	N	Atheromas formed grade	Authors
Hyperlipemic	6	$2.50 \pm 0.20^{+}$	Madar et al.[29]
	7	2.29 ± 0.30	DeCarli et al.[9]
	13	2.38 ± 0.25	pooled data
Hyperlipemic/Royal Jelly			
5 mg/kg inj.	7	1.43 ± 0.20**	DeCarli et al.[9]
10–15 mg/kg oral	7	1.71 ± 0.30**	DeCarli et al.[9]
15 mg/kg oral	6	1.70 ± 0.20**	Madar et al.[29]
	20	1.57 ± 0.23***	pooled data
Hyperlipemic/Heparin			
3 mg/kg inj.	7	2.57 ± 0.44	DeCarli et al.[9]
30 mg/kg inj.	3	1.33 ± 0.27*	Madar et al.[29]
	10	1.45 ± 0.35**	pooled data
Hyperlipemic/Clofibrate			
20 mg/kg oral	6	2.66 ± 0.20	DeCarli et al.[9]

* = $p < 0.05$; ** = $p < 0.0025$; *** = $p < 0.0005$; $^{+}$ = mean + SEM (Standard error of the mean).

Mechanism of action of Royal Jelly

The RJ is a secretion from the hypopharyngeal and mandibular glands of worker honey bees which is fed to the queen honey bee throughout their larval and entire adult lives. RJ consists of about 67% water, 12% proteins, 12% sugars, 5% fat, 1% minerals and about 2% of other not yet analyzed substances, i.e. vitamins, nucleic acids[17]. Considerable quantities of RJ are being distributed in Europe, Asia, South America and the United States for human consumption and medical use. RJ contains various biologically active compounds. Only those which may be effective in the prevention and treatment of atherosclerosis will be discussed in this review.

The mechanism by which the RJ prevents formation of atheromas in experimental atherosclerosis is not yet known. It is believed that RJ decreases resorption of cholesterol in the gastrointestinal tract (GIT) and increases its excretion in the bile[32], so that less cholesterol and other fat is available in the circulation.

Inhibition of dietary sterol absorption in GIT may be caused by the presence of large numbers of phytosterols (95 µg/100 mg) in RJ, mainly β-sitosterol[24,57]. It has been established that β-sitosterol competes for sterol binding sites on enterocyte membranes. The plant sterols in general are able to block the uptake of cholesterol by competition[51]. In addition, β-sitosterol may prevent intracellular accumulation of cholesterol esters in arterial intima even in situations where plasma sterol levels remain high; presumably the effect is similar to that of neomycin[48].

Another possible mechanism of RJ action in the regulation of plasma cholesterol concentration may be the suppression of hepatic sterol synthesis. Most of the authors[21,32,42,65] hypothesized that the hypolipidemic action of RJ is due to its effect on the endocrine system, especially its gonadotrophic and estrogenic effect. For a review of estrogen-like effects of RJ in experimental animals and humans see ref. 23 and 63. A glycoprotein with gonadotrophin-like activity was identified in RJ by Takahashi et al.[58], and an estradiol-like steroid by Vittek (unpublished). The estrogens are known to decrease the concentration of plasma cholesterol and LDL[48] by a suppression of HMG-CoA reductase, the rate limiting enzyme of hepatic cholesterol synthesis[53]. Metabolic studies have shown that, by inhibition of cholesterogenesis in the liver, there is activation of LDL receptors that in turn promote assimilation of the lipoproteins from the plasma[53]. In addition, unsaturated fatty acids i.e. essential fatty acids (EFA) (2.14 mg/100 mg), arachidonic acid (AA) (0.3 mg/100 mg) and 10-hydroxy Δ^2-decenoic acid or Royal Jelly acid (RJA) (1.8–2.7 mg/100 mg)[24], represent another possible component in the regulation of blood lipids. The n-3 fatty acids have been shown to have an anti-atherogenic effect by their ability to reduce postprandial lipemia[18]. RJA was implicated in the regulation of sterol metabolism in the honey bees[51] and the inhibition of lipid biosynthesis in the sebaceous gland of the hamster[31]. RJA probably regulates lipid metabolism in other organs as well, as shown by its accumulation in the liver, adipose and other tissues after its oral and intravenous application in rats and mice[25].

