Gut Microbiology And It's Relationship With Cancer.

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (B. Pharm.)

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "Gut Microbiology and Its Relationship with Cancer." submitted by Asheq Tanvir (19346006), of Summer, 2024 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This project does not involve any kind of animal and human trial.

Abstract/ Executive Summary

This paper explores the significant relationship between the human gut microbiome and cancer. It outlines how an imbalance in gut bacteria, known as dysbiosis. Dysbiosis can increase cancer risk, particularly in colorectal and gastric cancers, through mechanisms such as inflammation and immune modulation. The methodology involves a systematic review of literature focused on gut microbiota's influence on cancer, including data extraction, synthesis and identification of research gaps. Findings highlight specific microbial species linked to cancer progression and treatment, such as *Fusobacterium nucleatum* and *Bifidobacterium*. The discussion emphasizes the potential of personalized medicine based on gut microbiome analysis for improving cancer therapies. The conclusion calls for further research to bridge existing knowledge gaps, aiming to enhance cancer prevention strategies and treatment efficacy.

Keywords: Microbiota; Gut microbiome; Cancer; Dysbiosis; Immune modulation; Colorectal cancer.

Dedication

This project is dedicated to my parents.

Acknowledgement

Firstly, I would like to express my sincere gratitude to Dr. Mohd. Raeed Jamiruddin, whose exceptional mentorship has been invaluable. I am also profoundly grateful to the School of Pharmacy, Brac University. Furthermore, I would like to extend my heartfelt thanks to my family and friends. Their unwavering support and encouragement have been a constant source of motivation. Without their belief in me, this journey would have been much more challenging.

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List of Acronyms

H. pylori	Helicobacter pylori
SCFAs	Short-Chain Fatty Acids
CRC	Colorectal Cancer
IFN-γ	Interferon-Gamma

Chapter 1

Introduction

1.1 Background

The human gut microbiome is an extensive collection of billions of bacteria that live in the intestines. These include microorganisms such as bacteria, viruses and fungus (Arumugam et al., 2011). These microorganisms are important for many different aspects of our health. This includes digestion, immune system function and even mental wellness (Rooks & Garrett, 2016; Cryan & Dinan, 2012). The gut microbiome is frequently called the "second brain" because it has an impact on many biological functions, such as the absorption of nutrients and the creation of vitamins (Bienenstock et al., 2015).

Keeping a balanced gut microbiome is important to avoid dysbiosis. Dysbiosis is an imbalance linked to health issues like gut problems and autoimmune diseases, as well as mental health issues such as depression and anxiety (Zhao et al., 2020).The gut microbiome helps in digestion by breaking down complicated carbohydrates and fibres that the human body cannot digest on its own (Flint et al., 2012). Furthermore, gut microorganisms assist immune cells in distinguishing between hazardous invaders and safe molecules, which contributes to a healthy immune system (Belkaid & Hand, 2014).

Foods high in sugar, fat and processing can disturb microbial equilibrium and encourage the growth of detrimental bacteria. While diets abundant in fibre and fermentation foster a diversified and balanced microbiome (Singh et al., 2017). This imbalance has been associated with obesity, diabetes, and cardiovascular illness (Ley et al., 2006).

Recent studies have revealed a strong connection between gut microbes and cancer (Wu et al., 2020). Cancer is a complex illness characterized by uncontrolled cellular proliferation and the ability to invade surrounding tissues (Hanahan & Weinberg, 2011). Cancer is one of the leading causes of death worldwide. It is caused by a number of factors including genetic abnormalities, environmental effects and how one individual lives (Sung et al., 2021). New data indicates that the gut microbiota could play an important role in the connection between environmental factors and the development of cancer (Zhu et al., 2020).

The gut microbiome has an impact on the body's immune responses which in return affects the immune system's ability to recognise and destroy cancer cells (Zitvogel et al., 2018). Certain types of bacteria may help to prevent or contribute to the development of different kinds of cancer including colorectal, liver and gastric cancer (Gagnière et al., 2016). The relationship between gut microbiota and host cells provides a complicated web of information that can either encourage or prevent carcinogenesis (Zhu et al., 2020).

Furthermore, the use of antibiotics, dietary habits and lifestyle choices can significantly alter the composition of the gut microbiota. Thus it potentially affecting cancer risk and treatment efficacy (Alexander et al., 2017; Ma et al., 2019). By studying the link between gut bacteria and cancer, we can learn more about new ways to treat it, like using microbiome-based medicines and making changes to what we eat, which could help to prevent cancer and improve the effectiveness of treatments (Lee et al., 2021).

