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Strain-specific probiotic (microbial cell preparation) and omega-3 fatty acid in modulating quality of life and inflammatory markers in colorectal cancer patients: A randomized controlled trial

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Abstract

Aim: Colorectal cancer patients on chemotherapy usually have elevated levels of inflammatory markers and experience numerous side effects from chemotherapy thereby leading to poor quality of life. Omega-3 fatty acid and microbial cell preparation (MCP) have been known to provide significant benefits in patients on chemotherapy. The aim of this study was to determine the effect of supplementation of omega-3 fatty acid and MCP in quality of life, chemotherapy side effects and inflammatory markers in colorectal cancer patients on chemotherapy.

Methods: A double-blind randomized study was carried out with 140 colorectal cancer patients on chemotherapy. Subjects were separated into two groups to receive either placebo or MCP [30 billion colony-forming unit (CFUs) per sachet] at a dose of two sachets daily for 4 weeks, and omega-3 fatty acid at a dose of 2 g daily for 8 weeks. Outcomes measured were quality of life, side effects of chemotherapy and levels of inflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and C-reactive protein.

Results: The supplementation with MCP and omega-3 fatty acid improved the overall quality of life and alleviated certain side effects of chemotherapy. The supplementation with MCP and omega-3 fatty acid also managed to reduce the level of IL-6 ($P = 0.002$). There was a significant rise in the placebo group's serum TNF-α ($P = 0.048$) and IL-6 ($P = 0.004$).

Conclusion: The combined supplementation with MCP and omega-3 fatty acid may improve quality of life, reduce certain inflammatory biomarkers and relieve certain side effects of chemotherapy in colorectal patients on chemotherapy.

KEYWORDS

colorectal cancer, inflammatory markers, omega-3 fatty acid, quality of life, strain-specific probiotic

1 | INTRODUCTION

Colorectal cancer is the third most common cancer in men and the second most common cancer in women.[1] Current trend shows growing incidences of colorectal cancer in developing countries with global forecasts showing around 10% increase of mortality rates from 2005 to 2012.[2] The main treatment modality for colon and rectum cancer is resection of the tumor together with its associated lymphatic drainage. In locally advanced tumor, mainly high-risk stage 2 and stage 3 tumors, adjuvant chemotherapy is a norm. However, in stage 4 tumors, the treatment option remains palliative that is the possibility of surgery coupled with chemotherapy.[3]

Quality of life (QOL) assessment takes into account the subjective perceptions of the patient in terms of physical, emotional, social, cognitive functions, disease symptoms and side effects of treatment.[4] Studies have reported that colorectal cancer patients suffer from various symptoms during and after their chemotherapy courses, which negatively affects their QOL.[5] The evolution of medical care for colorectal

cancer has centered on prolonged survival rates of patients.[6] In line for a more holistic view of colorectal cancer treatment, there is growing emphasis on the assessment of QOL parameters to better ascertain the impact of the disease as well as its standard treatment regimens.[6]

The chemotherapy drug, 5-fluorouracil (5-FU), is regularly prescribed to treat a wide variety of cancers, including colon, lung, head and neck cancers. Although 5-FU is effective at killing neoplastic cells, its administration causes the upregulation of certain proinflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP), resulting in severe side effects, of which intestinal and oral mucositis are the most common.[7] CRP is primarily synthesized by hepatocytes in response to inflammation, with high levels associated with malignancy and disease stages, indicating worse prognosis.[8] The overall loss of intestinal barrier function caused by intestinal mucositis can lead to clinical complications, such as infection and malnourishment; resulting in a range of symptoms such as, nausea, vomiting, dyspepsia, dysphagia and diarrhea.[9] In many cases, these side effects of chemotherapy can have such severe effects on the patient that the treatment must be ceased until the patient recovers. The prevalence of intestinal mucositis remains high and there are constant efforts to explore new treatment alternatives.

Commonly, bacterial strains, such as *Lactobacillus* and *Bifidobacterium*, are defined as therapeutic preparations of microorganisms, which at the appropriate dosage can modulate the defense mechanism in the human gut.[10] It can also be defined as components of microbial cells that have a beneficial effect on the health and well-being of the host.[11] The term "probiotic" was coined by Lillyand Stillwell ;[12] however, probiotic can be referred to as microbial cell preparation (MCP).

Studies have suggested that MCP and omega-3 fatty acids, especially eicosapentaenoic acid (EPA), may have numerous applications in anticancer treatments. Besides inhibiting the progression of various cancers, including colorectal cancer, omega-3 fatty acids are also responsible for several immune-modulatory effects.[13] The mechanisms of these benefits include enhancing gastrointestinal barrier function, alteration of the gut microbiota by inducing host cell antimicrobial peptides, releasing probiotic antimicrobial factors, challenging for epithelial adherence and immune modulation to the benefit of the host.[10,14] The anti-inflammatory effect of MCP administration has been investigated in a limited number of animal and human studies. Studies have shown that animals fed with *Lactobacillus casei* had improved clinical manifestations and reduced levels of proinflammatory cytokines.[15] Human studies have applied different strains of MCP, and a majority of them have reported functional improvement or subjective well-being in those receiving the treatment. One such study that investigated the effects of two strains of *Lactobacillus* in modulating the production of TNF-α revealed that the strains of *Lactobacillus* played a role in the control of TNF-α production in macrophages.[16] Eicosapentaenoic acid (EPA), an omega-3 fatty acid can suppress the production of arachidonic acid–derived eicosanoids and is also a substrate for the synthesis of an alternative family of eicosanoids, which have many anti-inflammatory effects.[17] EPA is also known to improve the QOL and improve the side effects of chemotherapy in cancer patients.[18]

