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Effectiveness of royal jelly supplementation in glycemic regulation: A systematic review

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Abstract

BACKGROUND

Royal jelly (RJ) has been observed to have therapeutic properties in diabetic individuals, including the reduction of high blood sugar. This systematic review synthesized existing evidence to investigate the effectiveness of RJ supplementation in managing measures of blood glucose.

AIM

To determine the effectiveness of RJ supplementation on glycemic responses in healthy and non-insulin dependent diabetic adults, as well as animal models of diabetes.

METHODS

This was a systematic review employing the PRISMA strategy. Peer-reviewed, published articles were extracted from several databases using key words related to target population, intervention and outcome and hand-selected for inclusion. Included articles proceeded to data extraction phase, where information on target parameters and effectiveness of treatment was summarized. Following this, the risk of bias for each included study was evaluated. Then, the long-term and immediate effectiveness of RJ supplementation in glycemic control were assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool, which rates the quality of evidence.

RESULTS

Of 168 articles extracted from database searching, eighteen were included for analysis in this systematic review. Across the studies, studied populations, intervention styles and outcome measures were largely heterogeneous. Despite this, the results in studies indicate a general trend of positive effect of RJ in glycemic regulation *in vitro* and *in vivo*. Additionally, some dose-dependent glycemic effects were observed, along with some large effect sizes. The risk of bias for human and animal studies is generally low-unclear risk, although lack of

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blinding is a serious concern in both categories. Overall, as per the GRADE tool, the quality of evidence is low, and very low for long-term and immediate effectiveness of RJ, respectively. A major limitation affecting evidence quality is the heterogeneity among included studies. Fasting blood glucose and glucose clearance appear to be most affected by RJ supplementation.

CONCLUSION

Quality of evidence suggesting that RJ is an effective modulator of glycemic regulation is low for long-term effects of RJ, and very low for immediate effects.

Key words: Royal jelly; Type 2 diabetes; Dietary supplement; Glycemic control; 10-hydroxy-trans-2-decenoic acid; Hyperglycemia; Adults; Animals

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Core tip: Royal jelly (RJ) is a promising natural treatment to improve high blood glucose. Insulin sensitivity, fasting blood glucose levels, and rate of glucose clearance are among the glycemic parameters investigated in the current systematic review that are shown to approach normal levels due to regular RJ intake.

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INTRODUCTION

The incidence of type 2 diabetes (T2D) has drastically increased over the past thirty years, making it among the most taxing diseases for health agencies worldwide^[1-3]. As of 2017, projections for global prevalence of diabetes in 2030 have already been surpassed^[4,5]. By 2040, the prevalence of T2D is expected to reach 642 million worldwide^[5]. The epidemic is believed to stem from rapid changes in society since the 1980s that promote long periods of inactivity, energy and nutrient overconsumption; however, further epigenetic and genetic interactions continue to be explored^[1,2]. T2D is heavily associated with cardiovascular disease and obesity, which largely accounts for the morbidity and mortality in patients with the disease^[6]. Thus, to minimize risk of complications in patients, food intake and concentrations of blood glucose must be tightly managed^[6].

Numerous natural health products, including royal jelly (RJ), have been explored as potential hypoglycemic agents^[7,8]. RJ is a yellow, milky substance secreted by worker honey bees (*Apis mellifera*) through cephalic exocrine glands, such as the mandibular and hypopharyngeal glands^[9]. RJ functions to nourish larvae for the first three days after being reared, although larvae destined to be reproductive queen bees are fed the material throughout their entire larval and adult life^[9]. 10-hydroxy-2-decenoic acid (10H2DA), a fatty acid unique to RJ, is a major compound of interest in blood glucose management for its observed hypoglycemic effects^[7]. Takikawa *et al*^[7] found that 10H2DA significantly increases non-insulin dependent phosphorylation of AMP kinase (AMPK) in skeletal muscle, increasing translocation of glucose transporter type 4 (GLUT4) to cell surface and consequently, glucose transport into the cell. An *in vivo* study examining life-extending effects of RJ found that 10H2DA induces upregulation of molecules involved in caloric restriction, reducing energy intake^[10]. 10H2DA has demonstrated interactions with estrogen receptors leading to alterations in gene expression, potentially including those involved in glucose regulation^[11]. The glucose modulating role of 10H2DA is the most well-investigated mechanism by which RJ might benefit patients with T2D, although other RJ components, such as sebacic acid, may also be important.

In addition to *in vitro* studies, RJ administration has demonstrated therapeutic potential in human and rodent diabetic models. In a randomized controlled trial, Khoshpey *et al*^[12] found that daily ingestion of capsules containing 3000 mg RJ for eight weeks significantly decreased fasting blood glucose (FBG) in diabetic individuals compared to a placebo group. However, the effects of RJ administration

on glycemic control outcomes are inconsistent across studies, possibly due to considerable variation in studied population and intervention. For example, while Khoshpey *et al*^[12] found no significant change in carbohydrate (CHO) intake in the RJ-treated group, Pourmoradian *et al*^[13] found a significant decrease in CHO intake in diabetic individuals in response to daily ingestion of 1000 mg lyophilized RJ for eight weeks. Rodent studies have shown a more pronounced effect: Ghanbari *et al*^[14] found that addition of 100 mg/kg RJ in drinking solution improved circulating insulin and FBG in diabetic mice to levels similar to the healthy control group. Zamami *et al*^[15] observed a similar magnitude of effect in insulin-resistant rats following administration of 300 mg/kg enzymatically treated RJ. It is difficult to apply the results of rodent studies into a human context due to variation in physiologic processes, particularly absorption and distribution of nutrients such as 10H2DA^[16]. Presently, there is a lack of synthesis and analysis of these human and animal studies investigating the therapeutic effects of RJ.

This systematic review will investigate the effectiveness of RJ as a therapeutic agent in individuals with T2D. Specifically, we will assess animal, human and *in vitro* studies examining the effects of administration of RJ and its constituents on various outcomes that relate to glycemic control, such as plasma glucose levels, plasma lipid levels and hemoglobin A1c (HbA1c) levels in healthy and diabetic individuals. Included studies will investigate outcomes following both acute and long-term administration of RJ on glycemic control. The synthesis and evaluation of existing trials provides individuals and health care professionals with a resource to make informed decisions regarding T2D therapy. To our knowledge, no systematic review investigating RJ as a treatment for diabetes exists.

