NIGERIAN JOURNAL OF ENVIRONMENT AND HEALTH
Elucidating the Environment-Health Nexus in Nigeria
ISSN: 2616-0714 (print edition) eISSN: 2616-0706 (online, open access)

Nigerian Journal of Environment and Health 4 (2024) 14 -28

Microbiota Modulation in Oncology: Implications For Cancer Development And Therapeutic Strategies

Felix Oladele Okunlola[1*], Oluwakemi Semilore Omowumi[1], Odunayo Mariam Abidaku[1], Peace Abiodun Olajide[1], Opeyemi Ojueromi[1]

[1]*Department of Natural Sciences, Precious Cornerstone University, Ibadan, Nigeria.*

Abstract

In oncology, microbiota balance studies the complex relationship between the body's microbial networks and cancerous development. The billions of microbes that comprise the human microbiota are essential for maintaining homeostasis and affecting a number of physiological functions. Recent research suggests that modifications to this microbial ecosystem may have an impact on the onset and course of cancer. An imbalance in the microbiota known as dysbiosis has been linked to irritability, safe brokenness, and—surprisingly—direct effects on carcinogenesis. Comprehending the relationships between microbiota and malignant growth facilitates the development of innovative restorative techniques. Analysts are investigating the potential implications of targeted microbiota modification for malignant growth therapy outcomes. It is becoming evident that probiotics, prebiotics, and fecal microbiota transplantation may be utilized to improve the efficacy of traditional cancer therapies by reestablishing the microbial balance. Moreover, there is a growing body of research on the influence of the microbiome on immunotherapy responses. All things considered, deciphering the astounding relationship between microbiota and cancerous development promises to advance our understanding of the causes of disease and improve treatment approaches. In this review, the part microbiota plays in carcinogenesis, how microbiota can lead to cancer and different therapeutic strategies such as diet, probiotics, phytochemical and so on were discussed.

Keywords: Microbiota, cancer, therapeutic strategies, Carcinogenesis, Bacteria

1. Introduction

As the most common cause of sickness and death in the US last year, cancer accounted for 600,000 deaths and 1.7 million new cases of diagnosis (Siegel et al., 2019). Cancer not only causes great pain but also has a large financial cost; in the US, the yearly cost of healthcare for cancer patients exceeds $125 billion (Sung et al., 2019). Even in light of a recent high-profile report that asserted cancer is primarily stochastic or "bad luck" caused by the accumulation of spontaneous mutations during DNA replication in tissues where stem cells undergo a relatively large number of cell divisions, it is generally acknowledged that the environment has a major impact on cancer risk (Falzone et al., 2018).

Accepted 15 July 2024.
*Corresponding author
Email address: felixokunlola@pcu.edu.ng (Felix Oladele Okunlola)

Numerous epidemiologic and occupational health studies have shown that exposure to known or suspected carcinogens and lifestyle variables have a substantial impact on the development of cancer. It is estimated that 15–25% of cancer cases are caused by infectious agents, 20–30% are caused by tobacco use, and 30–35% are caused by food, exercise, and/or energy balance issues (such as obesity). Both individually and in combination (i.e., mixed exposure), UV radiation from sunshine, alcohol, and a variety of other chemicals (such as asbestos, benzene, and radon) also contribute (Stout et al., 2021; Xu et al., 2020).

It is possible to think of the bacteria that live in our stomachs and other parts of our bodies as a type of environmental factor that we are exposed to at high concentrations all our lives. Since commensal bacteria have been difficult to culture up until recently, our understanding of them has been restricted. The majority of these microbes are bacteria. However, metagenomics sequencing methods have emerged in the last 10 years. These methods combine computational analysis of whole-genome shotgun sequence reads or selected 16S rRNA Hypervariable areas with next-generation DNA sequencing technology. This has enabled for the culture-independent recording of the variety and quantity of microorganisms at diverse body locations (Rawla et al., 2019; Malesza et al., 2019). The alpha and beta diversity measures, derived from ambient microbial ecology, are useful for illustrating the microbiota's complexity. A diversity defines a sample's richness (number of species and evenness of distribution of those organisms), whereas beta diversity displays the degree of absolute or relative overlap in common taxa between samples (Xiao and Yu, 2021). The variety of microbial beta diversity in the microbiota varies greatly across individuals. Some humans may benefit from a certain organism that is underrepresented in others. Numerous metagenomics sequencing investigations have identified significant variations in the composition of microbial communities between individuals who are healthy and those who are ill, attributing these differences to environmental and lifestyle factors as well as genetics, place of residence, body mass index, and nutrition (Sheena et al., 2022). Consequently, microbiota have been linked to the development of some diseases, including cancer, or to their prevention. This idea has been confirmed by a large body of studies employing gnotobiotic mice models that have been colonized with one or more particular bacteria. A growing amount of evidence indicates that cancer and other diseases may be treated by changing the microbiome.

2.0. Human microbiome

More microbial cells than somatic and germ cells combined are found in the human body (Gavas *et al.,* 2021). In addition, the collective genome of our microbiota, referred to as the microbiome, has 100 times more genes than the human genome (Vivarelli *et al.,* 2019). The large bulk of this microbiota is made up of our GI tract's resident bacteria, but there are also viruses, eukaryotes like yeast and protozoans, and archaea (Liu *et al.,* 2021; Bolte *et al.,* 2021). Like the majority of other animals, humans receive significant amounts of microbiota from their mothers before birth. The composition of the microbiota is very dynamic during the first three years of life and subsequently becomes more stable and increasingly adult-like with higher complexity, despite the numerous tiny changes that occur during infancy, adolescence, middle age, and old age (Cryan *et al.,* 2019).

The variety of unrelated individual's is greater than that of dizygotic twins, who are more varied than monozygotic twins, according to twin study (Rinninellà *et al.,* 2019). Certain taxa are obviously more heritable than others. GWAS have started to identify loci in people and mice by treating the microbiome's composition as a multidimensional trait (Wastyk *et al.,* 2021). A portion of the human microbiome consists of loci next to loci that affect the likelihood of disease. It might be challenging to discern between related and causative single nucleotide polymorphisms (SNPs) because of linkage disequilibrium; yet, several potential genes, including the vitamin D receptor, are presently under investigation (Gomaa *et al.,* 2020; Abenavoli *et al.,* 2019). However, relatively tiny impact sizes that have proven hard to repeat have hindered the overall genetic architecture supporting microbiome traits (Ramirez *et al.,* 2020). This may not come as a surprise given the role that diet and other environmental factors play in creating "noise" that masks minute genetic effects. Considering this constraint, it might be advantageous to combine GWAS with dietary intervention research. A recent study identified a link between *Bifidobacterium* abundance and milk intake, but only in persons with a specific genotype (Zheng *et al.,* 2020).

Our diets do, as previously indicated, alter the composition of our microbiota; yet, regular dietary patterns are more crucial than transient dietary changes (Thursby and Juge, 2017). Given that different taxa within the gut microbiota have differing capacities for metabolism, it is not surprising that a particular diet favors some bacteria over others. A recent research (Sorboni *et al.,* 2022) suggests that some microorganisms could go extinct. The microbiome is impacted by alterations in lifestyle and cultural norms at every stage of life. The baby's microbiome is significantly impacted by breastfeeding versus formula feeding and vaginal versus cesarean section delivery techniques (Martino *et al.,* 2022). Some of these microbiome differences persist throughout adulthood, but the majority do not. However, even brief

aberrations in the infant can be relevant since infancy represents a developmental window of susceptibility to many disease circumstances, including those involving the still-forming of numerous cell types (such as neurons and lymphocytes). This notion is supported by the finding (Wilmanski *et al.,* 2022) that compositional alterations in the microbiota of three-month-old children were linked to the development of asthma later in life. Babies and early children may be more susceptible to low levels of antibiotics in food, which might alter the microbiota and lead to obesity, according to studies on animals (Aggarwal *et al.,* 2022). These cases of obesity and asthma have been linked to the hygiene theory, which postulates that a lack of exposure to microbiota throughout childhood decreases immunological tolerance and predisposes people to allergies and other chronic disease states. Lifestyle choices made later in life have an influence on the microbiome of the elderly, with those dwelling in long-term residential care institutions experiencing less diversity in their lives than those free to live in the community (Yao *et al.,* 2021). Although the issue of causality vs. correlation has not been addressed, these compositional alterations have been associated to nutritional inequalities, greater levels of inflammation, and frailty in patients residing in long-term care facilities (Hussain *et al.,* 2021).

Despite accounting for the bulk of cells in the human body, microbial cells are small, mitochondria-like structures that account for just a few pounds of body weight—roughly 2-7% of an individual's total biomass, excluding water weight. On the other hand, because of their high metabolic capacity and potent impacts on the immune system, our microbiota have a disproportionately huge influence on human biology. There are several aspects of the relationship between commensal microbiota and the human host, including advantages and disadvantages for human health. On the one hand, the microbiota in our stomach helps us absorb nutrients and produce energy from food. For instance, the gut microbiota has much more genes linked to glucose metabolism, such as 115 families of glycoside hydrolases and 21 families of polysaccharide lyases (Krautkramer *et al.,* 2021; Tett *et al.,* 2021). There is little genetic similarity in the human genome since the gut microbiota and microbiome co-evolved with mammals (and all animals) and their genomes in the absence of selective pressure. Additionally crucial to the growth and upkeep of the innate and adaptive immune systems are commensal gut bacteria. Eubiosis, the process by which bacteria maintain a commensal or symbiotic relationship with their hosts, is necessary for these advantageous roles. It is challenging to pinpoint a single, ideal eubiosis because of demographic variation, and what works well for one person might not work well for another.

