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A Protocol for Systematic Review and Metanalysis of Oral Turmeric and Curcumin Supplementation and Herb-induced Liver Injury

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ADMINISTRATIVE INFORMATION

Support - No external financial support. This planned systematic review and meta-analysis receives no external grants, contracts, pharmaceutical funding, or dietary supplement industry sponsorship. Non-financial institutional library and computing access will be provided by The Liver Institute, Rajagiri Hospital, Kochi, India. No commercial entity or external sponsor has participated in protocol design or will participate in study selection, data synthesis, or publication.

Review stage at the time of initial registration - Preliminary searches.

Conflicts of interest - None declared (financial or commercial). The corresponding author declares no financial, consulting, speaker, equity, or patent relationships with supplement manufacturers or pharmaceutical companies. Academic disclosure: Dr. Cyriac Abby Philips has authored peer-reviewed studies on herbal and complementary medicine hepatotoxicity. Should any record co-authored by a review team member be retrieved during formal screening, eligibility adjudication, extraction, and risk-of-bias scoring will follow pre-locked operational criteria and be verified independently by a non-authoring investigator.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 November 2026 and was last updated on 23 November 2026.

INTRODUCTION

Review question / Objective Among human individuals exposed to oral turmeric (Curcuma longa L.) or concentrated curcumin dietary supplements, with or without bioavailability enhancers such as piperine or lipid, phytosomal, micellar, or nanoparticulate delivery matrices (Population / Exposure), compared across bioavailability-enhanced versus unenhanced oral formulations, survey-weighted population supplement users, and empirical genotyped biobank and drug/herb-induced liver injury (DILI) comparator cohorts (Comparator), what are the biochemical liver injury patterns, clinical severity, autoimmune-like hepatitis features, clinical recovery versus acute liver failure (ALF) outcomes, and host pharmacogenomic susceptibility associations (Outcomes)?

-Objective 1 (Phenotypic Heterogeneity): To estimate descriptive study-level proportions and cross-cohort heterogeneity (95% prediction intervals) of hepatocellular, mixed, and cholestatic liver injury across deduplicated clinical HILI series,

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incorporating structured sensitivity bounds when eligible cohorts report qualitative injury-pattern predominance without main-text numeric R-ratios.
-Objective 2 (Formulation & Confounding): To evaluate published case-level latency, peak liver biochemistries, positive rechallenge episodes, and confounding from hepatotoxic co-medications or multi-botanical ingredients across piperine/bioenhanced versus unenhanced oral preparations.
-Objective 3 (Empirical Pharmacogenomics): To benchmark host HLA-B*35:01 allele carriage in genotyped turmeric HILI cases exclusively against published empirical genotyped biobank controls and empirical drug/herbal DILI cohorts.
-Objective 4 (RCT Surveillance Reconciliation): To audit primary adverse-event ascertainment in short-term RCT meta-analyses and model conditional binomial sample-size ceilings against rare idiosyncratic HILI incidence.
-Objective 5 (Spontaneous Vigilance & Product Integrity): To synthesize registry-specific spontaneous pharmacovigilance notifications alongside commercial supplement label and chemical adulteration audits without pooling non-commensurable surveillance units.

Rationale Oral turmeric (Curcuma longa L.) and concentrated curcuminoid supplements are among the most widely consumed botanical products globally. Published dose–response meta-analyses of short-term randomized controlled trials (RCTs) report modest mean reductions in serum aminotransferases and describe favorable short-term tolerability. Conversely, national phytovigilance outbreak investigations in Italy, prospective multicenter DILI registry cohorts in the United States, multicenter hepatic biopsy series [15], and independent safety evaluations by the United States Pharmacopeia (USP), Health Canada, the UK Committee on Toxicity, the Australian TGA, French ANSES, and NIH LiverTox document acute idiosyncratic hepatitis, drug-induced autoimmune-like hepatitis (DI-ALH), and rare fulminant liver failure.
Existing reviews remain narrative or methodologically vulnerable to four biases: (i) cross-publication double-counting where regional subseries or monograph vignettes overlap with national outbreak clusters or multicenter registries; (ii) unstated omission of cohorts describing qualitative cholestatic predominance without main-text numeric R-ratio tables; (iii) unadjusted conflation of piperine bioenhancement with concomitant hepatotoxic medications and multi-botanical formulas; and (iv) reliance on theoretical Hardy–Weinberg genetic denominators rather than empirical genotyped DILI comparator cohorts.

