The Gut-Brain Connection: Exploring the Influence of the Microbiome on Colon Cancer Development and Treatment

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Abstract. The gut-brain axis is an intricate bidirectional communication system between the gastrointestinal tract and the central nervous system that the gut microbiota can commonly influence. Recent studies have shown that the gut microbiome is crucial for colorectal cancer development and progression. The focus is on the close interaction between the gut microbiota and the development of colon cancer by explaining the microbial composition, metabolic byproducts and immune modulation. We also investigated how dysbiosis can promote carcinogenesis through inflammation, genotoxicity and immune evasion. In addition, we consider promising microbiota-targeted therapeutic approaches, such as the use of probiotics and faecal microbiota transplantation, together with the development of biotherapeutics and their ability to improve conventional colon cancer treatments. By elucidating the gut-brain-microbiome interplay, this manuscript aims to provide a comprehensive understanding of its impact on colon cancer, opening new avenues for innovative and effective treatment modalities.

Keywords: Gut-brain axis, colon cancer, probiotics, prebiotics, faecal microbiota transplantation, microbiome-based biomarkers.

Abbreviations: NF-kB, nuclear factor kappa B; iNOS, nitric oxide synthase; JNK, Jun N-terminal kinase; MNNG, N-methyl-N-nitro-N-nitrosoguanidine; MNU, N-methyl-N-nitrosourea; ILCs, Innate lymphoid cells; PTGS2, prostaglandin-endoperoxide synthase; Th 17, T helper 17.

1 Introduction

Colon cancer, or colorectal cancer (CRC), is a global health threat influenced by genetic, environmental, and lifestyle factors, ranking third in prevalence and fourth in cancer-related mortality worldwide [1].Colorectal cancer ranks third in women and fourth in men globally, with regional variations in prevalence; in 2023, the US reported 106,970 new cases, while worldwide, approximately 1.9 million new cases and 935,000 deaths occur annually, according to the WHO[2]. The gut microbiome, a community of bacteria, viruses, and eukaryotes, supports metabolism, immunity, and neurotransmitter production, notably serotonin, highlighting its role in the gut-brain axis[3].A healthy microbiome balances pro- and anti-inflammatory functions, preventing excessive inflammation while responding quickly to infections.[4]Age, diet, and environment influence the microbiome, but dysbiosis, linked to

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various disorders, causes pronounced changes affecting the gut's transcriptome, proteome, and metabolome[5]. Oxygen may play a role in altering the microbiota composition in individuals with dysbiosis. This concept suggests that increased gut permeability, such as inflammation, leads to increased oxygen availability in the intestinal lumen [6]The gut-brain axis, a bidirectional communication system, influences colon cancer by modulating microbiota composition, inflammation, neurotransmitters, immune responses, and gut barrier integrity, highlighting its role in cancer risk and potential interventions[7].

2. The role of microbial metabolites and their effects on colon cancer cells

Microbial metabolites, small molecules produced in the gut, influence colon health and behaviour, exerting protective or harmful effects based on their nature and context.Some key microbial metabolites and their effects are discussed below.

2.1 Short-chain fatty acids (SCFAs)

Short-chain fatty acids are produced by the gut microbiota from fermentable non-digestible carbohydrates [8]. Two main bacterial groups produce SCFAs: the Bacteroidetes phylum produces acetate and propionate, and *Firmicutes* produces butyrate. These bacteria are also capable of producing additional SCFAs[9]. SCFAs not only affect the colon but can also affect other organs through systemic circulation (Fig.1). Some research studies found that diseases such as diabetes, gastrointestinal distress, atherosclerosis and colorectal cancer can develop due to the influence of SCFAs [10]. Clinical case research has indicated that the concentration of SCFAs is lower than that in the control group, suggesting that there was a reduction in the number of bacterial colonies such as those of *Bifidobacterium* sp., *Roseburia* sp., *Lachnospiraceae*, and other bacteria [11, 12] SCFA receptors are G-Protein coupled receptors (GPCRs) and they are widely distributed throughout the human body. They can affect a variety of cellular pathways. GPR109A, also known as hydroxycarboxylic acid receptor 2 (HCA2, encoded by niacr1), is a receptor found on the apical membranes on the cell surface of macrophages, colonocytes, and adipocytes[13–15]. The role of GPR109A is to release stored fats in situations such as hunger.[16]The only SCFA with anti-tumor action that binds to the receptor GPR109A is butyrate. It can form tight junction proteins and fortify gut integrity by activating the Akt/mTOR signalling pathway in CRC cell line (Caco-2)[17, 18]. Along with downregulating NF-kB activity, it can also enhance the synthesis of cytokines like TNF-α, IL-1β, and IL-6 and decrease the expression of immune regulatory enzymes like COX-2 and iNOS[19]. GPCR43 and GPCR41 regulate appetite, gut function, electrolyte balance, and inflammation, with GPR41 found in enterocytes, renal epithelium, and neurons, while GPR43 is in colonocytes and endocrine cells. Acetate and propionate bind to these receptors, reducing tumor formation and inflammation by phosphorylating JNK and p38, thereby lowering MCP-1 synthesis in response to TNF-α.[20].

