

# Diet-Driven Alterations in Gut Microbiota and their Implications for Cancer Therapy: A Review

Saurav Raj, Megha Hegde\*, Sanatkumar Bharamu Nyamagoud, Shamita Shyam Sail, Chandrashekhar Patil, Kaushal Kumar, Nikhil Bohra

Department of Pharmacy Practice, KLE College of Pharmacy, Vidyanagar, Hubballi. A Constituent Unit of KLE Academy of Higher Education and Research, Belagavi, Karnataka, INDIA.

## ABSTRACT

The gut microbiome is being frequently acknowledged for its impact on intestinal and extra-intestinal conditions, notably cancer. Here, diet is the most extensively researched modulator of gut microbiota among various environmental factors, demonstrating the ability to enrich its diversity and composition. Recent insights from clinical and preclinical trials emphasize the reciprocal influence between gut microbiota and anticancer therapies, impacting treatment responses and mitigating associated toxicities. Understanding these intricate connections is pivotal, given the potential of the gut microbiota to enhance the efficacy of existing chemotherapeutic agents while reducing their adverse effects. A systematic literature review was conducted using PubMed and Google Scholar, employing keywords like "gut microbiome," "cancer therapy," "chemotherapy," "diet," and "microbial fermentation." Thus, this review seeks to examine the interplay between the gut microbiome and cancer therapies, while also delving into nutritional strategies that can modulate the gut microbiome to improve cancer treatments.

**Keywords:** Cancer treatment, Microbiome, Diet, Microbiota, Nutrition, Oncogenesis, Prebiotics, Probiotics, Efficacy, Toxicity.

## Correspondence:

**Ms. Megha Hegde**

Pharm D, Department of Pharmacy Practice, KLE College of Pharmacy, Vidyanagar, Hubballi. A Constituent Unit of KLE Academy of Higher Education and Research, Belagavi-590010, Karnataka, INDIA.

Email: dr.meghahegde@gmail.com

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## INTRODUCTION

The human digestive tract is home to approximately 100 trillion microorganisms, collectively known as the "microbiome." The microbiome harbours a minimum of 100 times the number of genes found in the human genome.<sup>1</sup> These microorganisms form a dynamic ecosystem that undergoes continuous changes throughout an individual's life.<sup>2</sup> Over the past few years, studies have emphasized the significant effect of the gut microbiome on various health and disease states. Various disease states such as Inflammatory Bowel Disease (IBD), atherosclerosis, multiple sclerosis, diabetes, Alzheimer's disease and others have been linked to dysbiosis, which refers to an imbalance in the gut microbiota.<sup>3</sup>

In the realm of oncology, an expanding corpus of preclinical and clinical data underscores an intricate interplay linking cancer development, anti-cancer immunity and the gut microbiota.<sup>4</sup> The gut microbiome plays a dual role in cancer, potentially contributing to both carcinogenesis and influencing the response to anti-cancer therapies.<sup>5</sup> Dysbiosis, often a consequence of

tumour therapy, is intricately linked to varied responses to treatment and disruptions in metabolic pathways, ultimately compromising immune function.<sup>6,7</sup> This complex relationship underscores the importance of the gut microbiota in shaping therapeutic outcomes in cancer treatment, where it can either enhance the effectiveness of chemotherapy or increase its toxicity.

The profound impact of diet on the functionality and composition of the gut microbiota resonates deeply, exerting significant influence on host homeostasis and biological processes by way of microbial fermentation of nutrients. Furthermore, specific dietary patterns have been associated with cancer risk in humans.<sup>8-10</sup> Understanding the links between diet, the microbiome and cancer is vital, as the intestinal microbiota offers promise in boosting the efficacy of existing chemotherapeutic drugs while reducing their adverse effects. This review aims to explore the interaction of the gut microbiome with cancer therapies and to delve into nutritional strategies capable of modulating the gut microbiome to enhance cancer treatments.

