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Efficacy of Cannabis Extracts in Preclinical Models of Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

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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 3 April 2025 and was last updated on 3 April 2025.

INTRODUCTION

Review question / Objective To systematically review and quantitatively analyze preclinical studies investigating the efficacy of cannabis extracts (e.g., CBD, THC) in animal models of inflammatory bowel disease (IBD), focusing on outcomes such as inflammation reduction, histological improvements, and disease severity.

Condition being studied Inflammatory Bowel Disease (IBD), encompassing Crohn's disease and ulcerative colitis, is a chronic inflammatory condition of the gastrointestinal tract. Crohn's disease can affect any part of the digestive system with discontinuous lesions and transmural inflammation, while ulcerative colitis is limited to the colon and rectum, involving only the mucosal layer. Globally, IBD affects approximately 4.9 million people (2019 estimate), with increasing incidence in newly industrialized countries, posing significant challenges to healthcare systems. The management of IBD aims to induce remission, prevent complications, and improve quality of life.

METHODS

Search strategy A comprehensive search will be performed across the following databases: PubMed, Embase, Cochrane and Web of Science, from their inception to March 5, 2025. The search strategy will combine keywords and Medical Subject Headings (MeSH) terms related to cannabis extracts and IBD. Specifically, the search terms will include ('cannabis', 'cannabinoids', 'Cannabidiol', 'Dronabinol', 'inflammatory bowel disease', 'Crohn's disease' and 'ulcerative colitis'. Additionally, the reference lists of included studies and relevant review articles will be manually searched to identify any additional studies.

Participant or population Animal models of inflammatory bowel disease (IBD).

Intervention Cannabis extracts or specific cannabinoids (e.g., cannabidiol [CBD], tetrahydrocannabinol [THC], cannabigerol [CBG], etc.), administered via various routes (e.g., intraperitoneal, oral, rectal).

Comparator Administration of cannabis extracts or isolated cannabinoids, such as cannabidiol (CBD), tetrahydrocannabinol (THC), or their derivatives, delivered via any route (e.g., oral, intraperitoneal, topical).

Study designs to be included Controlled experimental studies in IBD animal models, including randomized or non-randomized designs with an untreated model group as a comparator, evaluating cannabis extracts or cannabinoids' effects on IBD outcomes. Excludes observational, review, or in vitro-only studies.

Eligibility criteria

Inclusion Criteria:

Studies will be included based on the PICOS framework as follows: (1) Population: Animal models of inflammatory bowel disease (IBD), including but not limited to chemically induced (e.g., dextran sulfate sodium [DSS], trinitrobenzene sulfonic acid [TNBS]), regardless of species or strain; (2) Intervention: Administration of cannabis extracts or isolated cannabinoids, such as cannabidiol (CBD), tetrahydrocannabinol (THC), or their derivatives, delivered via any route (e.g., oral, intraperitoneal, topical); (3) Comparator: A control group receiving placebo, vehicle (e.g., saline, ethanol), or no treatment, matched to the intervention arm; (4)Outcome: At least one quantifiable measure of IBD severity or inflammation, including but not limited to disease activity index (DAI), histological inflammation scores, colon length/weight, or levels of inflammatory cytokines (e.g., interleukin-6 [IL-6], interleukin-1β [IL-1β], tumor necrosis factor-α [TNF-α]) assessed in tissue or serum; (5) Study Design: Experimental studies with a controlled design.

Exclusion Criteria:

Studies will be excluded if they:(1) Are not experimental studies (e.g., clinical trials, reviews, commentaries, or case reports);(2)Do not use animal models of inflammatory bowel disease (IBD);(3)Lack an untreated IBD model group as a control.(4)Do not report quantifiable outcomes related to IBD severity or inflammation (e.g., disease activity index [DAI], histological scores, or inflammatory cytokine levels such as IL-6, IL-1β, or TNF-α).(5)Are duplicate publications (i.e., studies reporting identical data from the same experiment, identified by overlapping authorship, sample size, and results).

Information sources A comprehensive search will be conducted in PubMed, Embase, Cochrane, and Web of Science from inception to March 5, 2025, using keywords and MeSH terms such as 'cannabis', 'cannabinoids', 'Cannabidiol', 'Dronabinol', 'inflammatory bowel disease', 'Crohn's disease', and 'ulcerative colitis'. Reference lists of included studies and relevant reviews will be manually searched.