Condition being studied Idiosyncratic herb-induced liver injury (HILI) / botanical drug-induced liver injury (DILI) associated with oral Curcuma longa L. or curcuminoid supplements in humans, defined per international CIOMS/RUCAM, EASL (2019) [22], and ACG (2021) [23] clinical consensus criteria:
-Acute HILI Biochemical Threshold: Serum ALT ≥ 5× upper limit of normal (ULN), ALP ≥ 2× ULN, or ALT ≥ 3× ULN with total bilirubin > 2× ULN (or biopsy-proven acute drug/herb-induced hepatitis) after exclusion of competing viral, biliary, vascular, autoimmune, and metabolic causes.
-Biochemical Injury Pattern (R-ratio): Computed at initial/peak presentation as R = (ALT / ULN_ALT) ÷ (ALP / ULN_ALP) (substituting AST only when ALT is unreported per CIOMS rules), classifying cases as hepatocellular (R ≥ 5), mixed (2 < R 3× ULN plus total bilirubin > 2× ULN without cholestatic predominance; ALF defined by coagulopathy (INR ≥ 1.5) and hepatic encephalopathy without pre-existing cirrhosis, or progression to liver transplantation or liver-related death.

METHODS

Search strategy Literature searches will follow PRISMA-S reporting standards from database inception through the formal search cut-off date (planned November–December 2026) with zero language or publication-year limits. Boolean search syntax combines controlled vocabulary (MeSH / Emtree) and free-text terms for turmeric/curcuminoids with hepatotoxicity, autoimmune hepatitis, liver failure, pharmacogenomic, and systematic-review descriptors, supplemented by backward and forward citation chasing.
MEDLINE via PubMed - ("Curcuma"[Mesh] OR "Curcumin"[Mesh] OR "Curcuma longa"[tiab] OR turmeric[tiab] OR curcumin*[tiab] OR diferuloylmethane[tiab] OR curcuma[tiab]) AND ("Chemical and Drug Induced Liver Injury"[Mesh] OR "Liver Failure, Acute"[Mesh] OR "Hepatitis, Autoimmune"[Mesh] OR "liver injury"[tiab] OR hepatotox*[tiab] OR "drug-induced liver injury"[tiab] OR DILI[tiab] OR "herb-induced liver injury"[tiab] OR HILI[tiab] OR "acute hepatitis"[tiab] OR "cholestatic hepatitis"[tiab] OR "autoimmune hepatitis"[tiab] OR "liver failure"[tiab] OR jaundice[tiab] OR "HLA-B*35:01"[tiab] OR ("liver enzymes"[tiab] AND ("systematic review"[pt] OR "meta-analysis"[pt] OR meta-analys*[tiab])))
PubMed Central (PMC) & Ovid / BPS - ("Curcuma longa" OR turmeric OR curcumin OR curcuminoids) AND ("herb-induced liver injury" OR "drug-induced liver injury" OR hepatotoxicity OR "acute liver failure" OR "autoimmune-like