According to certain studies, omega-3 fatty acids and MCP have synergistic effects whereby omega-3 fatty acids can potentiate the beneficial actions of MCP because of its anti-inflammatory and antibiotic-like actions. Omega-3 fatty acids exert growth inhibitory action against pathogenic bacteria and enhances the adherence potential of Lactobacilli to the mucosal surface of the gut, which aids the colonization of Lactobacilli in the gut.[19] Thus, adequate amounts of MCP and omega-3 fatty acids may help to restore normal and healthy gut microecology. Besides the administration of 5-FU, dietary intake and bowel microbiota can also influence the frequency and severity of chemotherapy-associated gastrointestinal adverse events (AEs). Studies have suggested that *Lactobacillus acidophilus*, *L*actobacillus *rhamnosus*, or a mixture of both strains may stop radiotherapy-induced diarrhea,[20] but to our knowledge, only a few controlled studies have evaluated MCP in the avoidance of chemotherapy-associated diarrhea. Nutritional therapy has been known to play a key role in improving the survival in cancer patients.

The aim of this study was to evaluate if the supplementation of MCP and omega-3 fatty acid helps to improve the QOL in colorectal cancer patients on chemotherapy, modulate the side effects of chemotherapy and alter the levels of inflammatory markers.

2 | MATERIALS AND METHODS

2.1 | Subjects

Sample size required for this study was calculated based on a previous study.[21] A minimum of 64 subjects per group was required to expect 80% power with a 5% significance level. We inflated this number by 10% to account for loss to follow up and nonrespondents. A total of 140 subjects, aged 18 and above, were recruited from the specialist clinic at University of Malaya Medical Centre, Malaysia. All subjects were on the XELOX chemotherapy regimen, which was a combination drug therapy of capecitabine and oxaliplatin. Subjects were administered with oxaliplatin 130 mg/m^2 as a 120-min intravenous infusion on day 1 and oral capecitabine 1000 mg/m^2 on days 1–14 every 3 weeks. The inclusion criteria were subjects who have been newly diagnosed with histologically or cytological confirmed colorectal cancer, subjects who have had surgery and have decided to completely receive chemotherapy and subjects who have sufficient organ and marrow function so that chemotherapy treatment can be administered. Subjects receiving other investigational agents, HIV-positive subjects receiving combination antiretroviral therapy, subjects on radiotherapy or chemotherapy prior to intervention were excluded. The study was explained to all recruited subjects and a written consent was obtained prior to enrolment.

2.2 | Study design

The study protocol was approved by the Institutional Review Board (IRB) of the University of Malaya Medical Centre (Reference No: 829.8) and registered with the Iranian Registry of Clinical Trials (Reference No: IRCT201106156814N1). Subjects were randomized into

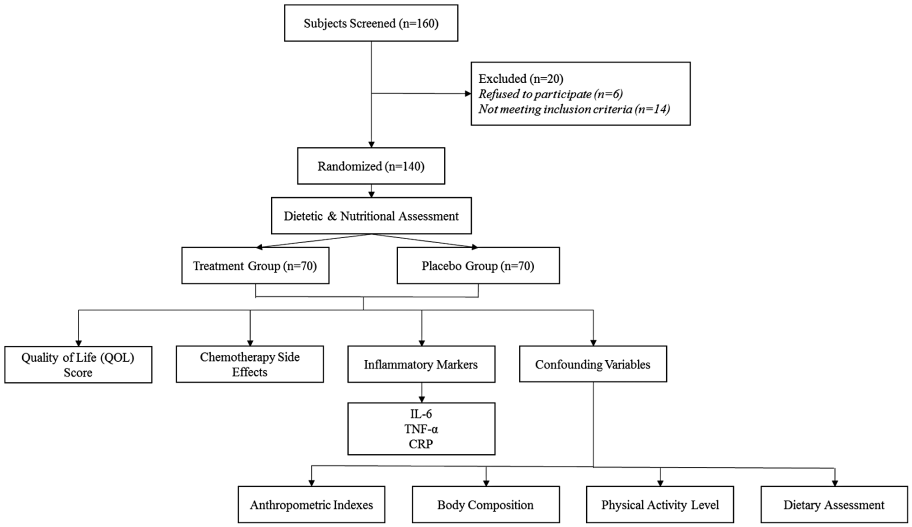

FIGURE 1 Consort diagram of subject recruitment and analysis

two groups: treatment (n = 70) and placebo (n = 70) groups. The treatment group received two sachets of MCP (Hexbio®, B-Crobes Laboratories Sdn. Bhd., Malaysia) (*L. acidophilus* BCMC® 12130, *L. casei* BCMC® 12313, *Lactobacillus lactis* BCMC® 12451, *Bifidobacterium bifidum* BCMC® 02290, *Bifidobacterium longum* BCMC® 02120 *and Bifidobacterium infantis* BCMC® 02129, 30 billion CFUs per sachet) daily for 4 weeks and omega-3 fatty acid (Nova Laboratories Sdn. Bhd., Malaysia) at a dose of 2 g daily for 8 weeks (each get had 700 mg of EPA and docosahexaenoic acid). Both the MCP and omega-3 fatty acid in the treatment group were administered orally. The placebo group received biologically inactive placebo preparations identical in appearance MCP and omega-3 fatty acid for 4 and 8 weeks, respectively; these placebo preparations were also administered orally. Blinding to treatment and placebo samples were carried out by an independent body; unblinding was only done upon the completion of data analysis. Evaluation parameters measured for both groups were: the QOL, side effects of chemotherapy and levels of inflammatory markers (CRP, IL-6 and TNF-α) (Figure 1). Readings were taken prior to the start of chemotherapy (baseline), postintervention (8 weeks from baseline) and after the completion of chemotherapy (6 months from baseline). Baseline characteristics of subjects are presented in Table 1.