The makeup of the microbiota might vary depending on the pathogen, the antibiotic being used, and dietary modifications. However, a person's microbiota is incredibly resilient to disruption and may progressively return to normal levels (Kolodziejczyk *et al.,* 2019). Unlike eubiosis, dysbiosis is indicative of altered community structure across a range of illnesses. For instance, a change in the ratio of the two main GI bacterial phyla, Firmicutes and Bacteroidetes, is linked to obesity, and this taxonomic shift increases mice's adiposity and ability to absorb calories (Dhar and Mohanty, 2020; Cheng *et al.,* 2020). Pathogenic microbiota can flourish in dysbiosis, producing poisonous compounds and antigens that cause erroneous immune reactions. These alterations are particularly significant in oncology as inflammation and dysregulated metabolism are thought to be characteristics of cancer (Fong *et al.,* 2020; Lee *et al.,* 2022).

3.0. Microbiota and Oncogenesis

Several studies have demonstrated the role of microbes in oncogenesis. According to Uphlenhopp *et al.* (2020), infectious organisms are thought to be the cause of almost 20% of cancer cases. Certain bacteria, such as *H. pylori*, have been directly connected to the emergence of cancer. The World Health Organization has designated *H. pylori* as a class I carcinogen, and it has been connected to stomach adenocarcinoma and mucosa associated lymphoid tissue (MALT) lymphoma (Alsina *et al.,* 2023) *Salmonella enterica*, *Chlamydia trachomatis,* and *Escherichia coli* have also been linked to malignancies of the gallbladder, colorectal, and cervical regions (Wong *et al.,* 2019). Furthermore, alterations to distinct microbiota species have been associated with microbiome dysbiosis, a condition connected to cancer (Makki *et al.,* 2020). Recent research indicates that antibiotic-mediated microbial dysbiosis has a major impact on carcinogenesis (Manor *et al.,* 2020). There have also been other new theories linking dysbiosis of the microbiota with cancer; nevertheless, comprehensive information about the roles played by each microbiota component and their potential importance in carcinogenesis is still lacking. Several studies have demonstrated a link between microbial dysbiosis and cancer. For example, the microbiota of a region associated with cancer differs from that of an adjacent healthy mucosa (Brennan and Garrett, 2019; Picardo *et al.,* 2019). Numerous studies have examined the alterations in microbiota components in various cancer types; nevertheless, further research is necessary to completely comprehend the relationship between these variations and carcinogenesis.

4.0. The Part Microbiota Plays in Carcinogenesis

Bacterial and viral infections have long been linked to the growth of tumors. They can affect a number of cellular processes, such as metabolism and immune response, and they may even contribute to the onset of cancer. There is ample

evidence to support this in the case of luminal gastrointestinal system malignancies, since microorganisms have been connected to the growth of *Helicobacter pylori* and *Fusobacterium nucleatum,* which cause stomach and colorectal cancers, respectively (Helmink *et al.,* 2019). It's been demonstrated that *H. pylori* alters key carcinogenic signaling pathways such the beta-catenin and Ras/MEK/ERK pathways, as well as the processes leading to stomach carcinogenesis by producing cytotoxins that disrupt the autophagy and apoptosis pathways. Furthermore, via generating IL8.15 and NFkB signaling, *H. pylori* modifies chronic inflammation (Wong and Yu, 2019).

The presence of *F. nucleatum*, which has been directly linked to colon cancer, attaches to and penetrates colonic epithelial cells via the FadA surface protein. Through its interaction with e-cadherin, beta-catenin and WNT signaling are altered, inducing inflammatory alterations and accelerating the growth of cancer. According to data from a large prospective cohort in the United States, *F. nucleatum* mediates interactions related to diet and offers information on molecular and prognostic alterations in colorectal cancer "sidedness" in tissue samples. It steadily reduces from cecum to rectum (Gomaa *et al.,* 2020). These and other findings had a major impact on the widespread use of the fecal microbiota as a proxy for the gut microbiome. A recent study that profiled the mucosal, luminal, and fecal microbiome of healthy individuals and mice along the entire gastrointestinal tract found significant compositional differences between the mucosa, lumen, and feces as well as between different anatomic locations (El Tekle and Garrett, 2023). The effects of cancer treatment might differ depending on the anatomical location of the microbiota in cancer and normal tissue.

A broader population of commensal "acte'Ia may impact cancer risk and progression through processes such as competitive exclusion, beyond the direct effects of particular microbiota on local tissues (Willis and Gabaldon, 2020). Microbial metabolites are crucial for intestinal homeostasis and overall health. Examples of these metabolites are short chain fatty acids (SCFAs), which are created in the colon by fermenting normally indigestible carbohydrates (fibers or resistant starches). Thus, the bacteria that are engaged in the metabolism and manufacture of SCFAs actively contribute to the stability and well-being of the gut flora. These microbial compounds also decrease inflammation, increase cancer cell apoptosis, and prevent the formation of Gram-negative infections (Green and Grivennikov, 2019). Additionally, they provide colonocytes and other bacteria with energy (a process known as cross-feeding). Lower concentrations of beneficial SCFA-producing bacteria have been consistently observed in colorectal cancer studies. Additionally, studies employing animal models have effectively demonstrated that dietary fiber inhibits the development of colorectal carcinogenesis in a manner dependent on butyrate and microbiota (Mager *et al.,* 2020).

However, it is becoming recognized that the secondary bile acids generated by gut microorganisms from the primary bile acids generated by the liver are carcinogenic. According to recent studies in animal and experimental settings, the gut microbiome may employ bile acids as a messenger (via the portal vein) to modify cancer via bile acid-regulated immune response (Cullin *et al.,* 2021). The importance of intra-tumoral bacteria in cancers, including pancreatic cancer, has also been brought to light by other recent investigations. It has been suggested that these bacteria may be found in the tumors of the majority of pancreatic cancer patients and may have a role in the development of treatment resistance (Lam *et al.,* 2021). In addition to the microorganisms previously discussed, viruses have also been shown to contribute to the development of cancer in a variety of histologies, including Merkel cell carcinoma, hepatocellular carcinoma, cervical cancer, and lymphoma (Belkaid and Hand, 2019). Though it's unclear if these are direct or indirect impacts, and causality hasn't been shown, more recent study has linked intestinal fungal and viral components to colorectal cancer.

There are several ways that viral infections might lead to cancer. Through the development of chronic inflammatory states or global immune system suppression that weakens anti-tumor immunity, they may indirectly contribute to carcinogenesis (examples: HIV, HCV, HBV). Furthermore, they may more directly induce cancer through viral oncogenes (like EBV) by directly integrating genetic material into the host genome and producing genes that both stimulate aberrant DNA damage response pathways and encourage cellular growth and proliferation (Grassiri *et al.,* 2010). Most importantly, it has been shown that viruses-driven cancers respond better to several forms of treatment, such immune checkpoint inhibition via the recognition of "non-self" antigens (Jacob *et al.,* 2022). Radiation therapy responses might be made worse by virally-induced DNA damage (Nagai and Otake, 2022). Responses to different forms of therapy may be associated with the identification of tumors. T cell-directed treatments are another method being used to target cancers infected with viruses (Wei *et al.,* 2023). By upregulating immunosuppressive molecules/pathways (PD-L1) or indolamine-2,3-dioxygenase (IDO) through the development of an interferon response, viruses can also negatively alter tumor immunogenicity and the local tumor immune microenvironment (Janagam *et al.,* 2017). The significance of viruses in malignancies becomes more evident as we understand more about them (Chang *et al.,* 2020). It's likely that useful strategies for preventing and treating cancer may soon be able to target these viruses.

5.0. Microbial infections are the cause of several cancers.

Some of the best evidence that microbiota are more than simply passengers or bystanders comes from *Helicobacter pylori*

and numerous other oncogenic viruses that cause cancer. *Helicobacter pylori* infections and stomach cancer caused by H. pylori are closely related. According to Bauer *et al.* (2020), gastritis brought on by *Helicobacter pylori* is thought to occur before cancer. During research that resulted in his 2005 Nobel Prize in Physiology or Medicine, Dr. Barry Marshall contracted an *influenzae* virus. *H. pylori* to validate Koch's claims and establish that it is the cause of stomach ulcers and arthritis (Levitt *et al.,* 2021). As a result, the *H. pylori* bacteria is disappearing from human populations all over the world. *H. pylori*, however, differently influences stomach pH and lowers acid reflux, which may protect against Barrett's esophagus and esophageal cancer (Patel *et al.,* 2020). This shows that there may be a lot more nuance to the interaction between dangerous bacteria and their human hosts than was previously thought. This is especially true for bacteria-derived carcinogens. Oncogenic bacteria infections do not always result in cancer; in contrast to viruses, which produce constitutively active viral mimics of cellular proto-oncogenes (Gomaa *et al.,* 2020), microbial dysbiosis-induced tumor development is a complicated process that involves "multiple hits." The incidence and severity of cancer are influenced by genetic variability in both the pathogen and the host, as well as environmental variables. As an example, only *H. pylori* strains that carry the cagA virulence factor are efficient in developing stomach cancer and gastritis. Another key factor in deciding whether an infected person gets cancer is the host's genetic composition, which influences the immune response. Obesity, alcoholism, and tobacco use are a few other dietary and lifestyle variables that are significant risk factors. Chronic inflammation is one such risk factor that is thought to be particularly important (Lam *et al.,* 2021).