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hepatitis") AND (RUCAM OR DILIN OR piperine OR "black pepper" OR "HLA-B*35:01" OR biopsy)
Embase / Scopus & Cochrane CENTRAL - TITLE-ABS-KEY(("Curcuma longa" OR turmeric OR curcumin OR curcuminoid*) AND ("liver injury" OR hepatotoxic* OR "acute hepatitis" OR "liver failure" OR DILI OR HILI OR phytovigilance OR nutrivigilance OR piperine OR "meta-analysis"))
Hepatotoxicity & Pharmacopeial Compendia - Latest published editions at search execution - NIH/NIDDK LiverTox 'Turmeric' monograph (NBK548561), United States Pharmacopeia (USP) Dietary Supplements Compendium safety reviews, and European Medicines Agency (EMA) HMPC herbal monographs.
Spontaneous PV & Regulatory Portals - Ingredient queries ('Curcuma longa', 'Turmeric', 'Curcumin', 'Curcuminoids') mapped to MedDRA SOC 'Hepatobiliary disorders' across WHO VigiBase/ VigiAccess, US FDA CFSAN CAERS, Australian TGA DAEN, French ANSES Nutrivigilance, Italian VigiErbe/ISS, New Zealand Medsafe SMARS, Health Canada SSR, UK COT, NIH DSLD, and US CDC NHANES.

Participant or population Human individuals (adults ≥ 18 years, and pediatric or adolescent cases if documented in clinical series or pharmacovigilance portals, stratified by age group where reported) exposed to oral turmeric or curcuminoid preparations across clinical HILI cohorts and case reports, nationally representative health surveys, published RCT syntheses, and spontaneous adverse-event registries. Non-human animal, in vitro, and in silico studies will be excluded.

Intervention Oral ingestion of any preparation containing Curcuma longa L. rhizome or concentrated curcuminoids (curcumin, demethoxycurcumin, bisdemethoxycurcumin), classified into: (a) unenhanced culinary/powdered rhizome capsules, tablets, or teas; (b) standardized curcuminoid extracts; (c) bioavailability-enhanced oral formulations incorporating piperine (Piper nigrum / BioPerine) or lipid, phytosomal, micellar, liposomal, colloidal, or nanoparticulate matrices; and (d) multi-botanical dietary supplements containing Curcuma longa (coded a priori with a binary multi-herb confounder indicator). Compounded intravenous/parenteral curcumin infusions (such as PEG-40 castor oil / diethylene glycol vehicle reactions), purely topical products, and non-Curcuma longa species lacking C. longa will be excluded.

Comparator -Within Tier 3 Published Case-Level Data: Bioavailability-enhanced oral formulations (piperine or lipid/micellar/nanoparticle delivery) versus unenhanced oral turmeric/curcuminoid preparations. A priori confounder rule: whenever an index episode involves hepatotoxic co-medications (e.g., NSAIDs) and a subsequent unconfounded monotherapy rechallenge episode is reported in the primary publication, laboratory values from the unconfounded monotherapy episode will be prioritized, paired with strict sensitivity restriction to cases free of concomitant drugs and multi-herb products.
-Population Demographic Benchmark (Tier 2): Survey-weighted national adult supplement consumer distributions (e.g., US NHANES) will provide descriptive demographic context without applying unweighted 2×2 Fisher tests to survey-weighted percentages.
-Host Pharmacogenomic Comparators (Tier 3 Genetic Module): Genotyped turmeric HILI HLA-B*35:01 carrier counts will be compared strictly against published empirical genotyped biobank controls (e.g., eMERGE) and published empirical DILI cohorts (e.g., US DILIN conventional drug DILI, non-polyphenol HDS DILI, green tea extract HILI, and Garcinia cambogia HILI). Synthetic Hardy–Weinberg equilibrium control denominators will not be constructed.
-Controlled Trial Syntheses (Tier 1): Placebo, lifestyle, or standard-of-care control groups within published RCT meta-analyses.

Study designs to be included This evidence synthesis comprises four hierarchical analytical tiers evaluating oral turmeric and curcuminoid hepatotoxicity: Tier 1 (Controlled Trial Syntheses) evaluates systematic reviews, dose–response meta-analyses, and umbrella reviews of human RCTs (excluding case reports) comparing oral turmeric/curcuminoids versus control in adults to generate pooled transaminase WMDs, hepatic AE reporting audits, conditional Clopper–Pearson upper risk bounds, and binomial sample-size ceilings; Tier 2 (Population, Label & Chemical Audits) analyzes nationally representative health surveys, label/dosage.