## Search Strategy

The search strategy employed a comprehensive approach to identify relevant literature from various databases, including PubMed and Google Scholar. The search terms utilized encompassed key concepts related to the gut microbiome, cancer therapy and dietary influences. These terms were employed



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individually or in combination to retrieve pertinent information. Key search terms included "gut microbiome," "microbiota," "cancer therapy," "chemotherapy," "immune response," "diet," "nutrition," "microbial fermentation," "cancer risk," and related keywords. The search strategy also incorporated relevant Medical Subject Heading (MeSH) terms to ensure comprehensive coverage of the literature. The gathered results underwent a rigorous assessment to include studies that provided insightful details of the role of the gut microbiome in cancer therapy and its modulation through dietary interventions. Exclusion criteria involved eliminating duplicate studies, those not written in English and studies lacking relevance to the topic. Hence, this review aims to provide a comprehensive understanding of the intricate relationship between the gut microbiome, cancer therapies and dietary interventions in optimizing treatment outcomes for cancer patients.

### The Bidirectional Interaction between Gut Microbiota and Anti-Cancer Therapies

The impact of gut microbes on the treatment of cancer, whether beneficial or detrimental, has been extensively demonstrated through large-scale mouse experiments. It has been observed in both mice and humans that certain microbes may contribute to a poor response to cancer treatments, including chemotherapy, radiotherapy, surgery and immunotherapy.<sup>11,12</sup> During cancer therapy, there is a bidirectional interaction between the gut microbiota and antineoplastic agents. On one hand, various interventions used to manage cancer have cytotoxic effects on intestinal bacteria, effectively promoting dysbiosis. Chemotherapeutic agents such as irinotecan and 5-fluorouracil have the potential to harm the gut microbiota, causing changes in its composition either through direct effects or by inducing an immune response. These therapeutic modalities may adversely affect the integrity of the intestinal barrier, precipitating undesired side effects. Anticancer interventions have the potential to incite two discernible forms of dysbiosis: detrimental dysbiosis, which compromises therapeutic efficacy or exacerbates treatment toxicity and beneficial dysbiosis, pivotal for or significantly augmenting its clinical effectiveness.<sup>13</sup> On the other hand, gut microbiota has an impact on both the therapeutic efficacy and toxicity of anticancer agents, operating through pharmacodynamic and immunological mechanisms.<sup>14,15</sup> (Figure 1).

### Pharmacological Mechanism

The presence and composition of gut microbiome can significantly influence the bioavailability and biological effects of ingested xenobiotics either by enhancing their therapeutic effect or by causing increasing toxicity. This phenomenon has been observed and established for various drugs; as seen in dose-limiting diarrhoea linked to irinotecan has been attributed to the gut microbiome's capability to locally reactivate the drug.<sup>16</sup> This microbial activity can alter the drug's behaviour within

the gut and contribute to specific adverse effects associated with the treatment. The gut microbiome can impact the Pharmacodynamics (PD) of anticancer agents beyond orally administered drugs and may affect any systemic interventions. Notably, Germ-Free (GF) or pathogen-free mice show differences compared to conventional, pathogen-free mice in the expression of various hepatic genes involved in xenobiotic metabolism.<sup>17</sup> This suggests that the gut microbiome can impact the metabolic processes of xenobiotics beyond the gastrointestinal tract. The gut microbiota is also implicated in the onset of acute Graft-Versus-Host Disease (GVHD), a significant barrier to the success of allogeneic stem cell transplantation. Dysbiosis, often characterized by enrichment in *Enterobacteriaceae* species, has been linked to infections and intestinal GVHD.<sup>18</sup>

Complications that arise after gastro-intestinal surgery in Colorectal Cancer (CRC) patients may also be influenced by the gut microbiota. Existing research suggests that *Lactobacillus species* and *Akkermansia muciniphila* potentially regulate the process of intestinal wound healing through mechanisms dependent on Reactive Oxygen Species (ROS). Moreover, colonizing GF mice with *Bacteroides thetaiotaomicron* impacted the absorption of nutrients, the integrity of the mucosal barrier and angiogenesis positively.<sup>19</sup> On the other hand, *Serratia marcescens*, a pathogenic bacteria, could worsen the occurrence of surgical complications. Among *Serratia marcescens*, one of its collagenolytic strains has been implicated in inducing anastomotic leakage, a severe complication linked with surgical interventions.<sup>20</sup>

