The efficacy of rosemary (Rosmarinus officinalis) in animal models of diabetes mellitus: A protocol for systematic review and meta-analysis

Citation

RenÃª Couto, Virgínia Oliveira, Gabriella Souza, Luiza Honorato, René Marchandeau Pinto Jr. The efficacy of rosemary (Rosmarinus officinalis) in animal models of diabetes mellitus: A protocol for systematic review and meta-analysis. PROSPERO 2021 CRD42021250556 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021250556

Review question

What are the effects of R. officinalis preparations in animal models for type 2 diabetes mellitus?

Context and rationale

Diabetes mellitus (DM) is a group of metabolic disorders characterized by high blood glucose level. Type 2 diabetes mellitus (DM2) is the most common form of DM, accounting for more than 90% of all cases of DM. Typically, it affects older adults, but is increasingly observed in children, adolescents and young adults. DM2 has been recognized as an important cause of morbidity and permanent disability in adults, compromising the social and economic well-being of all nations, regardless of their level of economy. Owing to the remarkable prevalence of DM2 worldwide, the research for alternative therapeutic options for the current pharmacological treatments, including herbal medicines, is drastically increasing over the last few decades.

Amongst the plants with the most pronounced antioxidant activity, the species Rosmarinus officinalis L. (Lamiaceae), popularly known as rosemary is noteworthy. Rosemary is a hold house herb widely used worldwide as a spice, food supplement, as well as in the production of phytocosmetics and phytomedicines. Furthermore, rosemary displays a powerful source of antioxidants such as phenolic acids (e.g., rosmarinic acid and coffee acid), diterpenes (e.g., carnosol and carnosic acid), triterpenes (e.g., ursolic acid) and essential oils, thereby standing out as an effective strategy for the treatment of ailments involving the oxidative stress e.g., inflammation, depression, cancer, etc. The antidiabetic and hypoglycemic effects of rosemary preparations have been showcased in several preclinical and clinical studies of metabolic syndromes, including DM2. Therefore, gathering, summarizing, and critically analyzing the scientific evidences regarding the efficacy of rosemary preparations for treating DM2 in animal models should be of utmost importance for validating their ethnopharmacological claims and promoting the rationale use in the folk and/or complementary medicine.

Searches

The electronic databases PubMed (MEDLINE), Scopus, ScienceDirect, Web of Science (Science Citation Index), and Health Virtual Library (BVS) will be searched for relevant publications. We also propose to perform citation searches and search reference lists of relevant included studies and any previously published reviews. The gray literature will also be searched in Google Scholar and Google to track unindexed works that may contribute to the study. The search will be performed by the DOI (Digital Object Identifier System) of the intended study through: .

Study designs to be included

Inclusion criteria:

Experimental studies with separate control group; cross-over design, randomized, and non-randomized study designs

Exclusion criteria:

in vitro and ex vivo, in silico study designs, before-after studies without control group.

Human disease modelled [1 change]

Diabetes mellitus (DM)

Animals/population [1 change]

Inclusion criteria:

All animal models of DM, all sex, all age, and all species of animals/strains

Exclusion criteria:

Studies in humans, animals with any co-morbidity

Intervention(s), exposure(s)

Inclusion criteria:

Treatment with R. officinalis preparations in any dosing, given at any time and frequency of dosing

Exclusion criteria:

Treatment with polyherbal preparation of R. officinalis; or isolated pure compounds; or R. officinalis combined with standard oral hypoglycemic agents.

Comparator(s)/control [1 change]

Inclusion criteria:

Animal models of DM treated with either vehicle/placebo, or standard treatment or health animal control

Exclusion criteria:

Animal models of DM treated with any other drug.

Other selection criteria or limitations applied

Original articles and short communications (published or ahead of print) will be considered. Neither the language nor the publication date will be restricted. Case reports, review articles, editorials, letters to the editor, papers will be excluded. presented in scientific events, news, comments, dissertations and theses will not be included.

Outcome measure(s)

Inclusion criteria:

Primary: Serum glucose level (SGL);

Secondary: Glycosylated hemoglobin A1c; Lipid profile (triglycerides, HDL, LDL, and total cholesterol); absolute body weight; alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total proteins (PT), albumin, globulin; and bilirubin total for hepatic function; urea nitrogen (BUN), uric acid (AUR) and creatinine (CRE) for renal function; and amylase (AMY) for pancreatic function; Noteworthy, the primary and secondary outcome measures will be collected at baseline and at the end of follow up period. Nevertheless, for glycosylated hemoglobin A1c, only data from studies that has a follow up of at least four weeks will be considered for analysis.