2.3 | Confounding variables

Anthropometric indexes, functional status of muscle, dietary assessments, basal metabolic rate (BMR) and body composition were our confounding variables, which were measured during the trial to ensure that both groups of patients were equally matched.

2.4 | Dietary intake assessments

The dietary assessment was carried out by using a questionnaire. Information from dietary assessment assisted the nutritionist in giving appropriate dietary counseling in relation to the total nutritional requirement in colorectal cancer (CRC) condition. This dietary assessment offers information concerning the status of individual or groups of specific population, besides looking into food intake pattern, choice and habits. The 24-h recall method was used to calculate the total and the daily average intakes of protein, carbohydrate (CHO), fat and energy intake for 3 days (2 weekdays and 1 weekend) via face-to-face interview, which had been recorded.

2.5 | Evaluation of energy expenditure and activity

By using the proprietary algorithms (Intelligent Activity Classification™), an individual's free-living activity is classified into periods spent for sitting, standing and walking. This information can be used to estimate daily energy expenditure, while changes in the free-living activity profile can be tracked against medication or intervention regimes. MET or simply metabolic equivalent refers to the measure of the intensity of aerobic exercise. Specifically, it reflects the ratio of metabolic rate during a specific physical activity to a reference rate of metabolic rate at rest. As for this study, the device was placed on the patients' leg for 24 h. After that, the device was placed into an analyzer. The color green shows standing time, while yellow means sitting and lying time and red reflects stepping time.1

2.6 | Evaluation of quality of life and chemotherapy side effects

The QOL of patients was evaluated based on the European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire (EORTC QLQ) C30. The EORTC QLQ-C30 incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional and social); three symptom scales (fatigue, pain and nausea and vomiting) and a global health and QOL scale. The reports of side effects of chemotherapy were evaluated based on the Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

TABLE 1 Demographic data baseline in treatment and placebo groups

Variable	Treatment Group ($n = 70$)	Placebo Group ($n = 70$)	*P* Value
Age, *n* (%)			0.40
≤56	20 (30.8)	28 (42.4)	
57–66	22 (33.8)	19 (28.8)	
≥67	23 (35.4)	19 (28.8)	
Ethnic, *n* (%)			0.768
Malay	13 (19)	13 (19)	
Chinese	41 (59)	46 (66)	
Indian	15 (21)	10 (14)	
Others	1 (1)	1 (1)	
Religion, *n* (%)			0.878
Islam	15 (21)	12 (17)	
Buddhism	40 (57)	39 (56)	
Christian	6 (9)	10 (14)	
Hindu	7 (10)	7 (10)	
Others	2 (3)	2 (3)	
Education level, *n* (%)			0.052
N.A.	15 (21)	5 (7)	
Primary	15 (21)	15 (21)	
Secondary	26 (37)	39 (56)	
Tertiary	5 (7)	7 (10)	
Others	9 (13)	4 (6)	
Marital status, *n* (%)			0.370
Single	1 (1)	4 (6)	
Married	55 (79)	59 (84)	
Divorced	0 (0)	1 (1)	
Others	14 (20)	6 (9)	
Living with, *n* (%)			0.460
Alone	2 (3)	1 (1)	
Wife	8 (11)	3 (4)	
Wife and children	46 (66)	50 (71)	
Children	7 (10)	9 (13)	
Others	7 (10)	7 (10)	
Job, *n* (%)			0.180
Government	7 (10)	8 (11)	
Private	5 (7)	13 (19)	
Self-employed	1 (1)	2 (3)	
Retired	51 (73)	42 (60)	
Unspecified	6 (9)	5 (7)	
Family history, *n* (%)			0.586
Yes	26 (37)	30 (43)	
No	35 (50)	31 (44)	
Unspecified	9 (13)	9 (13)	
Smoking, *n* (%)			0.458
Yes	12 (17)	7 (10)	
No	52 (74)	47 (67)	
Unspecified	6 (9)	16 (23)	

(Continues)

TABLE 1 (Continued)