Eligibility criteria Operational Inclusion & Exclusion Rules: Studies must satisfy Tier 1–4 design definitions with documented oral turmeric/ curcuminoid exposure; Tier 3 clinical records require acute liver injury with structured causality adjudication (RUCAM, DILIN expert panel, WHO-UMC, Naranjo, or national phytovigilance panel) and diagnostic exclusion of competing acute hepatobiliary etiologies. Preclinical models, parenteral infusions, editorials without primary numerators/denominators, and duplicate patient reports will be excluded.

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Prespecified 3-Rule Cross-Registry Deduplication Protocol: (1) Regional subcohorts nested within national outbreak series matching on surveillance network, calendar window, demographics, and product brands (such as regional Italian subseries nested within national Italian phytovigilance investigations) will be counted once under the parent national cohort denominator for study-level totals, retaining only unique granular patient laboratories in the case-level sheet with an explicit nesting flag; (2) Detailed patient vignettes reproduced inside clinical monographs (e.g., NIH LiverTox) originating from an included multicenter registry cohort will be linked to the parent cohort ID without study-level double-counting; and (3) Conference abstracts superseded by full-length peer-reviewed articles from the same clinical team matching on patient demographics, product, and biochemical trajectory will be merged into a single patient record.

Information sources Information sources comprise MEDLINE (PubMed), PubMed Central, Embase/Scopus, Cochrane CENTRAL/CDSR, Ovid/BPS archives, Google Scholar (top 200 records), NIH LiverTox, USP safety compendia, EMA herbal monographs, six spontaneous pharmacovigilance portals (WHO VigiBase/ VigiAccess, US FDA CAERS, Australian TGA DAEN, French ANSES, Italian VigiErbe/ISS, New Zealand Medsafe SMARS), regulatory dossiers (Health Canada, UK COT), NIH DSLD, US NHANES, and citation chasing. Every extracted case record will carry an explicit provenance code (Primary full-text article, Primary published conference abstract, or Secondary pharmacopeial/ monograph table when subscription paywalls prevent full-text access) to permit dedicated provenance sensitivity analyses.

Main outcome(s) The primary outcomes encompass biochemical injury patterns, clinical recovery, and severe hepatic endpoints. At index presentation or peak acute evaluation, biochemical injury will be classified via the R-ratio—calculated as (ALT/ULN) divided by (ALP/ULN)—into hepatocellular ($R \geq 5$), mixed (2 less than R less than 5), or cholestatic ($R \leq 2$) phenotypes, analyzed using descriptive Freeman–Tukey random-effects models (DL/REML/HKSJ) with 95% prediction intervals and sensitivity bounds (~30%, 50%, and ~70%) for qualitative-only cohorts. Clinical recovery, assessed from product cessation through 6–12 months of follow-up, will measure documented biochemical normalization alongside unresolved or missing follow-up counts, estimated via dual-denominator proportions across both complete-follow-up and conservative intention-to-follow cohorts. Finally, acute liver failure (INR ≥ 1.5 with encephalopathy), emergency liver transplantation, and liver-related or all-cause mortality will be evaluated from the acute episode through final follow-up using descriptive cohort-stratified reporting (remaining unpooled across incompatible selection frames) and an events-per-variable (EPV ≥ 10) threshold for regression modeling.

