SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

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Item #	Section/Subsection/Item	Description	Check for approval
	A. General		
1.	Title of the review	Natural plants in the treatment of experimental acute pancreatitis: a systematic review [provisional title].	
2.	Authors (names, affiliations, contributions)	**Danielle Gomes Santana**, MSc. Department of Physiology, Universidade Federal de Sergipe. Brazil. Danielle.GomesSantana@gmail.com **Fernando Kenji Nampo**, PhD. Latin-American Institute of Life and Natural Sciences, Universidade Federal da Integração Latino-Americana. Brazil and Department of Physical Therapy, Universidade Federal de Sergipe. Brazil. Fernando.Nampo@gmail.com **Alan Santos Oliveira**, MSc. Department of Physiology, Universidade Federal de Sergipe. Brazil. alansantos1991@hotmail.com **Enilton Aparecido Camargo**, PhD. Department of Physiology, Universidade Federal de Sergipe. Brazil. Enilton.Camargo@gmail.com	
3.	Other contributors (names, affiliations, contributions)	N/A	
4.	Contact person + e-mail address	**Enilton Aparecido Camargo**, PhD. Department of Physiology, Federal University of Sergipe (UFS), São Cristóvão, 49100-000, SE, Brazil. Telephone number: +55-79-2105-6644. Enilton.Camargo@gmail.com	
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6.	Conflicts of interest	Authors affirm that we have no financial affiliation or involvement with any commercial organization that has a direct financial interest in any matter included in this research.	
7.	Date and location of protocol registration	October 13, 2015. Syrcle.	
8.	Registration number (if applicable)		
9.	Stage of review at time of registration	Not started.	
	B. Objectives		

	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	Historically, medicinal plants and its compounds have been utilized to treat several illness conditions. Acute pancreatitis is a condition that should be further investigated since there is only adjuvant treatment and no drug effective in controlling its underlying progression mechanisms. This systematic review will compile preclinical research on medicinal plants and its compounds investigated in the treatment of acute pancreatitis; thus, this research will point strengths and limitations of available studies and offer future perspectives in this field.	
	Research question		
11.	Specify the disease/health problem of interest	Acute pancreatitis (AP).	
12.	Specify the population/species studied	Animals submitted to pancreatitis induction either surgically or not.	
13.	Specify the intervention/exposure	Treatment of AP based on natural plants or its secondary metabolites. Administration route: either oral or intraperitoneal.	
14.	Specify the control population	Control group (placebo, sham treatment.	
15.	Specify the outcome measures	Inflammatory response: nociception, histological analysis, myeloperoxidase activity or amylase activity.	
16.	State your research question (based on items 11-15)	1. Compared to placebo, is there any treatment based on natural plants that is effective in controlling AP inflammatory response? 2. What natural plants and secondary metabolites have already been investigated in the treatment of experimental AP? 3. What experimental models are most frequently used to investigate the efficacy of natural plants and its compounds in AP?	
	C. Methods		
	Search and study identification		
17.	Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science)	☑ MEDLINE via PubMed ☑ Web of Science ☑ SCOPUS ☑ EMBASE ☑ Other, namely: Grey literature (Google Scholar) □ 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])	Simplified PubMed search: Pancreatitis: (exp pancreatitis/OR pancreatitis.ti,ab. OR pancreatitides.ti,ab. OR ANP.ti,ab. OR (pancreas.ti,ab. AND inflammation.ti,ab.) OR (pancreatic.ti,ab. AND inflammation.ti,ab.) Natural plants: ethnobotan*OR Ethnopharmacolog* OR ethno botan* OR caatinga OR inner bark OR traditional chinese medicine OR chinese medicine OR chinese medicine OR natural products OR natural product OR plant OR plants OR phytother*	

