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# The safety of herbal medicine in pediatric randomized controlled trials

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**ADMINISTRATIVE INFORMATION**

**Support -** None.

**Review Stage at time of this submission -** The review has not yet started.

**Conflicts of interest -** None declared.

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**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 March 2025 and was last updated on 31 March 2025.

## INTRODUCTION

**Review question / Objective** Overview of safety data on herbal medicine in randomized controlled trials with a focus on the pediatric population.

**Rationale** Herbal medicine has been an integral component of traditional medicine systems for centuries, and its integration into modern healthcare is increasingly acknowledged. It is widely employed across numerous countries for both adult and pediatric populations, yet its usage prevalence varies considerably. For instance, approximately 10 % of parents in the United States administer herbal products to their children, compared to nearly 44 % in Turkey and over 85 % in Germany (Loman 2003; Ozturk und Karayagiz 2008; Hümer et al. 2010). This widespread use is largely driven by the perception that herbal medicine is natural and therefore inherently safe, offers a broad spectrum of therapeutic applications, and is associated with a low risk of side effects and drug interactions (Hümer et al. 2010).

Although many parents consider herbal medicine a safe treatment option, its use can still lead to unintended and harmful effects. These effects , known as adverse events, occur following the administration of medication (Gardiner et al. 2013). In the context of herbal medicine, these may result from excessive use, adulteration, contamination, herb- drug interaction or herb-herb interaction (Kongkaew et al. 2024). Despite the natural origin of herbal products, parents often overlook the possibility of herb–drug interactions, which can be particularly dangerous for medications with a narrow therapeutic index (Lim et al. 2011). Consequently, it is critical that healthcare professionals are informed about the use of herbal products, although studies indicate that parents frequently do not disclose this information to pediatricians (Hümer et al. 2010). Adverse events have also been reported resulting from improper administration, such as not adhering to the

recommended methods. For example, while aloe vera is beneficial when applied topically, its ingestion can lead to adverse events (Gardiner et al. 2013). Moreover, product descriptions often lack critical information on pre-existing conditions, concomitant diseases, and concurrent therapies (Lim et al. 2011).

Many herbal products contain multiple ingredients, making it difficult to determine the specific component responsible for an adverse event. A systematic review of umckaloabo by the Natural Standard Research Collaboration highlighted the challenges in standardizing herbal medicines due to their complex mixtures, which complicates safety assessments and quality control (Ulbricht et al. 2010).

Systematic research and evaluation of the potential adverse events associated with herbal treatments are essential. However, even in adult populations, the safety of herbal medicine remains inconclusive, and in pediatric populations, it has not yet been systematically investigated. Children differ from adults in terms of body surface area, physiological development, and pharmacokinetics, which may result in distinct responses to these treatments (Kraft 2010).

Despite its widespread use as a complementary treatment, the safety profile of herbal medicine in pediatric populations remains insufficiently studied. With few exceptions, there is a significant lack of systematic investigations into its potential adverse events (Anheyer et al. 2024; Anheyer et al. 2018). Therefore, this review aims to systematically analyze the existing evidence from randomized controlled trials regarding the safety of herbal medicine in children and adolescents.

**Condition being studied** The study will focus on herbal medicine for children and adolescents irrespective of the indication.

## 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:

("Pediatrics"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR "Pediatric*"[Title/Abstract] OR "Child*"[Title/Abstract] OR "Infant*"[Title/Abstract] OR "Adolescent*"[Title/Abstract])

