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Effects of Royal jelly on metabolic variables in diabetes mellitus: A systematic review

Vahid Maleki[a,b,c], Hamed Jafari-Vayghan[d], Sevda Saleh-Ghadimi[a,b], Mahsa Adibian[e], Sorayya Kheirouri[c], Mohammad Alizadeh[c,*]

[a] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Department of Clinical Nutrition, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Nutrition Research Center, Faculty of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran
[d] Faculty of Health, Arak University of Medical Sciences, Arak, Iran
[e] Department of Clinical Nutrition and Dietetics, Faculty of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

Diabetes mellitus is one of the most common endocrine disorders in the world. This systematic review was conducted with focus on the current knowledge on the effect of royal jelly on metabolic variables in diabetes mellitus. PubMed, Scopus, Embase, ProQuest and Google Scholar databases were searched from inception until June 2018. All clinical trials and animal studies that evaluated the effects of royal jelly on diabetes mellitus, and were published in English-language journals were eligible. Studies that provided insufficient outcomes were excluded. Out of 522 articles found in the search, only twelve articles were eligible for analysis. Seven studies showed a significant reduction in FBS, and one reported HbA1c decrease following royal jelly supplementation. Although royal jelly supplementation resulted in significant reductions in HOM A-I R in three studies, the findings on insulin levels were controversial. In addition, royal jelly substantially improved serum levels of triglycerides, cholesterol, HDL, LDL, VLDL and Apo-A1 in diabetes mellitus. In addition, royal jelly resulted in a decrease oxidative stress indicators and increase antioxidant enzymes levels. In conclusion, royal jelly could improve glycemic status, lipid profiles and oxidative stress in diabetes mellitus. However, exploring the underlying mechanisms warrants further studies.

1. Introduction

Diabetes mellitus is a main danger to human health in today's world.[1] The global prevalence of the disease is rising dramatically.[2] In 2015, the prevalence of diabetes mellitus was 415 million people in the world (8.8%), and it is estimated that the disease will affect439 and 642 million people in 2030 and 2040, respectively.[3,4] Diabetes mellitus includes a group of disorders characterized by hyperglycemia, which is caused by disruption of insulin secretion, its function, or both; this in turn, can be because of genetic predisposition or environmental risk factors or a combination of these.[7] Chronic hyperglycemia with increases oxidative stress and inflammation can lead to macrovascular and microvascular complications.[56] About 10% of these patients have type 1 diabetes, 85% have type 2 diabetes, and the rest are afflicted with other types of diabetes mellitus.[7,8] Hyperglycemia in type 1 diabetes is mainly due to an autoimmune disorder which subsequently leads to destruction of beta-pancreatic cells and decreased production of insulin, while type 2 diabetes occurs following insulin resistance.[9,10] Although various medications are available in the market to control and reduce the complications of diabetes, new strategies are required to provide patients with the most therapeutic benefits and the least adverse effects.[11]

Nowadays, antioxidant compounds and supplements are widely considered for their role in reducing oxidative stress and inflammation, which might help prevent the onset of diabetes or reduce its complications in those affected by the disease.[12,13]

Royal jelly (RJ) is known as a highly nutritious substance, containing major macronutrients, micronutrients and antioxidants. In particular, polyphenols with a viscous and creamy texture are produced by the mandibular glands of worker honeybees and are the essential food for the queen bee.[14–16] RJ is chiefly composed of water (60–70%), proteins (9–18%), carbohydrates (7–18%), lipids (3–8%), minerals

* Corresponding author at: Department of Clinical Nutrition, Faculty of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Golgasht St, I. R., Tabriz, Iran.
E-mail address: mdalizadeh@tbzmed.ac.ir (M. Alizadeh).

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(0.8 = 3%), vitamins, and polyphenols.[17] In addition, RJ has various biological activities such as insulin-like, anti-hypercholesterolemic, hypotensive and anti-tumor functions.[18–21] Also, several studies have revealed some pharmacologic, antioxidant and anti-inflammatory properties for RJ in both human and animal models.[21–23] Despite the several studies that investigated the effects of RJ on metabolic variables such as glycemic status, lipid profile, oxidative stress and inflammation in diabetes mellitus,[24–35] no comprehensive study has been conducted to summarize the findings yet. The purpose of this systematic review is to highlight the available information and to compare findings of the recent human and animal studies on the effects of RJ on metabolic status of patients with diabetes mellitus. Further, knowledge gaps will discuss and suggestions for future studies will provided.

