Food and Chemical Toxicology 125 (2019) 494–502

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

Antidiabetic effect of quercetin: A systematic review and meta-analysis of animal studies

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ARTICLE INFO

Keywords:
Diabetes
Quercetin
Flavonoids
Meta-analysis
Systematic review

ABSTRACT

Quercetin is a plant polyphenol with biological activities such as anti-inflammatory, anticancer, antidiabetic, neuroprotective and anti-allergic. The objective of this review is to provide a systematic evaluation of the evidence and a meta-analysis of data from previously published researches on the antidiabetic action of quercetin. A comprehensive literature search was conducted between July 2018 and August 2018 on PubMed, EMBASE, Web of Sciences and Scopus databases. A random-effects model was used to estimate the pooled effect size and studies were weighted according to an estimate of the mean difference. The heterogeneity between studies was assessed using a Higgins' I2 test with corresponding p values. Overall 13 eligible articles with appropriate data on serum glucose were included in the statistical analysis. The meta-analysis for serum glucose level (mg/dL) showed that at doses of 10, 25 and 50 mg/kg there was a significant difference between the means. Therefore, the results of the meta-analysis support the hypothesis that quercetin lowers serum glucose level, at doses of 10, 25 and 50 mg/kg.

1. Introduction

Diabetes mellitus is a serious global health problem characterized by hyperglycemia which is caused by an absolute or relative deficiency of insulin or by insulin resistance at the cellular level (Issa and Bule, 2015). Type 2 diabetes mellitus (T2DM) is the most prominent ailment accounting for approximately, 90–95% of patients with diabetes (Issa and Hussen Bule, 2015). T2DM is mainly marked by glucose intolerance, high fasting and postprandial serum glucose level, tissue insensitivity to insulin, decreased insulin secretion and obesity (Rahmani et al., 2018). Deterioration of diabetic conditions particularly poor glycemic control leads to life-threatening complications (Trikkalinou et al., 2017). Increased production of reactive oxygen species (ROS) and impaired antioxidant defense are the basic molecular mechanisms that enhance oxidative stress (OS) in diabetes (Kabel, 2014). Various evidences have shown a high level of free radicals and oxidative stress biomarkers in tissue samples of diabetic patients (Tabatabaei-Malazy et al., 2016). The excessive presence of free radicals and OS biomarkers is mainly due to hyperglycemia, which is responsible for overproduction of mitochondrial ROS in diabetes (Bhat et al., 2013). The ROS, including O_2^-, OH^-, and H_2O_2, are capable of damaging cellular macromolecules such as lipids, proteins, and DNA (Metere et al., 2012). Free radical-induced OS is involved in the pathogenesis of various diseases (Maqbool et al., 2016), which occurs through four basic mechanisms; DNA damage, protein oxidation, membrane lipid peroxidation and disturbance in reducing equivalents of the cell (Bhat et al., 2013).

Herbal medicines have been implicated in chronic disorders

Abbreviations: CI, confidence interval; Mesh, medical subject headings; PICOT, Participants, Interventions, Comparisons, Outcomes and Time; PRISMA, Preferred Reporting Items for systematic reviews and Meta-Analyses; ROS, reactive oxygen species; OS, oxidative stress; SD, standard deviation; SMD, standardized mean difference; T2DM, Type 2 diabetes mellitus; CVD, cardiovascular disease; HED, human equivalent doses; FDA, Food and Drug Administration

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https://doi.org/10.1016/j.fct.2019.01.037
Received 16 November 2018; Received in revised form 27 January 2019; Accepted 30 January 2019
Available online 05 February 2019
0278-6915/

treatment both in the developed and developing countries among the people and scientists working in the area (Baharvand-Ahmadi et al., 2016; Hasani-Ranjbar et al., 2009; Ríos et al., 2015; Tabatabaei-Malazy et al., 2018; Tiwari et al., 2018). Quercetin is the dietary flavonoid that has attracted the attention of the scientific community mainly because of its biological activity and its widespread availability in dietary sources. The daily dietary intake of quercetin accounts for approximately 75% of our total flavonol intake (Xiao et al., 2018). Quercetin exists in fruits and vegetables as glycoside and appears in the form of quercetin aglycone conjugated to sugar moieties such as glucose or rutinose (Guo and Bruno, 2015). For instance, the glycoside derivative of quercetine, quercetin-3-rhamnoglucoside or rutin is present in plants (Erlund, 2004). The glycoside quercetin is deglycosylated by lactase-phlorizin hydrolase (LPH) or cytosolic β-glucosidase (CBG) to its aglycone form in the intestinal cells and then will be absorbed after conjugation into glucuronide/sulfate conjugates. However, all quercetin glycosides are not substrate to the hydrolytic enzymes in the small intestine. Thus, the bioavailability of quercetin glycosides is mainly affected by the kind of sugar moiety. Nevertheless, studies have suggested that successive intake of quercetin can improve its bioavailability. In addition, the introduction of sugar moiety and glycosylation has been demonstrated to improve the absorption of quercetin (Rimbach and Schwarz, 2016; Terao, 2017). Onion is known to contain up to 1.3 g/kg dry matter and others like cranberry, black chokeberry, lettuce, tomato, chili pepper, broccoli, and apple also contain a high level of quercetin (Grzelak-Błaszczyk et al., 2018; Guo and Bruno, 2015). Dietary intake of quercetin is highly recommended and it is associated with health benefits (Petersen et al., 2018). Dietary supplementation is widely applicable at a dose of 200–1200 mg/day. Moreover, it is also taken as a nutraceutical via functional foods at an amount of 10–125 mg per serving (Lesjak et al., 2018). Quercetin has different pharmacological actions including anti-inflammatory, anticancer, antidiabetic, neuroprotective, cardioprotective, prophylaxis of osteoporosis and anti-allergic (Xu et al., 2017). In particular, the antioxidant potential of quercetin studied *in vitro* and *in vivo* in rodent models showed the effect by increasing the mitochondrial activity along with suppressing atrophic factors (Funakoshi et al., 2018). Structurally its antioxidant and strong chelating actions are the results of catechol groups in the ring B and free OH groups of the A ring and or C ring (Fig. 1) (Xiao et al., 2018). Although various preclinical studies have assessed the antidiabetic activity of quercetin the overall impact of these studies hasn't been investigated. Therefore, this review provides a systematic evaluation of the evidence of the antidiabetic action of quercetin. Besides, a meta-analysis of data from previously published researches is conducted to statistically evaluate the effect of quercetin on diabetes.