6.0. Through the production of metabolites and poisons, microbiota can lead to cancer.

While the role of the microbiome in carcinogenesis has been established, more investigation is needed to determine the exact mechanism by which these microbial components influence the course of cancer and its management. In addition to the indirect mechanism of microbiota-induced inflammation in carcinogenesis, a variety of bacterial metabolites directly contribute to the etiology of cancer (Mager *et al.,* 2020). One of these chemicals is bacterial toxins, which can influence biological processes associated with cancer, including as differentiation, apoptosis, proliferation, and cell cycle, by interacting with many signaling pathways (Mager *et al.,* 2020). For instance, the *Helicobacter pylori* bacterial oncoprotein known as cytotoxin-associated gene A (CagA) interacts with host cell proteins such as PAR1 (Partitioning-defective 1), SHP2 (Src homology two phosphatases), and E-cadherin to induce genetic instability (Lam *et al.,* 2021). This link has been associated to the prevention of apoptosis, enhanced cell survival and proliferation, polarity loss in cells, and neoplastic transformation (Lee *et al.,* 2022). Another example is the metalloprotease toxin generated by enterotoxigenic strains of Bacteroides fragilis (ETBF), which is associated to the development of mucosal inflammation and is a risk factor for colorectal cancer (Fong *et al.,* 2020). When intestinal epithelial cells with BFT overexpress the spermine oxidase enzyme (SMO), reactive oxygen species (ROS) and DNA damage are generated (Xu *et al.,* 2020). Furthermore, BFT exposure causes morphologic alterations, e-cadherin cleavage, and stimulation of cell proliferation, which is at least partly mediated by beta-catenin nuclear translocation, c-myc proto-oncogene activation, and e-cadherin cleavage (Wong *et al.,* 2019).

It's feasible that gut microbes' capacity to cause cancer Is influenced by their metabolism. The microbial community breaks down undigested dietary items into a range of compounds, some of which have been demonstrated to either aggravate or prevent the development of cancer (Yao *et al.,* 2021). Short-chain fatty acids, also known as butyrate, propionate, and acetate, are crucial byproducts of the fermentation of carbohydrates and have anti-inflammatory, anti-proliferative, and apoptotic-triggering properties (Hussain *et al.,* 2021). It also supports intestinal homeostasis by increasing the number of Foxp3 IL-10-producing Treg cells (Gomaa *et al.,* 2022). *Lactobacillus acidophilus, Lactobacillus bulgaricus, Lactobacillus plantarum, Bifdobacterium infantis, Bifdobacterium breve, Bifdobacterium longum,* and *Streptococcus thermophiles* all shown comparable anti-neoplastic and pro-apoptotic characteristics (Picardo *et al.,* 2019). Studies have indicated a correlation between the expression of GPR40 (G protein-coupled receptor 40), a CLAs receptor, and the development of colorectal cancer as well as a poor prognosis (Jacob *et al.,* 2022).

On the other hand, microbial fermentation of a high-fat or high-protein diet produces NOCs (N-nitroso compounds), polyamines, ammonia, hydrogen sulfide, and secondary bile acids that promote the formation of tumors by inflaming the body and destroying DNA (Patel *et al.,* 2020). According to Bernstein and colleagues, brief exposure to bile acid produced reactive oxygen and nitrogen species (ROS/RNS). DNA damage, mutation rates, and apoptosis all increased as a result. Mutant cells had development benefits over time, including resistance to apoptosis, which enhanced the risk of stomach cancer (Cammarota *et al.,* 2020). Furthermore, Cheng et al. (2020) reported that secondary bile acid, namely deoxycholic acid, increases the proliferation and invasion of cancer cells through the beta-catenin signaling pathway.

All things considered, the microbiome may target tumor cells directly or indirectly through immune system modulation to aid in the onset and spread of cancer. In this context, bacteria can affect cancer formation by direct (as an antigen) and indirect (by creating byproducts and cytokines) methods, as well as innate and adaptive immunity (including dendritic

cells, natural killer cells, myeloid cells, CD8 T cells, and so on). In the former, cross-reactive T cells, which can enhance anti-tumor immunity, were created due to similarities between microbial epitopes and tumor antigens (Wei *et al.,* 2023). As mentioned in a number of papers, cross-reactive T CD8 and T CD4 cells as well as molecular mimicry may boost the efficiency of anti-cancer therapy (Makki *et al.,* 2018). In addition, when pattern recognition receptors (PRRs)—like TLRs and NLRs—identify bacterial antigens, they start downstream signaling cascades that activate STAT3 and NF-B, which in turn release pro- and anti-inflammatory cytokines. Dendritic cells (DCs), which travel to mesenteric lymph nodes and activate T helper cells, are antigen-presenting cells that were activated by PAMPs. Notably, microbial dysbiosis and over-activation of the NF-B, STAT3, and wnt/-catenin signaling pathways contribute to cancer pathogenesis by altering anti-tumor immune responses, increasing inflammation, and causing cancer cell proliferation and metastasis (Xu *et al.,* 2020).

7.0. The microbiota may be employed as a biomarker in cancer treatment.

The variety and makeup of the gut microbiota are connected to the therapeutic efficacy of several forms of cancer therapy, according to accumulating data from pre-clinical models and human cohorts (Gavas *et al*., 2021). This study supports therapeutic manipulation of the microbiome and verifies the potential use of the gut microbiota as a biomarker of response to cancer treatment. This should be studied in conjunction with other prognostic indicators (tumor mutational burden and other factors). Perhaps the most exciting data to far about the possible use of gut microbiota signature for response was found in a research conducted on a cohort of patients with melanoma undergoing anti-PD1 treatment (Cryan *et al.,* 2019). Based on the baseline gut microbiota configuration, two different groups of patients were identified. It's important to note that one of these clusters, designated "Type I" due to its high *Clostridiales* abundance and low *Bacterioloides* abundance, was limited to responders. Notably, the signature kept its substantial connection with response in multivariable-adjusted models, outperforming other well-established prognostic biomarkers including mutational burden (Cryan *et al.,* 2019). This concept is highly relevant given the current efforts to characterize the gut and other microbiota in human health and disease (Liu *et al.,* 2021) and the fact that clinical trial designs are currently incorporating the profiling of the gut, tumor, and other microbiota. Some of the significant drawbacks to such an effort are the methods used to profile the microbiome (16S sequencing versus metagenomics versus metatranscriptomics versus metabolomic profiling) and the complexities and questions surrounding the appropriate timing and intervals for microbiome profiling (which will almost certainly depend on therapy). It's also probable that microbiota won't be a good enough "stand-alone" diagnostic; instead, it will work best in conjunction with other established and emerging biomarkers that alter the gut microbiome to enhance the treatment response in cancer patients. As we proceed, standardizing the pipelines for data collection, sequencing, and analysis will be essential (Falzone *et al.,* 2018; Sung *et al*., 2019).

8.0. Strategies for Treating Cancer

The gut microbiota influences the host's response to several anticancer treatments, as shown by preclinical research utilizing cell culture and animal models, meta-analyses of clinical trials, and human clinical trials. It has become clear that immunomodulation is a crucial mechanism that permits these distinct reactions. Dysbiosis is both a cause and an effect of variable reactions to treatment. For example, patients with hematological malignancies undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) had a greater chance of survival if their intestinal diversity was larger (Siravegna *et al.,* 2017). For patients getting allo-HSCT, the fact that immunological modulation brought on by higher microbial diversity limits the degree of graft vs host illness is a major concern. Furthermore, the compositional changes caused by chemotherapy may result in a variety of adverse effects.

8.1. Immunotherapy

The adaptive immune system, which is vital for identifying and getting rid of malignant cells, is primarily controlled by T cells. The existence of a second costimulatory or co-inhibitory signal, which is delivered by extra surface molecules on antigen-presenting cells, is essential for the gradual activation of T cells. Inhibitory molecules, such as PD-1, PD-L1 (PD-1 ligand), and CTLA-4 (cytotoxic T lymphocyte-associated protein 4) function as immunological checkpoints, reducing the immune response and halting autoimmune disorders. On the other hand, inhibitory ligands and receptors are frequently overexpressed by cancer cells and stromal cells inside the tumor microenvironment, helping the malignancy evade immune-mediated death. The FDA has approved immune checkpoint inhibitors, which stimulate the patient's own immune system to combat cancer. Examples of these inhibitors are monoclonal antibodies against CTLA-4 (ipilimumab), PD-1 (nivolumab), and PD-L1 (pembrolizumab). They have proven to be quite successful in treating lung, kidney, bladder, and melanomas in addition to Hodgkin's lymphoma.

