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Royal jelly does not improve markers of glycemia: A systematic review and meta-analysis of Randomized Clinical Trials

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ABSTRACT

Bee products including propolis, bee wax, pollen and royal jelly (RJ) have been used as medicine from ancient times. A vast number of in-vivo and in-vitro studies as well as clinical trials have been conducted to investigate potential health related properties of RJ. A growing number of clinical trials have been performed to assess effects of RJ ingestion on different metabolic markers including glycemia, with diverse results. In the current meataanalysis, we aimed to evaluate effects of RJ ingestion on glycemic markers compared with placebo and set directions for future research. Electronic databases including Scopus, Pubmed, Scholar, Cochrane, Proquest, SID and Magiran were searched and 5 eligible studies were included in the quantitative analysis. Review Manager Software was used for statistical analysis and random effects model was used for pooling data. A total of 205 participants for FPG and 130 participants for HbA1c were included. The overall analysis revealed that RJ consumption reduced FPG by 0.95 mg/dl (95% CI: −5.83 to 3.87; p = 0.69; I2 = 0%; Tau^2 = 0.00) and HbA1c by 0.32 (95% CI: −0.87 to 0.23; p = 0.25; I2 = 69 %; Tau^2 = 0.16) which were not statistically significant. Funnel plot demonstrated no publication bias. In conclusion, RJ supplementation did not beneficially affect markers of glycemia. However, due to methodology issues and potential confounders like diet as well as diverse populations, we recommend future studies well designed and well controlled for major confounders so we can update these data to more precise results and more accurate conclusion.

1. Introduction

Elevated blood glucose as well as dyslipidemia, hypertension, and abdominal obesity are features of metabolic syndrome (Mets)[1] that put individuals at higher risk of cardiovascular diseases (CVD).[2] According to available evidence, the prevalence of Mets is between 20% and 30% in most countries and accounts for a major proportion of CVD risk, worldwide.[3] Changes in lifestyle and dietary habits along with increasing physical exercise should be considered as first line therapy to decrease Mets and control glycemia.[4]

In recent years, research have focused on functional foods, nutraceuticals, and other bioactive compounds to control metabolic syndrome components. These include polyphenols found in different herbal teas and coca, lutein, lycopene and flavonoids found in fruits and vegetables, seaweed, cumin, cinnamon and so on.[5–7]

Bee products including propolis, bee wax, pollen and royal jelly (RJ) have been used as medicine from ancient times and growing research is now investigating health application for humans considering their antioxidant activities.[8] RJ is a white viscose substance secreted from hypopharyngeal and mandibular glands of worker bees that is only consumed by the queen bee and is also fed to the larvae for brood nutrition.[9] RJ is whitish to yellow in colour and the yellow colour increases during storage.[10] Its main constituents are proteins, sugars, lipids, free amino acids, vitamins and minerals.[11] 10-hydroxy-trans-2-decenoic acid (HDEA) is an unsaturated fatty acid and a unique component in RJ.[12] HDEA was found to have many pharmacological activities such as anti-tumor, antibiotic, and neuroprotective properties.[13]

A vast number of in-vivo and in-vitro studies as well as clinical trials have been conducted to investigate potential health related properties of RJ. Several animal studies have examined different outcomes such as osteoporosis,[14] fatigue,[15] wound healing,[16,17] hyperglycemia[18] and longevity.[19] Besides, a growing number of clinical trials have also been performed to assess effects of RJ ingestion on different metabolic markers including glycemia,[20–26] with diverse results.

Since a considerable number of trials had targeted glycemic markers, we were interested to pool these data and provide new directions

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for future research.

2. Materials and methods

2.1. Search strategy and data sources

The study was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Metaanalyses (PRISMA) guidelines.[27] The primary goal was to evaluate effects of royal jelly supplementation on markers of glycaemia. We searched the following electronic databases from inception till February 2019: Pubmed, Scopus, Cochrane library, Proquest, Scholar, SID and Magiran. Furthermore, reference lists of reviews related to our research topic were hand searched. The systematic search was conducted by two independent reviewers (S.M and S.J). Search terms used included "royal jelly" [All Fields] OR "royal jelly" [Text Word] AND "blood glucose" [MeSH Terms] OR "blood glucose" [Text Word] OR "diabetes mellitus [MeSH Terms] OR "diabetes insipidus" [MeSH Terms] OR "diabetes" [Text Word] OR "HbA1c" OR "insulin" OR "HOMAIR".

2.2. Study selection

Eligible studies for this systematic review and meta-analysis were randomized clinical trials in either English or Persian language that were placebo-controlled. There were no restriction on age or clinical condition. Studies had to report baseline and end-of-study measures for at least one glycemic marker (FPG, HbA1c, insulin or HOMAIR). Exclusion criteria were as follows: not being placebo- controlled, written in languages other than English/Persian, not reporting adequate data on outcome measures or reporting transformed data, pre-post ingestion trials, as well as all other types of studies other than RCTs (case reports, commentaries, animal and observational studies).