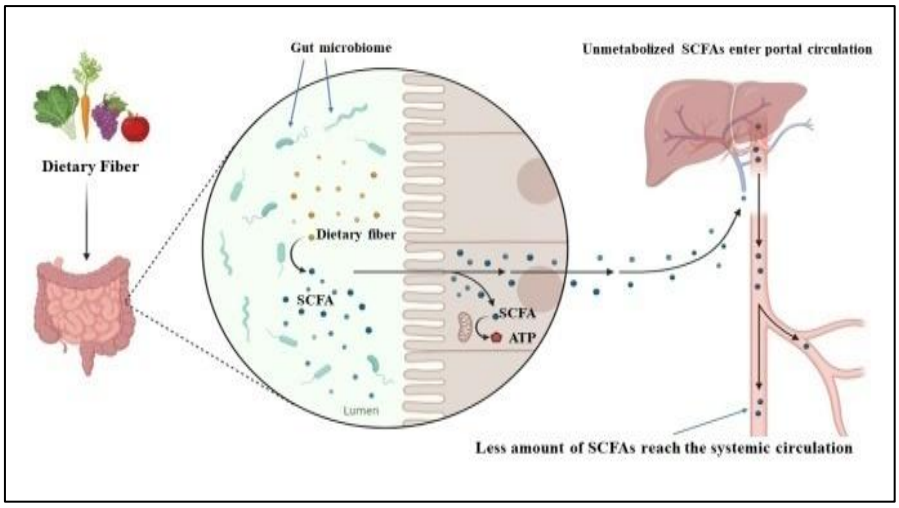

Fig.1. The microbiota ferments the dietary fiber and produces SCFAs

2.2. Conjugated linoleic acids (CLAs)

Conjugated linoleic acids (CLAs) are considered to be beneficial to health and useful food ingredients. A collection of linoleic acid's geometric and positional isomers is known as CLAs. They help in energetic metabolism and function in maintaining body composition [21, 22].Probiotics such as *Lactobacillus acidophilus, Lactobacillus bulgaricus, Lactobacillus casei,* and *Lactobacillus plantarum,*etc. use the byproduct of hydrogenation to create CLAs from linoleic acid[23].It has been demonstrated that CLAs have anti-carcinogenic activity, inhibiting cell proliferation *in-vitro* in human colon cancer cell lines such as HN-29 and Caco-2. It can affect the signalling pathway APC-β-catenin-TCF4, which suppresses genes linked to colonocytemultiplication of cells[24]. In addition to this activity, in colon cancer cells (SW 480), CLAs can cause caspase-dependent apoptosis by switching between caspase-3 and caspase-9, raising the level of Annexin V, and reducing the expression of Bcl-2 [25].