Additional outcome(s) Secondary outcomes evaluate formulation profiles, autoimmune-like features, genetic susceptibility, and trial or pharmacovigilance surveillance. From pre-onset exposure through peak illness, peak liver biochemistries (ALT, AST, ALP, total bilirubin, INR), latency, recovery duration, RUCAM scores, and positive rechallenge will be summarized using complete-case medians (IQR), 10,000-resample bootstrap 95% confidence intervals, Mann–Whitney U tests, and Hodges–Lehmann shifts (prioritizing rechallenge cases). During the acute episode, drug-induced autoimmune-like hepatitis (ANA/ASMA seropositivity, corticosteroid therapy), inpatient hospitalization, and female sex proportions will be synthesized via Freeman–Tukey random-effects models with 95% prediction intervals and contrasted against survey-weighted population supplement users. Time-invariant germline HLA-B*35:01 carrier status in genotyped turmeric herb-induced liver injury patients will be compared against empirical biobank and DILI cohorts using two-sided exact Fisher tests and Woolf/Haldane 95% confidence intervals. Lastly, randomized controlled trial adverse event ascertainment quality and sample sizes will be evaluated over trial durations via conditional binomial curves, alongside an unpooled, registry-stratified descriptive synthesis of cumulative spontaneous hepatobiliary adverse drug reaction counts.

Data management Search exports (RIS/NBIB) will undergo automated identifier deduplication (DOI, PMID, normalized title) followed by manual verification and two-stage screening (title/abstract then full text), logging all full-text exclusions with exact reasons per PRISMA 2020. Standardized relational extraction sheets will capture study metadata, deduplication links, provenance tags, product composition, concomitant medications, viral/biliary exclusion workup, peak laboratory values, causality scores, genotypes, and follow-up status.

Qualitative text descriptions in source reports (e.g., 'normal ALP' or 'normal INR') will be coded strictly as missing (NR) in continuous numeric analyses rather than imputed as synthetic normal midpoints.

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Broad culinary intake ranges lacking a point estimate will be preserved as text ranges and excluded from continuous mg/day dose correlations. Serum bilirubin reported in µmol/L will be converted via exact molecular stoichiometry (÷ 17.104). Per INPLASY v.12 Section 07, deterministic Python 3 verification scripts will support data auditing under 100% human investigator verification.

Quality assessment / Risk of bias analysis Part A — Study-Level Risk-of-Bias Appraisal: Internal validity will be assessed using design-specific validated tools: (1) the Joanna Briggs Institute (JBI) 8-item Critical Appraisal Checklist for Case Reports for individual HILI case reports and 2-case series; (2) the JBI 10-item Critical Appraisal Checklist for Case Series for clinical HILI cohorts (evaluating consecutive/complete inclusion and follow-up completeness); (3) the JBI 8-item Analytical Cross-Sectional Checklist for Tier 2 surveys and product audits; and (4) AMSTAR-2 (16 items, 7 critical domains) for Tier 1 RCT systematic reviews.
Part B — Outcome-Level Certainty of Evidence (GRADE): Cumulative certainty across primary clinical, formulation, and pharmacogenomic outcomes will be rated formally as High, Moderate, Low, or Very Low using the GRADE framework across risk of bias, inconsistency (I^2 and 95% prediction interval width), indirectness, imprecision, and publication/selective-reporting bias.

Strategy of data synthesis All quantitative models, non-pooling boundaries, and rare-event statistical guardrails are locked a priori. Where ≥ 2 non-overlapping Tier 3 clinical streams report commensurable numerator/denominator proportions, Freeman–Tukey double-arcsine random-effects models (DerSimonian–Laird and REML estimators with truncated Hartung–Knapp–Sidik–Jonkman t-intervals and Barendregt–Miller harmonic-mean back-transformation) will be reported strictly as descriptive summaries of selected published clinical series rather than population incidence estimates, leading with 95% prediction intervals ($df = k - 2$ for $k \geq 3$). Per Cochrane guidance, Egger and Begg–Mazumdar funnel-asymmetry tests require $k \geq 10$ independent studies and will be omitted whenever $k < 10$.
Rare-Event Prognostic Gate (EPV ≥ 10) & Surveillance Separation: Logistic or Firth penalized regression, ROC curves, and Youden cutoffs for fatal ALF / transplantation will ONLY be fitted if ≥ 10 unconfounded events are identified; if < 10 events occur, regression and data-derived cutoffs will be omitted in favor of structured individual case/confounder profiling anchored to EASL (2019) and ACG (2021) ALF referral criteria. Tier 4 spontaneous pharmacovigilance registries mix distinct reporting units and surveillance horizons and will be synthesized descriptively without cross-registry proportional pooling or small-k meta-regression.

