Received: 26 May 2016 | Revised: 22 August 2016 | Accepted: 26 August 2016

DOI 10.1002/ebm2.19

WILEY Evidence-based Preclinical Medicine

SYSTEMATIC REVIEW PROTOCOL

Medicinal plants and natural compounds in the treatment of experimental endometriosis: A systematic review protocol

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Funding Information

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Endometriosis is defined as the endometrial tissue growth (containing both glandular and stromal components) on the extra uterine places especially peritoneal and visceral surfaces of the pelvis. The current medical treatments are mainly based on inhibiting oestrogen or treating the symptoms rather than curing the disease. The recurrence rate is nearly high after both current medical and surgical treatments for endometriosis. In recent years, medicinal herbs and other botanical products have become popular for relieving the symptoms of several gynaecologic disorders such as endometriosis. The objective of this systematic review and meta-analysis is to provide the pre-clinical researches on medicinal plants (Not Chinese combinations) and its compounds studied in the treatment of experimental endometriosis. It will also prepare the strengths and limitations of available studies and offer future perspectives in this field. The following electronic databases will be searched up to December 2015: Medline (PubMed platform), Scopus. The grey literatures, Google scholar, and the reference list of all known primary articles, and relevant conference proceedings will also be checked. Only non-Chinese language papers will be placed in our searches or study selection. For assessing the risk of bias of the included studies, we will use the SYstematic Review Centre for Laboratory animal Experimentation risk of bias tool for animal studies (SYRCLE's RoB tool). If the studies are sufficiently comparable, outcome data will be pooled. For outcome measures where a meta-analysis is not possible a qualitative data synthesis of the results from individual studies will be performed.

KEYWORDS

animal models, endometriosis, experimental studies, medicinal plants, natural compounds

1 | STRENGTHS AND LIMITATIONS OF THIS STUDY

- The results of this systematic review will provide the pre-clinical researches on medicinal plants (Not Chinese combinations) and its compounds investigated in the treatment of experimental endometriosis. It will also prepare the strengths and limitations of available studies and animal models of endometriosis and offer future perspectives in this field.
- The risk of bias of the included studies will be assessed with the SYstematic Review Centre for Laboratory animal Experimentation risk of bias tool for animal studies (SYRCLE's RoB tool).[1] "This tool, based on the Cochrane Collaboration RoB Tool,[2] aims to assess methodological quality and has been adapted to aspects of bias that play a role in animal experiments."[1]
- In this study, databases in Chinese languages will not be searched or included. This limitation may cause language bias.

2 | INTRODUCTION

Endometriosis is defined as the extra uterine growth of endometrial tissue, most commonly on the peritoneal and visceral surfaces of the pelvis, and containing both glandular and stromal components.[3]

The treatment of endometriosis can be divided into medical or surgical treatments. The current medical treatments are mainly based on inhibiting oestrogen and its receptors which are not useful for every patient with endometriosis. The other treatments also focus on treating the symptoms rather than treatment the disease. In addition hormonal treatments interfere with infertility treatments and pregnancy and have different side effects.[4] The recurrence rate is nearly high after both current medical and surgical treatments for endometriosis.[5]

Endometriosis has a pleomorphic manifestation and no single theory can explain its pathogenesis. So single treatment focused one mechanism may not be beneficial.

In recent years, medicinal herbs and other botanical products have become popular for management of symptoms of several gynaecologic disorders such as endometriosis. Medicinal herbs and their active compounds have different potentials such as anti-proliferative, antioxidant, analgesic, and anti-inflammatory effects. These mechanisms may be useful and promising for treatment or regression of endometriosis.[6,7]

Several animal studies have demonstrated the effectiveness of medicinal herbs or natural compounds in endometriotic lesion regression,[8–10] however, they used different animal models for endometriosis and some have shortcomings in their methodology.

Systematic review for clinical studies is an accepted and common practice however, there is less common to summarize the evidences from animal experiments in a systematic review. The results of pre-clinical studies are very important for designing the future clinical studies. In recent years, some bias tools and formats have been adopted for animal or pre-clinical systematic reviews.[11]

The objective of this systematic review and meta-analysis is to provide the pre-clinical researches on medicinal plants (Not Chinese combinations) and its compounds investigated in the treatment of experimental endometriosis. It will also prepare the strengths and limitations of available studies and offer future perspectives in this field.