2.3. Polyamines (PAs)

Firmicutes in the gut produce microbial metabolites like cadaverine, putrescine, and spermidine, all of which are polyamines[26, 27].Host cells can also produce polyamines, Which the upper gut can absorb from food[28].Polyamines, as polycationic compounds, bind to cell's negatively charged components, such as phospholipids in membranes and nucleic acids [29].The production of siderophores, defence against free radicals and other acids, and stability of the cell wall are all facilitated by polyamines in bacteria[30].Founded on investigations utilizing cell cultures and animal models. Cancers of the breast, colon, lung, prostate, and skin have also been connected to altered levels of intracellular PAs and changes in their metabolism, in addition to clinical observations[31]. According to a study by Russell and Snyder, cells that are actively dividing, such as rat liver regeneration, chicken embryos, and different tumours, have higher levels of PA synthesis [32].The enzyme responsible for the rate-limiting process in PA biosynthesis is ornithine decarboxylase (ODC). Elevated ODC activity and, in turn, higher PA concentrations are associated with the development of colorectal cancer (CRC). Probiotic bacteria's ability to change the concentration of PAs in the intestinal lumen is one of their anticancer properties [33].After feeding the rats a probiotic

cocktail that was enhanced with Bifidobacterium, Lactobacillus, and Streptococcus spp., the rats' PA levels dropped. Additionally, it has been noted that colonocytes exhibit decreased ornithine decarboxylase (ODC) activity[34].

2.4. Polyphenols

It was found that an increase in the concentration of polyphenols in blood serum decreased the risk of breast cancer and colon cancer [35, 36]. Most of the polyphenols cannot be digested by host cells in the small intestine and enter into the large intestine where bacteria (*Clostridium* sp., *Eubacterium* sp., *Bifidobacterium* sp., *Lactobacillus* sp.) convert those polyphenols into a small number of aromatic compounds, which the body absorbs and circulates throughout the body [37, 38]. Polyphenol metabolites inhibit the cell cycle and induce apoptosis, which has anti-tumor activity [39, 40]Polyphenols suppress COX-2, modulate cytochrome P450, and induce apoptosis via the mitochondrial pathway. Their phenolic hydroxyl groups enable metal chelation, ROS reduction, and inhibition of NOX and ATPase. By activating the Nrf2/ARE pathway, compounds like resveratrol and curcumin enhance antioxidant defence, while flavonoids and gallic acid mitigate oxidative stress by promoting antioxidant enzymes and preventing lipid peroxidation[41].

2.5. Tryptophan (Trp)

The necessary amino acid tryptophan (Trp) is a substrate for the bacterial production of vitamin B3, serotonin, and melatonin[42].Indole lactic acid, indole acetic acid, indole propionic acid, indole acrylic acid, tryptamine, indole acetaldehyde, indole, indolic acid, and indicant skatole are the main Trp derivatives [43]. When there is a change in the composition of gut microbiota it can affect the concentration of Trp in plasma [44].Gut bacteria like *Lactobacillus sp.*, *Ruminococcusgnavus*, and *Clostridium sporogenes* are primarily responsible for the metabolism of tryptophan. Some pathogenic bacteria are also included such as *Escherichia coli*, *Proteus vulgaris*, *Paracolobactrum coliforme*, *Achromobacter liquefaciens*, and *Bacteroides* spp [45, 46].It has been demonstrated that Trp and the metabolites it produces in bacteria are essential for the development of many types of cancer. Additionally, certain research has indicated that Trp can enhance the malignant characteristics of cancer cells and inhibit the anti-tumor immune response [47].IDO, a key enzyme in tryptophan metabolism, is overexpressed in cancer and linked to poor prognosis; while Trp-like molecules inhibit IDO as anti-cancer therapy, gut microbiota metabolism may reduce treatment efficacy and impact immune function[48].

2.6. Bile acids

Cholesterol largely originates in the liver and is the source of primary bile acids, including chenodeoxycholic acid and cholic acid[49]. Bile acids do not directly cause colon cancer in rodents but enhance tumor formation by carcinogens. In humans, high-fat diets increase bile acid release, correlating with CRC risk. Lithocholic and deoxycholic acids induce DNA damage and apoptosis via ROS production. Chronic exposure to deoxycholate may select apoptosis-resistant cells, reducing colon crypt cell apoptosis and promoting cancer development.[50].

2.7. Lipopolysaccharides

Lipopolysaccharides (LPS) can promote colon carcinogenesis by activating Toll-like receptor 4 (TLR4) signaling pathways, as shown in a TLR4-mediated colon carcinogenesis model [51].Elevated TLR4 expression in chronic intestinal inflammation induces Cox-2 and PGE2

production, promoting colonocyte proliferation, while TLR4 signaling in tumor-associated macrophages and LPS-induced activation contribute to tumor development, immune evasion, DNA damage, and altered apoptosis in colon cancer cells[52].

