GUT MICROBES ACTION ON CDV'S AND CANCERTHEARPY

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ABSTRACT:

Recent advances in metagenomic sequencing and metabolomics have revealed a strong connection between gut microbiota and cardiovascular diseases (CVDs) such as coronary atherosclerosis, hypertension, and heart failure. Metabolites like trimethylamine-N-oxide (TMAO), short-chain fatty acids (SCFAs), and bile acids (BAs) play key roles in the development, prevention, and treatment of CVDs. This review summarizes the latest findings on how these microbiota-related metabolites impact CVD progression. Similarly, next generation sequencing has improved our understanding of the microbiota's role in cancer development and treatment. Evidence suggests that modifying gut microbiota can enhance the effectiveness of therapies like immunotherapy, chemotherapy, and radiation. This review also examines emerging microbial interventions for cancer therapy and their potential to improve treatment outcomes.

Keywords: Gut microbiota, cardiovascular diseases (CVDs), Cancer Immunotherapy, Chemotherapy, Fecal Microbiota Transplantation (FMT), Microbial Dysbiosis, Microbial Metabolites, Bacterial Consortia, Probiotics in Cancer, Gut–Tumour Interaction, Tumour Microenvironment (TME), Microbial Therapy, Immune System Modulation, Microbiome based Treatment, Biomarkers in Cancer Treatment.

INTRODUCTION:

Cardiovascular diseases (CVDs), such as coronary atherosclerosis, hypertension (HTN), and heart failure (HF), are leading causes of death worldwide, contributing significantly to both economic and health burdens. As a chronic condition, diabetes, alongside inflammation, plays a critical role in the onset and progression of CVDs. Other factors, including diet and nutritional status, also have a substantial impact on CVD development.[1] Additionally, advancements in microbial sequencing have revealed the presence of distinct gut microbiota associated with CVDs, highlighting the strong connection between gut microbiota and CVDs.

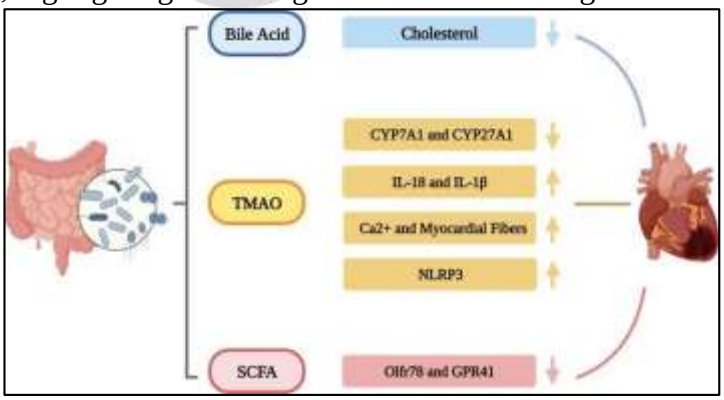

FIG 1: The roles of gut microbiota in CVDs.

The human gut serves as a vast microbial environment, hosting hundreds of bacterial species. Gut microbiota plays a crucial role in maintaining overall health. These microbiotas produce biologically active metabolites that influence various aspects of host physiology, earning the gut the designation of the "ninth system" of the human body.[2] The intestinal flora forms the epithelial barrier, regulates immune function, aids in nutrient

digestion, produces vitamins, and defends against pathogenic invasions, all of which are vital for human health. Disruptions in the gut microbiome caused by dietary habits, environmental factors, or intestinal infections can lead to malnutrition, trigger inflammation, and cause metabolic abnormalities, which, in turn, contribute to the onset and progression of CVDs.[3] This review explores the role of gut microbiota in CVDs and provides a summary of related metabolites, offering new insights into the relationship between gut microbiota and CVDs **(Table 1)**.

Table-1: The association between gut microbiota and CVDs.

Types of CVDs	**Changes in the Gut Microbiota**	**Involvement of Gut Microbiota Metabolites**	**Mechanism**
Coronary Atherosclerosis	Increased Streptococcus; Increased Roche; Increased Ruminococcus; Increased Clostridium	TMAO (Trimethylamine NOxide)	Cholesterol metabolism ↓; Foam cells ↑. Promote activation of NFκB; IL-18 ↑; IL1β ↑.
		BAs (Bile Acids)	Cholesterol ↑; Reduces the risk of atherosclerosis
		LPS (Lipopolysaccharide)	Foam cells ↑; Cholesterol ↑.
Hypertension (HTN)	Increased Prevotella; Increased Bifidobacterium; Increased Lactobacillus	SCFAs (Short-chain fatty acids)	Knockout of Olfr78 and GPR41 leads to high blood pressure.
		Propionate	Adjusts Th17 and lowers blood pressure
Heart Failure (HF)	Increased Candida. Decreased Faecal bacterium.	BAs	Regulates calcium ion concentration
		SCFAs	Disrupts the intestinal barrier; Promotes endotoxin translocation into the blood.
		TMAO	Ca2+ ↑; Myocardial fibres↑. Induces T-tubule network damage and calcium
			processing dysfunction. Activates NLRP3.

CVDs: Cardiovascular diseases; HTN: Hypertension; HF: Heart failure; TMAO: Trimethylamine-N-oxide; BAs: Bile acids; LPS: Lipopolysaccharide; SCFAs: Short-chain fatty acids.

Gut Microbiota and Coronary Atherosclerosis:

- Coronary heart disease (CHD), primarily driven by coronary atherosclerosis, is a significant representative of metabolic cardiovascular diseases (CVDs).
- Metagenomic sequencing has revealed that the gut microbiota in patients with atherosclerotic cardiovascular disease differs from that in healthy individuals, with elevated levels of Streptococcus and Enterobacteriaceae. Studies have shown that coabundant gut microbiota and serum metabolites are closely linked to the severity of CHD.
- Gut microbiota such as Roseburia, Ruminococcaceae, and Clostridium can regulate the metabolic activity of bile acids (BAs) and aromatic compounds, which further influence the progression of coronary atherosclerosis. This indicates a strong correlation between gut microbiota and coronary atherosclerosis (Table 1).
- Intestinal dysbiosis can also exert pro-atherosclerotic effects through metabolismdependent pathways by altering the production of various metabolites, including Trimethylamine-N-oxide (TMAO), BAs, serum indoxylate, protocatechuic acid, and lipopolysaccharide (LPS).[4] Among these, TMAO is one of the most important metabolites associated with gut microbiota.
- Research has shown that TMAO can affect immune system regulation, cholesterol metabolism, oxidative stress, and inflammatory responses, thereby increasing the risk of coronary atherosclerosis.
- Increased plasma TMAO concentrations are associated with a higher likelihood of developing CVDs.[5]Studies have found that TMAO-induced upregulation of macrophage scavenger receptor and CD36 expression impairs cholesterol metabolism in macrophages, promoting foam cell formation, which is an early cellular indicator of coronary atherosclerosis progression.

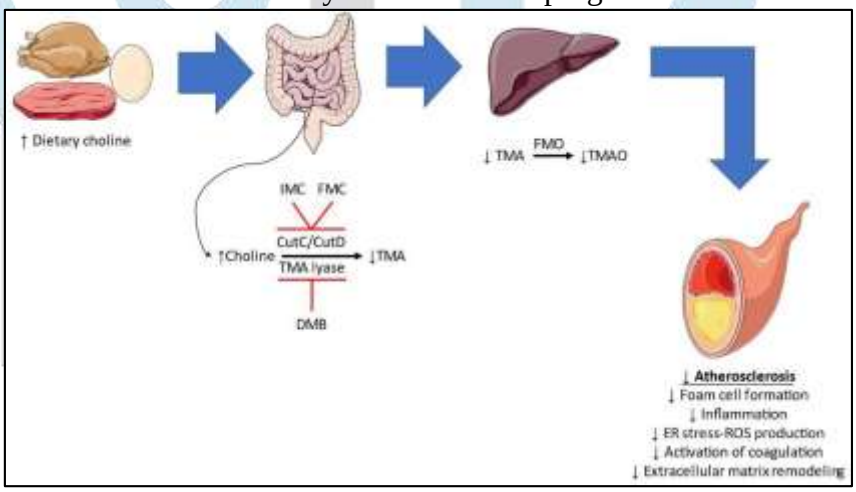

FIG 2: Therapeutic Perspectives of Gut Microbiota and Coronary Artery Disease

- Elevated TMAO levels also activate the NF-κB pathway and promote the release of inflammatory cytokines, such as IL-18 and IL-1β, indicating the role of inflammatory mediators in TMAO-induced endothelial dysfunction. Zhu et al., found that TMAO increases intracellular calcium release in platelets, promoting platelet aggregation and thrombosis.
- Furthermore, the choline analogy 3,3-dimethylbutanol (DMB), which inhibits choline TMA lyase activity, can reduce circulating TMAO and mitigate the proatherosclerotic effects of choline.
- In addition to TMAO, other factors like cholesterol metabolism, short-chain fatty acids (SCFAs), and tryptophan metabolites also affect coronary atherosclerosis development.[7] Deconjugated BAs, being hydrophobic, are excreted in feces, which lowers circulating cholesterol and reduces the risk of coronary atherosclerosis.
- Elevated levels of serum indoxylate have been found to correlate with coronary atherosclerosis and are predictive biomarkers of coronary artery disease severity. Protocatechuic acid also regulates atherosclerosis-related genes, including those associated with oxidative stress (AOX1, CYP2E1, TXNIP), adhesion molecules (JAM-A), and angiogenesis-related blood vessel endothelial growth factor receptor 2.

- Additionally, LPS has been reported to induce foam cell formation and cholesteryl ester accumulation from native low-density lipoprotein, further supporting its proatherosclerotic effect.
- Gut microbiota metabolites also play a role in arterial thrombosis. Fecal transplantation of TMAO-rich gut microbiota into germ-free mice promotes platelet function and arterial thrombosis.[8] found that phenylacetylglutamine can induce platelet hyperresponsiveness via adrenergic receptors. Additionally, phytoestrogens may have prothrombotic or proinflammatory effects.

