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Prebiotic Intervention in Chemotherapy Induced Adverse Effects A Systematic Review- Muscle Wasting and Gut Health as Major Thrust

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Abstract

Background: Cancer is the world's leading cause of death and considered as life threatening disease. Its treatment usually includes chemotherapy, radiotherapy, surgery, or combination of the therapies. However, most preferred is chemotherapy which can be applied at the early stage as well as late stages of the disease. The development of adverse effects from chemotherapy impedes therapeutic utilization and significantly impacts cancer patients' quality of life. Muscle wasting, gastro intestinal inflammation, cardiotoxicity neurotoxicity and nephrotoxicity to name a few.

Objective: To lessen the discomfort brought on by chemotherapy, traditional medications including antiemetic, multivitamins, diuretics, and antidiarrheal are recommended. However, these are known for secondary adverse effects as insomnia, hallucinations, intestinal cramping, etc. Natural drugs complementary and alternative therapies are employed to counteract these; however they lack scientific support and vary depending on the patient's personality. Certain contemporary approaches, such the use of probiotics and prebiotics, have been demonstrated to be effective in overcoming these disorders. Evidently, skeletal muscular atrophy and weakness are the tell-tale signs of cachexia brought on by chemotherapy, which reduces treatment tolerance, impairs daily functioning, and worsens survival in cancer patients. These conditions are referred to as sarcopenia and cancer cachexia. These therapies can also cause mucositis, a disorder marked by gastro-intestinal inflammation and disruption of the gut flora.

Methods: Findings of different researcher in this thrust are analyzed and outcomes are summarized. This review focuses to examine the known mechanisms of prebiotic action and explores their potential to reduce the severity of chemotherapy-induced with primary focus on muscle wasting and gastro intestinal inflammation.

Result and conclusion: The prebiotics are found to be effective in combating this chemotherapy induced adverse effects evidently focusing on the muscle wasting and GI inflammation. With a detailed literature survey, we conclude that this review will surely provide firm and better insights to the researchers to develop relevant option of prebiotics and establishing the possible mode of action.

1. Introduction

According to WHO Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, or nearly one in six deaths. It is a significant public health problem in both developed and developing countries[1].

As per National Centre for Health Statistics in 2023, 1,958,310 new cancer cases and 609,820 cancer deaths are projected to occur in the United States[2]. In Indian as per Global Cancer Observatory (GLOBOCAN) The estimated number of incident cases of cancer in India for the year 2022 was found to be 14,61,427 which is estimated to increase by 12.8 % in 2025. It is forecasted that cancer cases in India would increase to 2.08 million, accounting for a rise of 57.5 % in 2040 compared to 2020[3].

Cancer and treatment modalities:

Cancer develops as cells proliferate and spread abnormally throughout the body. Consequently, cancer was brought on by chemically injured cells or affected by radiation exposure. 10% of fatal cancers are influenced by nutrition, while 22% of fatal cancers are linked to tobacco smoking. Environmental factors like drug misuse, poor nutrition, stress, lack of exercise, and environmental toxins are to blame for

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90–95 percent of cancer cases. Inherited cancer genetics are responsible for the remaining 5–10 %.[4]

Cancer, also known as a malignant or benign neoplasm, all of which involve uncontrolled cell growth. There are several therapeutic approaches that can be utilized to slow the advancement of the disease and the proliferation of cells in which include surgery, chemotherapy radiation therapy of combination. The surgery and radiation therapy are more suitable for localized area. The radiation therapy consists of exposure of the ionizing radiation which will damage the DNA and kills the cancer cell in a localized area. This involves lot of adverse effects which depend on the area of exposure, frequency and the stage of the cancer. To name a few it develops fatigue, radiation dermatitis, seizures, lymphedema, low blood count, decreased bone density, radiation pneumonitis, sexual dysfunction, radiation cystitis. Moreover it is considered as age and condition specific treatment. [5]

Chemotherapy is used more profoundly which may have single drug treatment or combination of drugs. Sometimes it is vital to utilize combination treatments to maximize treatment effectiveness even though these method increases the risk of severe adverse effects which disturbs the quality of life during and post chemotherapy.[6, 7] There are a variety of situations in which chemotherapy may be used in cancer patients to cure the disease. It may be used as the primary or sole treatment for cancer, used after other treatments to kill any remaining cancer cells(adjuvant therapy), used to shrink a tumour so that other treatments (neoadjuvant therapy), such as radiation and surgery, can be more effective. Conclusively chemotherapy is found as the choice of treatment due to its wide drug choices and applications.

