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Potential and toxicity effects of fish omega-3 fatty acid as a chemopreventive agent in colorectal cancer: A scoping review

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Literature Review

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ABSTRACT

Colorectal cancer (CRC), a malignancy that affects the colon and rectum, is influenced by gene mutations, epigenetic changes, local inflammation, and lifestyle risk factors. New cases of CRC globally account for 10%, with mortality at 9.4%, while Indonesia occupies the top four incidence and mortality cases. A family history of CRC requires preventive measures, including consuming functional foods to maintain the colon microenvironment. This article aims to review the potency and toxicity effects of omega-3 fish fatty acids as a chemopreventive agent against CRC. The data sources were original articles about omega-3 fish fatty acids as CRC chemopreventive agents, published in 2012-2022 and in English or Indonesian. Databases used are Ovid, ScienceDirect, ProQuest, PubMed, Springer Link, EBSCO, and Google Scholar using Boolean search. The selection of studies followed the PRISMA-ScR method. Of the nine articles selected, fish omega-3 fatty acids had the potential as a chemopreventive agent against CRC, with several variations in daily dose ranges accompanied by a good lifestyle. Oral omega-3 fish supplementation gave benefits in the range of 96 mg–2,000 mg of eicosapentaenoic acid (EPA) and between 360 mg–1,000 mg of docosahexaenoic acid (DHA), with a daily intake varying between 0–14 grams/day. One study reported a toxic effect of fish omega-3 fatty acids, which raised the risk of post-operative infection after parenteral (intravenous) administration. There are no reported side effects across eight studies following oral preparation administration. The omega-3 fish fatty acid shows potential as a chemopreventive therapy for CRC; further studies are required to explore the parenteral administration-associated toxic effects.

INTRODUCTION

Colorectal cancer affects the tissues of the large intestine (colon) and rectum (lower part of the intestine to the anus). Like other types of cancers, CRC has its specific behaviors, such as keeping cell proliferation signals going, avoiding growth suppressive factors, activating cell invasion and metastasis, activating long-term gene replication, inducing angiogenesis, and fighting cell death (apoptosis) to form a tumor microenvironment.[1] The tumorogenic microenvironment consists of cancer stem-like cells (CSC) and mesenchymal stem cells (MSC) with high-level expression of vascular endothelial growth factor (VEGF) stimulated by tumor necrosis factor-α (TNF-α).[2] It can then recruit endothelial cells by making CXCL1 and CXCL2 and secreting interleukin-6 (IL-6), endothelin-1 (ET-1), IL-1β to increase angiogenesis, tumor development, and modulate oncogenic genes.[2,3] Pathways deregulated in colorectal cancer include the WnT-β-catenin signaling pathway, the growth factor signaling pathway, the epidermal growth factor receptor/mitogen-activated protein kinase (EGFR-MAPK)

pathway, and the phosphatidylinositol 3-kinase (PI3K) pathway.[2,4,5]

According to the Global Burden Cancer (GLOBOCAN) 2020, CRC cases are approximately 10% of the total estimated world cases and contribute to a 9.4% mortality rate.[6,7] In Indonesia, CRC ranks third in terms of case incidence and fourth in cancer mortality.[6]

A family history of CRC is one of the risk factors, so early diagnosis is necessary.[8] Aside from genetic factors, more than 30% of cancer deaths are contributed by some behavioral and dietary risk factors, including high body mass index, lack of consumption of vegetables and fruit, lack of physical activity, consumption of cigarettes, ways of consuming food, and excessive alcohol consumption. Thus, it is necessary to carry out preventive measures in cases of CRC by maintaining a healthy lifestyle, one of which is consuming healthy and nutritious foods.[2,8]

The optimal functioning of the immune system holds significant importance in maintaining overall health, playing a crucial role in preventing and eliminating infections, as well as overseeing immunosurveillance against tumor cells. Nutrition emerges as a pivotal factor in modulating the function of the immune system, acting both systemically and locally actions within the tumor microenvironment. This regulatory role extends to influencing cell metabolic pathways and shaping intestinal microbiota composition. The gut microbiota, in turn, has a crucial role in the immune system's ability to detect and respond to cancer and its treatment. Dietary regulation is essential in influencing the microbiota, making it a viable strategy to enhance the immune response against cancer.[9] Various components in the daily diet contribute to maintaining or improving immune system function. These include inhibiting pro-inflammatory mediators, augmenting anti-inflammatory function, modulating cell-mediated immunity, influencing the function of antigen-presenting cells (APCs), and facilitating communication between the natural and adaptive immune system.[10] The intricate interplay between nutrition, immune system function, and microbiota highlights the multifaceted role of dietary choices on promoting overall health and strengthening the body's ability to fight against infections and cancer.

