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Plant-derived (herbal) exosome-like nanoparticles and nanovesicles for inflammatory bowel disease: a combined scientometric mapping and modality-stratified meta-analysis of experimental evidence

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

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 26 October 2026 and was last updated on 26 October 2026.

INTRODUCTION

Review question / Objective Primary review question: In animal models of inflammatory bowel disease (IBD), do orally administered plant-derived exosome-like nanoparticles/nanovesicles (ELNs/PDEVs) and carrier-free herbal self-assembled nanoparticles improve disease activity and mechanistic endpoints compared with untreated or vehicle controls? And do engineered formulations (drug-loaded, hybridized, hydrogel-composited) truly enhance efficacy relative to native plant vesicles?

Objectives:

1.To quantitatively synthesize all experimental evidence (January 2013 – October 2026) on plant-derived (particularly herbal) vesicular nanoparticles for IBD, covering ulcerative colitis (UC), Crohn's disease (CD), colitis-associated cancer (CAC) and gut–brain comorbid outcomes;

2.To pre-specify and test three hypotheses:

○H1 (engineering-gain hypothesis): engineered/loaded plant vesicles (drug-loaded, hydrogel-

composite) are non-inferior or superior to native vesicles on disease-activity and inflammatory endpoints;

○H2 (source–evidence-strength hypothesis): studies using traditional herbal-medicine sources show systematically different (larger) effect sizes and higher risk of bias than studies using edible fruit/vegetable sources;

○H3 (hotspot–evidence-mismatch hypothesis): scientometrically identified research hotspots are discordant with pooled effect strength and GRADE certainty, to be visualized as a hotspot–evidence mismatch matrix defining the field's research agenda;

3.To map the evidence landscape with an integrated scientometric module (dual sources: Web of Science Core Collection as primary, OpenAlex as supplementary) and to identify translational gaps (CD, CAC, safety/CMC reporting, manufacturing–efficacy disconnect, gray literature).

Condition being studied Inflammatory bowel disease (IBD), including: (i) ulcerative colitis (UC) — chemically induced colitis models (dextran sulfate sodium [DSS], trinitrobenzene sulfonic acid [TNBS]); (ii) Crohn's disease (CD) — including intestinal fibrosis models; (iii) colitis-associated cancer (CAC) — AOM/DSS models; (iv) IBD comorbidity models (high-fat-diet-aggravated colitis; IBD-associated depression-like behaviour / gut-brain axis models); and (v) naturally occurring canine IBD (clinical veterinary evidence, synthesized separately).

METHODS

Participant or population Experimental animals with induced or spontaneous IBD/colitis: mice (all strains, e.g., C57BL/6, BALB/c), rats, and dogs (naturally occurring IBD — clinical case series, handled through a separate descriptive channel and not pooled with animal-model data). Human clinical trials are not expected in this literature domain; if any are identified during the update search, they will be reported descriptively and flagged in the evidence map. Cell-only (in vitro) studies are excluded.

Intervention Orally (or locally) administered vesicular/nanoparticulate preparations derived from plants, medicinal herbs, edible fungi, algae, or traditional decoctions, stratified into five pre-defined intervention modalities:

- A1 — Native plant vesicles: exosome-like nanoparticles / extracellular vesicles isolated directly from plant materials (juice, tissue, decoction supernatant) without synthetic modification;
- A2 — Engineered/drug-loaded plant vesicles: plant vesicles loaded with drugs (small molecules, nucleic acids, biologics such as infliximab), surface-modified, or hybridized (e.g., with bacterial outer-membrane vesicles or probiotics), including gene-editing-grade lipid nanoparticle platforms built on plant-derived lipids;
- A3 — Hydrogel/composite delivery systems: plant vesicles incorporated into hydrogel or composite matrices for oral/colonic delivery;
- A4 — Carrier-free herbal self-assembled nanoparticles: decoction-derived nanoparticles, herb-component co-assemblies (e.g., berberine-glycyrrhizic acid), and natural-phospholipid phytosomes (flagged as boundary form);
- A5 — Scale-up manufacturing studies: only if containing in vivo efficacy data.

Comparator Any of: (i) untreated/model-only control; (ii) vehicle/sham control (saline, PBS, buffer); (iii) free (unencapsulated) drug or plant

extract at equivalent dose; (iv) positive-drug control (e.g., 5-aminosalicylic acid, dexamethasone, sulfasalazine); (v) native (unengineered) plant vesicles — when an engineered formulation study includes this arm, it enables within-study head-to-head comparison for H1.

Study designs to be included Systematic review and meta-analysis of animal experimental studies, integrated with a scientometric (bibliometric) mapping module. Reporting will follow PRISMA 2020 (flow and checklist), CAMARADES recommendations for animal systematic reviews, and the PRISMA-ScR-informed transparency for the scientometric module. The protocol is registered before the start of data extraction and statistical synthesis.

