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REVIEW

Rosemary (*Rosmarinus officinalis* L.) improves biochemical outcomes in diabetes mellitus: a systematic review and meta-analysis of animal studies

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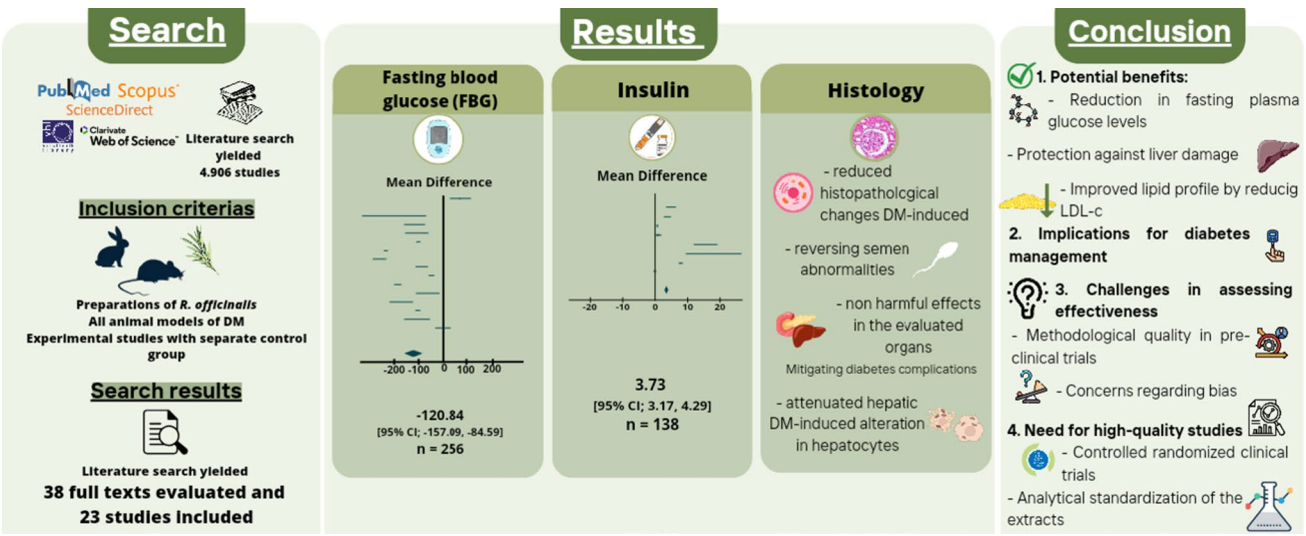
Abstract

We report on the systematic review and meta-analysis concerning the efficacy *of R. officinalis* in treating diabetes mellitus (DM) in animals. This study followed the PRISMA guideline and the protocol was registered in PROSPERO (CRD42021250556). The research was duplicated in the PubMed, Scopus, ScienceDirect, Web of Science, and Virtual Health Library (VHL) databases until December 31st, 2022. No restrictions have been set for language publication. Twenty-three (23) experimental studies of type-1 diabetes mellitus (T1DM) met the eligibility criteria and were included in the qualitative analysis, whereas eighteen (18) underwent a meta-analysis. The *R. officinalis* derivatives significantly decreased fasting plasma glucose (MD: −120.84 [95% CI; −157.09, −84.59]); increased insulin release (MD; +3.73 [95% CI; +3.17, +4.29]); dwindled blood urea nitrogen (MD: −24.84 [95% CI; −34.78, −14.90]) and creatinine (MD: −0.40 [95% CI; −0.74, −0.06]) levels; and ameliorated liver function or repaired liver damage by decreasing ALT (MD: −36.42; [95% CI; −55.69, −17.14]) and AST (MD: −24.05 [95% CI; −37.84, −10.27]) enzyme levels compared to vehicle control group. Moreover, *R. officinalis* derivatives improved the lipid profile of diabetic animals by reducing LDL-c levels (MD: −11.74 [95% CI; −21.27, −2.21]). *R. officinalis* is a nutraceutical that may help in the management of T1DM and its complications. However, some gaps need to be taken into account for this evidence. Greater attention is needed for an analytical standardization of Rosemary extracts besides the demand for high-quality clinical studies dealing with the efficacy of this phytomedicine.

Graphical abstract



Extended author information available on the last page of the article

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Keywords Diabetes Complications · Hypoglycemic Agents · Insulin · Medicinal Plant · Metabolic Syndrome · Nutraceuticals

Abbreviations

Alb	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUR	Uric acid
BUN	Blood urea nitrogen
CAMARADES	Collaborative Approach to Meta Analysis and Review of Animal Experimental Studies
CI	Confidence interval
CRE	Creatinine
D.O.I	Digital Object Identifier System
DeCS	Health Sciences Descriptors
DM	Diabetes mellitus
FPG	Fasting plasma glucose
HbA1c	Serum glycated hemoglobin
HDL-c	High density lipoprotein cholesterol
LDL-c	Low density lipoprotein cholesterol
MD	Mean difference
MeSH	Medical Subject Headings
OS	Oxidative stress
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RevMan	Review Manager software
ROs	Reactive oxygen species
SD	Standard deviation
SIL	Serum insulin level
SYRCLE	Systematic Review Center for Laboratory animal Experimentation
T1DM	Type-1 diabetes mellitus
T2DM	Type-2 diabetes mellitus
TC	Total cholesterol
Tg	Total triglycerides
VHL	Virtual Health Library

Introduction

DM is a metabolic disorder characterized by persistent hyperglycemia due to a deficiency in insulin production or its action or in both mechanisms. This chronic ailment has been classified as a troubling disease for the twenty-first century. According to the International Diabetes Federation Global Diabetes Atlas (10th Edition), DM reached about 537 million adults in 2021 was responsible for around 6.7 million deaths, and cost USD 966 billion in health spending in the last 15 years (International Diabetes Federation 2021).

Uncontrolled DM has deleterious consequences and several complications, such as circulatory problems (increased risk of heart disease, stroke, and peripheral blood vessels), kidney diseases, arterial hypertension, and a higher mortality rate when compared with non-diabetic and healthy patients; which can impair affected patients' quality of life and also reduction or loss of productive capacity (Almutlaq et al. 2021; Bjornstad et al. 2022; de Souza Stork et al. 2022; Shrestha and Ghimire 2012).

It is known that OS, which is a state of imbalance between the production of ROs and endogenous antioxidant capacity; triggers the complications of DM (Reis et al. 2021). The main molecular mechanisms associated with OS in DM are related to glucose and lipid metabolism (Giacco and Brownlee 2010).

Under conditions of hyperglycemia, the excessive production of ROs during glycolysis reactions leads to damage in both DNA and DNA repair enzymes, causing accumulation of glyceraldehyde-3-phosphate content, which is responsible for the activation of other pro-oxidant pathways and the auto-oxidation of glucose. Thus, a boost in the production of hydrogen peroxide, a precursor of oxidizing substances, is observed. Furthermore, the auto-oxidation of glucose leads to the formation of glyoxal, an advanced glycation end-product precursor, which promotes cellular OS (Darenskaya et al. 2021).

Even though the complications of DM are diverse and clinically relevant, the pharmacological treatment options for either T1DM or T2DM are narrowed to a few common approaches. The treatment of T1DM involves the administration of insulin, but there is a chance of developing so-called insulin resistance, manifesting in most cases itself at the cellular level through post-receptor defects in insulin signaling. In another hand, T2DM is treated with oral antihyperglycemic drugs, which are associated with several side effects. Therefore, more patients seek lifestyle modifications combined with natural and safer options like nutraceuticals for the management of DM (Buzzetti et al. 2020; Shi et al. 2019).

Some nutraceuticals, like super fruits and spices exhibiting high anti-radical and anti-inflammatory activity, are sources of copious phytochemicals that can regulate alpha-glucosidase and lipase activities, improve pancreatic function and insulin release and reduce blood glucose levels, boosting the effects of hypoglycemic or antihyperglycemic

agents (Alhujaily et al. 2022; Dehdashtian et al. 2020). Thus, they act as antioxidants, mitigating the imbalance of ROs and blocking the synthesis of prostaglandins, pro-inflammatory cytokines, and transcription factors, mainly the NF-κB factor. Consequently, such foodstuffs may be highly effective in the management of DM and its worsening (Alhujaily et al. 2022; Derosa et al. 2022; Zhang et al. 2015).

Rosemary (*Rosmarinus officinalis* L., *Lamiaceae*) is an aromatic household spice that has been used worldwide for culinary, food preservative, and medicinal purposes owing to its powerful antioxidant properties (Sánchez-Camargo and Herrero 2017). There is increasing scientific evidence supporting its efficacy in preclinical models in which the OS is involved, such as inflammation (Gonçalves et al. 2022), neurodegeneration (Capatina et al. 2020), cancer (Pérez-Sánchez et al. 2019) and DM (Bao et al. 2020; Hassani et al. 2016; Naimi et al. 2017). Its wide range of bioactivities can be due to the synergism of antioxidant phytochemicals such as diterpenes, triterpenes, phenolic acids, flavonoids, and volatile compounds (Ulbricht et al. 2010; Yashin et al. 2017).

Despite plenty of original papers and narrative reviews reporting the healing properties of *R. officinalis*, its efficacy in DM and DM complications has not been systematically reviewed and statistically compared so far. Therefore, healthcare professionals across the globe still lack high-level evidence that supports the use of *R. officinalis* in complementary and integrative medicine as a coadjutant in the management of DM.

Motivated by this scientific and clinical gap, this investigation aimed to provide a systematic review and meta-analysis concerning the effects of *R. officinalis* in the biochemical outcomes of animals that underwent pre-clinical models of DM. Insights on the overall methodological quality and bias of the included primary studies are also presented. Our findings are consistent with using *R. officinalis* in traditional medicine for managing DM. Besides, this scientific contribution is a step forward in evidence-based practices related to the rationale use of *R. officinalis* in primary healthcare and poses this nutraceutical as the target of further clinical investigations associated with DM and its complications.