AND

("Plants, Medicinal"[Mesh] OR "Herb*"[Title/Abstract] OR Angelica[Mesh] OR Angelica[Title/Abstract] OR Iberogast[Supplementary Concept] OR Iberogast[Title/Abstract] OR "STW 5"[Title/Abstract] OR Pimpinella[Mesh] OR Pimpinella[Title/Abstract] OR Anise[Title/Abstract] OR Arnica[Mesh] OR Arnica[Title/Abstract] OR Retterspitz[Supplementary Concept] OR Euphrasia[Mesh] OR Euphrasia[Title/Abstract] OR Eyebright[Title/Abstract] OR Valeriana[Mesh] OR Valeriana[Title/Abstract] OR Valerian[Title/Abstract] OR Arctostaphylos[Mesh] OR Arctostaphylos[Title/Abstract] OR Bearberr*[Title/Abstract] OR Comfrey[Mesh] OR Comfrey[Title/Abstract] OR Comfrey[Title/Abstract] OR Traumaplant[Supplementary Concept] OR Traumaplant[Title/Abstract] OR Betula [Mesh] OR Betula[Title/Abstract] OR “Menyanthes trifoliate” [Title/Abstract] OR Solanum[Mesh] OR Solanum[Title/Abstract] OR Bittersweet[Title/Abstract] OR "bitter nightshade"[Title/Abstract] OR “Cinnamomum camphora"[Mesh] OR "Cinnamomum camphora"[Title/Abstract] OR camphor[Title/Abstract] OR Cinchona[Mesh] OR Cinchona[Title/Abstract] OR "China bark"[Title/Abstract] OR Hedera[Mesh] OR Hedera[Title/Abstract] OR Ivy[Title/Abstract] OR Bronchipret[Supplementary Concept] OR Bronchipret[Title/Abstract] OR Prospan[Supplementary Concept] OR Prospan[Title/Abstract] OR Althaea[Mesh] OR Althaea[Title/Abstract] OR "Marsh Mallow"[Title/Abstract] OR Imupret[Supplementary Concept] OR Imupret[Title/Abstract] OR Quercus[Mesh] OR Quercus[Title/Abstract] OR "Oak bark"[Title/Abstract] OR Verbena[Mesh] OR Verbena[Title/Abstract] OR Vervain[Title/Abstract] OR Gentiana[Mesh] OR Gentian*[Title/Abstract] OR Sinupret[Supplementary Concept] OR Sinupret[Title/Abstract] OR Eucalyptus[Mesh] OR Eucalyptus[Title/Abstract] OR Pinimenthol[Supplementary Concept] OR Pinimenthol[Title/Abstract] OR Gelomyrtol[Supplementary Concept] OR Gelomyrtol[Title/Abstract] OR Foeniculum[Mesh] OR Foeniculum[Title/Abstract] OR Fennel[Title/Abstract] OR Picea[Mesh] OR Picea[Title/Abstract] OR Spruce[Title/Abstract] OR Psyllium[Mesh] OR Psyllium[Title/Abstract] OR Plantago[Title/Abstract] OR Alchemilla[Mesh] OR Alchemilla[Title/Abstract] OR "Lady's Mantle"[Title/Abstract] OR Eugenia[Mesh] OR Eugenia[Title/Abstract] OR Clove[Title/Abstract] OR Solidago[Mesh] OR Solidag*[Title/Abstract] OR Goldenrod[Title/Abstract] OR Grindelia[Mesh] OR Grindelia[Title/Abstract] OR Gumweed[Title/Abstract] OR Ononis[Title/Abstract] OR Ononidis[Title/Abstract] OR Restharrow[Title/Abstract] OR "Vaccinium