Young patients with Acute Myeloid Leukaemia (AML) undergoing chemotherapy, particularly those receiving antimicrobial prophylaxis, often exhibit a reduction in the anaerobic bacteria and a rise in potentially pathogenic aerobic bacteria like *Enterococci*. This shift in gut microbiota composition indicates an increased susceptibility to gram-positive aerobic infections in these individuals.<sup>21</sup>

Relatively, a noticeable reduction in *Akkermansia muciniphila* levels was observed in the B6 microbiota from day 0 of paclitaxel therapy to day 10 by a study investigating paclitaxel-induced effects. This decline hinted at the potential role of *Akkermansia muciniphila* in inhibiting the pain by supporting gut barrier function. However, paclitaxel might disrupt this barrier function, potentially leading to an increased exposure to bacterial products and metabolites systemically. This shift may contribute to systemic inflammation, increasing pain sensitivity as a result of decreased levels of *Akkermansia muciniphila*.<sup>22</sup> Therefore, in addition to affecting the gastrointestinal adverse effects of certain anticancer treatments, dysbiosis could potentially compromise their therapeutic efficacy. Conversely, a balanced gut microbiota (eubiosis) may help mitigate the undesired side effects of various antineoplastic agents.

## Immunological Mechanism

A growing body of evidence suggests that the gut microbiota influences the responses of various tumour types to anticancer therapy through immunological mechanisms, particularly in mouse models.<sup>23</sup> For instance, total body irradiation, which depletes lymphocytes, has been shown to lead to the translocation of gut microbiota components or by-products across the intestinal epithelium. This translocation is associated with increased activation of dendritic cells, elevated levels of proinflammatory cytokines in the blood and improved efficacy of CD8+ T-lymphocytes adoptively transferred. Accordingly, mice treated with antibiotics, injected with Lipopolysaccharide (LPS)-neutralizing antibody, or lacking specific immune response receptors (CD14<sup>-/-</sup> and Toll-Like Receptor 4 (TLR<sup>-/-</sup>) mice) show reduced sensitivity to lymphodepletion irradiation compared to their control counterparts.<sup>23</sup> A study on women with gynaecological cancer revealed that patients who suffered from diarrhoea as an adverse effect of radiotherapy exhibited, before treatment, higher levels of *Bacteroides*, as well as *Dialister* and *Veillonella*, along with lower levels of *Clostridium* XI and XVIII, *Faecalibacterium*, with *Oscillibacter*, *Parabacteroides* and *Prevotella* compared to those who did not develop diarrhoea. These findings imply a possible association between gut microbiota composition and the occurrence of radiotherapy-induced diarrhoea in gynaecological cancer patients.<sup>24</sup>

Likewise, the injection of cyclophosphamide into mice kept in a pathogen-free environment leads to mucosal injury and also leads to the translocation of particular Gram-positive bacteria through the intestinal epithelium. This translocation is associated with therapeutically significant T<sub>H</sub>1 and T<sub>H</sub>17 immune responses in the spleen. Tumour-bearing mice that are GF or treated with antibiotics and consequently unable to mount antibacterial T cell-mediated responses, exhibit greater resistance to the therapeutic effects of cyclophosphamide compared to their control counterparts. These findings imply that the gut bacteria may trigger the generation of a distinct subset of "pathogenic" T<sub>H</sub>17 cells, ultimately enhancing the response to cyclophosphamide treatment. Remarkably, in antibiotic-treated mice, the antineoplastic efficacy of cyclophosphamide can be completely reinstated by transferring T<sub>H</sub>17 cells that have been cultured and expanded in vitro. Albeit, not all Gram-positive bacteria induce beneficial T<sub>H</sub>17 immune responses. Certain prokaryotes, like *Parabacteroides distasonis* (known for stimulating regulatory T-cell responses) and segmented filamentous bacteria (which induce conventional T<sub>H</sub>17 responses), have the potential to mitigate the favourable outcomes of anticancer chemotherapy.<sup>25</sup>