MATERIALS AND METHODS

The guidelines of the 2009 PRISMA model strategy were followed throughout this review^[17].

Search strategy

We conducted a systematic search of peer-reviewed articles relating to the impact of RJ on glycemic outcomes. A set of keywords were developed by Kamel Omer and Genevieve Newton to yield trials with study variables that are appropriate for the research question. These were subsequently searched in five databases: Cochrane Library, CINAHL Plus, PubMed (*via* NCBI), Web of Science, and ProQuest. Operator commands were used to yield studies containing at least one keyword for each variable within the title or abstract. A review protocol does not exist for this systematic review.

Selection of articles

Following extraction and compilation of articles from the database results, duplicate studies were electronically removed. Bibliographies of studies were manually scanned to capture relevant studies. Titles and abstracts were manually screened and articles not meeting inclusion criteria were removed. Full text screening was completed for the remaining articles, where studies not meeting the inclusion criteria were removed. This was conducted in duplicate by Kamel Omer and Maxwell J Gelkopf; final decisions were settled by discussion. The resultant articles proceeded to the quality appraisal stage.

Inclusion criteria

(1) Population: Healthy or diabetic human adults or animal models; (2) Intervention: Oral administration of RJ or its constituents; (3) Outcomes assessed: Direct measures of glycemic control or measures pertinent to glycemic control; (4) *In vitro* studies: Effects of RJ (or constituents) administration were investigated on an outcome directly related to glycemic control; (5) Methodology includes control group for comparison with treatment; and (6) Available in English.

Data extraction

Data on study design, subjects, treatment, and relevant outcomes and results were abstracted for each included study, where applicable, qualitative and quantitative details were added to each of these study variables. For subjects, the extracted number of participants was those that completed the study. Data summaries of each included study were then classified into one of three different tables, depending on study population and intervention style. The classifications are: (1) Acute administration (examining immediate RJ effects) of RJ in human trials; (2) Long-term administration (examining long-term RJ effects) of RJ in human trials; and (3) Long-term

administration of RJ in animal trials and *in vitro* trials.

Risk of bias

For each included human and animal study, the Cochrane Collaboration's risk of bias assessment tool was used to determine the risk of bias^[18]. The tool covers five pre-specified areas of bias: Selection bias (allocation concealment and random sequence generation), performance bias (blinding of participants and researchers), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective reporting)^[18]. The tool also includes an "other bias" category for other sources of bias that do not fall within these prespecified areas^[18]. For each area of bias, the tool provides criteria to rate the study as low, high, or unclear risk of bias. A high risk of bias indicates a high possibility of bias that is likely to impact the study results, while a low risk suggests negligible risk^[18]. An unclear risk of bias indicates that insufficient information is provided to determine if results are impacted by bias, but some doubt is raised^[18].

Two authors, Kamel Omer and Maxwell J Gelkopf, assessed all included articles to reach a consensus on the risk of bias for each study. Higgins *et al*^[18] provides a detailed guide on the ranking procedure, which was applied by reviewers throughout the risk of bias assessment. Although the tool is designed for human trials, O'Connor and Sargeant^[19] developed a modified version for use in risk of bias assessment of animal trials. This modified version was used by the reviewers to guide ranking of risk of bias for the included animal studies. Justification was noted for each judgement, including paraphrases and direct quotes from the article when available.

Quality of evidence

Following determination of the risk of bias for each study, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool was used to rate the overall quality evidence across all included studies for a single outcome^[20]. In this review, GRADE was used to assess the quality of evidence for RJ's capacity to manage blood glucose levels following long-term supplementation of RJ as well as acute effects of RJ administration. The GRADE tool encompasses five domains to determine overall quality: risk of bias, indirectness to research question, imprecision of results, inconsistency between studies and publication bias^[20].

To represent the GRADE rating, a summary of findings table was created. Ranking begins at high quality due to the majority of trials being randomized controlled trial but are gradually degraded if serious concern exists in any of the five domains^[20]. Ranking can also be upgraded if there is no plausible confounding bias, or if magnitude of effect is large or dose-dependent^[20]. The overall ranking is determined by number and magnitude of all downgrades and upgrades^[20]. Each of the four possible rankings directly correspond to a certain overall quality of evidence (very low, low, moderate, high)^[19]. Ryan and Hill^[21] provide criteria for what constitutes a concern in these domains, which was used as a guide for reviewers when determining the GRADE ranking. To factor animal studies in, a modified version of GRADE for animal studies developed by Wei *et al*^[22] was used. Kamel Omer and Genevieve Newton reached a consensus on the GRADE score based on criteria and justification was provided for each decision on the summary of findings table.

Summary measures

To determine effect size and the precision of the quantitative data of the study results, appropriate measures were manually calculated. Standardized mean difference (SMD, also known as Cohen's d) was calculated as described by Faraone^[23] using a pooled standard deviation and sample means of the treatment and placebo group to estimate magnitude of treatment effect. A large effect size constitutes a SMD of > 0.8, while a small effect size is considered to have a SMD of < 0.2; all values in between are medium effect sizes^[23]. A negative value indicates that the treatment reduces the parameter being investigated^[23]. The SMD was calculated for values taken at the endpoint of the study. For studies with multiple treatment groups, the SMD was calculated for the group with highest dosage. Where numerical values were unavailable, values were interpolated from provided graphs. If values were reported as medians, these were used in place of the mean throughout the effect size calculation. As part of the GRADE evaluation, 95% CIs of SMDs for long-term, hypoglycemic outcomes were calculated to assess imprecision of the effect sizes. For simplicity of evaluation and comparison, SMDs were reported in this review for statistically significant outcomes only.

RESULTS

Study selection

The pre-specified search strategy was conducted on March 21st, 2018, yielding 168 results. Grey literature databases were searched, but no pertinent articles were found. One study was captured from scanning the bibliographies of collected studies. After removal of duplicates, the total number of unique studies was determined to be 83. These studies went on to the title and abstract screening. Fifty-seven studies were removed due to not meeting the inclusion criteria at this stage. The remaining 26 underwent a full-text screening to determine eligibility. Of these 26, eight were excluded: two because they were not written in English, two for assessing outcomes not related to glycemic control, one because it lacked an oral intervention in treatment groups, one because the study design did not have a control group, one because it lacked an intervention, and one because it did not target the desired population for this review. The resultant 18 articles were included in the systematic literature review for quality of evidence appraisal (Figure 1).