2. Methods

A systematic review of published studies reporting the effects of Quercetin on diabetes was undertaken using a pre-specified protocol (Participants, Interventions, Comparisons, Outcomes and Time (PICOT)) in accordance with the Preferred Reporting Items for systematic reviews and Meta-Analyses (PRISMA) (Moher et al., 2009).

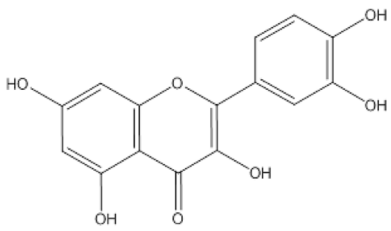

Fig. 1. Chemical structure of quercetin. MarvinSketch (Marvin JS 18.30.0, 2018, ChemAxon; http://www.chemaxon.com) was used for drawing the chemical structures.

2.1. Search strategy

A comprehensive literature search was conducted between 13 July 2018 and 03 August 2018 on: PubMed, EMBASE, Web of Sciences and Scopus databases. The search was updated on 16 Dec 2018 in order to include newly published articles. The following search terms were used in the search: hypoglycemic Agents, antidiabetic, diabetes, diabetes mellitus, type-1 diabetes, type-2 diabetes, glucose, insulin, insulin resistance, metabolic syndrome and quercetin. Similar search terms were used for EMBASE, Web of Sciences and Scopus databases. The search strategy includes keywords, explode search, and medical subject headings (MeSH) terms. There was no limit on language, type of publication, sample size, study design, and exposure or outcome measurement method (Supplementary Table 1).

2.2. Eligibility criteria

Studies were considered eligible if they satisfied the following criteria: a) experimental study design b) *in vivo* animal study c) administered quercetin d) measured serum glucose before and after intervention e) used appropriate control groups and f) published in English. In contrast, studies were excluded if they were *in vitro* or *ex vivo* model study, patient study, review articles, editorial or protocols, letters, conference abstracts, and abstracts without details. This study focused on *in vivo* animal studies in order to show the research gaps in the area and indicate future directions on the antidiabetic activity of quercetin.

2.3. Data collection, synthesis and extraction

Primarily, the articles were screened based on the title and abstract. Then, the relevant full-text articles were retrieved and evaluated for eligibility according to the inclusion and exclusion criteria. Discrepancies were resolved through discussion and consensus was reached. The data extraction was executed via a standard data extraction form based on first author's last name, year of publication, study design, study setting and country, study animal species, sex, sample size, rout of administration, and method of disease induction. The data from different species are treated separately to accommodate inter-species differences. Serum glucose level, glycated Hb, and serum insulin level are the main disease condition indicators in diabetes. However, the serum glucose level is the most consistently reported variable. Thus, we have utilized only the data on serum glucose level in the meta-analysis. In addition, in cases where there were missing data and results of the studies were presented in graphs, we have sent an email request to 16 authors to obtain the detailed data sets and only one replied (Ahmed et al., 2018b). We excluded those studies which lack appropriate control groups, appropriate outcome measurement and do not presents results in figures.

2.4. Quality of assessment

The quality and strength of the included studies were assessed by adopting a standard from SYRCLE's risk of bias tool (Hooijmans et al., 2014b) and CAMARADES checklist for study quality “Gold Standard Publication Checklist to Improve the Quality of Animal Studies”, published by Radboud University Nijmegen Medical Centre (Hooijmans et al., 2010) (Supplementary Table 2). Hence, the percentage quality score of the studies was calculated and those with a high score were subsequently used in the sensitivity analyses.

2.5. Statistical analyses

Meta-analysis was performed using StatsDirect. SDs of the mean difference were calculated using the formula: $SD = \sqrt{[(SD_{pretreatment})^2 + (SD_{posttreatment})^2 - (2R \times SD_{pretreatment} \times SD_{posttreatment})]}$, assuming a correlation coefficient (R) = 0.5 (Serban et al., 2016).