A balanced gut microbiota boosts the therapeutic benefits of a CpG-oligodeoxynucleotide-based immunotherapeutic regimen as well as platinum derivatives. Particularly, the gut microbiota played a role in enhancing the efficacy of CpG oligodeoxynucleotides when used alongside a monoclonal

antibody that neutralizes interleukin-10 receptor- $\alpha$  or IL10RA, thus fostering a clinically significant innate immune response against malignant cells, which relies on tumour necrosis factor- $\alpha$  or TNF- $\alpha$ . A healthy gut microbiota was found to be essential for oxaliplatin, which is an immunogenic platinum salt, approved for CRC patients, to enhance tumour infiltration by myeloid cells. These myeloid cells mediate antineoplastic effects by producing ROS. The impairment of chemotherapy effects, as seen with the usage of antibiotics, could be replicated by the *Cybb*<sup>-/-</sup> genotype (lack of a ROS-generating enzyme) and the administration of antioxidants systemically. Additionally, mice which lack critical components involved in sensing microbe-associated molecular patterns, such as myeloid differentiation primary response-88 (MYD88) or TLR4, were more resistant to chemotherapy with oxaliplatin compared to their wild-type counterparts. Hence, the complete therapeutic potential of oxaliplatin involves the immune system's detection of components from the gut microbiota, enabling the generation of tumour-infiltrating myeloid cells with antineoplastic activity.<sup>23,25</sup>

Such findings open up new possibilities for strategies to regulate the gut microbiota and enhance outcomes in oncological treatments. Diet is an established modulator of the gut microbiota composition as well as its function.<sup>26</sup> Studies exploring the effects of dietary interventions administered simultaneous to cancer therapy on both gut microbiota and the clinical outcomes are increasing in number. In the following sections, we delve into the potential role of various nutritional interventions as modulators of gut microbiota, aiming to improve responses to cancer therapy. Table 1 summarises the effects of microbiota on the efficacy and toxicity of various anticancer drugs.

## Nutritional Interventions in Cancer Therapy

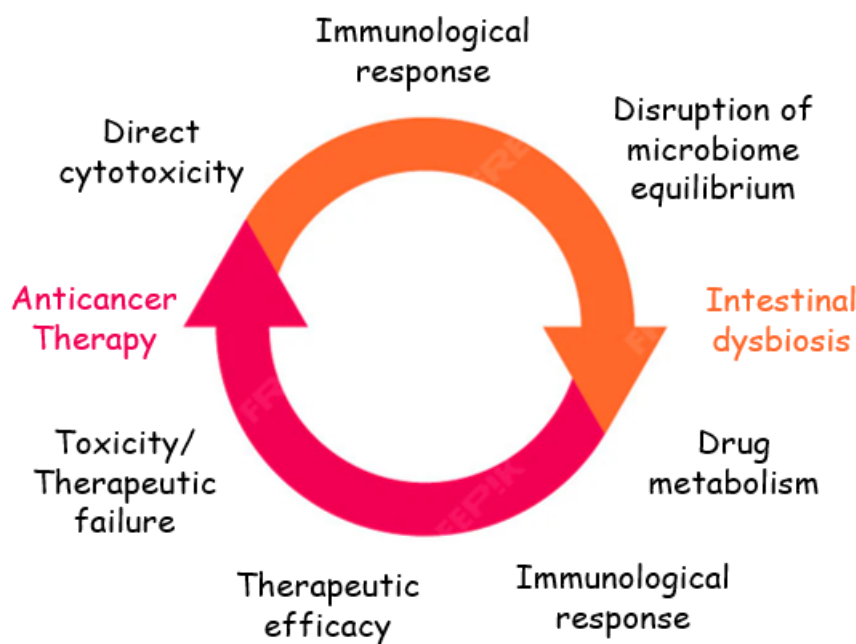
To address the effects of microbial changes during cancer treatment and their potential impact on treatment response, we suggest utilizing dietary interventions to alter the microbial composition as well as its function prior to or during treatment, thereby improving cancer outcomes. (Figure 2) Substantial research focusing on diet and the gut microbiome composition in healthy individuals provides compelling evidence for the positive effects of acute dietary interventions on the composition and function of the gut mucosa and systemic microbes, as detailed in the ensuing review. However, it is imperative to acknowledge that the favourable outcomes of dietary interventions may be relatively modest (e.g., 5%-16%) and variable due to the substantial diversity in the gut microbiome across individuals.<sup>26,33</sup>