Eligibility criteria Inclusion (PICOS):

- P: Animal models of IBD as defined in the "Condition" field;
- I: Plant/herbal/algal/decoction-derived vesicular nanoparticles as defined in the "Intervention" field (modalities A1–A5);
- C: Any comparator listed above;
- O: At least one quantitative efficacy or mechanistic outcome listed in the "Main outcome(s)" field, with extractable mean $\pm$ SD/SEM and group n;
- S: Original experimental studies (journal articles; dissertations via gray channel).

Exclusion (six hard rules with adjudication precedents from full-text screening):

1. Biomimetic vesicles/nanoparticles constructed from synthetic materials (niosomes, poloxamer/Pluronic, Eudragit, synthetic phospholipid-PEG, chitosan-only carriers), even when loading plant-derived compounds;
2. Mammalian- or microorganism-derived extracellular vesicles (unless hybridized with plant vesicles serving as the delivery chassis — flagged A2);
3. Studies without IBD efficacy data: pure manufacturing or isolation-methodology studies, in-vitro-only release kinetics, healthy-animal absorption/stem-cell studies, non-IBD disease models (stress models, non-IBD tumour metabolism);
4. Sister-paper duplication: same research group (author/affiliation overlap) + same intervention + same model + same molecular target → retain the most complete/most recent report only;
5. Non-English full text unavailable; Chinese-language literature is excluded by design (declared as a limitation; its potential directional impact on H2 will be discussed);

6. Duplicate versions of the same study (preprints, errata, conference versions) merged into the primary record.

Information sources Databases: PubMed (via NCBI E-utilities), Europe PMC, OpenAlex, Semantic Scholar (four complementary sources for the meta-analytic corpus); Web of Science Core Collection (primary source for the scientometric module and for cross-validation of corpus coverage).

Temporal window: 1 January 2013 (first foundational study) to one month before submission; a final update search will be re-run at submission and reported in the PRISMA flow.

Language: English only.

Gray literature: dissertations identified via DOI-registered repositories (e.g., RCSI Lenus/OpenAIRE).

Citation screening: backward/forward snowballing of all included studies and of 14 domain reviews.

Search strategy: three-block Boolean strings (plant-source block $\times$ vesicle/nanoparticle block $\times$ IBD block), adapted with database-specific field tags; the plant-source block is expanded iteratively with species identified from included studies. Full strings for all five sources, with run dates and hit counts, will be published in the manuscript supplement. Representative PubMed string:

("plant-derived"[tiab] OR "plant derived"[tiab] OR botanical[tiab] OR herbal[tiab] OR "traditional Chinese medicine"[tiab] OR phyto*[tiab] OR edible[tiab] OR ginger[tiab] OR ginseng[tiab] OR turmeric[tiab] OR garlic[tiab] OR tea[tiab] OR grapefruit[tiab] OR broccoli[tiab] OR aloe[tiab] OR mulberry[tiab] OR "medicine-food homology"[tiab] OR decoction*[tiab]) AND (exosome*[tiab] OR "extracellular vesicle"[tiab] OR "extracellular vesicles"[tiab] OR nanovesicle*[tiab] OR "exosome-like nanoparticle"[tiab] OR "exosome-like nanoparticles"[tiab] OR ELN[tiab] OR ELNs[tiab] OR PDEV*[tiab] OR PDEN*[tiab] OR GELN*[tiab] OR "plant-derived nanoparticle"[tiab] OR "plant-derived nanoparticles"[tiab] OR "self-assembled nanoparticle"[tiab] OR "self-assembled nanoparticles"[tiab]) AND ("inflammatory bowel disease"[tiab] OR IBD[tiab] OR colitis[tiab] OR "ulcerative colitis"[tiab] OR "Crohn disease"[tiab] OR Crohn*[tiab] OR "colitis-associated cancer"[tiab] OR dextran sulfate sodium[tiab] OR DSS[tiab] OR trinitrobenzene sulfonic acid[tiab] OR TNBS[tiab]).

Main outcome(s) Primary outcomes (disease activity): (i) Disease Activity Index (DAI); (ii) body weight change; (iii) colon length.

Secondary outcome families (mechanistic):

- Inflammatory mediators: IL-1 β , IL-6, TNF- α , IL-10, IFN- γ , MPO;
- Oxidative stress: SOD, MDA, GSH;
- Intestinal barrier proteins: ZO-1, occludin, claudin-1;
- Gut microbiota α -diversity: Shannon index, Chao1;
- Histological score.

Descriptive-only domains (pre-specified sparse-domain rule: outcome domains or indications with $k < 3$ studies are NOT pooled, but reported as a structured evidence map): Crohn's disease endpoints, CAC tumour burden, gut-brain behavioural scores, epigenetic markers (e.g., histone lactylation), veterinary clinical outcomes.