Summary estimates were obtained by means of a random-effects model and studies were weighted according to an estimate of the mean difference. The effect size was expressed as standardized mean difference (SMD) and 95% CI. The heterogeneity between studies was assessed using a Higgins' I^2test with corresponding p values. The I^2 statistics ranging from 0 to 100% (Higgins and Thompson, 2002). A large I^2 indicates that the total variation between studies is due to true heterogeneity rather than chance. In this study analysis, where $p \leq 0.1$ or $I^2 \geq 50\%$ was observed, subgroup analyses were conducted. Subgroup analyses were conducted to assess the source of heterogeneity and to examine the robustness of the pooled effect estimate, where subgroup analyses were defined based on the duration of the intervention. The effect of aberrant studies was examined via sensitivity analyses after the exclusion of studies with low and poor quality, as classified by the quality of the study (based on SYRCLE's risk of bias tool and CAMARADES quality assessment). To identify publication bias funnel plot, Begg's test and Egger's test were conducted (Egger et al., 2008). This systematic review was registered at PROSPERO, International prospective register of systematic review with registration number PROSPERO CRD42018107098 (http://www.crd.york.ac.uk/PROSPERO).

3. Results

3.1. Study selection

The electronic database search strategy retrieved a total of 6466 documents (1453 records from PubMed, 1082 from Web of Science, 1933 from EMBASE and 1998 from Scopus) of which 3776 were unique. These articles screened were assessed based on title, abstract and inclusion criteria, 3655 records were excluded and the rest 121 were retrieved and evaluated against the eligibility criteria. After detailed screening of the full-text articles, 108 of them were excluded and the rest 13 articles (Adewole et al., 2007; Anjaneyulu and Chopra, 2004; Bhutada et al., 2010; Elbe et al., 2015; Maciel et al., 2013; Mahesh and Menon, 2004; Maksymchuk et al., 2017; Narenjkar et al., 2011; Shetty et al., 2004; Srinivasan et al., 2018; Torres-Piedra et al., 2010; Velescu et al., 2017; Wu et al., 2014) were enrolled in the study (Fig. 2). In addition, Google Scholar was searched manually in order to avoid exclusion of potentially related study but none was found. Out of the 108 documents excluded, 16 authors were requested via email in order to obtain the detailed data sets and only one (Ahmed et al., 2018a) stated they have not worked on the requested data type.

3.2. Study characteristics

The characteristics of the studies included in this work are displayed in Table 1. Thirteen eligible articles with appropriate data on serum glucose were included in the statistical analysis. All the included studies were case-control and have measured the serum glucose levels before and after the intervention. Out of the total 13 studies included, 12 studies reported the mean serum glucose level and 1 study reported the mean difference of the serum glucose (Torres-Piedra et al., 2010). There was a large variation in the duration of intervention, age of the animal and the sample size, which ranges from 1 to 45 days (Ammar and Al-Okbi, 1988; Mahesh and Menon, 2004), 3–16 weeks (Coskun et al., 2005; Wu et al., 2014) and 10–40 animals (Maciel et al., 2013; Maksymchuk et al., 2017; Srinivasan et al., 2018; Torres-Piedra et al., 2010), respectively. The studies included were all conducted in rats. Two studies out of 13 were on female (15.4%), one study used both gender (5.7%) and 8 studies were on male (61.5%) rats. Two studies have not reported the gender of the animals (Ammar and Al-Okbi, 1988; Torres-Piedra et al., 2010).

3.3. Meta-analysis

The results of the outcome measures for serum glucose are summarized in Fig. 3. The overall meta-analysis included 13 studies and four doses; 5, 10, 25 and 50 mg/kg of quercetin. In the meta-analysis conducted for the dose, the 5 mg/kg dose included two studies, the 10 mg/kg and 25 mg/kg doses included four studies each and the 50 mg/kg dose included six studies. In the 5 mg/kg dose the overall pooled SMD was 0.26 (95%CI: -0.67, 1.19) and P value was 0.585 (Fig. 3). This showed that the serum glucose level was not significantly different between the intervention and the control group animals. In contrast, the trend observed for the 10, 25 and 50 mg/kg doses showed there is a significant difference between the means; where their overall pooled SMD and P values were −3.95 (95%CI: -7.92, 0.01), 0.051; −6.67 (95%CI: -9.77, −3.56), 0.000; and −5.46 (95%CI: -8.36, −2.55), 0.000 respectively (Fig. 3). These three doses (10, 25 and 50 mg/kg) included 12 studies with SMD (95% CI) and a P value that indicated quercetin has significantly reduced the experimentally induced rise in serum glucose level. Likewise, the linear regression analysis shows a similar dose-response relationship, with a decrease of 1.63 mg/dL serum glucose for one mg/kg increase in dose of quercetin (Beta = −1.63; 95%CI: -2.94, -x.xx; p = 0.0016). The overall study heterogeneity was high. It was recorded to be (I^2 = 80.7%, p = 0.000) at 5 mg/kg, (I^2 = 94.9%, p = 0.000) at 10 mg/kg, (I^2 = 94.6%, p = 0.000) at 25 mg/kg and (I^2 = 94.1%, p = 0.000) at 50 mg/kg.