Gut Microbiota and Hypertension:

- ✓ Hypertension (HTN) is the most prevalent risk factor associated with cardiovascular diseases (CVDs) and serves as the primary risk factor for both stroke and coronary heart disease morbidity and mortality.
- ✓ Recently, research has highlighted the involvement of gut microbiota in blood pressure regulation, with abnormal microbial populations being linked to hypertension.
- ✓ Compared to healthy individuals, hypertensive patients show a decrease in gut microbial diversity and abundance, with a notable increase in the genus *Prevotella*.
- ✓ Moreover, a fecal microbiota transplantation (FMT) study demonstrated that the microbiota from hypertensive patients could raise blood pressure in germ-free mice, emphasizing the close connection between gut microbiota and blood pressure regulation.
- ✓ This suggests a significant link between gut microbiota and HTN (Table 1).

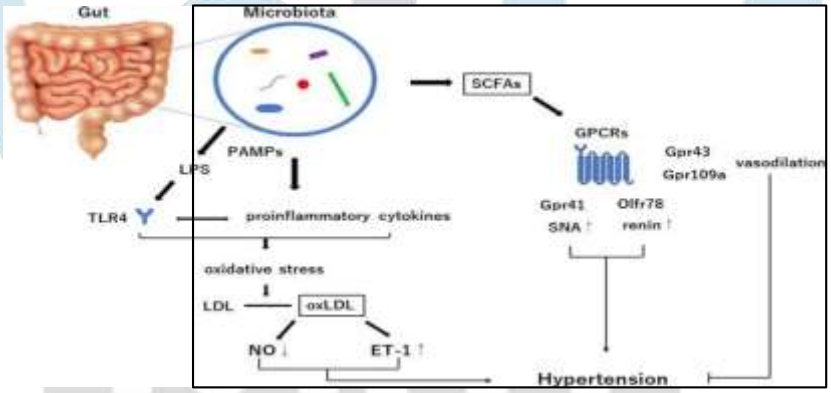

FIG 3: Mechanism of gut microbiota and hypertension

- ✓ Beyond changes in microbiota composition, the overproduction of metabolites by gut microbiota is also considered a crucial factor in the development of hypertension. Bacteria from genera such as *Bifidobacterium*, *Lactobacillus*, *Streptococcus*, and *Escherichia coli* produce neurotransmitters that interact with the autonomic nervous system, altering vascular tone and contributing to HTN.
- ✓ Additionally, elevated levels of circulating TMAO (trimethylamine-N-oxide) have been positively correlated with an increased risk of hypertension demonstrated that *Lactobacillus rhamnosus*[9] GG strain could prevent hypertension progression by reducing TMAO levels.
- ✓ Short-chain fatty acids (SCFAs), produced by gut bacteria, are also crucial in blood pressure regulation. SCFAs primarily influence blood pressure via Olfactory receptor 78 (Olfr78) and G protein-coupled receptor 41 (GPR41).
- ✓ Natarajan et al found that mice lacking GPR41 exhibited hypertension. Furthermore, activation of GPR41 reduced the abundance of SCFA-producing bacteria in hypertensive individuals with gut dysbiosis.[10] Similarly, showed that Olfr78-deficient mice also exhibited high blood pressure.
- ✓ Research has also suggested that propionate production is regulated by T regulatory cells, and blood pressure can be reduced through the action of regulatory T cells and angiotensin II-induced effectors.

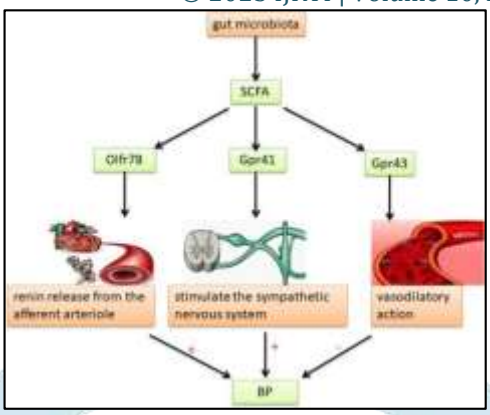

FIG 4: Flow chart of gut microbiotas effect on hypertension.

Although numerous studies have explored the mechanisms by which gut microbiota influence hypertension, the specific pathways remain unclear, and further research is needed. Understanding how gut microbiota metabolites such as TMAO, SCFAs, and propionate regulate blood pressure may provide new therapeutic approaches to treating hypertension by improving gut microbiota balance.

Gut Microbiota and Heart Failure:

- Heart failure (HF) is a terminal condition with high mortality, marked by symptoms such as edema and dyspnoea.
- The gut hypothesis proposes that reduced cardiac output and increased systemic congestion lead to ischemia and edema in the intestinal mucosa, promoting bacterial translocation and elevating circulating endotoxin levels,[(11)] which may contribute to the development of HF.
- Research has shown that HF patients exhibit an increase in pathogenic bacteria, such as Candida, and a decrease in anti-inflammatory bacteria, such as Faecalibacterium.
- This imbalance contributes to HF by influencing the regulation of mucosal immunity, highlighting the connection between gut microbiota and HF (Table 1).
- Gut microbiota metabolites, including short-chain fatty acids (SCFAs), trimethylamine-N-oxide (TMAO), indoxyl sulfate, and lipopolysaccharides (LPS), play significant roles in HF progression.
- Demonstrated that TMAO promotes calcium release in healthy mouse cardiomyocytes, affecting their contractility.[(12)] Direct dietary supplementation with TMAO results in higher systemic TMAO levels, which can increase myocardial fibrosis and trigger HF. TMAO also damages adult cardiomyocytes by disrupting the T-tubule network and impairing calcium handling.
- Furthermore, TMAO promotes myocardial fibrosis through the activation of NLRP3 inflammasome-related signaling, suggesting its potential as a therapeutic target for HF. Schuett et al.[(13)] found that TMAO enhances susceptibility to HF by increasing myocardial fibrosis, while Wang et al. showed that 3,3-dimethyl-1-butanol (DMB) alleviated adverse cardiac remodelling in HF mice by lowering TMAO levels.
- Additionally, indoxyl sulfate exacerbates cardiac fibrosis, cardiomyocyte hypertrophy, and atrial fibrillation.

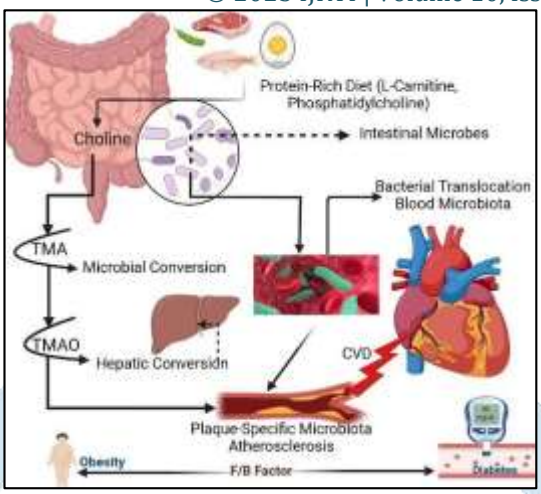

FIG 5: Therapeutic Regulation of Gut Microbiota in Cardiovascular Disease.

- Bile acids (BAs) have also been shown to influence cardiovascular function by modulating heart rate, channel conductance, and calcium dynamics in atrial and ventricular cardiomyocytes, as well as regulating vascular tone.
- SCFAs protect the gut by maintaining the intestinal barrier.
- A decrease in SCFAs can compromise the intestinal barrier, facilitating the translocation of endotoxins into the bloodstream,[14] which may ultimately contribute to HF. SCFAs also aid in cardiac repair following HF by inducing CX3CR1+ cells.
- Moreover, LPS damages the intestinal mucosal barrier, increasing intestinal permeability and elevating inflammatory cytokine levels, which are closely associated with HF development.
    - Thus, alterations in gut microbiota composition and the metabolites they produce play a critical role in the pathophysiology of heart failure.

Microorganism-Targeted Therapies:

Several microorganism-targeted therapies are being explored for the treatment of cardiovascular diseases (CVDs) (Table 2).

- Fecal microbiota transplantation (FMT) is one such approach, involving the introduction of fecal matter from healthy individuals into the gastrointestinal tract of patients to replace pathogenic microorganisms.
- This method effectively reintroduces beneficial gut microbiota. Studies have demonstrated that FMT can restore the balance of the gut microbiota by reducing the Bacteroides/Firmicutes[15] ratio and decreasing inflammation in cardiomyocytes, thereby alleviating myocarditis in mice.
- Furthermore, clinical trials have shown that FMT can rapidly restore the gut microbiota of healthy individuals following antibiotic treatment. However, the clinical application of FMT is currently limited due to the potential risks of transferring endotoxins or infectious agents, which may lead to new gastrointestinal complications.

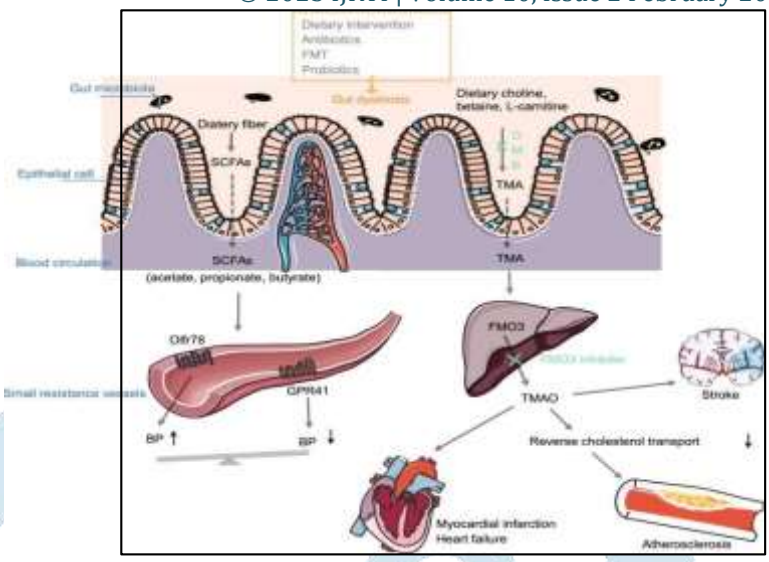

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FIG 6: Potential therapeutic applications of Gut microbes in cardiovascular diseases

Table-2: Microorganism-targeted therapies.

