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PROBIOTICS – INTERPLAY BETWEEN GUT FLORA, IMMUNITY, AND MENTAL HEALTH

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Abstract:
Probiotics are live microorganisms that provide health benefits when consumed in adequate amounts. The gut is home to trillions of microorganisms, collectively known as the gut microbiota, which play a crucial role in maintaining gut health and overall well-being. In recent years, there has been growing interest in the potential of probiotics to modulate the gut microbiota and improve various aspects of health, including immunity and mental health. In conclusion, probiotics have the potential to modulate the gut microbiota, enhance immune function, and improve mental health. Further research is needed to fully understand the mechanisms underlying these effects and to identify the most effective probiotic strains and dosages for different health outcomes.

Keywords: Probiotics, LAB, Gut Micro biota, Bifidobacteria, immunotherapy, AC-T, cancer treatment.

1. Introduction

Probiotics are defined as "live bacteria that, when supplied in sufficient quantities, provide a favorable health effect on the host." Although probiotics have been used to treat a variety of GI problems, including the prevention and treatment of diarrhoea, infection, and inflammation in CRC [colorectal cancer] is currently being studied thoroughly (Zhong et al.,2014). In this Probiotic microorganism should have potential traits relevant to the setting bio therapeutics development Lactic acid bacteria (LAB) which has been proven to protect against CRC via strengthening and altering the natural defensive systems of the host. LAB (Lactic acid bacteria) may also alter luminal secretions, strengthen the mucosal barrier, influence epithelial cell proliferation, and minimize exposure to harmful and carcinogenic substances found in the colon. This review will focus on the consequences of the effects of probiotics on gut micro biota regulation and reinforcing the gut integrity as well as the physicochemical conditions (Hemarajata et al.,2013).

2. Probiotics

Exogenous probiotics paired with functional colonization can lead to health benefits, as seen by the use of probiotics to treat IBD (Inflammatory bowel disease). Aside from the well-known Lactobacillus rhamnosus GG, which might cause cancer, reduce the expression of inflammatory proteins such as NF-B-p65, COX-2, and TNF-Lactobacillus species have immune modulatory properties, which help to reduce the occurrence of colon cancer qualities that prevent carcinogenesis. Lactobacillus casein BL23 has the capability of immune function (Śliżewska et al.,2020). Response in mice with TReg deficiency colitis-related cancer; and Lactobacillus plant arum prolonged the lives of Cd4 + T cells from tumor-bearing animals benefit from increased effector Cd8 + T cell activity, intratumoral infiltration of NK cells.

In a Randomized controlled trial (RCT), 15 colorectal cancer (CRC) patients were given probiotics (Lactobacillus acidophilus NCFM and Bifid bacterium lactic BI-04) (NCT03072641, 120). Butyrate-producing bacteria (such as Clostridiales and Faecalibacterium) are being boosted in the environment. Both tumor and non-tumor colonic mucosa environments, as well as a reduction in Fusobacterium and Peptostreptococcus are two genera related with CRC. Microorganisms found in faces were detected (Poggi et al.,2019). These findings highlight the probiotics' ability to heal dysbiosis and improve antitumor immunity, however it is unknown how such a shift in the microbial profile may occur benefit. Combining cancer immunotherapy has sparked renewed attention using probiotics.

As cancer immunotherapy adjuvants, E.coli targets gut micro biome. Micro biota-targeted treatments such as dietary modification, probiotics, and FMT (fecal microbiota transplantation) can boost immunotherapy effectiveness in four ways. These extrinsic measurements can be beneficial to cure dysbiosis by restoring the microbial imbalance population. The cancer-fighting drug Immunity in the body do not favor cancerous cells (Hibberd et al.,2017), hence the tumor microenvironment is diminished. Inhibited host immunity can be revived by replenishing the T cell repertoire fight cancer A number of immune cells (including NK and dendritic cells) enter the body. The blood tumor to contribute to cancer cell death, Other than direct these have antitumor immunity-stimulating effects on tumor inflammatory processes. Cytokines, hence lowering chronic inflammation Cancer (Hemarajata et al.,2013).

➢ *What is Gut Microbiota*

The human intestine micro biota is a varied and complex microbial community comprising of fungus, bacteria, Archaean's, viruses, bacteriophages, and protozoa that coexist with the host. The makeup and activity of the gut micro biota is a hotly debated topic. It is a topic in the cross-research field of human microbiology and health is intimately tied to probiotic research. Bacterial commensals create a sophisticated and tight interaction network with their hosts engaged in protecting the intestines from potentially toxins Met genomic (Li et al.,2022). The makeup and function of the gut micro biota, on the other hand, change with food, geography, gender, age, and race. Diet is the most important control of gut microbial function [Figure-1]. In general, the phylum Firmicutes/Bacteroidetes ratio is greater in those who eat a Western-style diet, whereas the abundance of the Bacteroidetes phylum's genus Prevotella is more abundant. The small intestine absorbs more than 90% of the ingested meal, while the complex carbs that pass through the small intestine undigested, fiber, protein residues, and main bile acids released by the intestine In reaction to fat consumption, the body digests it in the colon (Feng et al.,2019). These Dietary components have an impact on the makeup and function of the gut micro biota. SCFAs (Short chain fatty acids) are produced by colonic bacteria by saccharolytic fermentation of complex carbohydrates, with acetic, propionic, and butyric acids (in a molar ratio of 3: 1: 1) accounting for roughly Colonic SCFAs account for 90–95 percent of the total. Butyrate controls mucosal inflammation as well as anti-tumor action by contributing to gut microbial balance Proliferation control, immunological regulation, and epigenetic control More than 1,000 bacterial species make up the intestinal micro biota. It is dominated by helpful and harmful bacteria (Thursby et al.,2017). Thus, the gut micro biota may be regarded as an "organ" that plays crucial tasks such as the important utilization of complicated food elements, anabolism of diverse substances, and modulation of the immune system. Immune function and the integrity of the intestinal barrier hence,