2. Methods

2.1. Information sources and search strategy

PubMed, Scopus, Embase, ProQuest, Google Scholar electronic databases were searched using the keywords “royal jelly” or “major royal jelly” or “pure royal jelly” or “royal jelly supplementation” or “fresh royal jelly” or “RJ” and “diabetes mellitus” or “type 2 diabetes” or “type II diabetes” or “diabetes” or “T2DM”or “type 1 diabetes” or “type I diabetes”or“T1DM”or “noninsulin-dependent diabetes mellitus” or “insulin-dependent diabetes mellitus” or “NIDDM” or “IDDM” or “gestational diabetes mellitus” or “GDM” or “fasting blood sugar” or “glycemic outcomes” or” fasting blood glucose” or HOM A-I R” or “B-cell function” or “insulin secretion” or “impaired glucose tolerance” or “impaired fasting glycaemia” or “glucose intolerant or “glucose tolerant” or “glucose tolerance” or “glucose intolerance”. The search was limited to clinical trials and animal models and the English language papers published until June 2018.Guideline of the Preferred Reporting for Systematic Reviews (PRISMA) used for designing this systematic review. The review protocol has been registered at PROSPERO database of Systematic Reviews (registration number: CRD42018053375).

2.2. Eligibility criteria

Studies were eligible if they met the following criteria (1) all clinical trials (2) animal studies (3) published in English-language journals and studies with (1) insufficient information and (2) *in vitro* models were excluded.

2.3. Selection, extraction, and assessment of studies quality

Two researchers independently screened the titles and abstracts of the articles according to the inclusion criteria; studies that did not meet the criteria were excluded. For quality assessment and data extract at the next step, full-text studies that were eligible were analyzed according to a checklist of aims, research question, and inclusion and exclusion criteria. Then, a third reviewer assessed the quality of the included studies by the primary data extractor. Any disagreements between the reviewers during the processing were resolved through a discussion of the article among reviewers.

2.4. Findings

A summarized flowchart of the studies selection process for the systematic review is presented in Fig. 1. In total, 522 potentially eligible articles were retrieved by the search strategy. Following removal of duplicate records, 457 titles and abstracts remained for further screening. Of these, 438 were excluded as they did not meet the inclusion criteria; 19 full-text studies were reviewed. After reading the full texts of the articles, nine studies were removed for they had the exclusion criteria. Finally, 10 articles were selected for qualitative synthesis (Tables 1 and 2).

2.5. Royal jelly biological activities

In addition to water, protein, carbohydrates, lipids, mineral salts and vitamins, which are the main components of royal jelly, several bioactive compounds including 10-hydroxy-2-decenoic acid (10-HDA), acetylcholine, adenosine, adenosine monophosphate (AMP) N1 oxide, polyphenols and some hormones have been detected in royal jelly.[37] Many biological and health promoting activities are attributed to royal jelly. Protein content of royal jelly exhibits antibacterial and antimicrobial activity,[38,39] wound healing activity in foot ulcers of diabetic patients and hypocholesterolemia effect. [40] Peptides with amino acid residues have radical scavenging properties.[39] Moreover, royal jelly is considered as an antiaging product via its antioxidant effects. It also promotes the ovarian hormones synthesis and maintains follicle stimulating hormone (FSH) and luteinizing hormone (LH) expression in low amounts. In neurodegenerative diseases, mental and physical function is enhanced by royal jelly.[37] Therefore, royal jelly can be introduced as an agent with potent pharmaceutical properties.