Types of CVDs	**Treatment Methods**	**Role**
Myocarditis	FMT	Reduce inflammation and myocarditis
	FMT	Restore the healthy gut microbiota
	Fiber-rich diet	Promote growth of beneficial symbiotic bacteria and inhibit the growth of opportunistic pathogens.
	Dietary Intervention	Reduce Enterobacteriaceae pathogenic bacteria and increase intestinal protective bacteria.
Hypertension (HTN)	High-Fiber diet	Lower blood pressure.
	Bifidobacterium breve and Lactobacillus fermentum	Lower blood pressure.
Myocardial Infarction	Lactobacillus plantarum	Reduce myocardial infarction size
	Lactobacillus rhamnosus GR-1	Reduce myocardial infarction size
Heart Failure (HF)	Saccharomyces boulardii	Have therapeutic effect on patients with HF.
	Antibiotics	Reduce damage to cardiomyocytes.
	Rifaximin	Have anti-inflammatory effects and modulate gut microbiota.
	Polymyxin B and tobramycin	Reduce the level of inflammatory factors in the gut of patients with HF

	DMB	Reduce ventricular remodeling.
Atherosclerosis	Resveratrol	Alleviate TMAOinduced atherosclerosis.
Myocardial Infarction	Exercise	Prevent myocardial infarction
Atherosclerosis	Curcumin	Attenuate atherosclerosis

FMT, Fecal microbiota transplantation; DMB, 3,3-dimethylbutanol; HTN, Hypertension; HF, Heart failure; TMAO, Trimethylamine-N-oxide.

- Dietary interventions to manage cardiovascular diseases (CVDs) offer significant potential. Research indicates that Fiber-rich diets promote the growth of beneficial symbiotic bacteria while suppressing opportunistic pathogens.[16] demonstrated that dietary changes involving whole grains and traditional Chinese medicine foods reduce pathogenic Enterobacteriaceae and enhance beneficial intestinal bacteria like Bifidobacterium.
- Furthermore, a high-Fiber diet can stimulate acetic acid-producing microbiota, which helps lower blood pressure.
- The gut contains a variety of bacteria, some of which are beneficial, and enhancing these beneficial bacteria may lead to favourable outcomes, such as through the use of probiotics. Probiotics like Bifidobacterium breve and Lactobacillus fermentum have been shown to lower blood pressure by restoring gut microbiota balance and preventing endothelial dysfunction. Lam et al. found that Lactobacillus plantarum improved ventricular function and reduced the size of myocardial infarctions. Similar results were observed in rats with myocardial ischemia treated with Lactobacillus rhamnosus GR-1.[17] Saccharomyces boulardii has also demonstrated therapeutic effects in heart failure patients by reducing inflammatory markers and serum creatinine levels. However, despite their safety, probiotics lack sufficient regulatory oversight, potentially increasing the risk of probiotic translocation to the bloodstream and causing sepsis.
- Antibiotics also influence the gut microbiota structure, impacting CVD treatment. Studies show that antibiotics can reverse gut microbiota imbalances and reduce cardiomyocyte damage.[18] For instance, rifaximin has anti-inflammatory properties and modulates the gut microbiota, while polymyxin B and tobramycin reduce inflammatory markers in the guts of heart failure patients, offering valuable therapeutic implications for CVDs.
- DMB (dimethyl butyrate) treatment can lower TMA production, prevent the conversion of TMA to TMAO, and mitigate ventricular remodeling. Moreover, resveratrol from Polygonum cuspidatum has been found to alleviate TMAO-induced atherosclerosis by reshaping the microbiota and lowering TMAO levels.
- Exercise can also impact the gut microbiome by enhancing the Firmicutes to Bacteroides ratio,[19] increasing bacterial metabolites, and preventing myocardial infarction. However, the effects of exercise on the gut microbiome are transient and reversible.
- Additional treatments for CVDs include curcumin, which has been shown to attenuate atherosclerosis by improving intestinal barrier function, and berberine, a compound derived from Coptis chinensis,[20]which can modulate the gut microbiota and influence CVD outcomes. In conclusion, microorganism-targeted therapies for CVDs primarily focus on fecal microbiota transplantation (FMT), dietary modifications, and the use of probiotics.

GUT MICROBIOTA-CANCER THERPY OVERVIEW:

The human microbiota, consisting of about 40 trillion microorganisms, including bacteria, fungi, and viruses, is essential for maintaining homeostasis and functional stability, with over
97% residing in the gastrointestinal tract. The gut microbiota is crucial for immune development and nutrient synthesis, but disturbances (dysbiosis) are linked to various health disorders, including cancer. Recently, intratumorally microbiota in the tumour microenvironment (TME) has gained attention, as it may influence cancer progression and therapy responses. Despite being low in biomass, these microbes can impact tumour growth and resistance to treatments like chemotherapy and immunotherapy. Research has shown that gut

microbes can promote cancer through mechanisms like chronic inflammation and DNA damage. Clinical trials have demonstrated the potential of modifying the microbiota to enhance cancer treatments and reduce side effects, using strategies like probiotics, prebiotics, and fecal microbiota transplantation.[21] However, challenges remain in translating these findings from animal models to human clinical settings, particularly due to variability in human microbiota and the complexity of the TME. Emerging microbial interventions hold promise for personalized cancer therapy, but more research is needed to fully understand their potential and overcome clinical translation hurdles.

Multidimensional Roles of Microbes in Cancer Development:

Gut dysbiosis, a disruption of the balanced microbial ecosystem in the gastrointestinal tract, leads to a pathogenic microbiota that can adversely affect host physiological processes and contribute to various diseases, including cancer. Pathogenic microbes influence both cancer development and treatment. These effects can be contact-dependent, occurring locally at the mucosal surface or within the tumour microenvironment (TME), and contact-independent, involving microbial metabolites and outer membrane vesicles (OMVs) circulating through the bloodstream.[22] Contact-independent effects are more complex, as detrimental molecules like lipoteichoic acid (LTA) and deoxycholic acid (DCA), produced by gut bacteria, can enter the bloodstream and promote cancer progression. For instance, LTA and DCA can facilitate hepatocellular carcinoma development via the enterohepatic circulation, representing a typical contact-independent contribute to the development of hepatocellular carcinoma. These complex microbial contributions highlight the diverse roles microbes play in cancer.

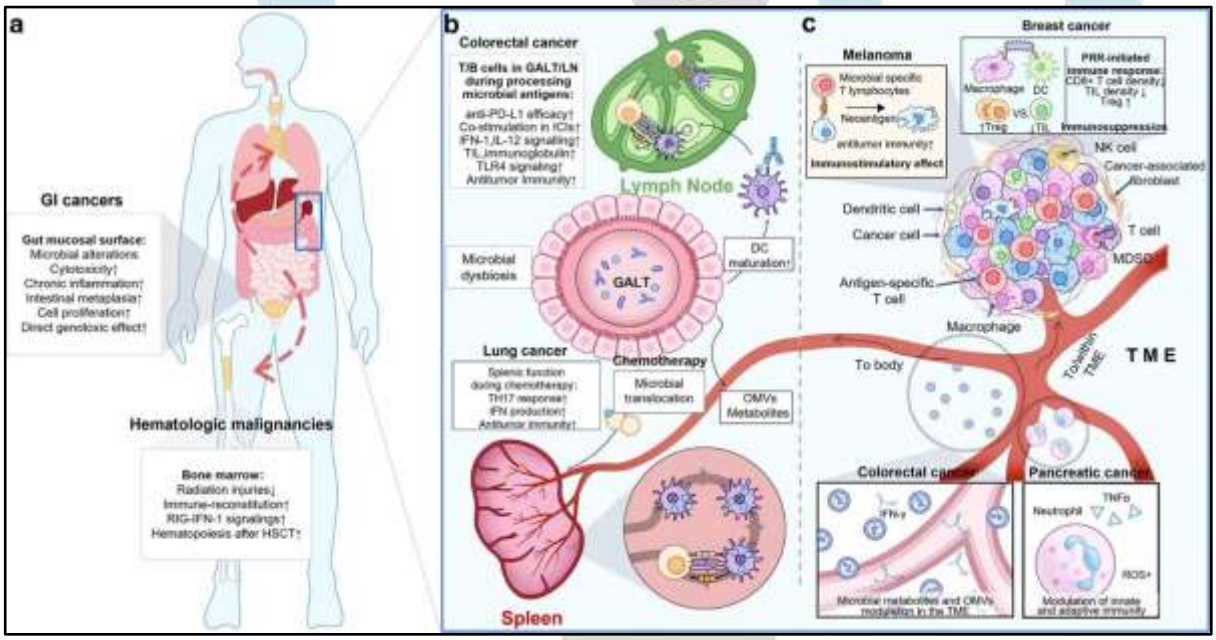

FIG 7: Role of the gut microbiota in anticancer therapy: from molecular mechanisms to clinical applications.

Interactions Between the Gut Microbiota and Cancer Development:

- ✓ The gut microbiota influences cancer development through both contact-dependent and contact-independent interactions. Contact-dependent interactions occur locally at the mucosal surface, primary lymphoid organs (bone marrow, thymus), secondary lymphoid organs (GALT, lymph nodes, spleen), or within the tumour microenvironment (TME).
- ✓ These interactions can promote epithelial cell proliferation, intestinal metaplasia, and immune responses, such as enhancing TH17 responses and IFN production. Contactindependent interactions involve microbial metabolites and outer membrane vesicles (OMVs) circulating through the body.
- ✓ These components can modulate the TME by activating innate immune cells (e.g., neutrophils, NK cells) and influencing adaptive immune responses, like T cell activation and Treg/TIL balance. (HSCT hematopoietic stem cell transplant, DC dendritic cell, GALT gut-associated lymphoid tissues, LN lymph node, TLR4 Tolllike receptor 4, TME tumour microenvironment, CTL cytotoxic T lymphocyte, NK cell natural killer cell, OMVs outer membrane vesicles, SCFAs short-chain fatty acids, TIL tumour-infiltrating lymphocyte, PRR pattern recognition receptor, MDSC myeloid-derived suppressor cells, ROS reactive oxygen species, TNF α tumour necrosis factor α).