The interplay between nutrition and the immune system plays a crucial role in modulating various inflammatory conditions, including cancer, highlighting the critical importance of dietary components. Micronutrients such as zinc, vitamins D and E, along with macronutrients like fatty acids, including omega-3 polyunsaturated fatty acids (PUFAs). Omega-3 PUFAs, which consist of DHA, EPA, alpha-linolenic acid (ALA), and docosapentaenoic acid (DPA), are particularly beneficial for health. Previous research on humans or animals demonstrates the therapeutic potential of vitamin D and omega-3 PUFAs in managing chronic inflammatory conditions, as well as the efficacy of omega-3 PUFAs in combating autoimmune disorders. Furthermore, vitamins D and E, zinc, and probiotics collectively play a crucial role in enhancing the body's defense against infection.[10] These fatty acids influence the structure and function of cell membranes, maintain intestinal microbiota, and modulate the immune system in the gastrointestinal tract.[11] Moreover, beyond their preventive effects against CRC, dietary habits involving fish consumption habits align with the potential of Indonesia's marine resources and support the government's program, known as *Gerakan Memasyarakatkan Makan Ikan (GEMARIKAN)* or Movement to Popularize Fish Consumption. [8,12]

Regarding therapeutic approaches for CRC, disrupting the interactions between tumor cells and their microenvironment has significant potential for chemoprevention strategies.[3] However, the outcomes of existing studies exploring the impact of the microenvironment on CRC pathogenesis have yielded inconsistent results. A review by Caini et al. noted that while some preclinical studies showed a protective effect with a reduced CRC risk, the data were inconsistent.[8] Moreover, cohort studies by Aglago et al. and Shin et al. provide additional insights. Aglago et al. indicated that fish consumption rich in omega-3 fatty acids reduced the risk of CRC12 while Shin et al. suggested a modest relationship between omega-3 PUFAs and CRC prevention.[13] Therefore, this scoping review aims to explore and compile evidence to provide information regarding the potential and toxic effects of fish omega-3 fatty acids as a chemopreventive agent in CRC, serving as a basis for further chemopreventive research.

METHODS

This study employed the scoping review method utilizing literature search strategies across 14 databases, including Ovid, ScienceDirect, ProQuest, PubMed, Springer Link, EBSCO, and Google Scholar, all accessible through Universitas Islam Indonesia. The Boolean search technique, incorporating keywords with AND, OR, and NOT was applied. The research literature search method used Population, Concept, and Context criteria (PCC criteria), focusing on individuals with a history and risk of CRC (population), exploring the potential and toxic effects of fish omega-3 fatty acids (concept) within all health and community research facilities (context).

Advanced search techniques were employed, combining keywords such as "omega 3", "colorectal cancer", and "chemoprevention". Variations like "omega-3 fatty acid", "polyunsaturated fatty acid", "omega-3 fish consumption", and "fatty acid fish" were used, along with alternative keywords for "colorectal cancer" such as "colorectal adenoma", "colorectal carcinoma", "colorectal tumor", "colorectal benign", "colorectal malign", and "colorectal metastasis". To broaden the search, terms like "chemopreventive", "prevention", "preventive", and "against" were used in place of "chemoprevention".

The inclusion criteria encompassed original research articles with randomized controlled trial designs and non-randomized control trials such as cohorts and case reports published between 2012 - 2022, in English or Indonesian. The exclusion criteria involved articles not meeting the PCC criteria, lack of full-text availability, redundancy across databases, and unclear research methodology. Following the article screening process, selected articles were entered into the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) diagram (Figure 1).[14] The final selected journals were categorized in a data extraction table based on research title, researcher's name, year of publication, location, study design, the number and type of participants, method of administration, dose, and frequency of administration, duration of administration, and results of the study. This comprehensive approach ensured a thorough exploration of the literature on omega-3 fatty acids and CRC prevention, providing valuable insights for future research and clinical applications.

RESULTS

The identification process across the 14 databases yielded a substantial pool of 898 articles that were selected based on predefined keywords and filter adjustments. Following a thorough analysis, 168 articles were duplicates, resulting in a refined pool of 730 articles. The application of rigorous inclusion and exclusion criteria further narrowed down the selection, with 141 articles deemed non-original or not classified as research articles. Additionally, 16 articles lacked full-text free access, 295 articles did not specifically involve subjects with CRC, 207 articles were not associated with omega-3 fish, 21 articles were not in English or Indonesian language, and one article was published before 2012, leaving the remaining 49 articles left. The rigorous screening process continued by scrutinizing the full-text content and excluding nine articles, leaving 40 articles for detailed analysis. Among these, 14 articles focused on subjects without a history and risk of CRC, 15 articles were not specifically relevant to omega-3 fish and CRC risks, three articles did not comprehensively explain the results of the study, seven articles reposted the use of a combination of omega-3 with other drugs, and one article involved subjects with CRC metastases. The final process synthesized and extracted nine articles for the subsequent analysis, as illustrated in Figure 1.