Among numerous bioactive compounds, 10-HDA is exclusively found in royal jelly.[40] 10-HDA is an unsaturated fatty acid involved in pharmacological properties of royal jelly including antibacterial, anticancer, immunomodulatory and collagen promoting activities.[41] Moreover, 10-HDA exhibits a unique effect in impaired endothelial cells (EC) exposed to high glucose concentration in diabetic condition. Dysregulated angiogenesis and abnormal de novo vascularization in EC following chronic exposure to high glucose level could be attenuated by royal jelly. 10-HDA contributes in improvement of this medical condition via inhibition of elevated metalloprotease activity and subsequently vascular endothelial growth factor -associated angiogenesis in EC.[42]

2.6. Royal jelly and glycemic control in diabetes mellitus

The first and most important goal in prevention, control and treatment of diabetes mellitus is improving glycemic status and maintaining it within normal range.[43] Antioxidant compounds to improve chronic hyperglycemia can prevent macrovascular and microvascular complications of diabetes mellitus.[44]

2.7. Animal models studies

The effects of RJ supplementation on glycemic parameters have been investigated in animal and human studies. In a study by Rezk et al. administration of 300 mg/kg RJ to diabetic rats for eight weeks resulted in a significant alleviation of glucose, insulin, homeostatic model assessment- insulin resistance index (HOM A-I R) index and insulin resistance. [24] Moreover, Asgari et al. reported significantly reduced glucose after four weeks of 100 and 200 mg/kg RJ administration in animal models of diabetes mellitus.[25]

In another study, mice receiving 10 mg/kg of RJ for eight consecutive weeks showed reductions in hyperglycemia as well as glucose-6-phosphatase (*G6Pase*) gene expression, and increased Glucose transporter type 4 (*GLUT4)* gene expression with no significant effect on fasting serum insulin levels.[26] Also, Ghanbari et al. showed that diabetic rats fed 100 mg/kg RJ for eight weeks had decreased fasting blood glucose, and increased serum insulin levels.[27] Nomura et al., administered 300 mg/kg RJ for four weeks to diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats, and reported that the intervention could reduce insulin and HOMA-IR without any significant changes in blood glucose.[29]

2.8. Human studies

Mousavi et al. conducted a randomized clinical trial on type 2 diabetic patients and reported that RJ reduced blood glucose (11%), but didn’t result in any significant changes in Hemoglobin A1c (HbA1c)

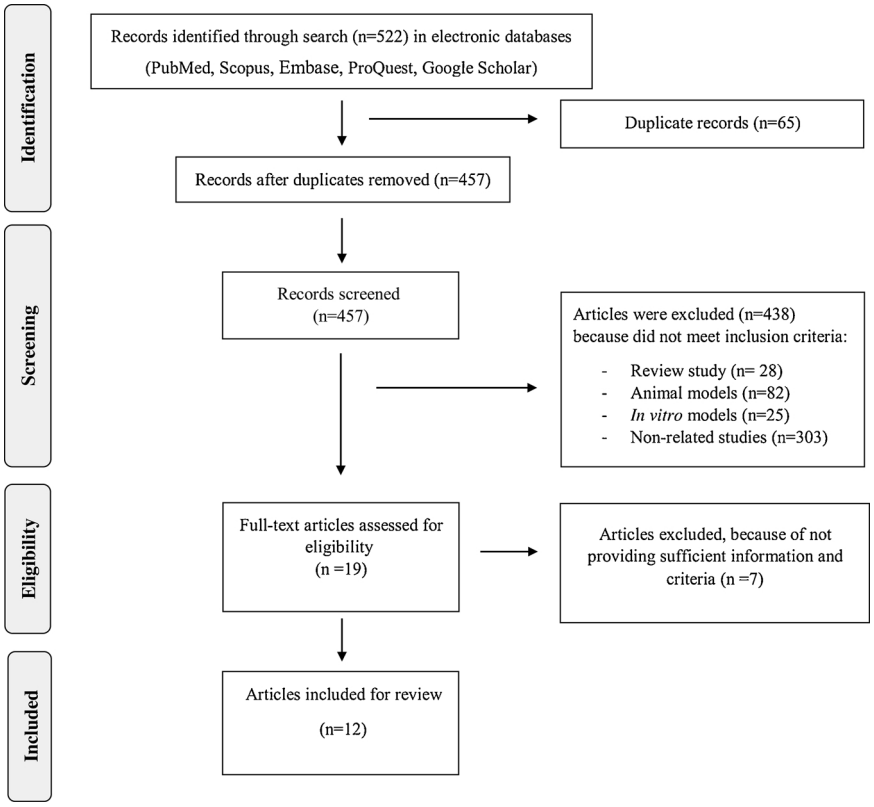

Fig. 1. Flow diagram of the literature search and study selection process.