Exclusion criteria:

HBA1c measure at less than four weeks of follow up

Study selection and data extraction [1 change]

Procedure for study selection

Research data will be extracted from database and exported to Rayyan QCRI web platform (https://rayyan.qcri.org/welcome) to facilitate the selection of potentially eligible studies. Titles and abstracts will be read from the electronic material obtained by an effective search strategy to identify potential eligible papers by two independent authors. Throughout the study, each reviewer will be blind to the decisions of the other, and any discrepancies will be discussed until consensus is achieved, or, if this is not possible, a third researcher will be consulted.

Prioritise the exclusion criteria

1. Not an R. officinalis preparation

2. Not an animal model

3. Not a DM

4. Experiments without comparison group

Methods for data extraction

Studies will be reviewed for relevance based on study design, types of animal models, exposures and outcome measures. Two review authors will extract data independently. Any disagreement over eligibility will be resolved through discussion with third author. The data will be extracted into a pre-piloted standardized data extraction form. In case of data presented in form of graph study authors will be contacted and obtain missing or additional data. The authors of the unavailable articles will be contacted twice by email, through which access to these articles will be requested.

Data to be extracted: study design

Experimental design will include randomized controlled, cross-over design, non-randomized controlled, number of experimental groups and duration of follow up, method of allocation to treatment group, method of assessing outcomes whether blinded or not.

Data to be extracted: animal model

Species of animals used, sex of animals, number of animals per group and age of animals

Data to be extracted: intervention of interest

Nature of intervention, taxonomical identification of plant, voucher number, method of preparation of rosemary extract, quality control parameters, chemical composition, dose, dosing frequency, time and route of administration (oral, intraperitoneal, subcutaneous)

Data to be extracted: primary outcome(s)

The SGL, a continuous variable, will be expressed in mg/dL. Herein, included studies with data expressed in different units of measurement will be converted to mg/dl.

Data to be extracted: secondary outcome(s)

1. Glycosylated hemoglobin A1c is a continuous data measured in %;

2. Triglycerides is a continuous data measured in mg/dL;

3. HDL cholesterol is a continuous data measured in mg/dL;

4. LDL cholesterol is a continuous data measured in mg/dL;

5. Total cholesterol is a continuous data measured in mg/dL;

6. Weight is a continuous data measured in g;

7. Urea is a continuous data measured in mg/dL;

8. Urea nitrogen (BUN) is a continuous data measured in mg/dL;

9. Serum creatinine (CRE) is a continuous data measured in mg/dL;

10. Serum total protein is a continuous data measured in mg/L or g/dL;

11. Albumin is a continuous data measured in g/dL;

12. Globulin is a continuous data measured in g/dL;

13. Alanine aminotransferase (ALT) is a continuous data measured in U/L;

14. Aspartate aminotransferase (AST) is a continuous data measured in U/L;

15. Bilirubin total is a continuous data measured in U/L;

16. Alkaline phosphatase (ALP) is a continuous data measured in U/L;

17. uric acid (AUR) is a continuous data measured in mg/dL;

18. amylase (AMY) is a continuous data measured in mg/dL;

Data to be extracted: other

Author, year, language of publication.

Risk of bias and/or quality assessment

By use of SYRCLE's risk of bias tool. By use of the CAMARADES checklist for study quality.

SYRCLE's risk of bias tool. Hence, the internal validity of studies will be evaluated through assessment of ten risk of bias domains i.e., sequence generation, baseline characteristics, allocation concealment, random housing, blinding of investigators/caregivers, random outcome assessment, blinding of assessor incomplete outcome data, selective outcome reporting and other source of bias. Each criterion will be assigned value as high, low or unclear risk of bias. Any disagreement between the two review authors will be resolved through discussion with a third reviewer.

Construct validity will be assessed in relation to the extent the experimental models mimic typical clinical presentation of intoxication due to internal exposure. The external validity will be assessed in relation to the replicability of cause-effect relationship under different condition. We will use CAMARADES checklist, which combines reporting of a number of measures to reduce bias, and several indicators of external validity. Such a checklist is based on 10 criteria i.e., peer-reviewed publication; statement of control of temperature; random allocation to treatment or control; blinded induction of intoxication; blinded assessment of outcome; any use of cointerventions/co-morbid without influence on toxicity; appropriate animal model (age, sex, strain); sample size calculation; compliance with animal welfare regulations; and statement of potential conflict of interests. Each study will be given a quality score out of a possible total of 10 points, and the group median will be calculated.

.

Strategy for data synthesis

Planned approach

Data from eligible studies will be described in narrative synthesis, and summarized in tables and figures. The narrative synthesis aims to provide summaries of results explained primarily in textual form. The variable for narrative

summarizing and analysis are: diabetes induction method; type of intervention studied; intervention content such as dose; route of administration; taxonomical identification of the plant species used; target animal characteristics; chemical composition and quality control results of the extracts; method of preparation of the extracts. Both the primary and secondary outcomes will be synthesized qualitatively. We will use sign to indicate increase (↑) and decrease (↓) or equal (↔) effect size measured at follow up between treatment and control groups. The narrative syntheses will therefore present data in form of tables to established patterns and variations. Meta-analysis will be conducted whether data from primary included studies meet the following criteria: Judged to be relatively similar through evaluation of I^2 statistic results; primary study methodological quality is within acceptable quality; there are sufficient studies with data on outcome to be pooled in meta-analysis. Meta-analysis is planned for all primary and secondary outcomes (continuous data).