2.3. Data extraction and management

Data extraction was conducted by two independent reviewers (S.M and S.J). Any disagreements were resolved through discussion with a third reviewer (M.H. E). All titles and abstracts were first screened to identify studies meeting inclusion criteria. In the next step, reviewers screened the full text of identified studies to determine eligibility. A data extraction form was developed in excel format and

completed by S.M. Extracted data from each study included first author, year, sample size, country, gender, clinical condition, age, type of intervention, dosage, duration, and baseline and end-of-study outcome measures. Necessary data calculations were performed by S.M and checked by S.J.

2.4. Quality assessment

Quality assessment for included RCTs were systematically assessed by first reviewer (S.M) and approved by second reviewer (S.J) according to JADAD checklist[28] using the following items[1]: Describing as randomized,[29] describing methods used to generate randomization sequence,[3] describing as double blind,[4] describing methods of blinding,[5] description of withdrawals and dropouts. Two minus points were assigned for inappropriate description of randomization and inappropriate method of blinding while describing the study as double blind. A JADAD score of 1–5 was assigned to each study. Studies with a score of 3 or more were categorized as high quality while scores below 3 were representative of low quality design.

2.5. Statistical analysis

Review Manager Software (Version 5:3; Oxford, England) was used for quantitative analysis. Before analysis, all units were checked to be in the same units (mg/dl for FPG). One study had logarithmically transformed glycemic data which was excluded from the analysis.

Mean net changes and Standard Deviations (SDs) were calculated for both intervention and control groups in each study. Effects sizes were calculated following the Cochrane handbook[30] using mean change from baseline to endpoint and its SD and expressed as between group WMD and 95% CI. A p-value < 0.05 was considered as statistically significant. Since various studies might stem from diverse nature with differences in patient characteristics and study design[31] we used random effects model to overcome heterogeneity.

One study had compared three different doses of RJ with placebo and therefore, we considered each dosage data as a separate arm.

2.6. Publication bias

Publication bias was assessed by visual inspection of asymmetry in funnel plot. When publication bias exists, this plot is asymmetric. "trim" and "fill" method is used to adjust for publication bias which were not used in this study since no publication bias existed for proxy variables.[32]

3. Results

3.1. Search results and study selection

A total of 372 citations were identified using the search keywords. 171 records remained after removing duplicates. Of this number, 156 studies were excluded for being animal studies (n = 53), reviews (n = 13), irrelevant (n = 50), other study types (commentaries, book chapters, case series, etc.) (n = 19), not being in English/Persian language and not having access to abstract or full text (n = 3). After the initial screening, 15 studies remained for full text evaluation. 10 other studies were excluded in this step for following reasons: using honey as control (n = 1), not reporting our markers of interest (n = 3), being a pre-post ingestion trial (n = 2), logarithmically transformed data (n = 1), not being placebo-controlled (n = 2), and not being published yet (n = 1). Therefore, 5 RCTs met our eligibility criteria. Since one study had 3 different arms, a total of 7 studies were included in the quantitative analysis. Fig. 1 demonstrates a detailed search process and study selection.

3.2. Risk of bias

All seven studies were reported to be randomized and 3 studies to be double blind.[21,25,33] Two studies described withdrawals and dropouts adequately.[25,33] In general, based on JADAD score, only two studies were categorized as high quality (JADAD score ≥ 3)[25,33] while other five studies were categorized as low quality ones (JADAD score $<$ 3).[20,21,34] It seems that clinical trials conducted in this area were not adequately well designed following standard guidelines such as CONSORT[35] and are rated as high risk of bias. Calculated JADAD scores for included studies are presented in Table 1.

3.3. Characteristics of the included studies

Table 2 provides information on characteristics of included studies. Studies were conducted between 2007 and 2017 in different regions. Two studies were conducted in Japan,[20,21] two studies in Iran,[25,33] and one in Turkey.[34] Duration of intervention was 4 weeks in two studies[20,34] and 8 weeks in three others.[21,22,25] The intervention dosage varied between 500 mg–6000 mg on a daily basis with no co-supplements. Furthermore, participants had various clinical conditions in different studies: one study recruited healthy adults,[20] two studies had subjects with type 2 diabetes,[25,33] one had patients with dry eye symptoms[21] and the other remaining one had trained male swimmers as participants.[34] Number of participants ranged from 15 to 50 across studies.