1.2 Gut Microbiology

The human gastrointestinal tract hosts a varied collection of bacteria referred to as the gut microbiome. This encompasses bacteria, viruses, fungi and archaea, all of which are essential for sustaining overall health. Certain gut bacteria generate chemicals that induce chronic inflammation, potentially elevating cancer risk (Garrett, 2015). These bacteria influence immunological responses, either augmenting or inhibiting the body's capacity to combat cancer (Schwabe & Jobin, 2013). Dysbiosis refers to an imbalance in the gut microbiota (Turnbaugh et al., 2006). Preserving a healthy gut microbiome via dietary measures and treatment approaches including probiotics, prebiotics and faecal microbiota transplantation (FMT) can profoundly influence overall health (El-Sahli et al., 2020).

1.3 Knowledge Gap

There are still significant gaps even although gut microbiology and its link with cancer have been studied in great progress. Particularly in Bangladesh, where modern research facilities and funding are lacking (Afzaal et al., 2022). There is a lack of large-scale, community-based research. It makes it harder to figure out how gut bacteria and cancer in Bangladeshi people are connected (Zyoud et al., 2022). Not enough is known about how gut bacteria affects cancer, which means that more study is needed to come up with specific treatments (Afzaal et al., 2022). Also, more research is needed to find out if gut bacteria transplantation and probiotics are safe and useful ways to treat cancer. It is important to understand these gaps if we want to make cancer prevention and treatment better.

1.4 Prevalence's and Consequences

The link between gut microbiome and cancer has gotten a lot of attention because it shows how microbes in the digestive system can affect cancer growth. Dysbiosis in the microbiota has been linked to multiple malignancies such as colorectal, gastric and liver cancers. It emphasize the potential of gut microbiota as both a risk factor and therapeutic target in cancer therapy (Guan et al., 2023). For instance, individuals with colorectal cancer (CRC) generally have a separate microbiota composition characterized by lower beneficial bacteria like *Bifidobacterium* and *Lactobacillus* and higher pro-inflammatory bacteria including *Fusobacterium nucleatum* and *Enterococcus faecalis* (Guan et al., 2023).

There are several ways that the gut bacteria affects cancer but the main way is by modulating the immune system. It controls the activities of T cells and macrophages (Zitvogel et al., 2018). Some bacteria make substances called short-chain fatty acids (SCFAs) that can help reduce inflammation and may even help avoid tumors (Shi et al., 2022). Short-chain fatty acid (SCFA) production is hampered by an imbalance in the bacteria. It will cause swelling and raise the chance of getting cancer (Shi et al., 2022). Studies show that the bacteria in the gut may affect the extent to which chemotherapy and immunotherapy work. It suggests that recovering a good mixture of bacteria in the gut could make cancer treatments work better (Shi et al., 2022).

Chapter 2

Aims and Objective

The main goal of this study is to find out how bacteria in the gut are linked to cancer. The primary aim of this study is to find out how gut bacteria impacts the growth and spread of cancer. It will focus on certain types of bacteria and the metabolic by-products they make that help cancer spread. Secondly, it gathers data and shows several examples that bacteria in the gut can be used to treat cancer. Additionally, a light has been shed on how variations in gut bacteria can be used to improve treatments for cancer while lowering their side effects.

Chapter 3

Literature Review

There are many kinds of bacteria in the human gut. It has been found that the bacteria in our gut can change how chemicals that cause cancer are broken down, mess with your immune system and make you inflamed. As Guan et al. (2023) say, *Fusobacterium nucleatum* and other harmful bacteria cause inflammation, which helps tumors grow. This has been connected to colorectal cancer. Good bacteria such as *Bifidobacterium* and *Lactobacillus* produce metabolites, which contain short-chain fatty acids (SCFA). These SCFAs may decrease inflammation and inhibit the development of cancer cells (Shi et al., 2022).

A research conducted by Gopalakrishnan et al. (2018) demonstrated how individuals with advanced melanoma reacted to immune checkpoint medications. Zackular et al. (2013) conducted a research that found that an imbalance in the gut flora of a mouse model may make it easier for colon cancer to develop.

The gut microbiome impacts both cancer formation and progression as well as cancer treatment results. According to Routy et al. (2018), a diversified and strong immune system may improve the efficacy of immune checkpoint inhibitors by strengthening the immune system's ability to defend against cancer. Shi et al. (2022) said that microbiome-targeted therapies such as probiotics and fecal bacteria transfers, may improve cancer patients response to treatment. The fact that the gut microbiome has a role in both cancer development and therapy highlights its importance as a potential predictor of cancer risk and new approaches to treatment (Zhou et al., 2021).

Chapter 4

Methodology

The project "Gut Microbiology and Its Relationship with Cancer" aims to systematically gather, assess, and integrate existing research on the subject of cancer. The process focusses on selecting research that examine the impact of gut microbiota on the development, progression and therapy of cancer. In the updated methodology, a consistent way to collect information from each study was used. This ensured that the data was reliable and easy to compare. Details about the study, its design, specific gut bacteria studied, results, the quality of the study, and the main conclusions were looked at. The feedback was addressed and the review was made more thorough and clear through this approach. The approach comprises the subsequent steps:

1. Literature search and article selection

The initial step included conducting an extensive search of databases. The literature search was conducted across three major scientific databases such as PubMed, Google Scholar and Web of Science. The search terms included combinations of keywords such as "gut microbiota and cancer," "gut microbiome and cancer progression," "microbial species and cancer treatment," and "bacteria and cancer." The search was restricted to peer-reviewed articles published in English between 2000 and 2025. This search strategy aimed to capture a broad range of studies.

