Review Article

Inflammation and colorectal cancer: The bioinformatics analysis of multifunctional role of microbiota and diet in colorectal cancer development

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ABSTRACT

Chronic inflammation in colorectal cancer can result in the progression of tumorigenesis. Inflammation in the colorectal part of the body can be affected by microbiota, as well as an individual diet. These two factors play a critical role in cancer types related to the colon and rectum. This inflammation could lose the protective epithelial layer of colorectal cancerous cells and, thus, translocation of healthy flora to inner layers. Pathogenic bacteria can also cause inflammation induction and tumorigenesis in the intestines. A change in the bacteria composition and some bacteria metabolites can also play a role in colorectal cancer. Dysbiosis can be affected by an individual diet. In this paper, the importance of diet and microbiota content on inflammation has been reviewed, and finally, in silico investigation confirmed their interplay.

***Keywords*:** Colorectal cancer, microbiota, inflammation, diet, bioinformatics analysis

INTRODUCTION

Colorectal Cancer (CRC) is a well-known disease. Each year, about 1 million cases are reported in the world and nearly half the evidence leads to death [1]. Additionally, according to statistical analysis prediction for 2018, there were 1096601 new cases of colon cancer with 551269 of them leading to death and Rectum cancer was predicted to be 704376 new cases, with 310394 deaths. It should be noted that diseases such as Lynch syndrome, Familial Adenomatous Polyposis (FAP), and other rare disorders that increase one's susceptibility to CRC are examples that have affected a small percentage of the population [2]. As a result, factors such as microbiota, diet, and inflammation caused by them are significant both in terms of helping the progression of the disease as well as its onset. There is a strong correlation between cancer and chronic inflammation, and almost twenty percent of patients diagnosed with cancer, have experienced the inflammation before the occurrence of cancer [3]. Furthermore, according to studies, the bacteria composition of colon mucosa alters in people suffering from colon adenoma compared to that of healthy people. Moreover, during the onset of tumorigenesis, a bacteria invasion to this part is observed [4]. Hence, a thorough study to analyze these factors in CRC patients seems necessary. Another impactful factor in CRC is diet and lifestyle. It could be thus concluded that an inflammatory diet could increase CRC risk noticeably [5]. It has been observed in studies that a change in bacteria composition of intestines, obesity-related mutations, and nutrition have helped the progression of the diseases in rats. Therefore, the effect of diet on CRC has been highlighted.

Overall, the general aim of this study is to analyze microbiota and diet-related inflammations, causing mechanisms that support tumors in patients. Further studies might shine a light on finding an effective way to treat CRC.

Inflammation and colorectal cancer

There is a strong relation between CRC and inflammation since 95% of CRC patients with no Inflammatory Bowel Disease (IBD) background, inflammation, and tumor progression has been observed [3]. Additionally, in IBD patients such as Crohn's Disease (CD) and Ulcerative Colitis (UC), there is a chance of colitis progression related to CRC, causing problems in the diagnosis [6].

Some of the CRC affecting molecular factors are transcription factors and inflammatory cytokines such as IL-22, NF-KB, STAT3, TGF-β, IL-17, IL-10, IL-21, and IL-23 (Figure 1). Progression support can be done by the effect of STAT3 and NF-KB transcription factors [7].

Also, TGF-β inhibits inflammation and, therefore, CRC progression at the beginning but then, helps its progress by epithelial stimulation and contributes to metastasis (Table 1).

The function of transcription factors in CRC

Activation of the NF-KB signaling pathway in cancerous cells and immune cells that have infiltrated tumors helps the progression of cancer by expression and production of pro-inflammatory cytokines such as TNF-α, IL-6, IL-17 and IL-23 due to activation of NF-KB in immune cells [8].

TNF-α induces inflammation and helps CRC progression by signaling immune cells and It also activates the NF-KB pathway in cancerous cells and promotes survival, metastasis, and angiogenesis. Also, BCL-XL, BCL-2, C-IAP2, and MCL-1 production help the survival of cancer cells by activating STAT3 [9]. Furthermore, transcription of C-MYC coding genes, as well as cyclin B and D, promote the progress if cancer cell cycle by STAT3 activation [9]. STAT3 activation in tumor cells can also be a result of IL-6 or IL-11 [10].

The regulatory role of CRC related cytokines

Th-17, NKT, Tγδ and other innate lymphoid cells cause the production of IL-17. Some bacteria-related infections, such as Bacteroides fragilis, result in the expression of IL-17 and This cytokine is involved in colitis formation and making CRC more sever and Also, signaling in tumor cells to activate NF-KB and ERK, facilitating IL-6 production, improving survivability and cell proliferation, and the myeloid-derived type 1 suppressor cell attraction are processes that are done by IL-17 [11].

IL-17A and IL-17F involve IL-17RA on altered cells of the colon and help facilitate CRC progression. This is because NF-KB and ERK signaling pathways are activated in intestines and cancerous cells, and as a result of the involvement of IL-17RA, the proliferation of cancer cells takes place [11]. IL-17c, IL-17A and IL-17F are produced by epithelial cells of the organs because of a change in the microbiota

composition of the lumen. It then affects the TLR-MYD88 signaling pathway and thus, increases BCL-2 and BCL-XL anti-apoptotic genes through an autocrine process, resulting in the survival of cancer cells [12]. Improving cell proliferation and survival of cancer cells is done by STAT3 activation; it can also be done by increased tumor-related inflammation by IL-21 [13]. It should be mentioned that IL-21 induces IL-17 production through signaling to T-cells, helping CRC progression [13]. IL-21R and gamma chain mediated signaling is one of the IL-21 characteristics, which is a member of Class 1 cytokines. IL-21 supports B cell development and TH2 enhanced function. Additionally, TH17 differentiation, which is autocrine, is facilitated by IL-21 that is produced by these cells [14].

Based on the studies conducted on rats, colitis reduction, tumor formation reduction in IL-21 deficient rats, and increased IL-21 expression in chronic colitis rats have been observed [15]. Due to the fact that IL-6 and IL-17 help tumor progression and IFN-ɣ results in the degradation of intestine tumors, it should be mentioned that increased expression of IFN-ɣ, as well as reduced levels of IL-6 and IL-17 in colon tumors, are a result of IL-21 degradation [15].