Material and methods

Study design and guiding question

This systematic review was carried out according to the PRISMA guideline (Page et al. 2021). This study was registered in PROSPERO with protocol number CRD42021250556 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021250556). Our guiding question was: Does *R. officinalis* improve the biochemical outcomes of animals in experimental models of diabetes mellitus?

Sources of information and search strategies

The electronic databases PubMed (MEDLINE), Scopus, ScienceDirect, Web of Science (Science Citation Index), and VHL were used for the search of relevant publications issued until December 31st, 2022. The authors also searched citation reference lists of relevant included studies and any previously published reviews and gray literature to include other studies in Google Scholar, through the D.O.I of the intended study. Thus, all the searches were performed by two independent researchers (V.M.O and L.R.S) on January 13th, 2023.

None of the collection language was restricted during the identification of the studies. The authors of the unavailable articles were contacted twice by e-mail, through which they were requested access to the articles and other information (raw data).

The descriptors were delimited and defined from the MeSH and DeCS tools. The research strategies used in this review were carried out using the PECOS acronym, i.e.: population (P); exposure (E); comparator (C); outcomes (O); and study design (S). The research terms were combined using the Boolean logical terms "AND" and "OR". Research filters (document type = "article") for the identification of preclinical studies in the Web of Science and VHL were applied to increase filtering and research efficiency. The research strategies used for each database are detailed in Table S1 of the Supplementary Material.

Eligibility criteria

The eligible and selected articles from the databases were read in full and evaluated according to the inclusion and exclusion criteria predefined from the PROSPERO protocol prioritized in terms of i) type of exposure/intervention, ii) type of population, iii) study design and, iv) type of publication.

Inclusion criteria:

(i) treatment with preparations of *R. officinalis* at any dosage, administered at any time, by any administration route, and any dose frequency;
(ii) all animal models of DM (deficiency in insulin production and failure of β cells to ensure construct validity), all sexes, all ages, and all species of animals/strains;
(iii) experimental studies with separate control groups; cross-design, randomized, and non-randomized study designs;

(iv) original articles and short communications (published or ahead of print) were considered.

Exclusion criteria:

(i) combined treatment of *R. officinalis* L., or isolated pure compounds or *R. officinalis* combined with standard oral hypoglycemic agents;
(ii) studies in humans, animals with any other comorbidity
(iii) in vitro and ex vivo study designs, in silico, studies before and after without a control group;
(iv) case reports, review articles, editorials, letters to the editor, and articles presented at scientific events, news, comments, dissertations, and thesis were excluded.

After searching the databases, the articles were transferred to the Rayyan QCRI application (Ouzzani et al. 2016) to organize, remove duplicates, and apply the eligibility criteria of each article and thus associate them with eligible or not for inclusion.

Throughout the selection of the articles, each reviewer (VMO, LRS) was blinded about the other's decisions, and the discrepancies were discussed until a consensus or, if it was not possible, a third author (ROC) was consulted. It is noteworthy that the final decision of the articles to be included is made by consensus among all the researchers involved.

The Kappa coefficient (Landis and Koch 1977) was used to assess the level of agreement between the two authors (VMO, LRS). In this pursuit, we considered a 95% CI and used the Stata 11.0 software package.

Data extraction

The primary and secondary data of the included studies were extracted for a standardized and pre-formatted electronic spreadsheet. Data were collected considering the animal models (species/strains of animals used; sex of animals; number of animals per group; age and weight of animals; type of feeding used); study design (number of experimental groups and duration of follow-up; method of allocation to the treatment group; type of diabetes whether T1DM or T2DM; and blind or non-blind evaluation method); intervention characteristics (taxonomic identification of the herb; voucher number; method of preparation of *R. officinalis* extract; methods and parameters of quality control; chemical composition; dose; dose frequency; time and route of administration; method of induction of DM and time to begin exposure; parameters to be considered diabetic; whether nephrectomy was performed or not); identification of the study (authors; year of publication; country where the research was conducted); and publishing language.

The main results evaluated were: FPG (mg/dL); HbA1c (%); SIL (mU/L); lipid profile [Tg (mg/dL), HDL-c (mg/dL), LDL-c (mg/dL), and TC (mg/dL); ALP (U/L), ALT (U/L), AST (U/L), and Alb (g/dL) for liver function; BUN (mg/dL), AUR (mg/dL), and CRE (mg/dL) for renal function.

Taxonomic evaluation

Taxonomic and nomenclature accuracy was evaluated by comparing the taxonomic information reported with existing patterns in an open botanical database accessible at https://wfoplantlist.org/plant-list. A classification was then elaborated according to methods proposed elsewhere (Rivera et al. 2014) to evaluate the taxonomy and identification of plant species used.

For studies that included complete information on plant species, identification and proof of the specimen presented, it was qualified as "LEVEL 1". For studies that did not present information on identification and proof of the specimen, a classification of "LEVEL 2" was then assigned; finally, studies with incomplete information or that did not present any information about the species, collection, identification, and proof of specimens, received a classification of "LEVEL 3" (Rivera et al. 2014).

Data synthesis

The qualitative data of the included studies were described in narrative synthesis and summarized in tables to establish patterns and variations. Statistically, we used signs to indicate significant increment (↑), decrement (↓), or equality (↔) effect size measured between treatment and control groups.

Quantitative data were grouped into a statistical meta-analysis using RevMan 5.3 (Copenhagen: The Nordic Cochrane Centre). The meta-analysis was carried out exclusively for two or more studies depicting data on a specific outcome of interest. Herein, given the great diversity of the experimental models, only the most effective dose and the greatest frequency of exposure were considered. As the same outcome could be reported in different measurement scales, we performed mathematic conversions to the same scale. Data of FPG (mg/dL), HbA1c (%), SIL (mU/L), Tg (mg/dL), HDL (mg/dL), LDL (mg/dL), TC (mg/dL), ALP (U/L), ALT (U/L), AST (U/L), Alb (g/dL), BUN (mg/dL), AUR (mg/dL), and CRE (mg/dL) underwent metanalysis. MD and SD were used to assess continuous variables with a 95% CI. The p-value < 0.05 was considered statically significant. For studies reporting, the standard errors of means, and the corresponding SD were calculated by multiplying by the square root of the respective sample size.

The inverse method of weighted variance was used to attribute the relative contribution of each study included to the effect of the grouped standard deviation of *R. officinalis* and its 95% CI. The random effects model was used for pooling effect estimates because the effect sizes from animal studies probably differ more due to the distinction in design features (Peter et al. 2021).

Heterogeneity assessment

We used the I^2 statistic to evaluate the severity of heterogeneity. The $I^2 \geq 75\%$ was considered indicative of substantial heterogeneity (Borenstein et al. 2010). Subgroup analysis was carried out to identify potential factors that influence heterogeneity in the FPG and SIL.

Assessment of the risk of bias and quality of the included articles

Two reviewers (VMO and LRS) independently evaluated the risk of bias using SYRCLE's tool (Hooijmans et al. 2014b). By using this tool, it was possible to evaluate selection bias, performance bias, detection bias, friction bias, reporting bias, and other types of biases.

The ten domains evaluated in this tool are random sequence generation; basic characteristics; allocation concealment; random housing; blinding of participants and staff; evaluation of random results; incomplete results data; reports of selective results; and other sources of bias. The risk of bias was assessed using RevMan 5.3 (Copenhagen: The Nordic Cochrane Centre). Then, two independent researchers (VMO and LRS) evaluated all the studies included through the CAMARADES checklist (Bahor et al. 2021) for study quality. Disagreements were resolved with discussion.

Results

Search results

Figure 1 depicts the PRISMA flowchart with the selection of studies performed in this systematic review. A total of 4909 studies were identified in the electronic databases search. After reviewing the title and abstract, 322 papers were excluded for being duplicates (coming from the two different databases). During the title, keywords, and abstract screening 4876 articles were further discarded. The full text of the 33 potentially relevant articles was assessed and 15 papers were excluded due to the following reasons: not an *R. officinalis* preparation (n = 6), not a DM model (n = 4), dissertation (n = 1), wrong experimental design (n = 1), in vitro experiments (n = 2), unseparated control group (n = 1).

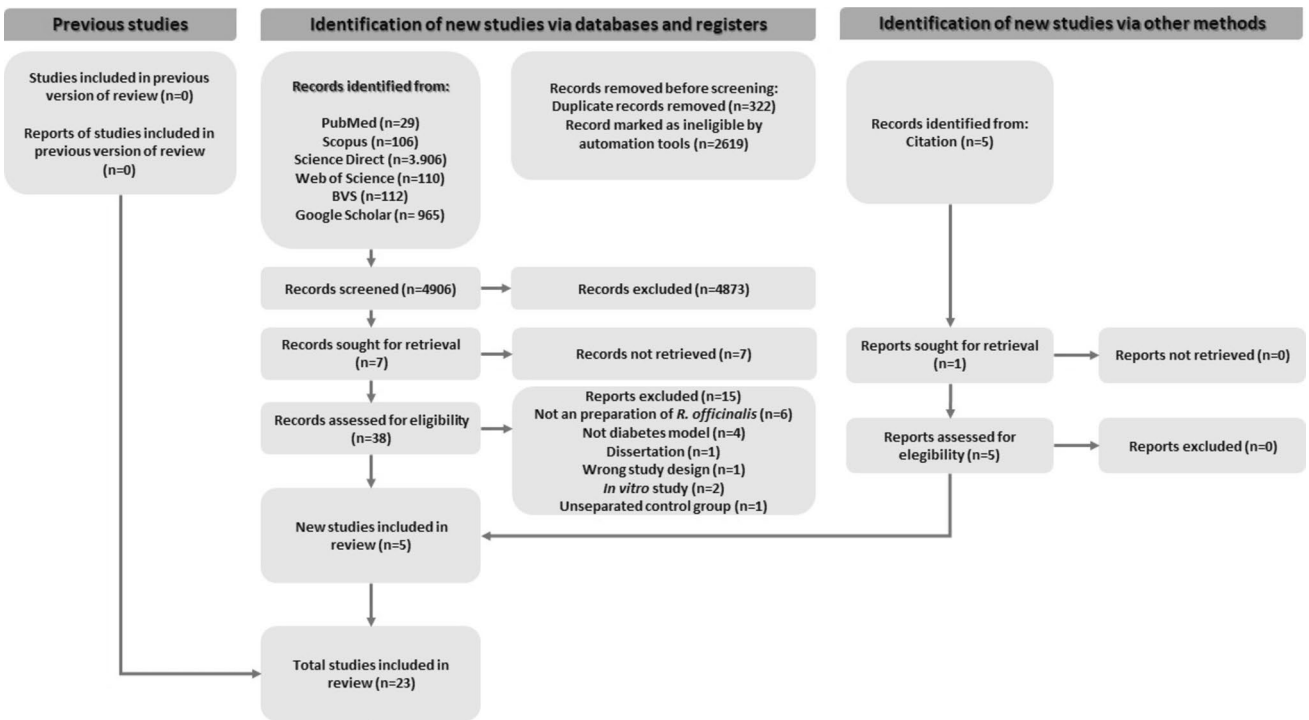


Fig. 1 PRISMA flow diagram of studies selected, included and excluded in the systematic review on the effect of *R. officinalis* in animal models of diabetes mellitus