3.4. Subgroup analysis

To assess the source of heterogeneity in the included studies a subgroup analysis based on the duration of intervention was performed. The result of overall subgroup analysis by duration of intervention (≤14 days, 14–28 days and ≥28 days) showed a significant beneficial effect of quercetin in all doses except at the dose of 5 mg/kg. The 5 mg/kg dose had an overall P value of 0.585 showing there was no significant difference between the two groups in all the three intervention periods. On the other hand, the 10 mg/kg dose showed a significant difference between its groups during the 14–28 days intervention period with a P value of 0.000. The other two doses (25 and 50 mg/kg) also demonstrated a significant difference between the control and their intervention groups with a corresponding overall P value of 0.000. The 25 mg/kg dose showed a significant difference between the groups during the ≥28 days period intervention with a P value of 0.017 while the 50 mg/kg showed a significant difference between the two groups during 14–28 days and ≥28 days intervention with respective P values of 0.046 and 0.013. However, the overall study heterogeneity remained high after subgroup analysis also (I^2 = 94.9%, 10 mg/kg; I^2 = 94.6%, 25 mg/kg; I^2 = 94.1, 50 mg/kg).

3.5. Methodological quality of studies

The results of the quality assessment of the 13 studies included in the meta-analysis are shown in (Supplementary Table 2). The average point reported for the studies is 10 out of 18 characteristics (57.3%) and the lowest is 7 out 18 items (38.9%) whereas the highest is 14 items out 18 (77.8%). The quality assessment in this study comprised 18 parameters adopted from SYRCLE's risk of bias tool and CAMARADES checklist for study quality in animal studies. Some of the points in the checklist were not scored by most studies assessed. In particular points such as sample-size calculation before the start of the experiment (0.00%), blinding (0.00%), numbers and reasons for exclusion (7.6%), and the total numbers of animals included in the statistical analyses (7.6%) were ignored by majority of the studies. Despite the unprecedented evidence of temperature's impact on animal behavior, 39% of the studies did not report whether the body temperature of the animals was properly regulated (Supplementary Table 2).

3.6. Sensitivity analysis

To assess the robustness of our findings, a sensitivity analysis was

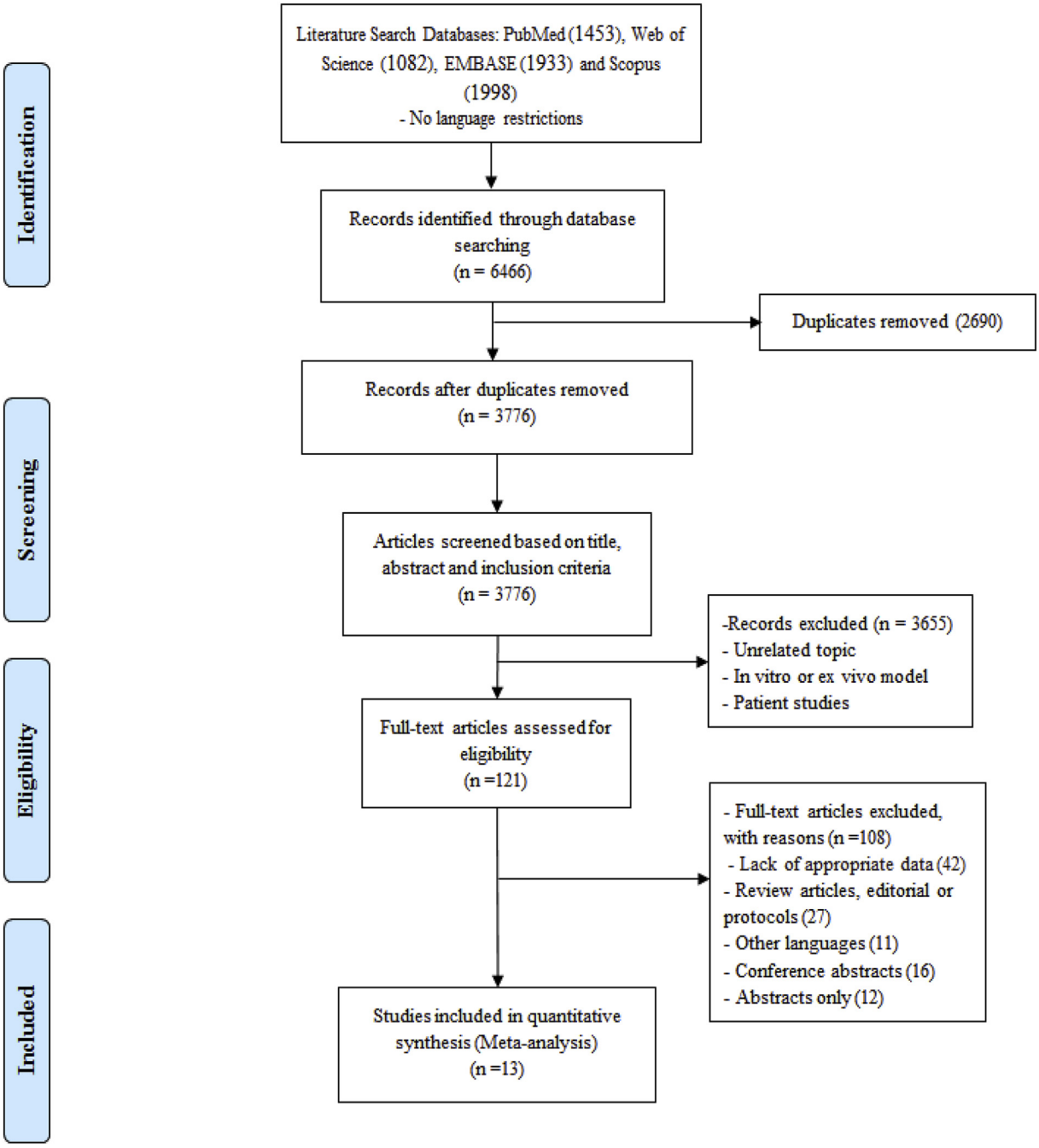

Fig. 2. Search strategy.