the gut's function 2 Cellular Longevity and Oxidative Medicine (Rinninella et al.,2019). A lot of attention in recent years Whether or not microbial dysbiosis is the root cause alternatively the outcome of CRC is yet uncertain, which remains a critical concern in comprehending CRC The prevalence of CRC is frequently linked to the mucosal microorganisms at the cancer site. The primary bacterial species that impact the development of CRC are not yet fully understood. However, research shows that the presence of Fusobacterium nucleatum (Fn), Escherichia coli, Helicobacter pylori, and Bacteroides fragilis is linked to CRC. It is also recommended that the incidence is linked to a decline in bacterial diversity cancers, although its significance in carcinogenesis has to be verified through more research (Den besten et al.,2013).

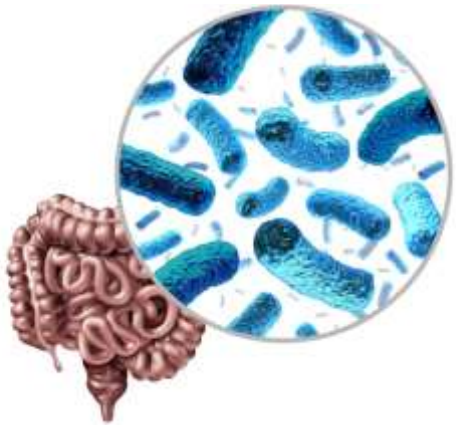

Figure 1: GUT MICROBIOTA
Source: https://www.istockphoto.com/search/2/image?phrase=gut+bacteria

- ***Probiotics And Intestinal Modulation***

Gram-positive bacteria L. reuteri is a heterofermentative symbiont found in the intestines of numerous animals, including humans, pigs, mice, and rats. L. reuteri controls the gut immune system through a variety of methods. Several in vitro experiments have been conducted and uncovered the chemical processes underlying its capacity to control the immunological system surprisingly, these behaviors appear to be both innate and adaptive immunity are strain dependent (Quigley et al.,2013). Numerous investigations have shown that L. reuteri has the potential to control Human immune cells that produce cytokines [Table-1]. IL-2 production was increased when these cells were treated with L. reuteri 100-23 and interacted with splenic T cells from ovalbumin T-cell receptor transgenic mice decreased whereas transforming growth factor (TGF) production rose in comparison to those of untreated cells Furthermore, Lactobacillus-free L. reuteri 100-23 colonized mice contained more FoxP3-positive cells in their spleen and mesenteric lymph nodes than the control group mice (mu et al.,2018).These findings indicated that, in addition to triggering intestinal L. reuteri 100-23 controlled immunological responses as well as development and T lymphocytes with regulatory functions are recruited to the gastrointestinal epithelium. L.reuteri may regulate gastrointestinal tract inflammation (Huang et al.,2017).

L.reuteri may create antimicrobial substances such as reuterin, organic acids, and ethanol. L. reuteri's antimicrobial activity enables it to prevent the colonization of pathogenic bacteria and alter the composition of the host's commensal micro biota. Lactobacillus reuteri soluble substances reduced the synthesis of pro-inflammatory cytokines and the signaling of immune cells. L.reuteri 6798 cell-free culture supernatants suppressed tumor necrosis factor (Hemarajata et al.,2013). TNF (tumor necrosis factor) generation by lipopolysaccharide (LPS)-activated and mouse macrophages treated with Helicobacter hepaticas. Moreover, ATCC PTA 6475 human-derived L. reuteri conditioned medium showed strains' capacity to decrease TNF production by THP-1 stimulated human monocytoid cells and primary isolated monocyte-derived macrophages from peripheral blood of folks suffering from Crohn's disease. TNF transcriptional regulation L. reuteri expression was inhibited by inhibiting c-Jun-dependent transcription. Signaling by activator protein 1 (AP-1) Furthermore, L.

reuteri was capable to generating biofilms and suppressing TNF production in human myeloid cells THP-1 cells were treated with culture supernatants produced from PTA6475 derived from L. reuteri biofilms (Lin et al.,2008).

