



SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

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VERSION 2.0 (DECEMBER 2014)

Item #	Section/Subsection/Item	Description	Check for approval
A. General			
1.	Title of the review	Herbal medicines and dietary supplements in the management of diabetes mellitus: A systematic review of animal studies	
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?	<p>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.</p> <p>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.</p>	
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	
16.	State your research question (based on items 11-15)	<p>What are the herbal medicines and dietary supplements that have been evaluated for their intended therapeutic effect for diabetes mellitus in various animal models?</p> <p>Sub-questions:</p> <p>Which herbal medicine and dietary supplement has been evaluated in most of the studies?</p> <p>Which aspect of diabetes mellitus in human beings has been modelled in animals?</p>	
C. Methods			
Search and study identification			
17.	Identify literature databases to search (e.g. Pubmed, Embase, Web of science)	<input checked="" type="checkbox"/> MEDLINE via PubMed <input type="checkbox"/> Web of Science <input type="checkbox"/> SCOPUS <input type="checkbox"/> EMBASE <input type="checkbox"/> Other, namely: <input type="checkbox"/> Specific journal(s), namely:	
18.	Define electronic search strategies (e.g. use the step by step search guide ¹⁵ and animal search filters ^{20, 21})	Search strategy has been added at the end of this document	
19.	Identify other sources for study identification	<input type="checkbox"/> Reference lists of included studies <input type="checkbox"/> Books <input checked="" type="checkbox"/> Reference lists of relevant reviews <input type="checkbox"/> Conference proceedings, namely: <input checked="" type="checkbox"/> Contacting authors/ organisations, namely: <input type="checkbox"/> 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)	<ol style="list-style-type: none"> 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	
<i>Define all inclusion and exclusion criteria based on:</i>			
23.	Type of study (design)	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Animal model appropriate for inducing diabetes mellitus • Evaluation of any herbal medicine or dietary supplement <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Studies evaluating only the <i>in vitro</i> or <i>ex vivo</i> effects on animal tissues • Studies having one or more groups of animals administered combination of interventions that can be either herbal/allopathic/dietary 	

		supplement	
24.	Type of animals/population (e.g. age, gender, disease model)	Inclusion criteria: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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 <i>in vitro</i> or <i>ex vivo</i> 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)	<ul style="list-style-type: none"> First author Title Journal Year 	
32.	Study design characteristics (e.g. experimental groups, number of animals)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> Name of the herbal medicine or dietary supplement 	

		<ul style="list-style-type: none"> Dose, duration, frequency and route of administration 	
35.	Outcome measures	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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)	<input checked="" type="checkbox"/> By use of SYRCLE's Risk of Bias tool⁴ <input type="checkbox"/> By use of SYRCLE's Risk of Bias tool, adapted as follows: <input type="checkbox"/> By use of CAMARADES' study quality checklist, e.g.²² <input type="checkbox"/> By use of CAMARADES' study quality checklist, adapted as follows: <input type="checkbox"/> 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	
<i>If a meta-analysis seems feasible/sensible, specify (for each outcome measure):</i>			
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	

46.	The statistical methods to assess heterogeneity (e.g. I^2 , Q)	I^2 test statistic	
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	Type of models	
48.	Any sensitivity analyses you propose to perform	Not planned	
49.	Other details meta-analysis (e.g. correction for multiple testing, correction for multiple use of control group)	Nil	
50.	The method for assessment of publication bias	Funnel plot	

Final approval by (names, affiliations):

Date:

References:

Yeh GY, Eisenberg DM, Kaptchuk TJ, Phillips RS. Systematic review of herbs and dietary supplements for glycemic control in diabetes. *Diabetes Care*. 2003;26(4):1277-94.

Althuis MD, Jordan NE, Ludington EA, Wittes JT. Glucose and insulin responses to dietary chromium supplements: a meta-analysis. *Am J Clin Nutr*. 2002;76(1):148-55.

Shekelle PG, Hardy M, Morton SC, Coulter I, Venuturupalli S, Favreau J, Hilton LK. Are Ayurvedic herbs for diabetes effective? *J Fam Pract*. 2005;54(10):876-86.

Sievenpiper JL, Kendall CW, Esfahani A, Wong JM, Carleton AJ, Jiang HY, Bazinet RP, Vidgen E, Jenkins DJ. Effect of non-oil-seed pulses on glycaemic control: a systematic review and meta-analysis of randomised controlled experimental trials in people with and without diabetes. *Diabetologia*. 2009;52(8):1479-95.

Smith DM, Pickering RM, Lewith GT. A systematic review of vanadium oral supplements for glycaemic control in type 2 diabetes mellitus. *QJM*. 2008;101(5):351-8.

Elia M, Ceriello A, Laube H, Sinclair AJ, Engfer M, Stratton RJ. Enteral nutritional support and use of diabetes-specific formulas for patients with diabetes: a systematic review and meta-analysis. *Diabetes Care*. 2005;28(9):2267-79.

Montori VM, Farmer A, Wollan PC, Dinneen SF. Fish oil supplementation in type 2 diabetes: a quantitative systematic review. *Diabetes Care*. 2000;23(9):1407-15.

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]