performed by removing data from the meta-analytic model. This is to examine the effect of low quality and high-bias-risk studies on the overall estimate. The result of the sensitivity analysis showed that the overall pooled SMD at 5, 25 and 50 mg/kg was 0.26 (95% CI: -0.67, 1.19; $I^2 = 80.7$), −3.60 (95% CI: -6.26, 0.95; $I^2 = 91.6$), and −1.41 (95% CI: -3.78, 0.96; $I^2 = 89.5$), respectively. The sensitivity analysis showed that quality scores did not significantly affect the overall pooled prevalence, and the heterogeneity remained significant (Table 2).

3.7. Publication bias

The existence of publication bias was assessed for all the doses used in the intervention. Visual analysis of funnel plots revealed that most of the studies have a publication bias. According to the Egger's test performed to evaluate the publication bias, there was a significant publication bias demonstrated with a P value of 0.037 at 10 mg/kg, 0.001 at 25 mg/kg and 0.018 at 50 mg/kg. However, the publication bias appears to be statistically not significant at 5 mg/kg dose with a P value of 0.462.

4. Discussion

Nearly 800 medicinal plants are reported to have antidiabetic activity according to ethnobotanical studies. For instance, the hypoglycemic drug metformin is a natural product isolated from the *Galegaethlinasis* (Fabaceae) plant. Hence, herbal medicines with known safety and efficacy can serve a better alternative for treating diabetes. The flavonoids are secondary plant metabolites with a demonstrated antidiabetic activity. The flavonoid quercetin is one of the dietary polyphenols with a strong antioxidant activity (Braga et al., 2013;

Table 1
Study characteristics.

Authors name	Year of publication	Country	Duration (Days)	Age (Wks)	Sex	Species	Diabetes induced	Rout of admn.	Freq./day	Sample size	Quality (%)
Maciel et al. (2013)	2013	Brazil	40	7–9	Male	Rat	STZ	P.o.	1	40	77.8
Velescu et al. (2017)	2017	Romania	28	–	Male	Rat	Alloxan	P.o.	1	16	72.2
Bhutada et al. (2010)	2010	India	30	–	Male	Rat	STZ	P.o.	2	24	66.7
Narenjkar et al. (2011)	2011	Iran	42	10–12	Male	Rat	STZ	I.p.	1	16	50.0
Anjaneyulu and Chopra (2004)	2004	India	28	–	Male	Rat	STZ	P.o.	1	14	38.9
Shetty et al. (2004)	2004	India	42	–	Male	Rat	STZ	P.o.	–	14	38.9
Adewole et al. (2007)	2007	S. Africa	30	12	Male	Rat	STZ	I.p.	1	32	50.0
Elbe et al. (2015)	2015	Turkey	30	–	Male	Rat	STZ	I.p.	1	14	66.7
Mahesh and Menon (2004)	2004	India	45	–	Female	Rat	STZ	I.g.	1	16	55.6
Maksymchuk et al. (2017)	2017	Ukrain	30	6	Male	Rat	STZ	P.o.	1	10	55.6
Srinivasan et al. (2018)	2018	India	28	7–8	Male	Rat	STZ	P.o.	1	10	61.1
Torres-Piedra et al. (2010)	2010	Mexico	5	–	–	Rat	STZ	I.g.	1	10	55.6
Wu et al. (2014)	2015	China	21	3	Female	Rat	HFD	I.g.	1	20	55.6

Shetty et al., 2004; Sirovina et al., 2013; Steyn et al., 2018; Tabatabaei-Malazy et al., 2015). It belongs to the class of flavonols that have the 3-hydroxyflavone backbone (D'Andrea, 2015). Quercetin's antioxidant action is mainly via two mechanisms; radical scavenging and metal chelating (Islam et al., 2013). A great number of experimental studies showed its valuable actions on metabolic disorders including CVD, diabetes and obesity. In human it is found to act through inducing nitric oxide release in CVD and reducing ROS production in metabolic disorders (Rezvan et al., 2018). In a randomized, placebo-controlled, double-blind trial on diabetic type-1 and type-2 patients with neuropathy. It is reported that quercetin topical preparation is well tolerated that improves symptoms of peripheral neuropathy (Eid and Haddad, 2017). In addition, a study in Finland has demonstrated that dietary quercetin intake reduces the risk of type-2 diabetes (Song et al., 2005).