2.8. Aryl hydrocarbon receptor (Ahr) ligands

The main sources of ligands for the aryl hydrocarbon receptor (AhR), which is present in host immunological and epithelial cells, are microbial metabolites of polyphenols and tryptophan[53–55]. It has been demonstrated that AhR affects gut barrier metabolic balance, mucosal immune response, and cell differentiation. Changes in AhR activity have been shown to induce both intestinal tumors and cell proliferation[56]. When Trp is supplemented during dextran sodium sulphate-induced colitis, AhR activity-induced acute inflammation is reduced, which in turn leads to less cytokines (IL-6, TNF-α, IL-1β) and chemokines (CCL2, CXCL1, CXCL2) being produced[57]. AhR promotes the growth of innate lymphoid cells (ILCs), which enhances gut integrity and the immune system[58]. ILCs have reduced IL-22 levels and a higher rate of apoptosis when AhR is absent. The onset of CRC corresponds with ILC's synthesis of IL-22. By lowering inflammation and inhibiting the immune system, AhR ligands can support cancer. Through Trp catabolism, cancer cells can create AhR ligands to ward off immune cells[59]. Urolithin A, a microbial metabolite of ellagic acid, exhibits anti-inflammatory effects by reducing PTGS2 and IL-6 expression, though its role in cancer remains under investigation[60].

3. The Gut-Brain Axis and Colon Cancer

There has long been acceptance of the theory that the brain is influenced by the gastrointestinal (GI) system and vice versa. Writers on medicine like Hippocrates, Galen, and Soranus recognized the importance of the stomach and its digestive processes in maintaining morality, physical and mental health, and general well-being[61]. According to Martin et al., and Mayer, the gut-brain axis is a complex communication and control system that connects the gut and brain. It is a bidirectional signalling network made up of neurons, hormones, immune cells, and microbial metabolites[62, 63]. Numerous pathways, including innervated and neuronal ones, as well as small molecule communication systems in the stomach and brain, could be used for communication between the gut and brain [64].The vagus nerve, key to the microbiota-gut-brain axis, links the CNS to gut immunity, where symbiotic bacteria regulate Th17 cell activity and gastrointestinal function[65, 66].Bacteria-derived neurotransmitters and metabolites stimulate the vagus nerve and cross the blood-brain barrier, influencing brain function and systemic responses.Examples of these metabolites are tryptophan derivatives, short-chain fatty acids, and secondary bile acids (Fig. 2). [62, 67–69].Depression and anxiety disrupt the ANS by increasing sympathetic tone, reducing parasympathetic activity, and activating the HPA axis to elevate CRF and cortisol levels[70]. Downstream effects include activation of local inflammatory systems and cytokines, as well as changes in gut flora and secretory activity. These changes may respond to signaling molecules like catecholamines or environmental changes [71].From various research studies, it was found that the progression of colorectal cancer can also occur due to stress, depression and anxiety, these factors change the microenvironment in the gut and due to the change of microenvironment tumor progression takes place [72, 73].

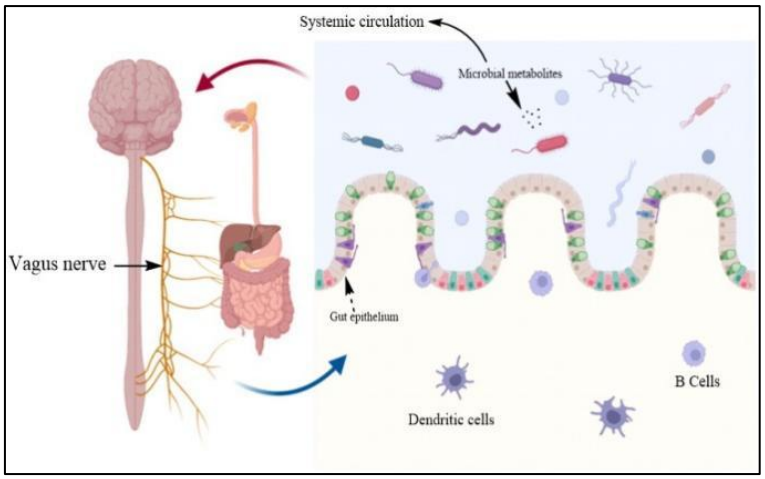

Fig. 2. The gut-brain axis communication is bidirectional and mediated by several pathways. This communication is performed through hormonal (hypothalamic-pituitary-adrenal axis), immunological and metabolic pathways (SCFAs and neurotransmitters). Furthermore, the gut microbiota can directly influence the vagus nerve and enteric nervous system, which in turn affects the brain through the gut microbiota, or indirectly through the pathway being affected locally by neuroactive substances (such as noradrenaline, serotonin, dopamine, tryptophan, and short-chain fatty acids).