A comprehensive search was conducted which resulting in numerous studied responses related to gut microbiota and cancer. However, only those studies that were strongly related to the topic were counted to ensure a focused and relevant review. Finally, the search yielded a total of 68 results.

2. Screening and review of articles

A two-step process was employed to screen and select articles for inclusion. In the first step, titles and abstracts were reviewed to assess the relevance of each study to the topic of gut microbiota and cancer. Articles focusing on non-cancerous conditions or those not involving gut microbiota were excluded. In the second step, full-text articles were examined to ensure they met the inclusion criteria. The inclusion criteria focused on studies involving human or animal models and clinical trials, observational studies were prioritized. Relevant studies were those that investigated the relationship between gut microbiota and cancer, specifically exploring mechanisms of cancer progression. Studies that did not meet these criteria or lacked methodological rigor were excluded from further analysis.

After applying the inclusion and exclusion criteria, 32 papers were included in the study.

3. Data extraction and analysis

Following the selection process, data extraction was carried out using a standardized form. Key data points included the type of cancer being studied, the microbial species implicated, study design (e.g., clinical, animal models), the mechanisms through which the microbiome influenced cancer, and the therapeutic implications of these findings. The data were then organized into flow charts for easier comparison across studies, allowing for the identification of trends in the literature.

4. Synthesis of information

The synthesis of the extracted data aimed to highlight the most frequently implicated microbial species in cancer such as *Fusobacterium nucleatum* and *Bacteroides fragilis* and to outline their proposed mechanisms in cancer progression. The extracted data was synthesized

to identify common themes, patterns, and differences among the studies. Meta-analyses and systematic reviews were particularly emphasized to provide a broader understanding of the gut-cancer relationship.

5. Evaluation and identification of research gaps

In evaluating the research gaps, particular attention was given to areas where the current literature is lacking, such as specific cancer types that have not been extensively studied in relation to gut microbiota, or microbial species that remain understudied. The studies were critically evaluated for quality, methodology and significance of findings. Research gaps and limitations were identified to highlight areas requiring further investigation.

6. Concluding the review by summarizing the main findings

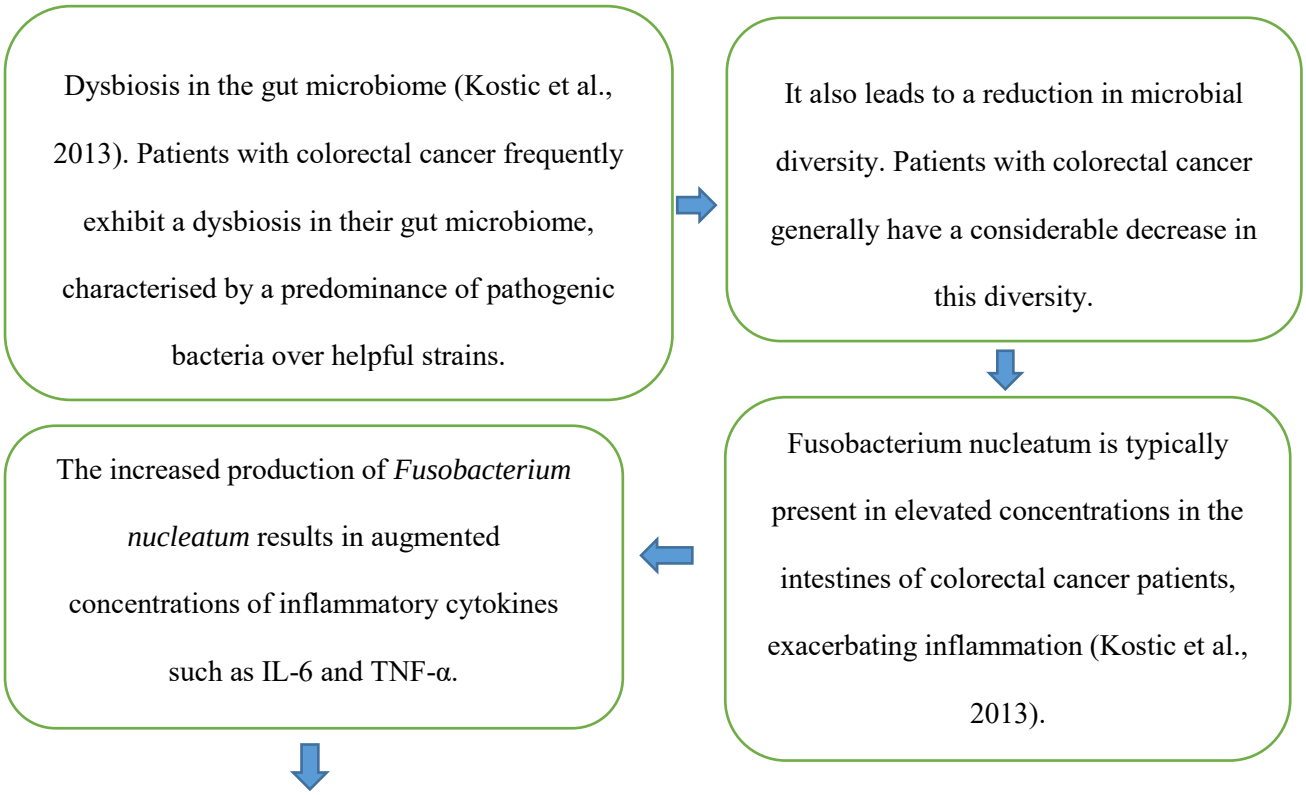
The main findings of the review were summarized, highlighting the role of gut microbiota in cancer development, progression, and treatment. The review concluded with recommendations for future research directions based on the identified gaps and emerging trends in the field.