Effect measure

1. SGL; measure of effect is standardized mean difference;

2. Glycosylated hemoglobin A1c; measure of effect is standardized mean difference;

2. Triglycerides; measure of effect is standardized mean difference;

3. HDL; measure of effect is standardized mean difference;

4. LDL; measure of effect is standardized mean difference;

5. Total cholesterol; measure of effect is standardized mean difference;

6. Weight; measure of effect is standardized mean difference;

7. Urea; measure of effect is standardized mean difference;

8. BUN; measure of effect is standardized mean difference;

9. CRE; measure of effect is standardized mean difference;

10. Serum total protein; measure of effect is standardized mean difference;

11. Albumin; measure of effect is standardized mean difference;

12. Globulin; measure of effect is standardized mean difference;

13. ALT; measure of effect is standardized mean difference;

14. AST; measure of effect is standardized mean difference;

15. Bilirubin total; measure of effect is standardized mean difference;

16. ALP; measure of effect is standardized mean difference;

17. AUR; measure of effect is standardized mean difference;

18. AMY; measure of effect is standardized mean difference;

The standardized mean difference calculated will be calculated by subtracting mean of the control group from mean of treatment group divided by the pooled standard deviation of the two groups.

Effect models

Random effect model is planned to be use for all continuous data aforementioned:

Heterogeneity

The Qui^2 (Qui squared) test and its P value will be used to evaluate heterogeneity between primary studies intervention effects. A low P value (or a large Qui2 statistic relative to its degree of freedom) provides evidence that, the observed variation in estimates of effect is not due to chance alone. We will use I^2 statistic for assessing heterogeneity severity. The $I^2 \geq 50$ will be considered as indicative of substantial heterogeneity. The heterogeneity severity will be evaluated before performing the analysis to decide whether to use random effects model or fixed effect model. Factors that influence heterogeneity such as primary study quality score and design, dosage amount, nature of intervention and animal strain will be assessed during sensitivity analysis.

Other

Not planned

Analysis of subgroups or subsets [1 change]

Subgroup analyses

If sufficient data will be available, subgroup analysis will be done by study design (randomized and nonrandomized design), type of extract, type diabetes model, duration of treatment, dose, and animal strains used.

Sensitivity

For all outcome measures sensitivity analysis will be performed by restricting study quality score and design, dosage amount, nature of intervention and animal strain used

Publication bias

Publication bias will be assessed by testing asymmetry of funnel plot using Egger's test. The test for funnel plot asymmetry will not be used when there are fewer than ten primary studies in the metanalysis because test power is generally too low to distinguish chance from real asymmetry. If publication bias is significant, trim and fill method will be used for correcting the probable publication bias. In addition, the significant asymmetry of funnel plot will be interpreted in the context of susceptibility to other biases that might explain it.

Contact details for further information

Rene Couto

rocouto@ufsj.edu.br

Organisational affiliation of the review

Federal University of Sao Joao del-Rei

Review team members and their organisational affiliations [2 changes]

Professor RenÃª Couto. Federal University of SÃ£o JoÃ£o del-Rei

Virgínia Oliveira. Universidade Federal de São João del-Rei, Campus Centro-Oeste Dona Lindu

Gabriella Souza. Universidade Federal de Sao Joao del-Rei

Luiza Honorato. UFSJ

René Marchandeau Pinto Jr. UFSJ

Collaborators

Dr Nayara Baldoni. Universidade Federal de Sao Joao del Rei

Review type

Pre-clinical animal intervention review

Anticipated or actual start date

21 April 2021

Anticipated completion date

28 February 2022

Funding sources/sponsors

Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)

Grant number(s)

21092

Conflicts of interest

Language

English

Country

Brazil

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Animals; DIABETES MELLITUS; Diabetes Mellitus, Type 2; GLUCOSE INTOLERANCE; HYPERGLYCEMIA; HYPERINSULINEMIA; INSULIN RESISTANCE; KETOSIS; Models, Animal; NIDDM; OBESITY; Phytotherapy; Plant Extracts; Rosmarinus

Date of registration in PROSPERO

23 April 2021

Date of first submission

21 April 2021

Stage of review at time of this submission [2 changes]

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Revision note

Owing to the lack methodological clarity and standardization on the diabetes inductionmodels (i.e., wether type 1 or type 2 DM), we decidde to include all types of DM.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

23 April 2021

11 June 2021

05 November 2021