After carrying out a thorough review of the literature, including both published articles and gray literature, a total of five articles were selected for full-text reading. In addition, two articles were identified as potentially relevant (Erenmemisoglu et al. 1997; Malek et al. 2020) and we contacted the authors requiring full access, but only one was obtained (Malek et al. 2020).

The study comprised 23 articles (Al-badry 2017; Al-Hader et al. 1994; Alnahdi 2012; Ayaz 2012; Bakirel et al. 2008; Belmouhoub et al. 2016, 2017, 2020; Benkhedir et al. 2022; El-Boshy et al. 2015; Emam 2012; Khalil et al. 2012; Koga et al. 2006; Malek et al. 2020; Mohamed 2021; Nazem et al. 2015; Ramadan et al. 2013; Rasoulian et al. 2019; Sebai et al. 2015; Selmi et al. 2017; Shen et al. 2020; Silva et al. 2011; Wahba 2022), of which 18 were eligible for the meta-analysis (Al-Hader et al. 1994; Alnahdi 2012; Ayaz 2012; Bakirel et al. 2008; Benkhedir et al. 2022; El-Boshy et al. 2015; Emam 2012; Khalil et al. 2012; Malek et al. 2020; Mohamed 2021; Nazem et al. 2015; Ramadan et al. 2013; Rasoulian et al. 2019; Sebai et al. 2017; Shen et al. 2020; Silva et al. 2011; Wahba 2022). Throughout the eligibility evaluation, the degree of agreement between the two researchers (Kappa coefficient) was of 0.992, which is considered almost perfect (Landis and Koch 1977).

Description of the included studies

General Features

Table 1 summarizes the experimental design of the studies herein included, Moreover, Table 2 presents the qualitative synthesis of their main findings. The majority of included studies used rats (69.6%; n = 16), while 21.7% (n = 5) used mice and 8.7% (n = 2) used rabbits. A total of 21 studies (91.3%) used only male animals, 1 (4.3%) study used only females and 1 (4.3%) used both sexes. About 56.5% of the studies (n = 13) did not specify the animal's age, being that the age of the animals ranged from 13 days to 3 months.

About 47.8% (n = 11) of studies used *R. officinalis* aqueous extract, 34.8% (n = 8) used hydroalcoholic extract, 8.7% (n = 2) used fortified power diet and 8.7% used the volatile oil. A total of 10 studies (43.5%) presented data of qualitative and quantitative analysis of the phytochemicals contained in the extracts.

The doses of *R. officinalis* administered ranged from 25 to 800 mg/kg (200.7 ± 156.8 mg/kg). Only two studies (8.7%) did not specify the dose (mg/kg) used, and the other 2 studies (8.7%) blended leaves powder in animals' diets with doses ranging from 0.05% to 10%.

Oral administration was the most frequent among studies (82.6%; n = 19), while 3 studies (13%) used intraperitoneal administration and 1 study (4.3%) used intramuscular administration. The once-a-day regimen of administration was performed in all the included studies (100%).

The histopathology and anatomopathological analysis were assessed in 8 studies (34.8%), which related to nonharmful effects in the evaluated organs. *R. officinalis* reduced histopathological changes induced by DM on the kidney and liver of the treated animals, also displayed amelioration in the degeneration of Langerhans islets, attenuated hepatic DM-induced alteration in hepatocytes, preserved renal architecture, decreased plasma inflammatory cytokine and enhanced the reproductive performance by reversing semen abnormalities.

Table S2 of the Supplementary Material presents the characteristics of DM induction protocols in the included studies. All of the studies carried out T1DM experimental models, with FPG levels at baseline greater than 200 mg/dL; since the researchers chemically induced the illness by using alloxan or streptozotocin (STZ) (King 2012).

About 39.1% of the studies (n = 9) used alloxan and 60.9% (n = 14) used STZ. The STZ doses used range from 40 to 110 mg/kg (60.8 ± 28.3 mg/kg). In turn, the doses of alloxan used ranged from 120 to 220 mg/kg (146.1 ± 32.0 mg/kg). The time taken to confirm that the diabetes is stabilized after the exposure to induction material was between 2 and 7 days. Only 5 studies (21.7%) reported pancreatectomy, which was used to prevent pancreatic beta regeneration.

The animal's diet was assessed in 13 studies (56.5%), in which 2 studies (8.7%) reported the amount of nutrients contained in the food. Concerning the exposure time, 5 studies (21.7%) carried out acute follow-up (up to 24 h), while 13 (56.5%) studies performed subacute follow-up (from 1 up to 21 days) and 7 studies (30.4%) performed subchronic follow-up (>22 days). Noteworthy, in some studies more than one follow-up period was investigated depending on the outcome assessed.

Taxonomic evaluation

The full taxonomic analysis of the included studies is presented in Fig. S1 of the Supplementary Material. The majority of the studies (56.5%, n = 13) were classified as LEVEL 1, with higher quality and complete information about the specimens; 8 studies (34.8%) were classified as LEVEL 2 because they did not use an appropriate style to formally differentiate the nomenclature from other text, and/or provide data and evidence of specimens used and/or provided data on how these specimens were identified. Finally, 2 studies (8.7%) were classified as LEVEL 3, because did not fulfill 3 or more specified items.

Table 1 General features of the studies included in the systematic review on the efficacy of *Rosmarinus officinalis* in animal models of diabetes mellitus

Study	Country	Animal strain	Sex	Age/weight	Groups/total individuals	Exposure	Study follow-up	Dose (mg/Kg)	Route of administration/frequency	Phytochemicals/analytical method
Al-badry (2017)	Iraq	*Norvegic's rattus*	♂	8–10 weeks/NI	4/28	Aqueous extract	30 days	NI	v.o/once daily	ND
Al-Hader et al. (1994)	Jordan	New Zealand Rabbits	♂	NI/2–2.5 kg	2 /12	Essential oil	6 h	25	IM/single	ND
Alnahdi (2012)	Saudi Arabia	Albino rats	♂	NI/150–200 g	5/25	Aqueous extract	21 days	200	v.o/once daily	ND
Ayaz (2012)	Saudi Arabia	Wistar Rats Albino	♂	NI/150–200 g	5/25	Aqueous extract	21 days	200	v.o/once daily	ND
Bakirel et al. (2008)	Turkey	New Zealand adult rabbits	♀♂	NI/2.2–3.1 kg	5/35	Ethanolic extract	6 h and 8 days	50, 100 or 200	v.o/single	ND
Belmouhoub et al. (2016)	Algeria	Swiss Albino Mice	♀	3 months/22 ± 3 g	4/20	Methanolic extract	3 h	800	v.o/single	209 ± 14 mg EAG/g polyphenols and 89.5 ± 13 mg QE/g flavonoids/UV–vis spectrophotometry
Belmouhoub et al. (2017)	Algeria	Swiss Albino Mice	♂	3 months/20–30 g	4/20	Methanolic extract	20 days	400	v.o/once daily	260 ± 7 mg EAG/g polyphenols and 114 ± 2 mg QE/g flavonoids/UV–vis spectrophotometry
Belmouhoub et al. (2020)	Algeria	Swiss albino mice	♂	3 months/25–35 g	4/20	Diethyl ether and n-butanol extract	14 days	400	v.o/once daily	BUT fraction, 260 ± 7 mg EAG /g of polyphenols and 113.33 ± 2 mg EQ /g of flavonoids. DE fraction 141.66 ± 2 of polyphenols and 70.33 ± 2 of flavonoids/UV–vis spectrophotometry
Benkhedir et al. (2022)	Algeria	*Rattus* novergicus,var. albinus	♂	2 months/200–220 g	9/54	Ethyl acetate extract	3 h and 21 days	150 or 300	v.o/once daily	ND
El-Boshy et al. (2015)	Saudi Arabia	Sprague–Dawley Rats	♂	NI/160–200 g	4/24	Aqueous extract	45 days	200	v.o/once daily	ND
Emam (2012)	Egypt	*Albino rats*	♂	NI/150–200 g	6/36	Aqueous extract	21 days	200	v.o/once daily	ND
Khalil (2012)	Saudi Arabia	*albino rats*	♂	2 months/150–200 g	4/20	Aqueous extract	21 days	200	v.o/once daily	ND
Koga et al. (2006)	Japan	*ddY mice*	♂	4 week/19–21 g	3/15	50% Ethanolic extract	30 min	0,1 g/mL	v.o/single	luteolin/NMR. IR and UV–vis spectrophotometry

Table 1 (continued)

