Animal review

Please complete all mandatory fields below (marked with an asterisk *) and as many of the non-mandatory fields as you can then click *Submit* to submit your registration. You don't need to complete everything in one go, this record will appear in your *My PROSPERO* section of the web site and you can continue to edit it until you are ready to submit. Click *Show help* below or click on the icon

to see guidance on completing each section.

This record cannot be edited because it has been marked as out of scope

1. * Review title.

Give the working title of the review. This must be in English. The title should have the interventions or exposures being reviewed and the associated health or social problems.

Neuroprotective effects of Urtica Dioica in diabetic animal models: A systematic review

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

Neuroprotective effects of Urtica Dioica in diabetic animal models: A systematic review

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

27/08/2024

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

30/04/2025

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review.

The review has not yet started: No

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

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Sayed Yousof Mousavi

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Mousavi

7. * Named contact email.

Enter the electronic mail address of the named contact.

mousavi@kavosh.org.af

8. * Named contact address.

Enter the full postal address for the named contact.

First street of Karte 4, 1004, Kabul, Afghanistan

9. Named contact phone number

Enter the telephone number for the named contact, including international dialling code.

+93796850084

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'none' if the review is not affiliated to any organisation.

Department of cognitive neuroscience, Neuroscience research center, Kavosh nonprofit educational research institute, Kabul, Afghanistan

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country are now mandatory fields for each person.**

Dr Sayed Yousof Mousavi. Department of cognitive neuroscience, Neuroscience research center, Kavosh nonprofit educational research institute, Kabul, Afghanista
Dr Kawsar Alami. Department of Cognitive Neuroscience, Neuroscience Research Center, Kavosh nonprofit educational research institute, Kabul, Afghanistan
Dr Zahra Nazari. Department of Cognitive Neuroscience, Neuroscience Research Center, Kavosh nonprofit educational research institute, Kabul, Afghanistan
Miss Raheel Bayat. Department of Cognitive Neuroscience, Neuroscience Research Center, Kavosh nonprofit educational research institute, Kabul, Afghanistan

12. * Funding sources/sponsors.

Give details of the individuals, organisations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.

None

Grant number(s)

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

Give details of the question to be addressed by the review, clearly and precisely.

Does administration of Urtica dioica exert a neuroprotective effect on diabetic animal models when compared to those receiving a vehicle or placebo?

Context and rationale

Provide a brief description of the context and rationale of the review, including information on the relevance of your review for human health (max 250 words).

Urtica dioica, commonly known as Nettle, has a long-standing history in traditional medicine and has been recognized for its anti-inflammatory and antioxidant properties. Recent studies have explored its potential as a promising treatment for type 2 diabetes, a condition characterized by hyperglycemia, chronic inflammation, and oxidative stress. These underlying mechanisms contribute to the development of neurologic complications. It has been established in several animal studies that nettle can exert significant neuroprotective effects in diabetic models, reducing its neurologic complications such as cognitive impairment, affective disorders, and peripheral neuropathy. However, despite this promising preclinical evidence, a comprehensive assessment of the quality of evidence supporting the neuroprotective effects of Urtica dioica in diabetes is lacking. Although a narrative review article has been published on the neuroprotective effects of Urtica dioica, it is not a systematic review and does not specifically focus on diabetic subjects. This systematic review aims to critically evaluate the quality of evidence on the efficacy of Urtica dioica in reducing neurologic complications of diabetes and exerting neuroprotective effects in diabetic animal models to enable the transition to clinical research. The review will focus on studies that have investigated the effects of Urtica dioica on neurologic complications in diabetic animal models, as well as the underlying mechanisms of these effects. The review emphasizes the need for continued investigation to bridge the gap between preclinical findings and clinical application, ultimately paving the way for potential therapeutic applications of Urtica dioica in the prevention and management of diabetic complications.

16. * Searches.

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

A comprehensive literature search will be conducted to identify articles on the neuroprotective effects of Urtica dioica on diabetic animal models published in English from 2000 (there is no available data before this year) to the present. The following electronic bibliographic databases will be searched: Web of Science,

PubMed, ScienceDirect, Scopus, and Cochrane. The full search strategy is based on the search components “animal”, “Urtica dioica”, “neuroprotection”, and “diabetes”. The search terms will be combined using relevant Boolean operators to optimize the search. In addition to the electronic database search, the reference lists of included studies will be screened to identify any eligible studies that may not have been retrieved by our search. To ensure the inclusion of the most recent studies, the search will be re-run just before the final analyses.

