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The effect of probiotics supplementation on the side effects of chemo radiotherapy for colorectal cancer: a literature review

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SUMMARY

Colorectal Cancer (CRC) is fourth leading cause of cancer-related deaths (8.5%) and ranks as the second most common cancer among women (9.2%) and the third among men (10.0%) worldwide. The main treatments modalities for CRC as all the different types of cancer are surgery, radiation therapy, and chemotherapy. However, such treatments (mainly radio and chemotherapy) have several side effects which cannot be ignored and mainly presented as gastrointestinal toxicity that include infections, mucositis, enteritis, diarrhoea, nausea and vomiting. Probiotics are one of Biological Radio protectors (BRPs) that have been reported to preserve gastrointestinal tract in patients treated with radiotherapy and/or chemotherapy. The main use of probiotics as BRPs is treatment of intestinal toxicity and inflammation induced by radiotherapy, chemotherapy or surgical interventions. These effects may explain by different abilities of the probiotics such as synergistic activity, toxin neutralization, antioxidant property, antagonistic activity, and immune system stimulation. Moreover, the probiotic effect on reducing the side effects during radio- chemotherapy may improve the quality of life in CRC patients during and after the treatment. Further studies on uses of probiotic to improve immune system, inflammatory response and the exact doses with optimum combination of strains to reduce or prevent the side effects occur during treating CRC is needed.

Key words: colorectal cancer, probiotics, radiotherapy, chemotherapy

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INTRODUCTION

Colorectal Cancer (CRC) is a multi-factorial disease that occur in the colon (mainly the sigmoid part) and the rectal. CRC has hereditary and non-hereditary types; the later type is the most frequent worldwide that caused mainly by somatic mutation as a result of environmental factors [1]. CRC is accounting for 9.7% of cancer incidences, and the fourth leading cause of cancer-related deaths (8.5%) worldwide as reported by the World Health Organization (WHO). Based on gender, CRC ranks as the second most common cancer among women (9.2%) and the third among men (10.0%) worldwide [2]. The incidence of CRC is associated with several modifiable and non-modifiable risk factors. The non-modifiable risk factors, which cannot be controlled, include genetic factors (family history, inflammatory bowel disease, and hereditary syndrome), age, gender and ethnicity [3, 4]. The modifiable risk factors include diet and dietary habits, lifestyle, inflammation, physical inactivity, the consumption of tobacco and alcohol, and as recently reported the gut microbiota imbalances [5]. The main treatments modalities for different types of cancer including CRC are surgery, radiation therapy, and chemotherapy [6]. The effectiveness of radiotherapy by itself or combined with chemotherapy has been proven to be the foundation in treating cancer patients including CRC patients [7]. However, radio and chemo-therapy have several side effects which cannot be ignored and mainly presented as gastrointestinal toxicity that include mucositis, enteritis, diarrhoea, nausea and vomiting [8]. Some of these effects are related to mucosal damage by ionizing radiation with subsequent alteration of intestinal flora, accelerated small and large bowel transit, and malabsorption of bile salts [9, 10]. The radiation also induces diarrhoea that causes changes in the intestinal flora and intestinal motility that contribute to impaired secretion, absorption and immune function of the digestive tract [11]. Moreover, some of these effects persist even after the conclusion of radiotherapy which may decline patient quality of [12, 13].

The Food and Agriculture Organization (FAO) and the WHO nutritional guidelines have defined probiotics as "live microorganisms when administered in adequate quantities confer a health profit to the host cell" [14-16]. Food and Drug Administration of the USA (FDA) endorses probiotics for their null safety issues, based on that probiotics have become a typical ingredient in many formulations and traditional foods as well as

the first Biological Radio Protectors (BRPs) [17-19]. Probiotics beneficial effects as radio protectors have been reported from investigations that used probiotics to preserve gastrointestinal tract in patients treated with radiotherapy [20]. Moreover, it has been reported that probiotics have different abilities such as synergistic activity, toxin neutralization, antioxidant property, antagonistic activity, and immune system stimulation [21]. In addition, the uses of probiotics to enhance immune responses, attenuate inflammatory responses, improve the intestinal microbial environment and reduce infectious complications were only studied in few researches on preoperative and postoperative treatment among CRC patients [22, 23]. Therefore, the objective of this review was to summarize the current research in using probiotics to prevent and/or reduces the side effects of CRC treatments.