Upon analyzing the nine selected articles, it is evident that there were variations in the method of drug administration, dosage, frequency, and duration of administration; all of which yielded diverse effects, as delineated in Table 1. Moreover, variations were observed in the characteristics of individuals' medical history and the risk of colorectal cancer, as well as its association with several factors such as genetic variations, age range, lifestyle, and nutrition.

DISCUSSIONS

Among the nine scrutinized, seven articles showed fish omega-3 fatty acids as potential chemopreventive agents in CRC. In contrast, one article asserted no significant relationship between fish omega-3 fatty acids and CRC prevention. Another article, however, showed the toxicity

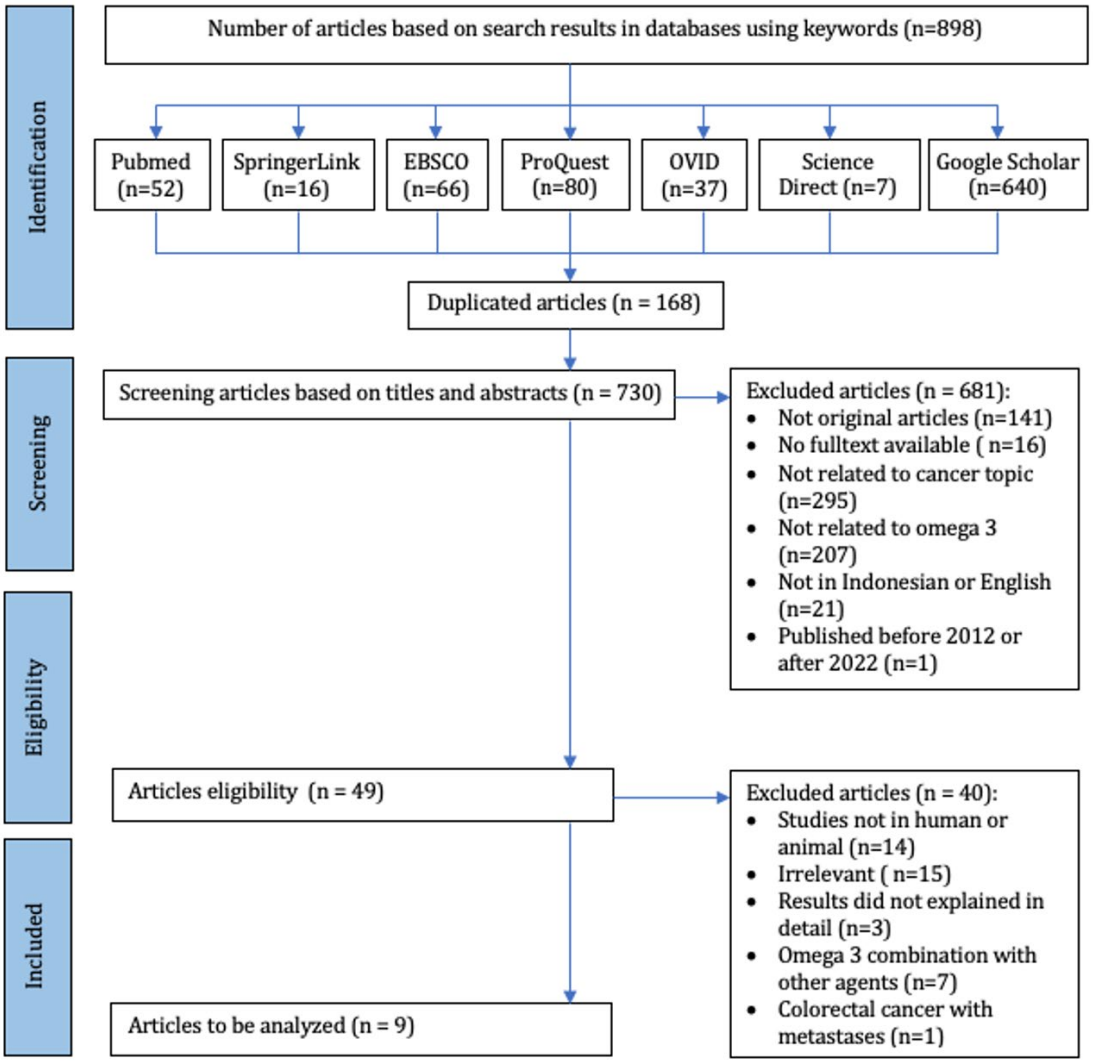

Figure 1. The selection process of articles

effects of these fatty acids, specifically noting an increase in infectious complications among patients with a history of CRC after surgery.

