INPLASY

Clinical adverse events, organ toxicities, supply-chain adulteration, and controlled-trial safety signals associated with Ayurvedic herbs, herbo-mineral formulations, and procedures in humans: a protocol for a systematic review and meta-analysis

INPLASY2026110100

doi: 10.37766/inplasy2026.11.0100

Received: 24 November 2026

Published: 24 November 2026

Corresponding author:
Cyriac Philips

abbyphilips@theliverinst.in

Author Affiliation:
Department of Clinical and Translational Hepatology and Monarch Liver Laboratory, The Liver Institute, Center of Excellence in Gastrointestinal Sciences, Rajagiri Hospital, Aluva, Kochi, Kerala, India.

Philips, CA; Oommen, TT; Theruvath, AH; Sreemohan, A; Baby, A; Ramesh, C; Kalal, CR.

ADMINISTRATIVE INFORMATION

Support - This systematic review and meta-analysis receives no external commercial, pharmaceutical, nutraceutical, or governmental grant funding. Non-financial institutional infrastructure, library access, and statistical computing support are provided by The Liver Institute, Center of Excellence in Gastrointestinal Sciences, Rajagiri Hospital, Aluva, Kochi, Kerala, India. No external sponsor or funding entity has had or will have any role in developing the protocol, designing the search architecture, screening records, extracting data, executing statistical syntheses, interpreting findings, or preparing the manuscript for publication.

Review stage at the time of initial registration - The review has not yet started.

Conflicts of interest - The corresponding author declares no financial, commercial, consulting, patent, or industry competing interests related to any pharmaceutical company, dietary supplement manufacturer, or traditional medicine enterprise. As a clinical hepatologist and physician-scientist who has previously authored peer-reviewed observational studies and toxicological investigations on herb-induced liver injury and complementary and alternative medicine safety in India, the corresponding author discloses an academic track record in this field. To mitigate intellectual or confirmation bias during the conduct of this review, strict pre-specified eligibility rules will separate defined Ayurvedic exposures from mixed complementary medicine cohorts, pre-specified leave-one-centre-out sensitivity analyses will omit cohorts originating from the corresponding author's institution, and if co-reviewers participate, risk-of-bias appraisal and data verification for any primary study authored by a review team member will be performed independently by a reviewer not involved in that primary study.

INPLASY registration number: INPLASY2026110100

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 November 2026 and was last updated on 24 November 2026.

Philips et al. INPLASY protocol 2026110100. doi:10.37766/inplasy2026.11.0100 Downloaded from https://inplasy.com/inplasy-2026-11-0100/

INTRODUCTION

Review question / Objective The primary objective of this systematic review and multi-tier meta-analysis is to comprehensively identify, appraise, and quantitatively synthesize the clinical spectrum, organ-system phenotypes, prognostic determinants, product toxicological correlates, and controlled-trial safety signals of adverse events associated with oral, topical, or procedural Ayurvedic interventions in humans. Framed using an integrated Population, Exposure/Intervention, Comparator, Outcome, and Study Design (PECOS/PICOS) structure, the review asks four linked questions: first, among humans exposed to defined Ayurvedic botanical extracts, polyherbal formulations, calcined herbo-mineral preparations, or procedures, what are the pooled clinical proportions of severe outcomes—specifically herb-induced liver injury case-fatality, patient-level mortality modification by pre-existing chronic liver disease, autoimmune-like histological and serological hepatotoxicity phenotypes, blood lead distributions, chelation requirements, and extrahepatic organ toxicities—across clinical cohorts and case series; second, across unselected retail and internet market surveys versus patient-linked forensic testing, what proportions of Ayurvedic products contain heavy metals above regulatory limits or undeclared synthetic pharmaceuticals; third, across randomized controlled trials comparing Ayurvedic interventions against placebo or active conventional controls, do active Ayurvedic arms exhibit higher risks of adverse-event treatment discontinuation, luminal gastrointestinal events, biochemical transaminase elevations, or mild and serious adverse events; and fourth, what statistical power do existing controlled trials possess to detect rare idiosyncratic organ injury compared with active hospital surveillance and national or international pharmacovigilance systems.

