INPLASY

Alterations of Serotonin System-Related Biomarkers and Their Association with Disease Activity in Patients with Ulcerative Colitis: A Systematic Review and Meta-analysis

INPLASY202690107

doi: 10.37766/inplasy2026.9.0107

Received: 24 September 2026

Published: 24 September 2026

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202690107

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

INTRODUCTION

Review question / Objective This systematic review and meta-analysis aims to evaluate alterations of serotonin system-related biomarkers in patients with ulcerative colitis (UC) and investigate their associations with disease activity.

Specifically, this review will assess whether circulating and intestinal mucosal serotonin-related biomarkers, including serotonin (5-hydroxytryptamine, 5-HT), tryptophan hydroxylase (TPH1/TPH2), serotonin transporter (SERT/SLC6A4), enterochromaffin (EC) cells, and 5-hydroxyindoleacetic acid (5-HIAA), differ between UC patients and non-UC controls, and whether these biomarkers are associated with clinical, endoscopic, or histological disease activity.

The review question will be structured according to the PICOS framework:

Population: Patients diagnosed with ulcerative colitis.

Exposure: Alterations in serotonin system-related biomarkers.

Comparator: Healthy controls or different disease activity states of UC.

Outcomes: Levels or expression of serotonin-related biomarkers and their association with disease activity indicators.

Rationale Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by recurrent inflammation of the colonic mucosa. Although immune dysregulation, genetic susceptibility, environmental factors, and intestinal microbiota alterations contribute to UC pathogenesis, the mechanisms underlying disease initiation and progression remain incompletely understood.

Serotonin (5-hydroxytryptamine, 5-HT) is an important gastrointestinal signaling molecule mainly produced by intestinal enterochromaffin cells. Beyond its classical role as a neurotransmitter, serotonin regulates intestinal motility, epithelial barrier function, immune responses, and inflammatory processes. The intestinal serotonergic system involves multiple components, including serotonin synthesis

enzymes such as tryptophan hydroxylase (TPH1/TPH2), serotonin transporters (SERT/SLC6A4), enterochromaffin cells, and serotonin metabolites such as 5-hydroxyindoleacetic acid (5-HIAA).
Previous clinical studies have reported altered serotonin-related markers in UC patients; however, the findings remain inconsistent regarding the direction and clinical significance of these alterations. Differences in biological samples, detection methods, and disease activity assessment may contribute to these discrepancies.
Therefore, a systematic review and meta-analysis is needed to comprehensively evaluate alterations of serotonin system-related biomarkers in UC and clarify their relationship with disease activity. This study may provide evidence for understanding serotonergic mechanisms and identifying potential biomarkers for UC assessment.

Condition being studied Ulcerative colitis (UC) is a chronic, relapsing inflammatory bowel disease characterized by continuous inflammation of the colonic mucosa. Patients commonly present with abdominal pain, diarrhea, and rectal bleeding. Disease severity varies from mild to severe, and assessment of disease activity is essential for treatment decision-making and prognosis evaluation. The pathogenesis of UC involves complex interactions among immune responses, epithelial barrier dysfunction, microbiota imbalance, and intestinal signaling pathways.

METHODS

Search strategy A comprehensive literature search will be performed in PubMed, Embase, Web of Science Core Collection, Cochrane Library, CNKI, WanFang Data, and VIP databases from inception to September 19, 2026.
The search strategy will combine terms related to ulcerative colitis and serotonin system-related biomarkers.
PubMed search strategy:
("Colitis, Ulcerative"[Mesh] OR "ulcerative colitis"[tiab] OR "ulcerative proctitis"[tiab] OR pancolitis[tiab])
AND
("Serotonin"[Mesh] OR "Tryptophan Hydroxylase"[Mesh] OR "Serotonin Plasma Membrane Transport Proteins"[Mesh] OR "Enterochromaffin Cells"[Mesh] OR "Hydroxyindoleacetic Acid"[Mesh] OR serotonin[tiab] OR "5-hydroxytryptamine"[tiab] OR "5-HT"[tiab] OR TPH1[tiab] OR TPH2[tiab] OR "serotonin transporter"[tiab] OR SERT[tiab] OR 5-HTT[tiab] OR SLC6A4[tiab] OR enterochromaffin*[tiab] OR "EC cell*"[tiab] OR "5-HIAA"[tiab]).
Similar strategies will be adapted for other databases.