Checkpoint inhibitors induce a wide variety of reactions in individuals, just as other cancer treatments (Dall'Olio *et al.,*

2022). Notably, since the gut flora of the patient interacts with the immune system, the efficacy of checkpoint inhibitors appears to be dependent on it. Therefore, it is not surprising that the gut microbiota and immune checkpoint inhibitors may work together to explain the observed variance in clinical responses. Two distinct studies have shown that gut bacteria can counteract distinct responses to immune checkpoint inhibitors in animal models of melanoma. Researchers discovered that tumor development differed depending on where the mice came from—from Taconic suppliers to The Jackson Laboratory (JAX). These mice (C57BL/6) have a different microbiota while having the same genetic composition. The tumors in JAX mice developed more slowly and reacted more strongly to anti-PD-L1 immunotherapy than in Taconic mice (Mo *et al.,* 2023). JAX donors' fecal microbiota transplantation increased the anticancer effectiveness of the recipients against PD-L1. The researchers determined that *Bifidobacterium* was necessary and that via modifying dendritic cell activity, "therapeutic feeding" (probiotics) of *Bifidobacterium* alone might mediate the effectiveness of anti-PD-L1 and increase CD8+ T cell responses to eliminate malignancies.

In the other study, other researchers noticed a sharp change in the microbiome after receiving an anti-CTLA-4 injection, which was characterized by a rise in the number of *Clostridiales* and a fall in *Bacteroidales* and *Burkholderiales* (Mo *et al*., 2023) In a germ-free environment, anti-CTLA-4 immunotherapy was unable to decrease tumor burden; however, this drawback was overcome by the addition of *Bacteroides fragilis* and/or *B. subtilis*. All things considered, by developing dendritic cells and changing TH1 responses that rely on IL-12, these microorganisms enhanced tumor selectivity. The microbiota and checkpoint blockades employed in the two research varied, but their mechanisms of action—which included tumor-infiltrating effector T cell function enhancement and dendritic cell maturation/activation—were very comparable. Hepatic and gastrointestinal adverse effects are linked to immune checkpoint drug efficacy (Rahman *et al.,* 2022). Hepatitis, diarrhea, and enterocolitis are often brought on by immune checkpoint inhibitors. These adverse effects are brought about by a complicated interaction between host genetics, immunological responses, environment, and microbiota. Compared to colitis-free persons who also get ipilimumab (Georgiou *et al.,* 2021) patients who acquire new-onset, immune-mediated colitis as a result of anti-CTLA4 monoclonal antibody treatment have a lower abundance of *Bacteroidetes*. Microbiological modules associated with polyamine transport and vitamin B (B1, B2, and B5) production provided protection, as there was a strong positive association between their relative abundance and the lack of colitis in humans. Synthetic CpG oligonucleotides, or CpG-ON, are TLR9 ligands that activate the immune system. Humans respond therapeutically to CpG-ON and inhibitory IL-10 receptor antibodies in combination with peptide vaccinations, which reduces tumor volume and lengthens survival (Wyres *et al*., 2020). Mice become ineffective when administered antibiotics or rendered germ-free; proinflammatory cytokines are generated from mouse tumors with introduction of CpG-ON and IL-10R antibodies, which decrease tumor burden (Jenney *et al.,* 2020).

8.2. Chemotherapy

It should come as no surprise that chemotherapy modifies the microbial ecosystems in patients; yet, it is still unknown how relevant these adjustments are for prognosis (Siravegna *et al.,* 2017). More significantly, research using animal models has demonstrated that the unique makeup of microbiota can alter the anticancer effectiveness of a number of traditional chemotherapy drugs. The platinum treatment oxaliplatin inhibits tumor growth in a way that depends on the microbiota. Elimination of the microbiota by broad-spectrum antibiotics has a significant impact on host gene expression, upregulating genes that promote the development and metabolism of cancer and downregulating pathways related to inflammation, phagocytic activity, and antigen presentation. Furthermore, the proinflammatory potential and the recruitment of immune cells—both necessary for tumor regression—were reduced by the injection of antibiotics.

Reactive oxygen species (ROS) were discovered to be produced less intratumorally in germ-free mice, an effect that oxaliplatin was demonstrated to be beneficial in mitigating. Furthermore, a decrease in intratumoral DNA damage was associated with a reduction in ROS generation. This work demonstrates that the line between immunotherapy and chemotherapy may be confounded by the immunomodulatory effects of microbiota in response to chemotherapeutic drugs. One common alkylating drug used in chemotherapy is cyclophosphamide (CP). It results in the rupturing of the intestinal barrier and the reduction of the height of the villus in the small intestine, which promotes the buildup of inflammatory cells and microbial translocation to secondary lymphoid organs. Some studies have noted that the anticancer effects of CP are lessened in mice that are administered antibiotics or kept germ-free. (Mo and others, 2023). In the latter scenario, antibiotics that target solely Gram-positive bacteria as opposed to Gram-negative bacteria greatly lowered the efficiency of CP. In a mouse model of nonmetastasizing sarcoma, it was demonstrated that certain Gram-positive bacteria, namely *Lactobacillus johnsonii, L. murinus, Enterococcus hirae,* and segmented filamentous bacteria, are crucial for mediating the anti-tumor response of CP. After translocation, the intratumoral CD8/TReg ratio of *E. hirae* rose, according to a follow-up investigation by the same team (Rahman *et al*., 2022). Additionally, it was demonstrated that one of the main ways CP exercised its anticancer effects was by enhanced infiltration of interferon-producing T cells

into cancer lesions caused by the Gram-negative *Barnesiella intestihominis.* Progression-free survival was expected to be prolonged by particular memory responses of TH1 cells to intestinihominis (but not to other bacteria). These studies bear the collective responsibility for incorporating certain *Enterococcus* and *Barnesiella* species into an optimal microbiota cocktail that might be delivered in conjunction with CP and perhaps other alkylating drugs. These bacteria or specific immunomodulatory products/metabolites could be added to already used chemotherapy medications in the future to increase their efficacy as adjuvants (Clay *et al.,* 2022).

8.3. Targets of antimicrobial drugs in oncology

The biotechnology and pharmaceutical industries are increasingly concentrating on cellular targets in order to develop customized medications and chemotherapy treatments. However, in not too distant a future, medicinal therapies involving bacteria may be the focus. Microbial drug targets may also be able to mitigate the negative effects on the gastrointestinal tract that many chemotherapy medicines have. Some adverse effects require limiting the dosage or duration of medication because they are so severe, such as those caused by irinotecan (camptothecin). Irinotecan, a topoisomerase I inhibitor, is used to treat colorectal and pancreatic cancer. In particular, it stops DNA replication in cells that are expanding quickly (Wright and Kelly, 2017). Irinotecan becomes the active chemotherapeutic agent when administered as a pro-drug (SN38). The resultant inactive SN38-G is then glucuronidated in the liver and eliminated via the GI tract. The glucuronic acid molecule, which bacteria need as fuel, is hydrolyzed by the -glucuronidase enzymes produced by microbiota. In the GI lumen, this mechanism reactivates SN38. Increased SN38 levels in the colon are the cause of severe and frequently fatal diarrhea, necessitating frequent dose adjustments and decreases.

Compared to ordinary mice with full microbiota (Enaud *et al.,* 2020) germfree animals showed less GI damage and were able to survive larger dosages of irinotecan. A clinical trial found that administering neomycin in addition to irinotecan reduced adverse effects (Zmora *et al*., 2019). On the other hand, broad-spectrum antibiotics can destroy a range of gastrointestinal commensals and create an environment that is conducive to the growth of illnesses like *Clostridium difficile (C. diff).* Alternatively, non-toxic to bacteria or mammalian cells, tiny chemical inhibitors of bacterial glucuronidases have been discovered that do not cross-react with human glucuronidases and do not (Silva *et al.,* 2020). In preclinical research, animals given both -glucuronidase inhibitors were protected against irinotecan-induced diarrhea. GI side effects from other chemotherapy drugs are comparable. For example, doxorubicin and irinotecan are similar in that they both need bacteria to generate gastrointestinal harm. These results imply that targeting microbiota may reduce the toxicity of certain chemotherapeutic drugs.

8.4 The transfer of fecal microbiota

A great deal of research has been done on fecal microbiota transplantation (FMT) in relation to dysbiotic gastrointestinal disorders, particularly inflammatory bowel disease (IBD) and *Clostridium difficile* infection (Wyres et al., 2020). Despite the fact that FMT has not been examined in relation to cancer until recently, the insights gathered from FMT's experience with these illnesses might potentially inform the design of future cancer trials. FMT transplants a full enteral microbial ecology from the donor or donors, which offers several potential benefits, as opposed to just a single beneficial bacteria. First, engraftment of imported bacteria may be stronger with whole community transplantation because the recipient microbiome is less competitively excluded. From an ecological point of view, there is a lot of functional redundancy and mutual dependency between cooperating microorganisms in the ecosystem as a whole. Taxonomic distinctions may be decreased at the functional level, despite the fact that many of the species that have been identified as advantageous share substantial overlap. When an ecosystem is transplanted as a whole, all of the supporting ecosystem and its overall diversity can be transplanted alongside the discovered "good" bacteria, which may or may not reflect markers of the ecosystem's general health (Wright and Kelly, 2017).