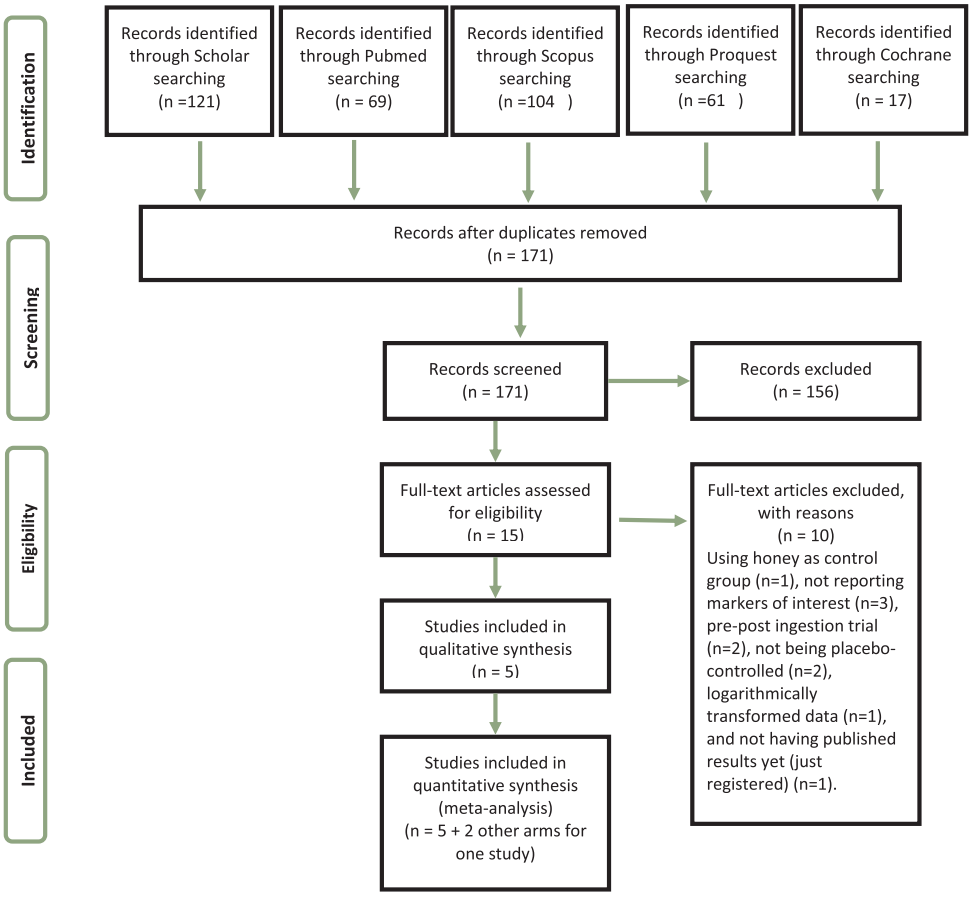

Fig. 1. Study selection flow diagram. PRISMA flow diagram of search results following study selection procedure evaluating effects of Royal Jelly supplementation on glycemic markers.

3.4. Pooled estimate of the effect of royal jelly on Fasting Plasma Glucose (FPG)

All included studies measured effects of RJ on blood glucose with 102 participants in experimental group and 103 participants in control group. Two studies showed remarkable decrease in FPG[25,33] while three others (including 5 arms) did not show any marked improvements in FPG following RJ consumption. The overall analysis revealed that RJ consumption reduced FPG by 0.95 mg/dl which was not statistically significant (95% CI: -5.83 to 3.87; p = 0.69; I^2 = 0%; Tau^2 = 0.00); Fig. 2(A)).

3.5. Pooled estimate of the effect of royal jelly on Glycated Hemoglobin (HbA1c)

Three of five included studies evaluated effects of RJ supplementation on HbA1c with a total of 65 participants in experimental and 65 in control group. One study showed significant reduction in HbA1c (25) while two other studies didn't show any positive and significant improvements in this marker.[21,33] The overall analysis demonstrated that RJ consumption reduced HbA1c by -0.32 which was not statistically significant (95% CI: -0.87 to 0.23; p = 0.25; I^2 = 69%; Tau^2 = 0.16); Fig. 2(B)).

3.6. Publication bias

In this meta-analysis, publication bias was examined by visually inspecting funnel plots for effects on FPG as proxy marker for glycemia. Funnel plot demonstrated that publication bias was not a source of bias in our study (Fig. 3).

3.7. Subgroup analysis

Subgroup analysis was performed based on clinical condition to

Table 1
Quality of the included studies based on JADAD score.

Study	Guo 2007	Inoue 2017	Khoshpey 2013	Pourmandian 2014	Saritas 2011 a	Saritas 2011 b	Saritas 2011 c
Described as randomized (0/1)	1	1	1	1	1	1	1
Describing methods used to generate randomization sequence (0/1)	0	0	1	1	0	0	0
Described as double blind (0/1)	0	1	1	1	0	0	0
Describing methods of blinding (0/1)	0	0	1	1	0	0	0
Description of withdrawals and dropouts (0/1)	0	1	1	1	0	0	0
Inappropriate description of randomization (-1)	−1	−1	–	–	−1	−1	−1
Inappropriate method of blinding (-1)	–	−1	–	–	–	–	–
Score	0	1	5	5	0	0	0

Table 2
Characteristics of included studies.