3. How Gut and Microbes are Connected to Brain-Biochemical Agents

There are several variables that affect how well the human body functions. Through the use of certain biological agents and the right supplements, the health status of the organism may frequently be improved. Probiotics, or living bacteria that improve host health when given in sufficient proportions, are frequently employed in over-the-counter nutritional supplements or functional foods, such as yoghurt. Irritable bowel syndrome, ulcerative colitis, Crohn's disease, or allergic disorders may all be treated with certain strains of microorganisms when given in the right dosages. These conditions include different types of diarrhoea (viral, antibiotic-related, or caused by Clostridioides difficile), IBS, ulcerative colitis, and Crohn's disease (Thomas et al.,2012). Contrarily, psychobiotics are living microorganisms that can affect the neurological system and mental health through interactions with the gut micro biome [Figure-2]. Prebiotics and live bacteria are frequently combined to create symbiotic which promote the development and/or activation of the metabolism of the healthy gut micro biome. For the development of probiotic strains or fermentation procedures, prebiotics may act as a substrate (Kailasapathy et al.,2000). Probiotic bacteria are more tolerant to environmental factors like oxygenation, pH, and temperature in an organism than prebiotic compounds are. It's important to note that post biotics and para probiotics, which are metabolites or cell components of living microbes, can also have an impact on the host's health. The mechanisms of probiotics, prebiotics, symbiotic, post biotics, Para probiotics, and psychobiotics' actions are discussed in this study, along with the findings of research demonstrating their efficacy and effects on consumer health (Nitzan et al.,2013). Interactions between intestinal bacteria and the enteric nervous system may modify immune responses in the gut and extra intestinal locations in addition to having an impact on behavior and pain perception. Gut microorganisms support immune development and homeostasis. The development of neuro immunological illnesses may, interestingly, be influenced by gut bacteria. Studies using a mouse model of experimental autoimmune encephalomyelitis (EAE) showed that the gut micro biota can cause autoimmunity to be sparked by myelin-specific CD4+ T cells (Zawistowska-Rojek et al.,2022).

The intestines and the brain are physically and chemically linked. Changes in the stomach can have an impact on the brain. The vagus nerve is a major nerve in the central nervous system that transmits information between the intestines and the brain. Estimates are also used to communicate between the brain and the intestines that imply that you have around 30 trillion human cells and 40 trillion bacteria. This suggests that you have more bacteria based on the number of cells than you are a human being. Microbes in your stomach create chemicals that transport data to the brain (Breit et al.,2018). This signifies that, according to this you are more bacteria than human in terms of cell count. The vast majority of bacteria can be found in your intestines. This means they have direct touch with the cells lining your intestines and everything else. Many additional microorganisms, including yeasts and fungus, coexist with your gut bacteria. These bacteria are referred to collectively as the gut micro biota or gut flora that penetrates your body's micro biome, this includes food, medications, and other items. Microbes and many additional germs coexist with your gut bacteria, Yeasts and fungus are two examples [Table-1]. These bacteria are referred together as the gut micro biome vs. gut micro biota. Each of these microorganisms has the ability to create several chemicals that can have an effect on the brain, Short chain amino acids is one of them. Amino acids, neurotransmitters, and fatty acids Gut bacteria can also cause via influencing the brain and central nervous system, Hormone production and inflammation (Sender et al.,2016).

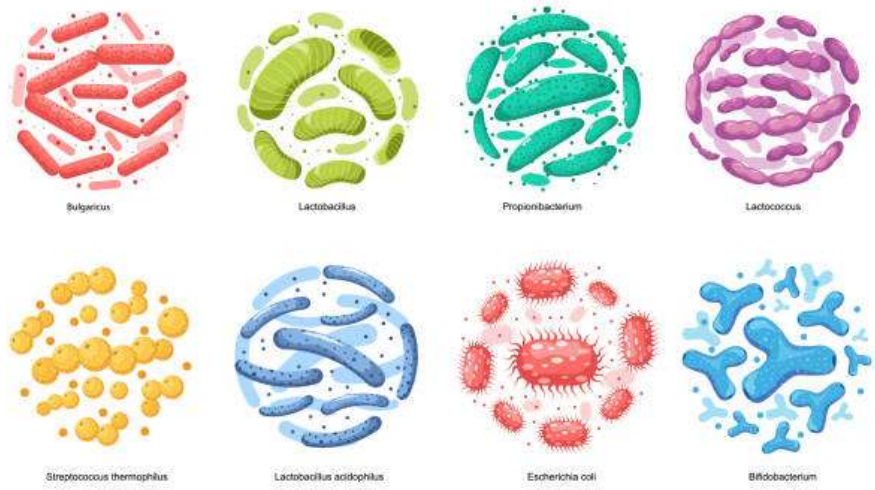

Figure 2: VARIOUS PROBIOTIC AGENTS
SOURCE: https://www.istockphoto.com/search/2/image?phrase=lactobacillus

➢ ***Probiotics Can Improve Mental Health***

stress and anxiety are becoming more widespread, and depression is one of the world's most serious mental health issues. A number of these illnesses, particularly stress and anxiety, are linked to elevated blood levels of the human stress hormone cortisol. Several researches have been conducted to investigate how probiotics have an effect on persons who have clinically diagnosed depression. According to one research shown the combining of three Lactobacillus and Bifidobacterium strains were considerably different after 8 weeks (Salleh et al.,2008). Depressive symptoms were lessened, they were also deficient in inflammatory process. A few more researches have looked into how probiotics work and Influence depressed symptoms in those who have not been formally diagnosed depression, such as:

- Symptoms of anxiety
- Depressive symptoms
- Psychological distress
- academic stress (Wallace et al.,2017).