Study	Country	Animal strain	Sex	Age/weight	Groups/total individuals	Exposure	Study follow-up	Dose (mg/Kg)	Route of administration/frequency	Phytochemicals/analytical method
Malek et al. (2020)	Syria	Wister albino rats	♂	NI/200 – 250 g	4/32	Ethanolic extract	36 days	300	v.o/once daily	presence of flavonoids, tannins, triterpenes, and saponins/colorimetric assays for phytochemical screening
Mohamed (2021)	Cairo	Albino rats	♂	NI/135–150 g	5/50	Leaves powder	28 days	diet at 0.05%	v.o/ND	ND
Nazem et al. (2015)	Iran	Wistar Rats	♂	NI/195–200 g	5/50	Aqueous extract	56 days	200	v.o/once daily	ND
Ramadan et al. (2013)	Saudi Arabia	Albino mice	♂	NI/150–200 g	5/25	Aqueous extract	21 days	200	v.o/once daily	ND
Rasoulian et al. (2019)	Iran	Wistar Rats	♂	NI/220–250 g	6/48	Aqueous extract	21 days	100, 150 or 200	v.o/once daily	4.5% rosmarinic acid/HPLC–UV
Sebai et al. (2015)	Tunisia	*Wistar Rats*	♂	15 weeks/220–230 g	6/72	Aqueous extract	15 days	50 or 150	i.p/once daily	1,8-cineole (34.38%), trans-caryophyllene (14.47%), borneol (9.66%), camphor (8.97%), α-pinene (7.83%), α-thujone (6.92%)/GC–MS
Selmi et al. (2017)	Tunisia	Wistar Rats	♂	15 weeks/220–225 g	4/48	Essential oil	15 days	220	i.p/once daily	1,8-cineol, trans-caryophyllene, borneol, camphor, α-pinene, α-thujone, β-thujone, δ-cadinene, germacrene-D, humulene, α-copaene, bornyl acetate, chrysanthenone, β-pinene, camphene/GC–MS

Table 1 (continued)

Study	Country	Animal strain	Sex	Age/weight	Groups/total individuals	Exposure	Study follow-up	Dose (mg/Kg)	Route of administration/frequency	Phytochemicals/analytical method
Shen et al. (2020)	China	*Sprague–Dawley Rats*	♂	NI/190 ± 10 g	3/24	Ethanolic extract	6 weeks	200	i.p/daily	protocatechuic acid (2.16 ± 0.01%), caffeic acid (0.02 ± 0.00%), ellagic acid (2.04 ± 0.01%), ferulic acid (0.01 ± 0.00%), rosmarinic acid (17.28 ± 0.74%), carnosol (4.45 ± 0.03%) and carnoic acid (8.31 ± 0.06%)/HPLC–UV
Silva et al. (2011)	Brazil	*Rattus* novergicus,var. albinus	♂	1 month and 15 days/220–240 g	5/40	Aqueous extract	30 days	25, 50 or 100	v.o/once daily	30.7 mg/g of total polyphenols/UV–vis spectrophotometry
Wahba (2022)	Egypt	*Sprague Dawley albino*	♂	ND/255–265 g	6/42	Powder extract	10 weeks	diet at 5% and 10%	v.o/ND	ND

i.m. intramuscular route, *i.p.* intraperitoneal route, *ND* non-determined, *NI* non-informed, *v.o.* oral route, *GC–MS* Gas chromatography–mass spectrometry, *HPLC–UV* High Performance Liquid Chromatography coupled to UV–vis detector

Table 2 Summary of the primary and secondary outcomes of the studies assessing the effects of *R. officinalis* in animal models of diabetes mellitus

Study	Study follow-up time	Biochemical parameters[a]	Physiological and pharmacological parameters	Histopathology and anatomopathological analysis	Safety issues	Main remarks
Al-badry (2017)	Sub chronic	ND	ND	Improvement of the harmful effects of drug-induced diabetes on the kidney and liver. Treated animals had kidneys with venial contraction of the glomeruli, most renal tubules were normal, and few tubules were damaged by degeneration and necrosis Reduction of histopathological changes in rosemary-treated groups	No deaths or adverse effects have been reported	Rosemary extracts alleviates the harmful effects of drug-induced diabetes on kidney and liver damages
Al-Hader et al. (1994)	Acute	↑FPG ↓SIL	ND	ND	No deaths or adverse effects have been reported	The volatile oil of Rosemary has hyperglycemic and insulin release inhibitory effects
Alnahdi (2012)	Subacute	↓FPG ↑Hb ↑AST heart ↑CPK heart ↑LDH heart ↓TG ↓TC ↓LDL-c ↑HDL-c	Treatment reduced the weight	ND	No deaths or adverse effects have been reported	Rosemary extract was effective in preventing diabetes and its complications, as well as improving lipid metabolism in diabetics
Ayaz (2012)	Subacute	↓FPG ↑ SIL ↑C-peptide ↓BUN ↓CRE ↓AUR	Treatment reduced weight loss	Administration of extract to control rats did not alter the structure of the kidney when compared with the control group	No deaths or adverse effects have been reported	Water extract of Rosemary exhibits strong antihyperglycemic activity and attenuates BUN, serum creatinine, and uric acid rise in diabetic rats
Bakirel et al. (2008)	Acute and Subacute	↓FPG ↑SIL ↑CAT ↑SOD ↓MDA	Treatment did not change weight loss	ND	No deaths or adverse effects have been reported	Rosemary extract exerts remarkable hypoglycemic, antihyperglycemic, and antioxidant activities

Table 2 (continued)

Study	Study follow-up time	Biochemical parameters[a]	Physiological and pharmacological parameters	Histopathology and anatomopathological analysis	Safety issues	Main remarks
Belmouhoub et al. (2016)	Acute	↓FPG	ND	ND	No deaths or adverse effects have been reported in the doses of 2,500 mg/Kg and 5000 mg/Kg	Rosemary extract showed antihyperglycemic activities
Belmouhoub et al. (2017)	Subacute	↓FPG ↓TC ↓LDL-c ↔TG	ND	Treatment groups displayed amelioration in the degeneration of Langerhans islets	No deaths or adverse effects have been reported	Rosemary extract showed both antidiabetic and anti-hypercholesterolemic activities
Belmouhoub et al. (2020)	Subacute	↓FBG	Treatment ameliorates the sexual behavior and sperm motility	ND	No deaths or adverse effects have been reported	*Rosmarinus officinalis* showed an effective protective effect against the deleterious impacts of diabetes on reproductive performances,
Benkhedir et al. (2022)	Subacute	↓FPG ↑SIL ↑Hb ↓ HbA1c ↑ HXK ↑G6PD ↓G6P ↓ FDPase ↓ GYS1 ↓ GP ↑GLY liver	The treatment restored a decrease in body weight and water and food consumption, as well as increased liver weight	Rosemary extract attenuated hepatic DM-induced alteration in hepatocytes, such as infiltration of inflammatory cells and degeneration of the sinusoids	No deaths or adverse effects have been reported	Extract of the ethanolic extract of RO was significantly efficient against plasma glucose and insulin levels, body weight, food consumption, Hb and HbA1c levels, and hepatic glycogen levels. Also, the altered activity of key carbohydrate metabolism enzymes is almost normal
El-Boshy et al. (2015)	Subchronic	↓FPG ↑GR ↑CAT ↔SOD ↓MDA ↓CRE ↓BUN ↓AUR	Treatment reduced weight loss	The treatment group displayed preserved renal architecture	No deaths or adverse effects have been reported. Computational calculations reinforced the safety of the main phytochemicals contained in the extract	Rosemary extract exhibited hypoglycemic and antioxidant effects, besides improving renal function and reducing renal damage caused by oxidative stress

Table 2 (continued)

Study	Study follow-up time	Biochemical parameters[a]	Physiological and pharmacological parameters	Histopathology and anatomopathological analysis	Safety issues	Main remarks
Emam (2012)	Subacute	↑TP ↑AMY ↓TC ↓Tg ↑ Gpx ↑CAT ↑ SOD ↓Alb ↓ceruloplasmin ↓ ferritin ↓glutathione ↓ AUR ↓Bilirubin	Treatment reduced weight loss	ND	No deaths or adverse effects have been reported	Rosemary extract was effective in the markers evaluated for diabetes and proved to be more effective than chamomile
Khalil (2012)	Subacute	↓FPG ↓MDA ↓NO ↑GST ↑CAT ↑Gpx ↑GR	ND	ND	No deaths or adverse effects have been reported	Rosemary extract brings back the blood glucose and also increases the antioxidant level in experimental rats
Koga et al. (2006)	Acute	↓FPG ↓AGc	ND	ND	No deaths or adverse effects have been reported	Distilled extract from 50% ethanol rosemary extract showed potent AGc inhibitory activities, that may play a role in controlling dietary glucose uptake in the small intestinal tract
Malek et al. (2020)	Acute and Subchronic	↓FBG ↑SIL ↓DPP-4	ND	ND	No deaths or adverse effects have been reported	Extract of RO has an antidiabetic effect, based on a crease in FBG levels, an increase in the level of insulin, and a decline in the activity of DPP-4
Mohamed (2021)	Acute	↓FPG ↑GSH ↑CAT ↑SOD ↓LDH ↓MDA	ND	ND	No deaths or adverse effects have been reported	Diet fortification with Rosemary mediated promising antidiabetic effects

Table 2 (continued)

Study	Study follow-up time	Biochemical parameters[a]	Physiological and pharmacological parameters	Histopathology and anatomopathological analysis	Safety issues	Main remarks
Nazem et al. (2015)	Subchronic	↓FPG ↑SIL ↑CAT ↑SOD ↑GPx ↓MDA	Treatment reduced weight loss	ND	No deaths or adverse effects have been reported	Rosemary extract has a hypoglycemic effect and ameliorates oxidative damage
Ramadan et al. (2013)	Subacute	↓FPG ↑SIL ↑C-peptide ↓AST ↓ALT ↓ALP ↔TP ↑Alb	ND	ND	No deaths or adverse effects have been reported	Rosemary extracts exerted hypoglycemic and hepatoprotective effects
Rasoulian et al. (2019)	Subacute	↓FPG	Treatment inhibited diabetic neuropathic pain; reduced the damage induced by high glucose levels and levels of apoptosis markers; and reduced the weight loss	ND	No deaths or adverse effects have been reported	Rosemary Extract improved hyperglycemia and provided hyperalgesia and neuroprotective properties
Sebai et al. (2015)	Subacute	↓FPG ↑CAT ↑SOD ↑GPx ↓MDA	Treatment reduced weight loss	The treated group reversed semen abnormalities and reproductive performance affected by diabetes	No deaths or adverse effects have been reported	The volatile oil of Rosemary has a hypoglycemic effect and protects against reproductive function damage and oxidative stress in male