IL-22 stimulates signaling to tumor cells and thus, activates STAT3 and increases CRC progression [16]. Additionally, IL-22, which belongs to cytokines of the IL-10 family group, plays a significant role in the restoration of intestine epithelial cells, alongside establishing a defensive barrier against microbes [17]. IL-22 production is mainly done by TH17/TH22 CD4+ cells, whose migration to tumor site is a result of CCL20/CCR6 chemical signaling [16]. Also, IL-22 signals via a heterogenic complex containing IL-22R1 and IL-10R2 sub-units. A higher level of IL-22 is observed in CRC patients who have a high chemical tolerance, also, there is a direct link between IL-22 and the chemical tolerance of CRC patients [18]. It should be noted that epithelial cells affected by IL-22 signaling induce nitric oxide signaling and help increase genetic abnormalities [19].

Reduction in cancer-related inflammation and the inhibitory effect on CRC are both a result of IL-10 secretion [10]. Additionally, increased production of inflammatory cytokines occurs in intestine polyps, and their increased growth as a result of IL-10 reduction takes place on T-cells.

IL-23 is composed of a p19 subunit and a p40 subunit, making it a heterodimer cytokine. IL-23, which intensifies inflammation and induces IL-17 production, helps CRC progression [4]. IL-23 is secreted mostly from M1 macrophages while involving toll-like receptors and it activates transcription factors such as NF-KB and STAT3. Signaling pathways such as STAT3 are mediated by IL-23 attachment to a heterodimeric receptor complex consisted of IL-12Rβ1 and IL-23R [20].

It should be noted that IL-23 is also involved in innate lymphoid cell activation alongside Tγδ cells with IL-1, Additionally, it is included in the proliferation induction of TH17 cells [21]. According to the provided information, cytokines and their impact on transcription factors can play an important role in colorectal cancer.

The interplay between microbiota and colorectal cancer

Studies regarding adenoma patients as well as acute carcinoma patients compared to healthy control group have shown those microbes, their genes, and their function increases in CRC patients [22]. Therefore, we will investigate intestine flora, pathogenic bacteria, mutagen bacteria, and the effect of dysbiosis and some other bacterial metabolites (Figure 2).

Healthy flora bacteria and inflammation

Lack of mucosa production and abnormalities in the production and placement of proteins in cell junctions has been observed in colorectal tumors [4]. Because of this reason, the bacteria composition of flora intestines can affect myeloid tumor cells of CRC [4]. Due to an inflammation caused by tumors in the colorectal area, followed by the weakening of protective epithelial cells in the colorectal region, tumor progress is intensified [4].

Pathogenesis of microbiota and its role in CRC progress through inflammation

Taking pathogen bacteria potential in the onset and progression of CRC into consideration, it should be noted that colon tumors are rich in virulence bacteria genes [23]. Based on this, cancer in intestines and colorectal tumors in humans could be a result of helicobacter pillory infection [24]. Additionally, increased levels of inflammatory cytokine expression, such as IL-1α, IL-1β, IL-6, IFN-ɣ, and TNF-α in intestine could be due to helicobacter interference [25]. Cytotoxin-associated

gene A (cag A), a pillory factor toxin, could cause progression in blood and digestive system cancer [26]. It should be noted that in immunodeficiency conditions, in terms of function or regulation, helicobacter hepaticus has been reported to cause colitis, CRC, and some other intestine-related diseases. Therefore, it can be concluded that secreted IL-10 by regulatory T cells has an inhibitory role, inhibiting helicobacter-induced colitis [27].

Other bacteria that are involved in intestine-related diseases of humans are Enterotoxigenic Bacteroides fragilis. IT results in the secretion of IL-17 from TH17 and Tγδ cells [28]. Also, particles secreted from Bacteroides stimulate intestine epithelium cells, producing exosome-like nanoparticles containing a noticeable amount of sphingosine-1-phosphate, CCL20, and E2 prostaglandin [29]. CCL20 and E2 prostaglandin are necessary for proliferation, and recruitment of TH17 cells, which make CRC progress more by IL-17 and other relevant cytokines secretion [29].

Fusobacterium nucleatum is another gram-positive bacteria that is linked to IBD and CRC. FadA adhesive protein, which is produced by Fusobacterium nucleatum, binds to E-cadherin and activates β-catenin signaling pathway in intestines epithelial cells and It also increases the expression of pro-inflammatory genes and oncogenes in CRC patients [30].

Mutagen bacteria, dysbiosis, and other impactful factors in CRC progression

According to the conducted studies, Enterococcus faecalis culture in mammalian cells resulted in a kind of chromosomal instability [31]. Induction of superoxide production by macrophages, which damages epithelial cells DNA, is caused by Enterococcus faecalis. Additionally, increased expression of cox-2, which is mediated by macrophages, increases the mutation rate in mammalian cells and This phenomenon is a result of the superoxide effect on macrophages [31].

Chronic inflammation in intestines alters the bacterial population of some genotoxic bacteria, helping tumor progression. Overall, tumorigenesis and its intensity in intestines can be a result of dysregulation of microbial compounds (dysbiosis) [32]. As a result, chronic inflammation can play a crucial role in dysbiosis formation and the formation of microbiota components [33].

Changes in the flora component, followed by alteration in their function, play an important role in CRC progression [34] (Table 2). Also, based on some studies on rats, it can be found out that dysbiosis could be transferred from a rat to another when they are placed next to each other [35].

It should be mentioned that Lipoteichoic Acid (LTA) in the Lactobacillus cell wall, which stimulates dendritic cells to produce cytokines, increases polyp formation, and increases colitis intensity [36]. Studies on rats have shown that resistance to cancer in the colon is a result of 1,2 dimethylhydrazine and Lactobacillus salivarius. It should be mentioned that bacterial metabolites, such as butyrate, could also affect CRC progress. GPR109A activation affects macrophages and dendritic cells in the colon through butyrate and thus, increases regulatory T-cell proliferation, which produces anti-inflammatory cytokines such as IL-10 [37]. Therefore, intestine microbiota does not always contribute to CRC and could sometimes help improve patients' conditions. Cancerous cell malignancies and anti-tumor immune reduction could be a result of some metabolites such as poly-amine [38].

Colorectal cancer and diet

There are pieces of evidence that show a link between specific diets and inflammation, as well as CRC [39] (Figure 3). It could be concluded that a change in diet could affect microbiota in intestines as well as their metabolites [40].