When treating recurrent *Clostridium difficile* infections in a highly dysbiotic condition, a single infusion of healthy donor FMT produces long-lasting microbiota engraftment as well as therapeutic benefit. However, in other conditions where the local microbiota is controlled by a single pathogenic strain and has not been frequently disturbed by medicines, lasting engraftment with single FMT has proven more difficult (Rahman *et al.,* 2022). In the end, investigations into FMT treatments to enhance responses to cancer therapy must carefully take into account a number of criteria (such as immune checkpoint inhibition); yet, as cancer research is a relatively new subject, the most effective approaches have not yet been identified. In these investigations, donor selection will be crucial and might be more complex than in the usual FMT indications defined by severe dysbiosis (e.g., *C. difficile*). Complete responder (CR) donor FMT is now being used in several trials for immune checkpoint-treated patients (NCT03353402; NCT03341143). It has been suggested that microbiome profiling be used for patient screening; yet, further research is required to fully comprehend the distinctions between a "favorable" and "unfavorable" microbiome (Silva *et al.,* 2020). In order to determine the effects of microbiome

alteration on engraftment, general immunity, and anti-tumor immunity, extensive biomarker evaluation—including longitudinal sampling of fecal samples, blood, and ideally tumors—is unquestionably an essential and critical part of early FMT for cancer studies.

8.5. Probiotics

Given to a person, probiotics are living microorganisms that are said to improve their health. Probiotic-containing supplements are available, as are fermented foods including sauerkraut, kimchi, miso, kombucha, yogurt, and kefir. Although probiotic supplements are easily obtainable and easy to use, there are significant issues and variations related to target modulation, bioavailability, quality control, and standardization (Zmora *et al.,* 2019). For the first commercial probiotic supplements, strains of easily produced bacteria from food sources, such *Lactobacillus* and *Bifidobacterium*, were employed. Despite extensive research, there is varying degrees of evidence on the therapeutic efficacy of certain probiotics in relation to specific gastrointestinal illnesses (Rothschild *et al.,* 2018). Nevertheless, depending on the species, dose, and method of preparation, as well as the natural host microbiome into which they are introduced, probiotics differ in their potential to tolerate stomach acids and colonize the intestinal tract (Mo *et al.,* 2023). Probiotics may actually lessen the reconstitution of a varied microbial environment after antibiotics, which means that these strategies need to be carefully studied in clinical trials. Antibiotic ablation can be used as a gut "conditioning regimen" to boost colonization (Rahman *et al.,* 2022).

It Is best to avoid using probiotic supplements off-trial in the setting of immunotherapy treatment since our present understanding of how they may alter immunity and therapeutic responses is limited. Furthermore, studies have shown that the quality of these supplements may vary significantly as they are virtually unregulated in both the US and the EU (Enaud *et al.,* 2020). This variability raises concerns, particularly in a vulnerable population, as it may impair the medicines' safety and efficacy (Patel *et al.,* 2020). Recently, there has been an attempt to combine the benefits of FMT with the capacity to create a diverse environment that can result in "synthetic stool" or "designer probiotics." Advances in technology have also contributed to the ongoing conversion of commensal bacteria that were formerly considered "unculturable" into probiotics. *Faecalibacterium prausnitzii,* an obligatory anaerobe bacteria that ferments fiber, is one example; it has been connected to a favorable reaction to immunotherapy (Janney et al., 2020). Lastly, tests are conducted on postbiotics, which are beneficial metabolites of bacteria.

8.6. Prebiotics and diet

The increasing importance of gut bacteria in customized cancer treatment has led to an emphasis on patient diet studies. Despite frenzied inquests and a widespread understanding that diet is crucial, we have no precise or evidence-based nutritional recommendations to provide patients upon diagnosis. This is partially due to the dearth of trials and clinical cohorts gathering dietary data, as well as the paucity of prospective interventional dietary research demonstrating improvements in cancer response and survival outcomes (Silva *et al.,* 2020). While a number of recently published studies (including those involving representatives of certain bacterial taxa, *Faecalibacterium prausnitzii, Akkermansia muciniphila, Bifidobacterium longum*, and others) demonstrate variations in their reactions to immune checkpoint blockade (Silva *et al.,* 2020). It has been demonstrated that a number of specific foods and/or food components (dietary fiber, for example) in the human diet can either raise or lower the risk of cancer. However, the likelihood that specific foods, nutrients, or other food-derived bioactive substances will either significantly increase or decrease the risk of cancer is decreasing. Instead, it is more likely that different dietary patterns will combine to create an inflammatory and metabolic state that will either significantly increase or decrease the risk of cancer. Diets that score highly on several metrics and worldwide recommendations (e.g., the Mediterranean diet, the Healthy Eating Index, and the Dietary Inflammatory Index) are associated with a lower risk of developing and dying from cancer. Studies on humans have also connected these diets to decreased inflammation and increased immune function through the utilization of cytotoxic and helper T-cells (Rahman *et al.,* 2022). However, there's still a lot of curiosity in specific dietary components that may Small differences in the immune system and microbiota have been seen in randomized controlled trials that examined the addition of certain nutrients or meals, such as whole grains rather than processed grains (Zmora *et al.,* 2019).

Short-term, provocative feeding studies on humans with gut microbiome endpoints have shown that significant dietary changes (such as switching from a vegetarian to a meat-based diet or restricting energy intake by more than 30%) can have equally significant effects on the microbiome and cancer biomarkers (Wong *et al.,* 2019). The microbiota may undo dietary improvements just as quickly if they are not maintained. To improve gut ecology and increase beneficial bacteria, food change would need to occur continuously, yet changing deeply ingrained dietary patterns is notoriously difficult. Well-designed and controlled human studies are required to advance our understanding of the relevance of diet-induced alterations in the makeup and function of the gut microbiome and their influence on response to cancer therapy. Prebiotics

(nutrients include resistant fibers) and synbiotics that enrich for possibly beneficial gut flora are being investigated in regard to the association between the microbiome and cancer (NCT01929122, NCT01549782, NCT03420443, NCT03072641, NCT01479907). However, unlike single-species probiotics, specialized prebiotics may not improve the total diversity of the microbiota and the clans of bacteria with complementary metabolic activities (Enaud *et al.,* 2020).

9.0. Using phytochemicals to stop the development of cancer

Phytochemicals are not believed to be necessary nutrients for humans, despite a growing number of well-conducted studies correlating increased intake to a reduced likelihood of getting cancer and a lower recurrence after initial treatment completion (Vona *et al.,* 2021). While there are numerous varieties of phytochemicals found in food, polyphenols are among the most abundant and well-recognized. According to research, consuming more than 1g of food offers almost 10 times the daily intake of polyphenols than the total daily intake of all other phytochemical groups and recognized dietary antioxidants (Sun *et al.,* 2023). Patients—especially those with cancer who are particularly interested in over-the-counter self-help strategies—are talking more about the health benefits of phytochemical-rich foods and concentrated nutritional supplements because they are frequently featured in the medical and popular media.

9.1. Clinical data supporting cancer prevention

As stated in other systematic reviews and the most recent comprehensive evaluation by the World Cancer Research Fund (Jideani *et al.,* 2021), a number of studies, though not all of them, have connected a lower risk of cancer to a higher consumption of foods high in phytochemicals, such as fruits, vegetables, nuts, legumes, and herbs. More precisely, several cohort studies have focused on specific meal components. Carotenoids are present in leafy green vegetables and carrots. Recent meta-analyses have linked carotenoids to a decreased risk of pancreatic and ovarian cancers, particularly in smokers, as well as a lower risk of these malignancies in studies using questionnaires or blood (Dey *et al.,* 2020). A decreased incidence of prostate cancer has been linked to eating more cruciferous vegetables, such as broccoli, cabbage, cauliflower, Brussel sprouts, radishes, and cauliflower, as well as foods high in isoflavones, such as pulses and soy products, and lycopene-rich colored fruits and tomatoes. Studies have demonstrated that eating foods rich in flavonoids, such onions, which have a high quercetin content, can lower the risk of developing a variety of malignancies, including lung cancer, especially in smokers (Mussa *et al.,* 2022). Anthroxanthins, which are contained in dark chocolate, have been proved to lessen the incidence of colon cancer. Moreover, it has been shown that drinking more green tea reduces the risk of ovarian, breast, prostate, and oesophageal cancers, especially in drinkers and smokers (Ververis *et al.,* 2020). In conclusion, research has indicated that coffee consumption reduces the likelihood of developing melanoma and non-melanomatous skin cancers, even after accounting for other factors including gender, age, body mass index, exposure to UV rays, physical activity, alcohol use, and smoking history (Wei *et al.,* 2022).

9.2. Clinical proof of an advantage in cancer

After a diagnosis, eating well still provides advantages, particularly when paired with other healthy lifestyle choices. Breast cancer survivors who routinely ate more fruit and vegetables than the government suggested five pieces per day had a third decreased chance of breast cancer recurrence when paired with regular physical activity (Giani *et al.,* 2022). According to a different study, the risk of death was lowest for women with breast cancer who consumed a healthy amount of cereals, legumes, cruciferous vegetables, and soya and had the highest blood lignan levels. Additionally linked to a decreased risk of colorectal cancer recurrence is a diet high in polyphenols and lignans (Tundis *et al.,* 2020).