### Prebiotics

Prebiotics, a category of dietary fibres, serve to foster the proliferation of anaerobic bacteria indigenous to the colon. Among these prebiotics are inulin, Fructo-Oligosaccharides (FOS) and Galactooligosaccharides (GOS). Microbiota-Accessible Carbohydrates (MACs) are a subset of carbohydrates that evade

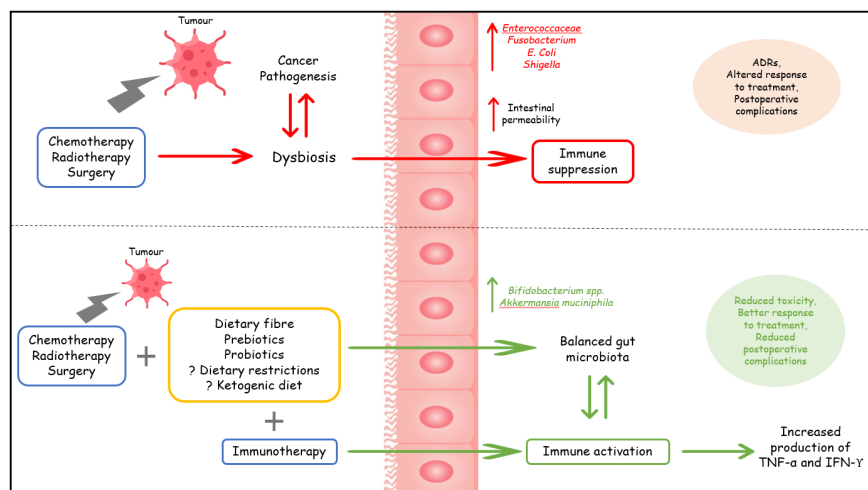
**Table 1: Effect of microbiota on various anti-cancer drugs.**

| Anti-cancer drug                       | Name of bacteria   | Potential mechanism   | Outcome                           |
|--|--|-----------------------|-----------------------------------|
| Oxaliplatin<br>(27)                    | <i>B. fragilis</i> (ileal microbiota)  | Immunomodulation      | Enhanced efficacy                 |
|  | Commensal microbiota   | Unclear               | Neurotoxicity                     |
| Irinotecan<br>(16)                     | Bacterial $\beta$ -glucuronidase   | Enzymatic degradation | Gastrointestinal toxicity         |
| Capecitabine<br>(28)                   | Bacterial uridine phosphorylase  | Enzymatic degradation | Decreased efficacy                |
| Gemcitabine<br>(29)                    | Bacterial cytidine deaminase   | Enzymatic degradation | Drug resistance                   |
| 5-Fluorouracil<br>(30,31)              | <i>F. nucleatum</i>  | Bacterial dysbiosis   | Oral mucositis                    |
|  | <i>P. oris</i>   |                       |                                   |
|  | <i>F. nucleatum</i>  | Immunomodulation      | Drug resistance                   |
| EGFR inhibitor<br>(32)                 | Skin microbiota  | Bacterial dysbiosis   | Skin toxicity                     |
| Immune checkpoint<br>inhibitor<br>(12) | <i>A. muciniphila</i> ,<br><i>B. adolescentis</i> , <i>B. fragilis</i> , <i>B.</i><br><i>longum</i> , <i>B. thetaiotaomicron</i> , <i>E.</i><br><i>faecium</i> , <i>E. hirae</i> , <i>B. obeum</i> , <i>F.</i><br><i>nucleatum</i> . | Immunomodulation      | Enhanced efficacy                 |
|  | Bacterial polyamine transport<br>system  | Immunomodulation      | Immune-related adverse<br>effects |

**Figure 1:** The bidirectional interplay between intestinal dysbiosis and anti-cancer therapy.

digestion by the host's metabolism, rendering them accessible for utilization by the gut microbiota as prebiotics. The microbiota ferments these MACs, converting them into Short-Chain Fatty Acids (SCFAs).<sup>34</sup> Research by Sonnenburg *et al.*,<sup>34</sup> showcased that a diet low in MACs results in an increase of *Bacteroides thetaiotaomicron*, which degrades intestinal mucus glycans. In

situations where dietary MACs are scarce, these bacteria possess the ability to utilize host mucus glycans, ultimately leading to a thinning of the intestinal barrier.<sup>35</sup> Higher levels of *Bifidobacterium* spp. are associated with a reduced incidence and/or growth of tumours. Both inulin and oligofructose demonstrated the ability to enhance the therapeutic efficacy of all six major cytotoxic