Chemotherapy and its adverse effects:

As said earlier chemotherapy is the commonly used as first line of treatment to control the disease. There are significant short- and long-term adverse effects associated with chemotherapy. The term “late effects" refers to adverse effects that may not be gone for several months or even years.[4]

According to the available literature the most frequently reported short term adverse effects were weakness (95%), fatigue (90%), nausea (77%), hair loss (76%) and vomiting (75%). Each of these adverse effects was experienced by more than 70% of the patients. Other prominent adverse effects include mouth sore (53%), dry mouth (21%) and numbness (51%) whereas diarrhea, abdominal cramps and memory impairment were less commonly occurring adverse effects.[8] The likelihood of experiencing long-term adverse effects following therapy is influenced by the patient's age, comorbidities, type of cancer, dose schedule, and length of treatment. Following is the prevalence rate of severe adverse effects of chemotherapy.[9]

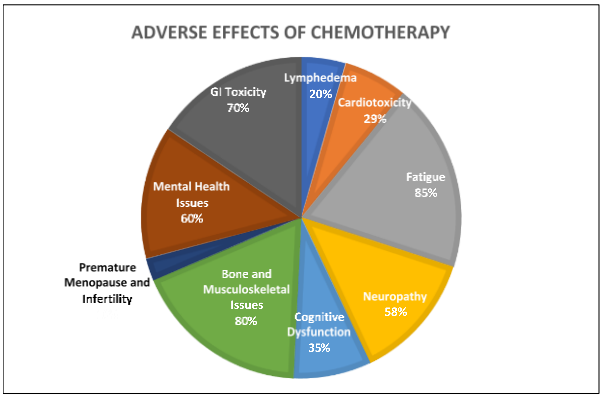

Figure 1 Adverse-effects of Chemotherapy and its prevalence rate

From the available literature data and findings, it is concluded that Fatigue, Musculoskeletal Issues and gastro intestinal inflammation was found to be most prevalent adverse effects of chemotherapeutic drugs. The fatigue and musculoskeletal are interlinked and seen as major adverse effects of promising chemotherapeutic agents used since ages. Hence they can be clubbed together under a wide title of muscle wasting. There effects are consider as long term adverse effects as they can be experienced during and post chemotherapy.[9]

2. Overcoming the Adverse Effects of Chemotherapy:

Conventional medicines and limitations Although the adverse effects and the probability of chemotherapeutic agents is also conferred, the conventional medicines are always provided to counteract these effects but eventually they also shows secondary harmful effects on body. The quality of life, morbidity, and total mortality of survivors are frequently significantly impacted by these adverse effects. Hence they are to be attended and treated as

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per the age, need and perspective of the patient which will eventually ease the day-to-day routine and improves the confidence, believe and quality of life.

1. Antiemetics: Ondansetron is prescribed to relieve nausea and vomiting during medication therapy. It has the same adverse effects as dexamethasone, including sleep issues, mood swings, indigestion, and weight gain.

2. Antidiarrheal are given like Loperamide or Diphenoxylate which has allied adverse effects as dizziness, nausea, and abdominal or stomach cramps and higher doses include severe drowsiness, hallucinations, and lethargy.

3.Diuretics like Furosemide & Hydrochlorothiazide are also conquered during the chemotherapy to manage the issues of swelling and edema will reflect low blood pressure, sensitivity to light, rash, nausea, and abdominal pain, dehydration, electrolyte depletion, yellowing skin and eyes (jaundice), ringing in the ears, pancreatitis, diarrhea, dizziness, increased blood sugar, and increased uric acid levels.

4.Vitamins and minerals and antioxidants like Vitamins A, C, & E; Carotenoids; Coenzyme Q10 are the choice of supplements by the survivor bit the use may provide the issues of vertigo, palpitation disturb bowel actions, increased urination, stomach bleeding, uneven heart rate, confusion, and muscle weakness or limp feeling.

5. Calcium booster and Vitamin D is being prescribed like frequent injection of bonimet which had side-effects of including gas, constipation, bloating, nausea/vomiting, loss of appetite, mental/mood changes, and bone/muscle pain.

In order to address the mentioned issues, different methods including CAM, utilization of beneficial microorganisms in their Prebiotic and probiotic are emerging. [8, 9]

COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM):

To overcome all these facts the survivors can uptake Complementary and alternative medicine (CAM). It is the term for medical products and practices that are not part of standard medical care.[10] There are Different methods of CAM like Mind Body Medicine (Meditation, Hypnosis, Yoga), Biologically Based (vitamins, minerals, and herbs, botanicals plants or parts of plants), Manipulative and body-based practices, Energy healing (Reiki), Ayurvedic medicine (diet, herbal medicines, exercise, meditation, breathing, physical therapy). [11]

Traditional Chinese medicine based on the belief that (the body's vital energy) flows along meridians (channels) in the body and keeps a person's spiritual, emotional, mental, and physical health in balance,[12] Naturopathic medicine (nutrition, acupuncture, and aromatherapy).