Variable	Treatment Group ($n = 70$)	Placebo Group ($n = 70$)	*P* Value
Alcohol, *n* (%)			0.991
Yes	5 (7)	6 (9)	
No	48 (69)	58 (83)	
Unspecified	17 (24)	6 (9)	
Chronic disease, *n* (%)			0.190
Diabetes	12 (17)	7 (10)	
Heart disease	20 (29)	14 (20)	
Arthritis	4 (6)	2 (3)	
Epilepsy	0 (0)	0 (0)	
Others	5 (7)	7 (10)	
None	29 (41)	40 (63)	
Cancer location, *n* (%)			0.141
Right ascending colon	6 (9)	3 (4)	
Left descending colon	5 (7)	3 (4)	
Left sigmoid colon	13 (19)	20 29)	
Rectum	17 (24)	9 (13)	
Transverse colon	4 6)	3 (4)	
Rectosigmoid	6 (9)	4 (6)	
Colon	4 (6)	13 (19)	
Duodenum	1 (1)	0 (0)	
Ileocecal	1 (1)	0 (0)	
Splenic flexure colon	0 (0)	2 (3)	
No record	13 (19)	13 (19)	
Type of surgery, *n* (%)			0.112
Radical	1 (1)	1 (1)	
Sigmoid colectomy	2 (3)	7 (10)	
Colectomy	5 (7)	7 (10)	
Right hemicolectomy	7 (10)	9 (13)	
Left hemicolectomy	3 (4)	4 (6)	
Hemicolectomy	4 (6)	11 (16)	
Pan-proctocolectomy and ileostomy	1 (1)	0 (0)	
Anterior resection	12 (17)	9 (13)	
High anterior resection	1 (1)	1 (1)	
Low anterior resection	10 (14)	3 (4)	
Ultralow anterior resection	5 (7)	0 (0)	
Abdominal perineal resection	2 (3)	1 (1)	
Colostomy	3 (4)	0 (0)	
Laparotomy	1 (1)	1 (1)	
Subtotal gastrectomy and omentomy	1 (1)	0 (0)	
Hartmann's procedure	3 (4)	2 (3)	
Omentectomy	0 (0)	1 (1)	
No surgery	3 (4)	1 (1)	
No data	6 (9)	12 (17)	

TABLE 2 Data of confounding variables in treatment and placebo groups

Variable	Treatment	Placebo	*P* Value[a]
Weight (kg), mean ± SD			
Baseline	54.24 ± 11.72	57.43 ± 10.91	0.106
Post intervention[b]	55.12 ± 11.88	58.08 ± 10.28	0.147
Post chemotherapy[c]	54.97 ± 12.21	58.08 ± 11.23	0.136
BMI (kg/m^2), mean ± SD			
Baseline	21.84 ± 4.12	22.98 ± 4.27	0.120
Post intervention[b]	22.04 ± 4.05	23.12 ± 5.11	0.234
Post chemotherapy[c]	22.51 ± 4.19	23.36 ± 4.67	0.426
Waist circumference (cm), mean ± SD			
Baseline	79.8 ± 11.61	81.85 ± 7.58	0.200
Post intervention[b]	79.62 ± 9.66	83.62 ± 9.90	0.051
Post chemotherapy[c]	82.27 ± 10.75	84.82 ± 10.69	0.340
Waist to hip ratio, mean ± SD			
Baseline	0.88 ± 0.10	1.07 ± 1.26	0.220
Post intervention[b]	0.86 ± 0.06	0.89 ± 0.06	0.100
Post chemotherapy[c]	0.87 ± 0.06	0.89 ± 0.05	0.294
Energy (calories), mean ± SD			
Baseline	1341.23 ± 360.69	1296.72 ± 307.94	0.472
Post intervention[b]	1336.70 ± 258.43	1489.43 ± 338.32	0.420
Post chemotherapy[c]	1343.54 ± 402.17	1392.24 ± 496.56	0.684
Protein (g), mean ± SD			
Baseline	65.44 ± 46.21	55.65 ± 16.35	0.130
Post intervention[b]	63.35 ± 23.90	64.93 ± 20.94	0.753
Post chemotherapy[c]	59.49 ± 19.41	57.15 ± 18.44	0.649
Carbohydrate (g), mean ± SD			
Baseline	188.27 ± 53.78	189.86 ± 54.061	0.872
Post intervention[b]	194.80 ± 56.27	217.04 ± 51.00	0.066
Post chemotherapy[c]	183.23 ±73.30	217.61 ± 106.09	0.153
Fat (g), mean ± SD			
Baseline	43.39 ± 24.15	34.47 ± 15.01	**0.019**
Post intervention[b]	40.858 ± 13.25	40.18 ± 13.91	0.822
Post chemotherapy[c]	39.14 ± 12.57	32.72 ± 10.36	**0.045**
BMR (kcal/day), mean ± SD			
Baseline	1156.08 ± 401.86	1264.46 ± 412.23	0.130
Post intervention[b]	1151.21 ± 555.28	1362.22 ± 498.80	0.057
Post chemotherapy[c]	1148.13 ± 430.23	1263.90 ± 438.14	0.276
Percentage of fat (%), mean ± SD			
Baseline	22.68 ± 7.54	22.06 ± 8.15	0.654
Post intervention[b]	22.55 ± 7.22	22.54 ± 8.44	0.995
Post chemotherapy[c]	23.64 ± 7.56	21.96 ± 8.49	0.385
Fat mass (kg), mean ± SD			
Baseline	12.58 ± 5.36	13.50 ± 6.73	0.394
Post intervention[b]	12.41 ± 4.93	13.41 ± 6.12	0.368
Post chemotherapy[c]	13.50 ± 5.26	12.56 ± 6.22	0.499
Lean body mass (kg), mean ± SD			
Baseline	41.86 ± 9.13	45.02 ± 9.01	0.053
Post intervention[b]	41.96 ± 9.49	45.05 ± 8.87	0.104

(Continues)

TABLE 2 (Continued)