Women who consumed the greatest quantities of phytoestrogenic polyphenols—found in soy and other legumes—such as flavanone and isoflavones—had a 29% reduced chance of passing away and relapsing, according to the big Shanghai Breast Cancer Survival Study (Li *et al.,* 2020). It was shown that green tea had similar advantages following colorectal and breast cancer (Lee et al., 2020). Furthermore, 30% of those with chronic leukemia showed a drop in aberrant white cell counts after drinking green tea. In males with prostate cancer, it also decreased the blood levels of numerous other indicators of proliferation, including PSA. Similar results of a slowdown of PSA growth have also been seen in other dietary studies, such as a phase II study of pomegranate juice (Martin-Diana *et al.,* 2021) and a randomized trial combining a plant-based diet with additional lifestyle adjustments. Another disease that is affected by diet is skin cancer, as shown by a study of patients who have had treatment for squamous or basal cell carcinoma and are at high risk of developing new lesions from prolonged sun exposure. The lowest odds of developing new cancer were seen in those whose diets were rich in lutein and zeaxanthin, which includes leafy green vegetables (Aune, 2019). The DietCompLyf prospective trial, which had 31,559 women receiving treatment for breast cancer and was conducted in the UK, is the largest and most likely thorough experiment assessing the advantages of phytochemicals (Qi *et al.,* 2022).

9.3. How can substances derived from plants combat cancer?

Because phytochemicals play so many complex functions, the precise biochemical processes by which they exert their anti-cancer properties are still being investigated; nonetheless, recent findings have substantially improved our comprehension of the mode of action. Their antioxidant effect, which is elicited either directly by absorbing free radicals or by stimulating antioxidant enzymes like glutathione, catalase, and superoxide dismutase (SOD) via a number of molecular pathways, is the most extensively studied strategy for preventing cancer (Aranda-Tivera *et al.,* 2022). According to Manessis *et al.* (2020), Nrf2 activation is one of these methods; it activates the genes responsible for detoxification and antioxidant enzymes. Moreover, phytochemicals, particularly those belonging to the thiol class like sulforaphane, have been demonstrated to block procarcinogens from converting into their electrophilic, DNA-damaging counterparts (Lee *et al.,* 2020).

Numerous studies have demonstrated the antioxidant qualities of phytochemicals utilizing well-known, everyday carcinogens. In an experiment with the well-known household carcinogen triclocarban, which is frequently included in detergents and cleaning products, they proved its protective effect. When curcumin was added to the petri dish culture diet, there was a substantial decrease in both the quantity and rate of carcinogenesis, a process that occurs when healthy cells exposed to triclocarban turn into pre-malignant cells (Wei *et al.*, 2022). According to blood and urine tests, people who consumed a lot of kaempferol had greater urine concentrations of these polyphenols (Elmo *et al.,* 2020) and better SOD activity. Rats exposed to cigarette smoke and given the phytochemical indole-3-carbinol, which is abundant in cruciferous vegetables, had a decreased risk of lung cancer than rats not given the phytochemical (Mussa *et al.,* 2022). Following their onion meal, the subjects' blood levels of quercetin rose. Alongside this was a drop in oxidative metabolites, including 8-hydroxydeoxyguanosine (8-OHdG), a hallmark of DNA damage and repair. It has also been found that supplementing with quercetin can ameliorate the mitochondrial dysfunctions produced by 3-nitropropionic acid toxin (Sun *et al.,* 2023). Giving Chinese smokers 170g of watercress per day—rich in indole-3-carbinol—had a comparable impact on urine indications of DNA damage, according to a clinical research conducted in Singapore (Aune, 2019). Lastly, studies have shown that marinating meat in rosemary and thyme lowers blood levels of carcinogenic heterocyclic amines (HCA) by 87% when compared to eating the meat unseasoned (Aranda-Rivera *et al.,* 2020). Phytochemicals' capacity to lower inflammation looks to be another significant anti-cancer approach. These days, it is commonly accepted that aberrant inflammation is essential to the Initial stages of cancer growth and propagation. Oxidative stress and the activation of the NF-kappa B transcription factor family are tightly linked to inflammation. These factors regulate over 150 genes that are involved in cell survival pathways; these target genes are pro-inflammatory and carcinogenic. Several phytochemicals, such as the phenol epigallocatechin-3-gallate (EGCG) present in green tea, quercetin, curcumin, caffeic acid, and caffeic acid phenethyl ester, as well as the phytochemicals present in bilberries, have been demonstrated to inhibit NF-kappa B activation (Qi *et al.,* 2022).

Recent research, most of which took place in labs, has shown that phytochemicals can influence a number of cancer processes by controlling cellular and signaling events related to metastasis, growth, and invasion (Tundis *et al.,* 2020). For instance, it has been demonstrated that pomegranates, which are high in the polyphenol ellagic acid, directly reduce cell proliferation and trigger apoptosis in androgen-sensitive and aggressive human prostate cancer cells (Qi *et al.,* 2022). In a study employing oestrogen-sensitive and -resistant breast cancer cell lines, pomegranate extract was also demonstrated to block the mechanisms involved in cancer metastasis. Increased markers of cell adhesion and migration were also found in cancer cells, but not in normal cells, according to the study. Additionally, it was discovered in a different research to suppress a chemokine that draws breast cancer cells to the bone (Dey *et al.,* 2020). By halting the cell cycle, accelerating apoptosis, and reducing cell invasion and migration, curcumin inhibits the proliferation of cancer cells (Vona *et al.,* 2021). Additionally, it has been demonstrated to preserve healthy breast stem cells while preventing the growth of breast cancer-causing stem cells. It has been demonstrated that curcumin controls the expression of miRNA in breast cancer cells. This results in a decrease in the expression of Bcl-250 and a stabilization of the tumour suppressor gene in colorectal cancer cell lines (Li *et al.,* 2020). Green tea has been found to drastically diminish various variables that promote the proliferation of cancer cells by blocking DNA synthesis, dedifferentiation, and angiogenesis due to its high epigallocatechin gallate (EGCG) concentration. It has also been demonstrated to inhibit ornithine decarboxylase, an enzyme that speeds up cell division and inhibits apoptosis. Resveratrol has proven epigenetic regulatory capabilities that control global gene expression, hence controlling cell survival, proliferation, and death in prostate cancer through the deacetylation of the FOXO transcription factor (Manessis *et al.,* 2020). Caffeine and phenethyl ester have been proven to decrease tumor model metastasis in vivo as well as cell motility in vitro and NF-κB activation. Apart from inhibiting the growth and spread of tumors, luteolin also suppresses the epithelial mesenchymal transition, a fundamental biological mechanism linked to the beginning and advancement of cancer (Aranda-Rivera *et al.,* 2022).

Lastly, a hormonal mechanism is one more way that some phytochemicals, such as polyphenols, may affect cancer.

Legumes, certain cruciferous vegetables, and soy products contain phytoestrogenic chemicals, primarily isoflavones and lignans. They do not encourage cell division and only bind sporadically to the oestrogen receptor. At the same time, they block the binding of more damaging oestrogens, particularly those generated endogenously (Aune, 2019). This explains why women who consumed the largest amounts of foods rich in isoflavones and flavanones had a decreased risk of developing ddyin in the previously published Shanghai Breast Cancer Survival Study. It has been demonstrated that 5 alpha reductase lowers endogenous testosterone levels in males exposed to phytoestrogenic substances. This might contribute to the explanation of why men who consume a diet high in foods high in phytoestrogenic compounds, such as beans and pulses, have a lower risk of developing prostate cancer (Mussa *et al.,* 2022).

Conclusion

Changes in dietary habits can prevent cancer, making chemotherapy a reasonably safe and economical strategy. Numerous preclinical and epidemiological studies have shown a strong case for the involvement of several dietary factors in both the prevention and treatment of cancer. Numerous clinical investigations pertaining to the chemopreventive characteristics of the natural substances mentioned above are now in progress. One major obstacle to the use of currently available chemotherapeutic medicines is drug-associated toxicity. On the other hand, the toxicity linked with using natural substances for cancer prevention may be reduced.

References

Stout, N. L., Santa Mina, D., Lyons, K. D., Robb, K., & Silver, J. K. (2021). A systematic review of rehabilitation and exercise recommendations in oncology guidelines. CA: a cancer journal for clinicians, 71(2), 149-175.

Klein, C. A. (2020). Cancer progression and the invisible phase of metastatic colonization. Nature Reviews Cancer, 20(11), 681-694.

Falzone, L., Salomone, S., & Libra, M. (2018). Evolution of cancer pharmacological treatments at the turn of the third millennium. Frontiers in pharmacology, 9, 1300.

Sung, H., Siegel, R. L., Rosenberg, P. S., & Jemal, A. (2019). Emerging cancer trends among young adults in the USA: analysis of a population-based cancer registry. The Lancet Public Health, 4(3), e137-e147.

Siegel, R. L., Miller, K. D., & Jemal, A. (2019). Cancer statistics, 2019. CA: a cancer journal for clinicians, 69(1), 7-34.

Vivarelli, S., Salemi, R., Candido, S., Falzone, L., Santagati, M., Stefani, S., … & Libra, M. (2019). Gut microbiota and cancer: from pathogenesis to therapy. Cancers, 11(1), 38.

Gavas, S., Quazi, S., & Karpiński, T. M. (2021). Nanoparticles for cancer therapy: current progress and challenges. Nanoscale research letters, 16(1), 173.

Sheena, B. S., Hiebert, L., Han, H., Ippolito, H., Abbasi-Kangevari, M., Abbasi-Kangevari, Z., … & Gholizadeh, A. (2022). Global, regional, and national burden of hepatitis B, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The lancet Gastroenterology & hepatology, 7(9), 796-829.

