IJBPAS, May, 2024, 13(5): 2206-2218

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

A DIVE INTO THE RELATIONSHIP BETWEEN GASTRIC CANCER AND GUT MICROBIOME

ABRAHAM R* & JIJU LA

Department of Biotechnology, Jyoti Nivas College Autonomous, Bangalore, Karnataka, KHB Colony, 5th Block, Koramangala, Bengaluru, Karnataka 560095

***Corresponding Author: Dr. Rini Abraham: E Mail: riniabr@gmail.com**

Received 15th May 2023; Revised 16th July 2023; Accepted 24th Aug. 2023; Available online 1st May 2024

https://doi.org/10.31032/IJBPAS/2024/13.5.8002

ABSTRACT

The gut, an area of expanding interest, is home to a plethora of microorganisms that are crucial to maintaining normal physiological function in humans, called eubiosis. Many metabolites and immunological reactions in the gut elicit a range of responses, sometimes which can cause negative consequences, causing dysbiosis. These may result in infections, inflammation, the growth of tumors, and other conditions. Current research suggests that there are several ways in which cancer and gut microbiome is interlinked. Stomach cancer, the fifth most prevalent cancer malignancy, has crippling effects brought about by a variety of factors, including age, obesity, food, alcohol, smoking, and infections caused by Helicobacter pylori. These often cause alterations in the composition of the gut. As a result, investigating and comprehending the impact dysbiosis has on gastric cancer and how different factors cause these perturbations can help with better therapeutic approaches and screening to aid in early identification. Attempts to reduce the risks of stomach cancer can be made by conducting more research in many therapeutic areas, such as fecal microbial transplantation and optimizing cancer treatment without or with less dependency on surgical procedures. This review elucidates the influence of dysbiosis and the role that many factors play in the gut microbiota, which results in gastric cancer.

Keywords: Gut microbiome, gastric cancer, factors, dysbiosis, carcinogenesis

INTRODUCTION

1.1 Background

Millions of people around the world have been impacted by cancer, the emperor of all maladies. According to various figures, the global increase in cases is expected to reach 50% during the next two decades. The total number of cases would be 28 million by 2040, while the fatality rate would be 16 million **[1]**. Owing to lifestyle, dietary patterns, environment, stochastic and inherent factors, the incidence and mortality rates differ country-wise. Gastric cancer, the third leading cause after lung and colorectal cancer, is responsible for cancer-related deaths worldwide. It has the fifth highest incidence rate, attributing 5.7% of all new cases. The frequency of oncological deaths attributed to gastric cancer is about 1 in 12 deaths. The rate of prevalence is seen more in men 2.2 more times than in women. The ratio is 1.83 in developing countries **[2]**.

A major causative factor of non-cardia-related gastric cancer is the chronic *Helicobacter pylori* infection. Furthermore, poor dietary habits such as drinking, smoking, salted food, and high-fat and low-fruit intake are other factors associated with an increased predisposition of non-cardia related gastric cancer. The exact pathogenesis of gastric cancer remains unknown, and the risk factors associated are similar to those for oesophageal adenocarcinoma such as acid reflux disease lesions and so on **[3]**. The treatment procedure for early gastric cancer is endoscopic resection. The first line of treatment for those with advanced gastric cancer is chemotherapy with platinum and fluoropyrimidine doublet. Other targeted therapies include monoclonal antibodies such as trastuzumab, ramucirumab, and nivolumab **[4]**.

During the 1800s, when Louis Pasteur and Robert Koch introduced and popularised the germ theory of disease, there were a lot of deaths due to cancer, particularly gastric cancer which made stomach an area of microbial research, focusing on the gastric luminal, mucosal bacteria and the role of Lactobacillus in the diagnosis of gastric cancer. However, this was replaced by the studies of the newly discovered *Helicobacter pylori* due to the nitrosamine production in the gastric microbiome during the 1970s-1980s **[5]**.