Consuming foods such as fruit, fish, vegetables, flavonoids, and antioxidants that possess anti-inflammatory qualities is recommended for CRC patients. On the other hand, absorbing nutrients such as bread, pasta, potato, cake, sweets, and sugar and overall, products that contain inflammatory ingredients such as trans fatty acids and saturated fatty acids are prohibited since they increase CRC risk [39].

Based on a study in the USA, which compared vegans to another group that had a healthy diet for ten days, a change was revealed in the intestine microbiota composition. It should be noted that a low-fiber diet reduces microbiome variety [41]. Fibers are regarded as the edible part of the plants or similar carbohydrates that are indigestible but are consumed in intestines by microbiota [42]. Based on the provided information, it can be concluded that one of the ways by which diet affects CRC is through microbiota.

From the previous studies regarding CRC, it could be concluded that bacteria growth in intestines provides an undesirable environment because of increased red meat consumption and reduced vegetables and fruit consumption. As a result, it can be concluded that a fiber-rich diet is more beneficial for CRC susceptible people. Fiber consumption could reduce CRC risk in two significant ways. The first one is that it increases bowel movement, and thus, carcinogens such as heterocyclic amines will not remain in the same environment as epithelial cells [43]. The other mechanism is that fibers are affected by a group of bacteria, and because of that, they will be turned into butyrate and other beneficial metabolites, reducing CRC risk [43].

Formation of N-nitrous compound and lipid oxidation, which acts as a carcinogen against intestines epithelial cells, is catalyzed by heme, which is found in red meat and increases the risk of cancer [44]. Additionally, based on the studies that have been carried on rats, heme destructive effect depends on intestines microbiota since some antibiotics could disrupt the above process in rats. Bile secretion, which changes microbiota composition of intestines, results in the flow of secondary gallbladder products such as deoxycholic acid and lithocholic acid, resulting in tumor progression, could be a result of consuming proteins of animal source [45].

Another metabolic change in cancer cells is increased glycolysis [46] because an increased glycolytic activity has been observed in malignant tumors, both in vitro and in vivo [46]. When glucose level is high, cancerous cell proliferation increases [46]. As a result, it should be noted that there is a direct link between Mellitus diabetes and an increased risk of CRC [46]. Therefore, diabetic individuals are at a higher risk of CRC [46].

In silico confirmation on diet and inflammation

Since inflammation is one of the most important affecting factors in different organs, cancer, such as colon and rectum cancer, a lot of research has been carried out on the effect of inflammation on colorectal cancer. CRC inflammation, regardless of its cause, if turned into chronic, especially during the late stages of cancer, can help the progress of CRC [3].

One of the adverse effects of chronic inflammation is the production of some inflammatory cytokines which are secreted during inflammation from a group of

immune system cells. For example, one of the functions of these cytokines is activating a group of transcription factors that result in the growth and survival of tumor cells (Table 1). It should be noted that the cytokines, which are mentioned in table 1, alongside transcription factors, can affect each other in a way that some increase the production level of the others, while some inhibit one another.

This chronic inflammation, based on what was mentioned before, can help cancer progress, especially at the end stage, depending on different affecting factors. An example of one of the significant affecting factors in the formation of this inflammation in CRC could be microbiota of this part as well as diet. These two factors, in addition to causing chronic inflammation in CRC patients, can under some circumstances directly contribute to the progress or onset of CRC. Additionally, intestine microbiota is profoundly affected by what a person eats (Figure3).

According to the details, as mentioned earlier, microbia related inflammation of the intestine can be caused by its natural flora. By entering further internal parts such as lamina propria, which are immune cell-rich, intestine flora can result in inflammation. This is because of a weakening of cell-cell attachment of cancerous cells of these parts [4].

Another factor that can cause colorectal inflammation because of microbia is pathogenic bacteria. They affect immune system cells of this part directly in a variety of ways [23]. Other than the indirect effect of CRC microbia, which helps CRC progress through inflammation, mutagen bacteria of this part can directly cause CRC through inducing mutations and making healthy cells unstable.

Alteration in the abundance of colorectal microbia (dysbiosis) is another factor contributing to the onset and progress of CRC [32]. Among the factors that have been mentioned previously, dysbiosis is of utmost importance. Intestinal dysbiosis can result in chronic inflammation. This increases the reproduction of pathogenic bacteria as well as genotoxic bacteria and alteration in their abundance in favor of tumor progression, which happens in this dysbiosis as follows: Pathogenic bacteria cause inflammation and genotoxic bacteria cause genetic instability for their surrounding cells and thus, help the progress of tumor in this part. Colorectal chronic inflammation, regardless of the

reason, can be one of the dysbiosis causes of this part.

A change in the abundance of intestine microbia can intensify dysbiosis. In other words, dysbiosis related inflammation can change the abundance of intestine microbia even more and intensify intestinal dysbiosis [33]. Lumen bacteria of large intestines do not always play a negative role in tumors of patients in this illness. For example, some bacterial metabolites such as butyrate can ultimately increase some anti-inflammatory cytokines such as IL-10[47]. Because of the vast number of intestine microbiota and their various functions, thorough research is to be done to find effective treatments for microbiota related illnesses.

Another critical factor affecting CRC is diet and lifestyle. Diet is closely related to the microbiota composition of intestines. For example, low fiber and inflammatory diet can change the microbiota of this part and cause dysbiosis (Figure3). Reduction in diversity and growth of pathogenic bacteria resulted from diet-related dysbiosis can result in inflammation and progression of colorectal tumors [41]. Creating an unsuitable environment in intestines resulted from dysbiosis, which is due to pathogenic and mutagen bacteria growth, involves immune system cells of that part. The secretion of inflammatory cytokines results in chronic inflammation of this part, usually leading to CRC progress in acute stages of the disease.

Besides and according to the given information, mutagen bacteria resulting from diet-related dysbiosis can cause genetic instability and form or help already existing tumor's progress, in addition to immune cell stimulation inflammation.

People who consume pasta, potatoes, sugar-rich desserts, and those who consume a lot of saturated fat are more likely to suffer from intestinal inflammation and are more prone to CRC[39]. Therefore, it is advised that people consume vegetables, fruit, fish, and antioxidant containing food in their diet[39].