Variable	Treatment	Placebo	*P* Value[a]
Post chemotherapy[c]	43.27 ± 10.75	43.39 ± 8.36	0.959
Sitting/lying (% of time/day), mean ± SD			
Baseline	87.59 ± 7.93	86.70 ± 8.08	0.596
Post intervention[b]	85.48 ± 6.92	86.08 ± 10.29	0.798
Post chemotherapy[c]	85.05 ± 8.36	85.57 ± 7.98	0.859
Standing (% of time/day), mean ± SD			
Baseline	6.94 ± 4.73	7.42 ± 6.25	0.677
Post intervention[b]	8.40 ± 5.03	8.04 ± 9.70	0.863
Post chemotherapy[c]	7.57 ± 6.42	6.42 ± 4.46	0.570
Stepping (% of time/day), mean ± SD			
Baseline	6.93 ± 6.16	6.40 ± 5.59	0.693
Post intervention[b]	6.41 ± 4.99	7.00 ± 4.77	0.677
Post chemotherapy[c]	7.83 ± 4.99	8.69 ± 5.66	0.658
Number of steps (steps/day), mean ± SD			
Baseline	7538.81 ± 7987.22	7310.82 ± 7441.11	0.890
Post intervention[b]	8040.97 ± 6742.00	8232.00 ± 6795.00	0.918
Post chemotherapy[c]	7668.90 ± 6605.36	10 547.00 ± 9524.00	0.684
Energy expenditure (%), mean ± SD			
Baseline	32.90 ± 3.04	32.86 ± 3.73	0.952
Post intervention[b]	33.39 ± 2.64	33.48 ± 2.59	0.904
Post chemotherapy[c]	33.97 ± 2.60	33.08 ± 4.92	0.505

[a]Significant *P* value <0.05 in bold.
[b]Reading taken at the end of intervention, 8 weeks from baseline.
[c]Reading taken at the end of chemotherapy, 6 month from baseline.

2.7 | Evaluation of inflammatory markers

Measurement of CRP aids in evaluation of stress, trauma, infection, inflammation and surgery. The IMMAGE CRP test measures the rate of increase in light scattered from particles suspended in solution as a result of complexes formed during an antigen–antibody reaction. Blood samples (10 mL whole blood) were collected in BD Vacutainer SST tubes. Approximately 30 min after blood collection, serum was separated by centrifugation at 1000 × *g* and aliquoted into cryovials for storage at −80°C before analysis. The serum samples were assayed using the IL-6/TNF-α enzyme-linked immunosorbent assay (ELISA) kit (CUSABIO, Hubei, China), according to the manufacturer's guideline. Briefly, 100 μL of standards and serum samples were added and incubated for 2 h at 37°C in microtiter plates coated with IL-6/TNF-α antibody. The plates were washed to remove unbound IL-6/ TNF-α protein, before the detection antibody and substrate solution were added. Approximately 15 min was allowed for color to develop. The colorimetric density of each well was measured at 450 nm using a microplate reader when standard dilutions were set as 1000, 500, 250, 125, 62.5, 31.3, 15.6 and 0 pg/mL. The standard curve was prepared and the values of the samples were calculated. Quantitative comparisons were then made from the triplicate analyses of each patient or control.

2.8 | Statistical analysis

The statistical analysis was performed using SPSS version 17. The results for quantitative data were expressed as means ± standard deviation (SD). For normal quantitative data between group comparisons, we used independent sample *t*-test and for within group comparison, we used repeated measures analysis of variance with post hoc test. For a nonnormal quantitative between groups and within groups' comparison, Mann-Whitney U-test was used. P values 0.05 were considered as statistically significant.

3 | RESULTS

3.1 | Baseline

The baseline characteristics of subjects in both the treatment and placebo groups are shown in Table 1. There were no significant differences between the two groups in terms of gender, ethnic religion, education level, marital status, job and chronic disease. Furthermore, other comorbidities such as alcohol consumption and smoking were comparable between the two groups. This illustrates that both groups were homogenous at baseline.

TABLE 3 Quality of life (QOL) parameters in treatment and placebo groups

	Treatment Group	Placebo Group	*P* Value[a]
Global Health Status			
Baseline	53.70 ± 2.10	60.70 ± 1.50	0.058
Post intervention[b]	68.70 ± 1.90	51.60 ± 2.20	**<0.001**
Post chemotherapy[c]	72.50 ± 2.17	44.80 ± 3.10	**<0.001**
Functional scales			
Physical function, mean ± SD			
Baseline	8.40 ± 1.80	3.02 ± 1.20	0.682
Post intervention[b]	2.70 ± 0.90	12.10 ± 1.80	**<0.001**
Post chemotherapy[c]	2.20 ± 1.10	19.10 ± 4.00	**<0.001**
Role functioning, mean ± SD			
Baseline	9.30 ± 2.30	7.50 ± 2.30	0.589
Post intervention[b]	1.80 ± 0.90	7.80 ± 1.70	**0.002**
Post chemotherapy[b]	1.10 ± 0.60	13.90 ± 4.10	**<0.001**
Emotional functioning, mean ± SD			
Baseline	18.30 ± 2.7	8.30 ± 1.90	0.064
Post intervention[b]	2.40 ± 0.90	7.60 ± 2.20	**0.032**
Post chemotherapy[c]	2.40 ± 1.20	14.30 ± 3.40	**0.001**
Cognitive functioning, mean ± SD			
Baseline	6.30 ± 1.40	3.60 ± 1.50	0.194
Post intervention[b]	1.30 ± 0.70	3.80 ± 1.50	0.123
Post chemotherapy[c]	1.50 ± 7.00	7.80 ± 2.80	**0.025**
Social functioning, mean ± SD			
Baseline	3.50 ± 1.10	4.70 ± 1.70	0.566
Post intervention[b]	1.80 ± 0.70	2.90 ± 1.40	0.472
Post chemotherapy[c]	1.00 ± 0.00	1.20 ± 0.50	0.206
Symptom scales based on evaluation			
Fatigue, mean ± SD			
Baseline	23.70 ± 2.80	14.23 ± 2.90	0.511
Post intervention[b]	11.97 ± 1.80	31.10 ± 3.00	**<0.001**
Post chemotherapy[c]	10.30 ± 1.90	35.40 ± 4.30	**<0.001**
Nausea and vomiting, mean ± SD			
Baseline	3.00 ± 1.56	4.10 ± 1.50	0.605
Post intervention[b]	0.50 ± 0.30	6.10 ± 1.90	**0.003**
Post chemotherapy[c]	1.10 ± 0.60	6.90 ± 3.00	**0.032**
Pain, mean ± SD			
Baseline	9.10 ± 1.50	6.70 ± 2.30	0.402
Post intervention[b]	4.10 ± 1.70	7.10 ± 1.90	0.265
Post chemotherapy[c]	4.90 ± 2.10	13.50 ± 3.80	**0.040**
Dyspnea, mean ± SD			
Baseline	3.00 ± 1.30	2.10 ± 1.20	0.615
Post intervention[b]	0.50 ± 0.50	0.60 ± 0.60	0.904
Post chemotherapy[c]	0.00 ± 0.00	1.00 ± 1.00	0.236
Insomnia, mean ± SD			
Baseline	16.10 ± 2.80	10.40 ± 2.70	0.148
Post intervention[b]	5.70 ± 2.00	10.50 ± 3.00	0.183
Post chemotherapy[c]	3.00 ± 1.80	11.80 ± 4.20	0.064
Appetite loss, mean ± SD			
Baseline	10.10 ± 2.20	9.50 ± 2.90	0.877