17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Human disease modelled.

Give a short description of the disease, condition or healthcare domain being modelled.

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder that serves as the modeled human disease in this context. T2DM is a chronic metabolic disorder characterized by hyperglycemia, insulin resistance, and impaired insulin secretion. T2DM is associated with neurologic complications, which can significantly impact the quality of life of individuals with T2DM, making the development of effective treatments a critical area of research.

19. * Animals/population.

Give summary criteria for the animals being studied by the review, e.g. species, sex, details of disease model. Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

All animal (rats, mice, and rabbits) studies with laboratory induced diabetes and neurologic complications will be included

Exclusion criteria:

In vitro, ex vivo, in silico, in human studies, and animals without neurologic complication

20. * Intervention(s), exposure(s).

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed (e.g. dosage, timing, frequency). Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

Administration of Urtica dioica extract (either orally or parenterally), including whole plant or standardized extracts in any dose, timing, and frequency

Exclusion criteria:

Administration of Urtica dioica extract in combination with other herbs or medications, without administering Urtica dioica extract alone as a treatment

21. * Comparator(s)/control.

Where relevant, give details of the type(s) of control interventions against which the experimental condition(s) will be compared (e.g. another intervention or a non-exposed control group). Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

Studies that used vehicle-treated control animals as a comparison group will be included.

Exclusion criteria:

Studies will be excluded if they used control animals that did not receive a vehicle treatment, such as no treatment or non-vehicle treatment or studies did not provide a clear comparison between Urtica dioica-treated diabetic animals and vehicle-treated control animals.

22. * Study designs to be included.

Give details of the study designs eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

Controlled animal studies with a separate control group for comparison

Exclusion criteria:

Human studies, Case studies, in vitro studies, and animal studies without a separate control group for comparison

23. Other selection criteria or limitations applied.

Give details of any other inclusion and exclusion criteria, e.g. publication types (reviews, conference abstracts), publication date, or language restrictions.

24. * Outcome measure(s).

Give detail of the outcome measures to be considered for inclusion in the review. Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

Studies that assessed the neuroprotective effects of Urtica dioica using behavioral tests (such as cognitive

functions, affective symptoms, motor activity or coordination, and pain sensitivity), histological analyses (such as changes in neural tissue structure or morphology), and neurochemical markers (such as oxidative stress markers and inflammatory markers)

Exclusion criteria:

Studies that do not report on any relevant neuroprotective outcomes

25. N/A.

This question does not apply to systematic reviews of animal studies for human health submissions.

26. * Study selection and data extraction.

Procedure for study selection

Give the procedure for selecting studies for the review, including the screening phases (title and/or title-abstract and/or full-text), the number of researchers involved, and how discrepancies will be resolved.

The systematic review will employ a two-phase screening protocol to ensure the inclusion of relevant studies after a comprehensive database search. In Phase 1, Title-abstract screening, two reviewers will independently screen the titles and abstracts of all retrieved articles based on predefined inclusion and exclusion criteria. This phase aims to exclude studies that do not meet the inclusion criteria based on the available information in the abstract. In phase 2, Articles that pass the title-abstract screening will proceed to a full-text assessment. Two reviewers will independently evaluate the full content of each study to confirm that it meets all the eligibility criteria for inclusion in the systematic review. This comprehensive evaluation will ensure that only relevant studies are included. Any discrepancies will be resolved through consensus or by consulting the third investigator. All decisions, including reasons for exclusion and resolutions of discrepancies, will be systematically documented to ensure transparency and reproducibility of the process.

Prioritise the exclusion criteria

Multiple exclusion criteria may apply to an abstract/paper, which can cause discrepancies between reviewers in the reason for exclusion recorded. To avoid this, it is helpful to prioritize the exclusion criteria (e.g. 1) not an animal study; 2) not a myocardial infarction model, etc.) and record the highest ranking applicable criterion as the reason for exclusion. Please sort the exclusion criteria defined in questions 19 to 24. If applicable, do so for each screening phase.