Limitation of CAM:

Although the patient shows interest in the above said CAM there are certain precaution that are to be care and need proper guidance and consultation is to be taken. Certain well known and explored herbal crude drugs like St. John's Wort, which some people use for depression or to improve the mental health, may cause changes in mechanism of action of certain anticancer drugs. Some Herbal supplements like kava, an herb that has been used to help with stress and anxiety, may cause liver damage or even high doses of vitamins like vitamin C, may affect how chemotherapy and radiation and interfere the Clotting time in an individual [11,13]. Adverse reactions to CAM products can be classified as intrinsic (innate to the product), or extrinsic (where the risk is not related to the product itself, but results from the failure of good manufacturing practice or the failure of the expert conduct). Moreover these do not have a classified standard protocol to be followed as they are customized according to the patient condition. This makes to fall for the risk of efficacy and safety parameter along with manual judgmental errors. [14]

Probiotics as live microbe feed supplements that positively affect the host animal by increasing the microbial balance in the intestine. They act by Adherence and colonization to the gut wall.[15] A portion of the widely utilized probiotic microorganisms are *Lactobacillus rhamnosus, Lactobacillus reuteri, Bifidobacteria and certain strains of Lactobacillus casei, Lactobacillus acidophilus-groups, Bacillus coagulans, Escherichia coli strain, certain enterococci, particularly Enterococcus faecium*, and the yeast *Saccharomyces boulardii.*[16]

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Journal of Coastal Life Medicine

Pathogenicity, infectivity, intrinsic characteristics, and virulence variables associated to toxicity and metabolic activities of bacteria must be considered during probiotic safety assessment. Probiotics must be viable and active during storage and GIT transit.[17]

Limitation of probiotics:

Sometimes associated with certain limitations like it may increase the bioburden, as it involves utility of live microbes immune regulation or provoke anti-inflammatory response may be noted. Other probiotic adverse effects include systemic infections, dysfunctional metabolic processes, and the spread of dangerous genes like antibiotic resistance. Utilizing Lactobacillus occasionally caused liver abscesses, sepsis, and endocarditis. Numerous studies show that *Bacillus subtilis* can cause bacteraemia, sepsis, and cholangitis. Additionally, it has been noted that *S. boulardii* may cause fungal sepsis. Probiotics' primary safety concern is the possibility of bacteremia, sepsis, or endocarditis, particularly in patients with severe immunodeficiency (such as those with HIV, cancer, or organ transplants), severe malnutrition, or an ineffective intestinal epithelial barrier (e.g., severe diarrhoea)[18]. Prebiotics may share some of the same safety issues as probiotics as potential substitutes or supplemental treatments.

Prebiotics as an emerging trend:

However, to overcome the certain negative aspects of probiotics another area called Prebiotics is being explore. Prebiotics are substrates that are selectively utilized by host microorganisms conferring a health benefit. These are not digested in the human gut but boost the growth and activity of bacteria that are good for our intestine; consequently they balance the intestine of an organism.[19]

The most commonly used bacteria that are good for our health is amplified by prebiotics comprise of genus *Bifidobacterium and Lactobacillus*, which control the growth of harmful bacteria.[20] Most commonly used prebiotics are mannan-oligosaccharides, lactose, inulin and oligofructose. Prebiotics functionality are not altered by any food processing treatment and require little or no regulatory requirements, hence making their consumption easier as compare to chemical treatment.[21] The probable mode of action would be, as these are non-digestible carbohydrates that are not digested by the upper gastrointestinal tract and travel in the ileum and colon where fermented by the resident microbes. They also work by coating or forming a layer on the host surface receptors. They produce bacteriocins which help to kill the harmful bacteria. Favorable bacteria produce short chain fatty acids with the help of non-digestible carbohydrates which are the energy source of epithelial cells and help to regulate metabolic function and modulate immune system.[22, 23]

Chemotherapy induced GI inflammation:

The capacity of chemotherapeutic drugs to cause GI inflammation is well reported in available literature. This is seen in different area ranging from the gastric section, small intestine, large intestine including colon region. Insight of this various possible mechanism are predicted which enable the drugs to cause inflammation.

Mechanism of chemotherapeutic agents to cause GI inflammation:

Although the mechanisms underlying mucositis development are complicated and still not fully understood, it is thought that the ailment develops over the course of five phases. Reactive oxygen species (ROS) are produced during the early stages of mucositis, which begins immediately after chemotherapy delivery. [24, 25] These subsequently cause the transcription factor nuclear factor-B (NF-B) to be activated, which is linked, to circumstances that promote the inflammatory response. Mucositis first becomes clinically evident during the fourth phase, termed ‘ulceration and inflammation’[26] It is during this stage that the epithelial layer increases in permeability, allowing the translocation of bacteria into the blood stream. This is accompanied by severe pain and discomfort, and sometimes secondary complications such as malnutrition and septicemia.