This systematic review and meta-analysis of literature also report on the antidiabetic activity of quercetin in animal models. In this review, random effect models were used for the meta-analysis and Higgins I^2 statistic was used considering the likelihood of significant heterogeneity among studies. The important outcome measure assessed in this study was the serum glucose level. The outcome measure was evaluated in different doses and durations. The forest plot of studies comparing the reduction in blood glucose showed a distinct reduction in the quercetin treated groups as compared to the control. Similarly, the pooled estimate of the SMD of the serum glucose in the control and intervention groups showed a statistically significant change in serum glucose level in all the doses administered except 5 mg/kg dose. A dose-response relationship that showed a decrease in blood glucose in a dose-dependent manner was observed among the individual SMDs of 10, 25 and 50 mg/kg doses. The linear regression analysis also revealed a statistically significant dose-response relationship in which the serum glucose decreases as the dose of quercetin increases. It was reported that consumption of total dietary flavonoids, in a dose-dependent manner, is associated with a significantly decreased risk of type 2 diabetes (Liu et al., 2014). In another meta-analysis of clinical trials that assessed intervention doses ranged between 16 mg and 1200 mg of flavonol, its clinical relevance was suggested (Menezes et al., 2017). The human equivalent doses (HED) calculated for the doses used in this study are translated by the formula for dose translation based on the body surface area (BSA) (Reagan-Shaw et al., 2008). The US Food and Drug Administration (FDA) has suggested that the extrapolation of animal dose to human dose is correctly performed only through normalization to BSA (Food and Administration, 2005). Accordingly, the respective human dosed for the 10, 25, and 50 mg/kg is 49, 122 and 243 mg for an adult human, which are in the ranges of doses reported by the above study.

Increase in serum glucose is believed to induce a rise in ROS production due to the change in mitochondrial oxidative metabolism related to high level of intracellular glucose concentration (Kawahito et al., 2009). Thus, it's important to consider oxidative stress as one of the underlying pathologies in diabetes and its complications (Tabatabaei-Malazy et al., 2015). The increase in ROS and oxidative stress in diabetes is accompanied by reduced antioxidant defense and lower insulin secretion and results in more hyperglycemia (Lazo-de-la-Vega and Fernández-Mejía, 2013; Lotfy et al., 2011). In particular, the insulin resistance could arise from numerous physiological stresses including genetics, physical inactivity, obesity, diet, medications, environmental toxicants, stress, and endocrine disturbances (Salek-Maghsoudi et al., 2018). The pancreas is highly susceptible to oxidative damage because of the low expression of the antioxidant enzymes in the organ (Giacco and Brownlee, 2010; Moreli et al., 2014). Consequently, the hyperglycemia-induced oxidative stress and high workload ultimately cause pancreatic β-cell death (Patel et al., 2013). Studies on its anti-glycemic action have reported quercetin acts to improve glycemic control in animal models of both type-1 and type-2 diabetes (Arias et al., 2014). Mechanistically quercetin decreases serum glucose mainly through antioxidant action or via modulating hepatic gene expressions (Jung et al., 2011). Quercetin has also been reported to reduce the blood glucose level through inhibiting α-glucosidase activity *in vitro* (Jo et al., 2009; Kim et al., 2011). Moreover, quercetin is reported to aid insulin action along with improving skeletal muscle mitochondrial biogenesis (Henagan et al., 2014). It has also been shown to upregulate mitochondrial activity in animal models (Funakoshi et al., 2018). The mitochondrial regulating function of quercetin is by controlling the production of ATP through inhibiting ATPase and hexokinase enzymes (de Oliveira et al., 2016). Henagan, T.M., et al., have reported that chronic dietary quercetin intake can diminish diet-induced insulin resistance and enhances mitochondrial function in the skeletal muscle through skeletal muscle PGC1α upregulation (Henagan et al., 2014). On the other hand, evidences demonstrated that quercetin stimulates the AMPK complex. Quercetin mediated AMPK activation mainly results in an increase in the intracellular levels of AMP or AMP-ATP ratio. Particularly, quercetin-induced AMPK activation downregulates the oxidative damage and augments the glucose uptake in mice (Antonioli et al., 2016). These actions of quercetin have great pharmacological implications in the treatment of metabolic disorders, cancer and neurodegenerative diseases (de Oliveira et al., 2016).

The effect of quercetin on diabetes based on the pooled estimate looks promising, however, the statistical heterogeneity was quite high and is not suitable to make a conclusion based on the pooled estimate alone. Therefore, further subgroup analysis was performed to specifically identify the source of heterogeneity. The subgroup analysis was done to investigate the possible sources of heterogeneity due to any of the study characteristics. Among the study characteristic species, sex, route of administration, and frequency of administration were more or