**Figure 2:** Gut microbiota modulating nutritional intervention and clinical outcomes in cancer therapy.

drugs like 5-FU, doxorubicin, cyclophosphamide, vincristine, cytarabine and methotrexate, representing diverse categories of cytotoxic drugs commonly used for treating cancer. Importantly, no detrimental effects on adjuvant therapy were noted from the inclusion of inulin or oligofructose.<sup>36</sup>

A clinical trial investigated the influence of a fibre blend (consisting of equal parts inulin and FOS) on the gut microbiota of patients with gynaecological cancer undergoing radiotherapy. The group receiving the prebiotic blend demonstrated a quicker restoration of *Lactobacillus spp.* as well as *Bifidobacterium spp.* counts two weeks after completing the radiotherapy, in contrast to the placebo group. This improvement led to enhanced stool consistency.<sup>37</sup> Diarrhoea is a frequent complication in enteral nutrition, significantly impacting recovery and prolonging the hospital stay, particularly in postoperative Gastric Cancer (GC) patients. A study involving 120 GC patients across the following groups: the 'fibre-free nutrition formula' group, the 'fibre-enriched nutrition formula' group and the 'fibre- and probiotic-enriched nutrition formula' group revealed that both fibre groups experienced a shorter Length of Hospital Stay (LOHS) compared to the fibre-free group. Additionally, they reported a reduction in diarrhoea symptoms.<sup>38</sup>

In another clinical trial, the impact of prebiotics, including FOS, xylooligosaccharides, polydextrose and resistant dextrin, on both gut microbiota composition and immune function was investigated in a cohort of 140 perioperative patients with CRC. During the preoperative period, the intake of prebiotics resulted in elevated levels of *Bifidobacterium* and *Enterococcus*, along with reduced levels of *Bacteroides*, compared to the placebo group. In the postoperative period, the control group exhibited an increase in the levels of *Enterococcus*, *Bacillus*, *Lactococcus* and *Streptococcus* compared to the prebiotic group. Following prebiotic consumption in the postoperative phase, there was an observed increase in the levels of benign strains of *Escherichia-Shigella*.<sup>39</sup>

Remarkably, the diversity of intestinal microbiota decreased from the preoperative to the postoperative period in patients not receiving prebiotics. Regarding immunological markers, prebiotic intake had a notable impact on immunologic indices both before and after surgery. Specifically, prebiotics led to a significant elevation in serum levels of immunoglobulins such as IgG, IgM and transferrin in the preoperative period. Furthermore, in the postoperative period, levels of IgG, IgA, cytotoxic T cells (CD3+ and CD8+ cells) and total B lymphocytes were higher compared to the control group.<sup>39</sup>

Therefore, utilizing inulin or oligofructose in dietary interventions could enhance the efficacy of cancer chemotherapy by altering gut microbial composition and influencing the immune system. Nevertheless, the existing studies on this are limited, necessitating larger-scale research to validate these observations.

## Probiotics

Probiotics, living microorganisms inhabiting the gut, play a pivotal role in maintaining health. These beneficial microbes are abundant in various fermented foods such as yoghurt, kefir, sauerkraut and kimchi.<sup>40</sup> Within the domain of fermented dairy products, natural yoghurt, sweetened yoghurt and matured cheese rank among the most popular choices. In a study conducted by Gonzalez *et al.*, which analysed the dietary patterns of 130 healthy adults, it was observed that individuals who consumed natural yoghurt had higher faecal levels of *Akkermansia* compared to those who did not consume it. Conversely, the consumption of sweetened yoghurt was associated with reduced levels of *Bacteroides*.<sup>41</sup>

A clinical trial was undertaken to assess the impact of yoghurt containing *Bifidobacterium* on the gut microbiome and clinical outcomes of patients diagnosed with metastatic Renal Cell Carcinoma (mRCC) initiating treatment with Vascular Endothelial Growth Factor-Tyrosine Kinase Inhibitors