Author	Guo et al	Inoue et al	Khoshpey et al	Pourmandian et al	Saritas et al (a, b, c)
Year	2007	2017	2013	2014	2011
Country	Japan	Japan	Iran	Iran	Turkey
Participants (sample size)	Healthy adults (15)	Patients who complained of subjective symptoms of dry eye (41)	Patients with type 2 diabetes (50)	Patients with type 2 diabetes (50)	Trained swimmers (40)
Sex	M/F	M/F	M/F	F	M
Duration	4 weeks	8 weeks	8 weeks	8 weeks	4 weeks
Intervention (dosage)	6 gr RJ daily	1200 mg RJ daily (6 tabs/day)	3000 mg RJ daily (three 1000 mg tabs/day)	1000 mg RJ daily	a) 500 mg RJ daily b) 1 gr RJ daily c) 2 gr RJ daily
Main findings	No significant improvement in FPG	No significant improvement in glycemic markers in RJ group, significantly higher increases in HbA1c in placebo group	Significant reduction in FPG levels and non-significant reduction inHbA1c	Remarkable decrease in FPG, significant reduction in HbA1c	Different doses of RJ were ineffective in reducing glycaemia, blood lipids or liver enzymes

Abbreviations: gr, grams; mg, milligrams; tabs, tablets; RJ, royal jelly; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin.

evaluate effects of RJ supplementation on glycemic markers in diabetic compared with non-diabetic subjects. Diabetic subgroup had greater albeit non-significant reductions in both FBG and HbA1c following RJ consumption compared with non-diabetic subjects (FBS: −11.7 [−25.53, 2.12], p = 0.10 in diabetic subgroup vs. 0.53 [−4.65, 5.71], p = 0.63 in non-diabetic subgroup and HbA1c: −0.63 [−1.47, 0.22], p = 0.15 in diabetic subgroup vs. −0.01 [−0.13, −0.11], p = 0.87 in non-diabetic subgroup). Table 3 summarizes results of subgroup analysis.

4. Discussion

The present meta-analysis aimed to evaluate effects of RJ supplementation on glycemic markers in human subjects. In overall, our results found no significant improvements in glycemic indices (FPG and HbA1c) following RJ consumption. The overall results are consistent with most individual studies regarding our primary outcome; five of seven arms included for FPG,[20,21,34] and four of six arms included for HbA1c found no significant effects following RJ ingestion compared with control group. RJ is secreted from hypopharyngeal and