In addition to the effect of diet-related inflammation, it can be the cause of CRC onset or progress. Consumption of certain foods that contain carcinogenic elements that can cause cancer, especially in the intestinal tract (Figure 3). Consumption of fiber-rich foods is one of the ways to prevent this type of adverse effect[43]. Based on bioinformatics analysis related to the impact of diet on inflammation-related

colon cancer and their role in the reduction of increase of some genes' expression, a functional study of these data was carried out (Figures 4,5).

Based on it, using the NCBI database regarding a group of signaling pathways and also biological processes that were involved in genes whose expression increased in colon cancer and inflammation, were identified (Figure 6). Additionally, considering the critical role of vegetable oils and unsaturated fatty acids in reducing CRC risk compared with animal fat, biological processes that reduce the expression of a group of genes related to inflammation and colon cancer by consuming corn oil and fish oil and the positive effect of these oils on the expression of a group of genes related to inflammation and colon cancer to reduce the risk of CRC was investigated (Figure 7,8 (partA)).

According to the analysis and investigations regarding the pathways of some genes that were linked to inflammation and cancer, such as ITGAV and IGF1, it was observed that diets that contained corn oil and fish oil reduce the expressions of those genes and pathways related to them (Figure 8 ,Part B).

Table 1 Some inflammatory and anti-inflammatory cytokines which regulate the STAT3 and NF-KB transcription factors

Cytokine	Function
IL-6	Activation STAT3
IL-11	Activation STAT3
IL-17	Increase production IL-6, Activation NF-kB, indirectly Activation STAT3
IL-21	Increase production IL-6, production IL-17, Activation STAT3
IL-22	Activation STAT3
IL-23	Increase production IL-21 and IL-22 and IL-17, Activation STAT3 and NF-kB
IL-10	Decrease production IL-21 and IL-22 and IL-23 and IL-6 and IL-11 and IL-17, Inactivation STAT3 and NF-Kb
TNF-α	Activation NF-kB
TGF-β	Decrease production IL-21 and IL-22 and IL-23 and IL-6 and IL-11 and IL-17, Inactivation STAT3 and NF-kB

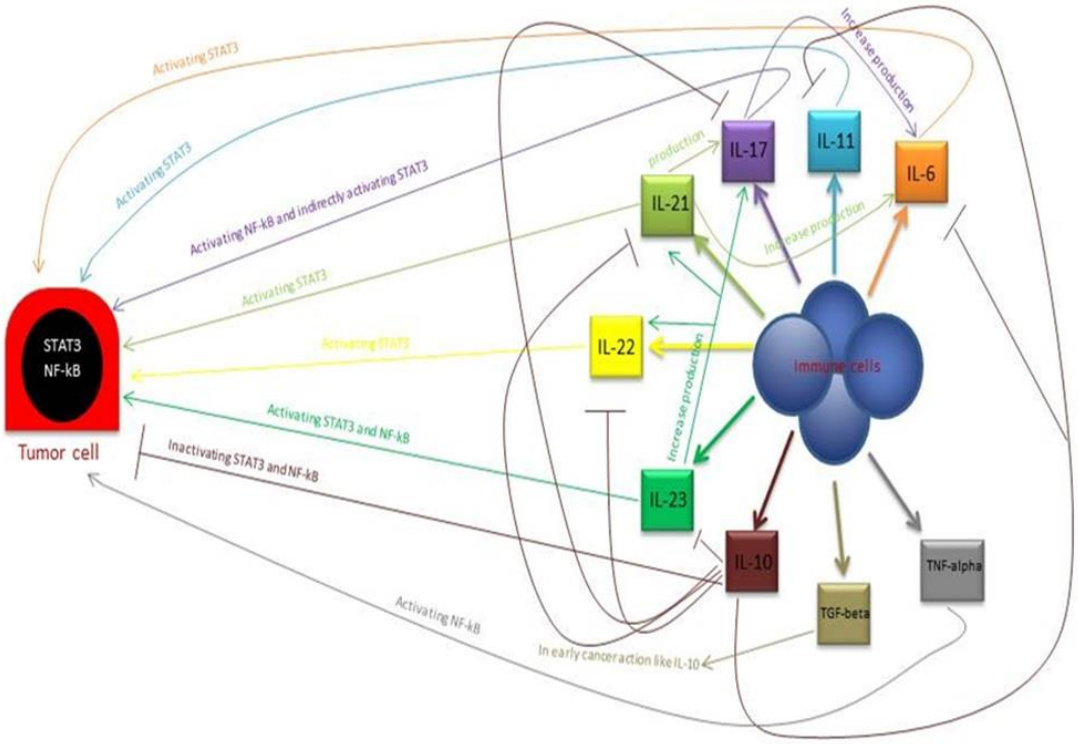

Figure 1. | The Effect of some inflammatory and anti-inflammatory cytokines on STAT3 and NF-KB transcription factors. Some inflammatory and anti-inflammatory cytokines such as TNF-α, TGF-β, IL-10, IL-23, IL-22, IL-21, IL-17, IL-11, and IL-6 which produced from different cells of the immune system, can activate and deactivate STAT3 and NF-KB transcription factors in multiple ways. Some of these cytokines can result in increased production or reduced production of some other cytokines of this group.