LITERATURE REVIEW

Colorectal Cancer (CRC)

CRC is one of the leading causes of mortality and morbidity worldwide (accounts for over 8% of all deaths annually) [24, 25]. Although the early detection of precancerous polyps significantly reduces the incidence of CRC [26], studies indicated that CRC is the third most common cancer after lung and breast cancers, and the fourth most common cause of cancer-related death, after lung, liver and stomach cancers [27]. CRC is the second most commonly diagnosed cancer in females and the third in males. It also accounts for over 9% cancer incidences, with 1.4 million cases occurring in 2012 worldwide [28]. In 2018, the total incidences of CRC worldwide were 18.1 million with 0.5 million new case [29], and with the spread of Western lifestyles CRC rates globally are expected to increase to 1.7 million by 2020 [30]. CRC known to be the disease of developed countries, however, due to shifting the behaviours and lifestyle in the developing countries to word westernization, the incidence in these countries has increased [31]. The exact causes of the most majority of CRCs still unknown, as it heterogeneous disease, however, the risk of CRC is associated with several risk factors include: family history of CRC, personal history of adenomatous polyps (precursor lesion of CRC) and inflammatory bowel disease, smoking, age (90% of diagnosed cases are 50 ≤ years old), gender (higher in male more than female), race (black population over white population), personal habit of alcohol consumption, lower socioeconomic status, obesity, physical inactivity, diets that high in meat, fat and low in fibre, and inherited syndromes (which account for only 2%-5% of all CRC cases) [32,33]. More than 80% of the incidence of colorectal neoplasms, occur sporadically, as a result of the interaction between the lifestyle and environmental factors with genetic factor that generate sequential accumulation of somatic mutations causing genomic instability that lead to CRC development [34].

Signs, symptoms and screening of CRC: CRC in early stage typically does not has symptoms, the symptoms often appear only after the growth and spreading of cancer [35]. The Signs and symptoms of CRC include rectal bleeding, blood in the stool, change in bowel habits like diarrhoea, constipation, or narrowing of the stool that continue for more than few days, the patient feeling of the bowel as not completely empty with need to have a bowel movement that is not relieved by doing so, abdominal cramping or pain, decreased appetite, intestinal obstruction, and weight loss. Sometimes the blood loss resulting from cancer leads to anaemia (low number of red blood cells), which resulting in symptoms such as weakness, dizziness and fatigue [36, 37]. As the symptoms of CRC usually does not appear until it is advanced, screening could help decreasing CRC mortality, prevent and reduce CRC incidence by identifying precancerous lesions (polyps) that can be removed, as well as detect some cancers early, when treatment is more often successful [38]. The 5-year relative survival rate of CRC is 65%, increased with early detection before spreading to 92%, which mean that at least 9 out of 10 people with early-stage cancer survive at least for 5 years.

Therefore, American Cancer Society new guidelines recommend regular CRC screening for people at average risk to begin at 45 years of age and continue up to age 85 depending on their health status and/or their life expectancy. Individuals with first-degree relatives with CRC or who have certain other risk factors, should begin screening at younger age [39]. Evidence support that considering the screening for CRC as a part of routine care for all adults aged 45 years and older, especially those with family history of CRC, through the adherence to either of the two types of testing (stool or structural exams) is important as the screening tests are relatively simple, accurate, resulting in reducing the incidence of the disease in those people, increasing the ability to identify high-risk groups, lowering the growth of primary lesions, and improving the survival rates of patients at early-stage lesions.

Pathophysiology of CRC: The intestinal epithelium is a hotspot for malignant transformations such CRC as it has a high turnover rate [1]. CRC results from complex interactions between inherited susceptibility and environmental factors [39]. The CRC start from development of specific types of colonic mucosa neoplastic polyps, called neoplastic polyps, colorectal neoplasms, or adenocarcinoma polyps (glandular cells in the wall of the colon and rectal) [40]. The neoplastic polyps grow slowly to invasive adenocarcinoma as a result of mutations activated by environmental/exogenous (e.g.: lifestyle factors), which caused and targeted mutations, activations, or deletions of oncogenes, tumour suppressor genes and/or genes related to DNA repair mechanisms such as genes including Adenomatous Polyposis Coli (APC), K-ras and TP53, through adenoma-to-carcinoma sequence [41].

Polyp histology is the critical parameter to be used for determining malignant potential in term of natural history [40]. Hyperplastic and adenomatous are the two most common types of histology and most CRC rise from adenomatous polyps [41]. Hyperplastic polyps histologically comprise increased number of glandular cells with decreased cytoplasmic mucus, however, its generally lack nuclear hyperchromatic, stratification, or atypia [42]. On the other hand, adenomatous nuclei (Adenomas) are histologically classified as tubular or villous and it's usually characterized as hyperchromatic, enlarged, cigar-shaped, and crowded together in a palisade pattern. The villous adenomas contain digit form villi arranged in a frond, whereas tubular adenomas are composed of branched tubules [43].