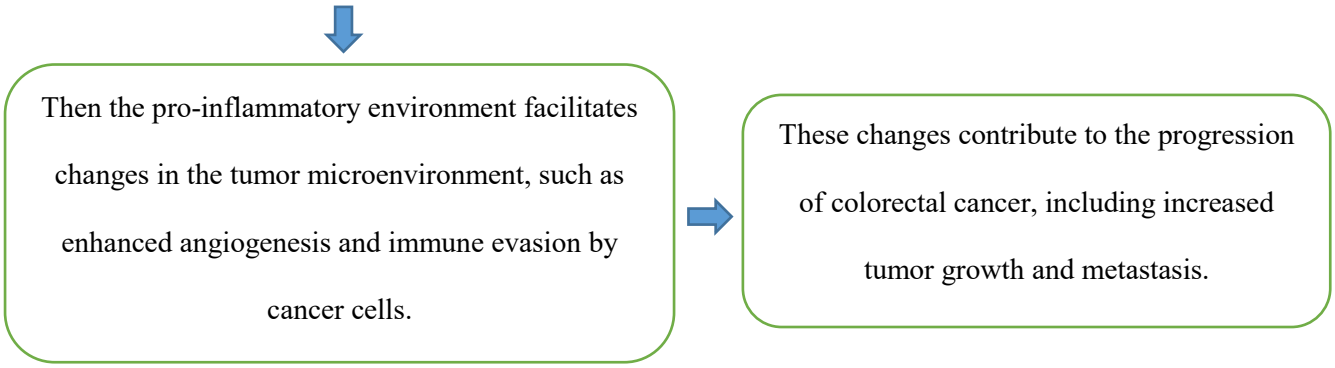
Chapter 5

Result

5.1 Description of specific microbial species implicated in cancer development

The literature review revealed several significant discoveries about the correlation between gut microbiota and cancer. Numerous studies indicate that dysbiosis, or an imbalance in the gut microbiome, correlates with a heightened risk of cancer. Patients with colorectal cancer frequently demonstrate notable alterations in their gut microbiota composition, characterised by diminished diversity and an overabundance of pro-inflammatory bacteria, such as *Fusobacterium nucleatum* (Kostic et al., 2013).