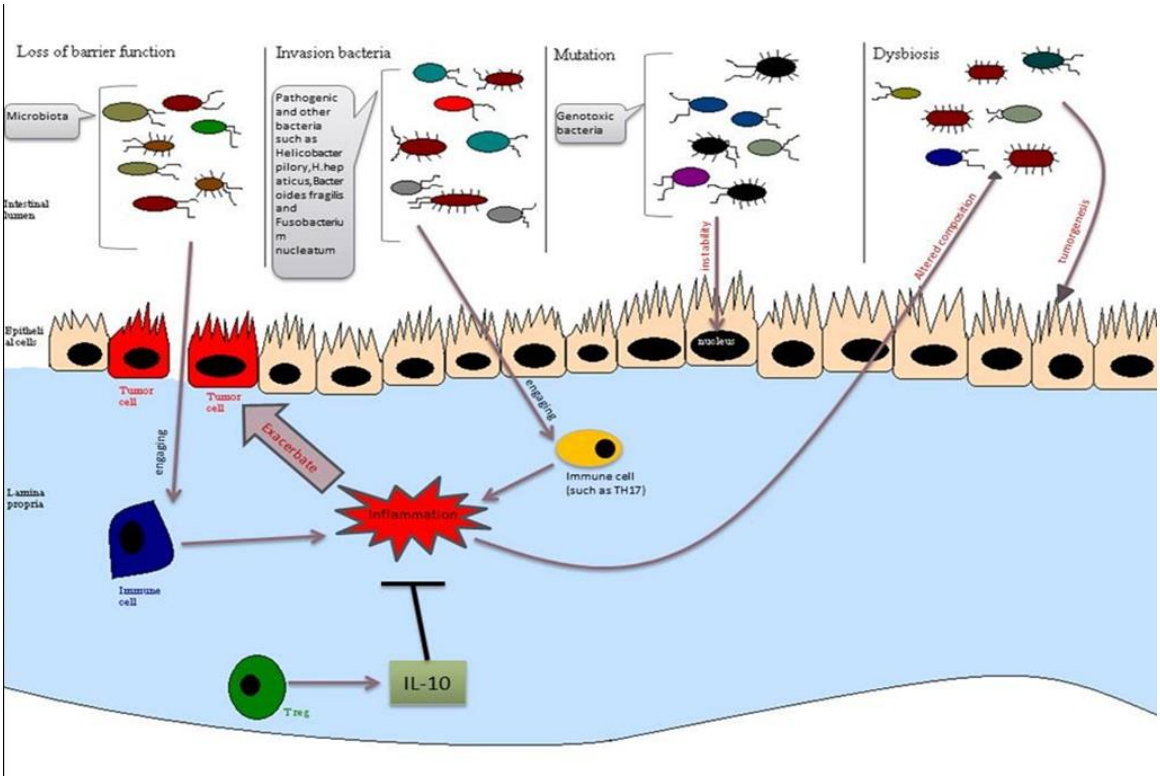

Figure 2. Lumen microbiotas and the onset and progression of CRC Weakness in intra-cellular connections in tumors allow flora bacteria to enter lamina propria, and they provoke immune cells, ultimately resulting in tumor formation. Invasive and pathogen bacteria in lumen stimulate and activate immune cells and result in inflammation induction of tumors in CRC. Mutated bacteria in lumen could result in instability or mutation in the genetic material of epithelial cells of the colon and lead to cancer. Alterations in the bacterial composition of a lumen could result in chronic inflammation and promote pathogen and mutated bacteria in this part and cause tumorigenesis. Regulatory T cells in the immune system inhibit inflammation by secreting cytokines such as IL-10, which can reduce dysbiosis as well as the progression of colorectal cancer.

Table 2. Function of some flora bacteria whose quantity changes in CRC

Phyla	Genus and species	Function
BACTEROIDETES	Alistipes finegoldii	Inflammation
	Bacteroides fragilis	Inflammation, Toxic performance of fragilisin
	Porphyromonas asaccharolytica	Inflammation
	Prevotella intermedia	Inflammation
	Bacteroides vulgatus	Inflammation
	Bacteroides uniformin	Inflammation
ACTINOBACTERIA	A. Collinsella	Not known
	A. Slackia	Anti-oxidantable
	Bifidobacterium (several)	Immune regulation, antiinflammation, butyrate manufacture
EURYARCHAEOTA	Methanobrevibacter	methane manufacturer
FIRMICUITES	Enterococcus faecalis	Inflammation, create oxidative stress
	Gemella	Not known
	Mogibacterium	Not known
	Parvimonas micra	Inflammation, Immune reaction
	Peptostreptococcus stomatis	create Oxidative stress
	Peptostreptococcus anaerobious	Not known
	Staphylococcus	Not known
FIRMICUITES	Solobacterium moorei	Not known
	Streptococcus gallolyticus (previously S.bovis biotypeI)	Inflammation
	Anaerostipes	Butyrate manufacturer
	Clostridium butyricum	Secondary bile acids manufacture,apoptosis cells of CRC, deterrence of tumorigenesis
	Eubacterium ventriosum	Inflammation, butyrate manufacture, DNA harm
	Faecalibacterium prausnitzii	Anti-inflammation, butyrate manufacturer
	Lactobacillus	Immune regulation (active T-cells), mucus barrier preservation
	Roseburia	Anti-inflammation, butyrate manufacturer
	Ruminococcus gnavus	SCFA maker,secondary bile acid manufacturer
FUSOBACTERIA	Fusobacterium nucleatum	Inflammation, butyrate manufacturer
PROTEOBACTERIA	Escherichia	Genotoxic(colibactin), mismatch repair of DNA, DNA harm checkpoint
PROTEOBACTERIA	Helicobacter pylori	Inflammation
	Klebsiella	change the biological process of hosts cell
	Citrobacter	Inflammation
	Cronobacter	Inflammation
	Kluyvera	Inflammation

	Salmonella	Inflammation
	Serratia	Inflammation
	Shigella	Inflammation
SYNERGISTETES	Thermanaerovibrio acidaminovorans	Not known
VERRUCOMICROBIA	Akkermansia muciniphila	Immune regulation (involved in PD-1 inhibite effect)
SPIROCHAETES	Treponema	Not known