(Continues)

TABLE 3 (Continued)

	Treatment Group	Placebo Group	*P* Value[a]
Post intervention[b]	4.70 ± 1.60	16.30 ± 3.40	**0.002**
Post chemotherapy[c]	4.50 ± 1.70	18.20 ± 5.00	**0.005**
Constipation, mean ± SD			
Baseline	7.50 ± 1.80	3.60 ± 1.60	0.122
Post intervention[b]	4.10 ± 1.30	3.00 ± 1.50	0.587
Post chemotherapy[c]	4.50 ± 2.00	5.30 ± 3.10	0.817
Diarrhea, mean ± SD			
Baseline	7.20 ± 2.10	2.60 ± 1.10	0.061
Post intervention[b]	3.60 ± 1.30	23.80 ± 3.50	**<0.001**
Post chemotherapy[c]	2.20 ± 1.20	20.80 ± 4.10	**<0.001**
Financial difficulties, mean ± SD			
Baseline	28.80 ± 6.80	10.40 ± 2.80	0.717
Post intervention[b]	9.90 ± 3.60	8.90 ± 2.80	0.838
Post chemotherapy[c]	6.80 ± 4.10	6.20 ± 2.70	0.917

[a]Significant *P* value <0.05 in bold.
[b]Reading taken at the end of intervention, 8 weeks from baseline.
[c]Reading taken at the end of chemotherapy, 6 month from baseline.

3.2 | Confounding variables

There was no significant difference between confounding variables including anthropometric indexes, functional status of muscle, dietary assessments, BMR and body composition (Table 2). There was no significant difference between confounding variables including anthropometric indexes, functional status of muscle, dietary assessments, BMR and body composition.

3.3 | Quality of life and chemotherapy side effects

The global health status of patients increased in the treatment group and decreased in the placebo group, indicating higher QOL in the treatment group in comparison to the placebo group (Table 3). Functional scales and symptom scales of QOL also improved in the treatment group in comparison to the placebo group as shown in Table 3. Overall patients receiving MCP and omega-3 fatty acid supplementations exhibited improved QOL. Based on Table 4, chemotherapy side effects such as nausea, vomiting and diarrhea significantly improved in the treatment group.

3.4 | Inflammatory markers

The administration of MCP and omega-3 fatty acid reduced the level of IL-6 and increased in placebo group. IL-6 level in between group after intervention was significantly different (0.002), but did not affect TNF-α and CRP level in the treatment group as compared to the placebo group. Within group, we had a significantly rise in IL-6 ($P = 0.004$) and TNF-α (0.048) level in placebo groups (Table 4).

4 | DISCUSSION

4.1 | Effect of microbial cell preparation and omega-3 fatty acid on quality of life

The results from this study support that the combined administration of MCP and omega-3 fatty acid improve the QOL and simultaneously modulates the inflammatory markers of cancer patients undergoing chemotherapy. This finding is in line with previous studies that suggest the synergistic effect of probiotics with omega-3 fatty acid in comparison to only probiotics.[22] Supplementation with MCP has been reported to significantly improve the functional outcomes and QOL parameters in postoperative colorectal cancer patients.[23] Studies have also reported that supplements of omega-3 fatty acids in patients with advanced cancer lead to the improvement of clinical, biological and QOL parameters.[24] In this study, the combined supplementation with MCP and omega-3 fatty acid resulted in improvement in QOL parameters in the treatment group, while the QOL parameters in the placebo group showed deterioration. For this reason, in the future insights on the effects of MCP and omega-3 fatty acid supplementation on the nutritional status of cancer patients undergoing chemotherapy, a study with a larger subject group should be conducted to oversee the various aspects and roles that a nutritionist may have on improving the nutritional statuses of these patients.