The analysis of the articles revealed a notable diversity that extended well beyond their concluding remarks. This includes variations in the method, dosage, frequency, and duration of fish omega-3 fatty acid administration. Methodologically, the administration of fish omega-3 fatty acids took on multiple forms across the articles, including parenteral or intravenous dosage forms, oral supplementation, and oral diet. The dosage of parenteral or intravenous omega-3 fish is 2 mL/kgBW. For oral supplementation, the range is 96 mg to 2 grams of EPA and 360 mg to 1 gram of DHA, resulting in a daily intake of omega-3 fish up to 2.5 grams. In the case of oral diet, the daily intake varies in the range of 0 to 1.4 grams per day. The frequency of administering omega-3 fish via parenteral or intravenous routes was 4 hours pre-surgery (18.00–22.00) and post-surgery (08.00–12.00). For oral supplementation, it was recommended 2–3 times/day, and for oral diet, the calculation was based on the usual daily intake. The duration of administering fish omega-3 fatty acids across the three dosage forms ranged from 3 months to 6.9 years.[12,15–22]

The characteristics of the subjects in the selected articles encompassed a diverse range of criteria. This included patients undergoing procedures such as colonoscopy or laparoscopy, those with a history of one or more adenomas, polyps, or CRC, patients possessing the rs174535 single-nucleotide polymorphism (SNP) and fatty acid desaturase 1 gene (FADS1) genotypes, subjects with histologically and pathologically confirmed colon adenocarcinoma in at least one lymph node, subjects who had undergone complete

Table 1. Results of selected articles

No.	References	Routes	Doses and durations	Notes	Results
1.	Bakker et al. (2020)	Parenteral; intravenous	Dosage : 2 mL/kg supplement (2 grams of oil fish) for 4 hours between 18.00 – 22.00 at evening pre-surgery and 08.00 – 12.00 in the morning post-surgery. Every 10% fish oil contains 1.25 – 2.82 grams of EPA and 1.44 – 3.09 grams of DHA. Duration: 3 months	Potency : No data Toxicity : • Whole blood IL-6 concentration, higher serum CRP on omega-PUFAs group (125 -175 mg/L) • Significantly increases the incidence of urinary tract infections, SIRS, and anastomotic leakage. Serum IL-6 levels are higher after surgery.	Omega-3 PUFAs infusion is more significant cause infectious complications.
2.	White et al. (2019)	Oral supplementation	Dosage : 3 capsules (containing 465 mg EPA and 375 mg DHA). A total of 2.5 grams of fish oil per day. Duration: 6 months	Potency : • Omega-3 fish lowers urinary PGEM levels • Omega-3 fish reduced rectal PGE2 levels in patients not taking NSAIDs. Toxicity : No reported data	Omega-3 associated with reduced urinary PGEM and PGE2 levels in patients not taking NSAIDs
3.	Song et al. (2019)	Oral diet	Dosage : Average intake • Men = 0.06 grams / day • Women = 0.05 gram/day Duration: median 6.9 years	Potency : • Patients with marine omega-3 PUFA (MO3PUFA) intake had lower median of proximal colon cancer, also dMMR and BRAF mutations • MO3PUFA consumption were significantly associated with better DFS rates at 3 years in patients with KRAS tumor patients. Toxicity : No reported data	Consumption of MO3PUFAs were associated with better survival in stage III colon cancer patients with wild-type KRAS and in tumors with MMR deficiency.
4.	Sorensen et al. (2020)	Oral supplementation	Dosage : 200 mL supplement 2x/day for 7 days before and after surgery with omega-3 PUFA supplements (2 grams EPA and 1 gram DHA), 2x/day. Duration: 3 years	Potency : No significant relationship between infectious rate, complications, survival rate and disease recurrent. Toxicity : No reported data	Perioperative omega-3 PUFA supplementation was not associated with a reduced risk of colorectal cancer recurrence after surgery.