TABLE-1: Probiotic agents and its effect

S.NO	PROBIOTIC AGENTS	FUNCTION	MECHANISM OF ACTION
1	*Lactic acid bacteria (LAB)*	Protection against colorectal cancer (CRC)	Strengthening and altering the natural defensive systems of the host cell [2]
2	*E coli strain*	Digestion of food	Stimulate intestinal mucosal adenylate cyclase [2]
3	*Lactobacillus casein BL23*	Immune function	Increase igA production [3]
4	*Lactobacillus Rhamnosus GG*	Barrier function	Decreased TNF-α production [3]
5	*Lactobacillus plant aurum*	Immune system modulation	Decreasing the levels of anti-inflammatory cytokines [4]
6	*Lactobacillus acidophilus*	Blocks communication between pathogenic bacteria	By secreting molecules which blocks quorum sensing signaling [4]
7	*Salmonella typhimurium VSL #3 probiotics*	Immune modulation	By attenuating IL-8 secretion or blocking the degradation of counter-regulatory factor lkB [13]
8	*Lactobacillus reuteri*	Improve digestion and restore normal flora	Inhibit colonization of pathogenic microbes and remodel the commensal microbiota composition in host [14]
9	*Yeasts (debaryomyces,torulaspora)*	Ensure gut barrier integrity	Tight junctions between gut cells enhance the intestinal barrier impermeability, separating the rest of body from intestine [22]

➢ ***The Relationship Between Probiotics and Cancer types***

Cancer is a disease with a high global fatality rate. Furthermore, this rate is rising on a daily basis. It is anticipated to become first position by 2030, overtaking cardiovascular disease, the most prevalent cause in the universe of death. Cancer is now acknowledged to be the second leading cause of death. The cancer process and therapy diminish the standard of living. The effects of probiotics on this process have been studied in order to enhance it (Nagai et al.,2017). Some kinds of cancer, particularly colorectal cancer studies are being carried out today, Probiotics have been shown in studies to be beneficial. However, some research contend that they should not be utilized, citing the possibility of harm infection in severely ill patients with weak immunity. The mechanisms behind probiotics' anticancer effects are yet unknown. It is linked to several pathways that mostly affect the stomach micro biota. The belief that probiotics have anti-cancer properties. As a general rule, depends on dosage, strain, and species conclusion. Furthermore, probiotics must be ingested on a regular basis, and the ingested product must contain a certain quantity of microorganisms (about 100 g/day) to achieve the desired effect. This review includes the effects of probiotics, including both good and negative effects individuals with cancer are still being addressed on many sorts of forums (Drago et al.,2019).

4. Immunotherapy and Gut Microbiota

Resistance to standard treatments, such as chemotherapy and radiation, is associated with significant tumor recurrence and has been a major issue in cancer treatment. In the recent decade, there has been a blossoming of Immunotherapy was shown promise in clinical studies for treating malignancies, for which numerous FDA-approved treatments are available long-term anticancer effects in individuals who were previously resistant to conventional therapy. In the meanwhile, aside from its involvement in carcinogenesis, the gut micro biota also has an impact on a variety of other factors. Cancer therapy's role of the gut is discussed in the next section. Microbiota in three primary immunotherapy methods that include AC-T, CpG-oligodeoxynucleotide treatment and immune checkpoint inhibition (Ventola et al.,2017).

➢ ***Transfer of Immune Cells for Adoption***

AC-T is a cancer therapeutic strategy that employs autologous immune cells such as tumor-infiltrating lymphocytes (TILs) and cytotoxic T lymphocytes (CTLs). It consists of three steps:
(1) Separation of T lymphocytes from tumor tissues or peripheral blood vessels;
(2) Co-culturing with interleukin (IL)-2 to enable for ex vivo growth
(3) Reintroduction of isolated T cells into patients (Wu et al.,2012).

Recent clinical trials have used genetically engineered T cells to increase the expression of antigen-specific T cell receptor (TCR) or chimeric antigen receptor (CAR) on retrieved T cells, resulting in greater immune responses to counteract antitumor immunological reaction following reinfusion Tumor cells' immune-resistance mechanisms (e.g., faulty antigens processing) (Tsai et al.,2016). ACT has a higher specificity than chemotherapy. Because autologous immune cells are employed and may be genetically modified ACT has been developed to detect and target certain tumor antigens; as a result, it is thought to be a highly customized cancer treatment. Currently, ACT, CAR-T cell therapy, in particular, has shown significant results in eliminating hematologic cancers and metastatic melanoma (Shsrpe at al.,2015).

While the effectiveness of ACT in gastrointestinal cancers such as colorectal cancer (CRC), hepatocellular carcinoma (HCC), and esophageal cancer is still being studied, restricted, which might be attributable to poor tumor trafficking TReg/effector T cell ratio deregulation and immunosuppressive tumor microenvironment. Extensive research is being conducted to improve AC-T (Bokaee et al.,2011).