The oral and parenteral application of RJ to rats significanlty influences liver metabolism by increasing the utilization of oxygen and decreasing adenosine triphosphatase activity[43]. This may be attributed in part to its effect on the increase of liver vitamins, i.e. niacin, riboflavin and thiamin, in rats fed RJ[15]. These vitamins are involved in hydrogen transfer during cell respiration and their increase suggests that RJ stimulates cell metabolism and respiration. Niacin also increases oxidative phosphorylation in the liver[53]. Although the most prominent pharmacodynamic action of niacin is vasodilation, it also decreases plasma cholesterol and free fatty

Table 3. The design of the included studies

Authors	Country	Patients		Preparation type/dose	Duration of study
		number	diagnosis		
Hammerl-Pichler[13]	Germany	68/43*	Atheroscler. Hypertension	Apifortyl 30 mg/day oral	5 weeks
Hammerl-Pichler[12]	Austria	111/43	Atheroscler. Hypertension	GR Holzinger 10 mg/day inj.	3 weeks
Kaczor et al.[21]+	Poland	20/12	Hypercholest	100 mg/day inj.	3 weeks
Kaczor et al.[21]+	Poland	7/7	Hypercholest. Smokers	100 mg/day inj.	6–11 weeks
Madar et al.[30]	Czechoslovakia	30/7	Advanced Atheroscler.	Vita-Apinol 50 mg/day oral	6 weeks
Pavero-Caviglia[42]	Italy	14/0	Atheroscler. Hypertension	Spintavit 20 mg/day inj.	4 weeks
Pejcev et al.[43]+	Bulgaria	12/10	Atherloscler. Geriatric	Royal Jelly 50 mg/day inj.	4 weeks
Sitar-Cernochova[56]	Czechoslovakia	14/14	Atheroscler. Coronary Sy.	Vita-Apinol 150 mg/day oral	4 weeks
Vinogradova-Zajcev[62]	USSR	N/A	Atheroscler	Apilak 30 mg/day sublingual	N/A
Vittek-Kresanek[64]	Czechoslovakia	100/0	Hypercholest	Vita-Apinol 100 mg/day oral	4 weeks

* = RJ/Placebo groups; + = used in meta-analysis; inj. = injection.

acids by lowering the cAMP level[8]. Thus the niacin content in RJ, together with its increase in the liver, may accelerate lipid catabolism in the liver and its excretion in the bile.

However, it was also found that RJ increases prothrombin time and thus fibrinolytic activity in rats[66]. While the mechanism of this increase is not known, it has been established that EFA, together with AA present in RJ, decrease capillary resistance, platelet aggregation and thrombus formation. EFA and AA are also the precursors for prostaglandins involved in many regulatory processes in the vascular and other systems. Niacin[11] and acetylcholine[61] may also play a vital role in the biosynthesis of prostaglandins and both are present in RJ in large quantities (57 µg/100 mg and 100 µg/100 mg respectively).

Moreover, injection of 0.01% RJ in saline dilated coronary arteries and hepatic veins[6,27] and also counteracted vasoconstriction caused by epinephrine in the eye[6,27]. When 1 mg of RJ was administered to a dog femoral artery it increased blood flow up to 75 times. This effect was blocked by atropine and cholinesterase, and was found to be caused by acetylcholine present in RJ[54]. Thus the vasodilation effect of RJ is mediated via acetylcholine receptors[20] and also in part by the niacin present in RJ. Both might also be responsible for a decrease in blood pressure in experimental animals and humans after application of RJ[10,20,27,35,42].

Hypolipidemic effect of Royal Jelly in the treatment of human atherosclerosis

The trials using RJ for treatment of atherosclerosis and its complications included in this study are summarized in table 3. One of the trials was a crossover study[29]; an additional six studies[12,13,21,30,42,43] used parallel group design. Two studies[42,64] did not include a placebo group, and in one study[62] no data were available on design or number of participants and duration of treatment. Only those studies showing data for both placebo and RJ groups were used for meta-analysis (table 3). A total of 496 subjects were enrolled in the trials, 374 in the RJ group and 97 in the placebo group. In all but one trial[43], patients were selected from the out-patient setting. In one trial[62], selection was not available.

Studies varied in terms of RJ preparations used. Four studies[12,21,42,43] used injectable forms of RJ and five studies[13,14,56,62,64] used oral forms (pills, tablets or capsules), of which one (Apifortyl) was in combination with B complex vitamins[13]. Doses of injectable forms varied from 10 to 100 mg/day[12,21,42,43], and from 30 to 150 mg/day for the oral preparations[13,30,46,56,62]. No reports were made of any dietary or other restrictions on participants.

Patients' age and sex were reported in only five studies[12,13,42,43,56]. The patient age range in these studies was from 21 to 94 years. The proportion of male and female was 63 to 37%. This proportion was different in two trials. In one the proportion was 92 to 8% (ref. 56) and trial (ref. 43) only included men.

All trials measured total serum cholesterol levels. In addition, five trials[12,13,21,30] measured total serum lipids, four trials[12,13,21] serum phospholipids and three trials[12,21,64] serum lipoproteins.

Meta-analysis of effect sizes for serum cholesterol. The results of five trials are summarized in table 4. The

Table 4. Effect of Royal Jelly on serum cholesterol.