Study characteristics

Following the systematic search, study characteristics, including intervention style, length, participants and results were manually extracted and summarized into the Tables 1, 2 and 3^[24-36].

Risk of bias within studies

For human trials, the pre-specified areas of bias are generally low risk. The biggest source of concern for bias stems from the lack of transparency of measures taken to prevent a given area of bias. This was particularly evident in the allocation concealment category, as evidenced by the high proportion of human trials at high or unclear risk in that category (Figure 2). Moreover, although many studies claimed that participants and personnel were blinded, description of the actual blinding methodology was rarely provided, suggesting that performance and detection bias are considerable concerns among included human studies. The next biggest source of concern for bias is apparent in the “other bias” section-this is largely due to confounding bias arising from the recruitment of participants from a single source (*e.g.*, common hospital). Overall, of the human trials, domains of bias at high risk are relatively few.

Across the animal studies, the risk of bias is a notably bigger concern. One hundred percent of the studies are considered high risk of detection bias (*i.e.*, group allocations known to outcome assessors), potentially due to blinding being uncommon in animal studies (Figure 3). Attrition bias is another serious concern across the animal studies; most included animal studies excluded some individual subjects from analysis without any explanation. Performance and selection bias, however, are well accounted for in the included animal studies, with nearly 100% of both domains at low risk. Like human trials, reporting bias is not a serious concern in the animal trials (Figure 4).

Overall quality of evidence

The quality of evidence was evaluated as per the GRADE criteria with results shown in Tables 4 and 5. This evaluation integrated study results with risk of bias across all studies included in this review.

Effectiveness

Direct measures of glycemic control (FBG, glucose clearance rate, insulin levels) appear to be appreciably impacted by RJ administration. Most of the included studies which examined FBG and rate of glucose clearance observed significant change from baseline due to oral supplementation of RJ. Of these results, the majority had large effect size estimates, substantiating the role of the intervention in the observations. Most of the studies investigating insulin levels also reported a beneficial effect. Furthermore, in studies with multiple experimental groups, a dose-response relationship was observed in plasma insulin levels and rate of glucose clearance, but not FBG levels. Abnormal regulation of these parameters give rise to other secondary conditions associated with T2D, such as high levels of HbA1c.

The beneficial effect of RJ supplementation was demonstrated by improved indirect measures of glycemic control. These indirect measures are precursors (*e.g.*, high circulating fat) or indicators (*e.g.*, HbA1c) of hyperglycemia. The effectiveness of RJ administration in improving these parameters was not as apparent, as there was no clear trend in outcome responses to RJ treatment. However, when significant changes were detected in the experimental group, these results mostly had large effect magnitude estimates. The inconsistency between observed effects may be due to heterogeneity among the included studies.

The wide range of supplementation forms included in the evidence may explain

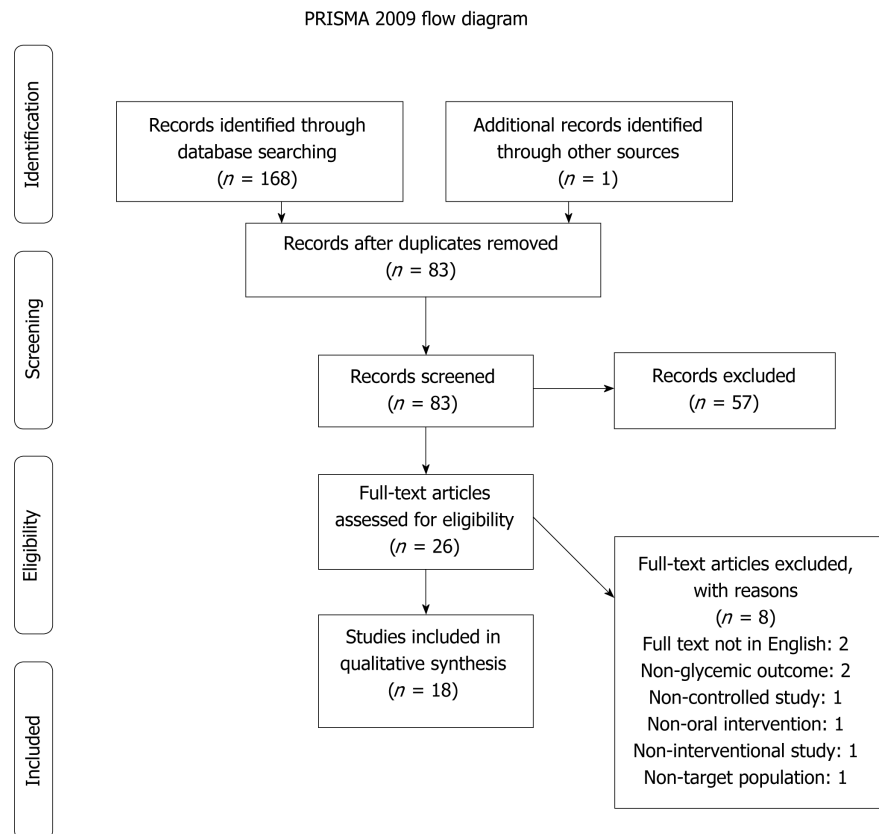


Figure 1 Flow diagram summarizing study selection process.

some of the observed inconsistency between results. For example, many studies used lyophilized RJ, which is known to be chemically different and less bioactive compared to fresh RJ^[27,37]. Numerous clinical trials used enteric coated capsules to deliver RJ, which is known to alter pharmacodynamic properties of compounds^[38]. Some animal and human studies added the supplementation to meals, which may affect effectiveness due to food-drug interactions^[39]. When similar populations were studied, some outcomes showed reduced, negated or contradictory effects in response to RJ as compared to 10H2DA and vice versa, such as between Yoshida *et al*^[36] and Watadani *et al*^[35]. This circumstance indicates the possibility of RJ constituents having interactions amplifying or diminishing effectiveness of certain glycemic outcomes.

Due to the different investigation types and subjects across the included studies, it is important to contextualize the effectiveness for the different populations. The largest improvements to blood glucose were observed in diabetic models, both human and animals. Healthy (human) models had some improvements in blood-glucose parameters; however, for most normal blood-glucose parameters, there is a limit on the possible difference from baseline. Only one *in vitro* was included and was used in this review primarily to elucidate mechanisms and support the *in vivo* results. Thus, the effectiveness of RJ as a glycemic regulator was determined through the lens of diabetic human patients, with the other populations used to support the findings.

