

INPLASY PROTOCOL

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Corresponding author:
Dennis Anheyer

dennis.anheyer@uni-wh.de

Author Affiliation:
Chair of Research in
Complementary Medicine,
Institute for General Practice
and Interprofessional Care,
University Hospital Tübingen,
Tübingen, Germany.

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None declared.

Herbal medicine for atopic dermatitis – protocol of a systematic review and meta-analysis

Anheyer, M¹; Cramer, H²; Ostermann, T³; Anheyer, D⁴.

Review question / Objective: To evaluate the effectiveness of topical and systemic herbal medicine in patients with atopic dermatitis.

Rationale: Atopic dermatitis is one of the most common skin diseases in both childhood and adulthood (1). Usually, the disease develops within the first year of life. In principle, all skin areas can be affected. However, there are age-dependent predilection sites (2). The diagnosis of atopic dermatitis is made clinically. Children and adults suffer primarily from the excruciating itching (1). As a result, atopic dermatitis not only affects quality of life, but also sleep, school, employment and social environment. The therapy includes a daily basic therapy with emollients. In acute episodes, topical glucocorticoids, in severe courses also systemically administered glucocorticoids or immunomodulators are used (1). Many parents and affected patients additionally use complementary and integrative medicine methods for various reasons (3, 4). Due to the increasing research in this field, an update of existing reviews is highly warranted. Therefore, this review aims to provide an overview of the current state of evidence in the overall field of both, topical and systemic herbal medicine.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 April 2023 and was last updated on 12 April 2023 (registration number INPLASY202340041).

INTRODUCTION

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Rationale: Atopic dermatitis is one of the most common skin diseases in both childhood and adulthood (1). Usually, the disease develops within the first year of life. In principle, all skin areas can be affected. However, there are age-dependent predilection sites (2). The diagnosis of atopic dermatitis is made

clinically. Children and adults suffer primarily from the excruciating itching (1). As a result, atopic dermatitis not only affects quality of life, but also sleep, school, employment and social environment. The therapy includes a daily basic therapy with emollients. In acute episodes, topical glucocorticoids, in severe courses also systemically administered glucocorticoids or immunomodulators are used (1). Many parents and affected patients additionally use complementary and integrative medicine methods for various reasons (3, 4). Due to the increasing research in this field, an update of existing reviews is highly warranted. Therefore, this review aims to provide an overview of the current state of evidence in the overall field of both, topical and systemic herbal medicine.

Condition being studied: The study will focus on clinically diagnosed atopic dermatitis.

METHODS

Search strategy: ("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 laricina"[Mesh] OR "terebinthina laricina"[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] OR juglandaceae[Title/Abstract] OR juglandis[Title/Abstract] OR “balloon vine” [Title/Abstract] OR Cardiospermum[Title/Abstract] OR Dulcamara [Title/Abstract] OR borago[MESH] OR borago[Title/Abstract] OR “borage oil”[Supplementary Concept] OR „Urtica dioica”[MESH] OR Urticae[Title/Abstract] OR nettle[Title/Abstract] OR “Avena stramentum”[Title/Abstract] OR “Oat straw”[Title/Abstract] OR “shepherd's purse”[Title/Abstract] OR “Bursae pastoris”[Title/Abstract] OR Taraxacum[MESH] OR Taraxacum[Title/Abstract] OR dandelion[Title/Abstract] OR mahonia[MESH] OR mahonia[Title/Abstract] OR propolis[MESH] OR propolis[Title/Abstract] OR deadnettle[Title/Abstract] OR “Lamii albi” [Title/Abstract] OR “tea tree oil”[MESH] OR “Tea tree oil”[Title/Abstract] OR melaleuca[MESH] OR melaleuca[Title/Abstract] OR hippophae[MESH] OR hippophae[Title/Abstract] OR “sea buckthorn” [Title/Abstract] OR aesculus[MESH] OR aesculus[Title/Abstract] OR chestnut[Title/Abstract] OR sanguinaria[MESH] OR sanguinaria[Title/Abstract] OR bloodroot[Title/Abstract] OR aloe[MESH] OR aloe[Title/Abstract] OR “Aloe vera gel”[Supplementary Concept] OR onions[MESH] OR onion[Title/Abstract] OR “Allium cepa”[Title/Abstract] OR “bellis perennis”[Title/Abstract] OR daisies[Title/Abstract] OR juglans[MESH] OR juglans[Title/Abstract] OR walnut[Title/Abstract] OR Azadirachta[MESH] OR Azadirachta[Title/Abstract] OR “neem tree” [Title/Abstract] OR “neem oil” [Supplementary Concept] OR bran[Title/Abstract])