Xiao, Y., & Yu, D. (2021). Tumor microenvironment as a therapeutic target in cancer. Pharmacology & therapeutics, 221, 107753.

Rawla, P., Sunkara, T., & Gaduputi, V. (2019). Epidemiology of pancreatic cancer: global trends, etiology and risk factors. World journal of oncology, 10(1), 10.

Gomaa, E. Z. (2020). Human gut microbiota/microbiome in health and diseases: a review. Antonie Van Leeuwenhoek, 113(12), 2019-2040.

Wastyk, H. C., Fragiadakis, G. K., Perelman, D., Dahan, D., Merrill, B. D., Feiqiao, B. Y., … & Sonnenburg, J. L. (2021). Gut-microbiota-targeted diets modulate human immune status. Cell, 184(16), 4137-4153.

Rinninella, E., Raoul, P., Cintoni, M., Franceschi, F., Miggiano, G. A. D., Gasbarrini, A., & Mele, M. C. (2019). What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases. Microorganisms, 7(1), 14.

Liu, X., Mao, B., Gu, J., Wu, J., Cui, S., Wang, G., … & Chen, W. (2021). Blautia—a new functional genus with potential probiotic properties?. Gut microbes, 13(1), 1875796.

Cryan, J. F., O'Riordan, K. J., Cowan, C. S., Sandhu, K. V., Bastiaanssen, T. F., Boehme, M., … & Dinan, T. G. (2019). The microbiota-gut-brain axis. Physiological reviews.

Martino, C., Dilmore, A. H., Burcham, Z. M., Metcalf, J. L., Jeste, D., & Knight, R. (2022). Microbiota succession throughout life from the cradle to the grave. Nature Reviews Microbiology, 20(12), 707-720.

Sorboni, S. G., Moghaddam, H. S., Jafarzadeh-Esfehani, R., & Soleimanpour, S. (2022). A comprehensive review on the role of the gut microbiome in human neurological disorders. Clinical Microbiology Reviews, 35(1), e00338-20.

Thursby, E., & Juge, N. (2017). Introduction to the human gut microbiota. Biochemical journal, 474(11), 1823-1836

Ramirez, J., Guarner, F., Bustos Fernandez, L., Maruy, A., Sdepanian, V. L., & Cohen, H. (2020). Antibiotics as major disruptors of gut microbiota. Frontiers in cellular and infection microbiology, 10, 572912.

Yao, Y., Cai, X., Ye, Y., Wang, F., Chen, F., & Zheng, C. (2021). The role of microbiota in infant health: from early life to adulthood. Frontiers in Immunology, 12, 708472.

Cammarota, G., Ianiro, G., Ahern, A., Carbone, C., Temko, A., Claesson, M. J., … & Tortora, G. (2020). Gut microbiome, big data and machine learning to promote precision medicine for cancer. Nature reviews gastroenterology & hepatology, 17(10), 635-648.

Aggarwal, N., Kitano, S., Puah, G. R. Y., Kittelmann, S., Hwang, I. Y., & Chang, M. W. (2022). Microbiome and human health: Current understanding, engineering, and enabling technologies. Chemical Reviews, 123(1), 31-72.

Wilmanski, T., Diener, C., Rappaport, N., Patwardhan, S., Wiedrick, J., Lapidus, J., … & Price, N. D. (2021). Gut microbiome pattern reflects healthy ageing and predicts survival in humans. Nature metabolism, 3(2), 274-286.

Kolodziejczyk, A. A., Zheng, D., & Elinav, E. (2019). Diet–microbiota interactions and personalized nutrition. Nature Reviews Microbiology, 17(12), 742-753.

Tett, A., Pasolli, E., Masetti, G., Ercolini, D., & Segata, N. (2021). Prevotella diversity, niches and interactions with the human host. Nature Reviews Microbiology, 19(9), 585-599.

Krautkramer, K. A., Fan, J., & Bäckhed, F. (2021). Gut microbial metabolites as multi-kingdom intermediates. Nature Reviews Microbiology, 19(2), 77-94.

Zheng, D., Liwinski, T., & Elinav, E. (2020). Interaction between microbiota and immunity in health and disease. Cell research, 30(6), 492-506.

Hussain, I., Cher, G. L. Y., Abid, M. A., & Abid, M. B. (2021). Role of gut microbiome in COVID-19: an insight into pathogenesis and therapeutic potential. Frontiers in immunology, 12, 4164.

Abenavoli, L., Scarpellini, E., Colica, C., Boccuto, L., Salehi, B., Sharifi-Rad, J., … & Capasso, R. (2019). Gut microbiota and obesity: a role for probiotics. Nutrients, 11(11), 2690.

Fong, W., Li, Q., & Yu, J. (2020). Gut microbiota modulation: a novel strategy for prevention and treatment of colorectal cancer. Oncogene, 39(26), 4925-4943.

Lee, J. Y., Tsolis, R. M., & Bäumler, A. J. (2022). The microbiome and gut homeostasis. Science, 377(6601), eabp9960.

Cheng, Y., Ling, Z., & Li, L. (2020). The intestinal microbiota and colorectal cancer. Frontiers in immunology, 11, 615056.

Dhar, D., & Mohanty, A. (2020). Gut microbiota and Covid-19-possible link and implications. Virus research, 285, 198018.

Xu, Y., Wang, N., Tan, H. Y., Li, S., Zhang, C., & Feng, Y. (2020). Function of Akkermansia muciniphila in obesity: interactions with lipid metabolism, immune response and gut systems. Frontiers in microbiology, 11, 219.

Malesza, I. J., Malesza, M., Walkowiak, J., Mussin, N., Walkowiak, D., Aringazina, R., … & Mądry, E. (2021). High-fat, western-style diet, systemic inflammation, and gut microbiota: a narrative review. Cells, 10(11), 3164.

Bolte, L. A., Vila, A. V., Imhann, F., Collij, V., Gacesa, R., Peters, V., … & Weersma, R. K. (2021). Long-term dietary patterns are associated with pro-inflammatory and anti-inflammatory features of the gut microbiome. Gut, 70(7), 1287-1298.

Manor, O., Dai, C. L., Kornilov, S. A., Smith, B., Price, N. D., Lovejoy, J. C., … & Magis, A. T. (2020). Health and disease markers correlate with gut microbiome composition across thousands of people. Nature communications, 11(1), 5206.