myrtillus extract"[Supplementary Concept] OR Vaccinium[Mesh] OR Vaccinium[Title/Abstract] OR Blueberr*[Title/Abstract] OR Capsella[Mesh] OR Capsella[Title/Abstract] OR Cress[Title/Abstract] OR Galeopsis[Title/Abstract] OR "Hemp nettle"[Title/Abstract] OR “Sambucus nigra”[Mesh] OR "Sambucus nigra"[Title/Abstract] OR Sinupret[Supplementary Concept] OR Humulus[Mesh] OR Humulus[Title/Abstract] OR Kytta[Title/Abstract] OR Tussilago[Mesh] OR Tussilago[Title/Abstract] OR Coltsfoot[Title/Abstract] OR Ginger[Mesh] OR Ginger[Title/Abstract] OR Zingiber[Title/Abstract] OR “Cetraria islandica”[Title/Abstract] OR “Icelandic moss”[Title/Abstract] OR Hypericum[Mesh] OR Hypericum[Title/Abstract] OR "St. John's Wort"[Title/Abstract] OR Tropaeolum[Mesh] OR Tropaeolum[Title/Abstract] OR "angocin Anti-Infekt N"[Supplementary Concept] OR Angocin[Title/Abstract] OR "Anti-Infekt N"[Title/Abstract] OR Nasturtium[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 Pinus[Mesh] OR Pinus[Title/Abstract] OR Pine[Title/Abstract] OR Coriandrum[Mesh] OR Coriandrum[Title/Abstract] OR Coriander[Title/Abstract] OR Carum[Mesh] OR Carum[Title/Abstract] OR Caraway[Title/Abstract] OR Lavandula[Mesh] OR Lavendula[Title/Abstract] OR Lavender[Title/Abstract] OR Thuja[Mesh] OR Thuja[Title/Abstract] OR Cedar[Title/Abstract] OR Esberitox[Supplementary Concept] OR Esberitox[Title/Abstract] OR Flax[Mesh] OR Flax[Title/Abstract] OR Tilia[Mesh] OR Tilia[Title/Abstract] OR Taraxacum[Mesh] OR Taraxacum[Title/Abstract] OR Dandelion[Title/Abstract] OR "Oenothera biennis"[Mesh] OR "Oenothera biennis"[Title/Abstract] OR "evening primrose"[Title/Abstract] OR Efamol[Supplementary Concept] OR Efamol[Title/Abstract] OR Malva[Mesh] OR Malva[Title/Abstract] OR “Milk Thistle”[Mesh] OR “Milk Thistle”[Title/Abstract] OR Thistle[Title/Abstract] OR Filipendula[Mesh] OR Filipendula[Title/Abstract] OR meadowsweet[Title/Abstract] OR Armoracia[Mesh] OR Armoracia[Title/Abstract] OR horseradish[Title/Abstract] OR Melissa[Mesh] OR Melissa[Title/Abstract] OR Commiphora[Mesh] OR Commiphora[Title/Abstract] OR myrrh[Title/Abstract] OR Myrtus[Mesh] OR Myrtus[Title/Abstract] OR Agrimonia[Mesh] OR Agrimonia[Title/Abstract] OR Orthosiphon[Mesh] OR Orthosiphon[Title/Abstract] OR Passiflora[Mesh] OR Passiflora[Title/Abstract] OR "Mentha piperita"[Mesh] OR "Mentha piperita"[Title/Abstract] OR peppermint[Title/Abstract] OR Pelargonium[Mesh] OR Pelargonium[Title/Abstract] OR "Balsanum Peruvianum"[Title/Abstract] OR "Balsam of Peru"[Title/Abstract] OR Citrus[Mesh] OR Citrus[Title/Abstract] OR "bitter orange"[Title/Abstract] OR Primula[Mesh] OR Primula[Title/Abstract] OR cowslip[Title/Abstract] OR "Thymus serpyllum"[Title/Abstract] OR "Wild Thyme"[Title/Abstract] OR Rheum[Mesh] OR "Rheum palmatum"[Title/Abstract] OR "Rhei radix"[Title/Abstract] OR Pieplant[Title/Abstract] OR "pyralvex berna"[Supplementary Concept] OR "pyralvex berna"[Title/Abstract] OR Calendula[Mesh] OR Calendula[Title/Abstract] OR Rosmarinus[Mesh] OR Rosmarinus[Title/Abstract] OR Rosemary[Title/Abstract] OR "Salvia officinalis"[Mesh] OR “Salvia officinalis”[Title/Abstract] OR Salvia[Title/Abstract] OR Sage[Title/Abstract] OR Rumex[Mesh] OR Rumex[Title/Abstract] OR Sorrel[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 "Iberis amara"[Title/Abstract] OR "Bitter Candytuft"[Title/Abstract] OR Chelidonium[Mesh] OR Chelidonium[Title/Abstract] OR celandine[Title/Abstract] OR Echinacea[Mesh] OR Echinacea[Title/Abstract] OR echinacin[Supplementary Concept] OR echinacin[Title/Abstract] OR Drosera[Mesh] OR Drosera[Title/Abstract] OR sundew[Title/Abstract] OR "Plantago lanceolata"[Title/Abstract] OR Ribwort[Title/Abstract] OR "Viola tricolor"[Title/Abstract] OR Heartsease[Title/Abstract] OR Glycyrrhiza[Mesh] OR Glycyrrhiza[Title/Abstract] OR liquorice[Title/Abstract] OR Centaurium[Mesh] OR Centaurium[Title/Abstract] OR centaury[Title/Abstract] OR Melaleuca[Mesh] OR Melaleuca[Title/Abstract] OR "Thymus Plant"[Mesh] OR "Thymus Plant"[Title/Abstract] OR thyme[Title/Abstract] OR "Balsanum tolutanum"[Title/Abstract] OR "Tolu balsam"[Title/Abstract] OR Potentilla[Mesh] OR Potentilla[Title/Abstract] OR "Xysmalobium undulatum"[Title/Abstract] OR "Milk bush"[Title/Abstract] OR Milkwort[Title/Abstract] OR “Artemisia absinthium”[Mesh] OR “Artemisia absinthium”[Title/Abstract] OR Artemisia[Title/Abstract] OR wormwood[Title/Abstract] OR Salix[Mesh] OR Salix[Title/Abstract] OR Assalix[Supplementary Concept] OR Assalix[Title/Abstract] OR "willow bark"[Title/Abstract] OR Triticum[Mesh] OR Triticum[Title/Abstract] OR Verbascum[Mesh] OR Verbascum[Title/Abstract] OR mullein[Title/Abstract] OR Hamamelis[Mesh] OR Hamamelis[Title/Abstract] OR "Witch hazel"[Title/Abstract] OR “Cinnamomum zeylanicum”[Mesh] OR “Cinnamomum zeylanicum” [Title/Abstract] OR Cinnamon[Title/Abstract] OR Garlic[Mesh] OR Garlic*[Title/Abstract] OR “Allium sativum”[Title/Abstract] OR “Ginkgo biloba”[Mesh]