Based on the origin of the mutation, colorectal carcinomas can

be classified as sporadic (70%); inherited (5%) and familial (25%) [1, 27]. Sporadic cancer has a heterogeneous molecular pathogenesis as mutations can target different genes. But, most of this type of CRC cases follow a specific sequence of mutations, first of them mutation occurs in APC. APC is a tumour suppressor gene, that triggering the formation of non-malignant adenomas, and also called polyps. This followed by mutations in KRAS, TP53 and, finally, DCC [44]. Inherited cancers, classified to two groups, polyposis form which involves Familial Adenomatous Polyposis (FAP), that characterized by the development of multiple potentially malignant polyps in the colon [45]. And non-polyposis form or Hereditary Non-Polyposis Colorectal Cancer (HNPCC), which related to mutations in DNA repair mechanisms and mainly caused by Lynch syndrome, that found in 2%-3% of all colorectal cancer cases, and result from inherited mutations in one of the alleles coding for DNA repair proteins such as MSH2, MLH1, MLH6, PMS1 and PMS2 [46]. The Familial colorectal cancer is also caused by inherited mutations, but they are not classified as inherited cancers per se as they cannot be included in any inherited cancer variant.

According to the degree of preservation of normal glandular architecture and cytological features CRC are classified as well-differentiated, moderately well differentiated, or poorly differentiated [47]. Progressively, more poor differentiation is a histologic marker that induct further sever underlying genetic mutations, with almost 20% of CRC are poorly differentiated. However, the mutations which associated with poor differentiation currently are unknown [47].

Stages of CRC: There are two frequently used classification for staging of CRC, Dukes' classification (the most commonly used), and Tumour, Node Metastases (TNM) classification (recently used) [48]. Dukes' classification is most commonly and staged cancer from A through D, with stage A means penetrating beyond the muscular is mucosa into the submucosa, stage B1 extends means penetrating beyond the submucosa into the muscularis propria; stage B2 mean extends through the muscularis propria into the serosa; stage C include regional lymph node metastases; and stage D include distant Metastases [49]. TNM classification staging the cancer by mural depth of the primary tumour (T), presence of local lymph node metastases (N), and the presence of distant metastases (M), which make it helpful particularly in endosonographic staging of CRC [50]. The invasive colon cancer in the TNM classification is classified from stage I to IV, where stage I in the TNM classification corresponds to Dukes' A or B1 lesions, stage II corresponds to Dukes' B2 lesion, stage III corresponds to Dukes' C lesion, and stage IV corresponds to Dukes' D lesion. Pathologic stage, as classified by either scheme, correlates highly with cancer prognosis [48].

Treatments of CRC

The treatment of CRC can be aimed either to cure or palliate the disease, depending on various factors such as the patient health and preferences, stage, site of the cancer, and the degree of spreading [51]. The current treatments for CRC include surgery, chemotherapy, and radiotherapy [52]. In the case of localized colon or rectum cancers, surgery is the most common treatment required. For early stage of CRC, a colonoscope may be used to remove the cancerous tissue or cancerous polyp/polyps, plus surrounding tissues and nearby lymph nodes. For advance stages (II, III) where the cancer has penetrated the bowel wall deeply or spread to lymph nodes, the neoadjuvant chemoradiotherapy is given either before the surgery to shrink tumors or following surgery to destroy small amounts of remaining cancerous tissue. The radiation therapy done either using external beams or surgically implanted radioactive pellets [36].

The metastatic colorectal cancer, which cancer has spread to other parts of the body, treatments typically include palliative chemotherapy and/or targeted therapy. The World Health Organization define the palliative care, as care that primarily aims to improve the quality of life of patients by the early identification, assessment, and treatment of physical, psychosocial, and spiritual issues. Palliative care can involve either treatments that directed at limiting tumor growth and associated symptoms (eg, pain), and/or treatments solely intended to relieve symptoms (ie, physical, emotional, and spiritual), which can prolong patients' life in case of CRC to >2 years overall survival [53]. However, these treatments are associated with high risk complications and are not proven to be successful in all cases, highlighting the need to develop new treatment strategies. Moreover, investigations reported that the current treatments can significantly reduce the quality of life [54]. Therefore, emerging therapeutic strategies have been proposed, including Capecitabine [55], Immunotherapy and antibodies such as the monoclonal Epidermal Growth Factor Receptor (EGFR) antibody "Cetuximab", which a newer option for some advanced cancers [56]. Probiotics have been also proposed as another emerging therapeutic option.