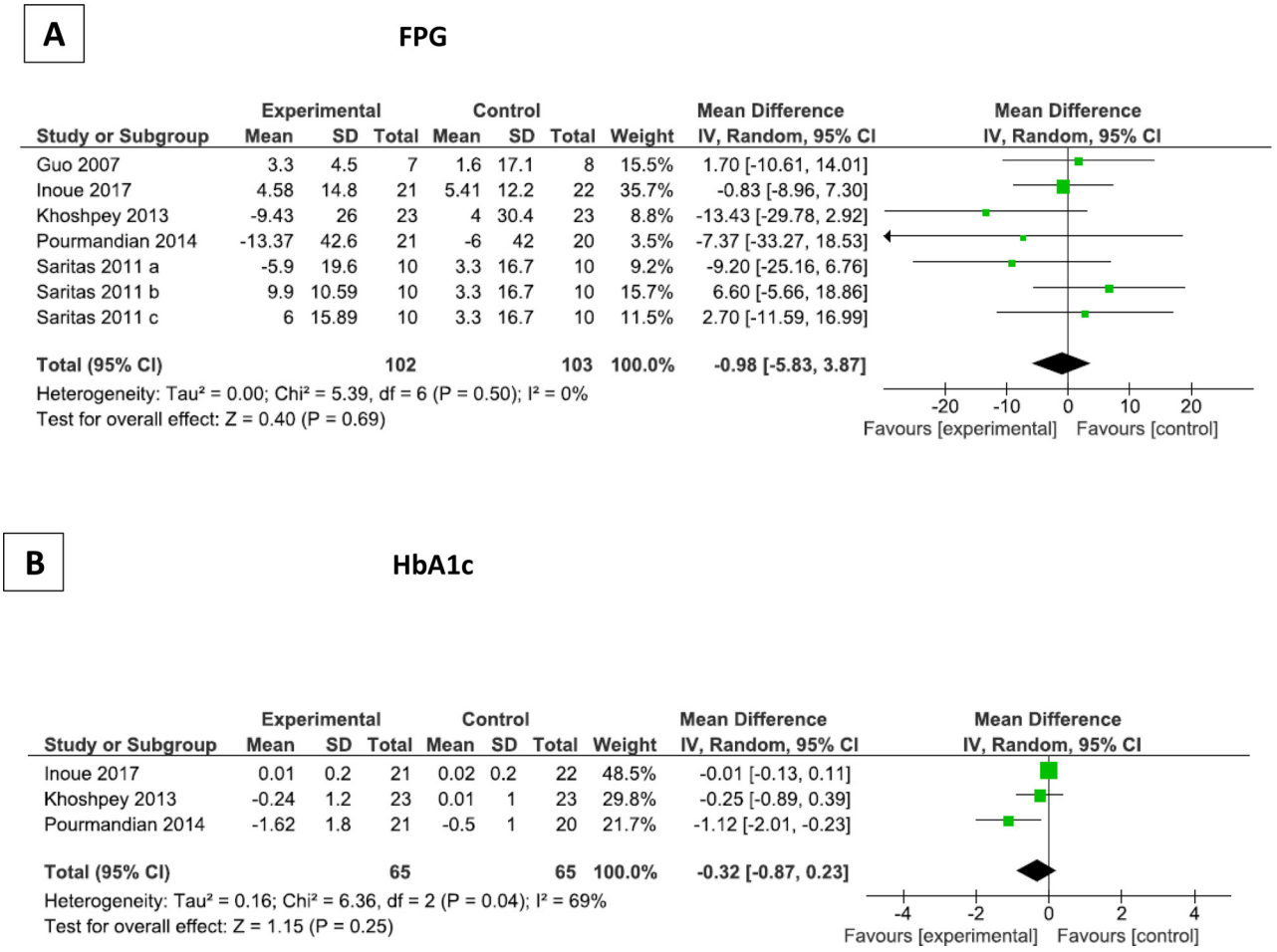

Fig. 2. Plots showing mean change of (A) Fasting Plasma Glucose (FPG) and (B) Glycated Hemoglobin (HbA1c) from baseline following royal jelly consumption compared with control. Random effects model was performed to pool the mean change of variables.

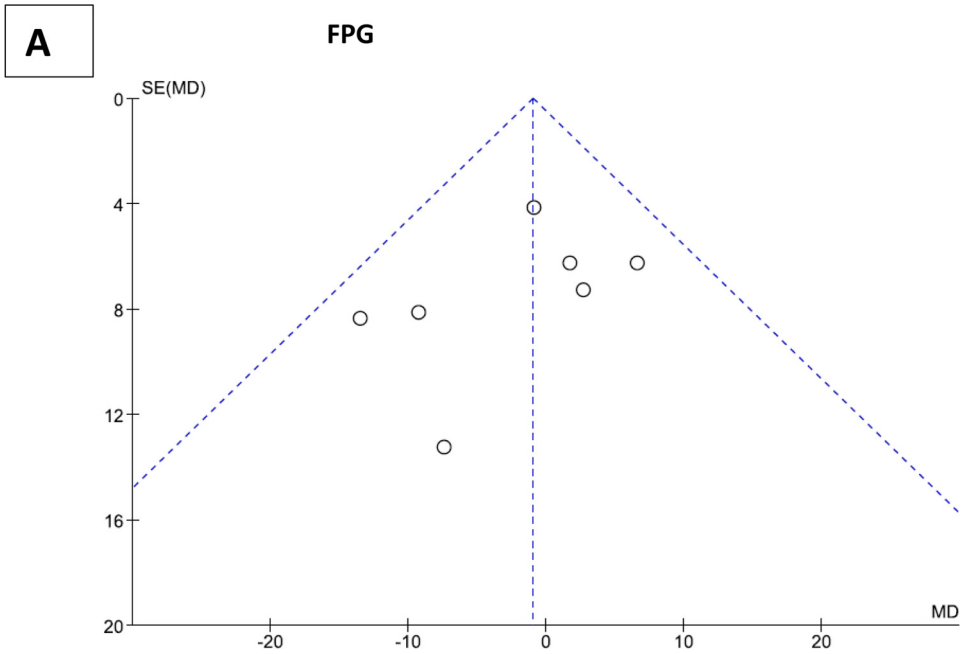

Fig. 3. Funnel plot of SE by standardized MD for FPG detailing publication bias in studies selected for meta-analysis. Abbreviations: SD, standard error; MD, mean difference; FPG, fasting plasma glucose.

Table 3
Subgroup analysis.

Subgroup Analysis	No. of Study	No. of Subjects		WMD(95% CI)	P value
		RJ	Placebo		
Clinical condition					
FPG					
Diabetic	2	44	43	−11.70 (−25.53, 2.12)	0.10
Non-diabetic	5	58	60	0.53 (−4.65, 5.71)	0.84
HbA1c					
Diabetic	2	44	43	−0.63 (−1.47, 0.22)	0.15
Non-diabetic	1	21	22	−0.01 (−0.13, 0.11)	0.16