following RJ supplementation with a 3000 mg/day dose. [30] In another study, Khoshpey et al. showed that RJ supplementation of 3000 mg/day reduced blood glucose levels.[31] However, in the study by Shidfar et al., RJ supplementation with the similar dose and duration, in patients with type 2 diabetes resulted in improved fasting blood glucose and HOMA-IR.[32] In the study by Pourmoradian et al., 1000 mg/day supplementation with RJ for eight weeks caused a reduction in HbA1c, an increase in insulin level; but, there was no significant change in blood sugar.[35] In Mobasseri et al. study, glycemic responses were evaluated after1500 mg of RJ supplementation in patients with type 2 diabetes; no significant changes were observed in glucose, insulin and C-peptide levels.[33]

2.9. Royal jelly and dyslipidemia in diabetes mellitus

Dyslipidemia is one of the most common features of diabetes mellitus which may havea substantial role in pathogenesis of microvascular complications of diabetes, atherosclerosis and coronary heart disease.[45] The effects of RJ on metabolism and serum lipoprotein levels have been reported both in human and animal studies.

2.10. Animal model studies

Asgari et al. showed that 100 and 200 mg/kg RJ supplementation for four weeks significantly decreased triglyceride (TG), High-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol (TC) in diabetic rats.[25] In another study in diabetic rats, administration of 300 mg/kg of RJ for four weeks led to a significant decrease in triglyceride, HDL and very low-density lipoprotein (VLDL) without significant changes in LDL and cholesterol.[24] By contrast administration of 300 mg/kg RJ in OLETF rats did not affect serum triglyceride levels, in another study.[29] Also, in a study by Ghanbari et al., 300 mg/kg RJ administration increased HDL in diabetic rats.[27]

2.11. Human studies

Mobasseri et al. reported that 1000 mg/day of RJ supplementation was able to decrease serum TG and TC in patients with type 2 diabetes, but had no significant effects on HDL and LDL.[34] In a clinical trial conducted by Khoshpey et al., it was found that supplementation with 3000 mg/day RJ for eight weeks in type 2 diabetic patients led to an increase in apolipoprotein (Apo) A-I, and reduction in the ApoB/Apo A-I ratio; but there was no significant change in Apo B levels.[31]

2.12. Royal jelly and oxidative stress and inflammation in diabetes mellitus

Oxidative stress and inflammation play a potential part in the pathogenesis of diabetes mellitus.[46] Chronic hyperglycemia can augment oxidative stress and inflammation, or the opposite way around.[47]

2.13. Animal model studies

In two animal studies, the antioxidant effects of 100 mg/kg RJ for six weeks on the levels of malondialdehyde (MDA) and antioxidant activity of catalase (CAT) were investigated in liver, pancreas and kidney tissues. The results showed that the activity of CAT and the levels of MAD increased and decreased, respectively by RJ supplementation.[27,28]

2.14. Human studies

There are several human studies addressing the effect of RJ on oxidative stress and inflammatory variables in patients with type 2 diabetes. In the study by Shidfar et al., supplementation with 3000 mg/day RJ for eight weeks resulted in an increase in total antioxidant capacity (TAC) in patients with type 2 diabetes, but no significant change was observed in MDA levels.[32] Pourmoradian et al. showed that 1000 mg/day RJ for eight weeks resulted in a significant decline in

Table 1
Characteristics of the included animal studies.