4. Microbiome-Based Interventions for Colon Cancer

Research studies have proven that probiotics have the potential anti-carcinogenic activity, among which colon and gastric cancer cells were commonly studied. A study by Lee et al., showed that the cytoplasmic fractions of *Lactobacillus acidophilus, Lactobacillus casei* and *Bifidobacterium longum* have anti-carcinogenic activity in some cancer cell lines [74]. Studies by Russo et al., and Orlando et al., have proved that cytoplasmic extracts of *Lactobacillus rhamnosus* strain GG (LGG) have anti-proliferative action in colon and gastric cancer cells,[75] while *Bifidobacterium adolescentis* SPM0212, a probiotic product, has inhibited the proliferation of three human colon cancer cell lines (HT-29, SW 480 and Caco-2) [76]. In addition to that, Cousin et al., reported that *Propionibacterium freudenreichii* present in fermented milk has enhanced the cytotoxic effect of camptothecin, used as a chemotherapeutic agent for gastric cancer [77].

4.1. Mechanistic effect of probiotics for decreasing the chance of colorectal cancer

4.1.1. Modulation of microbiota composition by probiotics

A balanced intestinal microbiota (eubiosis) helps prevent colorectal cancer (CRC), while dysbiosis disrupts this balance, leading to chronic inflammation and carcinogen production, increasing CRC risk[78, 79]. Sobhani *et al*. found significant gut microbiota differences in CRC patients, with higher Bacteroides, *Prevotella*, *Clostridium*, and lower *Lactobacillus*, while probiotics can help restore microbial balance by increasing protective lactic acid bacteria[80].*Bacteroides fragilis* is a particular concern because it produces a toxin called fragilysin (BFT). This toxin activates pathways in the body that lead to increased cell growth and inflammation, promoting cancer progression, especially in the advanced stages of CRC

[81]. *Fusobacterium nucleatum*, prevalent in CRC patients, promotes tumor progression and immune evasion, making it a potential CRC biomarker[82]. *Escherichia coli*, especially strains from groups B2 and D, produce harmful toxins that can interfere with cell processes and contribute to chronic inflammatory bowel diseases, increasing the risk of CRC [83]. Other bacteria, such as *Streptococcus gallolyticus* and *Enterococcus faecalis*, are also associated with CRC [84]. Probiotics aid cancer prevention by producing antimicrobial substances like lactic acid, hydrogen peroxide, and bacteriocins, inhibiting harmful bacteria and competing for space and nutrients in the gut[85].

4.1.2 Beneficiation of Probiotics for the Intestinal Epithelial Barrier

Intestinal barrier dysfunction allows allergen penetration and pathogenic invasion, triggering localized inflammation and impairing epithelial defense, increasing susceptibility to colorectal cancer (CRC)[86].According to Hsieh et al., certain strains of Bifidobacterium enhance the integrity of the epithelium and shield it from TNF-α-induced disruption[87]. Lactobacillus probiotics strengthen tight junctions (occludin, claudin-3), reduce oxidative stress and inflammation, and help restore intestinal barrier function after colitis[88]. Beneficial bacteria preserve the integrity of tight junction proteins and increase mucus defensins from the goblet cells, which aid in the reconstruction of the epithelial barrier. This process prevents harmful substances and antigens from leaking and enhances this barrier's integrity [86, 89].

