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The Role Of Microbiome in Colorectal Cancer – A Systematic Review

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 July 2025 and was last updated on 10 July 2025.

INTRODUCTION

Review question / Objective According to PRISMA's recommendation, we selected a specific framework of population (P), intervention (I), comparison (C), outcome (O), and study design (S). (PICOS) to define study eligibility: Population (P): Patients with colorectal cancer; Intervention (I): The composition of the gut microbiome in individuals undergoing the same therapy regimen; Comparison (C): Compare interindividual gut microbiome variations; Outcome (O): Understand how these variations may influence therapeutic outcomes; Research Design (S): Randomised controlled trials and Human Observational Studies.

Condition being studied Colorectal cancer (CRC) is among the most prevalent cancers worldwide and the second leading cause of cancer-related mortality, with a significant morbidity and recurrence rate associated. Modifiable and non-modifiable factors influence CRC risk. While age and genetics play a role, the rising incidence in younger adults suggests a greater importance of modifiable contributors, particularly gut microbiome alterations.

The gut microbiota includes 10^{14} microorganisms, which primarily reside in the gastrointestinal tract. Beyond the microbiota, the gut microbiome encompasses its structural elements, genes, and metabolites. It symbiotically associates with the host and is crucial in metabolism, immune regulation, and behavioural responses.

Treatment strategies for CRC are tailored to the individual patient's disease stage, tumour location, and presence of metastasis. In early-stage CRC, tumour resection is the first-line therapy. In contrast, stages II, III, and IV often necessitate the addition of systemic therapy to the treatment regimen, such as chemotherapy, immunotherapy, and radiotherapy.

In the context of CRC pathogenesis, it has been demonstrated that the gut microbiota not only plays a role in tumorigenesis, differentiation, and malignant progression, but it also plays a critical role in modulating the efficacy and toxicity of various cancer therapies. Conversely, it is

increasingly recognised that cancer treatments themselves can alter the composition and activity of the gut microbiota.
While surgical resection is a standard procedure for all CRC stages, emerging evidence suggests a link between postoperative complications and gut microbiome alterations. Preoperative interventions, like bowel preparation and antibiotics prophylaxis, significantly disrupt microbial composition. Given the microbiome's role in inflammation and tissue repair, such dysbiosis may contribute to postoperative complications, which in turn represent a risk factor of reduced overall survival and increased risk of recurrence.
The intestinal microbiome plays a crucial role in modulating the host response to systemic cancer therapies, including chemotherapy, radiotherapy, and immunotherapy. However, the tumour microenvironment and surgical procedures promote a state of dysbiosis characterised by reduced microbial diversity and richness, which can significantly impair therapeutic efficacy and exacerbate toxicity. The mechanisms by which the microbiome influences treatment outcomes are varied. Dysbiosis facilitates microbial translocation across the compromised intestinal barrier, potentially triggering inflammation. Additionally, direct microbial metabolism and its byproducts can alter therapeutic pharmacokinetics, efficacy, and toxicity by modulating metabolic pathways, reactivating inactive metabolites, and producing toxic products. Furthermore, the microbiome modulates both innate and adaptive immune responses, influencing the efficacy of immunotherapy by either enhancing antitumour activity or contributing to therapeutic resistance).
The gut microbiome may represent a promising prognostic biomarker and therapeutic target, with its modulation offering potential to enhance efficiency and reduce adverse effects on CRC treatment. Therefore, this review aims to outline the gut microbiome composition in individuals with CRC undergoing the same therapy regimen, compare interindividual variations, and understand how these differences may influence therapeutic outcome.

METHODS

Search strategy We selected relevant studies published between between January 2020 and January 2025, written in English, in PubMed and Cochrane databases on March 12 and 22, 2025, respectively.
The following keywords (Medical Subject Headings terms) were used to search all databases: : “Gastrointestinal Microbiome” (D000069196), “Colorectal Neoplasms” (D015179), “Host Microbial Interactions” (D000076662), “Drug Therapy” (D004358), “Immunotherapy” (D007167) and “Radiotherapy” (D011878). Searches were performed with AND or NOT.
The obtained literature was imported into "PICO Portal literature review" platform, which enhances the efficiency of the review process by consolidating all articles and their corresponding assessments in a centralised platform.

Participant or population Patients with colorectal cancer.

Intervention The composition of the gut microbiome in individuals undergoing the same therapy regimen.

Comparator Compare interindividual gut microbiome variations.

Study designs to be included Randomised Controlled Trials; Human Observational Studies.

Eligibility criteria Free full-text articles published in English between January 2020 and January 2025 were eligible for inclusion. Concurrently, randomised controlled trials and human observational studies were included. Simultaneously, any literature which didn’t meet these criteria was excluded. Furthermore, studies were excluded if they were considered to have limitations such as a high risk of bias, incomplete data reporting, or an unclear study objective.

Information sources PubMed and Cochrane.

Main outcome(s) Microbiome Composition, Treatment efficacy, Adverse Effects.

Quality assessment / Risk of bias analysis The risk of bias assessment for the studies included in this systematic review was conducted using the Risk-Of-Bias VISualization (Robvis) tool, a comprehensive and widely used tool to assess the quality and risk of bias in research studies. As both Randomised Controlled Trials (RCT) and human observational studies were included in this review, different Robvis tools were used to provide a clear and concise overview of the risk of bias assessment of the included studies.
The RoB 2 tool offers a structured framework for evaluating risk of bias in randomised trials, encompassing five domains where bias may be introduced: arising from the randomisation, deviations from intended intervention, missing outcome data, and selection of the reported result. This tool was applied to assess bias in the RCT studies included.

The ROBINS-I tool was employed in the evaluation of bias in non-randomised studies. It evaluates seven domains where bias may be introduced: due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. It was used to assess bias in the included human observational studies.

Strategy of data synthesis Given the study design, interventions, and outcome measures among the included studies, a narrative synthesis approach was employed for data analysis.

Subgroup analysis Although no formal subgroup analysis was conducted, the review organised findings by intervention type as an informal subgroup approach: Patients receiving standard cancer therapies and patients receiving microbiome-targeted interventions. This grouping allowed the review to identify patterns unique to each therapeutic approach and observe differences in microbiome composition, diversity, and associated clinical outcomes.

Sensitivity analysis A formal sensitivity analysis was not conducted, primarily due to the small number of included studies and the absence of standardised effect sizes or quantitative outcomes, being preferred a qualitative interpretation of the results.

Language restriction English.

Country(ies) involved Portugal.

Keywords Colorectal Neoplasms; Gastrointestinal Microbiome; Host Microbial Interactions; Drug Therapy.

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