(VEGF-TKIs). Patients were stratified into two cohorts: the probiotic-supplemented group, receiving two servings of 120 g probiotic yoghurt per day and the probiotic-restricted control group. Notably, probiotic supplementation significantly augmented the abundance of *Bifidobacterium spp.* Furthermore, among patients demonstrating clinical benefit-characterized by the complete or partial response, or sustained disease stability for over 6 months-there was a conspicuous elevation in the levels of *Barnesiella intestinihominis* and *Akkermansia muciniphila* compared to counterparts not experiencing clinical benefit.<sup>42</sup> This study marks a pioneering initiative in prospectively assessing the effects of fermented food on clinical outcomes in cancer patients receiving chemotherapy.

### The Ketogenic Diet (KD)

Tumour cells exhibit elevated glucose uptake compared to the surrounding tissue and have the ability to generate lactate via the aerobic glycolytic pathway.<sup>43</sup> As a result, limiting the availability of glucose to cancer cells could starve them of energy production, potentially resulting in decreased tumour growth. KD is characterized by a high-fat, isocaloric diet that significantly reduces carbohydrate intake.<sup>8,43</sup> It is specifically structured to induce ketosis and deprive the tumour cells of energy and in turn reduce their proliferation.<sup>43</sup> However, the precise role of the gut microbiota in mediating the anti-tumour effects induced by KD during cancer therapy is still not fully understood. This potential influence of the gut microbiota has been investigated in other health conditions such as autism and epilepsy. In infants with refractory epilepsy, KD led to a reduction in seizure frequency, an increase in the abundance of *Bacteroides* and *Prevotella* and a decrease in *Cronobacter* levels.<sup>44</sup> While these findings are promising, their specific impact on cancer patients undergoing cancer therapies remains an area that requires further research and empirical examination.

### Dietary restrictions

Dietary restrictions have the potential to counteract gut dysbiosis, offering a positive influence on the host's metabolism and the immune system. Specifically, gut permeability dysregulation and translocation of bacteria from the gut lumen to the underlying mucosa can significantly impact the immune system. The balance in intestinal immune regulation is maintained through intricate interactions between epithelial cells and dendritic cells. Therefore, modulating the microbiota through dietary changes holds promise in enhancing treatment outcomes for cancer patients. Dietary restrictions encompass a range of approaches aimed at improving health and potentially influencing disease outcomes.<sup>45</sup> One such approach is Caloric Restriction (CR), which involves reducing energy intake by 20-50% without causing malnutrition or compromising essential nutrients. Time-Restricted Feeding (TRF) is another approach, where food consumption is limited to a specific 4 to 12 hr time window daily. Intermittent Fasting

(IF) alternates between 24 hr fasting periods and 24 hr ad libitum eating periods. Lastly, the Fasting-Mimicking Diet (FMD) involves following a low-calorie, vegetable-based diet for five consecutive days, followed by a return to normal eating cycle, typically repeated once a month.<sup>46</sup>

Lee *et al.* conducted a study elucidating that cycles of fasting exhibited comparable efficacy to specific chemotherapeutic agents in retarding cancer progression. Furthermore, fasting was observed to potentiate the effectiveness of these drugs against malignancies such as melanoma, glioma and breast cancer cells. This enhancement was attributed to heightened oxidative stress, caspase-3 cleavage induction, DNA damages and apoptosis promotion. Subsequent *in vitro* and *in vivo* examinations corroborated these results, underscoring the favourable influence of short-term fasting on the efficacy of chemotherapy and radiotherapy.<sup>47</sup>

Nonetheless, comprehensive and dependable data in this field are presently lacking. It is imperative to recognize that while dietary constraints such as fasting may offer advantages, they could exacerbate cachexia syndrome. Future investigations should prioritize identifying optimal therapeutic windows for these nutritional interventions, taking into account factors like gut microbiota composition, cancer type and patient-specific characteristics.<sup>48</sup>

### Molecular Pathological Epidemiology: A Methodological Approach to Precision Nutrition Therapy

The intricate relationship between diet and the microbiome, especially during cancer treatment, remains a domain where understanding is currently limited. Several challenges hinder a comprehensive comprehension of this interaction. These include inadequate tools for accurate dietary data collection, suboptimal study designs, small sample sizes and the inherent difficulties associated with conducting research involving patients undergoing medical procedures, leading to a paucity of high-quality research.<sup>49</sup> As a result, achieving precision nutrition in cancer treatment, which necessitates a deep understanding of this interplay, remains a challenging goal without addressing these critical knowledge gaps.