During the ulcerative stage, other changes occur including crypt ablation and villus atrophy, which reduce the size of the intestine's overall absorptive area, diminish the levels of digesting enzymes, and increase intestinal permeability. The gut microbiota then undergoes changes as a result of this modifications.[27]

Further with insight of the cryptal stem cells and progenitor cells' cell mitosis and amplification

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Journal of Coastal Life Medicine

activities are hampered by apoptosis which is one of the major problems with chemotherapy. Depending on the cytostatic medication utilized, there are changes in the local cryptal alterations and the degree of apoptosis. Nevertheless, the epithelium's regular cell maturation and regeneration are compromised, so the constant shedding of intestinal epithelia cells that have undergone apoptosis at the tips of the villi is not accompanied by sufficient cellular renewal. Antineoplastic medications may potentially affect non-dividing cell populations in the intestine, amplifying any unfavorable effects of a changed cryptal cell renewal. Quoting an example the cytostatic doxorubicin (DOX) is associated with both production of reactive oxygen species and mitochondrial dysfunction.[28]

Moreover NF-KB activates TNF-α release, which in turn activates release of NF-KB which results in mucosal inflammation and ulceration. These overall effects of the strong biochemical reaction, and they are characterized by the destruction of epithelial villi, a breakdown of IEC adhesion, and an enhanced translocation of luminal components and immune cells into the lamina propria. Even more inflammation results from this series of actions.[29] The varied expression of pro- and anti-apoptotic proteins, such as Blc-2, which increases apoptosis in the small intestine region, has been suggested as the cause of the disparity in injury. The small intestine is, unsurprisingly, more susceptible to mucositis brought on by chemotherapeutics since spontaneous apoptosis occurs 10 times more frequently there than in the large intestine.[30] The larger intestine's lower frequency of apoptosis also adds to the lower digestive tract's increased risk of cancer.

Prebiotics intervention with gut microbiota:

Colonized bacterial communities make up a portion of the mucosal barrier on the intestine's epithelial surface, which may help to form the protective gut barrier, protect against the colonization of other pathogens, and reduce the possibility of bacterial translocation. A prebiotic oligosaccharide mixture administered to humans improved gut microbiota composition, as measured by an increase in Bifidobacteria and a reduction in the levels of pathogenic Clostridia-related species.[31] In a broiler chicken Escherichia coli challenge model, MOS consumption reduced mucosa-associated Coliform spp. in the jejunum. The same studies showed that FOS increased *Lactobacillus spp*. levels in the jejunum and lactic acid levels in the effect of E. coli. In addition, prebiotics are able to decrease gut pH and modulate the SCFA pattern, resulting in an inhospitable environment for pathogens.[32] concluding the prebiotics are responsible to create the effective environment for the growth of gut microbiota. Further it can be analyzed for interpreting the mechanism.

Prebiotics intervention with Mucin:

In the intestine, the mucin layer is a crucial part of barrier function. In order to protect the mucosa against bacterial overgrowth and/or penetration, mucins produce protective mucus gels that cover the epithelial surface.[33] An increase in mucin leads to less bacterial translocation and, as a result, less pathogenic infection. Contrarily, 5-FU-treated rats' jejunal epithelial mucin levels were considerably reduced by chemotherapeutics whereas irinotecan-treated rats showed an increase in mucus secretion in the large intestine.[34] Prebiotics, on the other hand, could be able to stop the harm that chemotherapy causes to the gut by preserving the integrity of the mucosa by mucin alteration. Future studies are necessary to determine whether prebiotics can affect the amounts of mucin in the various intestinal areas in the context of mucositis.

Prebiotics intervention with diarrhoea:

It is now generally recognized that the intestinal microflora through the gut ecosystem is involved in a number of biologic functions, such as direct and indirect anti-pathogen activity. A safe and effective way to beneficially influence the intestinal microflora is the administration of prebiotics, which selectively promote the growth and/or activity of beneficial bacteria, such as bifidobacterial. These prebiotics pass through the upper gastrointestinal system undigested and enter the colon, where they are fermented by the local microbiota into short chain fatty acids (SCFAs) and lactate. Prebiotics boost the population of health-promoting bacteria, like bifidobacterium and lactobacilli, at the expense of microorganisms that cause disease. Some protective organisms have the ability to hydrolyze prebiotic oligosaccharides, which causes them to multiply. Prebiotics can alter the environment in the gut as well. As previously indicated, most the prebiotics' fermentation products are acids, which lower the pH of the gut. The