The side effects of cancer chemo-radiotherapy treatment: Many side effects from gastrointestinal radiation can occur during or soon following radiotherapy. These symptoms are attributed to acute mucosal injury and inflammation. Acute radiation injury to the rectum and anal canal can result in a range of symptoms such as abdominal pain, diarrhoea, fatigue, tenesmus, rectal pain, urgency, rectal discharge, incontinence, and fresh rectal bleeding. These symptoms occur primarily as a result of direct mucosal damage [57-59]. Acute radiation injury to the colon can be severe and in 5%-15% can lead to therapy interruption or treatment plan alteration [60]. Delayed symptoms present a few months or years after radiotherapy and are associated with chronic process of transmural fibrosis and vascular sclerosis. Abayomi and colleagues [61] reported that 47% of women who received radiotherapy for cervical or endometrial cancer suffer from symptoms of radiation intestinal injury affecting quality of life within 3 months following therapy completion. These results are consistent with a previous structured questionnaire study which showed that 53% of patients had reported bowel symptoms significantly affecting their quality of life, while 81% of patients in the study described new-onset gastrointestinal problems after starting radiotherapy [62]. The severity of injury depends on the radiation dose and the volume of intestinal segment that falls within the radiation field [63, 64].

Probiotics

As the demands for healthy and functional foods that promote health and prevent or cure illness increased during the last decades, probiotics have received attention in the field of self-

care and complementary medicine [65]. The word "probiotic" comes from the Greek words "pro" and "biotic," meaning "for the life". In 2001, the Food and Agriculture Organization/ World Health Organization (FAO/WHO) defined probiotics as "live microorganisms which, when administered in adequate amounts confer a health benefits on the host" [66], and this concept was updated in 2013 to include the three main key aspects of probiotics: microbial, viable, and beneficial to health, to became "live microorganism that, when administered in adequate amounts, confer a health benefit on the host" [67]. Microorganisms that are considered as probiotics should have several characteristics including resistance to gastrointestinal environment (low pH and bile salt), antimicrobial activity, multidrug resistance, and antioxidant activity [68]. The chief

Tab. 1. Studies conducted on probiotic role in treating and prevention the side effect of CRC treatments from 2005-2019

Study	Main objective	Study design	Sample	Treatment type	Probiotics used	Main outcome
Osterlund *et al.* [97]	To assess the efficacy of probiotics on 5-FU-based chemotherapy toxicity	Randomized, phase III, single institution, 2*3 factorial design (duration: 24weeks)	140 CRC patients, aged 31-75 years	Chemotherapy intervention	*Lactobacillus rhamnosus GG* ($1\text{-}2 \times 10^{10}$)	Probiotics daily oral administration reported in reducing the frequency of severe 5-FU-based chemo-therapy related diarrhea
Mego *et al.* [98]	To determine the effectiveness of the probiotics in the prevention of irinotecan induced diarrhoea due to reduction of intestinal beta-D-glucuronidase activity	Randomized, double blind, placebo-controlled study (duration: 12 weeks)	46 CRC patients aged 42-81 years.	Chemotherapy	Colon Dophilus (*Bifidobacterium breve* HA-129, *Bifidobacteriumbifidum* HA-132 HA, *Bifidobacterium longum* HA-135, *Lactobacillus rhamnosus HA-111, Lactobacillus acidophilus* HA-122, *Lactobacillus casei* HA-108, *Lactobacillus plantarum* HA-119, *Streptococcus thermopilus* HA-110, *Lactobacillus brevis* HA-112, *Bifidobacterium infantis* HA-116. Additives includes: inulin, maltodextrine , magnesium stearate, ascorbic acid) (10×10^{9})	Probiotics reported to be safe and might lead to a reduction in the incidence and severity of gastrointestinal toxicity
Gianotti *et al.* [99]	To investigate whether probiotics might adhere to the colonic mucosa, reduce concentration of pathogens in stools, and modulate the local immune function.	A randomized, double blind clinical trial (duration: 7 days)	31 CRC patients aged 53-74 years.	Surgical intervention	*Lactobacillus johnsonii* and *Bifidobacterium longum* *(*2×10^{7}- 2×10^{9})	Probiotics reported to adhere to the colonic mucosa and affects intestinal microbiota by reducing the concentration of pathogens and modulates local immunity
Ohigashi *et al.* [100]	To investigate the functional outcome and health-related quality of life of patients who underwent a surgical resection of colorectal	Intervention study (duration: 3 months)	A 124 CRC patients aged 54-79 years.	Chemotherapy and surgical intervention	*Bacillus natto* (10 mg) and *Lactobacillus acidophilus* (30 mg)	Probiotics reported to be an effective treatment for improvement in functional outcome and quality of life after colorectal resection

