

# INPLASY PROTOCOL

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## Herbal medicine for herpes labialis – protocol of a systematic review and meta-analysis

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**Conflicts of interest:**  
None declared.

**Review question / Objective:** To evaluate the efficacy of herbal medicine in patients with herpes labialis.

**Condition being studied:** Clinically diagnosed herpes labialis.

**Eligibility criteria:** Inclusion:- All age - clinically diagnosed herpes labialis- topical or systemic herbal medicine  
Exclusion:- traditional Chinese medicine- traditional Indian medicine- traditional Korean medicine- traditional Kampo medicine- highly diluted / homeopathic preparations.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 May 2023 and was last updated on 10 May 2023 (registration number INPLASY202350038).

### INTRODUCTION

**Review question / Objective:** To evaluate the efficacy of herbal medicine in patients with herpes labialis.

**Rationale:** Herpes labialis is a common and widespread infectious disease caused by the herpes simplex virus (HSV). Worldwide, an estimated 3.7 billion people under the age of 50 (67 %) are infected with HSV [1].

After an initial infection, the virus spreads to the sensory neurons. There it remains dormant and reactivation, triggered by various factors, can lead to lifelong recurrent infections [2, 3]. Previous studies reported that 20-40 % of the adult population have recurrent herpes labialis [4]. Clinically it presents as inflamed and painful labial lesions with conditional distress [1, 4]. Therefore, although it is self-limiting and benign, it can significantly

affect quality of life [5]. To relieve symptoms and accelerate the disappearance of lesions, nucleoside antiviral drugs (NADs) like aciclovir are often used today. Both systemic and topical formulations are recommended, and they reduce the episode duration by an average of 0.74 days [6]. Also, various plant extracts show antiviral and anti-inflammatory effects [7]. Thus, herbal medicine may be a potential therapeutic option, as complementary and integrative therapies are increasingly in demand in dermatology [8]. Therefore, this review aims to provide an overview of the current state of evidence of herbal medicine for herpes labialis.

**Condition being studied:** Clinically diagnosed herpes labialis.

## METHODS

**Search strategy:** For literature search, search terms were created and modified upon requirements of other databases. As an example, the search term for PubMed is presented:

("Plants, Medicinal"[Mesh] OR "Herb\*" [Title/Abstract] OR Arnica[Mesh] OR Arnica [Title/Abstract] OR Retterspitz[Supplementary Concept] OR Comfrey[Mesh] OR Comfrey [Title/Abstract] OR symphytum [Title/Abstract] OR Traumaplant [Supplementary Concept] OR Traumaplant [Title/Abstract] OR Betula [Mesh] OR Betula [Title/Abstract] OR Quercus [Mesh] OR Quercus [Title/Abstract] OR "Oak bark" [Title/Abstract] OR Hypericum [Mesh] OR Hypericum [Title/Abstract] OR "St. John's Wort" [Title/Abstract] OR Hyperici [Title/Abstract] OR Matricaria [Mesh] OR Matricaria [Title/Abstract] OR Chamomile [Title/Abstract] OR Kamillosan [Supplementary Concept] OR Kamillosan [Title/Abstract] OR Kamillosan Liquidum [Supplementary Concept] OR Kamillosan Liquidum [Title/Abstract] OR Lavandula [Mesh] OR Lavandula [Title/Abstract] OR Lavender [Title/Abstract] OR Thuja [Mesh] OR Thuja [Title/Abstract] OR "Oenothera biennis" [Mesh] OR "Oenothera biennis" [Title/Abstract] OR "evening

primrose" [Title/Abstract] OR "evening primrose oil" [Supplementary Concept] OR Efamol [Supplementary Concept] OR Efamol [Title/Abstract] OR Malva [Mesh] OR Malva [Title/Abstract] OR Melissa [Mesh] OR Melissa [Title/Abstract] OR myrrh [Title/Abstract] OR Myrtus [Mesh] OR Myrtus [Title/Abstract] OR Agrimonia [Mesh] OR Agrimonia [Title/Abstract] OR "Mentha piperita" [Mesh] OR "Mentha piperita" [Title/Abstract] OR peppermint [Title/Abstract] OR "Balsanum Peruvianum" [Title/Abstract] OR "Balsam of Peru" [Title/Abstract] OR Calendula [Mesh] OR Calendula [Title/Abstract] OR "Salvia officinalis" [Mesh] OR "Salvia officinalis" [Title/Abstract] OR Salvia [Title/Abstract] OR Sage [Title/Abstract] OR Achillea [Mesh] OR Achillea [Title/Abstract] OR Yarrow [Title/Abstract] OR Equisetum [Mesh] OR Equisetum [Title/Abstract] OR horsetail [Title/Abstract] OR "Chelidonium" [Mesh] OR Chelidonium [Title/Abstract] OR celandine [Title/Abstract] OR "chelidonii herba" [Supplementary Concept] OR Echinacea [Mesh] OR Echinacea [Title/Abstract] OR echinacin [Supplementary Concept] OR echinacin [Title/Abstract] OR "Plantago lanceolata" [Title/Abstract] OR Ribwort [Title/Abstract] OR "Viola tricolor" [Title/Abstract] OR Viola [MESH] OR Heartsease [Title/Abstract] OR Centaurium [Mesh] OR Centaurium [Title/Abstract] OR centaury [Title/Abstract] OR Melaleuca [Mesh] OR Melaleuca [Title/Abstract] OR "Balsanum toltanum" [Title/Abstract] OR "Tolu balsam" [Title/Abstract] OR Potentilla [Mesh] OR Potentilla [Title/Abstract] OR Hamamelis [Mesh] OR Hamamelis [Title/Abstract] OR "Witch hazel" [Title/Abstract] OR Garlic [Mesh] OR Garlic\* [Title/Abstract] OR "Allium sativum" [Title/Abstract] OR "Agrimonia extract" [Supplementary Concept] OR agrimonia [MESH] OR agrimonia [Title/Abstract] OR agrimony [Title/Abstract] OR "plantaginis lanceolatae folium" [Supplementary Concept] OR ribwort [Title/Abstract] OR Plantaginis [Title/Abstract] OR Plantago [MESH] OR Plantago [Title/Abstract] OR "terebinthina larcina" [Mesh] OR "terebinthina larcina" [Title/Abstract] OR "turpentine" [MESH] OR "larch turpentine" [Title/Abstract] OR "clove