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Journal of Coastal Life Medicine

composition and population of the gut microbiota have been demonstrated to change when the gut pH is changed by one unit, from 6.5 to 5.5. The pH change can affect the population of species that are sensitive to acid, such as Bacteroides, and encourage the synthesis of butyrate by Firmicutes. The term for this action is "butyrogenic impact."[35]

Muscle wasting and Fatigue:

One of the most prevalent adverse effects of cancer treatment is fatigue, which presents in the clinic as weakness and an intolerance to physical activity. These adverse effects reduce physical activity, which limits treatment options and raises morbidity while also impairing patients' quality of life (QOL). There are two parts of physiological fatigue are central and peripheral fatigue. The central nervous system and neurological reflex inhibition are both involved in central fatigue.[36] Cancer patients often experience central fatigue, but it is uncertain how this condition interacts with chemotherapy, which further restricts the discussion of this aspect. Muscle weakness and fatigue are the two halves of peripheral fatigue, which affects individual muscles and results in the loss of muscle function. While muscular weakness is a reduced ability to generate force and is not restored by rest, muscle fatigue is described as a loss of force that is reversible by rest. The further complicated stage of fatigue induced by chemotherapeutic agents leads to a complex situation of muscle wasting.[37] Many of the chemotherapeutic agents kill tumor cells through a number of different mechanisms, including: inhibition of RNA and DNA transcription and replication, production of free radicals that cause DNA damage or lipid peroxidation, DNA alkylation, disruption of DNA unwinding or DNA strand separation and helicase activity, and inhibition of topoisomerase II. Tumor cell growth, division, and metastasis are inhibited as a result of some or all of these actions. Anthracyclines may also harm striated muscle and other non-cancerous tissues, which adds to muscle weakness and fatigue Muscle wasting is a widely seen condition that lowers overall resilience, causes psychologic discomfort, and causes gradual functional impairment.[38] Normally environmental stressors like physical activity and protein consumption have an impact on the balance between protein synthesis and breakdown. Although, throughout muscle wasting, this equilibrium changes towards muscle protein breakdown, which is frequently fuelled by inflammation, whether it is brought on by a disease or just ageing. Cachexia and sarcopenia are the names for these muscle-wasting disorders caused by inflammation, respectively. Sarcopenia and cachexia can co-occur because chronic inflammatory disorders like cancer typically manifest in elderly patients. Both disorders have detrimental effects on survival, quality of life, and life expectancy; however, present therapeutic options, particularly for cachexia, are palliative and frequently unable to restore the muscular atrophy.[39,40] Inflammatory mediators, which facilitate communication between these organs, affect fundamental functions like stress management, energy homeostasis, and appetite control. Due to the involvement of nutrition absorption, hormones that control appetite, and immunological responses, these processes are all intricately linked to gut health. Therefore, the organ crosstalk that causes cachexia may have a significant role in a disrupted gut function.[41] However, the insight for finding the correlation between the muscle wasting and gut health was not clear, hence more detailed study was carried out to establish the probable correlation between the wide terms of muscle cachexia and gut health.

3. Literature Findings:

Literature findings reveled that chemotherapeutic agents are prone to develop the adverse effects by different mode of action. Among the reported one's gastrointestinal inflammation and muscle wasting are considered as long term major effects. This review focuses on analyzing the potential of prebiotics to intervene on chemotherapy induced GI inflammation and muscle wasting.

Prebiotics in Chemotherapy induced GI Inflammation

1. In a case study conducted by Ruwiyatul Aliyah, et al. in the year 2022, a 42-year-old man with malignant lymphoma who had received chemotherapy and suffered from malnutrition, weight loss, and a decreased body mass index was given prebiotic as curcumin with a supplement of multivitamins at a dose of 5 grammes per day, which led to a clinical improvement in functional capacity and improved lab results. Constipation, a sore throat, nausea, and vomiting symptoms all improved while the chemotherapy dose was maintained.[42]

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Journal of Coastal Life Medicine

2.According to a data base review done by J.M. Deelemens (2021), 10 randomized controlled trials and 2 single-group trails were carried out with (N = 974) participants met the inclusion criteria. Ten trials active anticancer therapy and two were post chemotherapy. Three trials employed prebiotics as guar gum and blue agave and inulin, seven used probiotics lactobacillus species, and two used both. Prebiotics improved GI and psychological health just somewhat. Probiotics improved anxiety, depression, fatigue, QOL, and stomach discomfort (n = 2).[43]

3. Colorectal cancer patients (n=150) were randomly assigned to receive monthly 5-FU and leucovorin bolus injections or bimonthly 5-FU + continuous infusion as postoperative adjuvant therapy. During chemotherapy, study subjects received *Lactobacillus rhamnosus* and fibre guar gum at a dose of 11gm/day randomly. Lactobacillus patients had less grade 3 or 4 diarrhoea (22 Vs 37%, P=0.027), abdominal discomfort, hospitalization, and chemotherapy dose reductions due to bowel damage. Guar gum did not affect chemotherapy tolerance. The reduced the regimen had fewer grade 3 or 4 adverse effects (45 Vs 89%) and less diarrhoea. Lactobacillus GG supplementation is well-tolerated and may prevent 5-FUinduced severe diarrhoea and abdominal discomfort and shows good symbiotic relation with Guar gum as documented by Österlund, P et.al (2007).