Mostly displayed in the rodent trials, there was a marked difference on effectiveness of RJ administration between studies that investigated the effects of RJ between genders, with greater efficacy seen in males. The divergent effects may potentially be due to the estrogenic activity of compounds derived from RJ, particularly 10H2DA and a sterol, 24-methylenecholesterol^[11]. These have weak affinity for estrogen receptors that induce changes in gene expression^[11]. Because these compounds would compete with endogenous estrogen for receptor binding, RJ may not be effective in individuals with elevated estrogen levels (*i.e.*, premenopausal females). Correspondingly, estrogen perfusion has previously been linked to improved hyperglycemic symptoms in postmenopausal females and males, which is consistent with the evidence in this review^[40,41].

Although very few participants in the included study reported undesirable effects of RJ consumption, potential adverse effects in humans are an important factor in their feasibility as a glycemic regulator. One case report found an association between haemorrhagic colitis and daily RJ intake, which had never been documented

Table 1 Human trials examining acute effects of royal jelly treatment

Ref.	Study design	Subjects	Treatment	Outcome measures	Effectiveness
Iaconelli <i>et al</i> ^[24]	Crossover study	N = 10 + 10 healthy individuals and individuals with type 2 diabetes	Each subject went through three studies on different days: 0 g, 12 g, or 23 g of sebacic acid substituted fats in a meal	Glucose clearance: Postprandial Insulin secretion/clearance rate GLUT4 expression in L6 myotube cells	Significantly improved glucose clearance in diabetic subjects only in dose-dependent manner (d = -1.70) Significantly improved GLUT4 expression (d = 0.81) and glucose uptake in L6 cells (d = 0.67) Insulin secretion/clearance decreases significantly in similar fashion between healthy and diabetic patients. Dose-response relationship. For diabetics, d = -1.12
Mobasser <i>et al</i> ^[25]	Randomized controlled trial	N = 20 + 20 adults with type 2 diabetes aged 30-65 in control and treatment groups	15 g of royal jelly ingested orally after overnight fasting	Hyperglycemia: Fasting blood glucose, glucose clearance after royal jelly consumption Hyperinsulinemia: Serum c-peptide and insulin	No significant difference in outcome measures between two groups
Münstedt <i>et al</i> ^[26]	Controlled trial	N = 10 + 10 healthy males, split into experimental and control groups	20 g of fresh royal jelly ingested orally	Glucose clearance: Plasma samples during OGTT Insulin resistance: Serum insulin and c-peptide	Significantly increased rate of glucose clearance (insufficient information for effect size calculation) No significant change in serum insulin profile
Münstedt <i>et al</i> ^[27]	Randomized controlled trial	N = 15 healthy male adults aged 20-34, unspecified distribution between treatment and control groups	0.55 g lyophilized royal jelly in enteric-coated capsule ingested orally	Hyperglycemia: Glucose clearance (OGTT) Insulin resistance: Serum insulin and c-peptide	Improved glucose clearance and decreased plasma insulin, unspecified statistical significance (insufficient information for effect size calculation)

OGTT: Oral glucose tolerance test; GLUT4: Glucose transporter type 4.

previously^[42]. Bronchospasm and anaphylaxis have also been noted in individual cases^[43,44]. The aforementioned cases are possibly due to allergic reactions to RJ proteins^[42,43,44]. Harmful RJ-drug interactions should be considered; consuming RJ while taking warfarin has been associated with hematuria^[45].

DISCUSSION

The present systematic review suggests that RJ has a positive effect on both direct and indirect measures of glycemic control in diabetic and healthy individuals. This general trend was observed in both animal and adult human trials but was more pronounced in the former. In healthy individuals, supplementation of RJ may reduce risk of developing hyperglycemia and insulin resistance. With the evidence presented, RJ is likely more effective as a long-term dietary supplement rather than for acute treatment of hyperglycemia. Effective clinical doses appear to be as low as 1000 mg of fresh RJ daily for diabetic humans, but true values may vary between individuals and supplementation form.

Regulation of glycemic control by 10H2DA

In a normal state, intracellular protein-protein interactions arising from insulin binding to its surface receptor are critical to blood glucose regulation^[46,47]. One major result of the signaling cascade induced by insulin on various tissue types is the translocation of the GLUT4 glucose transporter to the cell surface, which works to import glucose into the cell^[46]. The insulin-dependent pathway also modifies gene

Table 2 Human trials examining effects of long-term royal jelly treatment

Ref.	Study design	Subjects	Treatment	Outcome measures	Effectiveness
Khoshpey <i>et al</i> ^[12]	Randomized double-blind controlled trial	N = 11 females + 12 males aged 20-65 with type 2 diabetes in control group (placebo) N = 13 females + 10 males aged 20-65 with type 2 diabetes in treatment group	3000 mg royal jelly oral capsules once per day for 8 wk. Control received placebo	Macronutrient intake Hyperglycemia: Fasting blood glucose	No significant change in macronutrient intake Fasting blood glucose significantly reduced in comparison to control group (d = -0.87)
Mobasserri <i>et al</i> ^[28]	Randomized controlled trial	N = 25 + 25 females with type 2 diabetes aged 30-65 in control and treatment groups	200 mg royal jelly powder prepared in gel form and served with breakfast for 8 wk. Control group received placebo	Plasma triglyceride	Significantly decreased plasma triglyceride in comparison to control (d = -0.476)
Morita <i>et al</i> ^[29]	Randomized double-blind controlled trial	N = 30 healthy adults 42-83 yr of age in control (placebo) N = 31 healthy adults 42-83 yr of age in treatment group	3000 mg royal jelly in 100 mL liquid daily for 6 mo. Control received placebo identical in appearance	Body weight: BMI Insulin resistance: HOMA-IR Hyperglycemia: HbA1c, fasting blood glucose Plasma triglyceride	Significantly improved fasting blood glucose (d = -0.9596) No significant changes in other outcomes of interest
Pourmoradian <i>et al</i> ^[13]	Human double-blinded randomized clinical trial	N = 23 females aged 30-65 with type 2 diabetes in treatment group N = 22 females aged 30-65 with type 2 diabetes in control group	1000 mg lyophilized royal jelly in soft gel form served after breakfast for 8 wk. Control group received placebo soft gel	Body weight: weight scale before and after study period Macronutrient intake: 24-h recall food questionnaire for 3 d before and after study period	Significantly decreased body weight within same group, before and after intervention (d = -0.3808) Significantly decreased energy intake within same group, before and after intervention (d = -9.52)
Pourmoradian <i>et al</i> ^[30]	Human double-blinded randomized controlled trial	N = 21 females aged 30-65 with type 2 diabetes in treatment group N = 20 females aged 30-65 with type 2 diabetes in control group	1000 mg lyophilized royal jelly in soft gel form served after breakfast for 8 wk. Control group received placebo soft gel	Plasma insulin HbA1c	Significantly decreased plasma insulin and HbA1c and insignificantly decreased fasting blood glucose compared to baseline within same group, before and after intervention. d = 0.016 (HbA1c)
Shidfar <i>et al</i> ^[31]	Human double-blinded randomized controlled trial	N = 23 + 23 adults 25-65 yr old with type 2 diabetes in experimental and control (placebo) groups	1000 mg royal jelly in soft gelatin capsules 3 times daily for 8 wk. Control group received placebo identical in appearance to treatment	Hyperglycemia: Fasting blood glucose Fasting blood sugar Macronutrient intake: 24-h recall diet questionnaire Insulin resistance: HOMA-IR	d = -0.0785 (plasma insulin) Significantly decreased fasting blood levels to more normal range (d = -0.3725) Did not significantly alter macronutrient intake Significantly decreased HOMA-IR: improved insulin sensitivity (d = -0.79)