The gut microbiome, abode of millions of bacteria, fungi, and viruses, plays a crucial role in the regulation and modulation of numerous processes by providing different energy and nutrient sources for the microbes' normal function and growth. This area of study has gained significant traction due to its interconnection to various diseases. Understanding etiologic pathways can further assist in the screening, diagnosis, and treatment options, and therefore the potential relationship between the gut microbiome and the cancer may present new chances for cancer prevention. The regulation between gastric microbiota and host is maintained by innate lymphoid cells (ILC) which are responsible for tissue homeostasis. A subtype called innate lymphoid cells 2, ILC2 is predominantly important in the stomach milieu as they stimulate IgA antibodies modulate balance and confer protection to the epithelium from bacteria-mediated damage from IgA-coated bacteria **[6]**.

The irregularity in the dynamic balance of the gut microbiome is due to factors such as lack of substrate availability, genetics, age, circadian rhythm, dietary habits, antibiotics, and environment **[7]**. These can lead to dysbiosis in the human gut microbiome, which plays a key role in a number of chronic diseases such as obesity, diabetes and cancer **[8]**. The role of microbiome plays a role in a few hallmarks of cancer, such as inflammation, cellular invasion, metastasis, apoptosis resistance and metabolic reprogramming **[9]**. Chronic inflammation, genotoxicity, host immune imbalance, and induction of oxidative stress responses promote carcinogenesis **[10]**. Other factors such as pH, mucin distribution, nutrients, ions and chemical levels influence the microbial diversity and composition, which vary in tumour and tumour-free tissues **[11]**. Thus, the interplay of cancer and the gut has led to significant advancements and key findings toward the development of therapeutics.

2. REVIEW OF LITERATURE

Stomach cancer, the fifth-most prevalent type of malignant tumour, is a multifactorial disease that has many risk factors, including food, obesity, radiation, and other factors. It is categorised based on two topographical and epidemiological distinctions: those emerging from the upper stomach are referred to as cardia gastric cancer, and those from the other sections are referred to as non-cardia. Adenocarcinomas, the most common form, can be diffuse or intestine-specific, depending on a number of other variables, including age and gender ratio, to name a few **[12]**. 8.3% of all cancer deaths are attributed to gastric cancer. Among males, 783,000 deaths are caused by gastric cancer, making it the third most deadly cancer among them worldwide. It has been observed that males in developed countries are 2.2 times more prone to stomach cancer than females **[13]**.

Classification of gastric cancer can be done based on staging: early stage and advanced stage. Irrespective of the size and metastasis of the lymph node, the former is localised to the mucosa and submucosa. Those which extend beyond the level of gastric submucosa and into the muscle layer are the middle gastric cancers. Further into the subserosa or to the other organs is termed the advanced stage. The efficacy of the treatment correlates directly to the stage of stomach cancer **[13]**.

The mortality and incidence have been declining owing to improved practices and the economic development of countries. Despite the improvements, the survival rates are low, implying that better prevention strategies should be explored. The highest incidence rates were observed in both males and females, predominantly in Eastern Asia, whereas the lowest incidence was in Africa. It is estimated that by 2040 the cases will increase to around 1.8 million, and about 1.3 million deaths will occur. At the national level, China is the leading country for the greatest number of cases. Following this are India and Japan. Almost 90% of the cases are due to infections caused by Helicobacter pylori. Significantly, this has been seen in East Asian, high-income Asia Pacific, and Andean South American regions. 33-50% were attributed to lifestyle and dietary factors **[29]**. The greater incidence rate, poor prognosis, and heterogeneity of the cellular and molecular basis of stomach cancer all play a role in its overall prevalence **[30]**.

2.1. Development and role of the normal gut microbiome

The first studies to comprehend the composition of intestinal microbiota utilized microscopic observations and culture methods which concluded that these predominant species: *Bacteroides, Eubacterium, Bifidobacterium, Peptostreptococcus, Fusobacterium, Ruminococcus, Clostridium and Lactobacillus*.

Gut microbiota develops from early infancy and it is affected by a range of factors such as mode of delivery, maternal antibiotic usage, form of feeding – formula, breast or mixed. During 12-36 months of life, the predominant phyla in neonates are Firmicutes and Bacteroidetes which make up more than 90% of the gut microbial population **[14]**. Over the course of life-time, it can change its composition depending on the dietary pattern and reducing in diversity as the age of a human progresses **[15]**. Thus, in a cascade manner, it can affect the overall health of a person with lasting repercussions.