Author, Year Country	Model	Diabetes induced	Daily dose	Duration	Main Outcomes
Rezk et al. 2017 KSA (24)	48 male wistar albino rats (150-200 g) were divided into eight groups (n = 6/group) including non-diabetic control, non-diabetic given RJ, diabetic control, diabetic given RJ, diabetic given glibenclamid, diabetic given metformin, diabetic given RJ with glibenclamide, diabetic given RJ with metformin.	Streptozotocin (60 mg/kg)	300 mg/kg	4 weeks	**Comparison between diabetes given RJ with diabetic control:** **Significant decrease**: Glucose: (46.70%), Insulin: (61.54%), TG: (62.86%), HDL: (18.42%) and VLDL: (51.61%) **Insignificant**: TC, LDL
Asgari et al. 2017 Iran (25)	40 male wistar rats (150-200 g) were divided into the five groups (n = 8/group)control, diabetic rats, glibenclamibe, diabetic given 100 mg/kg RJ and diabetic given 200 mg/kg RJ.	Streptozotocin (60 mg/kg)	100 and 200 mg/kg	4 weeks	**Comparison between diabetes given RJ 100 with control and RJ200 with control:** **Significant decrease**: Glucose (RJ 100: 0.36%) and (RJ 200: 0.87 %) TG (RJ 100: 27.27%) and (RJ 200: 27.27 %) HDL (RJ 100: 50%) and (RJ 200: 25%) LDL (RJ 100: 20%) and (RJ 200: 10%) TC (RJ 100: 14.29%) and (RJ 200: 17.14%)
Yoshida et al. 2017 Japan (26)	16 obese/diabetic KK-Ay mice were divided into the two groups (n = 8/group) including RJ and Vehicle groups.	Genetically were obese/diabetic KK-Ay mice as a model of type 2 diabetes	10 mg/kg	4 weeks	**Significant decrease**: hyperglycemia, expression of *G6Pase* gene. **Significant increase**: Expression of adiponectin, AdipoR1 and pAMPK genes. **Insignificant**: insulin resistance and expression of *GLUT4* gene.
Ghanbari et al. 2016 Iran (27)	32 male wistar rats (190 ± 10 g) were divided into the four groups (n = 8/group) including normal control and diabetic control, normal RJ-treated diabetic RJ-treated groups received RJ/kg.	Streptozotocin (60 mg/kg)	100 mg/kg	6 weeks	**Comparison between diabetes given RJ with diabetes control:** **Significant decrease**: Serum AST: (36.23%), ALT: (45.05%) ALP: (27.21%), FBS: (71.11%) and MDA in liver and pancreas: (41.03%) **Significant increase**: Serum insulin: (40%), HDL: (100%) and CAT in liver and pancreas; (125%)
Ghanbari et al. 2015 Iran (28)	32 male wistar rats (200 ± 10 gr)were divided randomly into four groups (n = 8 per group) including normal control, diabetic control, normal RJ-treated and diabetic RJ-treated groups.	Streptozotocin (60 mg/kg)	100 mg/kg	6 weeks	**Comparison between diabetes given RJ with diabetes control:** **Significant decrease**: Urine urea: (12.39%), Total protein: (62.5%) Albumin: (62%), MDA: (44.13%) **Significant increase**: CAT activity: (63.64%), Creatinine: (41.23%) and Uric acid: (63.37%) **Improve**: histological changes in kidney tissues
Nomura et al. 2007 Japan (29)	Otsuka Long-Evans Tokushima Fatty (OLETF) rats were divided randomly into three groups Effect of long-term treatment with RJ on insulin resistance in including Control, diabetic RJ-treated (10, 30, 300 mg/kg) groups.	OLETF rat as a genitival model of type 2 diabetes	300 mg/kg	4 weeks	**Comparison between diabetes given RJ (300 mg/kg) with control:** **Significant decrease**: insulin (RJ 300: 50%), HOMA-IR (25%) and SBP (7%) **Insignificant**: FBS, TG

RJ; Royal Jelly, **TG**; triglyceride, **HDL**; high density lipoprotein, **VLDL**; very low density lipoprotein, **TC**; total cholesterol, **LDL**; low density lipoprotein, **G6Pase**; glucose-6-phosphatase, **AdipoR1**; adiponectin receptor-1, **pAMPK**; phosphorylated AMP-activated protein kinase, **GLUT4**; glucose transporter type 4, **AST**; aspartate aminotransferase, **ALT**; alanine aminotransferase, **ALP**; alkaline phosphatase, **FBS**; fasting blood sugar, **MDA**; malondialdehyde, **CAT**; catalase, **HOM A-I R**; homeostatic model assessment- insulin resistance index, **SBP**; Systolic blood pressure.

Table 2
Characteristics of the included human studies.