Systematic review question

(1) Compared to placebo or control, is there any treatment based on medicinal plants that is effective in regression of endometriosis?
(2) Which medicinal plants and secondary metabolites have already been investigated in the treatment of experimental endometriosis?
(3) Which experimental models are most frequently used to investigate the efficacy of medicinal plants and its compounds in endometriosis?

PICO items

The disease/health problem of interest	Endometriosis
The population/species studied	All animal models used for induction of endometriosis
The intervention/ exposure	Effect of not Chinese medicinal herbs and its compounds on experimental endometriosis
The control population	Placebo, or sham treatment
The outcome measures	Endometriosis regression

3 | METHODS/DESIGN

This review will be reported according to the standards of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). This systematic review has been registered on SYRCLE (SYstematic Review Centre for Laboratory animal Experimentation).

3.1 | Criteria for considering studies for this review: types of studies

All animal and experimental studies with control groups will be eligible for inclusion. The complete criteria for inclusion and exclusion are mentioned in Table 1.

3.2 | Information sources

The following electronic databases will be searched up to December 2015: Medline (PubMed platform), Scopus. Grey literature will be searched via conference proceedings and abstracts for the last 5 y, as well as clinical trial and systematic review registries, and Google Scholar. Only non-Chinese language papers will be placed in our searches or study selection.

3.3 | Search strategy

Our initial search key words for PubMed will be:

(1) Medicinal plants or herbal medicine

Herbs[tiab] OR Herb[tiab] OR Polyphenolic Extract[tiab] OR Phenolic antioxidants[tiab] OR Green tea[tiab] OR Curcumin[tiab] OR

TABLE 1 The inclusion and exclusion criteria for selecting the studies

Type of study (design)	**Inclusion criteria:** Animal studies with control groups
	Exclusion criteria: Non-interventional studies, no control group
Type of animals/population (eg, age, gender, disease model)	**Inclusion criteria:** All animal models for endometriosis
	Exclusion criteria: in vitro studies or human studies
Type of intervention (eg, dosage, timing, frequency)	**Inclusion criteria:** Use of herbal or natural compounds for treatment of animal model of endometriosis (no restriction for dosage, timing or frequency)
	Exclusion criteria: Chinese herbal medicine (see Appendix S1)—Combination of different herbal compounds with un known origin—mixture of chemical and herbal treatments—mixture of herbal and other kinds of complementary therapy
Outcome measures	**Inclusion criteria:** Any outcome related to the severity, progression or reproductive consequences of endometriosis
	Exclusion criteria: no relevant outcomes assessed
Language restrictions	**Inclusion criteria:** Only restriction for Chinese language
	Exclusion criteria: Chinese language
Publication date restrictions	**Inclusion criteria:** Articles published up to December 2015
	Exclusion criteria: No past date restriction
Other	**Inclusion criteria:** Original, full-text publications containing unique data
	Exclusion criteria: Reviews or non-original papers

Resveratrol[tiab] OR Seed extract[tiab] OR Leaf extract[tiab] OR Fruit extract[tiab] OR Flower extract[tiab] OR Root extract[tiab] OR aqueous extract[tiab] OR methanol extract[tiab] OR ethanol extract [tiab] OR phenol contents[tiab] OR flavonoid contents[tiab] OR botanical extract[tiab] OR Puerarin[tiab] OR Medicinal Plant extract [tiab] OR botanical[tiab] OR dietary supplements[tiab] OR complementary and alternative medicine[tiab] OR CAM[tiab] OR anti-endometriotic agent[tiab] OR Western Herbal Medicine[tiab] OR herbal prescription[tiab] OR herbal extract[tiab] OR herbal medicinal products[tiab]

(2) Endometriosis

("endometriosis"[MeSH Terms] OR "endometriosis"[All Fields]) OR (endometriotic lesion[tiab] OR endometriotic lesions[tiab] OR endometriosis-like lesions[tiab] OR endometriotic implant[tiab] OR endometriotic implants[tiab] OR endometriosis model[tiab] OR experimental endometriosis[tiab] OR ectopic endometriotic tissues[tiab])

(3) Animals

Hooijmans CR, Tillema A, Leenaars M, Ritskes-Hoitinga M. Enhancing search efficiency by means of a search filter for finding all studies on animal experimentation in PubMed. Lab Anim. 2010; 44(3):170–175.