Condition being studied The condition under investigation encompasses all clinical adverse drug reactions, organ-specific toxicities, heavy-metal toxicity syndromes, synthetic pharmaceutical adulteration syndromes, and procedural harms occurring in humans in association with Ayurvedic medicine. Specific clinical entities include herb-induced liver injury classified by R-ratio and Roussel Uclaf Causality Assessment Method (RUCAM) criteria where available as well as presentations including autoimmune-like hepatitis, cholestatic hepatitis, portosinusoidal vascular disease, acute liver failure and acute-on-chronic liver failure, extrahepatic adverse events including but not limited to luminal gastrointestinal mucosal toxicity, plumbism, arsenicosis, nephrotoxicity and nervous system toxicity, cardiotoxicity, endocrinological disorders, cutaneous adverse reactions, and mechanical, metabolic, or infectious complications of Ayurvedic therapies.

METHODS

Participant or population Eligible participants include human subjects of any age, sex, ethnicity, geographic location, or baseline clinical status, encompassing healthy volunteers, outpatients with chronic medical conditions, pregnant individuals, children, and hospitalized patients with or without underlying chronic liver, renal, cardiovascular, neurological, or metabolic disease, who have documented oral, topical, inhalational, nasal, ocular, or procedural exposure to an Ayurvedic intervention, as well as commercial Ayurvedic medicinal products sampled directly from retail pharmacies, clinics, or internet marketplaces for laboratory toxicological analysis aimed at characterizing human exposure risk. Animal toxicology experiments, in vitro cellular assays without human clinical or market-exposure data, and botanical or agronomic field studies will be excluded.

Intervention Eligible interventions and exposures comprise any health product, botanical preparation, herbo-mineral formulation, or clinical procedure explicitly defined by the primary source as Ayurvedic (classical or proprietary Ayurvedic medicine), a calcined metallic or mineral supplement/drug, an Ayurvedic procedure, or a medicinal dosage form (standardized extract, capsule, tablet, powder/churna, decoction/kwatha, medicated ghee/ghrita, or fermented arishta/asava) of a codified single herb of the Ayurvedic pharmacopoeia, regardless of dosage, duration, or prescribing pathway. Non-Ayurvedic exposures, including culinary household spices, accidental ingestion of wild toxic plants or seeds outside medicinal prescribing, festival use of botanicals, non-Ayurvedic traditional medicines, non-Indian folk/alternative remedies, homeopathic dilutions will be excluded from primary Ayurvedic syntheses.

Comparator In controlled clinical trials (Tier 1), eligible comparators include matched placebo, no-treatment standard care, or active conventional pharmacotherapy; for multi-arm trials evaluating more than one Ayurvedic formulation against a shared control arm, active Ayurvedic arms will be combined into a single composite Ayurvedic group or analysed using shared-control adjustments to

Philips et al. INPLASY protocol 2026110100. doi:10.37766/inplasy2026.11.0100 Downloaded from https://inplasy.com/inplasy-2026-11-0100/

prevent double-counting of control participants, while non-Ayurvedic active comparator arms will be excluded from Ayurvedic numerators. In observational cohorts (Tier 2), internal comparators will include exposed patient subgroups stratified by baseline clinical status, specifically patients with versus without underlying chronic liver disease and in analytical market surveys (Tier 4), internal comparators will include herbo-mineral formulations versus herbal-only Ayurvedic preparations within the same sampling frame; single-arm case series and individual case reports without a comparator group will be eligible for proportional or qualitative phenotype synthesis as appropriate to study design.

Study designs to be included Because clinical safety evidence for traditional medicines spans experimental trials, hospital toxicology registries, rare syndrome case reports, chemical market surveillance, and spontaneous pharmacovigilance systems, eligible studies will be organized prospectively into four non-overlapping design tiers that will never be pooled indiscriminately across tiers: Tier 1 will include randomized controlled trials (parallel-group double-blind, investigator-blind, and crossover trials, with crossover designs isolated from parallel-group primary sensitivity analyses) reporting extractable arm-level a

Eligibility criteria Studies will be included in the primary synthesis only if they report original human clinical adverse-event data, arm-level trial safety denominators, unselected or patient-linked Ayurvedic product laboratory forensics, national Ayurvedic pharmacovigilance data, or official statutory regulatory warnings meeting the population, exposure, and design criteria specified above. Narrative reviews, editorials without primary cases, duplicate publications, preclinical studies, and clinical trials failing to report arm-level safety denominators will be excluded. Multi-etiology complementary and alternative medicine registries that aggregate Ayurvedic products with non-Ayurvedic supplements, homeopathy, or conventional hepatotoxins without reporting a separate Ayurvedic outcome denominator, as well as mercurial Siddha or unspecified traditional Indian medicine series where Ayurvedic provenance is unconfirmed, will be segregated a priori from all primary Ayurvedic meta-analyses and reported solely as explicitly labelled external benchmarks or contextual comparisons. Potential patient overlap across multicenter registries, single-centre series from overlapping calendar windows, and published literature compilations will be audited systematically by cross-checking participating hospital lists, recruitment dates, and individual case citations; literature-compiled case reviews overlapping primary reports will be excluded from de-novo pooling with constituent series.