Table 2 (continued)

Study	Study follow-up time	Biochemical parameters[a]	Physiological and pharmacological parameters	Histopathology and anatomopathological analysis	Safety issues	Main remarks
Selmi et al. (2017)	Subacute	↓FPG ↓Tg ↓TC ↔HDL-c ↓LDL-c ↓Tg/HDL-c ↓TC/HDL-c ↓ALT ↓AST ↓ALP ↑Alb ↓BUN ↑AUR ↓CRE ↓MDA liver ↑CAT liver ↑SOD liver ↓MDA kidney ↑CAT kidney ↑SOD kidney	Treatment reduced weight loss	Treatment protected against DM-induced increase in hepatic and renal relative weights	No deaths or adverse effects have been reported	The volatile oil of Rosemary has a hypoglycemic effect and protects against liver and kidney damage caused by oxidative stress
Shen et al. (2020)	Subacute and Subchronic	↓FPG ↔HDL-c ↓LDL-c ↓TC ↓Tg ↓ALP ↓ALT ↓AST ↑SOD ↓MDA	ND	ND	No deaths or adverse effects have been reported	Rosemary extracts exerted hypoglycemic, hypolipidemic, and hepatoprotective effects, Rosemary extract (50 mg/Kg) was efficient against the oxidative stress
Silva et al. (2011)	Subchronic	↔FPG ↓ A1c-Hb ↑CAT liver ↔SOD liver ↑GPx liver ↓GR liver ↑SOD brain ↔GPx brain ↔GR brain	Treatment did not change weight loss, water and food uptake	ND	No deaths or adverse effects have been reported	Rosemary extract (50 mg/Kg) was efficient against the oxidative stress

Table 2 (continued)

Study	Study follow-up time	Biochemical parameters[a]	Physiological and pharmacological parameters	Histopathology and anatomopathological analysis	Safety issues	Main remarks
Wahba, (2022)	Sub chronic	↓FPG ↑ SIL ↑NEU ↑EOS ↓LYM ↓MONO ↑PT ↑Alb ↑Glb ↓TG ↓TC ↑BUN ↑CRE ↑SOD ↑GPx ↑CAT	Treatment enhanced body weight improvement and enhanced feed efficiency ratio	Treatment decreased the elevated level of serum TNF-α, IL4, and IL8 in diabetic rats	No deaths or adverse effects have been reported	Rosemary diet supplementation Exhibits good immunostimulant and hypoglycemic

aResult was compared to vehicle control group; *AGc* intestinal α-glucosidase, *Alb* albumin; *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *AMY* α-amylase, *AUR* uric acid, *AST* aspartate aminotransferase, *A1c-Hb* serum hemoglobin glycated, *BUN* blood urea nitrogen, *CAT* catalase enzyme activity, *CPK* creatine phosphokinase, *CRE* creatinine; *EOS* eosinophils, *G6P* glucose-6-phosphatase, *G6PD* glucose-6 phosphate dehydrogenase, *Glb* globulin, *GLY* glycogen, *GP* glycogen phosphorylase, *Gpx* glutathione peroxidase, *GR* glutathione reductase, *GYS1* glycogen synthase, *Hb* blood hemoglobin, *FDPase* Fructose-1, 6-bisphosphatase, *FPG* fasting plasma glucose, *HDL-c* high density lipoprotein cholesterol, *HXK* hexokinase, *LDH* lactate dehydrogenase, *LDL-c* low density lipoprotein cholesterol, *LYM* lymphocytes, *MDA* malondialdehyde, *MONO* monocytes, *NEU* neutrophils, *ND* non-determined, *SIL* serum insulin level, *SOD* superoxide dismutase enzyme activity, *TC* total cholesterol, *Tg* triglycerides, *TP* total proteins

The effects of *R. officinalis* in the biochemical parameters of animals with DM

Lowering the FPG, but not the HbA1c levels

As can be seen in Fig. 2A, seventeen preclinical studies (n = 256) were pooled and indicated that *R. officinalis* derivatives significantly reduced FPG compared with vehicle control groups, representing −120.84 of MD (95% CI; −157.09, −84.59), $I^2 = 99\%$ (indicating a heterogeneity between the groups). The great majority of the studies (88.2%; n = 15) favored *R. officinalis*. In turn, Fig. 2B showcases that *R. officinalis* did not significantly reduce HbA1c as compared to the control groups (2 studies, n = 28; MD = −1.77 [95% CI; −6.16, + 2.61]; $I^2 = 70\%$).

Boosting the insulin release

Figure 2C depicts the metanalysis for SIL. The data from nine studies were pooled and provided evidence that *R. officinalis* significantly increases the release of insulin (n = 138; MD = + 3.73 [95% CI; + 3.17, + 4.29]) in comparison to the vehicle control groups. The I^2 was 100%, which showcases heterogenicity between the groups. Noteworthy, all studies consistently favored *R. officinalis*.

Decreasing hepatic damage

As reported in Fig. 3A, B, respectively, data of three studies (n = 38) were pooled and indicated that treating the animals with *R. officinalis* significantly reduced both ALT (MD = −36.42; [95% CI; −55.69, −17.14]; $I^2 = 99\%$) and

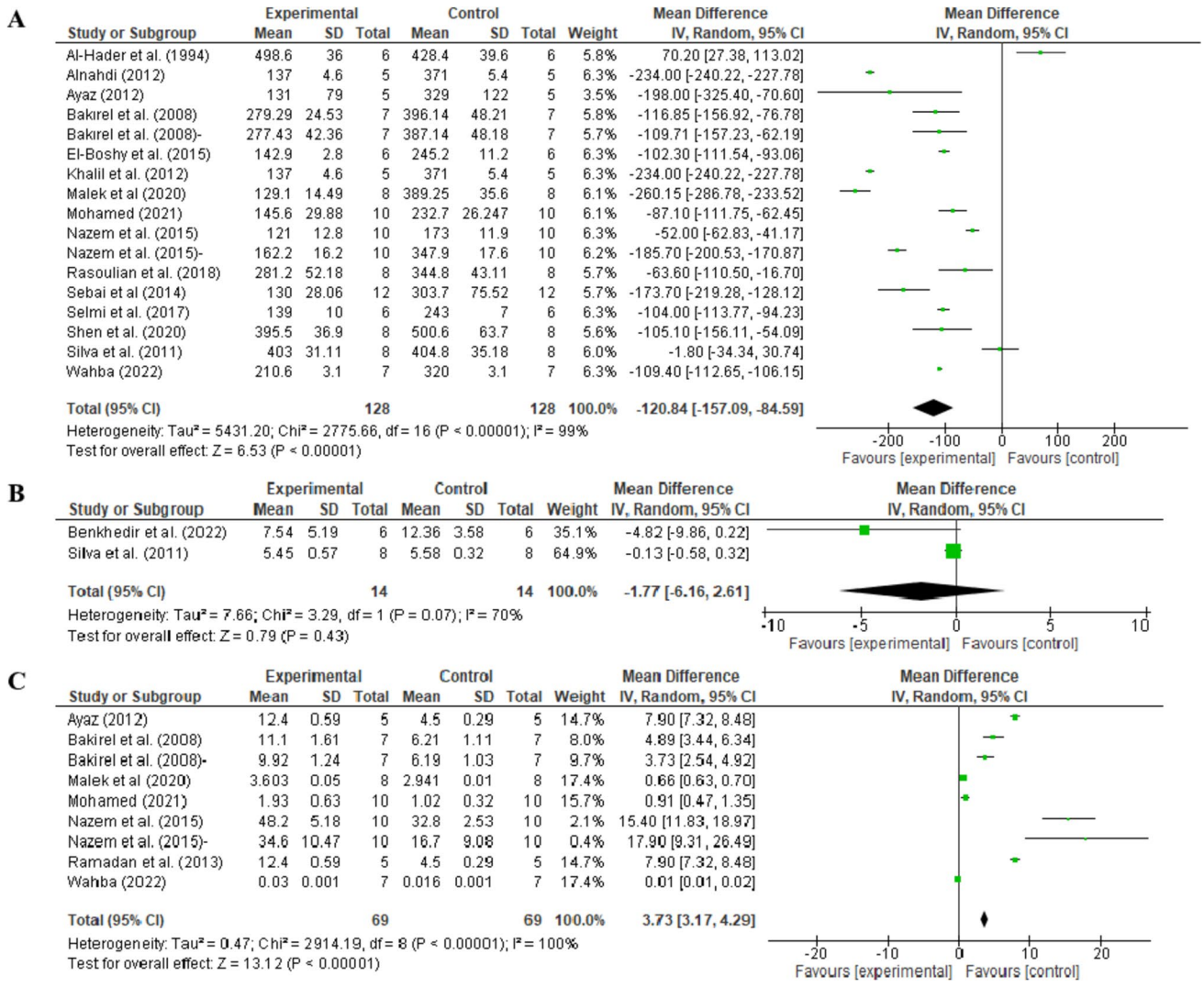


Fig. 2 Forest plot of preclinical studies of diabetes mellitus comparing *R. officinalis* and vehicle control; measuring FPG (**A**), HbA1c (**B**), and SIL (**C**)