- ✓ Microbial secreted molecules play a crucial role in both immunostimulatory and immunosuppressive effects within the TME.

Mechanisms by Which Microbes Contribute to Tumorigenesis:

Cancer-associated bacteria can promote oncogenesis through several molecular mechanisms. These mechanisms are generally categorized into four key pathways (Fig. 8): (1) DNA damage and epigenetic modifications, (2) disruption of the DNA damage response (DDR), (3) activation of abnormal signaling pathways, and (4) immune suppression.

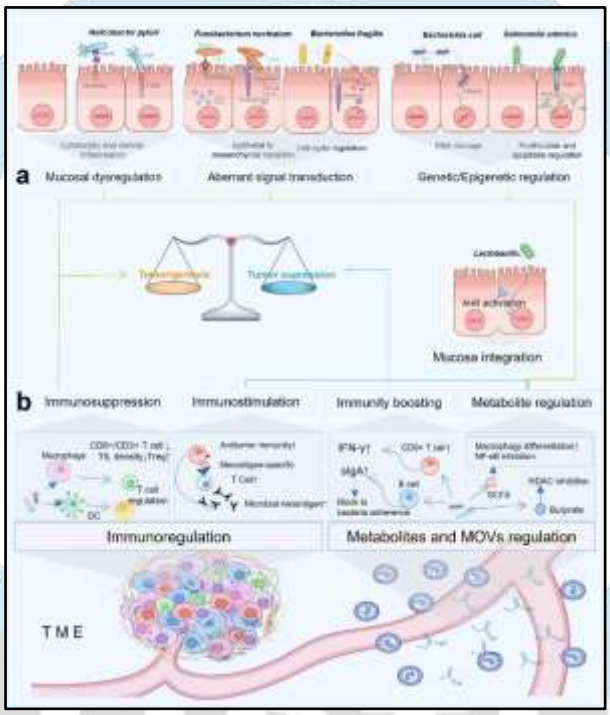

FIG 8: Microbial Mechanisms in Tumorigenesis

Inducing DNA Damage and Epigenetic Alterations:

- Cancer is fundamentally a genetic disease, and microbes can contribute to cancer initiation by inducing DNA damage in host cells. Several bacteria produce genotoxins, such as colibactin from E. coli and indolimines from Morganella morganii, which cause DNA damage and promote cancer progression.
- For instance, colibactin induces DNA alkylation and double-strand breaks, which disrupt DNA replication and transcription.[23] Additionally, bacteria like H. pylori and Bacteroides fragilis generate reactive oxygen species (ROS) that lead to DNA damage.
- Beyond direct DNA damage, microbes can also cause epigenetic changes, such as DNA methylation, which silences tumour suppressor genes. Studies have shown that bacteria like F. nucleatum and Hungatella hathewayi can upregulate DNA methyltransferases, contributing to colorectal cancer development by inducing promoter hypermethylation of key tumour suppressor genes.

Interference with the DNA Damage Response (DDR):

- ✓ The human genome constantly faces DNA damage from both external factors, like pathogens, and internal processes such as DNA replication stress. To manage this, cells have evolved the DNA damage response (DDR) to detect and repair DNA damage, leading to apoptosis, cell cycle arrest, or senescence.
- ✓ However, microbes can disrupt DDR, hindering DNA repair and promoting genetic mutations that may lead to cancer. For instance, C. trachomatis, associated with cervical and ovarian cancer, induces DNA damage and inhibits DDR by preventing the activation of key repair proteins like MRE11 and ATM.
- ✓ Similarly, H. pylori interferes with DNA mismatch repair, suppresses homologous recombination (HR), and promotes error-prone non-homologous end-joining (NHEJ) repair, leading to genomic instability.

Furthermore, H. pylori can degrade the tumour suppressor protein p53, which disrupts the DDR and promotes resistance to apoptosis, enhancing the risk of cancer development.

Triggering Aberrant Signaling Pathways:

- In addition to interfering with DNA damage response (DDR) mechanisms, microbes can also activate abnormal signaling pathways that contribute to cancer development. One key pathway is the Wnt/β-catenin signaling, which regulates cell processes like fate determination.
- However, its aberrant activation is linked to cancer initiation and progression. For example, Fusobacterium nucleatum produces a virulence factor, FadA, which disrupts the E-cadherin/β-catenin complex, promoting colorectal carcinogenesis. Similarly, Enterotoxigenic Bacteroides fragilis (ETBF) also activates Wnt signaling by cleaving E-cadherin.
- In addition, the MAPK signaling pathway, involved in cell growth and survival, can be triggered by bacterial factors. H. pylori produce CagA, which activates the ERK signaling cascade and promotes cell survival by inhibiting apoptosis. Salmonella Typhi can also activate both the MAPK and AKT pathways, further driving carcinogenesis by altering p53 and MYC activity.

Eliciting Immunosuppressive Effects:

- The immune system's immunosurveillance function is critical for detecting and eliminating abnormal cells, including cancer cells. However, cancer cells must evade immune detection to progress. Recent studies have shown that certain bacteria play a role in protecting cancer cells from immune surveillance, promoting tumorigenesis.
- For example, Fusobacterium nucleatum (F. nucleatum) inhibits natural killer (NK) cell attacks by binding to the TIGIT receptor on NK cells and promotes pancreatic cancer by reducing NK cell activity. Additionally, F. nucleatum recruits myeloidderived suppressor cells (MDSCs),[24]which suppress the immune response and may facilitate metastasis.
- Similarly, gut bacteria and lipopolysaccharides can recruit MDSCs in the liver, contributing to liver cancer. Helicobacter pylori (H. pylori) promote immune evasion in gastric cancer by inducing programmed death ligand 1 (PD-L1) expression on gastric epithelial cells. Microbial metabolites, such as indole compounds from Lactobacillus, can also suppress anti-cancer immunity, leading to rapid disease progression.
- Furthermore, pathogenic fungi like Aspergillus fumigatus and Candida albicans induce MDSCs to suppress immune responses, further aiding tumour growth. These findings highlight the critical role of microbes in immune evasion during carcinogenesis. Escape from immunosurveillance is a crucial step in carcinogenesis.
- In addition to the mutations within cancer cells themselves, substantial evidence indicates that microbes, as discussed in this article, also play a key role in suppressing immune surveillance of abnormal cells, thereby contributing to malignant transformation.

Microbial Mechanisms in Cancer Prevention and Tumour Suppression:

Microorganisms can not only promote cancer but also inhibit its occurrence and progression through two primary mechanisms: direct tumour-suppressive effects and positive immunoregulatory effects.

- **Direct Tumour-Suppressive Effects:** Some bacterial toxins, despite their genotoxic potential, also exhibit anticancer properties. For example, Clostridium perfringens enterotoxin (CPE) binds to claudin-3 and -4, which are highly expressed in various cancers like breast, prostate, and colon. This interaction triggers pore formation in cancer cell membranes, leading to cell death. Other bacteria, such as Pseudomonas aeruginosa and Salmonella typhimurium, also produce toxins that show anticancer activity. However, bacterial toxins can be toxic to normal cells, requiring genetic modifications to reduce systemic toxicity for potential therapeutic use.
- **Positive Immunoregulatory Effects:** The gut microbiota plays a crucial role in the development and function of the immune system, which is vital for cancer prevention. It promotes the maturation of lymphoid organs and the differentiation of immune cells. For example, commensal fungi in the gut help activate dendritic cells that trigger peripheral lymphatic development.[24] Additionally, gut microbiota influences immune homeostasis by modulating the development of thymic components and isolated lymphoid follicles, crucial for maintaining intestinal health and reducing the risk of cancers like

colorectal cancer (CRC). Moreover, certain bacterial strains can enhance anticancer immunity, as seen in studies where specific microbial consortia induced interferon-γ-producing CD8+ T cells, enhancing the effectiveness of immune checkpoint inhibitors in tumour models.

Cancer-Related Microorganisms and Effectors:

Key Cancer-Promoting Microorganisms:

Helicobacter pylori:

- H. pylori is a gram-negative, spiral-shaped bacterium that resides in the mucus layer of the human stomach and is a major risk factor for gastric cancer
- Classified as a Class I carcinogen by the WHO in 1994. In China, over 70% of noncardia and more than 60% of cardia gastric cancers are linked to H. pylori infection.
- The stomach's harsh acidic environment normally protects against pathogens, but H. pylori survive by producing urease, which neutralizes gastric acid and aids bacterial colonization.
- The bacterium's virulence factors, such as CagA and VacA, are delivered into host cells via a type IV secretion system, triggering carcinogenic pathways.
- In addition to gastric cancer, H. pylori infection has also been associated with other cancers, including colorectal cancer and gastric MALT lymphoma.

Fusobacterium nucleatum:

- Fusobacterium nucleatum (F. nucleatum) is a gram-negative, anaerobic bacterium traditionally associated with periodontal disease.
- It has recently been implicated in the development of colorectal cancer (CRC), with its presence detected in CRC tissues.
- Studies have shown that F. nucleatum strains from CRC and saliva samples are identical, suggesting the oral cavity as the origin of the bacteria in CRC.
- Although less prevalent in healthy gut microbiota, F. nucleatum can migrate to the tumour microenvironment (TME), raising questions about its colonization mechanisms.
- Research indicates that F. nucleatum can reach CRC tumours via the hematogenous route after being injected into the veins of tumour-bearing mice.
- F. nucleatum's surface protein Fap2, a galactose-binding lectin, helps the bacterium colonize CRC by binding to the Gal-GalNAc polysaccharide[(25)]overexpressed in CRC.
- The adhesin FadA is another key virulence factor that promotes colorectal carcinogenesis by activating the β-catenin signaling pathway.
- Other species within the Fusobacterium genus may also play a role in the precancerous stages of CRC, such as in ulcerative colitis.
- Clinical evidence suggests that targeting F. nucleatum in the gut could offer a potential strategy for CRC prevention and therapy.
- Similar, to how H. pylori eradication has been used for gastric cancer, F. nucleatum could become a target for future therapeutic interventions in CRC.