Authors	N	Treatment	Serum cholesterol (mg/dL)		
			inital	effect size	95% CI
Kaczor et al.[21]	20	Royal Jelly	258	−27.0	−14.2 to −39.8
	12	placebo	261		
Kaczor et al.[21]	7	Royal Jelly	259	−36.0	−31.9 to −40.1
	7	placebo	260		
Sitar-Cernochova[56]	14	Royal Jelly	291	−25.3	−15.3 to −35.3
	14	placebo	276		
Pejcev et al.[43]	10	Royal Jelly	210	−38.2	−33.4 to −43.0
	12	placebo	196		
Madar et al.[30]	30	Royal Jelly	326	−39.5	−28.8 to −50.2
	7	placebo	250		
Equally weighted average	81	Royal Jelly	269	−34.0	−25.1 to −42.9
	52	placebo	249		

N = Number of patients.

Table 5. Effect of Royal Jelly on serum lipids.

Authors	N	Effect size (mg/dL)	95% CI
Madar et al.[30]	30/7	−20.27	−5.76 to −34.88
Kaczor et al.[21]	7/7	−23.25	−20.00 to −26.49
Kaczor et al.[21]	20/12	−39.63	−21.08 to −58.19
Hammerl-Pichler[13]	68/43	−94.95	−76.89 to −113.00
Hammerl-Pichler[13]	111/43	−81.90	−65.40 to −98.40
Equally weighted average	236/69	−52.00	−37.80 to −66.19

N = Number of patients.

mean effect size of treatment for individual trials ranged from −25.3 to −39.5 mg/dL and were statistically significant in all included trials. The equally weighted average of effect size for the mean difference in cholesterol change between RJ and placebo group was estimated at −34.0 mg/dL ($p < 0.001$). The 95% CI was −25.1 to −42.9 mg/dL. Treatment effect sizes are shown in figure 3. The summary statistics for the five trials estimated the increased effect rate for RJ. Because the 95% CI does not include 0 the difference is statistically significant.

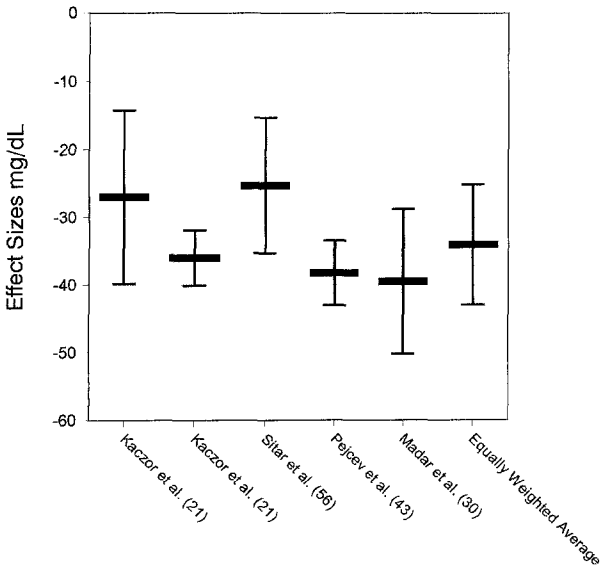

Figure 3. The effect sizes with 95% CIs for mean improvement during Royal Jelly therapy compared with placebo. Effect size for each trial was computed as the difference between the change of cholesterol level in the RJ and placebo groups. Any CI that includes zero indicates a nonsignificant result.

Sensitivity analysis for serum cholesterol. A total of nine studies[12,13,21,30,42,43,56,64] were included in this analysis. The effect sizes were determined to be homogeneous ($\chi^2 = 16.4$, $p > 0.1$) and were pooled to estimate the common effect size of treatment. The meta-analysis of the nine trials estimated a significant pooled effect size of −30.3 mg/dL after treatment with RJ. The 95% CI of this effect size was −19.0 to −41.5 mg/dL. Meta-analysis of the RJ-treated group of the five trials included in the primary analysis estimated a significant pooled effect size of −37.4 mg/dL and 95% CI of −27.6 to −47.2 mg/dL.

Meta-analysis for effect sizes for serum lipids. Study results of the five trials included are summarized in table 5. The mean effect size of treatment for individual trials ranged from −20.3 to −95.0 mg/dL and were statistically significant in all trials. The equally weighted average of effect size estimates for the mean difference in total serum lipids change between RJ and placebo group was estimated at −52.0 mg/dL ($p < 0.05$). The

Table 6. Effect of Royal Jelly on some serum lipids.