AND

(“Administration, cutaneous”[MESH] OR “skin diseases” [M E S H] OR dermatology[MESH] OR “Dermatitis, atopic”[MESH] OR Derm*[Title/Abstract] OR cutan*[Title/Abstract] OR “atopic dermatitis” [Title/Abstract] OR neurodermatitis[Title/Abstract] OR “diaper dermatitis” [Title/Abstract] OR

psorias*[Title/Abstract] OR ulcus[Title/Abstract] OR ulcer*[Title/Abstract] OR wound[Title/Abstract] OR herper[Title/Abstract] OR acne[Title/Abstract] OR eczem*[Title/Abstract] OR pruritus[Title/Abstract] OR urticaria[Title/Abstract]).

Participant or population: Participants with clinically diagnosed atopic dermatitis all age. No restriction regarding gender and ethnicity are made.

Intervention: Only articles studying herbal medicine treatment will be included in this review. Traditional Chinese, Korean, Indian or Kampo medicine will be excluded due to their often-unclear compositions and possible heavy metal contamination. In addition, studies on highly diluted herbal preparations will be also excluded. Herbal medicine treatment except for traditional Chinese, Korean or Indian medicine or Kampo due to the often-unclear compositions and possible heavy metal contamination. In addition, studies on highly diluted herbal preparations will be 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 atopic dermatitis- 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 outcomes are severity of atopic dermatitis and itching.

Additional outcome(s): Safety.

Data management: Citavi will be used as software tool to manage literature and to record decision making. First titles, then abstracts, and further full texts will be screened for eligibility independently by two authors.

If disagreements appear, a third author will be consulted. Further disagreements will be discussed until consent is reached.

Data extraction will be done in Excel, statistical analyses will be done 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: When there are two or more studies available on a particular outcome, combined analyses will be performed. For continuous outcomes, standardized mean differences (SMD) will be calculated, along with 95% confidence intervals (CI) using Hedges's correction for small study samples (5,6). In cases where standard deviations are not available, they will be estimated from standard errors, confidence intervals or t values. For dichotomous outcomes, odds ratios (OR) with 95% CI will be calculated (5,6). If there is missing data, attempts will be made to retrieve it from the trial authors. A random effects model will be used, and inverse variance method for continuous outcomes and the Mantel-Haenszel method for dichotomous outcomes (7). To improve comparability in cases of non-significant heterogeneity, fixed effects model estimates will be added to forest plots. The Hartung-Knapp small-sample correction will also be applied (8). The presence of statistical heterogeneity between studies will be assessed using the I² and τ^2 statistics. If there is statistical heterogeneity, subgroup analyses and meta-regression (if there are at least 10 studies available) will be conducted to explore possible reasons for heterogeneity (5,6,7).

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 the languages English and German, are included in the review.

Country(ies) involved: Germany.

Keywords: atopic dermatitis, herbal medicine, systematic review, meta-analysis.

Dissemination plans: publication in scientific journal; presentation on scientific congresses.

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.

m.anheyer@contilia.de

Author 2 - Holger Cramer - conceiving, designing and coordinating the review, interpretation of data, writing the protocol and review.

holger.cramer@med.uni-tuebingen.de

Author 3 - Thomas Ostermann - 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.

dennis.anheyer@uni-wh.de

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