Bacteroides fragilis:

- ✓ Bacteroides fragilis is a normal component of the human colon microbiota and plays a role in promoting the development of the host immune system.
- ✓ However, a pathogenic strain of B. fragilis, known as Enterotoxigenic Bacteroides fragilis (ETBF), is linked to colon tumorigenesis.
- ✓ The key virulence factor of ETBF is fragilysin, a zinc-dependent metalloprotease, which contributes to colon cancer development.
- ✓ Fragilysin triggers a pro-carcinogenic inflammatory response by activating IL-17 and NF-κB signaling in distal colonic epithelial cells.
- ✓ This inflammatory cascade leads to the infiltration of pro-tumoral myeloid cells in the distal colon, promoting tumour growth.
- ✓ ETBF also promotes intestinal inflammation and CRC progression by downregulating exosomal miR149-3p, a microRNA that inhibits tumorigenesis in other cancers.

- ✓ These findings suggest that ETBF plays a significant role in both inflammation and the promotion of colon cancer, highlighting its potential as a target for therapeutic intervention.

Epstein-Barr Virus (EBV):

- Epstein-Barr Virus (EBV) is a human herpesvirus, and the first virus identified to be associated with cancer.
- EBV infection is linked to several malignancies, including lymphoma, gastric cancer, and nasopharyngeal carcinoma.
- EBV exerts its carcinogenic effects through viral protein components that disrupt cellular processes.
- The viral protein BNRF1 induces centrosome amplification in B-lymphocytes, leading to chromosomal instability and an increased risk of malignant transformation.
- EBV infection promotes immune escape in tumours, particularly in gastric cancer and nasopharyngeal carcinoma.
- EBV miRNAs, such as BART11 and BART173p, inhibit tumour suppressor genes FOXP1 and PBRM1, respectively, resulting in increased PD-L1 transcription. PD-L1 is a key factor in immune evasion,[(26)] allowing tumours to escape immune surveillance.
- EBV infection also weakens the antitumor function of NK cells infiltrating EBVassociated epithelial malignancies.
- This impairment of NK cells further contributes to tumour progression and immune evasion in EBV-related cancers.
- These mechanisms highlight the complex role of EBV in promoting cancer development through both genetic instability and immune modulation.

Microbes with Tumour-Suppressive Properties:

Lactobacillus:

- ➢ **Lactobacillus spp. and Cancer Protection:** Lactobacillus species, commonly used in food supplements, have shown protective effects against cancer, particularly in animal models.
- ➢ **Effect on Colon Cancer:** Specific strains such as Lactobacillus rhamnosus, Lactobacillus acidophilus, and Lactobacillus fermentum have been demonstrated to reduce colon cancer development in mice.
- ➢ **Mechanism of Action (Type I Interferon Activation):** Lactobacillus rhamnosus GG stimulates type I interferon production via the cGAS/STING signaling pathway, enhancing the response to immune checkpoint inhibitors (ICIs).
- ➢ **Reduction in Inflammatory Factors:** Lactic acid bacteria (LAB) reduce inflammatory factors, which may help prevent colorectal cancer (CRC) initiation and progression.
- ➢ **Impact on Gut Microbiota:** LAB strains are known to modulate the gut microbiome, including decreasing the abundance of pro-inflammatory Bacteroides species.
- ➢ **Promotion of Gut Health:** Lactobacillus reuteri promotes intestinal epithelial renewal and repair, helping to maintain gut integrity.
- ➢ **Immune System Stimulation:** L. reuteri stimulates the immune system by converting intraepithelial CD4+ T cells into CD4+CD8αα+ double-positive intraepithelial lymphocytes.
- ➢ **Prevention of Alimentary Tract Cancer:** By promoting immune responses and gut health, L. reuteri may help prevent alimentary tract cancers, including those associated with inflammatory bowel diseases.

Bifidobacterium:

- ✓ **Cancer-Inhibiting Effects of Bifidobacterium:** Studies show that Bifidobacterium species, particularly Bifidobacterium bifidum, have cancer-inhibiting properties, such as inhibiting tumour growth in melanoma mice, comparable to PD-L1 antibody treatment.
- ✓ **Synergistic Effects with PD-L1 Antibody:** The combination of oral Bifidobacterium administration and PD-L1 antibody effectively suppresses tumour growth, highlighting their potential as complementary cancer therapies.

- ✓ **Maintenance of Intestinal Homeostasis:** In mice fed a Western-style diet, Bifidobacterium longum helps restore mucus secretion, improving gut barrier function and supporting intestinal homeostasis.
- ✓ **Regulation of Immune Response:** B. bifidum induces Foxp3+ T regulatory cells, which play a key role in immune regulation and suppressing inflammation, thus preventing experimental colitis and potentially cancer initiation.
- ✓ **Potential in Cancer Prevention and Treatment:** These findings underscore the potential of Bifidobacterium in cancer prevention and treatment, primarily through immune modulation and mucosal protection.

Faecalibaculum rodentium:

- **Absence in Tumorigenesis:** Faecalibaculum rodentium (F. rodentium) and its human homolog Holdemanella biformis are lost during tumorigenesis, but both produce SCFAs (short-chain fatty acids) that regulate tumour cell proliferation.
- **SCFA Production and Tumour Regulation:** These bacteria suppress calcineurin and NFATc3 activation, thereby controlling protein acetylation and influencing tumour cell growth.
- **Effect on CRC and APC Mutation:** In ApcMin/+ mice, a model for colorectal cancer (CRC), F. rodentium's presence prevents APC gene mutations, which are found in over 80% of CRC cases.
- **Tumour Growth Mitigation:** F. rodentium reduces tumour growth in mice treated with azoxymethane and dextran sodium sulfate, a common cancer-inducing regimen.
- **Potential of H. biformis in Cancer Therapy:** Holdemanella biformis suppresses tumour growth in the ApcMin/+ model, likely through butyrate production, suggesting its potential in cancer treatment development.

Streptococcus thermophilus:

- ✓ **Probiotic Benefits:** Streptococcus thermophilus (S. thermophilus) is a potent probiotic known for its digestive and immune benefits, but it is often depleted in colorectal cancer (CRC) patients.
- ✓ **Tumour Suppression in CRC Models:** Oral administration of S. thermophilus in CRC mouse models significantly reduces tumour formation, demonstrating its inhibitory effect on tumorigenesis.
- ✓ **Active Ingredient - β-Galactosidase:** The enzyme β-galactosidase, secreted by S. thermophilus, is identified as the active component that inhibits CRC growth, as confirmed by in vivo and cell-based experiments.
- ✓ **Mechanism of Action:** β-galactosidase inhibits CRC cell proliferation, colony formation, and induces cell cycle arrest, promoting apoptosis and suppressing tumour growth. It also enhances the growth of beneficial probiotics like Lactobacillus and Bifidobacterium, indicating a synergistic effect.
- ✓ **Folate Release and Immune Modulation:** S. thermophilus releases folate, which is important for DNA repair, replication, and cell metabolism, potentially contributing to tumour suppression. It also influences lymphocyte profiles, colitis severity, and regulatory T-cell responses, further supporting its role in cancer prevention.

Microbial Interactions and Their Role in Cancer Development:

- **Microbial Interactions:** Gut microbes can form symbiotic, antagonistic, or neutral relationships, with symbiotic and antagonistic ones playing roles in carcinogenesis.
- **F. nucleatum and S. gordonii Cooperation:** F. nucleatum, associated with CRC, benefits from its cooperative relationship with Streptococcus gordonii, a symbiotic oral bacterium. S. gordonii secretes ornithine, which supports F. nucleatum's growth and biofilm development in the oral cavity, potentially aiding its migration to CRC.
- **Impact on CRC Progression:** While the direct impact of this cooperation on CRC progression hasn't been fully confirmed, it likely enhances F. nucleatum's colonization in cancerous tissue, contributing to CRC development.

- **Probiotic Antagonism:** Some probiotics can antagonize carcinogenic microbes. For example, Bifidobacterium bifidum strain BF-1 suppresses Helicobacter pylori (Hp)-induced gene expression, particularly those linked to NF-κB signaling.
- **Protective Role of Probiotics:** By inhibiting Hp-induced NF-κB signaling, B. bifidum BF-1 helps reduce chronic inflammation, offering protection against carcinogenesis and potential CRC development.

Role of Metabolites in Cancer Development:

SCFAs/DCA:

- ✓ **SFAs and Their Role in Host Functions:** Short-chain fatty acids (SCFAs) like butyrate, propionate, and tryptophan, produced by gut microbes from dietary fibres, are crucial for maintaining intestinal barrier integrity, motility, and immune function, as well as regulating the gut-brain axis.
- ✓ **Butyrate's Protective Role in CRC:** Butyrate, a key SCFA, serves as an energy source for colonocytes and helps reduce colorectal cancer (CRC) risk. It enhances gut barrier function by promoting tight junction assembly and stimulating MUC2 expression, which strengthens the intestinal mucus layer.
- ✓ **Butyrate's Anti-cancer Effects:** Butyrate inhibits CRC cell proliferation by remodeling metabolism, suppressing the Warburg effect, and enhancing energy metabolism. It also works synergistically with cisplatin in gastric cancer, promoting cell apoptosis via the mitochondrial pathway.
- ✓ **DCA's Role in Cancer Development:** Deoxycholic acid (DCA), a secondary bile acid, influences cancer progression by activating various signaling pathways, including EGFR-MAPK, β-catenin, and p53. DCA has been linked to liver and CRC progression through its impact on metabolic and immune pathways.
- ✓ **DCA's Complex Role in Tumorigenesis:** DCA promotes CRC by antagonizing the intestinal farnesoid X receptor and stimulating tumour-promoting factors. However, it may also act as a tumour suppressor in gallbladder cancer, demonstrating its contextdependent effects on cancer.