To ensure the inclusion of high-quality studies that assess the neuroprotective effect of Urtica dioica in diabetic animals, the following exclusion criteria will be applied in each phase of the systematic review. In Title/Abstract screening phase: (1) not an animal study, (2) not a diabetic model, (3) no Urtica dioica intervention, and (4) no neuroprotective assessment. In the Full-text screening phase: As above, with the addition of (5) Inadequate control groups, and (6) Combination therapy of Urtica dioica, without administering

it alone as a treatment

Methods for data extraction

Describe methods for data extraction, including the number of reviewers performing data extraction, extraction of data from text and/or graphs, whether and how authors of eligible studies will be contacted to provide missing or additional data, etc.

We will develop standardized data extraction spreadsheet forms in Excel. Two reviewers will conduct the data extraction from each eligible study using a data extraction form. Each reviewer will extract data independently to ensure accuracy and minimize bias. If discrepancies arise between the two reviewers, they will discuss the differences to reach a consensus. If a consensus cannot be achieved, a third reviewer will be consulted to resolve the issue. Data will be extracted directly from the text or tables of the studies, including details on study design, sample size, interventions, outcomes, and results. If necessary, data presented in graphs will be extracted using digital data extraction tools or by manually digitizing the data, ensuring accuracy and reliability. If important data are missing or unclear, the authors of the eligible studies will be contacted to request additional information or clarification. Contact will be made via email, with a follow-up if necessary to ensure a response (max. 3 attempts).

Data to be extracted: study design

Specify the data to be extracted related to characteristics of the study design, e.g. controlled versus cross-over, number of experimental groups, etc.

Experimental groups, number of controls, type of controls, sample size calculation, number of animals per group, sampling methods.

Data to be extracted: animal model

Specify the data to be extracted related to characteristics of the animal model, e.g. species, sex of the animals, etc.

Type of animal, strain, species, age, gender, weight, housing, feeding conditions, method of induction of diabetes

Data to be extracted: intervention of interest

Specify the data to be extracted related to characteristics of the intervention of interest, e.g. dose, timing, etc.

Specific parts of Urtica dioica plant, Formulation of extract, dose, administration route, administration frequency and timing, duration, vehicle

Data to be extracted: primary outcome(s)

Define the primary outcome measure(s). For each outcome measure, specify in which format data will be extracted, including the eligible units of measurement, and data type (continuous/dichotomous). A description of any other manipulation or transformation of the extracted data that is planned may be included.

(1) Behavioral tests: type of behavioral tests for assessing neuroprotection (e.g., Morris water maze, open field test, Y-maze test), and specified behavioral parameters evaluated in each tests (e.g. escape latency and time spent in target quadrant in Morris water maze, spontaneous alteration in Y-maze test); Continuous. (2) Histological analyses: Type of histological staining used (e.g., hematoxylin and eosin, immunohistochemistry), brain regions or structures examined (e.g., hippocampus, cortex, substantia nigra), and parameters evaluated (e.g., neuronal density, gliosis, axonal degeneration); Continuous. (3) Neurochemical Markers: Type of marker (e.g., neurotransmitters, oxidative stress indices, neurotrophic factors, inflammatory cytokines), brain regions or structures in which examined (e.g., hippocampus, cortex, substantia nigra), and specific markers evaluated (e.g., dopamine, BDNF, TNF-alpha); Continuous. (4) Outcome of changes for above parameters including direction (e.g. increase, decrease, no change), magnitude (e.g. percentage change, mean difference) and statistical differences (e.g. p-value, confidence intervals); Continuous.

Data to be extracted: secondary outcome(s)

Define the secondary outcome measure(s). For each outcome measure, specify in which format data will be extracted, including the eligible units of measurement, and data type (continuous/dichotomous). A description of any other manipulation or transformation of the extracted data that is planned may be included.

Fasting blood glucose; Continuous; mg/dL

Data to be extracted: other

Specify any other data or study characteristics to be extracted, e.g. bibliographical details, such as author, year and language.

1st and corresponding author details and contact, country, publication year, journal name

27. * Risk of bias and/or quality assessment.

State whether and how risk of bias and/or study quality will be assessed. Assessment tools specific for pre-clinical animal studies include SYRCLE's risk of bias tool and the CAMARADES checklist for study quality

No risk of bias and/or quality assessment planned

No

By use of SYRCLE's risk of bias tool

Yes

By use of SYRCLE's risk of bias tool adapted as follows:

No

By use of the CAMARADES checklist for study quality

Yes

By use of the CAMARADES checklist for study quality, adapted as follows:

No

Other criteria, namely

No

Method for risk of bias and/or quality assessment

Give the procedure for the risk of bias and/or quality assessment, including the number of reviewers involved, their contribution, and how discrepancies will be resolved.