Information sources Planned information sources comprise MEDLINE (via PubMed), PubMed Central (PMC) full-text biomedical archives (capturing peer-reviewed Indian medical and AYUSH journals not indexed in MEDLINE), the Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews, ClinicalTrials.gov, and the Clinical Trials Registry–India (CTRI). Pharmacovigilance and grey-literature regulatory sources will include published World Health Organization VigiBase pharmacovigilance analyses, Indian National Pharmacovigilance Programme for Ayurveda, Siddha, Unani and Homoeopathy (NPvCC-AIIA and IPC NCC-PvPI) publications, United States Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report (CDC MMWR) outbreak archives, United States Food and Drug Administration Import Alerts (including Import Alert 66-41), Australian Therapeutic Goods Administration (TGA) safety advisories, United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) Drug Safety Updates, and European national food and medicines agency risk assessments (Danish Veterinary and Food Administration/DTU, German Federal Institute for Risk Assessment [BfR], Dutch National Institute for Public Health and the Environment [RIVM], and French Agency for Food, Environmental and Occupational Health & Safety [ANSES]), alongside backward citation tracking of all included full texts. If institutional subscription access to Embase is unavailable during search execution, mitigation via PMC full-text indexing, CENTRAL trial harvesting, and reference-list screening will be implemented and transparently reported as a methodological limitation.

Main outcome(s) Pre-specified primary outcomes are tailored to each non-overlapping evidence tier so that experimental trial denominators and hospital case-series denominators remain strictly segregated. In Tier 2 Ayurveda-defined herb-induced liver injury cohorts, the co-primary outcomes are overall case-fatality or liver transplantation rate (deaths or transplants divided by total Ayurveda-defined cases over the study follow-up window) and within-study patient-level mortality stratified by the presence versus absence of underlying chronic liver disease or cirrhosis. In Tier 4 unselected retail and online market surveys, the primary outcome is the prevalence of

Philips et al. INPLASY protocol 2026110100. doi:10.37766/inplasy2026.11.0100 Downloaded from https://inplasy.com/inplasy-2026-11-0100/

Ayurvedic products exceeding established regulatory permissible limits or reference thresholds for lead, mercury, or arsenic on inductively coupled plasma mass spectrometry or X-ray fluorescence testing, alongside within-survey comparisons of Rasa Shastra (Ayurvedic herbo-mineral) versus non-Rasa Shastra formulations. In Tier 1 randomized controlled trials, the co-primary safety outcomes are treatment discontinuations specifically attributed to adverse events (intention-to-treat arm denominators) and luminal gastrointestinal adverse-event incidence across placebo-controlled parallel trials.

Quality assessment / Risk of bias analysis Methodological risk of bias in individual studies will be appraised separately from overall certainty of evidence using design-specific validated instruments. Tier 1 randomized controlled trials will be evaluated across five domains using the revised Cochrane Risk of Bias 2 (RoB 2) tool supplemented by CONSORT Harms criteria, specifically distinguishing trials performing active scheduled biochemical hepatic and renal laboratory panels from trials relying solely on passive participant symptom self-reporting, and flagging period or carryover bias in crossover designs. Comparative Tier 2 observational cohorts will be assessed using the Newcastle–Ottawa Scale (0 to 9 stars), while single-arm clinical case series and analytical product surveys will be appraised using the Joanna Briggs Institute (JBI) 10-item critical appraisal checklist, alongside recording whether clinical causality was adjudicated via updated RUCAM, WHO-UMC, or Naranjo scales. Certainty of evidence across each pooled quantitative outcome will be graded separately using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework across risk of bias, inconsistency, indirectness, imprecision, and publication bias, recognizing observational prognosis and prevalence baselines appropriately and never conflating study-level appraisal scores with body-of-evidence certainty.