Tryptophan and trimethylamine N-oxide (TMAO):

- **Tryptophan's Role in Colon Cancer:** Tryptophan (Trp), an essential amino acid, is metabolized through the kynurenine pathway and microbial transformation. In colon cancer, Trp metabolism is altered, facilitating immune escape and tumour progression by enhancing protein synthesis and T cell inactivation in cancer cells.
- **c-Myc's Influence on Trp Metabolism:** The oncogene c-Myc upregulates Trp transporters (SLC7A5, SLC1A5) in colon cancer cells, promoting Trp absorption and metabolism.
- This accelerates carcinogenesis by modulating immune responses and protein synthesis in tumour cells.
- **Kynurenine and Immune Regulation:** Kynurenine, an intermediate product of Trp metabolism, accelerates pancreatic cancer progression and modulates immune responses. It promotes the nuclear translocation of AhR, a transcription factor involved in inflammation and immune regulation, contributing to tumour growth.
- **Lactobacilli's Role in Trp Metabolism:** Lactobacilli can convert tryptophan into indole-3-aldehyde, an AhR agonist that enhances the expression of IL-22 and activates Th17 cells, potentially promoting immune responses that affect cancer progression.
- **TMAO's Cancer Connection:** Trimethylamine N-oxide (TMAO), derived from trimethylamine (TMA) produced by gut microbes, is linked to increased cancer risk, including colorectal cancer (CRC).
- TMAO activates metabolic pathways that influence cancer development, highlighting the impact of diet, gut microbiota, and metabolites in cancer pathogenesis.

Insulin resistance and inosine:

- ✓ **Altered Gut Microbiota in Diabetes:** In patients with impaired glucose tolerance (IGT) or type 2 diabetes mellitus (T2DM), the pancreas microbiota shows significant changes, including a reduction in butyrate-producing bacteria, which is linked to insulin resistance and metabolic dysfunction.
- ✓ **Insulin Resistance and Cancer Growth:** Insulin resistance, a key feature of T2DM, is associated with microbial dysfunction and is linked to tumour growth through mTOR activation. The metabolite

imidazole propionate, produced by gut bacteria, contributes to insulin resistance and metabolic changes that support cancer progression.

- ✓ **Gut Microbiota's Role in Tumour Development:** Gut microbiota dysfunction that leads to insulin resistance may be a contributing factor to tumour development, as the metabolic alterations associated with insulin resistance create an environment conducive to cancer growth.
- ✓ **Inosine's Impact on Immunotherapy:** Certain bacteria, including Bifidobacterium pseudolongum, Olsenella, and Lactobacillus johnsonii, produce inosine, a metabolite that enhances the effectiveness of immunosuppressive treatments. Inosine has shown promise in improving immune responses in cancer models, including colon, bladder, and melanoma cancers.
- ✓ **Inosine as a Potential Cancer Treatment Adjuvant:** Inosine triggers the activation of Th1 cells via T-cell-specific A2AR signaling, promoting immune responses. This makes inosine a promising candidate for developing adjuvant therapies to enhance the efficacy of immune checkpoint inhibitors (ICIs) in cancer treatment.

Niacin, vitamin B and Diacetyl spermine/oncotoxins:

- **Niacin and NAD:** Niacin is a precursor for nicotinamide dinucleotide (NAD) and NAD phosphate (NADP), which are involved in redox reactions and cellular energetics, and play a role in regulating transcription and energy metabolism.
- **Niacin and Colon Cancer:** Niacin, through its receptor GPR109A (shared with butyrate), can inhibit the growth of colon cancer. This effect is linked to its impact on the regulation of cellular processes and the gut microbiota.
- **Niacin's Role in Colitis:** Niacin has beneficial effects on colitis by enhancing prostaglandin D2 production, which may help reduce inflammation in the gut.
- **Vitamin B and Tumorigenesis:** Vitamin B is crucial for DNA and protein synthesis and plays a significant role in metabolism. It impacts tumorigenesis through the Sergly one-carbon (SGOC) pathway, which is influenced by the gut microbiota's ability to synthesize B vitamins.
- **Bacterial Biofilm and Polyamine Metabolism:** Bacterial biofilms contribute to the polyamine pool, which is upregulated in cancer tissues. Antibiotic therapy can reduce bacterial membranes, lowering the levels of polyamine metabolites that promote cancer growth.
- **Urolithin and Anti-Tumour Effects:** Bacteria from the Eggerthellaceae family produce urolithin, derived from polyphenols, which has anti-inflammatory and antioxidative properties. Urolithin activates the AhR pathway to upregulate tight junction proteins, offering potential anti-tumour benefits.
- **Oncotoxins and Carcinogenesis:** Carcinogenic bacteria like E. coli and B. fragilis produce oncotoxins, such as cytolethal-derived toxins and colibactin, that damage DNA and accelerate carcinogenesis. Modifying microbial populations and their toxic byproducts may help in cancer treatment.

Targeting Gut Microbiota in Clinical Cancer Treatment:

- The gut microbiota functions as a unique organ whose composition can be influenced in various ways. Recent research has highlighted a strong connection between gut microorganisms and the effectiveness of cancer treatments.
- This has opened a new avenue for cancer therapy,[27]focusing on improving the efficacy and minimizing the toxicity of conventional treatments by modulating the gut microbiota.
- While microbial-based anticancer strategies hold great promise, they are still in the early stages of development. This section explores the relationship between gut microbes and cancer treatment, as well as current and emerging microbial interventions for cancer therapy.

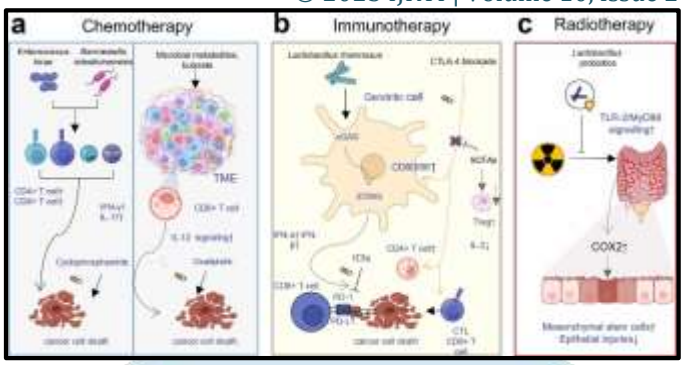

FIG 9: Gut Microbiota in Cancer Therapy: Molecular to Clinical Cancer

- **Impact on Chemotherapy:** Administration of Enterococcus and Barnesiella can enhance the effectiveness of cyclophosphamide-based chemotherapy by stimulating tumour-specific T cells and producing IFN-γ. Butyrate, produced by gut microbes from dietary Fiber, improves the effects of oxaliplatin-based chemotherapy by modulating CD8+ T cell function via IL-12 signaling.
- **Enhancement of Immunotherapy:** Lactobacillus rhamnosus can boost the antitumor response of PD-1 immunotherapy through the cGAS-STING pathway, activating IFNα/β signaling and promoting cytotoxic CD8+ T cell activity.
- **Influence on Immunotherapy Blockades:** Short-chain fatty acids (SCFAs) can reduce the effectiveness of CTLA-4 blockade by reducing Treg cell function. Elevated butyrate levels can diminish the anticancer effects of Ipilimumab by inhibiting the accumulation of CD4+ T cells.
- **Protection from Radiation Injury:** Probiotics can protect the gut mucosa from radiation damage through a TLR-2/COX-2-dependent mechanism, stimulating mesenchymal stem cells to promote crypt regeneration.

Impact of Gut Microbiota on Cancer Therapy:

Emerging Role of Microbiota in Immunotherapy:

- **Microbiota's Role in Immunotherapy:** Cancer immunotherapy, including immune checkpoint inhibitors (ICIs), adoptive T-cell therapy (ACT), and cancer vaccines, has revolutionized cancer treatment, but many patients still experience poor outcomes. Recent studies suggest that gut microbiota composition may influence the effectiveness of these therapies by modulating host immunity and tumour response.
- **Gut Microbiota and Immune Checkpoint Inhibitors:** The effectiveness of ICIs, such as PD-1 and CTLA-4 inhibitors, may depend on the gut microbiota. Microbes like Enterococcus can enhance anti-PD-L1 antitumor efficacy by activating immune pathways via NOD2 receptor recognition.[28] Gut microbes play a key role in enhancing immune responses, thus impacting the effectiveness of ICI therapies.
- **Specific Microbes Impacting Immunotherapy:** Lactobacillus rhamnosus stimulates the antitumor activity of PD-1 immunotherapy through the cGAS-STING signaling pathway. Bifidobacterium enhances antitumor immunity by activating dendritic cells and stimulating IFN-α and IFN-β signaling, ultimately promoting cytotoxic CD8+ T cell responses.
- **Vitamin B5 and Immune Response:** Vitamin B5 produced by gut microbes can support the generation of IL-22-producing Tc22 cells, which have strong antitumor effects and contribute to improved responses to immunotherapy, further highlighting the microbiota's impact on cancer treatment outcomes.
- **Microbial Diversity and Negative Effects on ICIs:** While some gut microbes enhance immunotherapy efficacy, others can have opposing effects. For instance, high levels of butyrate from SCFA-producing bacteria can reduce the anticancer effects of CTLA-4 blockade by inhibiting T cell accumulation, thereby complicating the relationship between diet, microbiota, immunity, and treatment outcomes.
- **Diet's Role in Modulating Microbiota and Immunity:** Diet influences gut microbiota composition, and a balanced microbiota is crucial for maintaining immunity. These microbes help metabolize nutrients that impact immune function, and therefore, diet and gut health directly affect the efficacy of immunotherapies like ICIs.