OR "Ginkgo biloba"[Title/Abstract] OR "Vaccinium macrocarpon"[Mesh] OR "Vaccinium macrocarpon"[Title/Abstract])

AND

("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR randomized[Title/Abstract] OR randomised[Title/Abstract] OR randomly[Title/Abstract] OR random[Title/Abstract] OR placebo[Title/Abstract] OR group[Title/Abstract] OR blind[Title/Abstract] OR Trial[Title/Abstract])

**Participant or population** Pediatric population aged from 0 to 18 years, with no restrictions regarding gender and ethnicity Intervention.

**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.

**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:
- Age group 0 - 18 years
- 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), direct communication with authors, trial registers.

**Main outcome(s)** Safety.

**Data management** The literature management and documentation of decision-making will be conducted using a literture manager (e.g. Citavi). The screening process will be carried out independently by two authors, starting with titles, followed by abstracts, and subsequently full texts to assess eligibility. In case of discrepancies, a third author will be consulted. Any remaining disagreements will be resolved through discussion until consensus is achieved. Data extraction will be performed using Excel, while statistical analyses will be conducted using R and R Studio.

**Quality assessment / Risk of bias analysis** The risk of bias assessment will be conducted using the Cochrane Risk of Bias Tool 2.0. Two authors will independently evaluate all included studies for potential bias. In case of discrepancies, a third author will be consulted. Any unresolved disagreements will be addressed through discussion until consensus is achieved.

**Strategy of data synthesis** If two or more studies are available for a particular outcome, a combined analysis will be performed. For continuous outcomes, standardized mean differences (SMD) with 95% confidence intervals (CI) will be calculated using Hedges's correction for small study samples (Borenstein et al. 2009; Higgins et al. 2019). In cases where standard deviations are not reported, they will be estimated from standard errors, confidence intervals, or t-values. For dichotomous outcomes, odds ratios (OR) with 95% CI will be computed (Borenstein et al. 2009; Higgins et al. 2019). If data are missing, efforts will be made to obtain them from the trial authors. A random-effects model will be applied, utilizing the inverse variance method for continuous outcomes and the Mantel-Haenszel method for dichotomous outcomes (Harrer et al. 2021). To enhance comparability in cases of non-significant heterogeneity, fixed-effects model estimates will be included in forest plots. Additionally, the Hartung-Knapp correction for small samples will be applied (Cornell et al. 2014). Statistical heterogeneity among studies will be assessed using the $I^2$ and $\tau^2$ statistics. If heterogeneity is detected, subgroup analyses and, if at least 10 studies are available, meta-regression will be conducted to explore potential sources of heterogeneity (Harrer et al. 2021; Borenstein et al. 2009; Higgins et al. 2019).

**Subgroup analysis** For each herb seperately.

**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** herbal medicine, adverse events, adverse effects, safety, complementary medicine, integrative medicine, children, adolescents, pediatric.

## Dissemination plans

- The review will be published in a peer reviewed scientific journal
- Results of this review will be presented at scientific congresses.

## Contributions of each author

Author 1 - Cosima Englert - conceiving, designing and coordinating the review, creation of search strategy, study selection, data collection, data management, interpretation of data, writing the protocol and review.
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Author 4 - Melanie Anheyer - conceiving, designing and coordinating the review, creation of search strategy, study selection, data management, interpretation of data, writing the protocol and review, supervision.
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