4.2 | Effect of microbial cell preparation and omega-3 fatty acid on side effects of chemotherapy

Side effects of chemotherapy are not uncommon among cancer patients. Chemotherapy-related diarrhea is a common adverse effect

TABLE 4 Comparison of chemotherapy side effects and inflammatory markers in treatment and placebo groups

Variable	Treatment Group	Placebo Group	*P* Value[a]
Chemotherapy side effects			
Alopecia, mean ± SD			
1 month after intervention	0.4 ± 0.7	0.3 ± 0.7	0.190
Post intervention[b]	0.4 ± 0.6	0.5 ± 0.8	0.675
Post chemotherapy[c]	0.4 ± 0.8	0.7 ± 0.9	0.204
Numbness, mean ± SD			
1 month after intervention	0.3 ± 0.5	0.7 ± 0.8	**0.010**
Post intervention[b]	0.4 ± 0.5	0.8 ± 1.0	0.066
Post chemotherapy[c]	0.5 ± 0.7	1.1 ± 1.1	**0.013**
Fatigue, mean ± SD			
1 month after intervention	0.2 ± 0.5	0.8 ± 1.2	**0.006**
Post intervention[b]	0.3 ± 0.5	1.1 ± 1.2	**<0.001**
Post chemotherapy[c]	0.2 ± 0.5	0.8 ± 1.0	**<0.001**
Nausea, mean ± SD			
1 month after intervention	0.2 ± 0.4	0.4 ± 0.7	**0.047**
Post intervention[b]	0.0 ± 0.2	0.3 ± 0.7	**0.015**
Post chemotherapy[c]	0.0 ± 0.2	0.2 ± 0.5	0.067
Vomiting, mean ± SD			
1 month after intervention	0.1 ± 0.4	0.4 ± 0.8	**0.014**
Post intervention[b]	0.0 ± 0.2	0.2 ± 0.6	**0.018**
Post chemotherapy[c]	0.0 ± 0.1	0.1 ± 0.4	0.206
Diarrhea, mean ± SD			
1 month after intervention	0.3 ± 0.5	1.0 ± 1.0	**<0.001**
Post intervention[b]	0.1 ± 0.4	0.8 ± 1.1	**<0.001**
Post chemotherapy[c]	0.1 ± 0.3	0.8 ± 1.1	**<0.001**
Hearing Impaired, mean ± SD			
1 month after intervention	0.0 ± 0.1	0.1 ± 0.3	0.073
Post intervention[b]	0.0 ± 0.1	0.1 ± 0.5	0.457
Post chemotherapy[c]	0.0 ± 0.1	0.0 ± 0.0	0.483
Constipation, mean ± SD			
1 month after intervention	0.1 ± 0.3	0.1 ± 0.4	0.595
Post intervention[b]	0.1 ± 0.3	0.1 ± 0.5	0.066
Post chemotherapy[c]	0.1 ± 0.3	0.1 ± 0.5	0.407
Dry mouth, mean ± SD			
1 month after intervention	0.3 ± 0.5	0.9 ± 0.9	**<0.001**
Post intervention[b]	0.3 ± 0.6	1.0 ± 1.0	**<0.001**
Post chemotherapy[c]	0.3 ± 0.5	1.1 ± 1.1	**<0.001**
Gastritis, mean ± SD			
1 month after intervention	0.1 ± 0.2	0.1 ± 0.5	0.589
Post intervention[b]	0.1 ± 0.3	0.1 ± 0.3	0.372
Post chemotherapy[c]	0.0 ± 0.0	0.2 ± 0.5	**0.013**
Heartburn, mean ± SD			
1 month after intervention	0.0 ± 0.2	0.2 ± 0.6	0.128
Post intervention[b]	0.0 ± 0.2	0.2 ± 0.6	0.296
Post chemotherapy[c]	0.0 ± 0.1	0.2 ± 0.7	**0.021**
Stomatitis, mean ± SD			
1 month after intervention	0.1 ± 0.3	0.2 ± 0.4	0.481

(Continues)

TABLE 4 (Continued)

Variable	Treatment Group	Placebo Group	*P* Value[a]
Post intervention[b]	0.1 ± 0.3	0.2 ± 0.6	0.119
Post chemotherapy[c]	0.1 ± 0.3	0.4 ± 0.9	**0.019**
Salivary gland changes, mean ± SD			
1 month after intervention	0.0 ± 0.1	0.1 ± 0.4	0.076
Post intervention[b]	0.0 ± 0.0	0.0 ± 0.1	0.274
Post chemotherapy[c]	0.0 ± 0.0	0.3 ± 0.6	**0.001**
Taste alteration, mean ± SD			
1 month after intervention	0.4 ± 0.5	0.9 ± 1.0	**0.005**
Post intervention[b]	0.4 ± 0.6	1.1 ± 1.1	**<0.001**
Post chemotherapy[c]	0.4 ± 0.7	1.3 ± 1.2	**<0.001**
Inflammatory side effects			
IL-6 (pg/mL), mean (normal range)			
Baseline	5.70 (2.25–9.40)	3.88 (1.70–8.70)	0.344
Post intervention[b]	3.50 (2.00–7.25)	7.75 (3.60–15.00)	**0.002**
Post chemotherapy[c]	4.50 (2.25–12.00)	3.40 (1.50–9.25)	0.313
TNF-α (pg/mL), mean (normal range)			
Baseline	2.40 (1.27–4.88)	3.29 (1.33–6.88)	0.275
Post intervention[b]	3.43 (2.06–5.25)	3.39 (1.43–9.54)	0.534
Post chemotherapy[c]	2.25 (0.83–4.80)	4.13 (1.13–11.13)	0.119
CRP (mg/dL), mean (normal range)			
Baseline	0.34 (0.18–1.02)	0.28 (0.17–0.88)	0.536
Post intervention[b]	0.45 (0.18–0.84)	0.24 (0.17–0.58)	0.497
Post chemotherapy[c]	0.40 (0.22–0.99)	0.30 (0.20–0.54)	0.234