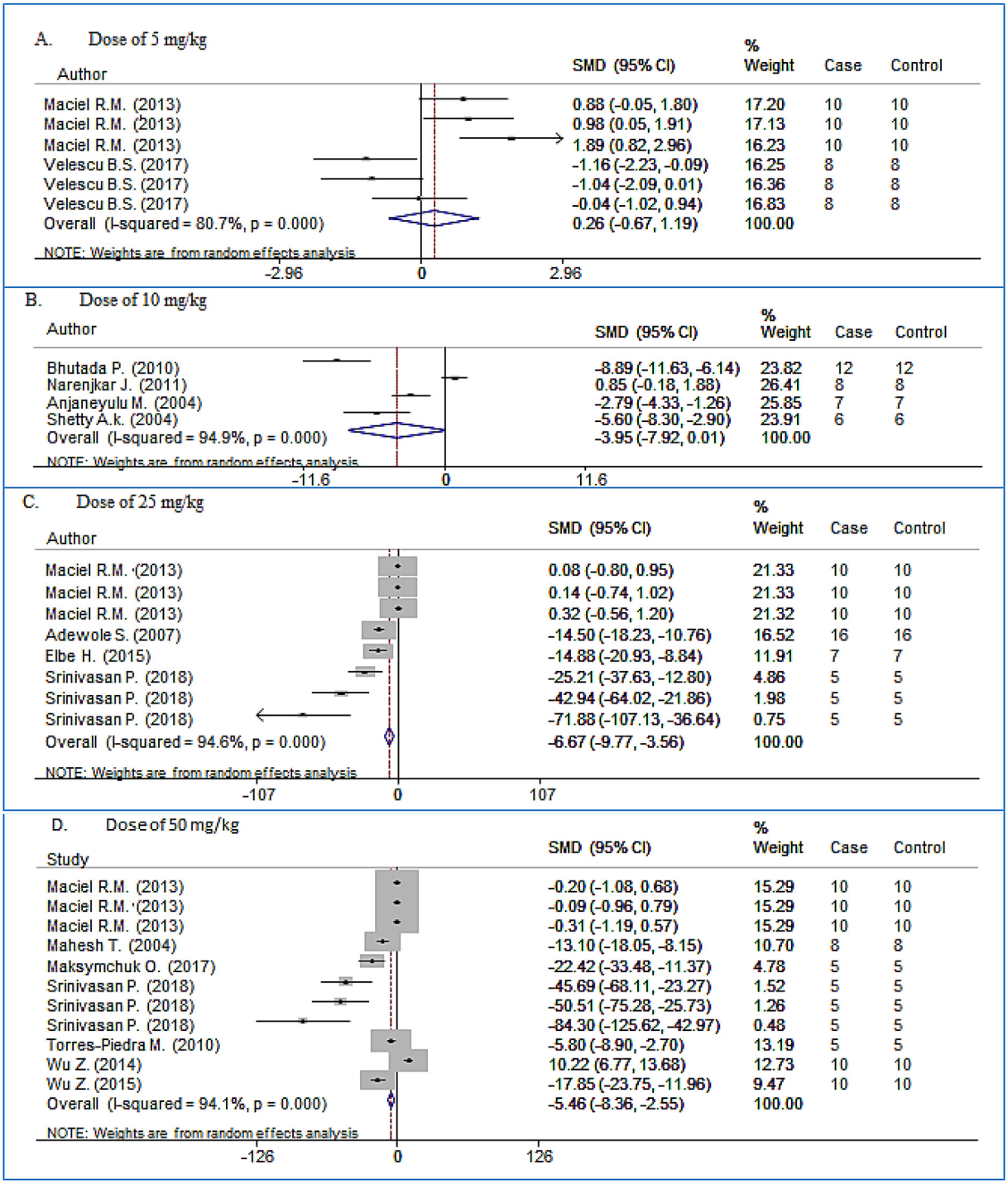

Fig. 3. Forest plot of standardized mean difference (SMD) and 95% confidence interval (CI) of serum glucose level of animals treated with different doses of quercetin (5, 10, 25 and 50 mg/kg).

less uniform in the studies included in the meta-analysis while age was not recorded in most of the studies. Therefore, duration of intervention (≤14 days, 14–28 days and ≥28 days) was used to perform the subgroup analysis in order to assess the source of heterogeneity. According to the subgroup analysis, a dose of 5 mg/kg did not produce a statistically significant effect. Yet, for the other doses, the subgroup analysis provided a varying result in relation to the duration of intervention. In these doses (10, 25 and 50 mg/kg) quercetin administered over a longer duration of intervention (14–28 days and ≥28 days) had a significant effect on the serum glucose level than shorter duration. Although the subgroup analysis has profoundly shown the dose-duration implications of quercetin's effect on serum glucose the heterogeneity was still significant.

Conducting systematic reviews is a helpful tool to criticize and summarize clinical evidence on the basis of statistics. Non-clinical and animal studies are also an important part of the evidence, but meta-analysis studies on animal experiments are rarely done (de Vries et al., 2015). The present review has several strengths and limitations. The major strength of this study is that to the best of our knowledge, it is the first systematic review and meta-analysis that assessed the effects of quercetin on diabetes in an animal model. Moreover, in this review, a comprehensive search strategy is used where most of the leading

Table 2
Subgroup and sensitivity analysis of the doses.

Subgroups	5 mg			10 mg			25 mg			50 mg		
	SMD (95% CI)	p	I^2	SMD (95% CI)	p	I^2	SMD (95% CI)	p	I^2	SMD (95% CI)	p	I^2
≤14 days	−0.12 (−2.12, 1.87)	0.903	87.5	–	–	–	−11.78 (−36.51, 12.96)	0.351	93.7	−2.53 (−10.00, 4.94)	0.507	95.3
14–28 days	−0.02 (−1.99, 1.96)	0.988	87.4	−2.79 (−4.33, −1.26)	0.000	–	−20.06 (−62.20, 22.08)	0.351	93.8	−18.15 (−35.99, −0.31)	0.046	96.0
≥28 days	0.91 (−0.99, 2.81)	0.346	85.3	−4.45 (−10.87, 1.97)	0.174	96.4	−15.02 (−27.37, −2.68)	0.017	96.8	−17.10 (−30.54, −3.66)	0.013	94.6
Overall	0.26 (−0.67, 1.19)	0.585	80.7	−3.95 (−7.92, 0.01)	0.051	94.9	−6.67 (−9.77, −3.56)	0.000	94.6	−5.46 (−8.36, −2.55)	0.000	94.1
Sensitivity analysis	0.26 (−0.67, 1.19)	0.585	–	–	–	–	−3.60 (−6.26, −0.95)	0.008	91.6	−1.41 (−3.78, 0.96)	0.242	89.5