mandibular glands of worker bees and is known as a superfood exclusively consumed by queen bee.[36] Due to its high bioactive content, including phenolic compounds, fatty acids and vitamins, RJ has been proposed to have functional benefits such as anti-oxidant, anti-diabetic, anti-microbial, wound healing, and cardioprotective properties. A vast majority of studies regarding health effects of RJ, are experimental studies with different outcomes of interest including: glycemia,[18,37] insulin resistance,[38,39] testicular damage,[40,41] wound healing,[16] immune response[42] and memory.[43] Rezk reported that 4 weeks supplementation with RJ could significantly decrease blood glucose levels and serum lipids, and was beneficial as an adjuvant therapy with oral hypoglycemic drugs in rats.[37] Similarly, Yoneshiro et al concluded that RJ can improve hyperglycemia and ameliorate diet-induced obesity in mice.[44] In another experimental study, 4 weeks administration of RJ improved hyperglycemia and suppressed the expression of glucose-6-phosphatase (G-6-pase) gene in KK-Ay mice.[18] Besides these experimental works, a considerable number of human studies have also been performed most of which investigated effects of RJ supplementation on blood lipids and glycemic markers. A recent meta-analysis have found RJ as an effective and relatively safe alternative approach for blood lipid modulation.[45] Several individual trials have also evaluated RJ consumption in association with glycemia reporting controversial results. Our meta-analysis is first to pool data from these studies. The overall results were not able to find any significant effects on FPG or HbA1c. These results are unexpected based on previous results of experimental and clinical literature. Different reasons might have led to this lack of association. Based on JADAD score, 3 of five studies have low quality design which also reported no significant effects regarding glycemic markers.[20,21,34] High quality studies on the other hand reported at least one significant result.[25,33] Based on this assumption we conducted a subgroup analysis but the results remained unchanged following this analysis (results are not shown in the paper). Studies were heterogeneous based on clinical condition. Two studies had type 2 diabetic subjects and reported some significant benefits[25,33] while the three remaining had healthy participants,[20] subjects with dry eye[21] and swimmers[34] which were not able to show any significant improvements in glycemia. Therefore, it can be assumed that RJ is more effective in diabetic subject with higher levels of glycemia. Regarding this assumption, we conducted a subgroup analysis based on clinical condition (Diabetic vs. non-diabetic). Diabetic subjects showed greater reductions in FPG and HbA1c after RJ consumption. However, these reductions were not significant. From a clinical point of view, RJ led to 11.70 units reduction in FPG in diabetic subjects which is considerable but the wide confidence interval has made it statistically non-significant. HbA1c, on the other hand had improvements in diabetic subjects with much narrower confidence interval but the P value is still non-significant. We can hypothesize that RJ might be more beneficial on glycemic markers in people with impaired glycemia and call for future well designed studies to establish this hypothesis. One study was excluded because of logarithm transformation of FPG and HbA1c.[24] In this study, 6 months of RJ consumption exerted beneficial effects on FPG but not HbA1c. Included studies had reported various markers besides FPG and HbA1c which were not pooled in the quantitative analysis; Inue et al found that oral RJ supplementation for 8 weeks can improve tear secretion in patients with dry eye.[21] Koshpey and her colleagues reported that RJ consumption can significantly improve total antioxidant capacity in type 2 diabetic patients.[33] In their clinical trial, Pourmandian et al observed significant improvements in markers of oxidative stress (MDA, SOD, and GSH –PX).[25] Mobasseri et al have also investigated effects of RJ on glycemia[23] whose results were not included in our analysis due to its different design. The results are indicative of a glucose- lowering effects of a single dose of RJ in type 2

diabetic patients. Different studies have used various amounts of RJ as their intervention which are summarized in Table 2. Dosage of RJ supplements does not seem to have considerable effects on results since no clear pattern is seen according to different dosages.

Modern spectrometric analyses have detected almost 185 compounds in RJ. RJ is composed of royalcaltin and a considerable number of bioactive compounds including fatty acids, proteins, adenosine monophosphate N1 oxide, hormones, polyphenols and other bioactive compounds which are responsible for a variety of its biological actions.[46,47]

RJ is used to combat diabetes because of its insulin-like action along with other compounds (like chromium, sulphur, vitamin B3 and Biotin). RJ has insulin-like peptides that are capable of optimizing blood sugar and interestingly resemble mammalian insulin.[48] Several limitations might be considered in our meta-analysis; included studies have low quality in design with heterogeneous populations and relatively low duration periods which might have led to non-significant results. As dietitians the authors of this study believe that dietary intake is one of the most important factors influencing glycemia and insulin responses. Except for Khoshpey et al,[33] none of other studies mentioned and controlled for dietary intakes of study groups which may probably confounded the results. Some results were unfortunately excluded from quantitative analysis for not meeting inclusion criteria. Publication bias is an inherent limitation in metaanalyses. However, visual inspection of funnel plots were not indicative of this type of bias. In spite of these limitations, our study has strengths, too. This study is the first meta-analysis evaluating effects of RJ on glycemic markers. Besides the statistical analyses, our study have evaluated the limitations of present research setting directions and hints for future studies. A comprehensive and predefined systematic search was applied to extract all relevant data.

Well-designed trials are needed with longer durations, and controlling for potential confounders especially diet and physical activity. We postulate that RJ might be more effective in diabetes regarding glycemic control. Therefore, more studies are suggested in this population to draw more accurate conclusions.

5. Conclusion

The present meta-analysis was not able to show beneficial effects of RJ supplementation on glycemic markers. However, due to methodology issues, lack of high quality studies, and possible confounders like diet, we cannot draw accurate conclusion and recommend further studies in this regard, well designed and well controlled for major confounders so we can update these data to more precise results.

Conflict of interest

None.

Authorship

S.M and S.J brought up the research hypothesis. Systematic search and screening was conducted by S.M and S.J and any disagreements were resolved by consulting M.H.E. Data extraction was conducted by S.M with guidance of S.J and M.H.E. Statistical analysis was performed and interpreted by SJ. Paper sections were written by S.M and M.H.E.