The gut microbiome constantly takes shape from various extrinsic factors which affect the development from birth to adulthood **[16]**. The first exposure to microorganisms occurs at birth, where they descend through the birth canal, get inoculated via the vaginal flora and begin to develop and establish themselves in the gut **[17]**. Thus, the neonatal gut can be an area to delve deeper into as these can be manipulated to train the immune system and have further long-term and short-term implications **[18]**. Breastfeeding also plays a role in the proliferation of symbiotic and commensal gut microbes. Furthermore, the oligosaccharides in milk function as prebiotics, anti-microbial agents, and antibiofilm compounds, which are bacteriostatic against selective pathogens. The adult microbiome is altered by various genetic, diet-based and environmental factors, including antibiotics more than 1000 drugs used by people affect the composition and at least 78% of more than 100 antibiotics impact at least one of the gut microbes **[19, 20, 21]**.

2.2. Role of gut microbiome in carcinogenesis:

The gastrointestinal microbiota in the gut not only modulates homeostasis and normal healthy functioning, termed eubiosis but also facilitates diseases due to dysbiosis which is any deviation from the normal gut composition. This can initiate inflammation and an overabundance of pathogenic bacteria. Dysbiosis promotes carcinogenesis mainly through chronic inflammation and toxic metabolite production. This mechanism was suggested by Meng *et al*., in 2018 **[25, 26, 27]**. This contributes to breaches in the epithelial barriers, immune reprogramming, metabolic signalling, inflammation, cell proliferation, promotion of angiogenesis, apoptosis, and various other hallmarks of cancer **[22]**. Cancer is caused by modification at the genetic or environmental level, and a similar effect is seen with the gut microbiome, which may be influenced by environmental factors, leading to various diseases. DNA damage promotes mutagenesis, triggering oncogenic signals, and disturbing the responses of the immune system. Thus, the relationship between the gut microbiome and its role in carcinogenesis is reinforced through various research studies.

Microbial-driven tumors are estimated to account for about 20% of all tumors worldwide **[28]**. Gut microbes can play a pivotal role in stimulating and preventing cancer. These can excessively activate CD8+T cells and then promote chronic inflammation and T-cell exhaustion. These abnormal activations damage the intestinal barrier and lead to various disorders and the growth of tumors encompasses this **[20]**. Another research conducted by Baxter *et al*. in 2014 in mice found that the various strains of the genus Bacteriodales correlated with the development of tumors **[23]**. Clostridiales, particularly Clostridium Group XIV a were associated with decreased cancer risk, owing to the production of butyrate, which has anti-inflammatory and anti-tumorigenesis properties, as inferred by Pryde *et al.* in 2002 **[24, 26]**.

Bacteria release various pro-tumor metabolites and genotoxins, which influence the progression of cancer by affecting the cell cycle negatively or causing damage to

DNA. For instance, Escherichia coli produces colibactin and P-cresol sulphate, which exerts its carcinogenic influence **[27]**.

2.4. Factors and their role on the gut microbiota in the progression of gastric cancer

2.4.1 *Helicobacter pylori*

Gastric cancer is one of the most common cancers resulting in worldwide deaths due to malignant tumors in the digestive tract and *Helicobacter pylori*, established as a class I carcinogen in 1994 by the International Agency for Research on Cancer a gram-negative bacterium is a well-established risk factor for gastric cancer **[10, 13, 31]**. It attributes 3% for gastric cancer cases alluding to the fact that there could be other bacteria which play a part in gastric tumorigenesis. Five such strains which have been found to do so are *Peptostreptococcus stomatis, Streptococcus anginosus*, *Parvimonas micra*, *Slackia exigua* and *Dialister pneumosintes* **[22]**.

Helicobacter pylori is divided into two strains: type I and type II, the difference lies in the presence of a 40kb pathogenicity containing CagA and VacA toxin. Type I is associated with an increased gastric cancer risk, whereas type II plays no role **[19]**. It exerts its oncogenic mechanism in two ways: an indirect inflammatory reaction on gastric mucosa and a direct epigenetic outcome on gastric epithelial cells. It leads to the suppression of Nei-like glycosylase 2, which is a DNA glycosylase found in mammals. These remove oxidised bases and increase the deposition of DNA damage, thereby aiding in the progression of tumour development in gastric cancer **[30]**. Other virulence factors, notably Cytotoxic associated gene A CagA or Vacuolating cytotoxin A (VacA) increase the risk of gastric cancer development. They cause the distal stomach to exhibit strong tissue reactions and lesions that are both premalignant and malignant. The infection in the gastric organoids produces various inflammatory cytokines. CagA activates the release of cytokine IL-8 which leads to alterations in the gastric epithelium and cell proliferation **[33]**. It was found that the production makes patients more vulnerable to duodenal ulcers, but protects them against gastric cancer. It also suppresses acid production via inflammatory mediators leading to atrophic gastritis. This altered microbiota in conjunction with *Helicobacter pylori,* induces carcinogenesis in ways that are not fully understood, but a popular hypothesis states that it could be due to nitrosating bacteria producing carcinogenic end products **[10]**.