No.	References	Routes	Doses and durations	Notes	Results
5.	Murff et al (2012)	Oral diet	Dosage : Average intake • Men = 0–1.4 gram/day • Women = 0–0.9 gram/day Time of Delivery : No data available	Potency : • High marine-derived omega-3 PUFA intake in women reduces the risk of non-advanced and advanced adenomas and is negatively related with PGEM concentrations. • No significant relationship between total calcium, linoleic acid, and arachidonic acid, omega-6 PUFAs with adenomatous polyps & hyperplastic polyps risk. Toxicity : No reported data	Consuming marine-derived content omega-3 PUFAs had lower colorectal adenomas & negatively correlated with PGEM production in women.
6.	Kantor et al. (2014)	Oral supplementation	Interventions: • High use = 4 + days/week for 3+ years • Low use = < 4 days/week or < 3 years • No use Duration: 2 years	Potency : • High consumption of supplements reduced the risk of colorectal cancer compared to the no use group. • Increased consumption of supplements associated with reduced the risk of colon cancer but not significant for rectal cancer. • Supplement consumption has a significant relationship with gender and increased dose. Toxicity : No reported data	The relationship between long chain-PUFA intake and colorectal cancer is influenced by variation gender, subsite, and genetic risk.
7.	Song et al. (2015)	Oral diet	Dosage: Average intake 1.3 – 1.4 grams/day of marine omega-3 PUFAs in the dietary intake Duration: 1 year	Potency : High intake of marine omega-3 PUFA has a linear relationship with lower risk of MSI-high tumors but not with MSS tumors. Toxicity : The MSI-high CRC hazard ratio value has changed 0.02 in 0.15 gram/day increase of omega-3 PUFA.	High marine-omega-3 PUFA intake is associated with risk MSI-high CRC low but not tumor-MSS so potentially protective.

No.	References	Routes	Doses and durations	Notes	Results
8.	Tokudome et al. (2015)	Oral supplementation	Dosage : 8 fish oil capsules/ day (per capsule contains 12 mg EPA+ 45 mg DHA) and dietary consumption.	Potency : Long chain omega-3 PUFA was not significantly associated with the incidence of colorectal tumors. Toxicity : No reported data	Long chain n-3 PUFA especially EPA and DHA had a competitive role in apoptosis. The long chain n-3 PUFA diet was well tolerated and effective.
9	Aglago et al. (2020)	Oral diet	Dosage : Intake of fish containing fish oil or not as much as 100-200 grams/week. Duration: 8 years	Potency: Weekly intake of 100-200 grams of fish omega-3 fatty acids, according to WHO recommendations reduced the risk of colorectal cancer by 7%. Toxicity : No data	Regular consumption of fish with intake according to daily nutritional recommendations is associated with a reduced risk of colorectal cancer. That matter possibly from exposure to long-chain omega-3 fatty acids PUFAs.

BRAF: V-Raf Murine Sarcoma Viral Oncogene Homolog B; CRP: C-reactive Protein; DFS: disease-free survival; DHA: docosahexaenoic acid; dMMR: deficient mismatch repair; EPA: eicosapentaenoic acid; IL: Interleukin; KRAS: Kirsten rat sarcoma virus homolog; MSI-high CRC: microsatellite instability-high colorectal cancer; MSS: microsatellite stability; MO3PUFA: Marine Omega-3 Polyunsaturated Fatty Acid; NSAIDs: Non-Steroidal Antiinflammatory Drugs; PGE2: prostaglandin E2;PGEM: prostaglandin E2 metabolite; PUFA/PUFAs: Polyunsaturated Fatty Acid/Polyunsaturated Fatty Acids; SIRS: Systemic inflammatory response syndrome; WHO: World Health Organization

surgery resection within 56 days before the study, patients undergoing CRC surgery referred from a surgical outpatient clinic, and those with grade 3–5 adenoma lesions. The age range of subjects varied from 30-85 years, encompassing both men and women. Furthermore, the characteristics of the subjects were explored about lifestyle and dietary nutrition, incorporating factors such as body mass index (BMI), smoking status, dietary habits involving dark fish (such as salmon and tuna) with an average intake from 0.26 to less than 0.80 servings per week, total energy and other micronutrients intake, history of regular multivitamin use, alcohol consumption, and physical activity.[15–22] This comprehensive set of criteria allowed for a thorough examination of the diverse profiles of individuals within the selected articles.

In one article, the characteristics of subjects included patients with a BMI falling within the range of 20–35 kg/m2.[22] This particular study examined the effect of perioperative oral supplementation of omega-3 fatty acid, administered at a dose of 200 mL (equivalent to 1 bottle) twice a day for seven days. Interestingly, the findings indicated that this supplementation regimen was not associated with a reduced risk of CRC recurrence following surgery.[19] This underscores the importance of considering appropriate dosage levels in research studies to accurately assess the potential benefits or lack thereof.