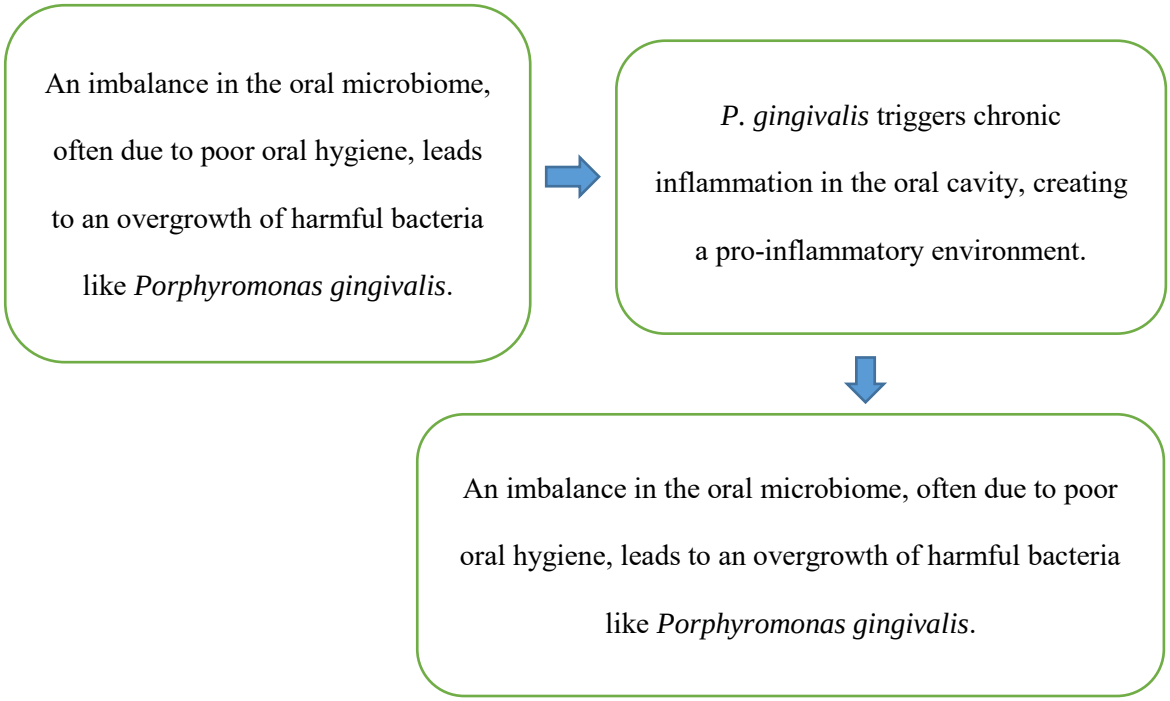




Flow chart 1: Progression of colorectal cancer by *Fusobacterium nucleatum*.

The flow chart illustrates the evolution of colorectal cancer, encompassing enhanced tumour growth and metastasis. To provide a clearer perspective, below are some examples of the association between dysbiosis and an elevated cancer risk:

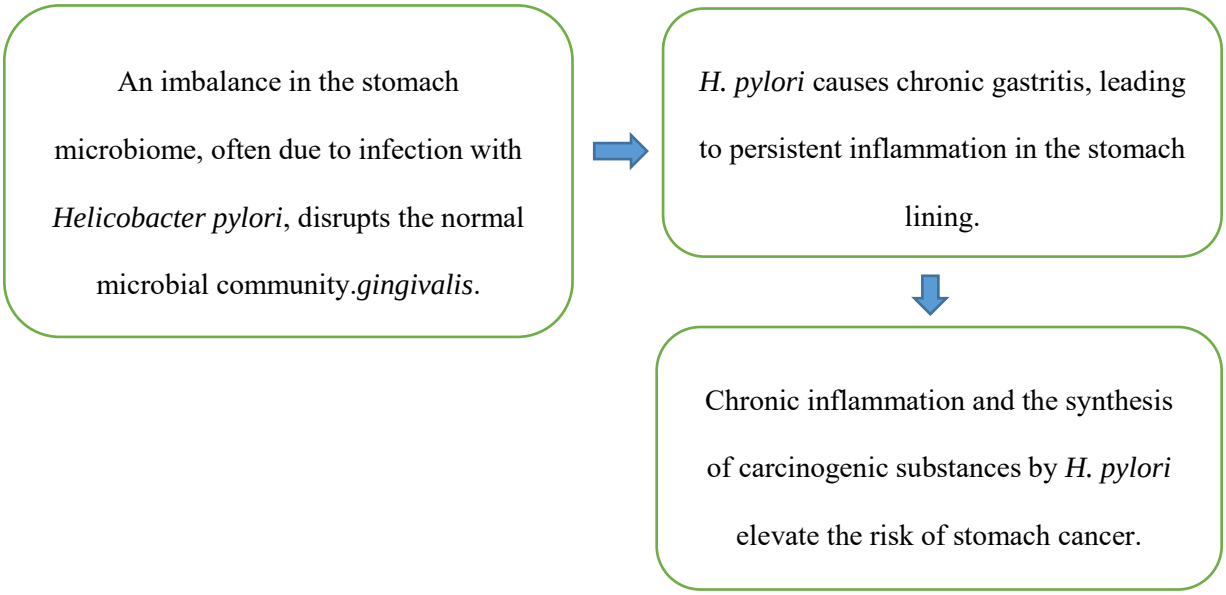
2. *Porphyromonas gingivalis* and Oral Cancer



Flow chart 2: Progression of oral cancer by *Porphyromonas gingivalis*.

The flow chart illustrates the evolution of oral cancer, encompassing enhanced overgrowth of harmful bacteria like *Porphyromonas gingivalis*.