Two independent reviewers will be involved in assessing the risk of bias and study quality. The Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool for animal studies will be used for assessing the risk of bias. It is adapted to assess methodological quality and features of bias such as selection bias, performance bias, attrition bias, and reporting bias. The CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies) checklist will be used to assess the methodological quality of animal experiments. This checklist evaluates various aspects of study design, conduct, and reporting. Each reviewer will independently assess the studies using the selected tools. After completing the assessments, the reviewers will compare their evaluations. Any discrepancies will be discussed and resolved by consensus. If the reviewers are unable to reach a consensus, a third reviewer will be consulted to make the final decision. The final assessment will be documented, including any changes made during the resolution process.

28. * Strategy for data synthesis.

Planned approach

For each outcome measure, specify whether a quantitative or narrative synthesis is planned and how this decision will be made.

We will conduct a narrative evaluation of the experimental outcomes of the included studies, focusing on the efficacy of Urtica dioica on neurologic complications of diabetic animals. The narrative synthesis will include the study setting, study design, population, intervention, outcome measures, and any other suitable findings of each study. If the results of the heterogeneity analysis suggest that the studies are sufficiently homogeneous, we will proceed with a meta-analysis to synthesize the results of the individual studies and provide an overall estimate of the efficacy of Urtica dioica on neurologic complications of diabetic animals. If meta-analysis is not possible, we will report data in a descriptive form.

If a meta-analysis is planned, please specify the following:

Effect measure

For each outcome measure, specify the effect measure to be used (e.g. mean difference, odds ratio etc.).

If the meta-analysis were possible, dichotomous data would be analyzed using risk ratios, while continuous data would be analyzed using mean differences or standard mean differences. Assuming that all behavioral tests, histological changes, and neurochemical parameters yield continuous data, the standardized mean difference would be used as the primary outcome measure for all relevant parameters.

Effect models

For each outcome measure, specify the statistical model of analysis (e.g. random-effects or fixed-effect model).

We will use random-effects model because of the nature and differences in animal studies.

Heterogeneity

Specify the statistical methods to assess heterogeneity (e.g. I^2, Q). For further guidance please refer to the introduction and practical guide to pre-clinical meta-analysis.

Statistical heterogeneity in our study will be assessed using ?² and quantified using the I^2 statistic.

Other

Specify other details of the meta-analysis methodology (e.g. correction for multiple testing, correction for multiple use of control group).

For corrections for multiple use of control group, we will use multivariate meta-analysis to model the covariance between estimates from the same study.

29. * Analysis of subgroups or subsets.

Subgroup analyses

Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.

In the narrative evaluation, we will also comment on whether the efficacy of Urtica dioica on neurologic complications of diabetic animals appears to vary according to the intervention subgroups. This may include subgroup analyses by:

Type of Urtica dioica extract used (e.g., aqueous, ethanolic, methanolic)

Dosage and duration of Urtica dioica administration

Type of diabetes model used (e.g., streptozotocin, high-fat diet)

Species of animal used (e.g., rat, mouse, rabbit)

Sensitivity

For each outcome measure, specify any sensitivity analyses you propose to perform.

If the findings of the meta-analysis are robust, we shall proceed with a sensitivity analysis using STATA software.

Publication bias

Specify whether an assessment of publication bias is planned. If applicable, specify the method for assessment of publication bias.

To evaluate potential publication bias, funnel plots will be generated, with the trim-and-fill method applied if required.

30. * Review type.

Type of review

Animal model review
No

Experimental animal exposure review
No

Pre-clinical animal intervention review
Yes

31. Language.

Select each country individually to add it to the list below, use the bin icon to remove any added in error.

English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Afghanistan

33. Other registration details.

List other places where the systematic review protocol is registered. The name of the organisation and any unique identification number assigned to the review by that organisation should be included.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one.

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

No

Give brief details of plans for communicating review findings.?

36. * Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line.

Systematic review; Urtica dioica; Nettle; Neuroprotection agent; Diabetes Mellitus; Animal model

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published.

Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any further information the review team consider relevant to the registration of the review.

40. Details of final report/publication(s) or preprints if available.

This field should be left empty until details of the completed review are available OR you have a link to a preprint. Give the full citation for the preprint or final report or publication of the systematic review.

Give the link to the published review or preprint.