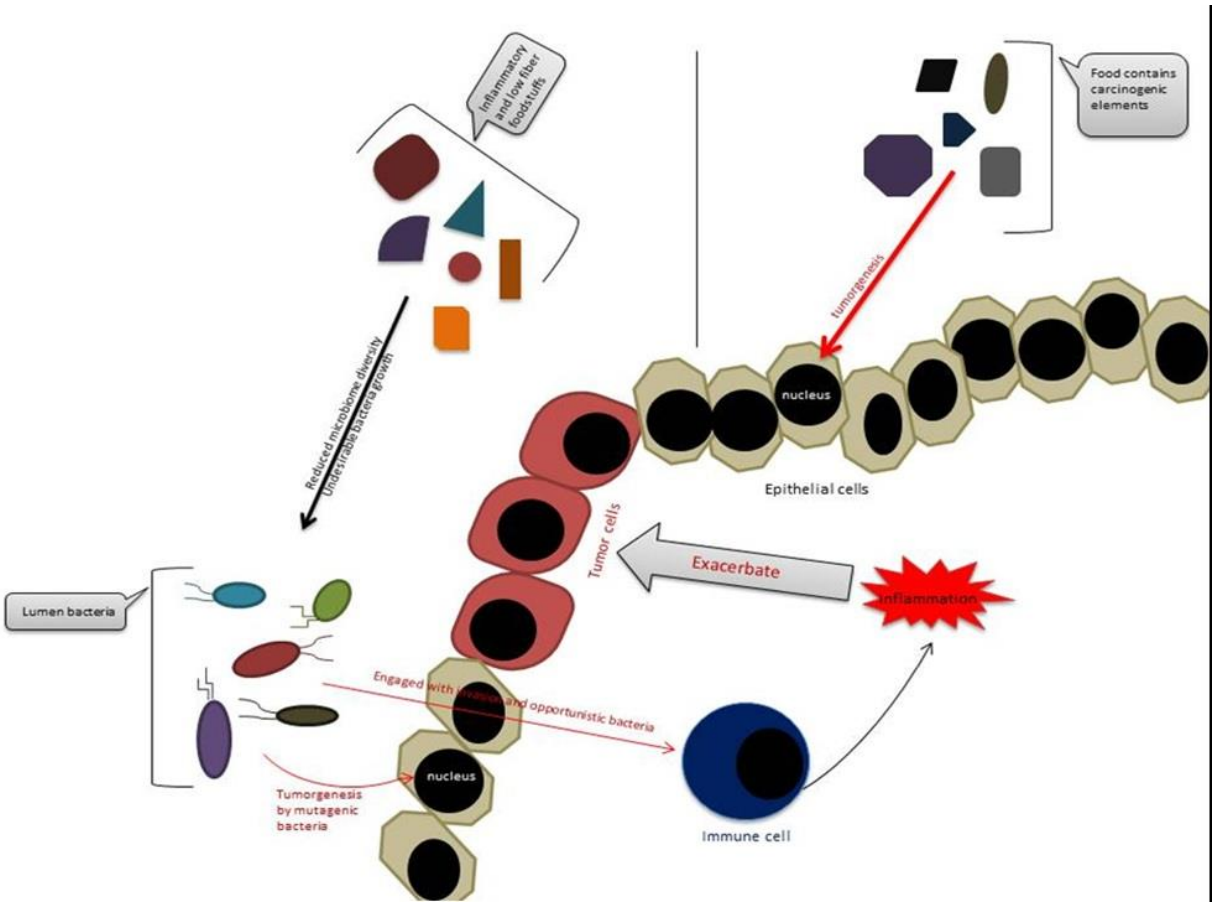

Figure 3. Effect of diet on CRC. Carcinogen containing food could affect intestine cells and change them to cancerous cells. Inflammatory and low fiber food products could result in a reduction in the diversity and growth of harmful bacteria in the lumen area. The dysbiosis caused by this process occupies immune cells with invasive bacteria that have had the chance to grow, leading to inflammation and the severity of these parts cancerous cells. Additionally, an alteration in lumen composition could result in the growth of some mutated bacteria, which can induce tumorigenesis.

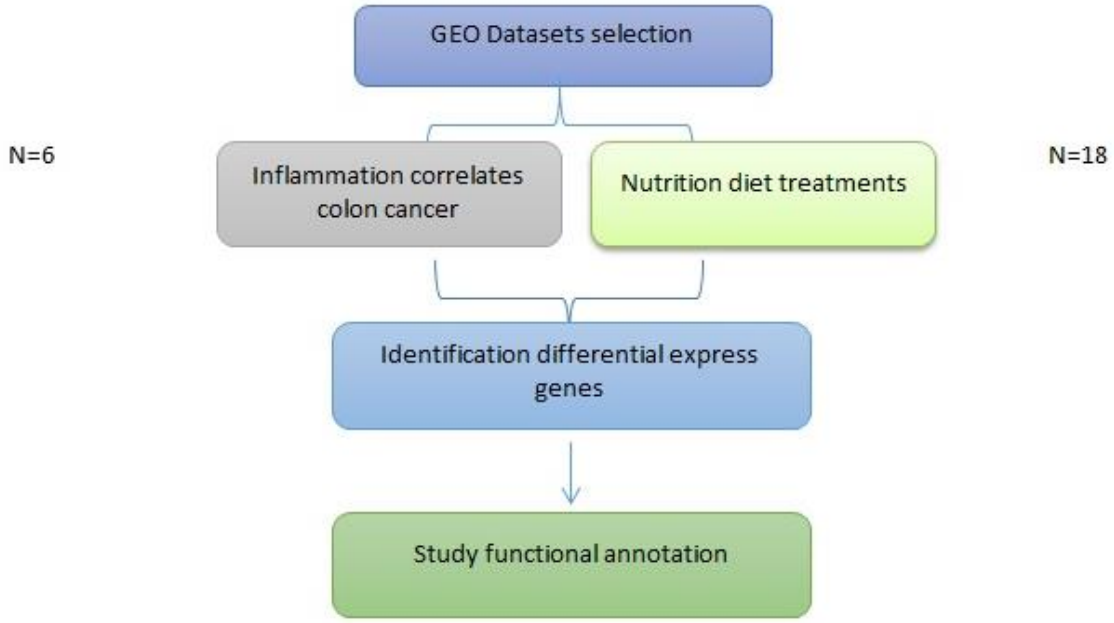

Figure 4. Schematic path of in silico analysis.

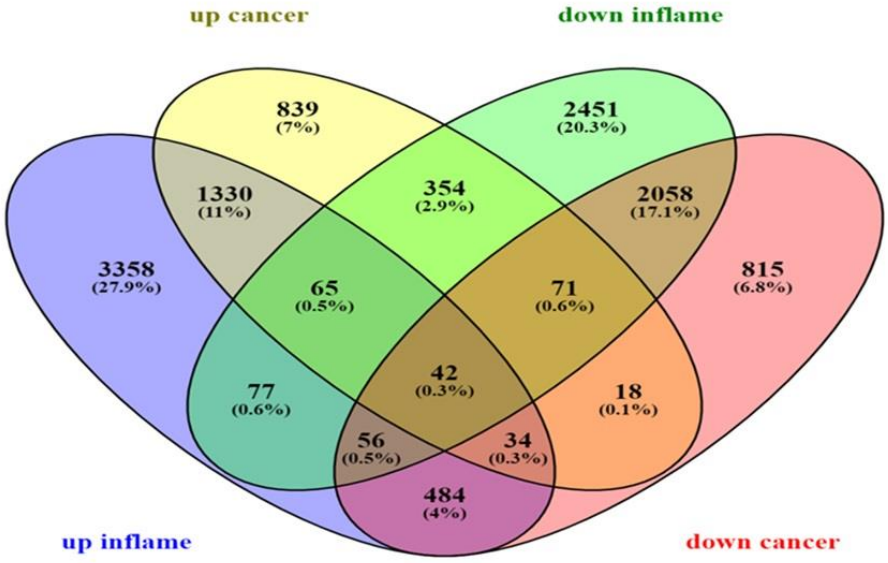

Figure 5. The above van chart shows the status of genes associated with inflammation and colon cancer, and those genes that are highly expressed and overlap in inflammation and cancer.