Authors	N	Difference between Royal Jelly and placebo			
		total lipids	phospho-lipids	cholest./phospholip.	lipoproteins beta/alpha
Kaczor et al.[21]	7/7	−6.2%	+5.5%	−13.5%*	+12.5%
Kaczor et al.[21]	20/12	−9.0%	+9.0%**	−17.0%*	−10.6%*
Hammerl-Pichler[13]	111/43	−15.0%	+9.0%*	−14.0%*	−61.0%*
Hammerl-Pichler[13]	68/43	−13.0%	−8.0%	−3.0%	-
Madar et al.[30]	30/7	−8.0%	-	-	-
Vittek-Kresanek[64]	100/0	-	-	-	−13.0%*

- = not reported; N = number of persons in group; *$p < 0.05$ and ** = $p < 0.01$.

95% CI was −37.8 to −66.2 mg/dL. The summary statistics for the five trials estimated the increased effect rate for RJ. Because the 95% CI does not include 0 the difference is statistically significant at the 5% level.

Analysis of other serum lipid components. As shown in table 6, while total serum lipids decreased in all five trials included in this study, serum phospholipids increased in three out of four trials in the RJ group as compared to placebo group. A statistically significant decrease in cholesterol/phospholipid quotient was also found in three out of four trials in the RJ group. In addition, in three out of four trials a statistically significant decrease in serum β/α-lipoprotein quotient was found in the RJ group.

Conclusion

This is the first quantitative review of literature suggesting that RJ decreases levels of serum cholesterol and other lipids. Effect size in the present analysis provided an estimate of the average improvement seen during RJ therapy compared to the placebo. RJ significantly lowered serum cholesterol levels by about 14% and total lipid levels by about 10% as well as levels of lipoproteins in the groups studied compared to placebo. There were some differences in the effect sizes between the individual studies, which made it difficult to establish a dose-response relation (table 7). This was due to the variety of RJ preparations and study duration. In addition, while the injectable forms of RJ caused a greater decrease in the blood cholesterol than the oral forms ($14.2 \pm 2.81\%$ and $13.28 \pm 3.6\%$ respectively), this difference was not statistically significant ($p > 0.6$). Although only officially-made preparations (by pharmaceutical companies under government control) were used in these trials, they were not standardized except by the amount of RJ used which was apparently analyzed for the basic compounds, i.e. water, protein, sugar, ash and various vitamin content/unit weight. The present analysis (table 7) would suggest that only a small amount of RJ ingestion per day is needed to produce a hypocholesterolemic effect. These results are consistent with experimental animal studies of the hypocholesterolemic effect of RJ.

Table 7. Relationship between Royal Jelly given and decrease in serum cholesterol.

Authors	Royal Jelly given	Decrease in serum cholesterol	
		mg/dL	%
Hammerl-Pichler[12]	10 mg inj.	−58	14.8
Pavero-Caviglia[42]	20 mg inj.	−55	11.8
Vinogradova et al.[62]	30 mg oral	−52	20.0
Hammerl-Pichler[13]	30 mg oral	−53	10.4
Madar et al.[30]	50 mg oral	−46	14.0
Pejcev et al.[43]	50 mg inj.	−40	19.0
Vittek-Kresanek[64]	100 mg oral	−32	12.0
Kaczor et al.[21]	100 mg inj.	−36	14.0
Kaczor et al.[21]	100 mg inj.	−27	11.0
Sitar et al.[56]	150 mg oral	−30	10.0

Although our data support the claim that oral or injectable RJ therapy decreases serum cholesterol and other lipids in people with increased levels, and possibly normalizes serum HDL and LDL as shown by results from α- and β-lipoproteins in these trials, the design of the included trials was not optimal. The number of people in the trials and in the arms of each trial varied greatly, and disease status was poorly characterized. In no trial was dietary intake, weight, or other medication assessed within or between groups during the trial period. In addition, different forms of RJ without standardization[35] were used, and in some trials[42,64] results from a comparable placebo group were not shown. Despite this heterogeneity, the sensitivity analysis showed that the inclusion of methodologically less rigorous trials did not appreciably alter the magnitude of the RJ effect. The sensitivity analysis also showed that the RJ effect was consistent across trials using different methods, preparations, and groups of participants. Although a significant hypocholesterolemic effect was detected by the use of RJ, the overall quality of the included studies weakens the validity of these findings and they should be considered as preliminary. In addition, in future studies the low density lipoprotein (LDL) subfraction should be used instead of cholesterol as the primary outcome measure, because it is a better marker of cardiovascular risk.

This meta-analysis combined people with hyperlipidemia of varying definition. Despite this heterogeneity, the results consistently show a significant reduction in total serum cholesterol by RJ, suggesting that RJ may act on some important step of cholesterol biosynthesis, degradation, transport, or uptake, common to many forms of hyperlipidemia[54]. Results from studies in experimental animals support this hypothesis and suggest that RJ may also be effective in the prevention of atherosclerosis in humans.

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