4.1.3. Probiotics metabolites against colorectal cancer and as an anti-oxidant

The probiotic bacteria produce short-chain fatty acids, conjugated linoleic acids, and phenols when they ferment dietary fibre. These compounds have anti-cancer properties that can fight colorectal cancer [78]. Butyric acid, produced by bacteria like *Clostridium* and *Roseburia*, supports gut health by promoting cancer cell apoptosis, regulating colon cell balance, strengthening the intestinal barrier, reducing inflammation, and modulating key proteins involved in apoptosis and antioxidant activity[78, 90].Probiotic strains of Lactobacillus and Propionibacterium produce conjugated linoleic acid (CLA), which exhibits anti-inflammatory and anti-cancer effects by suppressing eicosanoids and modulating the PPAR-γ receptor[91].Some probiotics like *Lactobacillus* and *Pedicoccus* can even produce antioxidants that may inhibit tumours from forming [92].

4.1.4. Probiotics as an anti-inflammatory agent

Probiotics support immune function by promoting immune cell growth, regulating responses, inducing antioxidants and anti-inflammatory compounds, and modulating cytokine expression to prevent immune-related diseases[93]. Probiotics interact with TLRs, modulate IL-8 and TNF production, inhibit NF-kB activation, and influence PPAR-γ and MAPK pathways, supporting immune regulation and anti-cancer responses. Lactobacillus strains modulate immune responses by influencing cytokine secretion, enhancing cellular immunity, producing SCFAs like butyrate and propionate, and stimulating T and B lymphocytes to support anti-cancer activity and intestinal protection[94]. Probiotics and their metabolic byproducts, including fatty acids, CLA, and phenols, support normal cell development, reduce DNA damage, inhibit cancer cell growth, and induce apoptosis, aiding in colorectal cancer prevention and treatment.

5. Fecal microbiota transplantation as a Therapeutic approach in Colon cancer treatment

Fecal microbiota transplantation (FMT) restores gut microbiota, treating Clostridium difficile infections, IBD, hematological malignancies, and antibiotic-resistant bacterial colonization, including resistant strains like *Klebsiella pneumoniae*, ESBL+ Escherichia coli, and Pseudomonas aeruginosa, with 75% achieving complete bacterial decolonization and 80% showing partial reduction, even in neutropenic patients[95,96]. FMT is gaining interest as a potential colorectal cancer treatment by reducing inflammation, slowing cell proliferation, and counteracting cancer-related pathways, but further research is needed to confirm its efficacy. [97,98]. Figure 3 represents the process of fecal microbiota transplantation from a healthy donor to a patient through endoscopy or oral capsules.

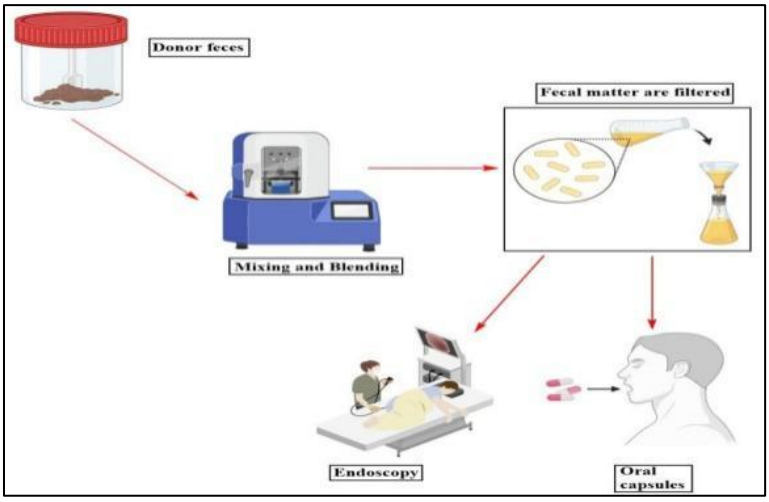

Fig. 3. Schematic diagram of fecal microbiota transplantation

6. Conclusions and Future Perspectives

Colon cancer risk is closely tied to the gut microbiome, with dysbiosis potentially promoting tumor growth. Factors like diet, lifestyle, and stress impact this microbiome, influencing cancer progression through microbial metabolites and the gut-brain axis. Innovations such as probiotics, prebiotics, and fecal microbiota transplantation (FMT) show promise for prevention and treatment, while microbial biomarkers may enable early detection. However, challenges like individual microbiome variability, ethical concerns, and limited understanding of mechanisms remain. Future research into microbial pathways, engineered probiotics, and integrated therapies could lead to personalized strategies, improving outcomes and addressing the multifaceted nature of colon cancer.

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