For final search, we combined three search key words "medicinal plants or herbal medicine key words," "endometriosis keywords," and "Animals key words" by using "AND." At this step, we don't use any filters for publication type. It will be checked at screening phase.

3.4 | Other sources

Reference lists of included studies and relevant reviews will also be checked by two reviewers for additional relevant references not yet identified by our search strategy, based on their title. Possibly relevant references will then be assessed for inclusion as indicated at item 21.

Search at Google scholar will be performed by using these key words:

(experimental endometriosis herb -Chinese - carcinoma - cancer - endometrial - menopausal)

We will also define 2015 as the final range of time. At Google scholar setting, we will exclude the Chinese language, and we will select the search articles and include patent. The final hits will be 180 results.

Search at Scopus will be performed by using these key words:

Part 1:

TITLE-ABS-KEY (medicinal plant OR plant, medicinal OR medicinal plants OR pharmaceutical plants OR pharmaceutical plant OR plants, pharmaceutical OR healing plants OR medicinal herbs OR herb, medicinal OR herbal medicine OR herbalism OR phytotherapy OR herbal therapy OR herb therapy OR plant extracts OR plants OR phytochemicals OR plant-derived chemicals OR phytosterols OR plant components OR plant drugs OR plant preparations OR pharmacognosy OR herbals OR herbal drugs OR herbal compound OR phytochemicals OR isoflavones* OR flavonoids OR genistein OR phytoestrogen OR phytoestrogen OR preparation OR plant OR herbal preparations OR biologics OR biologic products OR natural products OR antioxidants OR antioxidant effect OR anti-oxidant effects OR anti-oxidant effects OR anti oxidant effect OR scavengers,free radical OR quercetin OR catechin OR medicine,traditional OR complementary therapies OR alternative medicine OR complementary medicine) OR (herbs OR herb OR polyphenolic extract OR phenolic antioxidants OR green tea OR curcumin OR resveratrol OR seed extract OR leaf extract OR fruit extract OR flower extract OR root extract OR aqueous extract OR methanol extract OR ethanol extract OR phenol contents OR flavonoid contents OR botanical extract OR puerarin OR medicinal plant extract OR botanical OR dietary supplements OR

complementary AND alternative medicine OR cam OR anti-endometriotic agent OR western herbal medicine OR herbal prescription OR herbal extract OR herbal medicinal products) AND SUBJAREA (MULT OR MEDI OR NURS OR VETE OR DENT OR HEAL)

Part 2:

TITLE-ABS-KEY (endometriosis OR endometriotic lesion OR endometriotic lesions OR endometriosis-like lesions OR endometriotic implant OR endometriotic implants OR endometriosis model OR experimental endometriosis OR ectopic endometriotic tissues) AND SUBJAREA(MULT OR MEDI OR NURS OR VETE OR DENT OR HEAL)

Part 3:

TITLE-ABS-KEY ("animal experimentation" OR "models, animal" OR "invertebrates" OR "Animals" OR "animal population groups" OR "chordata" OR "chordata, nonvertebrate" OR "vertebrates" OR "amphibians" OR "birds" OR "fishes" OR "reptiles" OR "mammals" OR "primates" OR "artiodactyla" OR "carnivora" OR "cetacea" OR "chiroptera" OR "elephants" OR "hyraxes" OR "insectivora" OR "lagomorpha" OR "marsupialia" OR "monotremata" OR "perissodactyla" OR "rodentia" OR "scandentia" OR "sirenia" OR "xenarthra" OR "haplorhini" OR "strepsirhini" OR "platyrrhini" OR "tarsii" OR "catarrhini" OR "cercopithecidae" OR "hylobatidae" OR "hominidae" OR "gorilla gorilla" OR "pan paniscus" OR "pan troglodytes" OR "pongo pygmaeus" OR animals OR animal OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents OR pigs OR pig OR swine OR piglets OR pigle OR boar OR boars OR "sus scrofa" OR ferrets OR ferret OR polecat OR polecats OR "mustela putorius" OR "guinea pigs" OR "guinea pig" OR cavia OR callithrix OR marmoset OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbillinae OR gerbil OR gerbils OR jird OR jirds OR merione OR meriones OR rabbits OR rabbit OR hares OR hare OR diptera OR flies OR fly OR dipteral OR drosphilaor drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematoda OR nematode OR nematodes OR sipunculida OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthropoids OR saguinus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR pan OR paniscus OR "pan paniscus" OR bonobo OR bonobos OR troglodytes OR "pan troglodytes" OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR "bush baby" OR prosimian OR bush babies OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongo OR pygmaeus OR "pongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR fish OR fishes OR pisces OR catfish OR catfishes OR siluriformes OR arius OR heteropneustes OR sheatfish OR perch OR perches) AND SUBJAREA (mult OR medi OR nurs OR vete OR dent OR heal)