Tumor-immune microenvironment (TIM) modulation, genetic modification Engineering techniques or radiation integration Emerging trials creating replacements, such as CAR-expressing natural killer

(NK) cells treatment, as well as the combination of dendritic cells and cytotoxic-induced killer cells in the treatment of HCC and pancreatic cancer (Elahi et al.,2021).

➢ ***Adoptive Immune Cell Transfer and Gut microbiota***

The first indication of a link between gut micro biota and AC-T effectiveness was published in 2007, when AC-T and whole body irradiation (TBI; a type of lymph depletion) were given to a mouse model with a lymphoma [Figure-3]. Tlr-4.22 and a cluster of differentiation (Cd)-14 deficit Depleting antibiotics or inhibiting LPS signaling components micro biota Cd8 + T cells that had been adoptively transplanted performed poorly. Lowered the amount of activated dendritic cells, resulting in antitumor activity In contrast, LPS treatment to TBI patients Mice deficient in microbiota may boost the proliferation and function of reinfused T cells, and may even be able to heal animals with huge tumors TBI, in particular, might cause microbial translocation mechanically. PS-producing gram-negative bacteria entering the mesenteric lymph nodes (Wang et al.,2021).

These Trans located microorganisms subsequently activate the Tlr4 pathway by producing different Tlr4 agonists (e.g., LPS, peptidoglycan), resulting in greater activation of dendritic cells and release of pro-inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor (Tnf) - via the gut notably, and LPS administration might be enhanced. Adoptively transplanted Cd8 + T cells trigger an antitumor response in untreated TBI mouse. Uribe-Herranz et al. (2018) used AC-T on tumor-bearing C57BL/6 mice from two suppliers (JAX and HAR) and discovered that tumor development is nearly totally eliminated in HAR mice but not in JAX animals (Ahmed et al.,2013). 21 The 16S the variation in fecal content was identified by rRNA sequencing. JAX and HAR mice micro biome – a varied spectrum of Bacteroidetes taxa were found in HAR mice, but not in JAX mice. Bacteroidales S24-7 predominated, suggesting that ACT efficacy may be related to multiple Bacteroidetes species, including Bacteroides as well as Parabacteroides. The antibiotic vancomycin was then administered. Remove the gram-negative phylum Bacteroidetes from JAX and HAR mice In terms of effectiveness, no difference was seen in HAR mice, however Tumor regression in JAX mice was considerably accelerated. These findings offer a potential strategy to improve responsiveness to AC-T by modifying the gut microbiota, however it is unclear whether specific microorganisms are involved are in charge of such advancement. An in-depth mechanistic investigation is required. As a result, it is critical to find dependable microbial targets for modulation of the ACT efficacy before going to clinical studies (Lau et al.,2021).

5. Immune Checkpoint Inhibition

The goal of immune checkpoint blockade is to restore and increase the anticancer response by blocking the intrinsic immuno-inhibitory pathways that tumor cells typically use to grow Immune defense.

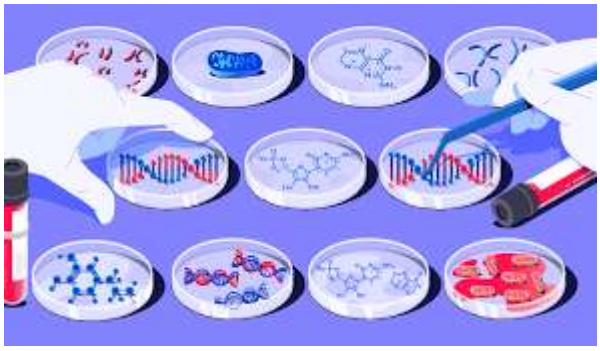

Figure3: Lactic acid probiotics
Source: https://atlasbiomed.com/blog/top-12-lactobacillus-probiotics/

Massive attempts have been made to capitalize on the effectiveness of treating cancer patients with completely humanized monoclonal antibodies against two of the most extensively researched immunological checkpoint regulators – CTLA-4 (cytotoxic T lymphocyte-associated antigen)

(CTLA-4) and PD-1 (programmed cell death protein-1) or PD-1-ligand 1 (PD-L1). CTLA-4 and PD-1 are TCRs that belong to the members of the immunoglobulin superfamily, although they have distinct characteristic methods for controlling host immunity (Kreamer et al.,2014).
Some immune checkpoint inhibitors (ICIs) have achieved FDA clearance to date, including PD-1 (nivolumab, pembrolizumab, and cemiplimab) and PD-L1 (atezolizumab, avelumab, and durvalumab) blockers.CTLA-4 (ipilimumab) for the treatment of cancer, particularly metastatic malignancy Melanoma and non-small cell lung cancer are two examples [Table-2]. These ICIs can also be employed against HCC, gastric cancer, and other gastrointestinal malignancies DNA mismatch repair defective or esophageal cancer CRC with high microsatellite instability (dMMR/MSI-H) (Wojtukiewicz et al.,2021). However, immune-related adverse events (irAEs) such as colitis and pneumonitis are often associated with ICI treatment. Increasing research has established a linicik between the occurrence of irAEs and the effectiveness of ICI therapy. In addition to a wide range of therapeutic response (45–60% for individuals with melanoma or MSI-H tumors; and 15–30% for patients with other cancers) As a result, developing techniques to treat patients with solid tumors is crucial and decrease the prevalence of irAEs and improve treatment efficacy (Das et al.,2019).