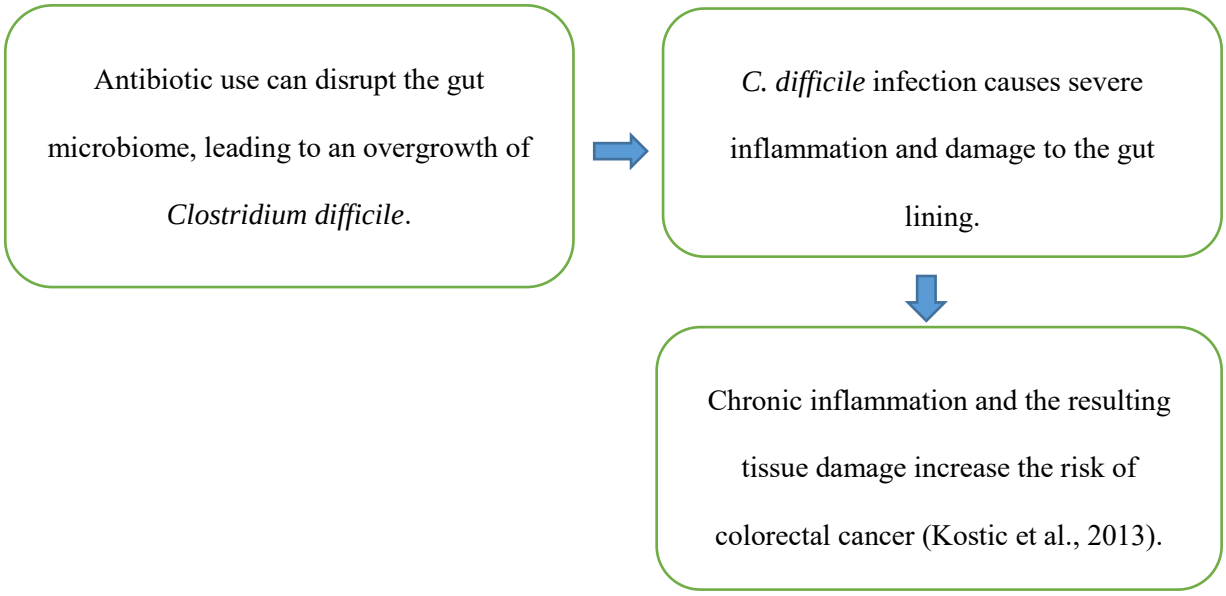
3. *Helicobacter pylori* and Gastric Cancer



Flow chart 3: Progression of gastric cancer by *Helicobacter pylori*.

The flow chart describe Progression of gastric cancer by *Helicobacter pylori*. *H. pylori* causes chronic gastritis, leading to persistent inflammation in the stomach lining.

4. *Clostridium difficile* and Colorectal Cancer



Flow chart 4: Progression of colorectal cancer by *Clostridium difficile*.

5.2 Description of specific microbial species implicated in cancer treatment

The gut microbiota significantly influences the immune system's modulation. Specific gut bacteria may enhance the function of immune cells that participate in anti-tumor responses.

1. **The activity of *Bifidobacterium* contributes to cancer treatment:**

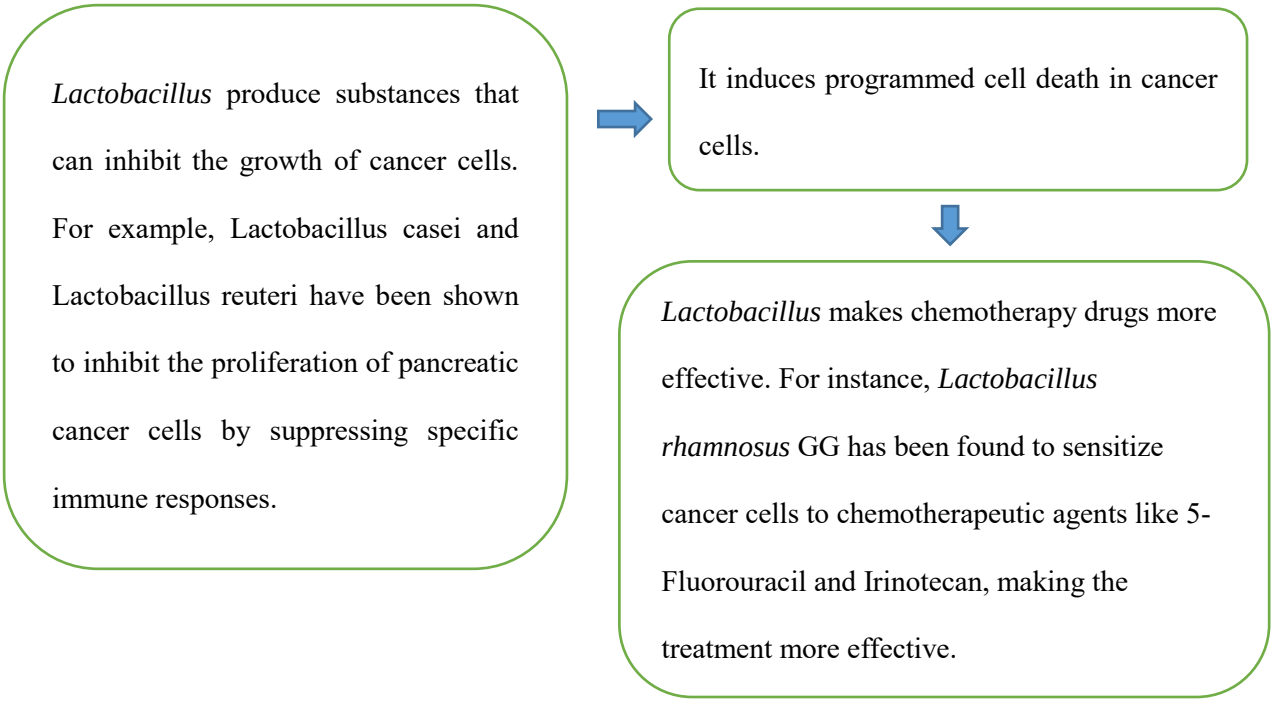
- *Bifidobacterium* generates metabolites that activate the immune system. These metabolites augment the synthesis of cytokines, including interferon-gamma (IFN-γ), which are essential for anti-tumor immune responses (Sivan et al., 2015).
- *Bifidobacterium*, when used in conjunction with immune checkpoint inhibitors, increases the body's immunological response to cancer cells. Immune checkpoint inhibitors (ICIs) function by obstructing proteins that suppress the immune system's capacity to target cancer cells.
- Research indicates that *Bifidobacterium* strains can diminish tumour burden in animal models by enhancing the immune system's capacity to identify and eliminate cancer cells. This results in enhanced treatment outcomes (Sivan et al., 2015).
- In clinical settings, patients exhibiting a greater prevalence of Bifidobacterium in their gut microbiome have demonstrated enhanced responses to immune checkpoint inhibitors, indicating that manipulating the gut microbiome may serve as a viable way to augment cancer treatment efficacy (Afzaal et al., 2022).