All three parts will be combined with using "AND."

The grey literature such as thesis will be searched in Google by combining the key words of "herbs or plants," "endometriosis," "animal models."

3.5 | Study records—selection process and screening phase

First, the titles and abstracts from the electronic databases will be assessed by two reviewers independently (KK and NS), then full papers of the eligible articles that were likely to meet the predefined inclusion criteria will be obtained.

For each screening phase, KK and NS will independently assess eligibility. Disagreements in inclusion will be discussed between the two reviewers until consensus is reach.

Sorting and prioritizing our exclusion criteria per selection phase:

Selection phase 1: (First screening based on title/abstract)

1. Review papers or non-original papers
2. Not an in vivo animal model
3. Not on disease of interest (endometriosis)
4. Not about usage of medicinal plants or phytochemicals
5. Combination therapy or use of Chinese herbal medicine

Selection phase 2: (Second screening based on full text)

1. Review papers or non-original papers
2. Not an in vivo animal model
3. Not on disease of interest (endometriosis)
4. Not about usage of medicinal plants or phytochemicals
5. Combination therapy or use of Chinese herbal medicine
6. No relevant outcome measures
7. No appropriate control group
8. Full-text not retrievable

3.6 | Data extraction, collection and management

After the final selections, data extraction will be performed independently by two researchers and then discrepancies will be resolved by consensus. If this is not possible, one of the senior authors will be asked to make a judgement on the data entered (see Appendix S2, Supporting Information).

Methods for data extraction/retrieval (eg, first extraction from graphs using a digital screen ruler, and then contacting authors)

(1) Extract data from text or tables
(2) Extract data from figures
(3) Contact authors for data not presented in paper

In case of no response within 3 wk including a reminder, the study will be excluded from analysis

3.6.1 | Data items

The data extraction form will be comprised the following items:

(1) General information about the article, including authors and contact information (of first or corresponding author), Study ID (eg, authors, year), Authors, title, year of publication, contact author email

(2) Study design characteristics (eg, experimental groups, number of animals)

(i) Experimental groups
(ii) Type of control group (eg, placebo treatment)
(iii) Number of animals in experimental and control groups
(iv) Type of randomization

(3) Animal model characteristics (eg, species, gender, disease induction)

(i) Animal species, Supplier of the animals
(ii) Strain
(iii) Age
(iv) Weight

(4) Endometriosis induction technique (Autologous, homologous, heterologous transplantation by surgery), (injection of endometrial tissues)

(i) Scratching of myometrium layer or not
(ii) Type of sham surgery in control group
(iii) Estradiol usage during model induction (Dosage, duration, frequency)
(iv) With or without ovariectomy
(v) Type of anaesthesia
(vi) Number of tissues transplanted in surgery model
(vii) Size of transplanted tissues
(viii) Transplantation site or location at surgery
(ix) Number of surgery
(x) Timing for endometriosis induction before treatment

(5) Intervention characteristics (eg, intervention, timing, duration)

(i) Intervention (drug name)
(ii) Type of plant extract
(iii) Dosage of drug
(iv) Duration of treatment
(v) Frequency of drug administration
(vi) Route of administration (oral or intraperitoneal injection)
(vii) Placebo solution (saline, vehicle, control)