TABLE-2: Immunotherapy methods

S NO	IMMUNOTHERAPY METHOD	FUNCTION	TREATMENT
1	AC-T Adriamycin, cyclophosphamide and Taxol	Damage DNA inside cancer cell, therefore stops the cells from dividing which causes them to die	Used in treatment of breast cancer, it can also be given after surgery as adjuvant therapy [28].
2	Immune check point inhibitors (ICIs) also called as immunotherapy drugs	Works by blocking checkpoint proteins from binding with their partner protein, thereby allowing the T-Cells to kill cancer cells. For example checkpoint proteins such as PD-L1 on tumor cells and PD-1 on T-Cells, help keep immune response in check.	Used in treatment of breast, bladder, cervical, liver and few other cancers [37].

- ***Preclinical Studies on Gut microbiota and Immune Checkpoint Blockade***

CTLA-4 inhibition discovered in 2015 that tumor-bearing mice treated with broad-spectrum antibiotics or confined in cages had a substantial drop in activated effector Cd4 + T cells and TILs. In germ-free settings, CTLA-4 blocking is ineffective. Bacteroidales and Burkholderiales reduction in the faces of these Microbiota-depleted mice were discovered. Specifically, re-colonization of Bacteroides thetaiotaomicron is one of the species from these two taxa. Bacteroides fragilis and/or Burkholderia cepacia are introduced into CTLA-4 blockade resistance was restored in mice lacking microbiota enhancing TH1-mediated immunity and dendritic cell maturation in tumor-draining lymph nodes, while also relieving Colitis caused by anti-CTLA-4 (Vétizou et al.,2015).
Adoptive transfer of B. fragilis-specific TH1 cells may also restore CTLA-4 sensitivity. In another study, mice were given vancomycin before being given anti-CTLA-4 antibodies with sodium dextran sulphate (a colitogen model) Blockade-induced colitis resulted in a more severe and often deadly type of the illness, suggesting that gram-positive bacteria have a role in disease mitigation Colitis caused by CTLA-4 inhibition of 31 Notable is the oral gavage of a combination of Four gram-positive Bifidobacterium species may help. Immunopathology related with CTLA-4 inhibition via T cell activation cell-mediated metabolic processing, saving mice from Dysbiosis caused by vancomycin (Wang et al.,2015).

- ***Clinical trials on Gut microbiota and Immune Checkpoint Blockade***

Antibiotic therapy: Clinicians frequently administer broad-spectrum antibiotics to patients with extended immunosuppression to prevent opportunistic infections, as well as individuals with HIV,

diarrhoea caused by immune checkpoint inhibition, accompanied by fever or leukocytosis. Several clinical trials were conducted to investigate the compositional changes in the gut microbiota undertaken to portray the influence of antibiotics on ICI patients Derosa et al. conducted the biggest independent retrospective study by far the most extensive study to investigate the efficacy of antibiotic therapy prior to the first_dosage of anti-PD-1/PD-L1 medication in 360 RCC patients (Seddon et al.,2011). 74 Reduced progression-free survival (PFS) and overall Survival was found in RCC patients who were given antibiotics for 30 or 60 days. As well as NSCLC patients who were given antibiotics 30 days before therapy began. AL retrospective's research, which included 172 participants, RCC, NSCLC, melanoma, sarcoma, and gastrointestinal cancer. Antibiotics were given to patients with stromal tumors (n = 54), 30 (n = 30) or 60 days (n = 14) before PD-1 and/or CTLA-4 treatment blockade In contrast, neither PFS nor overall survival showed any improvement. At all times, there is a distinction between antibiotic-treated and untreated patients, except that there was a decline in overall survival in patients with antibiotics 30 days before therapy (Petrelli et al.,2020).

Scientists conducted more research on how the timing of antibiotic administration affects patient outcomes. Broad-spectrum antibiotics were administered to 29 and 68 patients, respectively (malignant melanoma or NSCLC) 30 days before or during anti-PD-1/PD-L1 treatment, respectively. Only pretreatment antibiotic usage was permitted, but not concurrent use linked with worse overall survival and a greater risk of main illness refractory, implying that antibiotic use is still safe (Pinato et al.,2019). patients receiving ICI treatment Nonetheless, this clinical work has established a proof-of-concept link between microbiota and antibiotics, as established in preclinical trials Despite the fact that the outcome is debatable, it is evident that antibiotics provide no major advantages, or possibly decreases therapy response As a result, extensive effort is necessary to assure the safety and necessary before giving antibiotics to patients who will get immune checkpoint blockade, extensive study is necessary to establish the safety and necessity (Derosa et al.,2021).

Several CpG-ODNs, including CpG-7909, have been used in clinical studies [Table-3]. However, underwhelming findings were frequently reported, since immunotherapy appeared to be insufficient to create a powerful anticancer impact can be explained by different TLR9 expression patterns among patients, and The immuno stimulatory impact of CpG-ODNs was overshadowed by the tumor microenvironment immunosuppressive (Zhang et al.,2021).