Subgroup analysis -Oral Bioavailability Enhancement (Primary Biological Subgroup): Published case-level records with documented formulation type will be compared across piperine/lipid/micellar/nanoparticle-enhanced versus unenhanced oral preparations using two-sided Mann–Whitney U tests, Hodges–Lehmann median shifts, and rank-biserial correlations across peak ALT, AST, ALP, total bilirubin, INR, latency, and recovery days (prioritizing unconfounded monotherapy rechallenge labs where index episodes involved hepatotoxic co-medications, and noting algebraic coupling between ALT and R-ratio).
-Surveillance & Geographic Ascertainment Setting: Contrasting prospective hepatology registries and biopsy series against national spontaneous phytovigilance outbreak investigations to evaluate geographic batch, formulation, or ascertainment differences.
-Host Genotyping Context: Stratifying registry-enrolled versus standalone case-report HLA-B*35:01 data alongside empirical green tea and Garcinia cambogia DILI comparator cohorts.

Sensitivity analysis -Qualitative-Cohort R-Ratio Sensitivity Bounds: Testing ~30%, 50%, and ~70% hepatocellular allocations alongside complete-case numeric R-ratio streams whenever an eligible cohort reports qualitative injury-pattern predominance without main-text numeric R-ratio counts.
-Complete-Follow-Up vs. Intention-to-Follow Outcome Bounds: Reporting clinical recovery and unresolved proportions across both known-outcome denominators and total enrolled cohort denominators.
-Unconfounded Monotherapy & Non-Nested Case Restriction: Repeating formulation comparisons after (a) excluding registry/nested vignettes, (b) excluding multi-botanical supplements, and (c) restricting strictly to patients with zero concomitant hepatotoxic medications and zero multi-herb confounders.
-Provenance, Study Quality & Leave-One-Out Checks: Repeating case-level and study-level analyses restricted to primary full-text articles, excluding records with high JBI risk of bias, excluding serving-size dose approximations, and running jackknife (k – 1) stream omission.

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Language restriction This registration protocol and the resulting manuscript are prepared in English. No language restrictions will be applied during database searching or study selection; eligible reports in Italian, French, Spanish, German,.

Country(ies) involved India, United States, United Arab Emirates, Saudi Arabia.

Other relevant information Prior Registry Scoping Audit: Scoping searches prior to submission identified short-term RCT efficacy meta-analyses on transaminases and narrative regulatory reviews, but no prospective protocol integrating 4-tier non-overlapping stratification, 3-rule cross-registry case deduplication, qualitative-cohort sensitivity bounds, confounder-adjusted formulation analysis, and empirical DILIN/biobank HLA-B*35:01 benchmarking. Amendment Policy: Any protocol amendment required during review execution will be logged with date and rationale via INPLASY's formal amendment process and reported transparently in the final publication.

Keywords Curcuma longa; herb-induced liver injury; drug-induced liver injury; piperine; herb induced liver injury; HILI; DILI.

Contributions of each author

Author 1 - Cyriac Philips - Cyriac Abby Philips (CAP) conceptualized and designed the systematic review and meta-analysis, developed the clinical research question and eligibility criteria, supervised the overall project execution, resolved screening and data extraction disagreements, conducted clinical causality and hepatotoxicity interpretation, and drafted and critically revised the protocol.
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Author 5 - Shinsmon Jose - Shinsmon Jose (SJ) designed the statistical analysis plan, performed quantitative data synthesis, meta-analytic pooling, heterogeneity and sensitivity analyses, and evaluated certainty of evidence.
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