(6) Outcome measures

(i) Primary outcome:
  a. Size or weight of lesions
  b. Secondary outcomes:
  c. Histopathological score of endometriotic lesions
  d. Stress oxidative assessments
  e. Molecular assessments
  f. Immuno-histochemical assessments
(ii) Other (eg, drop-outs)
  a. -Age of sacrificing animals
  b. -Anesthetics used for sacrificing
  c. -Side effects of drug (weight loss, death, etc.)
  d. -Number of animals excluded from statistical analysis
  e. -Reason for excluding animals

3.6.2 | Risk of bias in individual studies

For assessing the risk of bias of the included studies, we will use the SYstematic Review Centre for Laboratory animal Experimentation risk of bias tool for animal studies (SYRCLE's RoB tool).[1] "This tool, based on the Cochrane Collaboration RoB Tool,[2] aims to assess methodological quality and has been adapted to aspects of bias that play a role in animal experiments."[1] The evaluated domains will be judged as "low," "unclear" or "high" risk of bias. A "yes" judgement indicated a low risk of bias; a "no" judgement indicated high risk of bias; the judgement will be "unclear" if insufficient details will be reported to assess the risk of bias properly (see Appendix S3).

KK and NS will independently assess the risk of bias/study quality in each study and disagreements will be discussed between the two reviewers by discussion or by a third reviewer (when no agreement is met by the two reviewers).

3.6.3 | Data synthesis

Outcome data will be pooled if the studies are sufficiently comparable (with regard to design, etc.). Subgroup analyses will only be performed, if the overall meta-analysis contains a minimum of 4 studies.

For outcome measures where a meta-analysis is not possible a qualitative data synthesis of the results from individual studies will be performed.

Standardized mean differences (SMD) with 95% Cis will be calculated for outcome measures of continuous and semi-continuous scales or all outcome measures reported as incidences (eg, number of lesions, we use a risk ratio. Whenever sham data are available or can be inferred, we will consider using the Normalized Mean Difference instead of the SMD.

3.7 | Assessment of heterogeneity

A random effects model will be conducted as heterogeneity is expected due to differences in animal model, interventions, outcome measures, etc. I-squared statistic will be used to assess heterogeneity.

3.8 | Subgroup and sensitivity analysis

If there are an adequate number of studies (at least four studies in at one of the subgroup categories), we will conduct subgroup analyses to interpret the heterogeneity between the studies, including the following:

The study characteristics that will be examined as potential source of heterogeneity (subgroup analysis):

Animal species
Endometriosis induction method
Medicinal plant
Dose of drug
Route of administration
Duration of treatment

Time between model induction and start of drug
Route of administration

We need to perform a Holm-Bonferroni correction for testing multiple subgroups. If one or more subgroup analyses cannot be performed due to insufficient data, the *P*-value will be adjusted accordingly. Also correction for multiple uses of control group will be performed by dividing the number of animals in the control group by the number of comparisons performed with this control group.

3.9 | The method for assessment of publication bias

The publication bias will be investigated using a funnel plots and visual analysis of these plots for outcome measures containing 20+ studies. We are aware that funnel plots of SMD are susceptible to distortion and will omit the assessment of publication bias if this is suspected for our dataset. In addition, we aim to perform Egger's test for small study effects for outcome measures containing 20+ studies.

4 | DISCUSSION

This systematic review and meta-analysis is to provide the pre-clinical researches on medicinal plants (Not Chinese combinations) and its compounds investigated in the treatment of experimental endometriosis. It will also prepare the strengths and limitations of available studies and offer future perspectives in this field.

4.1 | Ethics and dissemination

Research ethics approval is not required for this review, because the work will be carried out on published documents. The results of this systematic review will be published in related peer review journals.

Conflict of Interests

The authors declare no potential conflict of interests.

Author Contribution

KK has designed and performing research, analysing data, and writing paper. SNS has performing research, data extraction, Quality assessment, reviewing manuscript. MWL, HMA, MM, SNO, RA and AM have drafted the manuscript. All the authors contributed to the revision of the manuscript and approved the final version.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Kiani K, Sadati Lamardi SN, Laschke MW, MalekAfzali Ardakani H, Movahedin M, Ostad SN, Aflatoonian R, and Moini A, Medicinal plants and natural compounds in the treatment of experimental endometriosis: A systematic review protocol, *Evidence-based Preclinical Medicine*. 2016. doi:10.1002/ebm2.19