RJ: Royal jelly; HOMA-IR: Homeostatic model assessment of insulin resistance; BMI: Body mass index; HbA1c: Hemoglobin A1c.

expression and protein activity such as those involved in glycogen breakdown^[46]. Insulin receptor substrate (IRS) proteins are key intermediates in the pathway^[47]. With elevated levels of circulating fatty acids as in diabetic individuals, phosphorylation of IRS proteins is inhibited *via* activation of protein kinase C (PKC)^[47,48]. As a result of decreased sensitivity to insulin, the cellular responses involved in regulating blood

Table 3 Animal and *in vitro* trials examining effects of long-term royal jelly treatment

Ref.	Study design	Subjects	Treatment	Outcome measures	Effectiveness
Ghanbari <i>et al</i> ^[14]	Randomized controlled trial	N = 8 healthy male Wistar rats aged 10-12 wk (control) N = 8 diabetic male Wistar rats aged 10-12 wk N = 8 healthy male Wistar rats aged 10-12 wk receiving treatment N = 8 diabetic male Wistar rats aged 10-12 wk receiving treatment	100 mg/kg BW royal jelly dissolved in 1 mL of water daily for 6 wk	Hyperinsulinemia: ELISA test on plasma sample Hyperglycemia: Fasting plasma glucose	Treatment significantly improved insulin levels (d = 1.67) and hyperglycemic fasting blood glucose (d = -2.72) levels to levels similar to healthy control group
Fujii <i>et al</i> ^[32]	Controlled trial	N = 80 male streptozotocin-diabetic rats aged 5 wk equally split into three experimental groups and one control group	Each experimental group had one of 1, 10, and 100 mg/kg body weight royal jelly administered orally by force for 4 wk. Control group received purified water	Hyperglycemia: Blood glucose (unknown whether fasting) Body weight	Royal jelly administration overall slightly decreased blood glucose levels in non-dose dependent manner (no information on statistical significance) No significant change in body weight between groups
Membrez <i>et al</i> ^[33]	Randomized controlled trial	N = 15 male db/db mice aged 6-8 wk in control group N = 30 male db/db mice aged 6-8 wk equally split in two experimental groups	1 g/kg body weight of sebatic acid was added to chow food in one experimental group, and 10 g/kg body weight SA to second experimental group's chow for 6 wk	Hyperglycemia: OGTT and fasting (plasma samples) HbA1c: Plasma samples Liver gene expression: RNA extracted from liver samples Food intake: Chow consumed	In more heavily supplemented group: Hyperglycemia significantly improved (d = -1.86) and improved glucose clearance (d = -3.20), HbA1c significantly decreased (d = -1.89), ketone bodies significantly increased (d = 1.16), dose response relationship observed, gluconeogenic and lipogenic enzyme expression significantly decreased (insufficient information for SMD estimation), food intake was significantly decreased (d = -1.82).
Takikawa <i>et al</i> ^[7]	<i>In vitro</i>	L6 myotubes grown in cell culture and collected from healthy male mice 7 wk of age	Cell cultured myotubes treated with 10H2DA Mice fed 1.6 mmol/kg 10H2DA	Glucose clearance: GLUT4 translocation to plasma membrane	Significantly improved GLUT4 translocation to plasma membrane in skeletal muscle cells compared to non-treated myotube cells (d = 0.4698)
Yoneshiro <i>et al</i> ^[34]	Controlled trial	N = 8 3-wk old healthy male mice (control) N = 11 3-wk old healthy male mice fed HFD N = 11 3-wk old healthy male mice fed high fat diet with treatment	High fat diet with 5% lyophilized royal jelly powder for 17 wk	Body weight gain Hyperlipidemia: Plasma sample Hyperglycemia: Plasma sample Insulin resistance: HOMA-IR	Body weight gain due to white adipose tissue significantly reduced compared to HFD group (d = -2.82) Significantly decreased levels of NEFA compared to HFD (d = -1.6072) Significantly improved hyperglycemia compared to HFD group (d = -2.04) HOMA-IR significantly decreased compared to HFD group, not significantly different from control group (d = -1.23)