2.4.2 Cigarettes

Cigarettes, a complex chemical mixture that comprises nicotine, aldehydes, polycyclic aromatic aldehyde hydrocarbons, nitrosamines, and heavy metals, play a role in the gastrointestinal microbiota dysbiosis via various mechanisms and regulation of the intestinal microenvironment, thereby increasing lipid peroxidation, oxidative stress and decrease the antioxidant levels **[32]**. Particularly, nicotine promotes proliferation, tumour growth, metastasis, and invasion of cancer cells in vitro by activating nicotinic acetylcholine receptors. Acetylcholine, a neurotransmitter produces various outputs. This functioning is mediated by the nicotinic acetylcholine receptors and muscarinic acetylcholine receptors. As demonstrated in the research, the binding of the tobacco-specific nitrosamine, 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK), to nicotinic acetylcholine receptors with higher affinity than acetylcholine. The NNK formation posits great carcinogenic potential to stomach, lung and colorectal cancer cells **[11]**.

Furthermore, smoking tobacco causes a rise in the phylum Bacteroidetes and a decline in the phyla Firmicutes and Proteobacteria. It also decreases the concentrations of organic acids such as acetic acid, butyric acid, and so on **[38]**. Smoking modifies various functions in the gut, such as mucin production, alterations in tight functions in the small intestine, and gut barrier disruptions, to name a few. There were certain experiments conducted, which tested the intra-gastric exposure of smoke condensate to mice which led to an increase in *Erysipelotrichaceae and a decrease in Rikenellaceae.* They also had mild gut inflammation, crypt cell damage, Paneth cell modifications and reduced expression of anti-microbial peptides. It also led to fecal microbial dysbiosis and activation of multiple microbial metabolic pathways resulting in increased levels of dimethylglycine and N-acetyl glycine **[25]**.

2.4.3 Diet

There is a direct establishment in the relationship between diet and gut microbiome by supplying substrates and promoting bacterial colonization. A high intake of saturated fat increases bile acid secretions, and in the intestine, it produces secondary bile acid, changing the composition of the gut microbiome **[9]**. Broiled, charbroiled meats from animals and salt-preserved food enhance the progression of gastric cancer. The carcinogens in the food would interact with the epithelial gastric cells and change the expression of genes. Diet participates in the generation of signals with distal organs and shapes the metabolism of the host. Alterations in these patterns can lead to different compositions and functions of microbial communities, energy consumption, permeability and fermentation processes **[13]**. Mucosal deregulation due to the deficiency in fibre-rich diets can cause breaches in mucosal barriers which causes degradation of host glycans and allows gut bacteria to utilize mucus glycoproteins as a nutrient source **[30]**. The effect of fat in diets also affected the gut microbiota composition. Upon comparison of sedentary high-fat and low-fat diets fed in mice in a study, it was found that the high-fat-fed mice contained an increased abundance of *Clostridiaceae*, *Lachnospiraceae, Ruminococcaceae* and a decrease in *Bifidobacteriaceae, Turicibacteraceae,* and *Erysiplotrichaceae* **[14]**.

2.4.4 High salt intake

High salt intake predisposes people to the development of gastric adenocarcinoma, the common type of gastric cancer. This association can be explained in two ways: First, Salt irritates the stomach wall, promoting chemical gastric carcinogenesis. Second, excess salt production promotes gastric *Helicobacter pylori* colonisation in the stomach. These could also alter the viscosity of the protective mucous barrier, disrupt immune homeostasis, increased susceptibility to infections caused by *Helicobacter pylori*, inflammation and ulcers, the last two being signs of precancerous diseases. The gastric mucosa affected by the high concentrations leads to hyperplasia of the gastric pit epithelium and the possibility of mutations and glandular atrophy. These could also further catalyse intestinal metaplasia and lead to early gastric cancer. Salty foods contain N-nitroso compounds such as nitrates and nitrites which could exert carcinogenic effects **[15]**.