Makki, K., Deehan, E. C., Walter, J., & Bäckhed, F. (2018). The impact of dietary fiber on gut microbiota in host health and disease. Cell host & microbe, 23(6), 705-715.
Wong, S. H., & Yu, J. (2019). Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. Nature Reviews Gastroenterology & Hepatology, 16(11), 690-704.
Alsina, M., Arrazubi, V., Diez, M., & Tabernero, J. (2023). Current developments in gastric cancer: from molecular profiling to treatment strategy. Nature Reviews Gastroenterology & Hepatology, 20(3), 155-170.
Uhlenhopp, D. J., Then, E. O., Sunkara, T., & Gaduputi, V. (2020). Epidemiology of esophageal cancer: update in global trends, etiology and risk factors. Clinical journal of gastroenterology, 13(6), 1010-1021.
Picardo, S. L., Coburn, B., & Hansen, A. R. (2019). The microbiome and cancer for clinicians. Critical reviews in oncology/hematology, 141, 1-12.
Brennan, C. A., & Garrett, W. S. (2019). Fusobacterium nucleatum—symbiont, opportunist and oncobacterium. Nature Reviews Microbiology, 17(3), 156-166.
Willis, J. R., & Gabaldón, T. (2020). The human oral microbiome in health and disease: from sequences to ecosystems. Microorganisms, 8(2), 308.
El Tekle, G., & Garrett, W. S. (2023). Bacteria in cancer initiation, promotion and progression. Nature Reviews Cancer, 23(9), 600-618.
Helmink, B. A., Khan, M. W., Hermann, A., Gopalakrishnan, V., & Wargo, J. A. (2019). The microbiome, cancer, and cancer therapy. Nature medicine, 25(3), 377-388.
Wong, S. H., & Yu, J. (2019). Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. Nature Reviews Gastroenterology & Hepatology, 16(11), 690-704.
Gomaa, E. Z. (2020). Human gut microbiota/microbiome in health and diseases: a review. Antonie Van Leeuwenhoek, 113(12), 2019-2040.
Belkaid, Y., & Hand, T. W. (2014). Role of the microbiota in immunity and inflammation. Cell, 157(1), 121-141.
Lam, K. C., Araya, R. E., Huang, A., Chen, Q., Di Modica, M., Rodrigues, R. R., … & Goldszmid, R. S. (2021). Microbiota triggers STING-type I IFN-dependent monocyte reprogramming of the tumor microenvironment. Cell, 184(21), 5338-5356.
Cullin, N., Antunes, C. A., Straussman, R., Stein-Thoeringer, C. K., & Elinav, E. (2021). Microbiome and cancer. Cancer Cell, 39(10), 1317-1341.
Mager, L. F., Burkhard, R., Pett, N., Cooke, N. C., Brown, K., Ramay, H., … & McCoy, K. D. (2020). Microbiome-derived inosine modulates response to checkpoint inhibitor immunotherapy. Science, 369(6510), 1481-1489.
Greten, F. R., & Grivennikov, S. I. (2019). Inflammation and cancer: triggers, mechanisms, and consequences. Immunity, 51(1), 27-41.
Janagam, D. R., Wu, L., & Lowe, T. L. (2017). Nanoparticles for drug delivery to the anterior segment of the eye. Advanced drug delivery reviews, 122, 31-64.
Wei, J., Mu, J., Tang, Y., Qin, D., Duan, J., & Wu, A. (2023). Next-generation nanomaterials: advancing ocular anti-inflammatory drug therapy. Journal of nanobiotechnology, 21(1), 282.
Nagai, N., & Otake, H. (2022). Novel drug delivery systems for the management of dry eye. Advanced Drug Delivery Reviews, 114582.
Jacob, S., Nair, A. B., Shah, J., Gupta, S., Boddu, S. H., Sreeharsha, N., … & Morsy, M. A. (2022). Lipid Nanoparticles as a Promising Drug Delivery Carrier for Topical Ocular Therapy—An Overview on Recent Advances. Pharmaceutics, 14(3), 533.
Grassiri, B., Zambito, Y., & Bernkop-Schnürch, A. (2021). Strategies to prolong the residence time of drug delivery systems on ocular surface. Advances in colloid and interface science, 288, 102342.
Patel, M. I., Lopez, A. M., Blackstock, W., Reeder-Hayes, K., Moushey, A., Phillips, J., & Tap, W. (2020). Cancer disparities and health equity: a policy statement from the American Society of Clinical Oncology. Journal of Clinical Oncology, 38(29), 3439.
Levitt, H. M., Morrill, Z., Collins, K. M., & Rizo, J. L. (2021). The methodological integrity of critical qualitative research: Principles to support design and research review. Journal of Counseling Psychology, 68(3), 357.
Bauer, G. R., Churchill, S. M., Mahendran, M., Walwyn, C., Lizotte, D., & Villa-Rueda, A. A. (2021). Intersectionality in quantitative research: A systematic review of its emergence and applications of theory and methods. SSM-population health, 14, 100798.
Chang, E. S., Kannoth, S., Levy, S., Wang, S. Y., Lee, J. E., & Levy, B. R. (2020). Global reach of ageism on older persons' health: A systematic review. PloS one, 15(1), e0220857.
Mussa, A., Mohd Idris, R. A., Ahmed, N., Ahmad, S., Murtadha, A. H., Tengku Din, T. A. D. A. A., … & Hassan, R. (2022). High-dose vitamin C for cancer therapy. Pharmaceuticals, 15(6), 711
Dey, P., Kundu, A., Kumar, A., Gupta, M., Lee, B. M., Bhakta, T., … & Kim, H. S. (2020). Analysis of alkaloids (indole alkaloids, isoquinoline alkaloids, tropane alkaloids). In Recent advances in natural products analysis (pp. 505-567). Elsevier.
Jideani, A. I., Silungwe, H., Takalani, T., Omolola, A. O., Udeh, H. O., & Anyasi, T. A. (2021). Antioxidant-rich natural fruit and vegetable products and human health. International Journal of Food Properties, 24(1), 41-67.
Sun, W., & Shahrajabian, M. H. (2023). Therapeutic potential of phenolic compounds in medicinal plants—Natural health products for human health. Molecules, 28(4), 1845.
Vona, R., Pallotta, L., Cappelletti, M., Severi, C., & Matarrese, P. (2021). The impact of oxidative stress in human pathology: Focus on gastrointestinal disorders. Antioxidants, 10(2), 201.
Wei, S., He, Y., Yang, J., Li, Y., Liu, Z., & Wang, W. (2022). Effects of exogenous ascorbic acid on yields of citrinin and pigments, antioxidant capacities, and fatty acid composition of Monascus ruber. Lwt, 154, 112800.
Georgiou, K., Marinov, B., Farooqi, A. A., & Gazouli, M. (2021). Gut microbiota in lung cancer: where do we stand?. International journal of molecular sciences, 22(19), 10429.
Rahman, M. M., Islam, M. R., Shohag, S., Ahasan, M. T., Sarkar, N., Khan, H., … & Rauf, A. (2022). Microbiome in cancer: Role in carcinogenesis and impact in therapeutic strategies. Biomedicine & Pharmacotherapy, 149, 112898.
Mo, S., Dai, W., Wang, H., Lan, X., Ma, C., Su, Z., … & Cai, G. (2023). Early detection and prognosis prediction for colorectal cancer by circulating tumour DNA methylation haplotypes: A multicentre cohort study. EClinicalMedicine, 55.
Dall'Olio, F. G., Marabelle, A., Caramella, C., Garcia, C., Aldea, M., Chaput, N., … & Besse, B. (2022). Tumour burden and efficacy of immune-checkpoint inhibitors. Nature reviews Clinical oncology, 19(2), 75-90.
Siravegna, G., Marsoni, S., Siena, S., & Bardelli, A. (2017). Integrating liquid biopsies into the management of cancer. Nature reviews Clinical oncology, 14(9), 531-548.
Clay, S. L., Fonseca-Pereira, D., & Garrett, W. S. (2022). Colorectal cancer: the facts in the case of the microbiota. The Journal of Clinical Investigation, 132(4).
Brennan, C. A., & Garrett, W. S. (2019). Fusobacterium nucleatum—symbiont, opportunist and oncobacterium. Nature Reviews Microbiology, 17(3), 156-166.

Janney, A., Powrie, F., & Mann, E. H. (2020). Host–microbiota maladaptation in colorectal cancer. Nature, 585(7826), 509-517.
Wyres, K. L., Lam, M. M., & Holt, K. E. (2020). Population genomics of Klebsiella pneumoniae. Nature Reviews Microbiology, 18(6), 344-359.
Enaud, R., Prevel, R., Ciarlo, E., Beaufils, F., Wieërs, G., Guery, B., & Delhaes, L. (2020). The gut-lung axis in health and respiratory diseases: a place for inter-organ and inter-kingdom crosstalks. Frontiers in cellular and infection microbiology, 10, 9.
Zmora, N., Suez, J., & Elinav, E. (2019). You are what you eat: diet, health and the gut microbiota. Nature reviews Gastroenterology & hepatology, 16(1), 35-56.
Rothschild, D., Weissbrod, O., Barkan, E., Kurilshikov, A., Korem, T., Zeevi, D., … & Segal, E. (2018). Environment dominates over host genetics in shaping human gut microbiota. Nature, 555(7695), 210-215.
Wright, S. L., & Kelly, F. J. (2017). Plastic and human health: a micro issue?. Environmental science & technology, 51(12), 6634-6647.
Silva, Y. P., Bernardi, A., & Frozza, R. L. (2020). The role of short-chain fatty acids from gut microbiota in gut-brain communication. Frontiers in endocrinology, 11, 25.
Aranda-Rivera, A. K., Cruz-Gregorio, A., Arancibia-Hernández, Y. L., Hernández-Cruz, E. Y., & Pedraza-Chaverri, J. (2022). RONS and oxidative stress: An overview of basic concepts. Oxygen, 2(4), 437-478.
Lian, M. Q., Chng, W. H., Liang, J., Yeo, H. Q., Lee, C. K., Belaid, M., … & Pastorin, G. (2022). Plant-derived extracellular vesicles: Recent advancements and current challenges on their use for biomedical applications. Journal of Extracellular Vesicles, 11(12), 12283.
Qi, X., Jha, S. K., Jha, N. K., Dewanjee, S., Dey, A., Deka, R., … & Hou, K. (2022). Antioxidants in brain tumors: current therapeutic significance and future prospects. Molecular Cancer, 21(1), 1-32.
Aune, D. (2019). Plant foods, antioxidant biomarkers, and the risk of cardiovascular disease, cancer, and mortality: a review of the evidence. Advances in Nutrition, 10(Supplement_4), S404-S421.
Manessis, G., Kalogianni, A. I., Lazou, T., Moschovas, M., Bossis, I., & Gelasakis, A. I. (2020). Plant-derived natural antioxidants in meat and meat products. Antioxidants, 9(12), 1215.
Martín-Diana, A. B., García-Casas, M. J., Martínez-Villaluenga, C., Frías, J., Peñas, E., & Rico, D. (2021). Wheat and oat brans as sources of polyphenol compounds for development of antioxidant nutraceutical ingredients. Foods, 10(1), 115.
Lee, K. J., Baek, D. Y., Lee, G. A., Cho, G. T., So, Y. S., Lee, J. R., … & Hyun, D. Y. (2020). Phytochemicals and antioxidant activity of Korean black soybean (Glycine max L.) landraces. Antioxidants, 9(3), 213.
Li, Q., Wang, Y., Mai, Y., Li, H., Wang, Z., Xu, J., & He, X. (2020). Health benefits of the flavonoids from onion: Constituents and their pronounced antioxidant and anti-neuroinflammatory capacities. Journal of agricultural and food chemistry, 68(3), 799-807.
Tundis, R., Leporini, M., Bonesi, M., Rovito, S., & Passalacqua, N. G. (2020). Salvia officinalis L. from Italy: A comparative chemical and biological study of its essential oil in the mediterranean context. Molecules, 25(24), 5826.
Giani, M., Gervasi, L., Loizzo, M. R., & Martínez-Espinosa, R. M. (2022). Carbon source influences antioxidant, antiglycemic, and antilipidemic activities of Haloferax mediterranei carotenoid extracts. Marine Drugs, 20(11), 659.