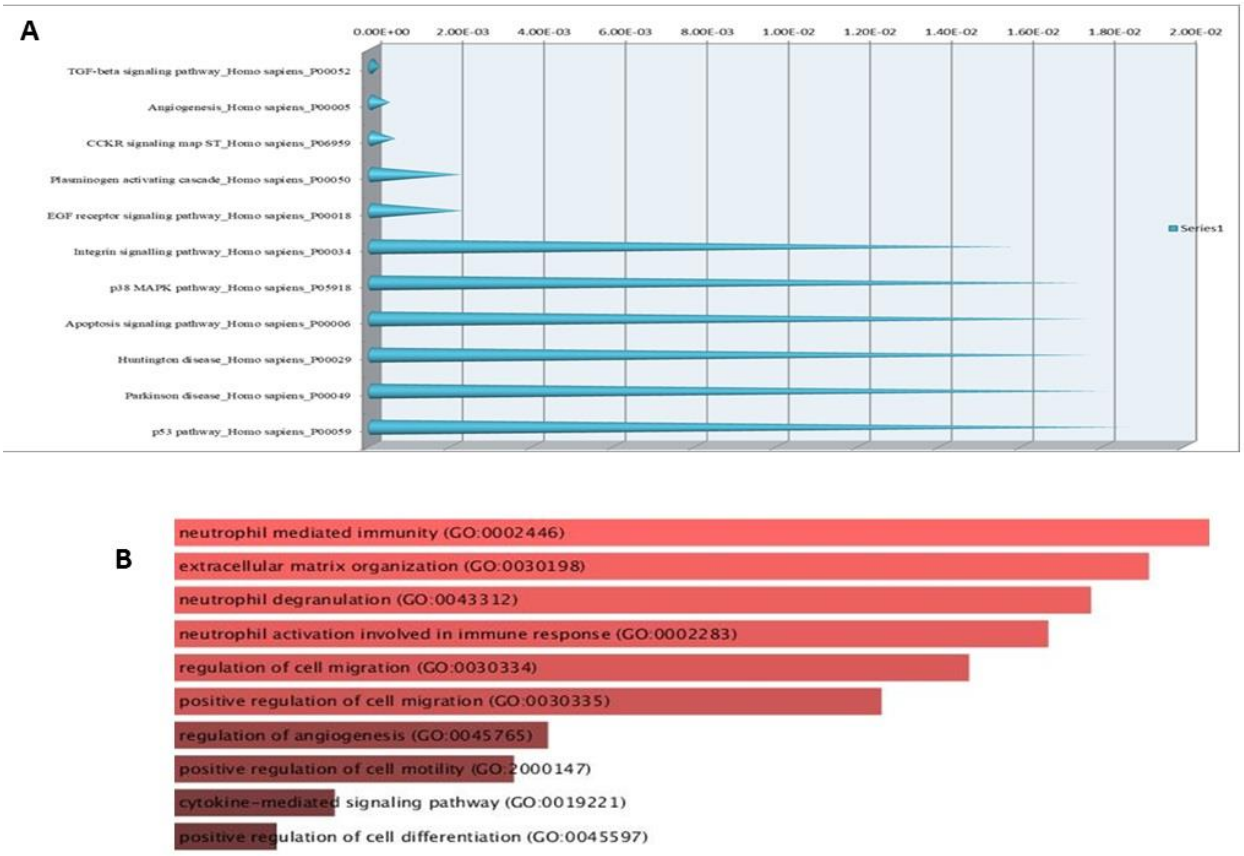

Figure 6. A- Identified signal pathways between commonly expressed genes in inflammation and colon cancer. **B-**Biological processes involved between common genes in inflammation and colon cancer that were more expressed.

Based on the analysis of ITGAV gene expression in the extracellular matrix, the correlation between the expression of this gene and CRC has been revealed [48].PI3K/AKT is one of the signaling pathways whose regulation is disrupted and is over-activated in CRC. Moreover, it should be noted that ITGAV is one of the genes that activate PI3K.Therefore it is probable that overexpression of ITGAV and its protein is involved in progression and environmental invasion of CRC [48].

Studies on integrin related genes' expression showed that ITGAV expression increased in invasive colorectal cancer [49]. Furthermore,

ITGAV is one of the genes whose expression increases in venous invasive colorectal cancer[49]. Also, ITGAV is one of the genes whose expression increases in stage III and IV compared to phase I and II in CRC [49]. As a result, reduced expression of this gene and its pathways caused by a diet that contains fish and corn oil can help contribute to CRC risk reduction.

The link between Mellitus diabetes and increased CRC risk is specific [1]. Elevated CRC risk related to Mellitus diabetes type II might be because of unfeasible alleles in the IGF pathway[50]. In Mellitus diabetes type II patients, several single nucleotide polymorphisms have been observed in the IGF pathway, which increases colorectal cancer risk [50]. Based on the analysis of data, consumption of the oils, as mentioned above, can affect IGF expression and its pathways, reducing CRC risk (Figure 8,part B).

Due to the critical role of diet and its link to inflammation and microbiota in gastrointestinal tract cancer, especially CRC, more studies are to be carried out to help prevent the disease and treat patients.