4. F Shao et. al (2014) performed the study to investigate the effect of microbial immune enteral nutrition and deep sea fish oil on the patients with acute enteritis in bowel function and immune status.24 patients received the said prebiotics whereas 22 patients as control. The concentration of serum albumin and pre-albumin and the number of CD3 + T cell, CD4 + T cell, CD8 + T cell, CD4 +/CD8 + and natural killer cell of the two groups were detected after treatment. Abdominal pain, bloating and diarrhoea were seen better than the control group and conclude that the prebiotics potential helps in Chemotherapy induced GI issues and immunity parameter.[45]

5. A study focused to evaluate the benefit of Fructo-oligosaccharides (FOS) in improving the quality of life as defined by the Gastrointestinal Quality of Life Index (GIQLI) and quantification of faecal Bifidobacteria was conducted on 57 individuals. And performed by N J. Wierdsma et.al (2009) .Following 6 weeks' intervention, GIQLI scores remained stable (65±14 versus 67±17) in the FOS group, whereas the non-FOS group values decreased (68±17 versus 64±19) compared to initial baseline data. While for the Bifidobacteria, the count remained stable in the FOS group (0.7×106±1.3×106 versus 1.0×106±1.3×106 baseline versus end-point), but decreased in the non-FOS group (3.6×1 06±8.0×106 versus 2.5×104±4.0×104). This suggests that prebiotic tube feeding may lead to a change in intestinal microbiota that could induce an increased quality of life in this patients.[45, 46]

6. A randomized double blind clinical trial was performed by R. Agustina et.al. (2007), where of Lactobacillus rhamnosus LMG P-22799 (probiotic: 5 x 108 CFU/100mL), inulin (prebiotic: 0.15 g/100mL), dietary fibre (soy polysaccharides: 0.2 g/100mL) were added as active ingredients for the early dietary management of 58 Indonesian well-nourished male infants aged 3-12 months suffering from diarrhoea. Where one group received the above (Study group) and other did not receive above formula (control group) along with rice meal. The weight gain and duration of diarrhoea was studied. Study group showed reduced diarrhoea compared to control, hence concludes that the prebiotics improves the gut health and cures the situation.[47]

7. As per the clinical trial review performed by J. A. Krumbeck et.al. (2016)The intestinal microbiota of patients following cytotoxic and radiation therapy significantly changes, most typically with an increase in Enterobacteriaceae and Bacteroides and a decrease in Bifidobacterium, Clostridium cluster. Mucositis may develop as a result of these alterations, especially if they cause diarrhoea and bacteraemia. In randomized clinical trials, the prevention of cancer therapy-induced mucositis by probiotics and prebiotic combination has been studied. In three out of six trials, the incidence of diarrhoea was significantly lower. In one study, there was a reduction in infection complications.[48, 49]

8. Smith et.al. (2008) tested FOS supplement (3 and 6%) on 5-FU (150 mg/kg)-induced intestinal mucositis in mice.[50] FOS reduced jejunum myloperoxidase activity. FOS (6%) also improved intestinal mucositis caused by 5-FU (300 mg/kg) (Galdino et. al., 2018).[51] FOS supplementation may prevent and treat intestinal mucositis by decreasing

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Journal of Coastal Life Medicine

inflammatory infiltration, partially preserving the intestinal epithelium, reducing body weight loss, and increasing catalase levels.

9. In a post biotic investigation on 5-FU-induced intestinal mucositis, Prisciandaro et. al. (2011) discovered that Escherichia coli supernatant partially protected the mouse gut (150 mg/kg).[52] this post biotic protected villus height and crypt depth and acidic mucin-producing goblet cells. Oral butyrate (9mM) reduced intestinal mucosa damage induced by this antineoplastic agent in another investigation. Hemorrhage, ulceration, and intestinal permeability decreased. TNF-α and IL-6 were reduced, and ZO-1 (zonulin) gene expression increased (Ferreira et al., 2012).[53]

10.N.S. Oh et.al. (2017) analyzed the effect of the supernatant of L. acidophilus A4-fermented mulberry leaf extract reduced gene expression of pro-inflammatory cytokines IL-1β and MPO and stimulated mucin gene overexpression (MUC2 and MUC5AC), reducing intestinal mucositis caused by 5-FU (150 mg/kg).[54]