flower extract"[Supplementary Concept] OR Caryophylli[Title/Abstract] OR "clove oil"[MESH] OR clove[ Title/Abstract] OR Syzygium[MESH] OR Sycygiu[m] [Title/Abstract] OR Theae[Title/Abstract] OR juglandaceae [ M E S H ] O R juglandaceae[Title/Abstract] OR juglandis[Title/Abstract] OR "balloon vine" [Title/Abstract] OR Cardiosperm.

**Participant or population:** Patients of any age with clinically diagnosed herpes labialis without gender or ethnicity restrictions.

**Intervention:** This study includes only articles dealing with herbal medicine treatment. Due to their often-unclear composition and possible heavy metal contamination, Traditional Chinese, Korean, Indian or Kampo medicines are excluded. Furthermore, studies on highly diluted herbal preparations are also excluded.

**Comparator:** 1. placebo 2. active control options (e.g. other herbs; treatment as usual).

**Study designs to be included:** Only randomized controlled trials will be included.

**Eligibility criteria:** Inclusion:- All age - clinically diagnosed herpes labialis- topical or systemic herbal medicine Exclusion:- traditional Chinese medicine- traditional Indian medicine- traditional Korean medicine- traditional Kampo medicine- highly diluted / homeopathic preparations.

**Information sources:** Electronic databases (cochrane, scopus, pubmed), contact with authors, trial registers.

**Main outcome(s):** The primary outcome is severity of herpes labialis. Secondary outcome healing of lesions.

**Additional outcome(s):** Safety.

**Data management:** Citavi is used as a software tool to manage the literature and record decision making. First, the titles,

then the abstracts, and finally the full texts are independently checked for suitability by two authors.

If discrepancies occur, a third author is consulted. Further disagreements are discussed until agreement is reached.

Data extraction is done in Excel, and statistical analyses are performed in R and R Studio.

**Quality assessment / Risk of bias analysis:**

Risk of bias analysis will be measured by the Cochrane risk of bias tool 2.0 . Two authors will independently assess all included studies for their risk of bias. If disagreements appear, a third author will be consulted. Further disagreements will be discussed until consent is reached.

**Strategy of data synthesis:** If there are at least two studies available for a particular outcome, combined analyses will be carried out. For continuous outcomes, standardized mean differences (SMD) along with 95% confidence intervals (CI) will be computed, with the use of Hedges's correction for small study samples (6,7). In cases where standard deviations are missing, they will be derived from standard errors, confidence intervals, or t values. For dichotomous outcomes, odds ratios (OR) with 95% CI will be calculated (6,7). If there is any missing data, attempts will be made to obtain it from the trial authors. Random effects model will be used to calculate inverse variance method for continuous outcomes, and Mantel-Haenszel method for dichotomous outcomes (8). For better comparability in case of non-significant heterogeneity, fixed effects model estimates will be added to the forest plots. Furthermore, the Hartung-Knapp small-sample correction will be employed (9). The I<sup>2</sup> and τ<sup>2</sup> statistics will be used to explore statistical heterogeneity between studies. If there is statistical heterogeneity in the meta-analysis, subgroup analyses and meta-regression (provided there are at least 10 studies for the respective analyses) will also be conducted to investigate possible reasons for heterogeneity (6,7,8).

**Subgroup analysis:** Subgroup analyses will be performed for adults, children and

mixed samples if appropriate data are available.

**Sensitivity analysis:** Sensitivity analyses will be conducted for studies with high risk of bias versus low risk of bias in respective domains.

**Language restriction:** Studies in English and German will be included in the review.

**Country(ies) involved:** Germany.

**Keywords:** - Herbal medicine- herbs-herpes labialis- Complementary medicine-dermatology.

**Dissemination plans:** - The review will be published in a peer reviewed scientific journal.

#### Contributions of each author:

**Author 1 - Melanie Anheyer** - conceiving, designing and coordinating the review, creation of search strategy, study selection, data collection, data management, interpretation of data, writing the protocol and review.

**Author 2 - Thomas Ostermann** - conceiving, designing and coordinating the review, interpretation of data, writing the protocol and review.

**Author 3 - Holger Cramer** - conceiving, designing and coordinating the review, interpretation of data, writing the protocol and review.

**Author 4 - Dennis Anheyer** - conceiving, designing and coordinating the review, creation of search strategy, data management, statistical analysis of data, interpretation of data, writing the protocol and review.

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