Flow chart 5: The activity of *Bifidobacterium* contributes to cancer treatment.

The flow chart illustrates the role of *Bifidobacterium* in cancer treatment. It has been shown that *bifidobacterium* can make immune checkpoint drugs work better in cancer treatment (Sivan et al., 2015). It is shown here how the gut bacteria changes the immune system by looking at how *Bifidobacterium* is used to treat cancer.

To provide a clearer perspective, other examples illustrating the gut microbiome's critical function in influencing the immune system are included below:

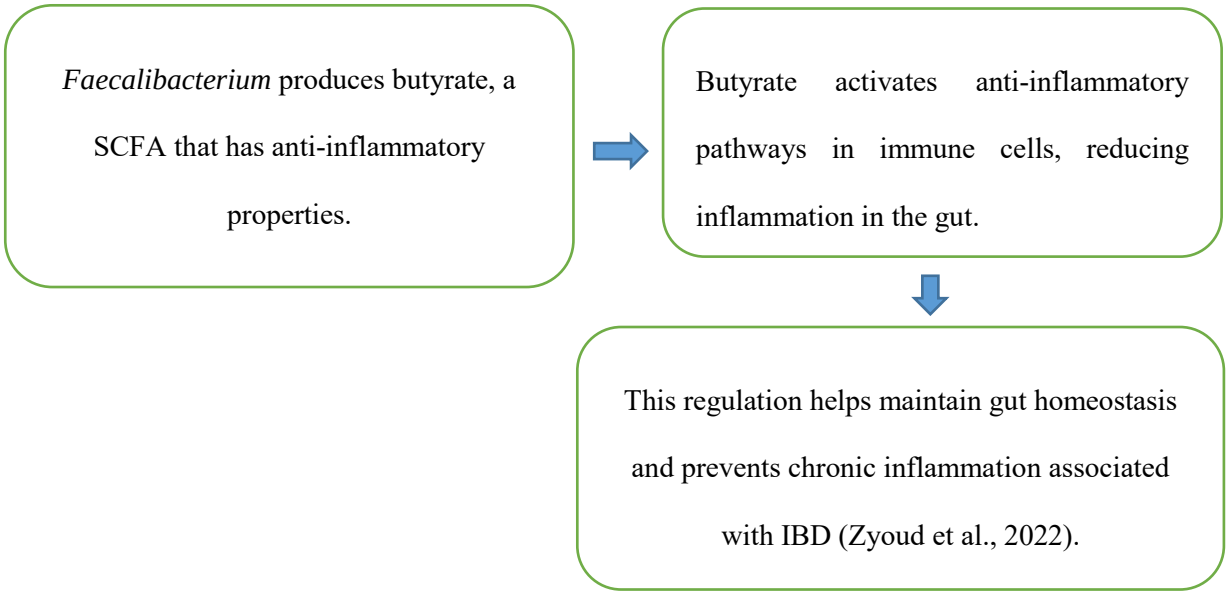
1. ***Lactobacillus***



Flow chart 6: The activity of *Lactobacillus* contributes to cancer treatment.

The flow chart illustrates the activity of *Lactobacillus* contributes to cancer treatment. *Lactobacillus* makes chemotherapy drugs more effective. For instance, *Lactobacillus rhamnosus* GG has been found to sensitize cancer cells to chemotherapeutic agents like 5-Fluorouracil and Irinotecan, making the treatment more effective.