References

1. Mamchur V, Zhyliuk V, Lievykh A, Markhon N. Effect of Piracetam, resveratrol and propylene glycol extract of Royal jelly on behavioral functions and markers of oxidative stress in rats with experimental metabolic syndrome. *Pharma Innov.* 2015;4(8 Part B):72–76.
2. Alexander CM, Landsman PB, Grundy SMJ. Metabolic syndrome and hyperglycemia: congruence and divergence. *Am J Cardiol.* 2006;98(7):982–985.
3. Grundy SMJA. Metabolic syndrome pandemic. *Arterioscler Thromb Vasc Biol.* 2008;28(4):629–636.
4. Andersen CJ, Fernandez ML. Dietary strategies to reduce metabolic syndrome. *J Rev Endocr Metab Disord.* 2013;14(3):241–254.
5. Cicero AF, Colletti A. Role of phytochemicals in the management of metabolic syndrome. *Phytomedicine.* 2016;23(11):1134–1144.
6. Mirmiran P, Bahadoran Z, Azizi F. Functional foods-based diet as a novel dietary approach for management of type 2 diabetes and its complications: a review. *World J Diabetes.* 2014;5(3):267.
7. Mohamed S. Functional foods against metabolic syndrome (obesity, diabetes, hypertension and dyslipidemia) and cardiovasular disease. *Trends Food Sci Technol.* 2014;35(2):114–128.
8. Kocot J, Kiełczykowska M, Luchowska-Kocot D, Kurzepa J, Musik I. Antioxidant potential of propolis, bee pollen, and royal jelly: possible medical application. *Oxid Med Cell Longev.* 2018;2018:1–29.
9. Pasupuleti VR, Sammugam L, Ramesh N, Honey Gan SH. Propolis, and royal jelly: a comprehensive review of their biological actions and health benefits. *Oxid Med Cell Longev.* 2017;2017:1–21.
10. Bogdanov S. Royal jelly, bee brood: composition, health, medicine: a review. *Lipids.* 2011;3(8):8–19.
11. Guo H, Kouzuma Y, Yonekura M. Structures and properties of antioxidative peptides derived from royal jelly protein. *Food Chem.* 2009;113(1):238–245.
12. Genç M, Aslan A. Determination of trans-10-hydroxy-2-decenoic acid content in pure royal jelly and royal jelly products by column liquid chromatography. *J Chromatogr A.* 1999;839(1-2):265–268.
13. Ito S, Nitta Y, Fukumitsu H, et al. Antidepressant-like activity of 10-hydroxy-trans-2-decenoic acid, a unique unsaturated fatty acid of royal jelly, in stress-inducible depression-like mouse model. *Evid Based Complement Altern Med.* 2012;2012:6.
14. Hidaka S, Okamoto Y, Uchiyama S, et al. Royal jelly prevents osteoporosis in rats: beneficial effects in ovariectomy model and in bone tissue culture model. *Evid Based Complement Altern Med.* 2006;3(3):339–348.
15. Kamakura M, Mitani N, Fukuda T, Fukushima M. Antifatigue effect of fresh royal jelly in mice. *J Nutr Sci Vitaminol.* 2001;47(6):394–401.
16. Rashidi MK, Mirazi N, Hosseini A. Effect of topical mixture of honey, royal jelly and olive oil-propolis extract on skin wound healing in diabetic rats. *Wound Med.* 2016;12:6–9.
17. Shirzad H, Sedaghat A, Ghasemi S, Shirzad M. Effect of royal jelly on sterile wound healing in Balb/C mice. *Armaghane danesh.* 2010;15(1):38–46.
18. Yoshida M, Hayashi K, Watadani R, et al. Royal jelly improves hyperglycemia in obese/diabetic KK-Ay mice. *J Vet Med Sci.* 2017;79(2):299–307.
19. S-i Inoue, Koya-Miyata S, Ushio S, Iwaki K, Ikeda M, Kurimoto M. Royal Jelly prolongs the life span of C3H/HeJ mice: correlation with reduced DNA damage. *Exp Gerontol.* 2003;38(9):965–969.
20. Guo H, Saiga A, Sato M, et al. Royal jelly supplementation improves lipoprotein metabolism in humans. *J Nutr Sci Vitaminol.* 2007;53(4):345–348.
21. Inoue S, Kawashima M, Hisamura R, et al. Clinical evaluation of a royal jelly supplementation for the restoration of dry eye: a prospective randomized double blind placebo controlled study and an experimental mouse model. *PLoS One.* 2017;12(1) (no pagination).
22. Khoshpey B, Djazayeri S, Amiri F, et al. Effect of royal jelly intake on serum glucose, apolipoprotein A-I (ApoA-I), apolipoprotein B (ApoB) and ApoB/ApoA-I ratios in patients with type 2 diabetes: a randomized, double-blind clinical trial study. *Can J Diabetes.* 2016;40(4):324–328.
23. Mobasseri M, Ghiyasvand S, Ostadrahimi A, Ghojazadeh M, Noshad H, Pourmoradian S. Effect of fresh royal jelly ingestion on glycemic response in patients with type 2 diabetes. *Iran Red Crescent Med J.* 2015;17(9).
24. Morita H, Ikeda T, Kajita K, et al. Effect of royal jelly ingestion for six months on healthy volunteers. *Nutr J.* 2012;11(1):77.
25. Pourmoradian S, Mahdavi R, Mobasseri M, Faramarzi E, Mobasseri M. Effects of royal jelly supplementation on glycemic control and oxidative stress factors in type 2 diabetic female: a randomized clinical trial. *Chin J Integr Med.* 2014;20(5):347–352.
26. Shidfar F, Jazayeri S, Mousavi SN, Malek M, Hosseini AF, Khoshpey B. Does supplementation with royal jelly improve oxidative stress and insulin resistance in type 2 diabetic patients? *Iran J Public Health.* 2015;44(6):797–803.
27. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.
28. Berger VW, Alperson SY. A general framework for the evaluation of clinical trial quality. *Rev Recent Clin Trials.* 2009;4(2):79–88.
29. Ramanathan A, VethaSundaram Sugunan AKAN. Antimicrobial activity of royal jelly from Indian honeybee, Apis Cerana. *Int J Allied Pract Res Rev.* 2012;5(2):7–12.
30. Higgins J, Green S. *Cochrane handbook for systematic reviews of interventions [Internet]. Version 5.1. 0.* London, England, UK: Cochrane Collaboration; 2011 [cited 24 Aug 2018].
31. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials.* 2007;28(2):105–114.
32. Mirhosseini N, Vatanparast H, Mazidi M, Kimball SM. Vitamin D supplementation, glycemic control, and insulin resistance in prediabetics: a meta-analysis. *J Endocr Soc.* 2018;2(7):687–709.
33. Khoshpey B, Shidfar F, Jazayeri S, Malek M, Fatemeh Hosseini A. Effect of royal jelly intake on serum glucose, HbA1c, and total antioxidant capacity (TAC) in type 2 diabetic patients: a randomized, double blind clinical trial study. *Razi J Med Sci.* 2013;19(103).
34. Saritas N, Yildiz K, Buyukipekci S, Coskun B. Effect of different levels of royal jelly on biochemical parameters of swimmers. *Afr J Biotechnol.* 2011;10(52):10718–10723.
35. Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT statement for randomized trials of nonpharmacologic treatments: a 2017 update and a CONSORT extension for nonpharmacologic trial abstracts. *Ann Intern Med.* 2017;167(1):40–47.