Zamami <i>et al</i> ^[15]	Controlled trial	N = 6 6-wk old healthy male Wistar rats (control, received water)	Two experimental groups: One fed 100 mg/kg and the other 300 mg/kg of dilute enzymatically treated royal jelly supplementation daily for 8 wk	Insulin resistance: HOMA-IR	High fructose diet induced insulin resistance in rats
		N = 5 6-wk old healthy male Wistar rats as vehicle-treated group (received high fructose consumption)		Food intake	Plasma insulin levels and HOMA-IR similar between healthy control group and fructose drinking rats supplemented with 300 mg/kg royal jelly. Dose dependent relationship observed $d = -0.7063$ (effect size of 300 mg/kg royal jelly on fructose drinking rats)
		N = 6 + 6 6-wk old healthy male Wistar rats (received high fructose consumption) in two treatment groups		Body weight	No significant difference in body weight and FBG between groups
				Plasma triglycerides	Plasma triglycerides significantly decreased compared to control dose-dependently ($d = -1.62$)
Watadani <i>et al</i> ^[35]	Controlled trial	N = 7 female KK-Ay mice 5 wk of age in control group	3 mg/kg 10H2DA for 4 wk	Hyperglycemia: Plasma glucose samples collected in intervals after OGTT	Significantly improved glucose clearance ($d = -1.33$) and fasting blood glucose ($d = -1.23$)
		N = 8 female KK-Ay mice 5 wk of age in treatment group		Body weight: Adiposity index of abdominal, mesenteric and retroperitoneal fat tissue	Body weight did not differ between groups
				Insulin resistance: HOMA-IR	Significantly improved insulin sensitivity ($d = -4.44$)
				Glucose regulatory proteins: AMPK, G6Pase, Pck1 levels, GLUT4, GS/GSK in tissue homogenates	Significantly increased levels of G6Pase ($d = 1.22$) and Pck1 ($d = 0.77$) mRNA in liver cells. Significantly increased levels of pAMPK in muscle ($d = 3.13$), but no change in liver. Insignificant increase in GLUT4 in muscle cells. No change in GS/GSK levels between groups
Yoshida <i>et al</i> ^[36]	Controlled trial	16 female KK-Ay mice split into control and experimental groups	10 mg/kg royal jelly in 1/15M phosphate buffer 5 d/wk for 4 wk		Significantly improved rates of glucose clearance ($d = -1.25$)
					Insignificantly decreased body weight
					Significantly increased pAMPK levels in liver ($d = 2.39$) and skeletal muscle ($d = 1.73$). Significantly decreased G6Pase mRNA levels in liver ($d = -1.65$), but no change in Pck mRNA levels. Insignificantly increased GLUT4 levels in skeletal muscle
					Significantly decreased plasma NEFA ($d = -1.42$). No change in plasma TG No significant change in plasma insulin

GLUT4: Glucose transporter type-4; 10H2DA: 10-hydroxydecanonic acid; OGTT: Oral glucose tolerance test; HOMA-IR: Homeostatic model assessment of insulin resistance; GS(K): Glycogen synthase (kinase); AMPK: AMP-dependent kinase; NEFA: Non-esterified fatty acids; HFD: High fat diet.

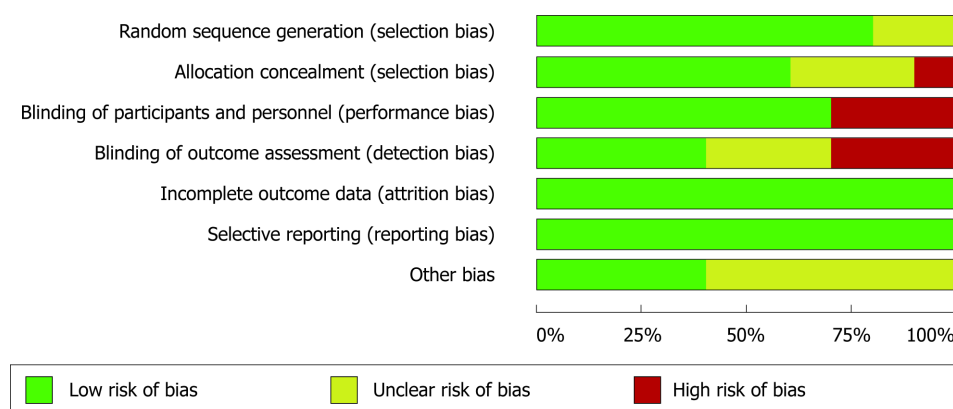


Figure 2 Risk of bias graph showing proportion of bias risk ratings across all included human studies.

glucose are impaired, leading to hyperglycemia^[48].

Intracellular AMPK, which induces similar glycemic responses to insulin in a non-insulin dependent pathway, has been observed to be activated by 10H2DA, the fatty acid derived from RJ that is thought to underlie its glycemic effects^[7,49]. Takikawa *et al*^[7] found AMPK to be activated by 10H2DA *via* activation of CaMKK β (calcium/calmodulin-dependent protein kinase kinase beta). In skeletal muscle, pathways mediated by AMPK have been observed to increase GLUT4 gene expression and translocation^[7,50]. In addition to this, AMPK-mediated regulation of GLUT4 has been observed to improve insulin-stimulated GLUT4 regulation, thus potentially improving response (sensitivity) of insulin receptors bound to ligand^[51]. Moreover, activated AMPK in adipocytes and skeletal muscle are also responsible for enhancing enzymes involved in fatty acid oxidation, thus potentially leading to a decrease in body weight and circulating fatty acids^[36]. Finally, in Yoshida *et al*^[36], increased levels of AMPK following oral administration in mice appeared to stunt activity of glucose-6-phosphatase in hepatocytes, thus suggesting that the kinase can also regulate gluconeogenesis (and therefore glucose export) independently of insulin. By activating an enzyme that works to increase cellular energy levels in the cell, 10H2DA from RJ may mediate the desired hypoglycemic effects in diabetic subjects.

In the hypothalamus, AMPK plays an important regulatory role in food intake^[52]. When activated, a signaling cascade that leads to increased energy intake is initiated^[53]. Downstream of this cascade, mammalian target of rapamycin (mTOR) signaling is known to play a direct and important role^[52]. However, in the presence of 10H2DA, mTOR activity has been observed to be decreased *in vitro*, resulting in decreased energy intake in hypothalamic cells^[10,53]. The beneficial effect of RJ on food intake and body weight is observed in Pourmoradian *et al*^[13], where both parameters were significantly decreased in diabetic female subjects. Following a decrease in macronutrient intake, there is a decrease in fatty acid synthesis and circulating lipids, leading to a decrease in activation of PKC. Thus, RJ's possible action to decrease body weight and food intake is a mechanism that adds to its beneficial effects on glycemic regulation.