Quality assessment / Risk of bias analysis Risk of bias of all included animal studies will be assessed with the SYRCLE RoB tool (10 items covering selection, performance, detection, attrition, reporting and other bias), each item judged as low/high/unclear risk with a one-sentence justification anchored to the full-text location. Gray-literature records (dissertations) receive an additional source-transparency checklist. Certainty of evidence per outcome domain will be graded using GRADE adapted for animal evidence (downgrading for risk of bias, inconsistency, indirectness, imprecision, publication bias). The SYRCLE summary score will additionally serve as a continuous moderator in meta-regression to test H2 (botanical source $\times$ RoB interaction). Assessment is performed by Reviewer 1 and independently verified on a $\geq 20\%$ random sample by Reviewer 2; disagreements resolved by discussion.

Strategy of data synthesis Effect measure: Hedges' g (small-sample-corrected standardized mean difference) with 95% confidence intervals for continuous outcomes; 95% prediction intervals reported alongside pooled estimates.

Model: Random-effects meta-analysis (τ^2 estimated by REML); heterogeneity quantified by I^2 , Cochran's Q and τ^2 .

Unit of analysis: one effect size per outcome per study-arm vs comparator; multi-arm studies share the control group with sample-size splitting per the Cochrane Handbook. For multi-dose arms of the same intervention, the pre-specified primary rule is to use the middle dose (or the arm most comparable to the control regimen); all alternatives enter sensitivity analysis.

Primary stratification (H1 test): intervention modality A1 (native) vs A2 (engineered/loaded) vs A3 (hydrogel-composite) vs A4 (self-assembled), with formal subgroup-difference tests; complemented by an engineering-complexity

gradient meta-regression (simple drug loading < hybridization/surface modification < gene-editing-grade platforms).

Publication bias: funnel plots + Egger's regression test for domains with $k \geq 10$; trim-and-fill as supplementary; a conference-abstract monitoring table serves as an unpublished-evidence stress test.

Data provenance and conversion: outcome values extracted from text/tables preferred; figure-only data digitized with WebPlotDigitizer (double-checked); corresponding authors contacted where feasible (2-week window); SEM converted to SD ($SD = SEM \times \sqrt{n}$); doses harmonized to $\mu\text{g/kg/day}$ with particle-number dosing retained as a separate moderator; every extracted value is tagged by provenance (text/table/figure-digitized/author-provided).

Software: Python 3 (numpy/scipy/statsmodels/matplotlib), with the random-effects implementation cross-validated against R metafor on a 10-study subset.

Scientometric-meta integration (H3): hotspot-evidence mismatch matrix plotting scientometric salience (publication volume $\times$ keyword burst strength) against synthesis strength (pooled effect $\times$ GRADE certainty $\times$ k) per research theme; quadrant membership defines research-agenda priorities. The scientometric module and the meta-analytic module share one de-duplicated corpus registry so that both are computed on identical records.

Subgroup analysis Pre-specified subgroup analyses:

1. Intervention modality: A1 native vs A2 engineered/drug-loaded vs A3 hydrogel-composite vs A4 self-assembled (primary H1 test);
2. Botanical attribute: traditional herbal medicine vs medicine-food homology vs edible fruit/vegetable vs algae/microalgae (H2, with RoB interaction term);
3. Plant organ/source part: root/rhizome vs fruit vs leaf vs flower vs whole herb vs decoction/formula-derived;
4. Isolation process: differential ultracentrifugation vs PEG precipitation vs density gradient vs tangential-flow filtration vs other;
5. Dosing timing: preventive (before/at induction) vs therapeutic (after colitis onset);
6. Model type: DSS (by concentration/duration) vs TNBS vs AOM-DSS (CAC) vs comorbidity models;
7. Animal species: mouse vs rat (pooled separately); canine clinical evidence narratively synthesized, not pooled;
8. Publication era: 2013–2021 vs 2022–2024 vs 2025–2026 (temporal trend comparable to the existing meta-analysis).

Sensitivity analysis Pre-specified sensitivity analyses:

1. Leave-one-out: iterative removal of each study to assess influence on pooled effects;
2. Boundary-form exclusion: re-running after excluding three form-ambiguous studies (inulin-prebiotic-encapsulated Cortex Fraxini EVs [A1/A3 boundary]; resveratrol phytosome [natural-phospholipid complex boundary]; polydopamine-coated modified Pulsatilla decoction [semi-synthetic shell]);
3. Gray-literature inclusion/exclusion: re-running with and without the dissertation channel;
4. Data-provenance restriction: restricting to text/table-sourced values only (excluding figure-digitized data);
5. Multi-dose handling: alternative rules (highest dose / all doses pooled) vs the pre-specified middle-dose rule;
6. Veterinary clinical evidence: confirming that canine case-series data do not enter any pooled estimate (narrative-only channel verification).

Country(ies) involved China.

Keywords plant-derived exosome-like nanoparticles; extracellular vesicles; herbal nanovesicles; inflammatory bowel disease; ulcerative colitis; Crohn's disease; colitis-associated cancer; traditional Chinese medicine; meta-analysis.

Contributions of each author

- Author 1 - Guibin Liao
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