2.4.5 Alcohol

Alcohol is another factor that alters the gut microbiota, and bacterial overgrowth is also seen after consumption. Alcohol dehydrogenase (ADH) primarily metabolizes alcohol in the liver, converting it to acetaldehyde and causing substantial toxic damage to tissues and gut bacteria. The by-products, such as ethanol directly exert their influence through various unknown mechanisms causing toxicity, oxidative stress, and accumulation of fatty acid ethyl ester. The intestinal hyperpermeability due to alcohol makes it easier for bacterial cells and their metabolites to enter and cause changes in the microbiota which can affect the gastrointestinal tract and other organs [17].

2.5. STRATEGIES FOR THERAPEUTIC TARGETS

The interplay between intestinal microbiota and carcinogenesis provides therapeutic areas to treat cancer. One such area worth exploring is the Faecal microbiota transplantation, a direct applicative method which impacts the therapeutic responses to cancer immunotherapy. This involves the transfer of Faecal material from a healthy donor. Usually, it involves a healthy, unrelated donor and this is best sourced when it is taken from a centralized stool bank. A prior screening round should be undertaken to minimize any adverse infections through this procedure **[34]**. It has been successfully implemented to treat Clostridium difficile infections with a cure rate of 90% **[36]**. Additionally, various case reports have shown that Faecal microbial transplantation can ameliorate cancers related to intestinal dysbiosis and associated treatment. However, further studies on a larger scale, randomized controlled trials are required to test its validity and long-term repercussions.

Optimization of cancer treatment utilizing the microbiota is a potential avenue for personalized medicine. The interplay between gut microbiota and the response to the drug effect assesses the modification of drug absorption, elimination, and varying sensitivity to pharmacological effects **[35]**. One such area under this is the effect of proton pump inhibitors on gut microbiota. These are one of the commonly used acid suppressants to treat acid-related disorders, however, the repercussions of this on the gastric microbiota include decreased mucus viscosity and gastric acidity, increased bacterial load and translocation and one such abundant family observed is of *Streptococcus*, which is an indicator of gastric dysbiosis, others include *Prevotellaceae*, *Campylobacteraceae* and *Leptotrichiaceae*. Albeit, robust studies must be done to infer its role in gastric cancer progression, nonetheless, there is an increased risk for long-term proton pump inhibitor users **[37]**. The decreased acidity has led to oral bacteria colonizing the gut microbiome and causing modifications in taxonomic homeostasis **[38]**.

CONCLUSION

Given the interconnectedness of the gut microbiome with numerous other organs and the immense research potential it offers, this area of research is fascinating to concentrate on. The gut microbiome is a vast area that can be targeted and altered much more easily. A plethora of therapeutic targets can be made in the gut microbiome, and it can also prove to be a biomarker that could aid in the early detection of diseases.

While they may not be a panacea, nevertheless there are a lot of treatment techniques, which once weighed out its pros and cons, not only can enhance research in terms of knowing the pathway, but also could become more prevalent once clinical and other regulations are established. It is important to research not only malignancies but also conditions like gastrointestinal, bowel, neurological, and other diseases. Even though there might be many other risk factors besides the effect of the gut microbiota, this discovery could also result in novel screening methods and possibly less expensive medications.

ACKNOWLEDGEMENT

We express thanks to our institution, Jyoti Nivas College Autonomous, and Dr. Sr.

Lalitha Thomas, Principal, for giving me the opportunity to undertake my project on "Nanotoxicology- A study of toxic properties of nanomaterials."

REFERENCES

[1] Mao J. J, Pillai G. S, Andrade C. J, Ligibel J. A, Basu P., Cohen L, Khan I. A, Mustian K. M, Puthiyedath R, Dhiman K. S, Lao L, Ghelman R., Guido P. C, Lopez G, Gallego-Perez, D. F, & Salicrup L. A, Integrative oncology: Addressing the global challenges of cancer prevention and treatment, CA Cancer Journal for Clinicians, 72(2), 2021, 144–164

[2] Rawla P, Barsouk A, Epidemiology of gastric cancer: global trends, risk factors and prevention, Przeglad Gastroenterologiczny, 14(1), 2019, 26–38.