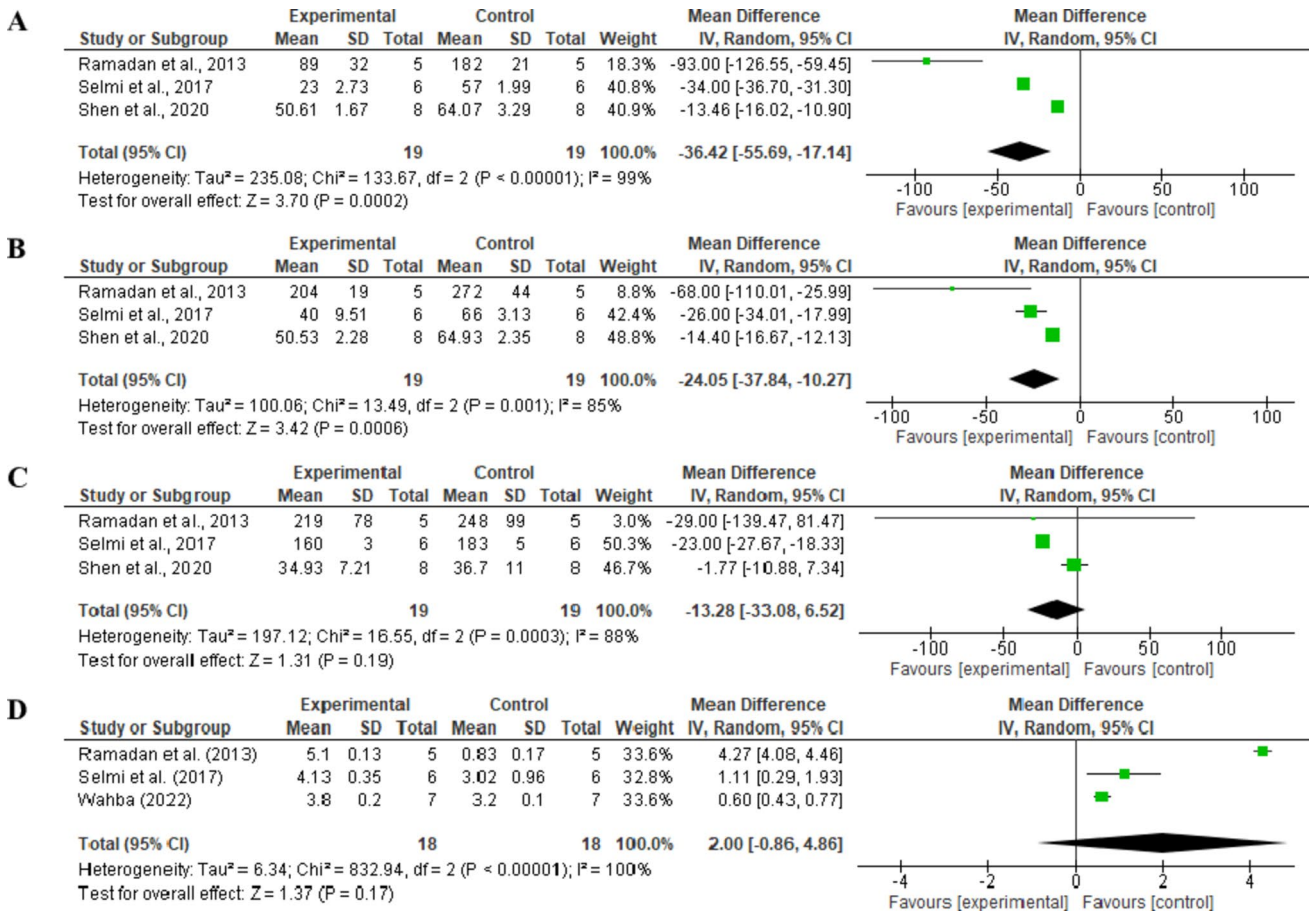


Fig. 3 Forest plot of preclinical studies of diabetes mellitus comparing *R. officinalis* and vehicle control; measuring ALT (**A**), AST (**B**), ALP (**C**) and Alb (**D**)

AST (MD = −24.05; [95% CI; −37.84, −10.27]; $I^2 = 85\%$) enzyme levels compared to vehicle control groups. On the other hand, *R. officinalis* did not significantly decrease the ALP enzyme levels (MD = −13.28; [95% CI; −33.08, +6.52]; $I^2 = 88\%$) as shown in Fig. 4C. Moreover, the Alb levels (Fig. 4D) were not significantly affected following the treatment with *R. officinalis* (3 studies, n = 36; MD = +2.00 [95% CI; −0.86, +4.86]; $I^2 = 100\%$).

Slightly recovering the kidney function

Figures 4A–C show the metanalysis for the several biochemical markers herein used to assess the kidney function of the diabetic animals treated with *R. officinalis* or vehicle. The data of 4 studies (n = 48) were pooled and indicate that *R. officinalis* significantly decreased both BUN (MD = −24.84 [95% CI; −34.78, −14.90]; $I^2 = 93\%$) and CRE (MD = −0.40 [95% CI; –0.74, −0.06]; $I^2 = 98\%$) levels compared to vehicle control groups. However, the data of these same studies were pooled and indicate that *R. officinalis* did not significantly reduce AUR (MD = −0.43 [95% CI; −2.05, + 1.19]; $I^2 = 100\%$) level in comparison to the vehicle control group.

Improving the lipid profile

Figure 5A indicates that there was a significant lowering in LDL-c level of diabetic animals receiving *R. officinalis* compared to the vehicle control group (3 studies, n = 38; MD = −11.74 [95% CI; −21.27, −2.21]; $I^2 = 92\%$). Nor the HDL (3 studies, n = 38; MD = + 3.66 [95% CI; −1.89, + 9.20]; $I^2 = 93\%$), neither the TC (4 studies, n = 52; MD = −27.18 [95% CI; −60.21, + 5.86]; $I^2 = 99\%$) or Tg (4 studies, n = 52; MD = −18.52 [95% CI; −37.96, + 0.93]; $I^2 = 97\%$) serum levels were significantly affected following the treatments with *R. officinalis* in comparison to vehicle control groups (Fig. 5B–D, respectively).

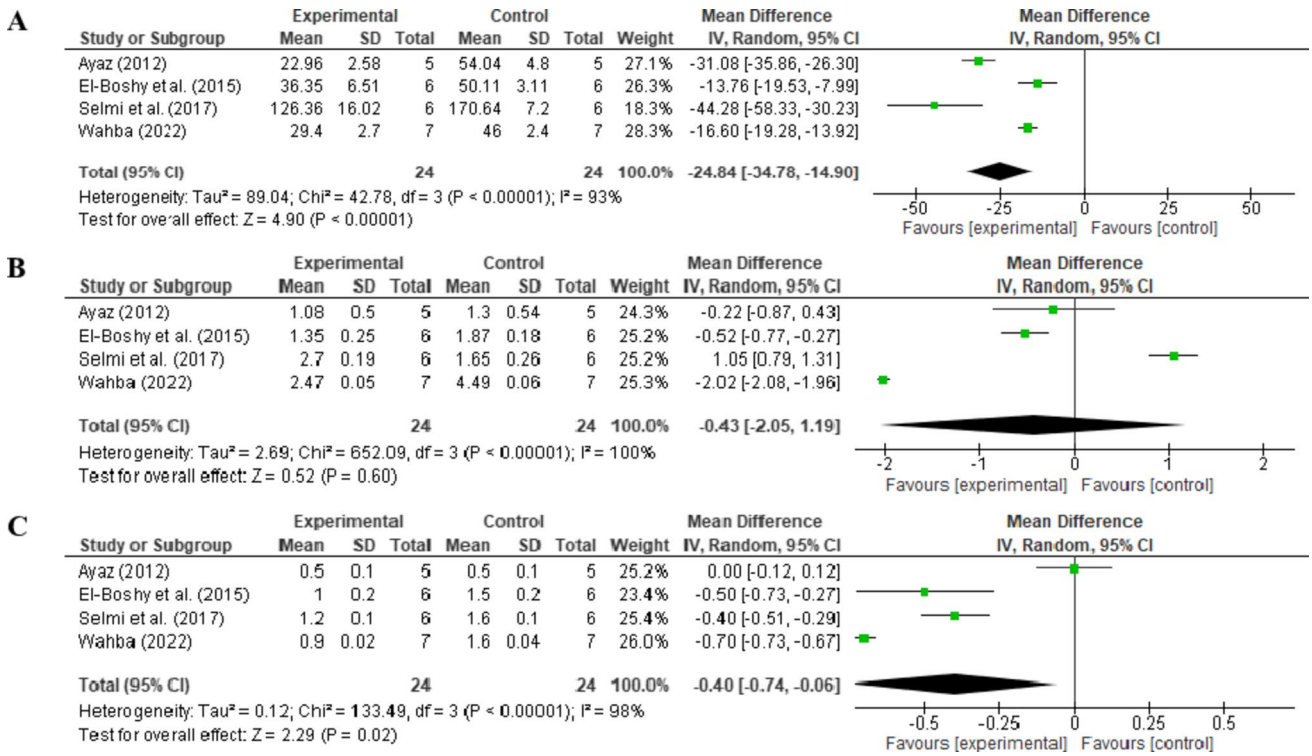


Fig. 4 Forest plot of preclinical studies of diabetes mellitus comparing *R. officinalis* and vehicle control; measuring BUN (**A**), AUR (**B**), and CRE (**C**)

Subgroup analysis

The subgroup analyses for FPG enabled us to compare the results for the exposure time and type of extracts. As shown in Fig. S2, there was a subgroup effect statistically significant ($p < 0.00001$; $I^2 = 79.3\%$), i.e., the exposure time and/or the extract type impact the antihyperglycemic effect of *R. officinalis*.

Based on this analysis it's possible to assert that either the volatile oil (2 studies, $n = 24$; $MD = -18.20$ [95% CI; $-188.89, +152.50$]; $I^2 = 98\%$) or the acute exposure (2 studies, $n = 26$; $MD = -19.45$ [95% CI; $-195.76, +156.86$]; $I^2 = 97\%$) do not yield significant outcomes in decreasing the FPG.