- **Gut Microbes Affecting ACT Efficacy:** Gut microbiota also influences the efficacy of adoptive T-cell therapy (ACT). Studies have shown that depleting gut microbes in tumour-bearing mice slowed tumour growth during ACT, indicating a potential link between microbiota and ACT response.
- **Antibiotics and ACT Outcomes:** Observational studies in patients with leukaemia or lymphoma found that exposure to certain antibiotics prior to CAR-T therapy worsened clinical outcomes.
- The abundance of specific gut microbes, like Ruminococcus, Bacteroides, and Faecalibacterium, was correlated with better responses to CD19 CAR-T-cell therapy.
- **Microbiota Composition and Clinical Outcomes:** Research indicates that gut microbial composition significantly impacts both ICIs and ACT outcomes, suggesting that optimizing the microbiome may improve cancer treatment responses. However, the mechanisms behind these effects require further investigation.
- **Future Directions for Microbiota-Based Therapies:** As gut microbiota plays a critical role in modulating cancer therapy efficacy, novel strategies are being explored to manipulate the microbiome to enhance treatment outcomes and reduce toxicity, presenting new avenues for improving cancer therapy.

Impact of Gut Microbiota on Chemotherapy Efficacy:

- **Chemotherapy and gut microbiota composition:** The efficacy of chemotherapy varies among cancer patients, with some not responding well despite receiving identical treatments. A key factor in this variability may be the differences in the gut microbiota composition among individuals.
- **Role of gut microbes in chemotherapy:** Certain gut microbes are involved in regulating chemotherapy efficacy, with some promoting and others inhibiting the treatment's effectiveness.
- **Gemcitabine and gut microbes:** Gemcitabine, a chemotherapy drug used for pancreatic cancer, is metabolized by gut microbes like Gammaproteobacteria, which converts it to an inactive form. Targeting these microbes with antibiotics may enhance gemcitabine's anticancer effects.
- **Butyrate's positive effect on gemcitabine:** Butyrate, a metabolite produced by gut microbes, can enhance gemcitabine's efficacy by inducing apoptosis in cancer cells, highlighting the potential of microbial metabolites as adjuncts in cancer therapy.
- **Cyclophosphamide efficacy and gut microbes:** Cyclophosphamide, an immunostimulatory chemotherapy drug, has shown reduced antitumor efficacy in antibiotic-treated or germ-free mice. However, the administration of Enterococcus and Barnesiella bacteria can restore its effectiveness by stimulating tumour-specific immune responses.
- **Erlotinib and gut microbiota:** The efficacy of erlotinib, a tyrosine kinase inhibitor used for non-small cell lung cancer, has been found to be positively correlated with certain gut bacteria, such as Bacteroides xylanisolvens and Bacteroides ovatus. These bacteria help enhance the drug's effectiveness by inducing immune responses.
- **Gut microbes and oxaliplatin response:** The efficacy of oxaliplatin, a chemotherapy drug, can vary based on gut microbial metabolites, particularly butyrate, which enhances its anticancer effects by modulating CD8+ T cell function in the tumour microenvironment (TME).
- **Microbial modulation of myeloid-derived cells:** Commensal gut microbes influence how myeloid-derived cells within the TME respond to chemotherapy. Disruption of the microbiota impairs the function of these cells, reducing the effectiveness of chemotherapy drugs like oxaliplatin.
- **Impact of antibiotic treatment on chemotherapy:** Antibiotic treatment or germ-free conditions can reduce the efficacy of chemotherapy by impacting tumour-infiltrating immune cells, which leads to a decline in reactive oxygen species production and cytotoxicity, ultimately reducing drug efficacy.
- **Gut microbiota dysbiosis and chemotherapy resistance:** Dysbiosis, or microbial imbalance, in the gut can contribute to chemotherapy resistance in cancer patients. Targeting the gut microbiota to restore a healthy microbial composition may improve the response to chemotherapy and enhance therapeutic outcomes.

Gut Microbiota and Radiotherapy: Bidirectional Interactions:

Bidirectional Relationships Between Gut Microbiota and Cancer Therapies: Radiotherapy, Chemotherapy, and Side Effects.

- **Impact of Radiotherapy on Gut Microbiota:** Radiotherapy (RT) has long been used in cancer treatment but induces changes in the gut microbiota. It can cause dysbiosis, characterized by a reduction in beneficial microbes like Bifidobacterium and an increase in harmful ones such as Fusobacteria and Proteobacteria. This imbalance can worsen radiation-related side effects like radiation enteropathy.
- **Gut Microbiota's Role in Enhancing Radiotherapy Efficacy:** Despite its adverse effects, the gut microbiota can also positively influence RT outcomes.
- In studies with breast cancer mouse models, depletion of gut microbes led to faster tumour growth and reduced survival, indicating that certain microbes are critical for improving RT efficacy.
- Conversely, antibiotic treatment alone slowed tumour growth, suggesting microbial metabolites might play a role in cancer progression.
- **Microbial Influence on Immune Responses During RT:** The gut microbiota can also affect the immune response during radiotherapy. For example, depletion of specific gut microbes can alter metabolism,[29] impacting immune cell functions and tumour-promoting metabolites, which could influence the effectiveness of RT.
- **Gut Microbiota and Chemotherapy Side Effects:** Chemotherapy, while effective in killing cancer cells, also induces side effects such as gastrointestinal toxicity, including intestinal flora imbalance, mucositis, and diarrhoea.
- For instance, the chemotherapy drug irinotecan causes gastrointestinal toxicity by altering the gut microbiota and increasing levels of β-glucuronidase, which prolongs irinotecan's toxicity.
- **Probiotics to Mitigate Chemotherapy Toxicity:** Certain probiotics, such as E. coli Nissle 1917, can help alleviate chemotherapy-induced intestinal damage by improving gut barrier function and reducing dysbiosis. This indicates a potential therapeutic strategy of combining chemotherapy with microbiota-modulating agents to reduce side effects.
- **Impact of Gut Microbiota on Immune Therapy Side Effects:** The gut microbiome is linked to immune therapy-related side effects like colitis. In immune checkpoint inhibitor (ICI) therapy, a decrease in Lactobacillus in patients with severe colitis correlates with worse outcomes. Probiotics like Lactobacillus reuteri can moderate these effects by modulating immune responses.
- **Postoperative Outcomes and Gut Microbiota:** Post-surgical complications such as infections and anastomotic leaks are influenced by gut microbiota composition. Specific microbiota profiles,[30] such as low diversity or a dominance of Bacteroidaceae and Lachnospiraceae, have been linked to worse surgical outcomes. Probiotics may help prevent infections and promote recovery by inhibiting harmful microorganisms like MRSA, showing promise for improving postoperative care through microbiota modulation.

In summary, both radiotherapy and chemotherapy significantly impact the gut microbiota, influencing treatment efficacy and side effects. Emerging research highlights the potential of microbiota modulation, including probiotics and microbial therapies, as a strategy to enhance cancer treatment outcomes and alleviate therapy-related toxicity.

Advancing Microbial Interventions in Cancer Therapy: Current and Emerging Strategies:

Recent advances in gut microbiome research have led to the development of microbial interventions for cancer therapy, such as FMT, prebiotics, probiotics, antibiotics, and dietary changes.[31] These strategies show significant potential and may become widely accepted cancer treatments in the future.

Therapeutic Potential of Fecal Microbial Transplantation (FMT) in Cancer Treatment:

- ✓ Fecal microbiota transplantation (FMT) involves transplanting functional flora from healthy donors into patients' intestines to treat diseases and was historically used over 1600 years ago in ancient China for severe diarrhoea.
- ✓ FMT has shown potential in cancer therapy, specifically improving the response to immune checkpoint inhibitors (ICIs) in immunotherapy-refractory melanoma patients by altering the gut microbiota.
- ✓ After FMT, the abundance of beneficial microorganisms like Ruminococcus and Bifidobacteriaceae increases in the recipient's gut, enhancing immune infiltration both in tumours and intestines, leading to better cancer treatment outcomes.

- ✓ FMT has also proven effective in curing treatment-related side effects, such as immune checkpoint inhibitor-induced colitis, by remodeling the gut microbiome when other treatments, like corticosteroids, failed.
- ✓ Studies have demonstrated the success of FMT in alleviating side effects like tyrosine kinase inhibitor-induced diarrhoea in patients with renal cell carcinoma, highlighting its potential as a therapeutic strategy in cancer treatment.

Defined microbial consortia and probiotics:

- ✓ Fecal Microbial Transplantation (FMT) has limitations due to the nonspecific insertion of an entire healthy microbiome, prompting the development of more targeted microbial interventions for better cancer treatment outcomes.
- ✓ Defined microbial consortia, composed of specific microbial strains, have shown promise in enhancing the efficacy of cancer therapies,[32] such as immune checkpoint inhibitors (ICIs). For instance, CBM588, a bifidogenic bacterial product, improved progression-free survival and response rates in metastatic renal cell carcinoma patients treated with ICIs.
- ✓ A consortium of 11 bacterial strains from healthy donors was found to stimulate CD8+ T cells, promoting therapeutic effects of ICIs in mice without causing inflammation, indicating the potential of microbial consortia to optimize cancer treatments.
- ✓ Microbial consortia, through mechanisms like increasing regulatory T cells, may help manage ICI-related colitis, enhancing the overall effectiveness of immunotherapy, but challenges such as administration route, dosage, and cross-infection still need to be addressed.
- ✓ Probiotics also play a role in cancer treatment, with some compounds improving postoperative recovery in gastric cancer patients[33] and alleviating side effects of other therapies, though caution is needed, as certain probiotics can negatively affect cancer treatment responses, like in melanoma patients treated with ICIs.