		Animals: Filter for animal studies	
19.	Identify other sources for study identification	☑Reference lists of included studies □Books ☑Reference lists of relevant reviews □Conference proceedings, namely: □Contacting authors/ organisations, namely: □Other, namely:	
20.	Define search strategy for these other sources	Google Scholar, Google.	
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	1. Title/abstract screening. 2. Full text screening.	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	a. Two reviewers will independently screen for relevant studies. b. Discrepancies will be resolved either by discussion or by a third reviewer (when no agreement is met by the two reviewers).	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	Inclusion criteria: Pre-clinical study. Exclusion criteria: N/A.	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: Laboratory animals with AP. Exclusion criteria: Animals with associated comorbidities (e.g. with altered hormone metabolism – either physiologically (age) or induced), aged).	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Inclusion criteria: Natural plants or its secondary metabolites, independently of timing of treatment. Exclusion criteria: Mixture of treatments.	
26.	Outcome measures	Inclusion criteria: Nociception, histological analysisof the pancreas, myeloperoxidase activity or amylase activity. Exclusion criteria: N/A.	
27.	Language restrictions	Inclusion criteria: No restriction. Exclusion criteria: N/A.	
28.	Publication date restrictions	Inclusion criteria: Studies published up to search date. Exclusion criteria: No past date restriction.	
29.	Other	Inclusion criteria: N/A. Exclusion criteria: No original papers (e.g. reviews).	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase: Title and abstract screening. 1. Type of study. 2. Type of animals. 3. Type of intervention. Selection phase: Full text screening. 1. Type of study. 2. Type of animals. 3. Type of intervention. 4. Outcome measures.	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	Authors, title, year, language, contact author e-mail	
32.	Study design characteristics (*e.g.*	Experimental groups.	

	experimental groups, number of animals)	Number of animals per group.	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	Animal species, strain, age or weight, gender,Pancreatitis induction technique.	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	Type of analgesics, Route of administration, dose, frequency, timing relative PA induction, duration of treatment, type of control group	
35.	Outcome measures	Nociception (stimuli threshold (Δ g), histological scores of the pancreas (count), myeloperoxidase activity or amylase activity.	
36.	Other (*e.g.* drop-outs)	Country of origin. Age of sacrificing animals, anesthetics used for sacrificing	
	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	a. Two reviewers will independently assess risk of bias of included studies. b. Discrepancies will be resolved either by discussion or by a third reviewer (when no agreement is met by the two reviewers).	
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)	☑By use of SYRCLE's Risk of Bias tool[4] □By use of SYRCLE's Risk of Bias tool, adapted as follows: □By use of CAMARADES' study quality checklist, e.g [22] □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)	Nociception: stimuli threshold (Δ g); continuous. Histological analysis: histological scores (count); discrete. Myeloperoxidase activity: uMPO/mg protein or uMPO/mg tissue; continuous. Amylase activity: U/dL, mU/DL or U/L; continuous.	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	Data will be extracted preferably from published data (explicit numeral). Whenever necessary, an electronic mail will be send to the correspondent author for further information. If no answer is obtained within a week or there is no contact information, other authors will be randomly contacted. After five weeks, if no answer is received, the study will be excluded from analysis.	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	a. Two reviewers will independently extract data from included studies. b. Discrepancies will be resolved either by discussion or by a third reviewer (when no agreement is met by the two reviewers).	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	To all outcomes meta-analysis is intended.	
43.	Specify (per outcome measure) how it will be decided whether a meta-	To all outcomes: - At least two studies.	

	analysis will be performed		
	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)	To all outcomes: - Mean differences or Standardized Mean Difference and 95% confidence intervals will be calculated for all the variables.	
45.	The statistical model of analysis (*e.g.* random or fixed effects model)	To all outcomes: - Random effects model -	
46.	The statistical methods to assess heterogeneity (*e.g.* I^2, Q)	I-square.	
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	Animal species. Gender. Pancreatitis induction method. Natural plant. Dose.	
48.	Any sensitivity analyses you propose to perform	Risk of bias.????	
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)	Correction for multiple use of control group.	
50.	The method for assessment of publication bias	Funnel plot, if applicable.	
Final approval by (names, affiliations):		Date:	