Concerning the SIL, it was possible to compare the results for the type of extract and animal strain whether rabbits or rats. The results of the subgroup analyses are presented in Fig. S3. The test for subgroup differences indicated that there was a significant subgroup effect statistically ($p < 0.00001$; $I^2 = 96.6\%$) so that both extract type and animal strain significantly impact the efficacy of *R. officinalis* in increasing the release of insulin when compared to vehicle control.

The treatment effect favored *R. officinalis* over vehicle control for all animal strains and extract types; which suggests that the subgroup effect is quantitative. Both FPG and SIL heterogeneity between results in studies within subgroups requires further exploration.

Risk of bias and methodological quality

Figure 6A displays the summary of the results concerning the bias risk assessment according to the SYRCLE tool for controlled preclinical trials herein included. The results reveal that all studies did not perform allocation concealment, blinding of outcome assessment, and blinding of evaluation of random results. In addition, an important risk of bias was verified by checking whether there was a pancreatectomy to assess outcome bias or indicating that there was no pancreatic beta regeneration not attributed to *R. officinalis* exposure.

Complementarily, Fig. 6B reports the methodological quality evaluated by the CAMARADES checklist for the pre-clinical studies included. The quality score of the majority of studies in this analysis was in mean, 5.3 ± 1.0, indicating an average methodological quality. All 23 studies reported statements of compliance with regulatory requirements and the use of animals with hypertension or diabetes.

However, none of these studies described the blinded assessment of outcome and sample size calculation, and 15 studies did not report how the animals used in the study were

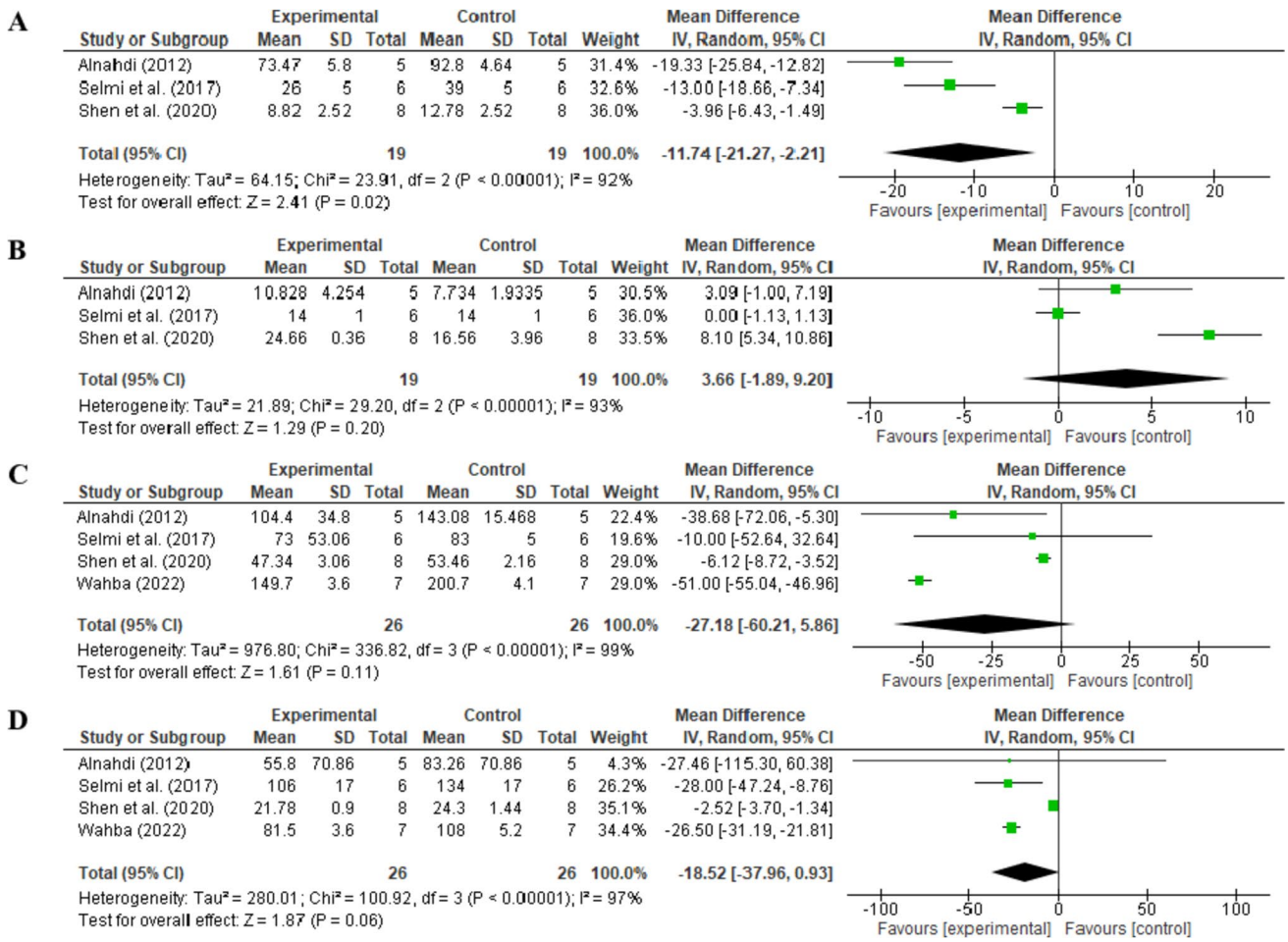


Fig. 5 Forest plot of preclinical studies of diabetes mellitus comparing *R. officinalis* and vehicle control; measuring LDL-c (**A**), HDL-c (**B**), TC (**C**), and Tg (**D**)

euthanized (avoidance of anesthetics with marked intrinsic properties).

Discussion

The efficacy and safety of *R. officinalis*

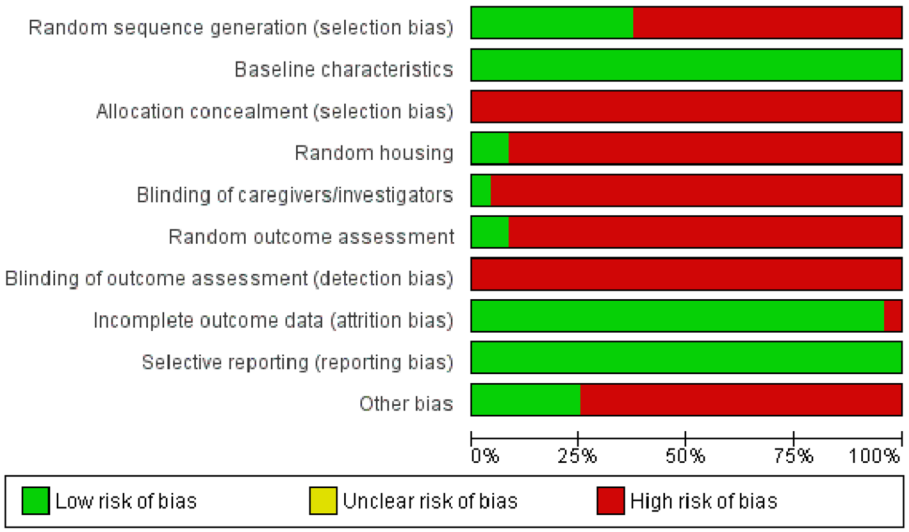
To the best of our knowledge, this is the first systematic review and meta-analysis shedding light on the antihyperglycemic, hepatoprotective, nephroprotective, and antihyperlipidemic effects of *R. officinalis* extracts in preclinical experimental models of T1DM. Our meta-analysis confirmed the beneficial effect of this nutraceutical in reducing FPG besides kidney and hepatic injury markers; in decreasing the LDL-c and increasing SIL in animals.

The reduction in the FPG of the diabetic animals treated with the different *R. officinalis* extracts is outstanding and, on average, greater than that observed with *Momordica charantia* L. (n = 815; SMD = −6.86 [95% CI; −7.95, −5.77]; $I^2 = 90\%$), which is a nutraceutical widely consumed in Asia and Africa as adjuvant in the management of DM (Peter et al. 2021). Moreover, *R. officinalis* displays a more appreciable antihyperglycemic effect when compared to the Brazilian superfruit *Eugenia uniflora* (n = 36; MD = −49.97 [95% CI; −57.18, −42.75]; $I^2 = 67\%$) (Máximo et al. 2022) and to the medicinal plant *Moringa oleifera* (n = 699; MD = −3.92, [95% CI; − 4.65, − 3.19; $I^2 = 90.15\%$) (Watanabe et al. 2021).

It's important to consider that in all studies herein included, the treatment with *R. officinalis* was not able to reduce the FPG to normal levels, i.e., < 100 mg/dL (Elsayed et al. 2023). Therefore, using *R. officinalis* does not ensure controlling the hyperglycemia by itself but may be helpful to enhance the hypoglycemic effects achieved with insulin administration. In turn, decreasing the dose of insulin or its administration frequency can increase patient compliance and adherence to the treatment, and reduce the adverse effects often associated with insulin administration errors.

The chance of herb-drug interactions following the long-term intake of *R. officinalis* with either insulin or oral

A



B

	n	%
Number of publications	23	-
Publication in peer-reviewed journal	23	100
Statement of control of temperature	15	65
Randomization of treatment or control	9	39
Allocation concealment	0	0
Blinded assessment of outcome	0	0
Avoidance of anesthetics with marked intrinsic properties	14	61
Use of animals with hypertension or diabetes	23	100
Sample size calculation	0	0
Statement of compliance with regulatory requirements	23	100
Statement regarding possible conflict of interest	11	48

Fig. 6 The risk of bias assessment results using SYRCLE's tool criteria (**A**) and methodological quality of the studies included (**B**) based on CAMARADES checklist

hypoglycemic drug administration is to be taken into account because this may exacerbate the hypoglycemic effect. On one hand, it would be beneficial when envisioning the deprescribing of oral hypoglycemic drugs and decreasing their major side effects such as vomiting, flatulence, and diarrhea, which impair the patient's adherence to the treatment (Ghadge and Kuvalekar 2017). On the other hand, it could provoke hypoglycemia (FPG < 70 mg/dL) which brings several undesired symptoms to patients (e.g., shakiness, sweating, fatigue, difficulty concentrating, etc.) (Nakhleh and Shehadeh 2021).

