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Effects of anthocyanin on Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis of Preclinical Studies

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ADMINISTRATIVE INFORMATION

Support - No external funding.

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 21 May 2025 and was last updated on 21 May 2025.

INTRODUCTION

Review question / Objective To conduct a systematic review and quantitative analysis of preclinical studies that explore the effectiveness of anthocyanins in animal models of inflammatory bowel disease (IBD).

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 The search strategy employed free-text keywords and Medical Sub-ject Headings (MeSH) terms, specifically "anthocyanins", "inflammatory bowel disease", "Crohn's disease", and "ulcerative colitis", with no language restrictions.

Participant or population Animal models of IBD, with no restrictions on age, sex, species, or modeling strategy.

Intervention At least one group received anthocyanins, with no restrictions on the source, dosage, duration, or route of administration.

Comparator An untreated IBD control group was required.

Study designs to be included Only controlled experimental studies were considered.

Eligibility criteria
Inclusion Criteria:
1. Population: Animal models of IBD, with no restrictions on age, sex, species, or modeling strategy.
2. Intervention: At least one group received anthocyanins, with no restrictions on the source, dosage, duration, or route of administration.
3. Comparison: An untreated IBD control group was required.
4. Outcomes: The primary outcomes included Disease Activity Index (DAI) scores, histopathological scores, colon length, and the colon weight-to-length ratio. Secondary outcomes comprised levels of interleukin-1β (IL-1β), interleukin-6 (IL-6), interleu-kin-10 (IL-10), tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), in-ducible nitric oxide synthase (iNOS), myeloperoxidase (MPO) activity, malondialde-hyde (MDA), superoxide dismutase (SOD), glutathione (GSH), occludin, mucin-2, zon-ula occludens-1 (ZO-1), claudin-1, and goblet cell count.
5. Study Design: Only controlled experimental studies were considered.

Exclusion Criteria:
The exclusion criteria included studies that were case reports, clinical trials, com mentaries, reviews, or in vitro studies; studies investigating whole-food interventions or anthocyanins in combination with other food components, as the presence of additional components could confound the evaluation of the therapeutic effects of anthocyanins; studies that did not include an untreated IBD model group as a control; studies that did not report sample size information; studies whose data were unusable; and studies whose full text could not be retrieved. Additionally, for studies with duplicate publications, only one version was included.

Information sources An extensive literature search was conducted across four major databases: PubMed, Embase, Cochrane Library, and Web of Science, from their inception up to April 22, 2025.

Main outcome(s) The primary outcomes included Disease Activity Index (DAI) scores, histopathological scores, colon length, and the colon weight-to-length ratio. Secondary outcomes com-prised levels of interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), inducible nitric oxide synthase (iNOS), myeloperoxidase (MPO) activity, malondialdehyde (MDA), superox-ide dismutase (SOD), glutathione (GSH), occludin, mucin-2, zonula occludens-1 (ZO-1), claudin-1, and goblet cell count; (5) Study Design: Only controlled experimental stud-ies were considered.

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.
Two researchers will independently extract data from each included study and record it using Excel. The following details will be collected: 1. Basic information: authors and publication year. 2. Animal model characteristics: species, sex, age, weight, sample size, and method of IBD induction for both experimental and control groups. 3. Intervention Details: type of anthocyanin, administration route, treatment duration, and dosage. 4. Outcome Measures: Disease Activity Index (DAI) scores, histopathological scores, colon length, colon weight-to-length ratio, and levels of IL-1β, IL-6, IL-10, TNF-α, IFN-γ, iNOS, MPO activity, MDA, SOD, GSH, occludin, mucin-2, ZO-1, claudin-1, and goblet cell count. For studies reporting results at multiple time points, data from the final time point will be extracted. If outcome measures are presented only graphically, we will first contact the study authors to request the raw data. If unavailable, data will be extracted from the figures using Engauge Digitizer (version 11.3) for quantification. Since all outcome measures are continuous, the mean, standard deviation (SD), and sample size (n) for each group will be extracted. Any disagreements during data extraction will be resolved through discussion or by consulting a third reviewer.

Quality assessment / Risk of bias analysis The risk of bias in the included animal studies will be assessed using the SYstematic Review Center for Laboratory Animal Experimentation (SYRCLE) risk-of-bias tool. This tool will comprehensively evaluate potential biases across several critical domains: selection bias (sequence generation, baseline characteristics, allocation concealment), performance bias (random housing, blinding of trial caregivers and researchers), detection bias (random outcome assessment, blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective outcome

reporting), and other sources of bias. The evaluation will be independently conducted by two researchers, and any discrepancies will be resolved by consulting a third assessor.

Strategy of data synthesis Data will be synthesized quantitatively through meta-analysis to assess the efficacy of anthocyanin on preclinical IBD models, using Review Manager (RevMan 5.4). Continuous outcomes will be analyzed with standardized mean differences (SMD) and 95% confidence interval(95%CI), 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 anthocyanin 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% CI 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 anthocyanin in preclinical IBD models, ensuring reliable conclusions.

Country(ies) involved China.

Keywords anthocyanins, Inflammatory Bowel Disease, Crohn's disease, Ulcerative colitis, Preclinical studies, Systematic review, Meta-analysis.

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