[3] Yang Y, Meng W, Wang Z, The origin of gastric cancer stem cells and their effects on gastric cancer: Novel therapeutic targets for gastric cancer, Frontiers in Oncology, 12, 2022.

[4] Smyth E. C., Nilsson M., Grabsch H. I., Van Grieken N. C., Lordick F, Gastric cancer, The Lancet, 396 (10251), 2020, 635–648.

[5] Engstrand L., Graham D. Y, Microbiome and Gastric Cancer, Digestive Diseases and Sciences, 65(3), 2020, 865–873.

[6] Kaźmierczak-Siedlecka K, Daca A, Roviello G, Catalano M, Polom K, Interdisciplinary insights into the link between gut microbiome and gastric carcinogenesis—what is currently known? Gastric Cancer, 25(1), 2021, 1–10.

[7] Chen X, Wang A, Chu A, Gong, Y, Yuan, Y, Mucosa-Associated Microbiota in Gastric Cancer Tissues Compared with Non-cancer Tissues, Frontiers in Microbiology, 2019, 10.

[8] Huybrechts I, Loobuyck A, Vandenbulcke Z, Zouiouich S, Gunter M. J, Smelov V, Michels N, The Human Microbiome in Relation to Cancer Risk: A Systematic Review of the Literature, Journal of Global Oncology, 4(2), 2018, 14.

[9] Mathebela P, Setlai B. P., Mulaudzi T. V, Mkhize-Kwitshana Z. L, Gaudji G. R, Dlamini Z, Influence of the Microbiome Metagenomics and Epigenomics on Gastric Cancer, International Journal of Molecular Sciences, 23(22), 2022, 13750.

[10] Weng M, Chiu Y, Wei P, Chiang C, Fang H, Wei S, Microbiota and gastrointestinal cancer, Journal of the Formosan Medical Association, 118, 2019, 32–S41.

[11] Smet A, Kupcinskas J, Link A, Hold G. L, Bornschein J, The Role of Microbiota in Gastrointestinal Cancer and Cancer Treatment: Chance or Curse? Cellular and Molecular Gastroenterology and Hepatology, 13(3), 2022, 857–874.

[12] Ilic M., & Ilic, I, Epidemiology of stomach cancer, World Journal of Gastroenterology, 28(12), 2022, 1187–1203

[13] Chen Z., Zhang P., Xi H., Wei B., Chen L., & Tang Y, Recent Advances in the Diagnosis, Staging, Treatment, and Prognosis of Advanced Gastric Cancer: A Literature Review, Frontiers in Medicine, 8, 2021.

[14] Niu J., Xu L., Qian Y., Sun Z., Yu D. B., Huang J., Zhou X., Wang Y., Zhang T., Ren R., Li Z., Yu J., & Gao X, Evolution of the Gut Microbiome in Early Childhood: A Cross-Sectional Study of Chinese Children, Frontiers in Microbiology, 11, 2020.

[15] Shock T., Badang L., Ferguson B. S., & Martinez-Guryn, K, The interplay between diet, gut microbes, and host epigenetics in health and disease, Journal of Nutritional Biochemistry, 95, 2021, 108631

[16] Ronan, V., Yeasin R., & Claud E. C., Childhood Development and the Microbiome—The Intestinal Microbiota in Maintenance of Health and Development of Disease During Childhood Development, Gastroenterology, 160(2), 2021, 495–506.

[17] Moore R., & Townsend S. D., Temporal development of the infant gut microbiome, Open Biology, 9(9), 2019, 190128.

[18] Ahearn-Ford S., Berrington J. E., & Stewart C. J, Development of the gut microbiome in early life, Experimental Physiology, 107(5), 2022, 415–421.

[19] Doocey C. M., Finn, K. Murphy, C. N. & Guinane C. M., The impact of the human microbiome in tumorigenesis, cancer progression, and biotherapeutic development, BMC Microbiology, 22(1), 2022.

[20] Xu J., Liu M., Tao T., Zhu X. X., & Fangqin F, The role of gut microbiota in tumorigenesis and treatment, Biomedicine & Pharmacotherapy, 138, 2022, 111444.