Still, in the wake of this food or herb-drug interaction scenario, it has been witnessed in the literature that the rosmarinic acid, the major phytochemical comprising *R. officinalis* acts in vitro as a weak or moderate inhibitor (even mixed or competitive mechanisms) of some human cytochrome P450 monooxygenases (CYP2C19 and CYP2E1) and, mainly, uridine diphosphate glucuronosyltransferases (UGT1A1/1A6/2B7) isoforms (Kim et al. 2019). This last group of enzymes is needful for the hepatic metabolism of some antidiabetic drugs such as canagliflozin and troglitazone (Zhou et al. 2016), besides antitumoral (etoposide and SN-38), antilipidemic (ezetimibe) and non-steroidal anti-inflammatory (acetaminophen, diclofenac, and naproxen) drugs (Kim et al. 2019).

These concerns are of utmost importance because diabetic patients can be up to two-fold more susceptible to using oral anti-diabetic agents associated with medicinal plants (Chelghoum et al. 2021). Therefore, the use of *R. officinalis* in association with other pharmaceutical drugs in the management of DM must be closely accompanied by a multidisciplinary healthcare professional team.

The overall mechanisms of action behind the antihyperglycemic effect of *R. officinalis* are not yet fully understood, but it has been suggested that the increment in insulin secretion somehow plays a key role in lowering the FPG (Bao et al. 2020). This is because an increased insulin level can help to the lowering of glucose levels by promoting glucose uptake and storage in the cells, then, inhibiting glucose production in the liver, and stimulating glycogen synthesis while inhibiting glycogenolysis (Rahman et al. 2021).

For clarification sake of this hypothesis, herein we plotted the MD obtained for SIL versus the respective MD of FPG arising from our meta-analyses (Figs. 2A and 3, respectively). There was a very low correlation between the increment of SIL and the decrement of FPG ($R^2 = 0.027$, data not

shown), thus further investigations with a greater number of studies are still required to ratify or refute this.

Non-alcoholic fatty liver disease and chronic kidney disease, which are metabolic conditions putatively interdependent, are often reported as DM complications (Byrne and Targher 2020). In a study included in the meta-analysis regarding the biochemical markers of hepatic damage related to DM (Selmi et al. 2017), the administration of *R. officinalis* lowered the ALT and AST serum levels to normal values, i.e., < 40 U/L (Kim et al. 2004).

Even though all the treatment effects favored *R. officinalis* over vehicle control in the meta-analysis of BUN, the decrement observed for this parameter associated with kidney injury did not reach normal levels, i.e., $5 \leq \text{BUN} \leq 20$ mg/dL (Hosten 1990). Nonetheless, in the group treatment with *R. officinalis* the CRE blood levels have been lowered to the normal ranges, which are 0.7–1.3 mg/dL for adult males and 0.6–1.2 mg/dL for adult females (Hosten 1990). Therefore, *R. officinalis* may promote hepatoprotection more markedly than nephroprotective effects in DM.

The hepatoprotective effects of *R. officinalis* have been confirmed by several in vitro and in vivo investigations irrespective of the method used to induce liver damage (Amin and Hamza 2005; Guimarães et al. 2023; Hegazy et al. 2018; Ielciu et al. 2021; Mohamed et al. 2022; Rašković et al. 2014). The lipid alterations that occur in DM, such as the increment of the LDL-c, are related to cardiovascular diseases, one of the main causes of mortality and morbidity in people with DM (Cole and Florez 2020).

Among the hypotheses related to these alterations, we have the high formation of advanced glycation end products and the increment in reactive oxygen species that are favored by hyperglycemia (Méndez et al. 2010). This process can lead to the accumulation of oxidized lipids, which can contribute to the development of lipid metabolism disorders and the progression of related diseases. Furthermore, a study published by Jiang et al. 2020, suggested that oxidative stress-induced lipid peroxidation can contribute to the development of insulin resistance, which is a key feature of DM.

Thence, besides the other benefits aforementioned, *R. officinalis* may reduce cardiovascular risk to a certain extent by decreasing the serum LDL-c level and avoiding the fatty deposits assembled in the arteries.

The role of OS in the pathogenesis of DM is extensively revised elsewhere (Darenskaya et al. 2021). Since *R. officinalis* is an outstanding source of antioxidants (Andrade et al. 2018; Celiktas et al. 2007; Gonçalves et al. 2011; Sánchez-Camargo and Herrero 2017; Takayama et al. 2022), several studies herein included assessed in vivo antioxidant activity of the tested extracts (Bakirel et al. 2008; El-Boshy et al. 2015; Emam 2012; Khalil et al. 2012; Mohamed 2021; Nazem et al. 2015; Sebai et al. 2015; Selmi et al. 2017; Shen et al. 2020; Silva et al. 2011; Wahba 2022). However, the methods used by the authors in pursuit of this and the antioxidant outcomes varied widely. For this reason, it was not possible neither to perform metanalysis nor to correlate the in vivo biochemical markers of antioxidant activities with the preventive effect in DM.

Noteworthy, none of the preclinical studies included in this systematic review reported any adverse effects, mortality, or behavioral changes in the tested animals that were attributed to *R. officinalis* exposure. These findings hint that *R. officinalis* is safe in all of the tested doses (25–800 mg/kg for extracts and 0.5% to 10% for leaves powder). Indeed, the European Food Safety Authority has classified *R. officinalis* extracts as a Generally Recognized as Safe (GRAS) food (CFR182.10; 182.20)(Aguilar et al. 2008), not showing high levels of toxicity at therapeutic doses.

Study limitations

Some studies evaluated in this work reported having assessed FPG in diabetic animals but did not demonstrate the raw results in the tables or figures (Belmouhoub et al. 2016, 2017, 2020; Ramadan et al. 2013). Hence, as we did not receive any answer about these raw data from the authors, it was not possible to include them in our meta-analysis.

Regarding the experimental design of the included articles, a large number of studies included only male rats in their experimental protocols, and it was not possible to compare the effects between males and females.

We also point out the lack of standardization when reporting the dose of extract administered to the animals. One study did not report the weight of the animals or the concentration of extract administered (Al-badry 2017), so it was not possible to define the dose administered (mg/Kg).

Many articles did not inform how the sample size calculation, housing, allocation, and blinding were carried out, thus revealing a high risk of bias for these domains and impairing the internal validity of these investigations. This trend is not an exclusivity of our findings, since it has been very often reported in systematic reviews and meta-analyses dealing with preclinical trials in animals (Gupta 2019; Máximo et al. 2022; Mignini and Khan 2006; Peter et al. 2021; Rostamkhani et al. 2022; Shojaei-Zarghani et al. 2022).

Furthermore, a scanty number of studies assessing the HbA1c levels in the animals was included, and *R. officinalis* displayed no appreciable impact in this parameter, which represents an index of average glucose and is considered the gold standard for monitoring the patient's glucose control over time (Sherwani et al. 2016). This inefficacy is likely related to the short-lasting of the studies assessing this biochemical marker., i.e., much lower than 90 days (the average time required for erythrocyte turnover). which might have been insufficient to adequately capture such effects.

The meta-analysis of animal studies has been considered a valuable statistical toolset for improving healthcare since it can be further used to generate new hypotheses and guide the design of clinical trials in humans (Hooijmans et al. 2014a; Sauvant et al. 2020).

The high heterogeneity displayed in our meta-analysis is likely attributed to the various methodological design aspects of the included articles, e.g., variability related to the animals used (strains, age, etc.), small sample sizes, different drugs administrated to induce DM and their doses, diverse intervention features (plant origin, harvesting time, solvents and procedures used to prepare the extract, route of administration, doses administrated, and treatment period), distinct outcome measurement methods, etc. This is also a recurrent trend for animal studies, that can restrict but not prevent the animal-to-human translation of findings arising from systematic reviews and meta-analyses (Bahadoran et al. 2020).

Finally, a few articles reported the accurate quantitative phytochemical analysis of the extracts administered in the animals (Rasoulian et al. 2019; Sebai et al. 2015; Shen et al. 2020), thereby revealing warning analytical standardization issues. Although displaying a great challenge, the standardization of herbal extracts plays a key role throughout the rationale development of phytopharmaceuticals once it is required for i) assessing the seasonal and batch-to-batch variability to assure consistent chemical profile; ii) identifying and controlling critical processing parameters such as extraction, drying, transportation and storage; iii) establishing the major active compounds involved in the biological activities and their putative mechanisms of action; and iv) enabling to achieve improved and reproducible treatment outcomes (Alamgir 2017).

Conclusions

The administration of *R. officinalis* derivatives dwindles the FPG besides hepatic damage in diabetic animals, thence this nutraceutical may help in the management of DM and some of its complications. The pre-clinical trials herein analyzed display relevant issues concerning the risk of bias and methodological quality. Therefore, although plausible, so far, it's not possible to draw a solid conclusion regarding the efficacy of this nutraceutical as an alternative in the primary care of DM.

Patients and healthcare professionals would greatly benefit from further high methodological quality studies, especially controlled randomized clinical trials performed with accurately standardized extracts and assessing HbA1c as a primary outcome.

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Declarations

Ethical statement This article does not contain any studies involving animals performed by any of the authors. This article does not contain any studies involving human participants performed by any of the authors.

Conflict of interest Virginia Moura Oliveira has no conflict of interest. Letícia Rafaela Silveira has no conflict of interest. Kitete Tunda Bunnel has no conflict of interest. Caroline Pereira Domingueti has no conflict of interest. André Oliveira Baldoni has no conflict of interest. Nayara Ragi Baldoni has no conflict of interest. Renê Oliveira do Couto has no conflict of interest.

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