Participant or population Patients diagnosed with ulcerative colitis according to recognized diagnostic criteria will be included, regardless of age, sex, disease duration, or disease severity.

Intervention Not applicable. This review evaluates biomarker alterations rather than therapeutic interventions.

Comparator Healthy individuals or UC patients with different disease activity states, including remission, mild, moderate, or severe disease, will serve as comparators.

Study designs to be included Observational studies, including case-control studies, cross-sectional studies, cohort studies, and clinical studies reporting serotonin system-related biomarkers in human UC patients will be included.

Eligibility criteria Inclusion criteria:
(1) Human studies involving patients with ulcerative colitis;
(2) Studies reporting at least one serotonin system-related biomarker, including 5-HT, TPH1/TPH2, SERT/SLC6A4, enterochromaffin cells, or 5-HIAA;
(3) Studies providing quantitative data or sufficient information for effect size calculation;
(4) Studies evaluating associations with UC status or disease activity.
Exclusion criteria:
(1) Animal or cell studies;
(2) Reviews, case reports, conference abstracts, and editorials;
(3) Studies without relevant biomarker data;
(4) Duplicate publications.

Information sources Electronic databases including PubMed, Embase, Web of Science Core Collection, Cochrane Library, CNKI, WanFang Data, and VIP will be searched. Reference lists of included studies and relevant reviews will also be manually screened.

Main outcome(s) The primary outcomes will include differences in serotonin system-related biomarkers between UC patients and controls, including:
- Circulating serotonin levels;
- Intestinal mucosal serotonin expression;
- TPH1/TPH2 expression;
- SERT/SLC6A4 expression;
- Enterochromaffin cell density;

- 5-HIAA levels.
Effect measures will include standardized mean difference (SMD), mean difference (MD), odds ratio (OR), or correlation coefficients where appropriate.

Additional outcome(s) Secondary outcomes will include associations between serotonin system-related biomarkers and clinical disease activity indicators, including Mayo score, endoscopic activity, histological inflammation, disease severity classification, and remission status.

Data management Literature records will be managed using EndNote software. Data extraction will be performed independently by two reviewers using a standardized data extraction form. Extracted information will include study characteristics, participant demographics, biomarker measurements, detection methods, disease activity assessment, and effect estimates.

Quality assessment / Risk of bias analysis The methodological quality of included observational studies will be assessed using the Newcastle-Ottawa Scale (NOS). Two reviewers will independently perform quality assessment, and disagreements will be resolved through discussion or consultation with a third reviewer.

Strategy of data synthesis Meta-analysis will be conducted using Review Manager and R software when sufficient homogeneous data are available. Continuous outcomes will be summarized using standardized mean differences (SMDs) with 95% confidence intervals. Random-effects models will be applied considering potential clinical and methodological heterogeneity.
Statistical heterogeneity will be evaluated using Cochran's Q test and I^2 statistic. Publication bias will be assessed using funnel plots and Egger's test when sufficient studies are available.

Subgroup analysis Subgroup analyses will be performed according to:
(1) Biological sample type (serum/plasma versus intestinal mucosa);
(2) Biomarker category (5-HT, TPH1/TPH2, SERT, EC cells, 5-HIAA);
(3) Disease activity status;
(4) Detection methods.

Sensitivity analysis Sensitivity analyses will be conducted by sequentially excluding individual studies and repeating meta-analyses to evaluate the robustness of pooled estimates.

Language restriction No language restriction.

Country(ies) involved China.

Other relevant information This systematic review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol will be registered prospectively to improve transparency and reproducibility.

Keywords ulcerative colitis; serotonin; 5-hydroxytryptamine; serotonin transporter; tryptophan hydroxylase; enterochromaffin cells; biomarker; meta-analysis.

Dissemination plans The findings of this systematic review and meta-analysis will be submitted for publication in a peer-reviewed scientific journal and presented at relevant academic conferences.

Contributions of each author
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