36. Buttstedt A, Moritz RF, Erler S. More than royal food-major royal jelly protein genes in sexuals and workers of the honeybee Apis mellifera. *Front Zool.* 2013;10(1):72.
37. Rezk MYA. Comparative study on the effect of royal jelly on blood glucose and serum lipids in Streptozotocin induced diabetic rats. *Eur J Pharm Med Res.* 2018;4(4):39–44.
38. Nomura M, Maruo N, Zamami Y, Takatori S, Doi S, Kawasaki H. Effect of long-term treatment with royal jelly on insulin resistance in Otsuka Long-Evans Tokushima Fatty (OLETF) rats. *Yakugaku Zasshi.* 2007;127(11):1877–1882.
39. Zamami Y, Takatori S, Goda M, et al. Royal jelly ameliorates insulin resistance in fructose-drinking rats. *Biol Pharm Bull.* 2008;31(11):2103–2107.
40. Ghanbari E, Nejati V, Khazaei M. Antioxidant and protective effects of Royal jelly on histopathological changes in testis of diabetic rats. *Int J Reprod Biomed.* 2016;14(8):511–518.
41. Karaca T, Demirtas S, Karaboga I, Ayvazz S. Protective effects of royal jelly against testicular damage in streptozotocin-induced diabetic rats. *Turk J Med Sci.* 2015;45(1):27–32.
42. Okamoto I, Taniguchi Y, Kunikata T, et al. Major royal jelly protein 3 modulates immune responses in vitro and in vivo. *Life Sci.* 2003;73(16):2029–2045.
43. Zamani Z, Reisi P, Alaei H, Pilehvarian AA. Effect of Royal Jelly on spatial learning and memory in rat model of streptozotocin-induced sporadic Alzheimer's disease. *Adv Biomed Res.* 2012;1:26.
44. Yoneshiro T, Kaede R, Nagaya K, et al. Royal jelly ameliorates diet-induced obesity and glucose intolerance by promoting brown adipose tissue thermogenesis in mice. *Obes Res Clin Pract.* 2018;12(1s1):127–137.
45. Hadi A, Najafgholizadeh A, Aydenlu ES, et al. Royal jelly is an effective and relatively safe alternative approach to blood lipid modulation: a meta-analysis. *J Funct Foods.* 2018;41:202–209.
46. Ramadan MF, Al-Ghamdi A. Bioactive compounds and health-promoting properties of royal jelly: a review. *J Funct Foods.* 2012;4(1):39–52.
47. Sugiyama T, Takahashi K, Mori H. Royal jelly acid, 10-hydroxy-trans-2-decenoic acid, as a modulator of the innate immune responses. *Endocr Metab Immune Disord Drug Targets.* 2012;12(4):368–376.
48. Pavel CI, Mărghitaş LA, Bobiş O, et al. Biological activities of royal jelly-review. *Sci Pap Anim Sci Biotechnol.* 2011;44(2):108–118.