Meanwhile, significant attempts have been made to use CpG-ODNs as an adjuvant in other therapies like as chemotherapy and immunotherapy. In preclinical studies, intratumoral or peritumoral injection of CpG-ODNs in combination with ICIs raised circulating levels and tumoral growth. Infiltration of effector Cd8 + T cells, extending the lifespan of tumor-bearing mice with blockade resistance. Investigated two Inpatient-like mice models of anti-PD-1 resistance were created and developed, When CpG-ODN SD-101 was combined, a synergistic effect was seen SD-101 anti-PD-1 antibodies were also administered intravenously (Huang et al.,2022). TIM promotes T cell invasion and the development of multifunctional cells Cd8 + T cells expanded more after being blocked by PD-1,Cd8 + T cells stimulated by CpG differentiated into short and long-lived effector cells and memory precursors.

These findings give justification for moving forward with clinical studies using this novel CpG-ODN-immune checkpoint blocking method (Bennett et al.,2020).

In germ-free or antibiotic-treated mice, injections of CpG-ODNs plus anti-IL-10 R antibodies failed to inhibit subcutaneous tumor development and resulted in shorter survival when compared to controls reduced pro-inflammatory cytokine secretion (Il-1, Il-1) and Tnf was generated in these with decreased Cd45+ TILs. Mice deprived of microbiota after injection There was also ineffective therapy seen in Tlr4/- animals, whereas Tlr4 agonist LPS administration potentially improve myeloid cell response to therapy in Mice with a compromised micro biome. This suggests that the stomach Tlr4 might be used by microbiota to activate tumor-associated myeloid cells. CpG-ODN activation results in a Tlr9-dependent immunological response injection (lida et al.,2013).

Several gram-negative (e.g., Ruminococcus and Alistipes shahii) and gram-positive (e.g., Lactobacillus fermentum, Lactobacillus intestinalis) fecal bacteria were associated with CpG-ODN effectiveness and Lactobacillus murinum) genera were both favorably and adversely correlated. Tnf

production induced by CpG-ODN, respectively. Notably when Alistipes shahii was given to microbiota-depleted CpG-ODN-treated mice Tnf production by tumor-associated myeloid cells in mice was studied and restored. In contrast, L. fermentum oral gavage (a well-established method) CpG-ODN anticancer response was reduced by anti-inflammatory species in antibacterial-treated mice. Overall it is now obvious that the effectiveness of CpG ODNs or other immunotherapies is directly connected to Communal microbiota because various microorganisms might cause conflict, Clinical interventions that change the microbial community Interventions such as probiotics and FMT may be a viable option (lida et al.,2013).

Table3: Micro biota and immune checkpoint blockade

S NO	IMMUNOTHERAPY METHOD	FUNCTION	TREATMENT
1	CPG-oligodeoxy nucleotide (Cytosine, phosphate, guanine)	The dendritic cells migrate to the reginol lymph nodes where they encounter and activate tumor specific cytotoxic T cells. In this the primary effect of CPG-ODN is to enhance activation, antigen uptake, and maturation of the dendritic cells.	CPG-ODN has potent immune stimulatory effects and enhances anticancer activity of various cancer treatments. They enhance both chemotherapy and radiation therapy.[45]
2	Treatment by Gram positive and gram negative bacteria	Species such as ruminicoccus and L.fermentum were associated with CpG-ODN effectiveness. It also decreases the tumor necrosis factor production	Both gram positive and gram negative bacteria are effective in treatment of certain cancers.[49]

7. Immunotherapy Adjuvants based on Gut Microbiota and Dietary modification

Given its therapeutic potential, there is rising interest in targeting the gut microbiota to treat dysbiosis or related inflammation, as well as using it as immunotherapy adjuvants. Three issues are addressed here .Dietary intervention, probiotics, and FMT (fecal microbiota transplantation) techniques that attempt to change the microbial community to provide more clinical advantages to patients who received immunotherapy, as summarized (Zhou et al.,2021).

Long-term unbalanced diets have been linked to cancer; for example, a diet low in fiber and high in protein from red meats is enough to increase CRC development. In the meanwhile, dietary Nutraceuticals have been shown in thousands of studies to prevent carcinogenesis. Recently nutraceuticals, particularly polyphenols (a kind of polyphenol) have been used. It has become possible to use natural plant-derived compounds to cure cancer .For example, resveratrol in grapes may boost antitumor immunity (Donaldson et al., 2004). Tumor-bearing mice by altering TIM to make it unfavorable for tumor formation e.g. Encouraging the accumulation of effector Cd8+ T cells and monocytic cells and inhibiting the number of myeloid-derived suppressor cells (MDSCs). Cd4+ Cd25+ TReg and Cd8 + T cell-suppressing tumor cells MDSCs (granulocytic). When supplying resveratrol to Tumor-bearing mice treated with immunotherapy had their tumors completely eradicated, as well as metastatic retardation without generating therapy-induced normal epithelial cells are injured. There are currently no experiments testing the short-term resveratrol-adjuvant immunotherapy effectiveness, Resveratrol treatment (14 days) to CRC patients may inhibit tumor growth, cell proliferation 102 and the induction of apoptosis. Other polyphenols, such as flavonoids, genistein, and pomegranate, have demonstrated anticancer activity in preclinical but not clinical research, which is concerning proposed because the amount of nutraceuticals necessary for displaying some effects in patients For example, despite the fact that curcumin is one of the most promising polyphenols as a CRC adjuvant Because of its limited water solubility, therapy and therapeutic usage are frequently restricted. As well as bioavailability Liposomes and other Nano formulations are examples. As a result, micelles are being developed to increase curcumin delivery into patients (Calvani et al.,2020).