[a]Significant *P* value <0.05 in bold.
[b]Reading taken at the end of intervention, 8 weeks from baseline.
[c]Reading taken at the end of chemotherapy, 6 month from baseline.

in the treatment of colorectal cancer, as the administration of 5-FU, capecitabine and irinotecan commonly result in diarrhea.[23] Severe diarrhea may lead to nutritional and metabolic imbalances. Studies have reported on the potential of MCP to reduce radiation therapy-related diarrhea.[20] Studies have shown that the administration of *Lactobacillus* in cancer patients on chemotherapy was able to reduce the frequency of diarrhea, thereby improving food intake and maintaining body weight.[23] The findings of this study are very much in line with that of previous studies, whereby results obtained also show that the chemotherapy side effects alleviated were mainly that related to the gastrointestinal tract function such as diarrhea, nausea and vomiting (Table 4). However, no studies have been done to investigate the synergistic effect of MCP and omega-3 fatty acid in alleviating the adverse effects of chemotherapy. The mode of action on how MCP reduces chemotherapy side effects is not fully understood. However, it is believed that bowel colonization with pathogenic bacteria is the main causal factor of infections in cancer patients undergoing chemotherapy. Certain theories suggest that MCP may be involved in cytoprotective processes, such as the induction of heat-shock protein expression in intestinal epithelial cells[25] and prevention of cytokine-induced epithelial cell damage,[26] thereby restoring the integrity of the intestinal cells. The previous claim that supplementing the diet with omega-3 fatty acids defends against chemotherapy-induced intestinal damage[27] is held by evidence of this result. Long-chain polyunsaturated fatty acids (LCPUFAs) have also been known to enhance the adhesion of MCP to the gut mucosal cells, thus augmenting the effect of MCP. This direct interaction between MCP and the lymphoid tissue in the gut is essential in enhancing the development of gut-associated lymphoid tissue and exhibit antibiotic-like actions.[19] A limitation in this study was that the incidence of chemotherapy side effects was only taken 1 month after the initiation of chemotherapy and supplementation with treatment and placebo samples. In the future, other studies should take into account the baseline record of chemotherapy side effects for better comparison.

4.3 | Effect of microbial cell preparation and omega-3 fatty acid on inflammatory markers

Individual studies on both MCP and omega-3 fish oil have reported on their immune-modulatory potential. Studies have shown that MCP possesses the ability to modulate the immune system, thus being able to benefit those with either an immune deficiency or an oversensitive immune system.[14] A study by de LeBlanc et al.[28] reported that mice models administered with the bacterium *L. casei* DN-114001 had a significant increase in TNF-α producing cells in the large intestine and higher levels of the anti-inflammatory cytokine IL-10. The results of

this study further consolidate the fact that MCP has the potential to modulate the immune system, and since IL-10 is an anti-inflammatory cytokine, MCP may also help to stimulate anti-inflammatory processes. Probiotic bacteria may counteract the inflammatory process by stabilizing the gut microbial environment and the intestine's permeability barrier, and by enhancing the degradation of enteral antigens and altering their immunogenicity. Another reason for the gut stabilizing effect could be improvement of the intestine's immunological barrier, particularly intestinal IgA responses. Probiotic effects may also be mediated via control of the balance between pro- and anti-inflammatory cytokines. Modification of intestinal flora to increase the predominance of specific nonpathogenic bacteria and thereby to alter the intestinal milieu may thus be taken as an alternative to attain prophylactic or therapeutic effects in intestinal infections and inflammatory conditions.[29]

It has been demonstrated that omega-3 fatty acids significantly lowered levels of CRP and IL-6 in overweight subjects.[30] This is indicative of the anti-inflammatory potential of omega-3 fatty acid. In our study, the levels of the proinflammatory cytokine IL-6 was reduced after intervention in the treatment group in comparison with the placebo group. Levels of TNF-α were unchanged in the treatment group during the study, whereas there was a significant rise in serum TNF-α and IL-6 in the placebo group. These results suggest that patients in the treatment group had decreased inflammatory rates, while patients in the placebo group had an increase of inflammatory rates.

In this study, we extrapolate that MCP serves as means to restore the integrity of intestinal cells, while omega-3 fatty acid ensures the preservation of the intestinal cells postrestoration. Future studies should evaluate the separate effects of MCP and omega-3 fatty acid in comparison to its synergistic effects. Further studies should also focus on eliciting the exact mechanism of synergism between MCP and omega-3 fatty acid.

A significant limitation of the current study is that no evaluation of the changes posed by MCP and omega-3 fatty acid to intestinal bacterial flora. Hence, more studies should be done to focus on fecal analysis to further elucidate in the changes in intestinal bacterial flora caused by the administration of MCP and omega-3 fatty acid.

5 | CONCLUSIONS

In this study, the combined supplementation of MCP and omega-3 fatty acid improved the QOL, reduced the levels of IL-6 and improved side effects of chemotherapy in colorectal cancer patients. This combined supplementation could thereby be further investigated, in turn, may be adapted as an adjuvant in colorectal cancer patients on chemotherapy.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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