Although an official definition for precision nutrition therapy is lacking, it can be broadly described as a tailored nutritional intervention aimed at enhancing treatment efficacy based on an individual's distinct attributes. These attributes encompass genetics, gender, race/ethnicity, health background, lifestyles and microbiome composition. One method embracing these elements for precision nutrition is Molecular Pathological Epidemiology (MPE).<sup>50</sup>

Growing evidence underscores the association between germline genetic variations and fundamental aspects of tumorigenesis,

immune responses and notably, the microbiome.<sup>51</sup> Research involving mouse strains has indicated a heritability range of 26% to 65% in gut microbiota, emphasizing the genetic influence on microbial composition. Moreover, this influence is intricate, entailing interactions between genes and the environment, especially concerning dietary factors. Genetic backgrounds have been shown to significantly affect responses to specific diets, while the microbiome plays a crucial role in regulating metabolism, as demonstrated through cross-fostering experiments.<sup>52</sup>

Intriguingly, studies employing the Molecular Pathological Epidemiology (MPE) approach have shed light on diet-immune interactions within the context of cancer. Notably, individuals exhibiting higher levels of Forkhead Box Protein 3 Gene (FOXP3+) T regulatory cells demonstrate a reduced risk of colorectal cancer.<sup>53</sup> MPE research further underscores the significance of dietary patterns, specifically those conducive to a balanced microbiome, in mitigating the development of *Fusobacterium nucleatum*-positive CRC. The role of the immune system is paramount, as evidenced by low immune infiltration being associated with *Fusobacterium nucleatum*-related microsatellite instability, intricately linked with tumour genetic features.<sup>54</sup> In the realm of cancer treatment, precision nutrition therapy must meticulously account for the genetic and environmental factors that contribute to the pathogenesis of cancer. This approach holds great promise in enhancing the efficacy of conventional cancer treatments.

## CONCLUSION

Integrating nutrition and the microbiome into cancer therapy holds immense promise for enhancing treatment outcomes in cancer patients. However, there is a significant dearth of comprehensive data regarding how nutritional support impacts the composition of gut microbiota and its correlations with clinical outcomes in cancer therapy. The hypothesis that a diverse and thriving microbiota could positively influence oncological results is compelling. To translate this vision into reality, a multi-pronged approach is essential and we must deepen our understanding of crucial genetic, dietary and microbial markers that can predict treatment response, adverse effects and drug resistance. Rigorous and extensive studies are necessary to answer pivotal questions, such as a) which biomarkers indicate a positive microbial response to nutritional intervention during cancer therapy and b) the specific microbial elements that mediate or alter the impact of diet on treatment efficacy. Advancing research in these domains represents a critical stride toward achieving precision nutrition in the context of cancer.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**5-FU:** 5-Fluorouracil; **AML:** Acute Myeloid Leukaemia; **CR:** Caloric Restriction; **CRC:** Colorectal Cancer; **FMD:** Fasting-Mimicking Diet; **FOS:** Fructo-oligosaccharides; **GOS:** Galactooligosaccharides; **GC:** Gastric Cancer; **GF:** Germ-free; **GVHD:** Graft-versus-Host Disease; **IF:** Intermittent Fasting; **KD:** Ketogenic diet; **LOHS:** Length of hospital stay; **mRCC:** Metastatic Renal Cell Carcinoma; **MACs:** Microbiota-accessible Carbohydrates; **MPE:** Molecular Pathological Epidemiology; **MYD88:** Myeloid Differentiation Primary Response-88; **ROS:** Reactive Oxygen Species; **SCFAs:** Short-chain Fatty Acids; **TRF:** Time-restricted Feeding; **VEGF-TKIs:** Vascular Endothelial Growth Factor-Tyrosine Kinase Inhibitors.

## AUTHORS' CONTRIBUTION

All authors contributed equally to conceptualising the study and conducting the literature review and they collaborated in writing and revising the manuscript. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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