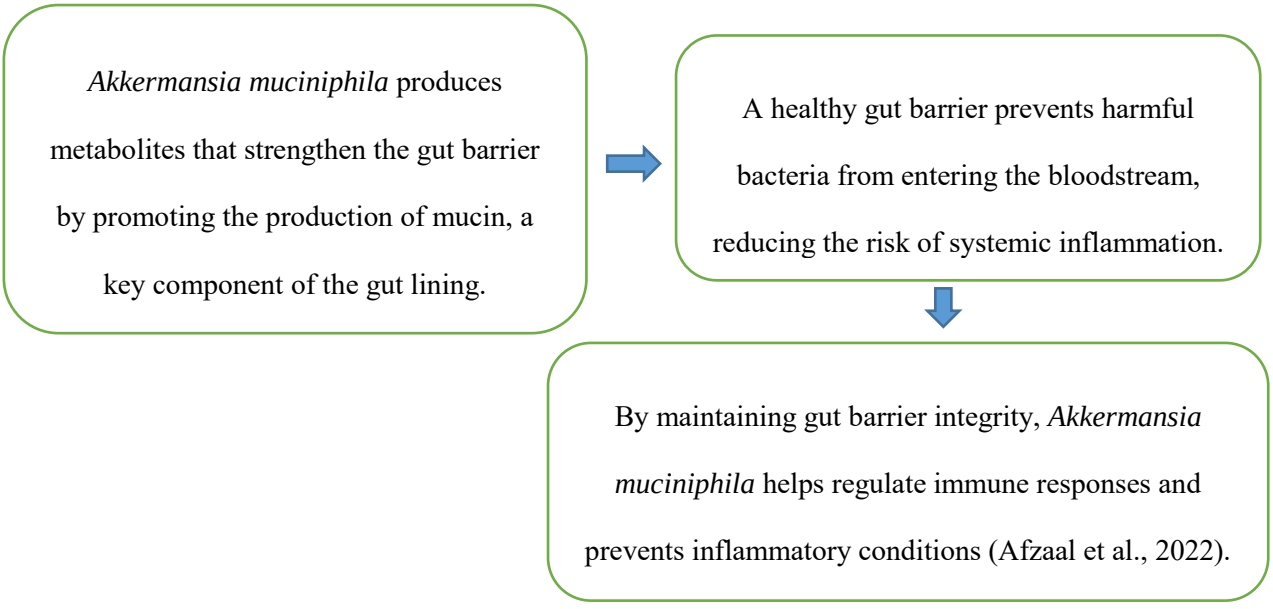
2. ***Faecalibacterium* and Inflammatory Bowel Disease (IBD)**



Flow chart 7: *Faecalibacterium* and Inflammatory Bowel Disease.

The flow chart illustrates the activity of *Faecalibacterium* that helps in Inflammatory Bowel Disease, which further leads to cancer. *Faecalibacterium* produces butyrate, a SCFA that has anti-inflammatory properties.

3. ***Akkermansia muciniphila* and Gut Barrier Integrity**



Flow chart 8: *Akkermansia muciniphila* and Gut Barrier Integrity.

Chapter 6

Discussion

The gut microbiome, a collection of bacteria and other microorganisms in the intestines, significantly influences cancer progression and therapy. Disruption of the equilibrium of these bacteria, termed dysbiosis, can elevate the risk of cancer. In colorectal cancer, there is frequently an overproliferation of detrimental bacteria such as *Fusobacterium nucleatum*, which exacerbates inflammation and facilitates tumour development.

The microbiome significantly impacts cancer by modulating the immune system. Specific gut bacteria can enhance the body's capacity to combat cancer. *Bifidobacterium*, a genus of gut bacteria, has demonstrated the ability to augment the efficacy of cancer therapies such as immune checkpoint inhibitors. These therapies facilitate immune cells in identifying and eliminating cancer cells. The presence of *Bifidobacterium* enhances the efficacy of these treatments by bolstering the immune response.

The gut microbiota additionally influences cancer through many mechanisms. It can impact the body's processing of carcinogens, modulate inflammation, and influence food absorption, all of which can affect tumour proliferation. These findings underscore the significance of a robust gut microbiota in the prevention and treatment of cancer. Preserving a balanced microbiota may enhance cancer therapy efficacy and diminish cancer risk.

Chapter 7

Conclusion

To sum up, the gut bacteria has a big effect on how cancer starts and spreads. Dysbiosis, microbial metabolites, and immunological regulation are critical processes by which the gut microbiome affects cancer risk and outcomes. Despite considerable advancements about the gut microbiome-cancer link but there are still big gaps in our knowledge that need to be filled in.

7.1 Future direction

Future studies should focus on identifying the specific cancer-causing microbes. They should also consider changes in gut microbes when treating cancer. Understanding the gut bacteria-cancer link might lead to new cancer prevention and treatment options. According to Thompson (2023), personalized medicine that is based on a person's unique gut microbiome might make treatment more successful and lower side effects by looking at how gut bacteria affect the immune system. So, researchers need to find out more about how microbe in the gut affect the growth and treatment of cancer.

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