Additional information provided includes the subjects' history of non-steroidal anti-inflammatory drugs (NSAIDs) usage and the presence of V-Raf Murine Sarcoma Viral Oncogene Homolog B (BRAF) and Kirsten rat sarcoma virus homolog (KRAS) mutations. This study elucidated the role of omega-3 fatty acids in reducing urinary prostaglandin E metabolite (PGE-M) and rectal prostaglandin E2 (PGE2) levels among patients with a history of CRC who did not consume NSAIDs. This effect was achieved with a total daily dose of 2.5 grams of fish oil, administered through the consumption of three capsules of omega-3. Each capsule contained 465 mg of EPA and 375 mg of DHA.[22] Remarkably, this dosage not only reduced the rectal mucosal proliferation index but also demonstrated excellent tolerance with no reported side effects. This dosage must align with the daily consumption recommended by the 2020 FDA, which advises against exceeding four capsules at once or consuming more than two capsules twice a day.[23] This aligns with the FDA guidelines aimed to ensure the safety and efficacy of omega-3 supplementation. Four other articles explored the effects of fish omega-3 fatty acids when integrated into daily or weekly dietary intake, shedding light on the diverse approaches taken to examine the potential benefits of these fatty acids in various consumption contexts.[12,17,18,21]

The toxic effect of fish omega-3 fatty acids is limited to a single article that used parenterally or intravenously administration.[15] This study revealed an elevated risk of post-operative infection, underscoring the importance of considering the mode of administration in assessing potential risks. The fish omega-3 fatty acids used were 2 mL/kg, equivalent to 2 grams of fish oil given for 4 hours during the evening (pre-surgery, between 18:00-22:00) and morning (post-surgery, between 08:00-12:00) over three months. This preparation, containing 1.25–2.82 grams of EPA and 1.44–3.09 grams of DHA in every 10% fish oil, resulted in significantly increased incidence rates of urinary tract infections, systemic inflammatory response syndrome (SIRS), and anastomotic leakage. The elevated serum IL-6 levels after surgery indicated a potential link to these effects.[15]

In adherence to the FDA recommendation, the infusion of fish omega-3 fatty acids was given up to 2 mg/dL for 8–24 hours, with the duration depending on the patient's clinical conditions and spanning for two weeks.[24] Notably, the lipid emulsion in this preparation was identified as a substantial substrate for microbial growth in the bloodstream. The increased risk of infection primarily occurs in patients with immunosuppression related to factors such as malnutrition, long-term drug use, poor intravenous catheter maintenance, and other conditions associated with concurrent multidrug use.[25] It was in line with a meta-analysis study by Bae et al. suggesting an increased risk of infectious morbidity and extended hospital stay associated with omega-3 fatty acid emulsions.[26] Moreover, it aligns with a study by Linecker et al., which argued that perioperative omega-3 fatty acids did not confer a protective effect for patients undergoing liver surgery and are consequently not recommended for these patients.[27] In contrast, studies examining the toxicity of fish omega-3 fatty acids from oral supplementation and dietary sources reported no toxic effects.

Several articles thoroughly investigated potential side effects throughout the studies and found no observable adverse effects during oral fish omega-3 fatty acid supplementation.[18,19,21] This notable difference underscores the significance of the route of administration in comprehending the safety profile of fish omega-3 fatty acids and highlights the necessity for careful consideration in clinical applications.

Some mechanisms have been proposed to elucidate the chemoprotective effects of omega-3 fatty acids, particularly PUFAs, against CRC. The fish omega-3 fatty acids in diets containing PUFAs, EPA, and DHA, exhibit potential as chemopreventive agents for CRC through various mechanisms. A study demonstrated that the consumption of fish omega-3 fatty acids led to a reduction in prostaglandin E2 metabolite (PGE-M) levels and rectal prostaglandin E2 (PGE2) levels in patients with a history of CRC in three months, even in the absence of NSAID intake.[22] Urinary PGE-M, an indicator of systemic PGE2 production, predicts the risk of advanced colorectal neoplasia and thus has potential as a biomarker.[28] This reduction may be related to the pathogenesis of CRC, as it modulates the tumor-inducing effects of the cyclooxygenase-2 (COX-2) enzyme through the regulation of the chronic inflammatory PGE2 pathway.[28–31] In the COX pathway, cellular membranes release n-6 PUFAs that are enzymatically converted into various bioactive lipid molecules, including PGE2. PGE2 promotes carcinogenesis by stimulating cellular proliferation, inhibiting apoptosis, promoting angiogenesis, and increasing invasiveness.[28–31] The EPA and DHA mitigate CRC risk through several mechanisms, such as reducing PGE2 levels, diminishing 1,2-dimethylhydrazine (DMH)-induced microscopic preneoplastic lesions, and exerting a protective effect against azoxymethane (AOM)-induced carcinogenesis. Furthermore, they inhibit epidermal growth factor receptor (EGFR) and human epidermal growth factor-2 signaling, thereby impeding cell proliferation.[2,8]