Author, Year Country	Subjects/ Type of Study	Sample Size	Age (years)	Daily dose	Duration	Main Outcomes
Mousavi et al. 2017 Iran [30]	T2DM/RCT	46	25-65	3000 mg	8 weeks	**Significant decrease**: Glucose (11%), SBP (0.6%), DBP (7 %) and IL-6 (18%) **Insignificant**: Hb A1c
Khoshpey et al. 2016 Iran (31)	T2DM/RCT	56	20–35	3000 mg	8 weeks	**Significant decrease**: FBS (12.25%) and ApoB/ApoA-I (0.88%) **Significant increase**: ApoA-I (0.34%) **Insignificant**: Apo B
Shidfar et al. 2015 Iran (32)	T2DM/RCT	46	25-65	3000 mg	8 weeks	**Significant decrease**: Glucose (1.35%) and HOMA-IR (0.17%) **Significant increase**: TAC (0.76%) **Insignificant**: MDA and insulin
Mobasseri et al. 2015 Iran (33)	T2DM/RCT	40	30 - 65	1500 mg	1 and 2 hours	**Insignificant**: C-peptide, insulin, glucose
Mobasseri et al. 2014 Iran (34)	T2DM/RCT	41	30 -65	1000 mg	8 weeks	**Significant decrease**: TG (1.25%) and TC (0.61%) **Insignificant**: HDL (0.14%), LDL (1.86%) and hs-CRP (0.63%)
Pourmoradian et al. 2014 Iran (35)	T2DM/RCT	41	30–65	1000 mg	8 weeks	**Significant decrease**: HbA1c (1.10%) and MDA (33.5%) **Significant increase**: Insulin (712%), SOD (0.99 %) and GSH-px (0.91%) **Insignificant**: FBS, TAC, BMI

T2DM; type 2 diabetes mellitus, **RCT**; randomized controlled trial, **SBP**; systolic blood pressure, **DBP**; diastolic blood pressure, **IL-6**; Interleukin 6, **HbA1c**; Hemoglobin A1c, **FBS**; fasting blood sugar, **ApoB;** Apo lipoprotein B, **Apo A-I**; Apo lipoprotein A1.**HOM A-I R**; homeostatic model assessment-insulin resistance index, **TAC**; total antioxidant capacity, **MDA**; malondialdehyde, **TG;** triglyceride, **TC;** total cholesterol, **HDL**;high density lipoprotein, **LDL**; low density lipoprotein,**hs-CRP**; high-sensitivity C-reactive protein, **SOD**; superoxide dismutase, **GSH-px**; glutathione peroxidase, **BMI**; body mass index**A-I**

MDA levels and an increase in superoxide dismutase (SOD) and glutathione peroxidase (GSH-px) activity; no significant change was observed in TAC levels.[35] The study by Khoshpey et al. is the only available report to evaluate serum levels of Interleukin 6 (IL-6) following supplementation with 3000 mg/day RJ for eight weeks; IL-6 was remarkably decreased in the intervention group.[30]

3. Discussion

In this systematic review, the effect of RJ, as a nutrient substance with antioxidant and anti-inflammatory properties was evaluated on metabolic variables in diabetes mellitus. In total, seven studies showed a significant reduction of fasting blood sugar (FBS) following RJ supplementation,[24–27,30–30–32,] but reduced HbA1c was reported only in one study.[35] Although a significant effect of RJ supplementation on HOM A-I R was reported in three studies,[24,29,32] the results regarding insulin levels were controversial; in two studies its levels increased [27,35] and in one study it decreased, following RJ administration.[24]

All the human studies were conducted among patients with type 2 diabetes. The mean of age and body mass index (BMI) were adjustable between studies. All the studies except Mobasseri et al. 2015 [33] were treated patients with RJ for 8 weeks [31–34,35,] Therefore, regarding to the dose response reaction, we observed that the effect of RJ by 1000 and 1500 mg/ day for 8 weeks on FBS or glucose were no significant[33–35]; but by increase the dose of RJ to 3000 mg/ day for 8 weeks, the mean of FBS or glucose decreased significantly.[30–30–32]

Regarding to the HbA1C%, Mousavi et al reported insignificant decrease in HbA1C% by 3000 mg RJ per day.[30] While the reduction of HbA1C% was significant in the Pourmoradian et al study after treating patients with 1000 mg RJ.[35] This contradiction especially in opposite with what was mentioned about the effect of higher dose of RJ on glucose and FBS may be explained by the base of HbA1C in the patients in the beginning of the two studies. Diabetic patients with the HbA1C% between 7–9% were included to the Mousavi et al study[30]; but there is no statement about the base of HbA1C of diabetic patients in the Pourmoradian et al study.[35] However, the definite conclusion in this regard needs to conduct randomized controlled trials (RCTs) with different dose of RJ.