As previously mentioned, rodent studies showed a difference between effectiveness of RJ as administered to males compared to females. Fatty acids and sterols in RJ putatively have weak affinity for estrogen receptors, which when activated principally affect gene expression^[11,54]. In addition to affecting transcriptional and translational activity that may regulate glycemic activity, estrogen receptors are able to induce activation of AMPK intracellularly^[54]. Moreover, activated estrogen receptors in skeletal muscle have been shown to amplify GLUT4 translocation^[54]. In the hypothalamus, estrogen suppresses energy intake through mechanisms not fully understood^[54]. Thus, in accord with the evidence collected in this systematic review, activation of estrogen receptors in the body work to increase energy expenditure and decrease energy intake^[54].

Study limitations

Generally, the principal limitation within the included evidence is the wide range of intervention methodology between the included studies. Although this heterogeneity provides data on the various ways to supplement RJ orally (*e.g.*, prandial), there may not be sufficient evidence for one particular intervention method, including duration and dosage of supplementation, to be adopted by health care providers or researchers. As previously described, this variation in intervention methodology also

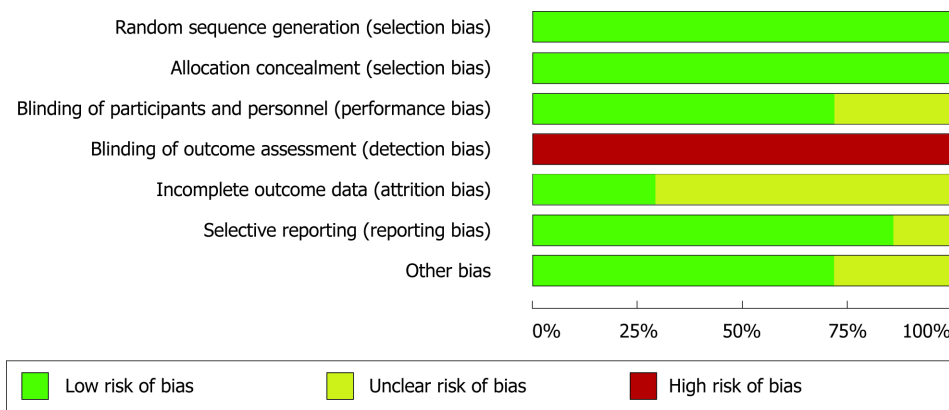


Figure 3 Risk of bias graph showing proportion of bias risk ratings across all included animal studies.

likely contributes to the inconsistency across study results. Moreover, outcomes associated with different interventions at times contradict each other-Watadani *et al*^[35] observed significantly increased expression of G6Pase in liver cells following 10H2DA administration, while Yoshida *et al*^[36] observed significantly decreased expression of G6Pase in liver cells following RJ administration. The source of RJ also differs between studies, which is a potential confounder of the evidence, as the chemical composition of RJ is known to differ between time of year, honeybee age, and geographic location^[55]. Thus, the inconsistency across intervention methods and resultant outcomes is a notable limitation of the overall evidence.

Across human studies, limitations exist largely due to the study populations. Although most of the clinical trials included a balance of male and females, few studies examined exclusively females, and none examined males exclusively. Considering RJ's potential estrogenic activity, a comparison of effects on male and female populations might have provided clearer evidence on the effectiveness of RJ as treatment for diabetes. Notably, the animal studies, which examined exclusively either male or female rodents, displayed differential responses to similar treatment between sexes. Similarly, the age ranges of included subjects in the included trials were relatively wide; inclusion criteria based on tighter ranges (*e.g.*, younger adults, menopausal women) might have determined if certain groups are more affected by the treatment than others, once again potentially due to RJ's activation of estrogen receptors. Moreover, the exclusion and inclusion criteria of the clinical trials affect the generalizability of RJ as treatment for diabetes: For example, many studies excluded individuals who had not taken glucose-lowering medications, or those who had diabetes for a certain length of time. Information on quality of participant dietary patterns and management of diabetes were rarely provided in the included studies but have a large impact on the effect of a supplement such as RJ. These factors are all important when considering the external validity of the synthesized evidence for clinical application.

The main limitation associated with animal studies is the physiological variability between animals and humans. Rodent studies, which comprise a considerable portion of the evidence, are good models of T2D in humans, but lack key pathologies in the disease, including pathologies found in pancreatic islets, the secretion site of insulin^[8]. Moreover, when investigating the effects of an oral agent such as RJ, bioavailability is critical: absorption, distribution and metabolism of nutrients such as fatty acids found in RJ may vary between rodents and humans^[16]. Our preliminary research indicates that bioavailability and metabolism of RJ in human models has not yet been established, so the enhanced response of RJ observed in animal trials may not be applicable to human patients.

Another limitation stems from the similarity between aspects of some studies. A considerable number of the included studies share the same authors, such as Pourmoradian *et al*^[13], Pourmoradian *et al*^[30], Mobasseri *et al*^[28], and Mobasseri *et al*^[25]. As a result, there is noteworthy overlap in the methodology of these studies, although different outcomes are assessed in each. In maintaining very similar study population and methodology, there is the potential for similar undetected bias to affect the results of these studies. Because it presents the risk of the overall evidence misrepresenting RJ's true effect, overlapping methodology between studies is an important factor to consider when interpreting the evidence.

Review limitations

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Fujii 1990	+	+	?	-	+	?	?
Ghanbari 2015	+	+	+	-	+	+	+
Iaconelli 2010	+	+	-	-	+	+	+
Khoshpey 2016	?	?	+	?	+	+	?
Membrez 2010	+	+	?	-	?	+	?
Mobasserri 2014	+	+	+	+	+	+	?
Mobasserri 2015	+	+	+	+	+	+	?
Morita 2012	+	?	+	?	+	+	?
Münstedt 2009	+	+	-	-	+	+	+
Münstedt 2010	?	-	-	-	+	+	+
Pourmoradian 2012	+	+	+	+	+	+	?
Pourmoradian 2014	+	+	+	+	+	+	+
Shidfar 2015	+	?	+	?	+	+	?
Watadani 2017	+	+	+	-	?	+	+
Yoneshiro 2017	+	+	+	-	?	+	+
Yoshida 2017	+	+	+	-	?	+	+
Zamami 2008	+	+	+	-	?	+	+

Figure 4 Risk of bias summary: Judgements about each risk of bias item for all included *in vivo* studies.