Liu *et al* . [101]	To determine the effects of perioperative administration of probiotics on the gut barrier function and the surgical outcome in patients undergoing elective colorectal surgery	Randomized placebo-controlled trial (duration: 6 days intervention)	100 CRC patients aged 51-76 years.	Surgical intervention	*Lactoba-cillus plantarum, Lactobacillus acidophilus, Bifido-bacterium longum* ($0.5\text{-}0.7 \times 10^{10}$)	Probiotics reported to improve the integrity of gut mucosal barrier by benefiting the faecal microbiota, and decreasing infectious complications in patients with CRC undergoing colorectomy
Zhang *et al.* [102]	To elucidate the effects of oral bifid triple viable probiotics among patients with CRC.	Randomized controlled study (duration: 8 days preoperative intervention)	60 CRC patients aged 45-87 years.	Surgical intervention	*B longum, L acidophilus* and *Enterococcus faecalis* (3×10^{8})	Probiotics reported to minimize the postoperative occurrence of infectious complications, with possible mechanisms attributed to the maintenance of the intestinal flora and restriction of bacterial translocation from the intestine
Liu *et al.* [103]	To determine the effects of the perioperative administration of probiotics on serum zonulin concentrations and the subsequent effect on postoperative infectious complications in patients undergoing colorectal surgery	Randomized placebo-controlled trial (duration: 16 days intervention)	150 CRC patients aged 50-77 years.	Surgical intervention	*Lactoba-cillus plantarum, Lactobacillus acidophilus, Bifido-bacterium longum* ($0.5\text{-}0.7 \times 10^{10}$)	Perioperative probiotic treatment reported to reduce the rate of postoperative septicemia and associated with the reduction of serum zonulin concentrations in patients undergoing colectomy
Lee *et al*. [104]	To investigate the effects of 12 weeks of probiotics administration in colorectal cancer patients	Randomized, double blind, placebo-controlled study (duration: 12 weeks)	60 CRC patients aged 45- 67 years.	Chemotherapy or chemo +radiotherapy	*L. rhamnosus R0011* and *L. acidophilus R0052* (2×10^{9})	Probiotics reported to improve bowel symptoms as well as quality of life in CRC survivors
kotzampassi *et al*. [105]	To assess the efficacy of probiotics as prophylaxis for complications after colorectal surgery	Randomized, double blind, placebo-controlled study (duration: 17 days intervention)	164 CRC patients aged 56-78 years.	Surgical intervention	*Lactobacillus acidophilus LA-5, Lactobacillus plantarum, Bifidobacterium lactis* BB-12 and *Saccharomyces boulardii* (9×10^{9})	Probiotics reported to decrease the risk of postoperative complications, including mechanical ventilation, infections and anastomotic leakage

Yang *et al.* [106]	To evaluate the anti-infective effects of perioperative probiotic treatment in patients receiving confined CRC respective surgery	Randomized, double blind, placebo-controlled study (duration: 12 days)	60 CRC patients aged 51-76 years	Surgical intervention	*Bifidobacterium longum* (≥ 1.0 ×10^7 cfu/g), *Lactobacillus*	Perioperative probiotic administration significantly influenced the recovery of bowel function, which might be important clinical significance in reducing the short-term infectious complications such as bacteremia

and most widely used probiotics bacterial species belong to the genera *Lactobacillus* and *Bifidobacterium*, which belong to lactic acid bacteria group [69, 70].

Probiotics Health Benefits: The human Gastrointestinal Tract (GIT) is a complex microbial ecosystem inhabited by more than 400 bacterial species, which can be influenced by different factors, and one of the most important factors is the diet of the host [71, 72]. Recent scientific research showed that the deficiency or imbalance of intestinal microbiota leads to some of the infections and disorders. Probiotics have been considered as one of control strategies for several gastrointestinal disorders such as GIT infections, constipation, irritable bowel syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis), antibiotic-induced diarrhoea, food allergies, and certain cancers such as colorectal cancer [73].