Prebiotics in Chemotherapy induced Muscle wasting:

1. J.E.Inglis et.al. (2019), depending on the review of database quoted that the traditional Chinese medicine herb Astragalus membranous possesses anti-inflammatory, immunomodulating, and anticancer actions. NF-B and AP-1 signaling pathways and antioxidant mechanisms may reduce inflammation and oxidative stress in fatigued people. Huang et al. (2016) observed that astragalus polysaccharides, a significant bioactive element from Astragalus membranous, reduced fatigue-related oxidative stress and mitochondrial dysfunction and can be proposed as potent prebiotic.[55]

2. According to the study of Bindels L et.al (2016) a symbiotic strategy that included both a probiotic (L. reuteri) and prebiotic (inulin-type fructans) was performed. They went on to further explain this evidence. Both the colon cancer (C26) and leukaemia (BaF) mice models of cancer cachexia were used to assess the effects of this combination. They discovered that administering this mixture was linked to lessened muscle atrophy and cancer cell proliferation. In addition, mice given L. reuteri and inulin-type fructans had longer life times and reduced morbidity.[56, 57]

3. As per the study reported by G. Huang et.al. (2017), the non-toxic dosages of the triterpene saponins (ginsenoside-Rb3 and ginsenoside-Rd) that, when used as prebiotics, successfully restored the intestinal milieu and dysbiotic-gut microbial composition in an ApcMin/+ mouse model. The down regulation of oncogenic signaling molecules (iNOS, STAT3/pSTAT3, Src/pSrc), together with the reduction in polyp size and number, was achieved by Rb3 and Rd. By increasing the number of goblet and Paneth cells and restoring the expression of E-cadherin and N-Cadherin, both substances enhanced the gut epithelium and eventually improved the muscle restoration and weight loss.[58]

4. Malignant treatment involving chemotherapy is known to produce cachexia wherein muscle wasting and skeletal muscle fatigue are major parameters. B. Obermüller et.al. (2020) assess the effect of prebiotic supplementation with OMNi-LOGiC® FIBRE on intestinal microbiome, bacterial metabolism, gut permeability, and accordingly evaluate the weight gain and muscle wasting. For this study, 2,000,000 NB cells (MHH-NB11) were implanted into a thymic mice followed by daily supplementation with water or 200 mg prebiotic oligosaccharide (POS) OMNiLOGiC® FIBRE (NB-Aqua, n = 12; NB-POS, n = 12). Three animals of each tumor group did not develop NB. The median time of tumor growth (first visibility to euthanasia) was 37 days (IQR 12.5 days) in the NB-Aqua group and 37 days (IQR 36.5 days) in the NB-POS group ($p = 0.791$). Prebiotic supplementation with OMNi-LOGiC® FIBRE seemed to induce modifications of the fecal microbiome and improved the VOC profile and shown weight gain but did not improve gut permeability.[59]

5. Another study N.E.P Deutz et. al. (2011) found that, in comparison to a standard dietary supplement, a high-protein formula comprising high quantities of leucine, certain oligosaccharides, and fish oil was able to increase muscle protein anabolism in advanced cancer patients. A recent study found that individuals with stage III/IV NSCLC showed a robust whole-body anabolic response to 14 g of essential amino acids, providing more evidence for a maintained anabolic capability. Like that shown in healthy

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Journal of Coastal Life Medicine

matched controls, this effect was not affected by recent weight loss, muscle mass, mild to moderate systemic inflammation, or survival rates.[60, 61]

6. Buigues C et.al. (2016) examined the prebiotic fibers fructooligosaccharides (FOS), inulin, and peptic oligosaccharides (POS) on aged test subjects. According to a randomized controlled research on frailty in older adults, supplementing with inulin and fructooligosaccharides (FOS) for 13 weeks reduced fatigue and enhanced hand grip strength, whereas POS had little effect. This suggests that prebiotics might improve muscle performance. It is currently unknown whether prebiotics can improve muscle mass in older people who are fragile because muscle mass was not assessed.[62]

Some medicinal herbs and food as prebiotics:

The herbal remedies that are frequently utilized in Ayurvedic medicine and other conventional systems of medicine for gastrointestinal health and sickness. Christine Tara Peterson et al. looked at the potential of the Ulmus rubra (also known as slippery elm), Glycyrrhiza glabra (also known as liquorice), and the well-known polyherbal medicine blend (also known as triphala) of Emblica officinalis, Terminalia bellerica, and Terminalia chebula to enhance gut health by boosting the microbiota.[63]