Main outcome(s) Primary outcomes: inflammation reduction (e.g., levels of inflammatory cytokines such as IL-6, IL-10, IL-1β, TNF-α), histological improvements (e.g., histopathology scores), and disease severity (e.g., disease activity index [DAI]). Secondary outcomes: colon length, colon weight/colon length ratio, myeloperoxidase (MPO) activity, and macroscopic score.

Data management Records and data will be managed systematically to ensure transparency and reproducibility. Literature identified from PubMed, Embase, Cochrane, and Web of Science will be imported into EndNote 20 for management. Duplicates will be removed using EndNote's deduplication function. A two-stage screening process will be conducted: titles and abstracts will be screened independently by two reviewers against inclusion criteria, with discrepancies resolved through discussion or a third reviewer. Full-text articles will then be retrieved and assessed similarly.

Data extraction will be performed independently by two reviewers using a standardized, pre-piloted form in Microsoft Excel, capturing study characteristics (e.g., author, year, species), IBD model details, intervention specifics (e.g., cannabinoid type, dosage), control group data, and outcome measures (e.g., DAI, cytokine levels). For data presented in figures, digital software (e.g., Engauge Digitizer) will be used to extract numerical values accurately. Extracted data will be cross-checked for consistency, with disagreements resolved via consensus or a third reviewer's input. All extracted data will be stored in Excel spreadsheets, organized by study and outcome, with backups maintained on a secure, password-protected cloud server (e.g., Google Drive or institutional repository) to prevent data loss.

Risk of bias assessments using SYRCLE's tool will be recorded in a separate Excel sheet, with scores (low, high, unclear) documented for each domain per study. Statistical data for meta-analysis (e.g., means, standard deviations) will be compiled in Review Manager (RevMan 5.4) format, ensuring

compatibility with analysis. Version control will be implemented by timestamping files (e.g., "Data_Extraction_2025-03-10"), and a detailed audit trail of screening, extraction, and analysis steps will be maintained in a Word document. All records and datasets will be securely stored for at least five years post-publication, accessible to the research team, and available upon reasonable request, adhering to PRISMA guidelines and ensuring data integrity throughout the review process.

Quality assessment / Risk of bias analysis The risk of bias in the included animal studies will be systematically evaluated using the SYRCLE's Risk of Bias Tool (Hooijmans et al., 2014), which comprehensively assesses potential biases across critical domains such as selection bias, performance bias, detection bias, attrition bias, reporting bias, and additional sources of bias. This standardized approach ensures rigorous appraisal of methodological quality and internal validity, aligning with best practices for systematic reviews in preclinical research.

Strategy of data synthesis Data will be synthesized quantitatively through meta-analysis to assess the efficacy of cannabis extracts or cannabinoids in preclinical IBD models, using Review Manager (RevMan 5.4). Continuous outcomes (e.g., disease activity index [DAI], histological scores, cytokine levels) will be analyzed with standardized mean differences (SMD) and 95% confidence intervals (CIs), employing a random-effects model to account for expected variability in effect sizes across studies due to differences in models, interventions, or dosages. This model assumes heterogeneity beyond sampling error, providing a conservative estimate of effect.
Forest plots will be used to present the results. Statistical significance will be set at $p < 0.05$. This approach ensures a robust, streamlined synthesis, focusing on overall efficacy while addressing heterogeneity and bias, suitable for guiding future research and clinical translation.

Subgroup analysis No subgroup analyses will be conducted in this meta-analysis. The focus is on estimating the overall efficacy of cannabis extracts or cannabinoids in preclinical IBD models using a random-effects model. Heterogeneity will be assessed with I^2 and Cochran's Q test and reported, but not explored through subgrouping, as the primary objective is to provide a pooled effect size across all included studies without stratification by specific variables.

Sensitivity analysis Sensitivity analyses will assess result robustness by excluding studies with high risk of bias (per SYRCLE's tool) or outliers with extreme effect sizes. Using RevMan 5.4, pooled standardized mean differences (SMD) and 95% CIs will be recalculated after removing these studies. Changes in effect size, significance, or heterogeneity (I^2) will be reported to confirm the stability of findings on the efficacy of cannabis extracts in preclinical IBD models, ensuring reliable conclusions.

Country(ies) involved China.

Keywords Cannabis extracts, Cannabinoids, Cannabidiol, Tetrahydrocannabinol, Inflammatory Bowel Disease, Crohn's disease, Ulcerative colitis, Preclinical studies, Systematic review, Meta-analysis.

Contributions of each author

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