The health promoting benefits of probiotics include modulation of the immune system reducing colitis and inflammation, antioxidant activity, toxin-binding and detoxification activity, maintenance of mucosal integrity, decreasing incidence and duration of diarrhoea, and regulation of gut motility to control constipation or irritable bowel syndrome [74-76]. Additionally, probiotics may reduce allergy symptoms, improve nutrient absorption, alleviate symptoms of lactose intolerance, and produce beneficial compounds, such as vitamins, Short-Chain Fatty Acids (SCFAS), and conjugated linoleic acid [77-81].

Probiotics Role in Colorectal Cancer (CRC): Anti-cancer properties of probiotics have been emphasized in recent years [82, 83], and the ingestion of probiotics represent a novel new therapeutic option for CRC [52]. Oral administration of probiotics was found to normalize the intestinal microflora by altering and suppressing the growth of microbiota implicated in the production of mutagens and carcinogens and increasing the concentrations of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, [84]. Furthermore, it improves the GIT barrier and enhances the local and systemic immune or/and anti-inflammatory activities, that lead in reducing the levels of pathogenic micro-organisms and protection of DNA from oxidative damage, all of which play a part in the suppression of tumour formation and growth [85, 86].

Probiotics may inhibit the development and progression of neoplasia and reduce the invasion and metastasis of cancer cells [87, 88]. These effects and mediated by decreasing the intestinal inflammation, enhancing the immune function and anti-tumorigenic activity, preventing biofilm formation, and binding to potential food carcinogens including toxins found in meat products [89].

The effects of probiotics on colorectal cancer treatment and treatment side effects: Probiotics are the first Biological Radioprotectors (BRPs) [7]. BRPs can be defined as "any living biological systems and processes that can modify the radiation responses of biological tissues" and act through their actions as antioxidants, anti-inflammation, anti-apoptosis and anti-aging agents [90].

The main use of probiotics as BRPs is treatment of intestinal toxicity and inflammation induced by radiotherapy alone, chemotherapy alone, combined chemotherapy and radiation or surgical interventions [91]. Table 1 summarizes the studies conducted between 2005-2019 on uses of probiotics to prevent, treat or reduces the side effects of different CRC treatments. Several clinical trials with varying design, patient populations and probiotics products have been stated that cancer patients who received probiotics during radiation therapy revealed fewer episodes of high-grade diarrhoea and less abdominal discomfort, and therefore, improving their quality of life [92].

It has been reported that probiotics might provide a favourable role to reduce the GIT toxicity and inflammation induced by radiotherapy [93]. Probiotics down regulate NF-κB activity, which balances the production of TNF-α and other pro-inflammatory cytokines and production of antioxidant enzymes (e.g. glutathione peroxidase, superoxide dismutase and catalase). Therefore, free-radical scavenging is the main mechanism of which using of probiotics protect from radiation side effects [94-96].

To prevent the side effects of chemo-radiotherapy, different doses of probiotics were used. For example, Mego et al. [95] used 6-18 × 10^9 per day of *Enterococcus faecium* M-74 to prevent the febrile neutropenia among testicular cancer and acute leukemia patients, which revealed no effect. Sharma et al. [96] used at least 2 × 10^9 six time per day of *Lactobacillus brevis* CD2 lozenges to prevent radiation-induced mucositis among head and neck cancer patients treated with and result in strong effect. For colorectal cancer, consumption a dose of 1-3 ×1010 per day of *Lactobacillus rhamnosus* GG1 or probiotic formula Colon Dophilus, which contain 4 strains of *Bifidobacterium* and 4 strains of *Lactobacillus*, found to prevent the gastrointestinal toxicity of chemotherapy and radiotherapy and give a strong effect [97].

CONCLUSION AND FUTURE DIRECTIONS

The use of probiotics may reduce different side effects of CRC chemo-radiotherapy treatment, and therefore, improving the patient's quality of life. Further interventional studies aiming to investigate the effectiveness of probiotics supplementation intervention in reducing inflammatory markers and the side effects of radiation therapy as well as enhancing the immune system response and the quality of life among CRC patients who undergo chemo-radiotherapy are needed. Moreover, studies providing sold base of using probiotics as adjuvant therapy for CRC patients and other types of cancer to reduce the side effects of radiotherapy and to enhance the immune system as well as improving their quality of life are recommended. Studies that clearly define the exact dose needed and beast combination of different probiotics strains to be used for preventing or reducing the CRC treatments side effects are required.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

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