Previous studies suggest that RJ may lead to improved dyslipidemia.[21,49] According to the evidence and the results of current studies investigating the effects of RJ on the components of lipid profile in diabetes mellitus, RJ improved levels of TG,[24,25,34] cholesterol [24,25,34] HDL,[24,25,27] LDL,[25] VLDL,[24] and Apo-A1(31).

Oxidative stress and inflammation play a key role in insulin signaling, in insulin-sensitive tissues[50]; increased oxidative stress and inflammation lead to decreased insulin sensitivity, increased insulin resistance and mitochondrial dysfunction.[51,52]

Reducing oxidative stress and inflammation caused by chronic hyperglycemia in diabetes mellitus, is the target of many medications and dietary supplements to decrease complications of diabetes mellitus.[13,53–55] Studies have shown that diminishing oxidative stress and inflammation can lead to improvement of hyperglycemia, insulin resistance, dyslipidemia, macrovascular (Cardiovascular diseaseand stroke) and microvascular (retinopathy, nephropathy and neuropathy) complications of diabetes mellitus.[46,56] The antioxidant and anti-inflammatory effects of RJ have been reported in previous studies.[57–62] The results of this systematic review showed that RJ resulted in a decrease in the oxidizing index MDA,[27,28] and increased levels and activity of the antioxidant enzymes CAT,[27,28] SOD,[35] TAC,[32] and GSH-px35. Also, Levels of IL-6 were reduced following RJ supplementation.[30]

The adipose tissue, as an endocrine organ, can release inflammatory and anti-inflammatory adipokines, which can regulate insulin signaling in the skeletal muscle and liver.[63,64] Adiponectin is an anti-inflammatory adipokine, whose secretion decreases from adipose tissue under oxidative stress and inflammation.[65] This adipokine is reported to improve insulin signaling, and decrease hyperglycemia and dyslipidemia via activating AMP-activated protein kinase (AMPK) pathway.[66,67] Yoshida et al. reported that 10 mg/day RJ administration for four weeks in led to increased genes expression of adiponectin, adiponectin receptor and *G6Pase*diabetic rats; it also improved hyperglycemia, but had no significant effect on gene the expression of