[21] Abenavoli L., Scarpellini, E., Colica C., Boccuto L., Salehi B., Sharifi-Rad J., Aiello V., Romano

B., De Lorenzo A., Izzo A. A., & Capasso R., Gut Microbiota and Obesity: A Role for Probiotics, Nutrients, 11(11), 2019, 2690.

[22] Lee M. H, Harness the functions of gut microbiome in tumorigenesis for cancer treatment, Cancer Communications, 41(10), 2021, 937–967.

[23] Baxter N. N., Zackular J. P., Chen G. Y., & Schloss P. D., Structure of the gut microbiome following colonization with human faeces determines colonic tumor burden, Microbiome, 2(1), 2014.

[24] Pryde S. E., Duncan S. H., Hold G. L., Steward C. J., & Flint H. J, The microbiology of butyrate formation in the human colon, Fems Microbiology Letters, 217(2), 2002, 133–139.

[25] Meng C., Bai C., Brown T. D., Hood L., & Tian Q, Human Gut Microbiota and Gastrointestinal Cancer. Genomics, Proteomics & Bioinformatics, 16(1), 2018, 33–49

[26] Grochowska M., Perlejewski K., Laskus T., & Radkowski M., The Role of Gut Microbiota in Gastrointestinal Tract Cancers, Archivum Immunologiae Et Therapiae Experimentalis, 70(1), 2022

[27] D'Antonio D., Marchetti S., Pignatelli P., Piattelli A., & Curia M. C., The Oncobiome in Gastroenteric and Genitourinary Cancers, International Journal of Molecular Sciences, 23(17), 2022, 9664.

[28] Morgan E., Arnold M., Camargo M. C., Gini A., Kunzmann A. T., Matsuda T., Meheus F., Verhoeven R. H., Vignat J., Laversanne M., Ferlay J., & Soerjomataram I., The current and future incidence and mortality of gastric cancer in 185 countries, 2020–40: A population-based modelling study, EClinicalMedicine, 47, 2022, 101404.

[29] Song Y., Liu X., Cheng W., Li H., & Zhang D., The global, regional and national burden of stomach cancer and its attributable risk factors from 1990 to 2019, Scientific Reports, 12(1), 2022.

[30] Park J. Y., Seo H., Kang C., Shin T., Kim J. M., Park J., Kim J. N., & Kim Y., Dysbiotic change in gastric microbiome and its functional implication in gastric carcinogenesis, Scientific Reports, 12(1), 2022.

[31] Gui X., Yang Z., & Li M., Effect of Cigarette Smoke on Gut

Microbiota: State of Knoledge, Frontiers in Physiology, 12, 2021.

[32] Sharma M., Li Y., Stoll M. L., & Tollefsbol T. O., The Epigenetic Connection Between the Gut Microbiome in Obesity and Diabetes, Frontiers in Genetics, 10, 2020.

[33] Lee E., & Lee J., Impact of drinking alcohol on gut microbiota: recent perspectives on ethanol and alcoholic beverage, Current Opinion in Food Science, 37, 2021, 91–97.

[34] Scherübl H., Alcohol Use and Gastrointestinal Cancer Risk, Visceral Medicine, 36(3), 2020, 175–181.

[35] Chen D., Wu J., Jin D., Wang B., & Cao H., Fecal microbiota transplantation in cancer management: Current status and perspectives, International Journal of Cancer, 145(8), 2019, 2021–2031.

[36] Conti G., D'Amico F., Fabbrini M., Brigidi P., Barone M., & Turroni S., Pharmacomicrobiomics in Anticancer Therapies: Why the Gut Microbiota Should Be Pointed Out, Genes, 14(1), 2022, 55.

[37] Ting N. T., Lau H. C. H., & Yu J., Cancer pharmacomicrobiomics: targeting microbiota to optimise cancer therapy outcomes, Gut, 71(7), 2022, 1412–1425.

[38] Tomoda K., Kubo K., Asahara T., Andoh A., Nomoto K., Nishii Y., Yamamoto Y., Yoshikawa M., & Kimura H., Cigarette smoke decreases organic acids levels and population of *Bifidobacterium* in the caecum of rats, Journal of Toxicological Sciences, 36(3), 2011, 261–266.