# Systematic Review Protocol for Animal Intervention Studies

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<table>
<thead>
<tr>
<th>Item #</th>
<th>Section/Subsection/Item</th>
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<tbody>
<tr>
<td><strong>A. General</strong></td>
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<tr>
<td>1.</td>
<td>Title of the review</td>
<td>Herbal medicines and dietary supplements in the management of diabetes mellitus: A systematic review of animal studies</td>
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</table>
| 2. | Authors (names, affiliations, contributions) | 1. Kannan Sridharan, Associate Professor in Pharmacology, Department of Health Sciences, Fiji National University  
2. Gowri S, Assistant Professor in Prosthodontics, Department of Oral Health, Fiji National University | |
| 3. | Other contributors (names, affiliations, contributions) | Nil | |
| 4. | Contact person + e-mail address | skannandr@gmail.com | |
| 5. | Funding sources/sponsors | Nil | |
| 6. | Conflicts of interest | None | |
| 7. | Date and location of protocol registration | 12 Jan 2016; SYRCLE | |
| 8. | Registration number (if applicable) | | |
| 9. | Stage of review at time of registration | Not initiated | |
| **B. Objectives** | | | |
| **Background** | | | |
| 10. | What is already known about this disease/model/intervention? Why is it important to do this review? | Many herbal medicines such as American ginseng, Coccinia indica and dietary supplement such as chromium were allegedly reported to improve glycemic control in some of the individual human studies. But, there is no synthesis of existing available evidence for their effect in various animal models.  
It is difficult to assess the efficacy of these herbal medicines/dietary supplements in human beings through clinical trials and so synthesising the evidence in animal studies shall throw light on the potential utility of these interventions. | |
| **Research question** | | | |
| 11. | Specify the disease/health problem of interest | Diabetes mellitus | |
| 12. | Specify the population/species studied | Non-human animals | |
| 13. | Specify the intervention/exposure | Any herbal medicine or dietary supplement | |
| 14. | Specify the control population | Any allopathic medicine that has been proven to be effective for managing diabetes mellitus or placebo or alternative herbal drug evaluated/proved for its efficacy in the treatment of diabetes mellitus | |
| 15. | Specify the outcome measures | Details regarding outcome measures include but not limited to blood glucose – random/fasting/post prandial; Lipid profiles (LDL and HDL cholesterol, triglycerides); Body | |
weight; Insulin levels; C-peptide will be collected in the present study.

**State your research question (based on items 11-15)**

What are the herbal medicines and dietary supplements that have been evaluated for their intended therapeutic effect for diabetes mellitus in various animal models?

**Sub-questions:**

Which herbal medicine and dietary supplement has been evaluated in most of the studies?

Which aspect of diabetes mellitus in human beings has been modelled in animals?

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**C. Methods**

**Search and study identification**

17. Identify literature databases to search (e.g. Pubmed, Embase, Web of science)  
   - [X] MEDLINE via PubMed  
   - [ ] Web of Science  
   - [ ] SCOPUS  
   - [ ] EMBASE  
   - [ ] Other, namely:

18. Define electronic search strategies (e.g. use the step by step search guide, and animal search filters)
   - Search strategy has been added at the end of this document

19. Identify other sources for study identification  
   - [X] Reference lists of included studies  
   - [ ] Books  
   - [X] Reference lists of relevant reviews  
   - [ ] Conference proceedings, namely:  
   - [X] Contacting authors/ organisations, namely:  
   - [ ] Other, namely:

20. Define search strategy for these other sources  
   - All the relevant studies to be included will be screened and authors of the relevant cross-references will be contacted for the same

**Study selection**

21. Define screening phases (e.g. pre-screening based on title/abstract, full text screening, both)  
   1. Pre-screening of the title/abstract  
   2. Screening the full-texts of the eligible studies

22. Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved  
   - Both the authors will independently be involved in both the pre-screening and screening phases and any disputes/discrepancies between the authors will be resolved by discussion