- ***Fecal microbiota transplantation***

FMT is a therapy that uses colonoscopy or oral administration to transport feces from healthy donors into the gastrointestinal tracts of recipients in order to cure disorders by restoring the balance and activities of gut microbiota. FMT is frequently used to treat recurrent Clostridium difficile infection with a high success rate. It also demonstrates its therapeutic promise against graft versus-host disease, neuropsychiatric (e.g., depression and Parkinson's disease), or autoimmune illness, additional digestive issues (e.g. IBD and ulcerative colitis). In contrast, the evidence on the use of FMT to treat gastrointestinal cancer is quite restricted (Choi et al.,2016).

Transfer of fecal samples from CRC patients into carcinogen-treated environments despite the fact that microbiota-depleted animals had higher intestinal tumor genesis, whether obtaining feces from healthy people may slow the onset of CRC testing is required. In addition, animals with high-fat diet-induced gut microbial diversity restoration (e.g., enrichment of Lactobacillus and butyrate-producing taxa) and decreased intrahepatic lipid accumulation were found, steatohepatitis after ingesting feces from healthy mice, indicating that FMT might be involved and reduce the incidence of HCC caused by nonalcoholic fatty liver disease (Wong et al.,2017).

- ***Current constraints and future prospects***

It is now apparent that the gut microbiota plays an important role in cancer immunotherapy. Such discoveries have offered solid foundations for improving therapeutic effectiveness by changing the microbial profile in patients via diverse mechanisms. Probiotic supplements and FMT are the two examples of techniques (Li et al.,2021).

Once again, the absence of comprehension of the molecular interactions between host immunity and particular antigens clinical progress has been hampered by microorganisms or the total microbial ecosystem investigation. To improve the translational potential of microbiota-targeted research ICMC emphasized the significance of developing uniform recommendations for therapy. When presenting "metaomics" data in academia, with more openness to enable repeatability. ("Gut microbiota: implications on gastrointestinal cancer") In addition, merging micro biome research with other new approaches Technologies may provide fresh insights into previously unexplored scientific fields have been studied well (Belkaid et al.,2014). The patient-derived organoid model, for example, is a recently established and robust in vitro system that has shown tremendous promise in predicting treatment outcomes due to perfect phenotypic preservation and the genotypes of the malignancies that gave rise to them. In 2020, a study used whole-genome sequencing on human CRC organoids that had been exposed to genotoxic pks+ E.coli to disclose its oncogenic mutational markers, demonstrating the utility to portray microbe-associated carcinogenesis at the genomic level, researchers used organoids ("Influences of gut microbiota on gastrointestinal cancer immunotherapy") (Yang et al.,2018).

Furthermore, it is becoming increasingly clear that metabolites (intermediate end products of microbe-mediated metabolism) play different roles in cancer development. For instance, there is a group of metabolites called as dysbiotic conditions, bile acids have been shown to promote cancer conditions. Changes in the micro biota's makeup might raise the risk of infection in the presence of deoxycholic acid (a kind of bile acid known to cause DNA damage), Enterohepatic circulation is disrupted, and resulting in a breakdown of the gut barrier and additional complications encouraging carcinogenesis in the intestines or the liver Evidence on how metabolites work is noteworthy (Staley et al.,2017). Until recently, the ability to modulate immunotherapy has been lacking, by which in a 2020 research, it was discovered that a molecule called inosine (made by bacteria) Bifidobacterium pseudolongum) may improve immunological checkpoint response. In mice, blockage is achieved by activating anticancer T cells. In addition to bacteria, the role of the gut viral, fungal, and archaeal microbiota in gastrointestinal malignancies, including CRC, has been demonstrated in a growing number of articles. It is, nonetheless, notable that their involvement in cancer therapy have received little attention. As a result, new research (for example, shotgun metagenomic sequencing, which permits cross domain profiling with higher taxonomic precision and genome coverage than traditional methods) is needed To determine whether nanobacterial pathogens are present, 16S rRNA sequencing is recommended Immunotherapy effectiveness may be influenced by the micro biome (Mager et al.,2020)

8. Conclusion

Combining cutting-edge sequencing technology with mechanistic research has contributed in the discovery of new interactions between the human immune system and the microbial population in both healthy and cancer-prone states. Here, we'll focus on the relevance of gut commensals in influencing cancer treatment efficacy and immunotherapy. Particularly noteworthy are efforts that target the micro biome as a cancer risk factor. The use of monotherapy or adjuvant therapy as a first-line treatment is becoming commonplace were studied. In conclusion, despite the knowledge gap between gut microbiota and humans, as the gap between gastrointestinal cancer and other cancers is shrinking, significant efforts are surely being made needed to properly understand the underlying systems, therefore amplifying the effect in clinical practice, the use of microbiota-targeted medicines.

Authors' contributions

Conflict of interest

'The authors declare no conflict of intrest'

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