SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

FORMAT BY SYRCLE (WWW.SYRCLE.NL)
VERSION 2.0 (DECEMBER 2014)

Item #	Section/Subsection/Item	Description	Check for approval
	A. General		
1.	Title of the review	Natural products for experimental orofacial pain: a systematic review	
2.	Authors (names, affiliations, contributions)	**Janaíne Prata de Oliveira** Department of Physiology, Federal University of Sergipe . Brazil. Janaineprata@gmail.com **Fernando Kenji Nampo,** PhD**.** Latin-American Institute of Life and Natural Sciences, Federal University of Latin-American Integration. Brazil. Fernando.Nampo@gmail.com **Marília Trindade de Santana Souza**, MSc. Department of Physiology, Federal University of Sergipe. Brazil. biomari@hotmail.com **Luana Mendonça Cercato**, MSc Department of Physiology, Federal University of Sergipe. Brazil. lucercato@gmail.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	Janaíne Prata de Oliveira Department of Physiology, Federal University of Sergipe (UFS), São Cristóvão, 49100-000, SE, Brazil. Telephone number: +55-79-3431-8500. Janaineprata@gmail.com	
5.	Funding sources/sponsors	Enilton Aparecido Camargo is beneficiary of *Conselho Nacional de Pesquisa e Desenvolvimento Científico* (CNPq) productivity grant. Remaining authors had no financial support for the submitted work	
6.	Conflicts of interest	The authors report no conflict of interest.	
7.	Date and location of protocol registration	April, 2019. Syrcle.	

8.	Registration number (if applicable)	Update:	
9.	Stage of review at time of registration	Started	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	Orofacial pain is defined as all pain associated to soft and mineralized tissues of oral cavity and face. Oftentimes, orofacial pain is related to temporomandibular disorders (TMD) (LEEUW, 2010). The treatment of orofacial pain and TMD is done with different drugs, however, these drugs are inefficient to treat many patients (SHEPARD et al., 2013). Natural products possesse biological and pharmacological effects that bring benefits to therapeutic treatment of many diseases (BAKER et al, 2007). Therefore, the use of natural products can be an alternative for orofacial pain and TMD treatment. The aim this systematic review is to determine the efficacy of natural products and its secondary metabolites in controlling nociceptive and inflammatory reaction in animals with orofacial pain.	
	Research question		
11.	Specify the disease/health problem of interest	Orofacial pain.	
12.	Specify the population/species studied	Experimental animals submitted to any model of orofacial pain.	
13.	Specify the intervention/exposure	The use of natural products or its secondary metabolites to reduce nociceptive and inflammatory responses following orofacial pain induction in “in vivo” animal experimentation.	
14.	Specify the control population	Control group (placebo treatment).	
15.	Specify the outcome measures	Nociceptive responses.	
16.	State your research question (based on items 11-15)	Compared to placebo, are natural products efficacious in controlling nociceptive and inflamatory responses of animals submitted to orofacial pain models? What natural products and secondary metabolites have already been investigated in the treatment of experimental orofacial pain?	
	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 ☑ SciELO ☑ LILACS ☐Other, namely: ☐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])	When available, please add a supplementary file containing your search strategy: [insert file name] Search strategy applied to Pubmed and adapted to the other databases: **PARTICIPANTS / CONDITION:** facial pain OR face pain OR pain, face OR pain, facial OR orofacial pain OR pain, orofacial OR neuralgia facial pain OR facial pain, neuralgia OR pain, neuralgia facial OR craniofacial pain OR pain, craniofacial OR myofacial pain OR pain, myofascial **INTERVENTION:** 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* OR terpene OR flavonoid OR coumarin OR xanthone OR chromone OR lignan OR neolignan OR tannin OR saponin OR alkaloid OR xanthine OR methylxanthine	
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	a. Two reviewers will independently screen for relevant studies.	

	and (b) how discrepancies will be resolved	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 with intervention and control group. Exclusion criteria: N/A	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: Laboratory animals submitted to orofacial pain. Exclusion criteria: Dental comorbity and TMD model	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Inclusion criteria: Natural product or its secondary metabolites, any dosage, timing, frequency or via administration. Exclusion criteria: Mixture of treatment	
26.	Outcome measures	Inclusion criteria: Orofacial nociception, immunohistochemistry , inflammatory parameters. Exclusion criteria: N/A	
27.	Language restrictions	Inclusion criteria: No language restrictions. 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: N/A	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase: Title and abstract screening 1. Type of study 2. Type animals 3. Type of intervention Selection phase: Full text screening 1. Reviews or non-original papers 2. Type of study 3. Type animals 4. Type of intervention 5. Outcome measure	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	Authors, title, year of publication, language, contact author e-mail	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	Experimental groups Number of animals per group	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	Animal species, Strain, Age, Weight, Orofacial pain induction technique	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	Type of drug, type of natural product, dosage of drug, duration of treatment, frequency of drug administration, route of administration, timing relative orofacial pain induction, type of control group	

35.	Outcome measures	All	
36.	Other (*e.g.* drop-outs)	Age of sacrificing animals , form of sacrifice, side effects of drug (weight loss, death, etc.)	
	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 (g); continuous. Histological analysis: histological scores; discrete. Myeloperoxidase activity: unit of MPO/mg protein, units of MPO/mg tissue or optical densitiy; continuous. Orofacial nociception (time of behavior, percentage)	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	1)Extract data from text or tables 2)Extract data from figures 3)Contact authors for data not presented in paper If no answer is obtained within a week or there is no contact information, other authors will be randomly contacted. After three 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 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).	
	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 network meta-analysis is intended.	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	To all outcomes: - at least two studies; - same specie investigated.	

	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 - Markov Chain Monte Carlo	
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. Orofacial pain models. Natural plant. Dose.	
48.	Any sensitivity analyses you propose to perform	Risk of bias of included studies	
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 (i.e. 10+ studies included).	
Final approval by (names, affiliations):		Date:	

Notes:
The results of initial database research proposed for the protocol offered material for confection of two independent systematic reviews. Then, we decided divide it. Due to this protocol need to be altered for update the methods of search.
The other review, about the use of natural products in laboratory animals submitted to TMD models, was done using the same methodology, except the search strategy, and the condition (TMD). This strategy used was:

(temporomandibular joint disorders OR disorder, temporomandibular joint OR disorders, temporomandibular joint OR joint disorder, temporomandibular OR joint disorders, temporomandibular OR temporomandibular joint disorder OR tmj disorders OR disorder, tmj OR disorders, tmj OR tmj disorder OR temporomandibular disorders OR disorder, temporomandibular OR disorders, temporomandibular OR temporomandibular disorder OR temporomandibular joint diseases OR disease, temporomandibular joint OR diseases, temporomandibular joint OR joint disease, temporomandibular OR joint diseases, temporomandibular OR temporomandibular joint disease OR tmj diseases OR disease, tmj OR diseases, tmj OR tmj disease) AND (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* OR terpene OR flavonoid OR coumarin OR xanthone OR chromone OR lignan OR neolignan OR tannin OR saponin OR alkaloid OR xanthine OR methylxanthine)

Referências Bibliográficas:

LEEUW R. **Dor orofacial: guia de avaliação, diagnóstico e tratamento**. São Paulo: Quintessence, 2010.

SHEPHARD, M. K et al. Orofacial Pain: A Guide for the Headache Physician. *Headache*, v. 54, p. 22-39, 2014.

BAKER, D.D et al. The value of natural products to future pharmaceutical discovery. Natural Product Report, v.24, p. 1225-1244, 2007.