*Define all inclusion and exclusion criteria based on:*

23. Type of study (design)  
   - Inclusion criteria:  
     - Animal model appropriate for inducing diabetes mellitus  
     - Evaluation of any herbal medicine or dietary supplement  
   - Exclusion criteria:  
     - Studies evaluating only the *in vitro* or *ex vivo* effects on animal tissues  
     - Studies having one or more groups of animals administered combination of interventions that can be either herbal/allopathic/dietary
| 24. | Type of animals/population (e.g. age, gender, disease model) | Inclusion criteria:  
- Any non-human animal of any age with appropriate model for diabetes mellitus  
Exclusion criteria: Nil |
| 25. | Type of intervention (e.g. dosage, timing, frequency) | Inclusion criteria: Any  
Exclusion criteria: Nil |
| 26. | Outcome measures | Inclusion criteria: Any  
Exclusion criteria: Nil |
| 27. | Language restrictions | Inclusion criteria:  
- Only articles published in English language  
Exclusion criteria: Nil |
| 28. | Publication date restrictions | Inclusion criteria: Any  
Exclusion criteria: Nil |
| 29. | Other | Inclusion criteria: NA  
Exclusion criteria: NA |
| 30. | Sort and prioritize your exclusion criteria per selection phase | Selection phase for pre-screening and screening:  
1. Non-animal studies  
2. Not a model for diabetes mellitus  
3. Either *in vitro* or *ex vivo* analysis of laboratory parameters  
4. Combination of interventions that can be either herbal/allopathic/dietary |

### Study characteristics to be extracted (for assessment of external validity, reporting quality)

| 31. | Study ID (e.g. authors, year) |  
- First author  
- Title  
- Journal  
- Year |
| 32. | Study design characteristics (e.g. experimental groups, number of animals) |  
- Number of groups  
- Number of animals in each group  
- Laboratory settings- temperature; humidity; food; lighting  
- Type of animal model  
- Randomization/non-randomization  
- Blinding/open |
| 33. | Animal model characteristics (e.g. species, gender, disease induction) |  
- Animal  
- Strain  
- Line  
- Supplier  
- Sex  
- Animal weight (start & end)  
- Animal temperature  
- Specific diet  
- Administration of laxative / other co-medication  
- Special bedding  
- Method of model induction (mutation / other)  
- Animal age at model induction (if not innate)  
- Time & duration of model induction (for non-genetic models) |
| 34. | Intervention characteristics (e.g. intervention, timing, duration) |  
- Name of the herbal medicine or dietary supplement |
| 35. | Outcome measures | • Dose, duration, frequency and route of administration  
• Details regarding outcome measures include but not limited to blood glucose – random/fasting/post prandial; Lipid profiles (LDL and HDL cholesterol, triglycerides); Body weight; Insulin levels; C-peptide will be collected in the present study |
| 36. | Other (e.g. drop-outs) | • Attrition will be considered in each of the included groups |

**Assessment risk of bias (internal validity) or study quality**

| 37. | Specify (a) the number of reviewers assessing the risk of bias/study quality in each study and (b) how discrepancies will be resolved | Both the authors will independently be involved in assessing the risk of bias and study quality and any disputes/discrepancies between the authors will be resolved by discussion |
| 38. | Define criteria to assess (a) the internal validity of included studies (e.g. selection, performance, detection and attrition bias) and/or (b) other study quality measures (e.g. reporting quality, power) | X By use of SYRCLE’s Risk of Bias tool  
☐ By use of SYRCLE’s Risk of Bias tool, adapted as follows:  
☐ By use of CAMARADES’ study quality checklist, e.g.  
☐ By use of CAMARADES' study quality checklist, adapted as follows:  
☐ Other criteria, namely: |

**Collection of outcome data**

| 39. | For each outcome measure, define the type of data to be extracted (e.g. continuous/dichotomous, unit of measurement) | All the outcome measures will be collected quantitatively |
| 40. | Methods for data extraction/retrieval (e.g. first extraction from graphs using a digital screen ruler, then contacting authors) | Nil |
| 41. | Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved | Both the authors will independently be involved in extracting the data and any disputes/discrepancies between the authors will be resolved by discussion |

**Data analysis/synthesis**

| 42. | Specify (per outcome measure) how you are planning to combine/compare the data (e.g. descriptive summary, meta-analysis) | For all the outcome measures when more than one study has evaluated the same and no significant heterogeneity has been observed, meta-analysis will be attempted for that outcome measures |
| 43. | Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed | For all the outcome measures when more than one study has evaluated the same and no significant heterogeneity has been observed, meta-analysis will be attempted for that outcome measures |

If a meta-analysis seems feasible/sensible, specify (for each outcome measure):

| 44. | The effect measure to be used (e.g. mean difference, standardized mean difference, risk ratio, odds ratio) | For quantitative variables, standardized mean difference will be used and for the qualitative variables, risk ratio will be used |
| 45. | The statistical model of analysis (e.g. random or fixed effects model) | Random effects model will be applied when significant heterogeneity is observed otherwise only fixed effects model will be used |
References:


Search strategy in PubMed:
Animal studies filter on.
Diabetes mellitus [Mesh] AND Herb [Mesh]
Diabetes mellitus [Mesh] AND Vitamins [Mesh]
Diabetes mellitus [Mesh] AND Minerals [Mesh]