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Harnessing the Gut Microbiome in Cancer Immunotherapy: Mechanisms, Challenges, and Routes to Personalized Medicine—A Systematic Review

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

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 10 July 2025 and was last updated on 10 July 2025.

INTRODUCTION

Review question / Objective In this systematic review, we have studied the precise mechanism of immune checkpoint inhibitors, interaction of immunotherapy and microbiome, and also we have discussed MPE and its potential role in improvement of personalized medicine. Challenges and limitations ahead in using the microbiome to improve cancer treatment outcomes and future directions have also been discussed.

Rationale Immunotherapy has transformed cancer treatment, yet patient responses vary widely. Emerging evidence suggests that the gut microbiome significantly influences immune modulation and treatment outcomes. However, findings are diffused between clinical and preclinical studies, and comprehensive synthesis is lacking. A systematic review is needed to consolidate current knowledge on how microbial composition and probiotic interventions affect immunotherapy, identify gaps in the literature, and guide the development of personalized microbiome-based therapeutic strategies.

Condition being studied Cancer is a group of diseases characterized by uncontrolled cell growth and immune evasion. Immunotherapy, particularly immune checkpoint inhibitors, has emerged as a powerful treatment option by reactivating the patient's immune system to attack tumors. However, not all patients respond equally. Recent studies suggest that gut microbiota composition plays a role in modulating immune responses, influencing treatment effectiveness and side effects. This review focuses on understanding how the gut microbiome affects immunotherapy outcomes in cancer patients.

METHODS

Search strategy Literature Search Strategy
A comprehensive literature search was conducted using several reputable academic databases,

including PubMed, Scopus, Web of Science, and Google Scholar. Keywords and phrases covering "probiotics", "cancer therapy", "immunotherapy", "microbiome", "immune checkpoint inhibitors (ICIs)", "personalized medicine", "SCFA", "polysaccharide A", "indole-3-carbaldehyde", "molecular pathological epidemiology", "environmental factor", and "lifestyle" were used to identify relevant articles. Boolean operators (AND, OR) were applied to refine search results. Additionally, the references of relevant articles were reviewed to find more related studies as well as papers that cited our selected references to ensure we covered all important literature. The search was conducted to capture the most relevant and recent advancements in the field. No restrictions on study type or geographical scope were applied. Also, the search was included publications from 1995 to 2024, capturing the most relevant and recent advancements in the field.

Participant or population This systematic review includes both clinical and preclinical studies examining the role of gut microbiota in cancer immunotherapy. Clinical evidence includes trials involving cancer patients treated with immune checkpoint inhibitors (ICIs) such as PD-1/PD-L1 blockers, where modulation of the microbiota—via probiotics or fecal microbiota transplantation (FMT)—was associated with improved therapeutic outcomes. Animal studies using murine models complement these findings by identifying microbial strains like Lactobacillus, Akkermansia muciniphila, and Alistipes shahii, which enhance immune responses.

Intervention The review focuses on observational data (or other study type), and does not involve any intervention.

Comparator Not applicable.

Study designs to be included The search was conducted to capture the most relevant and recent advancements in the field. No restrictions on study type or geographical scope were applied.

Eligibility criteria Inclusion and Exclusion Criteria
• Inclusion Criteria: Studies were considered for inclusion if they:
o Focused on the use of probiotics in cancer treatment.
o Explored the microbiome's role in modulating immune responses during cancer therapies.
o Provided clinical data, case studies, or insights on the safety and efficacy of probiotics.
o Explained the role of SCFA, polysaccharide A, and indole-3-carbaldehyde in regulating immune system.
o Discussed molecular pathological epidemiology, environmental factors, and lifestyle and their relation to cancer and its treatment.
o Were peer-reviewed articles, clinical trials, meta-analyses, or systematic reviews.
• Exclusion Criteria: Articles were excluded if they:
o Were not available in English.
o Had no full-text available.
o Had unclear methodology or reporting.
o Focused on topics unrelated to cancer therapy or probiotics.

Information sources A comprehensive literature search was conducted using several reputable academic databases, including PubMed, Scopus, Web of Science, and Google Scholar.

Main outcome(s) Gut microbiome has wide effects on immune responses through different pathways like production of short chain fatty acids (SCFAs), polysaccharide A, and indole-3-carbaldehyde. Also, probiotics were found to enhance Anit-inflammatory responses and increase CD8+ T-cell activity, suggesting a synergistic effect with ICIs. The efficacy of immunotherapy was identified as being determined importantly by the composition of the gut microbiota, especially in patients with treatment resistance. For optimized treatment outcomes, personalized probiotics tailored to an individual's microbiota showed potential. Important challenges are treatment resistance and compromised mucosal integrity because of microbiome alterations. Effective drug delivery systems do also remain as important barriers to common adoption.

Additional outcome(s) No additional outcomes.

Data management No specific software was used for data management; all records were kept and organized manually by the research team.

Quality assessment / Risk of bias analysis After collecting resources, duplications were removed manually and were evaluated for risk of bias by assessing key methodological aspects including randomization, blinding, sample size, completeness of outcome data, selective reporting, and reviewing the conflict-of-interest statement.

Strategy of data synthesis A two-phase screening process was performed: First, the abstract of articles was reviewed, and then the full text of all articles was examined by five

independent authors to extract key information from each selected article including details on study design, patient demographics, types of probiotics administered, treatment protocols, outcomes measured, and key findings related to the effectiveness of probiotics in cancer therapy. The findings were categorized based on themes such as the impact of probiotics on therapeutic application, treatment side effects, immune modulation, microbiome diversity, and overall patient outcomes. Three authors retrieved the studies and any disagreements were resolved by twoauthors.

Subgroup analysis No subgroup analyses are planned.

Sensitivity analysis No sensitivity analysis is planned for this review.

Language restriction Exclusion Criteria: Articles were excluded if they: Were not available in English.

Country(ies) involved Iran, USA.

Other relevant information No supplementary information to provide.

Keywords Immunotherapy, Immune checkpoint inhibitors (ICIs), Probiotics, Microbiome, Personalized Medicine, SCFA, Polysaccharide A, Indole-3-carbaldehyde.

Dissemination plans The results of this review will be disseminated through publication in peer-reviewed scientific journals.

Contributions of each author

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