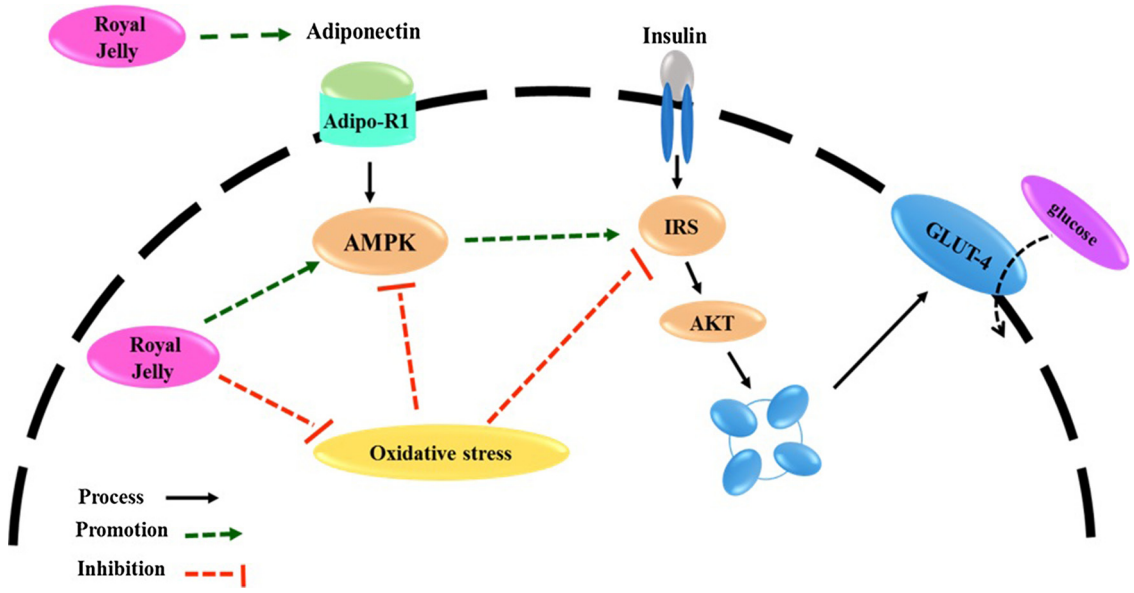

Fig. 2. The possible mechanism for the effect of royal jelly on insulin signaling in skeletal muscle cell. RJ induces secretion of adiponectin and activation of AMPK pathway leading to improved insulin signaling in skeletal muscle cell. Also, RJ reduces oxidative stress, consequently enhancing *GLUT4* translocation to the cell surface.
Abbreviations: RJ; Royal Jelly**, AMPK**; AMP-activated protein kinase**, IRS**; Insulin Receptor Substrate, **AKT**; Protein kinase B, **GLUT4**; Glucose transporter type 4.

GLUT4(26).

According to the current evidence, it seems RJ increases glucose uptake by reducing oxidative stress and inflammation, and enhancing insulin signaling and activating the AMPK pathway. On the other hand, RJ augments secretion of adiponectin and activates the AMPK pathway in the skeletal and liver muscle.[26] Activating this pathway in the muscle leads to an increase in glucose uptake, decrease in gluconeogenesis as well as lipogenesis, and increased glycogen, which ultimately leads to decreased glucose production and improved glycemic index.[68,69] The possible mechanism of RJ effects on insulin signaling is shown in Fig. 2.

3.1. Knowledge gaps and future directions

To find out the exact mechanism of the effects of RJ on metabolic variables in diabetes mellitus, future studies should focus on the effect of RJ on serum levels and gene expression of the factors involved in the AMPK pathway, such as sirtuin-1, fibroblast growth factor-21 and Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α).[70,71]

Studies suggest that AMPK in interaction with sirtuine-1 and fibroblast growth factor 21 (FGF-21) may lead to augmentation of Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) gene expression, and improve mitochondrial function and enhance *GLUT4* translocation to the cell surface.[72]

Also, AMPK pathway activation in liver leads to inhibition of Forkhead transcription factor FKHR (Foxo1), robust increase of gluconeogenic enzyme gene expressions, and decrease of lipogenesis enzyme gene expressions, inhibiting sterol regulatory element-binding protein-1c (SREBP-1C) and acetyl coenzyme A carboxylase (ACC).[73] Therefore, it is recommended that in future studies, the effects of RJ on other activities involved in AMPK signaling pathways be investigated.

Studies have recommended that antioxidant compounds can reduce microvascular complications (retinopathy, neuropathy, and nephropathy) caused by diabetes mellitus.[74] One of the most important mechanisms for development of these complications is increased production of advanced glycation end products (AGEs) due to chronic hyperglycemia.[75,76] Evidence suggests that antioxidant compounds can reduce the production of AGEs.[77–79] Therefore, assessing the effects of RJ on AGEs levels in future studies can increase our knowledge about the effect of RJ on microvascular complications of diabetes.

Patients with diabetes mellitus are at a higher risk for atherosclerosis.[80] It is associated with an increase in the incidence of cardiovascular diseases and stroke.[81–83] Studies suggest that antioxidants can prevent the onset and progression of the disease by reducing oxidative stress and inflammation.[84–86] It is suggested that future studies investigate the effect of RJ on the variables involved in vascular injury and atherosclerosis.[87,88] Myokines are new markers secreted from skeletal muscle, which regulate oxidative stress, inflammation, insulin signaling, and mitochondrial function.[89–92] Therefore, evaluation of the effects of RJ on gene expression and serum levels of “myokines” are recommended in future studies.

Increased secretion of inflammatory adipokines leads to exacerbation of chronic inflammation and oxidative stress.[93,94] Future clinical trials on the effects of RJ on adipokines can increase our knowledge and understanding in this regards.

4. Conclusion

As a whole, the results of this systematic review study showed that RJ may help improve glycemic status and oxidative stress in diabetes mellitus. However, the effects of RJ on lipid profile are contradictory. Also, studies on the effect of RJ on inflammatory markers in diabetes mellitus were not enough. Due to the gaps in our knowledge, and the future direction in this area, more studies are required to determine the exact mechanisms by which RJ improves diabetes mellitus.

Conflict of interest

The authors declare that they have no conflict of interests.

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