Strategy of data synthesis Quantitative synthesis will be conducted strictly within homogeneous design and exposure tiers in Python using validated numerical optimization and quadrature routines. For single-group clinical and market proportions, we will report exact pooled raw fractions with Clopper–Pearson 95% confidence intervals alongside a primary one-stage binomial-normal random-intercept generalized linear mixed model (GLMM) estimated via 35-node mode-centered adaptive Gauss–Hermite quadrature around each study's conditional posterior mode and verified against adaptive Gauss–Kronrod integration to avoid fixed-grid quadrature failure in large samples; Freeman–Tukey double-arcsine random-effects restricted maximum likelihood (REML) proportions back-transformed via Miller's harmonic mean will be computed as a secondary estimator and flagged wherever small-sample back-transformation overshoots raw fractions. For pairwise controlled-trial harms and within-study patient-level chronic liver disease mortality comparisons, model selection will follow Cochrane Handbook principles rather than heterogeneity p-values alone: heterogeneous or unbalanced trial syntheses will be led by inverse-variance random-effects REML risk ratios (Haldane–Anscombe 0.5 continuity correction for single-zero cells) accompanied by Hartung–Knapp t-distribution confidence intervals, 95% prediction intervals, Sweeting's treatment-arm continuity-corrected odds ratios (accounting for unequal allocation ratios such as 5:1 multi-arm randomization), all-trial REML risk differences (incorporating double-zero trials), and fixed-effect Peto one-step odds ratios reserved as primary only for sparse, balanced, homogeneous contrasts. Small-study asymmetry tests (Egger, Begg, Peters) and contour-enhanced funnel plots will be generated but interpreted strictly as underpowered and uninformative whenever fewer than 10 non-zero trials contribute weight. Unconditional exact two-sided Fisher power curves will be computed across observed trial sample sizes relative to population herb-induced liver injury benchmarks.

Subgroup analysis Pre-specified subgroup analyses will evaluate biologically and methodologically plausible effect modifiers where three or more studies are available. Within primary Ayurveda-defined herb-induced liver injury cohorts, case-fatality will be stratified by geographic setting (Indian hepatology referral cohorts versus Western drug-induced liver injury registries) and, at the individual patient level within single-herb cohorts, by presence versus absence of pre-existing chronic liver disease or cirrhosis tested via stratified Peto odds ratios and exact Fisher tests. Within analytical market surveys, heavy-metal exceedance will be compared directly between classical herbo-mineral preparations and herbal-only formulations within the same survey sampling frame. As an explicitly labelled secondary ecological analysis across broader mixed-complementary and alternative medicines and external benchmark strata, random-effects meta-regression and dichotomized subgroup contrasts (=50% baseline cirrhosis or acute-on-chronic liver failure) will be evaluated using between-group Cochran Q interaction tests and framed strictly as

Philips et al. INPLASY protocol 2026110100. doi:10.37766/inplasy2026.11.0100 Downloaded from https://inplasy.com/inplasy-2026-11-0100/

study-level ecological associations rather than individual causal proof.

Sensitivity analysis Pre-specified robustness checks will test key methodological and analytical assumptions independently of subgroup hypotheses: first, in controlled-trial adverse-event discontinuation and gastrointestinal syntheses, excluding crossover trials to restrict pooling to parallel-group double-blind randomized controlled trials, further restricting to placebo-controlled parallel trials (excluding active standard drug comparators), when trials report symptom-level tables without a composite patient denominator, and contrasting intention-to-treat against per-protocol denominators. Second, performing single-study leave-one-out omissions across pooled trial and observational models. Third, performing leave-one-centre-out sensitivity analyses omitting cohorts originating from the corresponding author's tertiary hepatology centre to test institutional referral influence; fourth, omitting potentially overlapping municipal series when national multicenter registries span overlapping calendar periods. Fifth, comparing exact adaptive-quadrature GLMM against Freeman–Tukey double-arcsine REML back-transformation; and finally, excluding non-Ayurvedic external benchmark registries from secondary ecological meta-regression models.

Country(ies) involved India.

Other relevant information Current review status: Ongoing.

Keywords Ayurveda; herb-induced liver injury; CAM; HILI; DILI; traditional medicine; cirrhosis; ACLF.

Contributions of each author

Author 1 - Cyriac Philips.
Email: abbyphilips@theliverinst.in
ORCID: 0000-0002-9587-336X
Author 2 - Tharun Oommen.
Author 3 - Arif Theruvath.
Author 4 - Aryalakshmi Sreemohan.
Author 5 - Ambily Baby.
Author 6 - Chandrasekhar Ramesh.
Author 7 - Chetan Kalal.

Philips et al. INPLASY protocol 2026110100. doi:10.37766/inplasy2026.11.0100 Downloaded from https://inplasy.com/inplasy-2026-11-0100/