The association between cancer and the inflammation process has been well-documented in scientific literature for over a century. Chronic inflammation is recognized as an important factor in the development of gastrointestinal cancer, involving various components of both the innate and adaptive immune system.[32] Inflammatory bowel disease (IBD) is a notable risk factor for CRC, highlighting the impact of chronic inflammation in carcinogenesis. Within the context of IBD, chronic inflammation stimulates aberrant alterations in deoxyribonucleic acid (DNA) methylation patterns and facilitates the recruitment of inflammatory cells to the site of inflammation. This creates a microenvironment that conducive to tumorigenesis.[33] Additionally, some cytokines secreted in inflammatory areas can act as growth and survival factors, contributing to the progression of malignancy. [32] These facts urged the importance of modulating the immune system in cancer therapy, highlighting the potential for immunomodulatory strategies to disrupt the inflammatory cascade and impede tumor progression.

The oral supplementation of fish omega-3 fatty acids has emerged as a promising strategy for enhancing immune function by activating the innate immune response and enhancing the activity of phagocytic and cytotoxic natural killer (NK) cells. Additionally, fish omega-3 fatty acids are associated with the promotion of anti-inflammatory cytokine profiles within the body, thereby mitigating chronic inflammation, which is linked to cancer development and progression In the context of CRC where chronic inflammation plays a crucial role in carcinogenesis, immunomodulatory effects of fish omega-3 fatty acids have particular significance. By attenuating inflammation and enhancing immune surveillance against tumor cells, omega-3 fatty acids may offer valuable therapeutic benefits in the prevention and treatment of CRC.[34] The acknowledged role of nutrition in carcinogenesis confirms the significance of the microenvironment in CRC development.[35–37] Food components, such as fish omega-3 fatty acids, have been identified as potential chemopreventive agents in CRC.[12,17,18,21] Immune cells involved in the inflammatory response are typically rich in fatty acids, which can be modulated in composition by omega-3 PUFAs. Oral administration of omega-3 PUFAs induces alterations in eicosanoid production during the inflammatory process, leading to the generation of resolvin, a novel anti-inflammatory agent that helps to resolve inflammation and promote tissue repair. These changes in fatty acid composition within the inflammatory milieu further impact the production of inflammatory mediators, including

adhesin molecules like E-cadherin and various cytokines, suggesting the anti-inflammatory role of omega-3 PUFAs in enhancing immune function within the colonic microenvironment. Omega-3 fatty acids have been observed to modulate several components in the immune system, including macrophages (reducing cytokine production, promoting polarization towards the M2 phenotype, enhancing phagocytosis), neutrophils (increasing of production pro-healing mediators, reducing migration, enhancing phagocytosis), eosinophils (decreased infiltration), basophils (decreased activation), dendritic cells (diminished antigen presentation), mast cells (attenuated activation), T cells (reduced activation, increased Treg differentiation), B cells (enhanced IgM production).[35]

The hypothetical mechanism of action for omega-3 PUFAs as a chemopreventive agent in CRC, drawn from various resources as discussed in the preceding paragraph, is illustrated in Figure 2, providing a visual representation of the complex interaction among omega-3 fatty acids, immune system function, and the prevention of CRC.