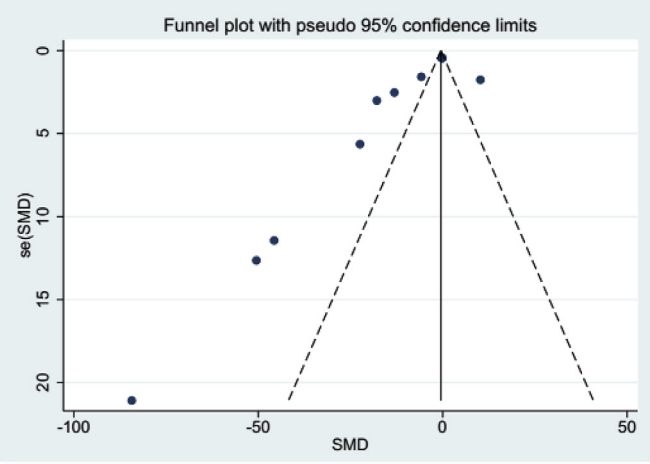

Fig. 4. Funnel plot of the standardized mean difference (SMD) in serum glucose level of quercetin treated and control animals.

databases such as Scopus, Web of Science, PubMed and EMBASE as well as manual searching of Google Scholar are included. The included original studies were all *in vivo* animal studies, which likely reduce the risk of selection bias. A sensitivity analysis was performed to assess the robustness of the findings of the meta-analysis. In contrast, there were a number of limitations in view of conducting the present work. The most prominent is the heterogeneity of the extracted data, which is likely due to the inconsistency in the experimental design and variation of quality among the studies. This is also reflected in our subgroup analysis which has an almost similar level of heterogeneity with the pooled estimate despite the use of the random effect model and sensitivity analysis. In addition, the methodological quality assessment performed also shows most of the studies have not done randomization and blinding in their experiment, thus increasing the possible source of bias. Visual analysis of funnel plots also showed that most of the studies have a publication bias (Fig. 4). This may indicate that publication bias is present, which could cause overestimation of the effect sizes. Importantly, funnel plot asymmetry can result from non-publication of negative results, but may also be caused by other factors, such as true study heterogeneity, or differences in study quality (Egger et al., 1997).

A systematic review of preclinical studies is done mostly to identify possible sources of bias and their impact on the studies as well as to generate hypothesis for the design of clinical studies (Vesterinen et al., 2014). Most preclinical studies are not always done perfectly in all steps and hence it is not easy to interpret their results straightforward. Consequently, the possible sources of bias are many and most animal studies are replicates of previous studies (Hooijmans et al., 2014a). Unlike clinical trials where randomization of experimental units and blind assessment of the treatment are mandatory, these techniques are left unmentioned in most animal model experiments (Hooijmans et al., 2010). Moreover, the sample size of animal studies is small (on average 10 animals per group) and the difference in studies of an individual intervention are common among different laboratories. Besides, in animal model studies it is considered important to minimize the variance, for example by the use of inbred strains, pathogen-free environments, and specific handling conditions. For instance, of all the studies included only one mentioned the numbers and reasons why the animals were excluded, although it's very likely to exclude animals in diabetes experiment due to animal's serum glucose not reaching the diabetic range. Similarly, only three studies explicitly stated the time schedule (day and time of intervention within an experiment). Moreover, sex and age of the animals and the duration of study varies among the studies as there is no standard protocol for conducting animal studies. Therefore, the differences among animal model studies (using different strains, different conditions) are disproportionately larger. This has important implications to perform, analyze and interpret a meta-analysis of data from preclinical studies (Vesterinen et al., 2014).

5. Conclusion

In this meta-analysis and systematic review of the antidiabetic activity of quercetin in an animal model the pooled estimate of the serum glucose level has shown that the flavonoid quercetin has anti-hyperglycemic activity in diabetic animals. Similarly, the subgroup analysis based on the duration of intervention also confirmed the anti-hyperglycemic action, particularly at higher doses. However, the heterogeneity was high in both the pooled estimate and the subgroup analysis. Moreover, the assessment of publication bias has shown a significant publication bias among studies. The higher heterogeneity and publication bias might be due to limitations and variations related to animal studies. Therefore, further quality preclinical studies need to be done so as to avoid the bias among studies and to assess the antidiabetic effects of quercetin. In addition, since the quercetin has a generally recognized as safe (GRAS) status according to FDA (Serban et al., 2016); further clinical studies are important and should be done to investigate its antidiabetic effects.

Author contributions

All authors have directly participated in the planning or drafting of the manuscript and read and approved the final version.

Conflicts of interest

The authors declare no conflict of interest.

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2019.01.037.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.01.037.

Funding

This article is the outcome of an in-house financially non-supported study.

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