According to Pamela Iheozor-study, Ejiofor's certain investigations have indicated that foods with high phenolic content have prebiotic properties. For instance, researchers discovered that giving 15 human participants 300 mg of catechin daily for three weeks greatly raised the amount of lactobacilli and bifidobacteria in their faeces while significantly lowering the amount of enterobacteriaceae, bacteroidaceae, and eubacteria. Additionally, it was assessed and reported that high levels of Lactobacillus acidophilus encourage and maintain the balance of the intestinal microflora in vitro while inhibiting harmful microorganisms. Accordingly, aqueous extracts of the herbs mint, thyme, and basil, which have various phenolic contents, have also been suggested as an alternate prebiotic compound to catechin, the major phenolic component of tea.[64]

Although there are many distinct types of prebiotics, short-chain fatty acids, especially acetic, propionic, and butyric acids, which are used as an energy source by the host organism, are the crucial final steps in the metabolism of carbohydrates. They can also be obtained from a variety of sources, including chicory, onion, garlic, asparagus, artichoke, leek, bananas, tomatoes, and many more plants, all of which have the potential to be used as prebiotics. [65]

Market review of prebiotics

The Prebiotics Market is projected to reach $6.61 billion by 2029, at a CAGR of 7.6% during the forecast period 2022–2029. The growth of this market is driven by the increasing consumption of prebiotics, the rising demand for nutraceuticals, and the increasing demand for plant-based food ingredients. [66, 67]

Key Findings in the Prebiotics Market Study:

The global market for prebiotics is divided into inulin, fructo-oligosaccharides, galactooligosaccharides, mannan-oligosaccharides, and other components based on the constituents they contain. The inulin market segment held the greatest market share for prebiotics globally in 2022. The usage of inulin in dietary items, which increases gut flora and limits the growth of dangerous organisms by enhancing gut function, is responsible for the huge market share of this category. Additionally, the demand for prebiotic inulin will rise due to the growing interest in natural products.[66]

Global market by geographic region:

The global market for prebiotics is divided into five key geographic regions: North America, Europe, Asia-Pacific, Latin America, and the Middle East & Africa. The region with the biggest share of the global prebiotics market in 2022 was Asia-Pacific. The significant market share is primarily attributed to consumers' growing interest in digestive health ingredients, the increased focus on boosting infant immune health, innovations in prebiotic formulations, the growing ageing population, and consumers' growing awareness of the connection between digestive health, immunity, and overall wellness.[67]

Current market formulations

There are combinations available with Fructo oligosaccharide (FOS) with coffee and curcumin selling as chocolate or green tea and mint flavor by

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Journal of Coastal Life Medicine

Happytizer Pvt. Ltd. Also, the combination of Guar gum FOS, and papaya with brand name of Prebiotic gut drink, combination of FOS, Inulin, and Dietary fibre as a drink. There are market products available in form of drinks, powders, chocolate bars etc.[68]

4. Conclusion:

Chemotherapy is regarded as the primary treatment for cancer, employing strong medicines with their well-known and well-documented significant adverse effects with which survivors must contend for a long or short length of time. To combat this prebiotic is found to be emerging trend which can be used together with chemotherapy medicines without diminishing their efficacy but these are not proven with a scientific mechanism of action. The field of Prebiotics is emerging, advantageous, and ripe for exploration due to its potential utility in the treatment of several prevalent and difficult-to-treat disease conditions, whereas the Probiotics field focuses on its personal benefits and deficiencies as it relates to living organisms. The use of prebiotics is a promising therapy strategy which is found to be safe in different preclinical settings although the clinical yet to be explored well.

The utilization of well documented prebiotics like inulin, fructans, FOS and certain herbs which release the SCFA during the metabolism are found to be promising in the field to cure chemotherapy adverse effects. Prebiotics drastically alter the microbiota population, boosting the number of bacteria that produce SCFA, amplifying the functional pathways that lead to SCFA, and increasing the concentrations of SCFA metabolites. Notably, most of the researches have demonstrated that a rise in SCFAs is associated with a considerable fall in tumor burdens. Prebiotics have antibacterial effects against gut pathogens, immune system modulation, and reduction of colitis and gut inflammation, prevention of CRC, gut homeostasis, and control of the host's energy metabolism.

With a focus on biologically active substances found in foods of plant origin that can lessen or alleviate the adverse effects of chemotherapy, prospects suggest that the inclusion of prebiotics can enrich and manage the gut microbiota. Depending on the literature findings it may be concluded that the prebiotics have the shown the proven capacity to reduce the mucositis, diarrhoea and other GI inflammation caused by chemotherapeutic agents.

Some studies demonstrated the correlation of muscle wasting and muscle fatigue as a crosstalk of disturbed gut health and loss of nutrients which can be cured by prebiotics. More over lack of well documented evidence in proving the mechanism of action of prebiotics in muscle wasting and GI inflammation and their correlation can be a major thrust area to explore.

DECLARATION OF CONFLICT OF INTEREST:

All authors declared that no conflict of interest regarding this review paper.

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