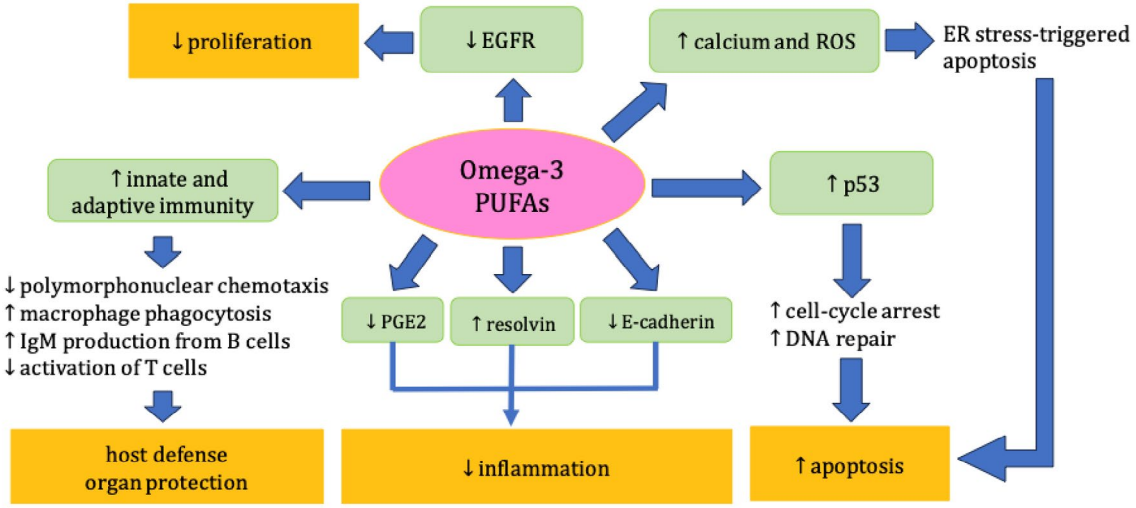

Figure 2. The hypothetical mechanism of omega-3 polyunsaturated fatty acids (PUFAs) as a chemopreventive agent in colorectal cancer. DNA: deoxyribonucleic acid; EGFR=endothelial growth factor receptor; ER=endoplasmic reticulum; PGE2=Prostaglandin E2; ROS=reactive oxygen species

CONCLUSION

This scoping review highlights the promising potential of fish omega-3 fatty acids administration as a chemopreventive strategy in CRC. The evidence suggests that the effect can be achieved through various approaches, including the consumption of supplementation or an oral diet incorporating omega-3 fatty acids at appropriate doses, coupled with the adoption of a healthy lifestyle and balanced daily nutritional intake. Notably, the observed toxic effect of fish omega-3 fatty acids is confined to a specific article associated with parenteral or intravenous fish omega-3 fatty-acid administration methods, revealing an increased risk of post-operative infection. However, articles that examined the administration of fish omega-3 fatty acids through oral supplementation and dietary preparations did not report any adverse effects. This absence of negative outcomes in these routes of administration contributes to the overall body of evidence supporting the safety and tolerability of integrating fish omega-3 fatty acids into daily nutritional practices. The comprehensive findings of this review not only underscore the potential benefits of fish omega-3 fatty acids in preventing colorectal cancer but also provide valuable insights for future research and clinical considerations in the realm of chemoprevention.

CONFLICT OF INTEREST

Competing interests: No relevant disclosures.

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AUTHOR CONTRIBUTION

IS contributed to planning of research and data collecting; IM contributed to data collecting,

writing the manuscript, and English editing; RR contributed to data analysis and proofread. All authors have read and approved the final manuscript.

LIST OF ABBREVIATION

ALA: alpha-linolenic acid; AOM: azoxymethane; APC: antigen-presenting cell; BRAF: V-Raf Murine Sarcoma Viral Oncogene Homolog B; BMI : body mass indeks; COX-2: cyclooxygenase-2; CRC: colorectal cancer; CSC: cancer stem like's cell; CXCL1 and CXCL2: CXC motif chemokine ligand 1 and CXC motif chemokine ligand 2; DFS: disease-free survival; DHA: docosahexaenoic acid; DMH: 1,2-dimethylhydrazine; dMMR: deficient mismatch repair; DNA: deoxyribonucleic acid; DPA: docosapentaenoic acid; EGFR: epidermal growth factor receptor; EPA: eicosapentaenoic acid; ER: endoplasmic reticulum; ET-1: endothelin-1; FADS1: fatty acid desaturase-1; FDA: Food and Drug Administration; GLOBOCAN: Global Burden Cancer; IBD: Inflammatory bowel disease; IgM: immunoglobulin M; IL-6: interleukin-6; IL-1β: interleukin 1- β; KRAS: Kirsten rat sarcoma virus homolog; MAPK: Mitogen-activated protein kinase; MSC: mesenchymal stem cells; MSI-high CRC: microsatellite instability-high colorectal cancer; MSS: microsatellite stability; MO3PUFA: Marine Omega-3 Polyunsaturated Fatty Acid; NSAIDs; NK: natural killer; NSAIDs: non-steroidal antiinflammatory drugs; PCC: population, concept, context; PGE: prostaglandin E; PGEM: prostaglandin E2 metabolite; PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews; PUFAs: polyunsaturated fatty acids; ROS: reactive oxygen species; SIRS: systemic inflammatory response syndrome; SNP: single nucleotide polymorphism; TNF-α: tumor necrosis factor-α; Treg: T cell regulator; VEGF: vascular endothelial growth factor; WHO: World Health Organization

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