Targeted antibiotics:

- **Impact of Broad-Spectrum Antibiotics:** Long-term use of broad-spectrum antibiotics can lead to gut dysbiosis, negatively impacting cancer patients' clinical outcomes by disrupting the gut microbiome balance.
- **Targeted Antibiotic Therapy:** Selective use of antibiotics can improve cancer treatment outcomes by targeting oncogenic or pathogenic microorganisms, thus reducing treatment complications and enhancing therapeutic efficacy.
- **Prevention of Cancer with Targeted Antibiotics:** Antibiotics targeting carcinogenic organisms may help prevent cancer in high-risk populations or those with precancerous lesions, offering an additional preventive strategy.
- **Antibiotics and Colon Cancer Prevention:** Specific antibiotics, such as ampicillin, metronidazole, and neomycin, can prevent colon cancer by strengthening the gut's mucus barrier and preventing harmful metabolites from damaging the gut epithelium.

Bacteriophage-based strategies:

- ➢ **Phage-Based Gut Microbiome Modulation:** Researchers are exploring the use of phages to modulate the gut microbiome for anticancer therapy. One approach involves covalently linking phages with irinotecan-loaded nanoparticles to target Fusobacterium nucleatum (F. nucleatum) and enhance chemotherapy efficacy in colorectal cancer (CRC).
- ➢ **Phages Targeting F. nucleatum in CRC:** The M13 phage has been shown to specifically bind to F. nucleatum and, when combined with silver nanoparticles (M13@Ag), can reduce the presence of this bacterium in the gut, improving the response to chemotherapy in CRC.
- ➢ **Remodeling the Tumour Microenvironment (TME):** The M13@Ag phage strategy reduces the amplification of immunosuppressive myeloid-derived suppressor cells (MDSCs) in tumour sites, remodeling the TME and enhancing the body's immune response against CRC.
- ➢ **Activating the Immune System:** Beyond modulating the microbiome, the M13 phage can activate antigen-presenting cells, further stimulating the immune system and supporting CRC suppression.

Genetically engineered/surface-modified bacteria strategies:

- **Genetically Engineered Bacteria for Cancer Therapy:** Genetic engineering has been used to enhance bacteria for direct anticancer purposes.
- For instance, researchers have transferred the violacein biosynthetic cluster into Salmonella strain VNP20009, an oncolytic bacterium, to improve the anticancer activity of violacein under hypoxic conditions, while also utilizing Salmonella as a tumour-targeting delivery vehicle.
- **Oncolytic Bacteria as Tumour-Targeting Agents:** The engineered VNP20009 strain of Salmonella has tumour-colonizing properties, allowing it to specifically target and deliver therapeutic agents, such as violacein, directly to tumour sites, enhancing the anticancer efficacy in hypoxic environments.
- **Surface Modification of Bacteria:** Surface modification of bacteria involves altering the envelope structure to impart new biological properties. This modification can improve the bacteria's ability to interact with the tumour microenvironment, enhancing their anticancer effects.
- **Checkpoint-Blocking and Tumour-Specific Antigens:** In a novel approach, bacteria were surface-modified with checkpoint-blocking antibodies and tumour-specific antigens.
- These modifications led to significant antitumor efficacy in tumour models that overexpressed the targeted antigens, providing a promising strategy for enhancing cancer immunotherapy.

Diet and prebiotic strategies:

- **Dietary Intervention for Cancer Therapy:** Dietary strategies offer a moderate approach to modulate gut microbiota indirectly. Studies have shown that certain diets can reduce chemotherapy-induced toxicity and enhance immune surveillance during cancer immunotherapy, supporting their role in cancer treatment.
  - **Types of Dietary Strategies:** Common dietary interventions include fastingmimicking diets (FMDs), high-Fiber diets, and ketogenic diets. FMDs, such as cyclic fasting and calorie restriction, can reshape anticancer immunity by enriching immune responses like IFN-γ, boosting Th1/cytotoxic responses, and promoting favourable immune signatures.
- **Prebiotics and Their Role in Cancer Treatment:** Prebiotics are indigestible food components that selectively promote beneficial bacterial growth in the colon. These compounds can modify gut microbiota metabolism, making it more favourable for anticancer therapies and improving treatment efficacy.
- **Specific Prebiotic Examples:** Prebiotics like inulin enhance gut T lymphocyte function, overcoming resistance to MEK inhibitors. Ginseng polysaccharides boost responses to PD1 inhibitors by increasing beneficial microbial metabolites like valeric acid, which helps induce Teff cells and suppress regulatory T cells.

Nanotechnology-Driven Modulation of Gut Microbiota for Enhanced Cancer Therapy:

- **Nanotechnology in Cancer Therapy:** While nanotechnology has been extensively researched for cancer treatment, its potential to modulate the gut microbiota to indirectly enhance cancer therapy is still emerging. Recent studies have explored innovative ways to use nanotechnology for this purpose.
- **Helicobacter pylori Membrane-Coated Nanoparticles:** Researchers have used the membrane of Helicobacter pylori to create nanoparticles capable of competing with H. pylori to inhibit pathogen adhesion. While this study did not directly link pathogen inhibition to cancer therapy, it opened the possibility of using targeted bacterial membranes in nanoparticles to reduce harmful bacteria and enhance anticancer efficacy.
- **Targeted Nanoparticles for Microbial Modulation:** The concept of using specific nanoparticles to modulate gut microbiota by inhibiting the adhesion and reducing the abundance of target bacteria is a promising direction for improving cancer therapy outcomes. These nanoparticles could potentially improve the gut microbial environment and facilitate better treatment responses.
- **Nano formulations from Yeast Cell Walls:** Yeast cell walls have been used to create nano formulations that remodel the immune microenvironment in tumours and lymph nodes, enhancing anticancer effects.Smaller-sized nanoparticles have been shown to be more effective in accumulating in tumour-draining lymph nodes and stimulating a stronger T-cell-mediated immune response.

Spore-Driven Cancer Therapeutics: Targeted Drug Delivery and Tumour Treatment:

- **Definition of Spore-Based Strategies:** Spores are dormant or reproductive bodies produced by plants, fungi, and some microorganisms, which can develop into new individuals or remain dormant until conditions allow for germination.
- In cancer therapy, spore-based strategies typically refer to bacterial or fungal spores used for their robust properties in harsh environments.
- **Spore-Based Drug Delivery Systems:** Bacillus cagulans, a probiotic spore, is used in drug delivery systems due to its resistance to acidic environments, temperature, and chemicals in the gastrointestinal tract. The spores can germinate in response to nutrients, releasing drugs into the body while protecting them from degradation, thus enhancing chemotherapy efficacy.
- **Oral Drug Delivery System:** Researchers have developed a system where B. cagulans spores are modified with deoxycholic acid (DCA) and loaded with chemotherapeutic agents.[34] This system survives the acidic stomach environment, and upon reaching the gut, it disintegrates, releasing nanoparticles containing the drugs for improved tumour targeting and enhanced drug absorption.
- **Clostridial Spores for Tumour Targeting:** Clostridium butyricum spores have been investigated as a delivery system for pancreatic cancer chemotherapy. These spores localize in hypoxic tumour areas, leading to increased drug accumulation in tumours, offering targeted therapy with reduced systemic side effects.
- **Therapeutic Potential of Clostridial Spores:** Clostridial spores, which thrive in the anaerobic conditions of tumours, are explored for delivering anticancer drugs or genes specifically targeting the tumour microenvironment (TME).
- Additionally, genetic modification of these spores allows them to convert harmless prodrugs into active drugs, reducing chemotherapy side effects.

Clinical Applications of Cancer Microbiota Therapy:

- **Increasing Clinical Trials on Microbial Therapy:** With growing evidence on the microbiota's role in cancer development, numerous clinical trials focused on microbial therapy are ongoing or completed, aiming to translate these findings into clinical applications.
- **Two Primary Therapeutic Approaches:** Clinical trials generally focus on two directions: boosting therapeutic efficacy, such as enhancing tumour sensitivity to immune checkpoint inhibitors (ICIs) and reducing therapy-related toxicity or side effects.
- **Examples of Ongoing Trials:** For example, the NCT04116775 trial explores fecal microbiota transplantation (FMT) from pembrolizumab-sensitive to resistant prostate cancer patients to improve antitumor efficacy. Another trial (NCT05032014) evaluates the effect of probiotics (Probio-49) on enhancing PD-1 inhibitor efficacy in liver cancer treatment.
- **Reducing Therapy Side Effects:** Some trials aim to reduce immune-related toxicity in renal cell carcinoma patients using FMT, while others assess the use of probiotics to alleviate radiation-induced enteritis during pelvic chemoradiotherapy or prevent chemotherapy-related toxicity in breast cancer patients.
- **Exploring Probiotic Benefits:** Probiotics are being tested for their potential to mitigate chemotherapy-related cognitive impairment (CRCI) and thyroid hormone withdrawal-related complications in thyroid cancer patients, with ongoing research expected to provide fundamental evidence for clinical microbiota applications.

CONCLUSION:

In conclusion, gut microbes have a significant role in both cardiovascular disease (CVD) and cancer therapy, with their relationship being complex and multifaceted:

- **CVD and Gut Microbes:** The gut microbiota composition in individuals with CVD differs from that of healthy individuals. Microbial metabolites such as trimethylamine N-oxide (TMAO) and phenylacetyl glutamine (PAG) can influence CVD risk.

Dysbiosis of the gut microbiota also contributes to the development of CVD.

- **Cancer Therapy and Gut Dysbiosis:** Cancer treatments often lead to gut dysbiosis, which can negatively impact cardiac function.[35] While the link between gut dysbiosis and therapy-induced

cardiotoxicity remains unclear, gut microbes are known to influence the effectiveness of cancer treatments like chemotherapy and immunotherapy.

- For instance, fecal microbiota transplantation (FMT) has shown to enhance the efficacy of anti–PD-1 therapy in melanoma models.
- **Other Health Impacts of Gut Microbes:** Gut microbes also affect health through various mechanisms, such as producing genotoxins that damage DNA, metabolizing bile acids that influence cardiac function, and acting as an endocrine system, communicating with other organs via metabolic processes.

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