The evidence synthesized in this review relied completely on the included studies, which may be unrepresentative of RJ's true effect on the probed outcomes. The exclusion of non-English studies may have removed a considerable number of studies; this is a concern particularly for this topic because almost all the included studies have non-English speaking origins. Also, despite having known insulin-like properties and thus potentially a role in glycemic regulation, no studies on RJ proteins were included in this review^[56]. Lastly, while this review focused on RJ as a dietary supplement, other forms of administration (*e.g.*, topical) may improve effectiveness or bioavailability.

In conclusion, RJ supplementation presents promising potential for treatment of glycemic T2D symptoms. The evidence synthesized in this review complements

Table 4 GRADE assessment for long-term effectiveness of RJ treatment on glycemic control

GRADE criteria	Rating	Support for judgement	Overall quality of evidence
Outcome: Long term glycemic control (<i>n</i> = 14 studies)			
RoB (assessed on Cochrane RoB Collaboration Tool)	No Serious (-1) ¹ Very serious (-2)	Only one study had low RoB for all categories. Most studies had at least one item at high or unclear RoB	High
Inconsistency	No Serious (-1) ¹ Very serious (-2)	Generally, positive clinical effects demonstrated but some studies indicate null effects. There are also large variations in magnitude of effect. Heterogeneity is notable between the studies (in population, intervention and outcome assessment)	Moderate
Indirectness	No ¹ Serious (-1) Very serious (-2)	Evidence synthesized from studies addresses review question with respect to population, interventions and outcome	Low ¹
Imprecision	No Serious (-1) Very serious (-2) ¹	All studies have groups with small sample sizes (≤ 20), with no indication that they meet required sample sizes to detect difference in outcome; observable but statistically insignificant measures in many studies suggest sample sizes were too small to detect difference. 95% confidence intervals of effect size estimates mostly suggest an appreciable benefit for treatment, but there are several that suggest possibility of no meaningful effect	Very low
Publication bias	Undetected ¹ Strongly suspected (-1)	There is chance of publication bias considering the review is entirely "small-scale" trials; this area of research is not well-established and there is potential for publication bias, but none was overtly detected	
Other	Large effect (+1 ¹ or +2) Dose response (+1 ¹ or +2) No plausible confounding (+1 or +2)	Standardized mean difference of studies (effect size) indicates large magnitude of effect of treatment. Dose-response relationships observed	

¹Indicates decision. RoB: Risk of Bias. Adapted from Ryan and Hill^[21] and Wei *et al*^[22].

existing research that demonstrates other therapeutic effects of RJ administration in T2D symptoms, such as oxidative stress, impaired wound-healing and inflammation^[32,57,58]. Future studies should examine the pharmacodynamic properties of RJ, particularly with respect to dosage forms, effectiveness and bioavailability in different populations to further elucidate the effectiveness of RJ as a therapeutic agent of hyperglycemia.

Table 5 GRADE assessment for acute effects of RJ administration on glycemic control

GRADE criteria	Rating	Support for judgement	Overall quality of evidence
Outcomes: Acute glycemic control outcomes (<i>n</i> = 4 studies)			
RoB (assessed on Cochrane RoB Collaboration Tool)	No Serious (-1) Very serious (-2) ¹	Majority of studies had overall high RoB, likely affecting the study results	High
Inconsistency	No Serious (-1) ¹ Very serious (-2)	Outcome effects are somewhat consistent, and studied population are similar enough to not be considered detrimental to evidence quality. Intervention, however, was heterogeneous across all relevant studies	Moderate
Indirectness	No ¹ Serious (-1) Very serious (-2)	Research question is addressed by majority of the animal studies	Low
Imprecision	No Serious (-1) Very serious (-2) ¹	All studies have groups with small sample sizes (≤ 20), with no indication that they meet required sample sizes to detect difference in outcome. For those with calculable effect sizes, the confidence intervals suggest potential for no appreciable benefit	Very low ¹
Publication bias	Undetected ¹ Strongly suspected (-1)	There is chance of publication bias considering the review is entirely “small-scale” trials; this area of research is not well-established and there is potential for publication bias, but none was overtly detected	
Other	Large effect (+1 or +2) Dose response (+1 or +2) No plausible confounding (+1 or +2)	Some dose response relationships observed, however not enough studies to confirm this relationship. Insufficient effect size estimates to determine if effect is large or not	

¹Indicates decision. RoB: Risk of Bias. Adapted from Ryan and Hill^[21] and Wei *et al*^[22].

ARTICLE HIGHLIGHTS

Research background

Existing evidence suggests that royal jelly (RJ) is a promising therapeutic option in hyperglycemic cases. Few studies have specifically examined the clinical viability of RJ as treatment, and no study has critically analyzed the existing evidence. Knowledge of the factors that influence effectiveness of RJ intake provides an alternative treatment for hyperglycemia, which is often associated with diabetes.

Research motivation

This systematic review demonstrated that the intervention style (*e.g.*, length of supplementation, ingestion form) as well as pre-existing patient characteristics may be important factors in its effectiveness, and future research should further investigate these factors to inform patients and health care providers.

Research objectives

This review sought to examine whether there is support for RJ as a glycemic regulator in models of type 2 diabetes as well as healthy individuals. Our analysis found that the existing evidence suggests that RJ is a promising therapeutic option in hyperglycemic cases, with effective doses as low as 1000 mg of fresh RJ daily for diabetic patients.

Research methods

This was a systematic review employing the PRISMA strategy. Five databases were searched using keywords pertinent to the research objectives. Two reviewers conducted full-text screening to select included articles that met eligibility criteria. Relevant information (*i.e.*, intervention style, results, participant characteristics) was extracted from the included articles. Risk of bias was assessed by two reviewers. GRADE, a novel tool developed by Cochrane used to assess overall quality of evidence, was also determined by two reviewers.

Research results

Effective doses of RJ may be as low as 1000 mg of fresh RJ for a diabetic patient. Overall, the quality of evidence for RJ as a treatment is low for long-term effectiveness, and very low for acute effects of RJ consumption.

Research conclusions

Synthesis and analysis of existing studies shows that RJ may be viable as part of a treatment plan in lowering blood sugar. Due to the heterogeneity in studied population and intervention, RJ may have more pronounced effects in certain dosage forms (*e.g.*, fresh RJ) and in certain populations (*e.g.*, postmenopausal females). This information may be useful for individuals and health care practitioners wishing to explore hyperglycemia treatment options.

Research perspectives

Future clinical trials should consider the potential effects of intervention form and length, as well as the effect of participant characteristics to clarify which patient populations or conditions would benefit most from RJ supplementation.

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