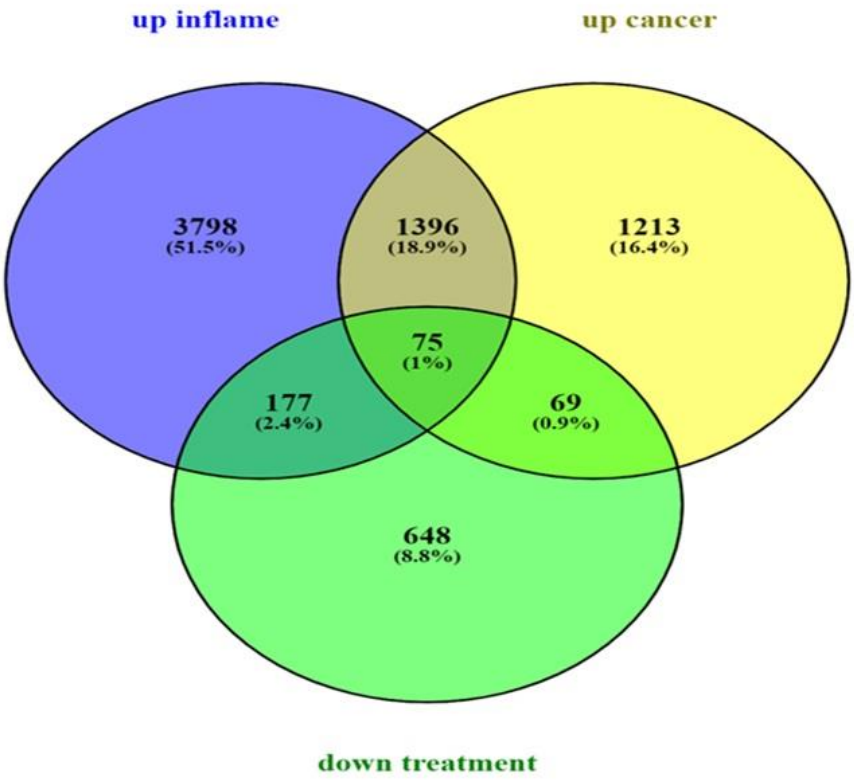

Figure 7. The chart above shows a decrease in the expression of a group of common genes in inflammation and cancer due to fish oil / pectin and corn oil / cellulose.

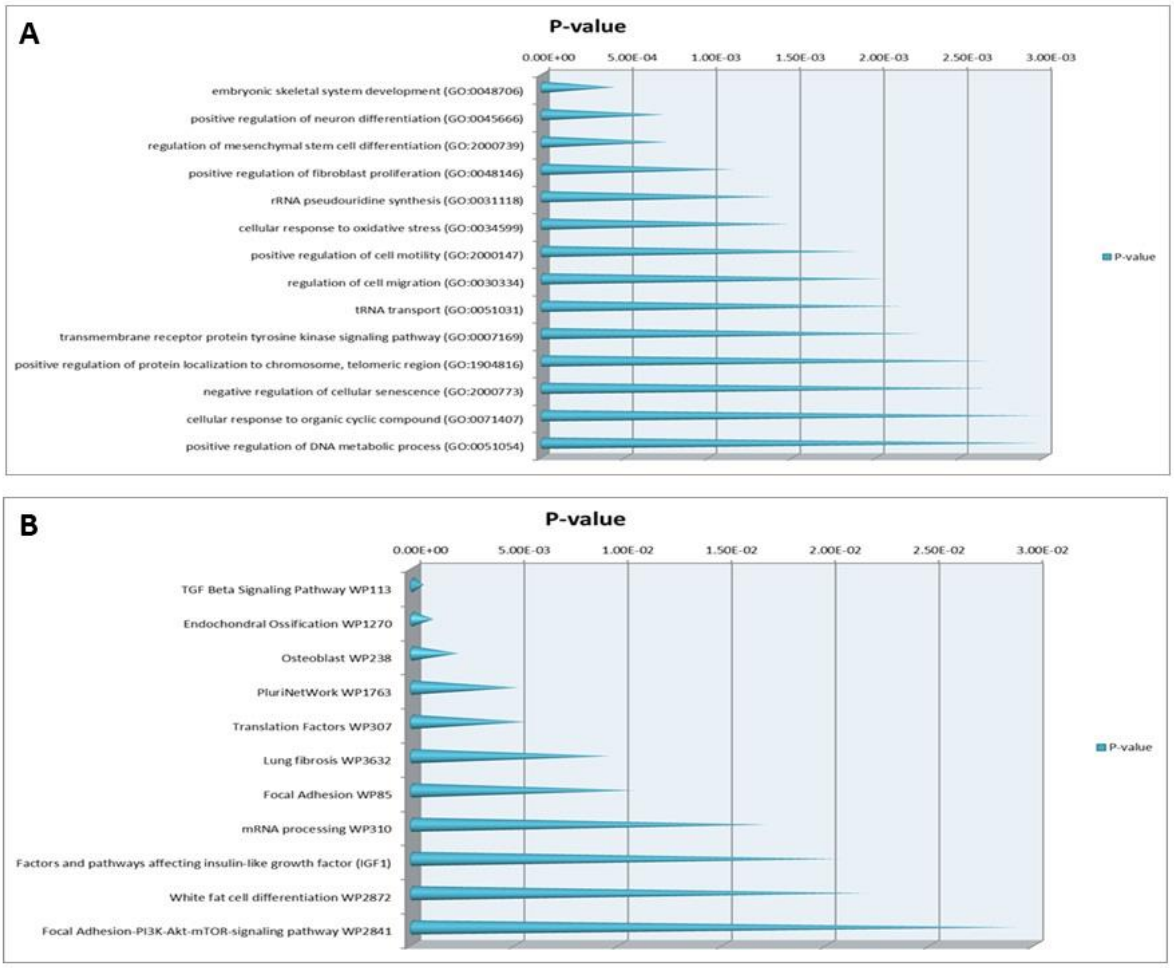

Figure 8. A- Involved biological processes have been identified through the use of corn oil / cellulose and fish oil / pectin that have reduced the expression of groups of genes in the pathways associated with colon cancer and inflammation. **B-** The pathways identified show genes that have been reduced jointly and individually with inflammation and cancer by the corn oil / cellulose and fish oil / pectin diets.

CONCLUSION

Because CRC is a disease which has complicated causes [46], it can be said that epigenetic and inherited factors are not the only responsible factors that cause CRC. It can be concluded, according to what has been investigated, that inflammation plays a crucial role in malignant CRC and can make it worse. This inflammation could be a result of the microbiota of the intestines. Additionally, diet can play a role by affecting the microbiota of this part and

worsen the inflammation. Other than the indirect effect of microbiota and diet through inflammation on CRC, the direct impact of genotoxic bacteria and some nutrition that contain carcinogens could also affect this disease.

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