IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Probiotics a promising approach in colorectal cancer treatment: A Review

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Abstract: Probiotics are the "live microorganisms which when administered in adequate amounts and certain numbers confers a health benefit to the host". Traditionally these healthy bugs are used as an ingredient of food and are generally regarded as functional food and dietary health supplements. With the increasing health benefits and negligible side effects of probiotics they are widely used as medicine in the treatment of a wide range of clinical disorders. Probiotics plays an important role in relieving the symptoms associated with Inflammatory Bowel Disease (IBD), eczema, traveler's diarrhea, peptic ulcer, colon cancer, colorectal cancer etc. The present review focuses on the mechanism of action of probiotics in treatment of cancer. Additionally, how probiotics will be choice of drug in cancer therapy apart from antibiotics is also been discussed.

KEYWORDS:

Probiotics, carcinogen, Meta statis , invasion, colorectal cancer (CRC), prebiotics, synbiotics , prevention, Colon Cancer

INTRODUCTION:

Probiotics are the live bacteria and yeasts that are microorganisms which are good and safe for our body specially for our digestive system, by helping us to digest our food, also used to destroy some disease-causing microorganisms. They also help to treat other conditions and diseases, including skin infections, cancer and allergies. They are live microorganisms that are believed to offer a good health benefit to the person when taken in sufficient quantities. [1]

Probiotics Produce Lactic acid as it lowers the Ph of intestines and inhibiting bacterial enemies such as clostridium, salmonella, shigella, E. coli. They decreases the production of a variety of toxic or carcinogenic metabolites and also help in the Production of beta-D-galactosidase enzymes that break down lactose and By increase the absorption of minerals and vitamins, it can also improve digestion especially of milk products. It can help to improve appetite and growth performance. They Also act as barriers to prevent harmful bacteria from colonizing the intestines.[2]A cancer of the colon or may be rectum, is located at the digestive tract's lower end mainly. This type of cancer often have no symptoms but can be detected by screening. And For this , doctors recommend the screenings for those who are at higher risk or over the age of 50.The Symptoms of Colorectal cancer mainly depends on the size and where is the cancer located. Some patients commonly experienced the symptoms like changes in bowel habits, changes in stool consistency, blood in the stool and abdominal discomfort. Colorectal cancer treatment mainly depends on the size, and location of

the cancer and how far the cancer is spreading. Common treatments include surgery to remove the cancer, chemotherapy and radiation therapy.[3}

Colorectal cancer (CRC) is already the third leading cause of cancer death in the world, and its incidence is steadily rising in developing nations. Also known as colorectal adenocarcinoma, CRC usually emerges from the glandular, epithelial cells of the large intestine. The cancer arises when certain cells of the epithelium acquire a series of genetic or epigenetic mutations that confer on them a selective advantage [4]. With abnormally heightened replication and survival, these hyper-proliferative cells give rise to a benign adenoma, which may then evolve into carcinoma and metastasize over decades [5].

To prescribe as a common cancer for the list, the estimated annual cases for 2019 had to be 40,000 cases or more.

The most common type of cancer which is listed is breast cancer, in 2019. The other most common cancers which are found are lung cancer and prostate cancer.

colon and rectal cancers are referred to as "colorectal cancers," these two cancer types are combined for making the list. For 2019, and adding to a total of 145,600 new cases of colorectal cancer.

THE FOLLOWING TABLE SHOWS THE NUMBERS OF NEW CASES AND DEATHS FOR EACH COMMON CANCERS:

Cancer Type	Estimated New Cases	Estimated Deaths	Reference
Bladder cancer	80,470	17,670	AMERICAN CANCER SOCIETY : CANCER FACTS
Breast (Female – Male) cancer	268,600 – 2,670	41,760 – 500	AND NUMBERS 2019. ATLANTA,
Colon and Rectal cancer (Combined)	145,600	51,020	GA: AMERICAN CANCER SOCIETY, 2019.
Endometrial Cancer	61,880	12,160	ALSO AVAILABLE ONLINEEXIT DISCLAIMER.
Kidney (Renal Cell and Renal Pelvis) Cancer	73,820	14,770	LAST ACCESSED FEBRUARY 5, 2019.[6]

Leukemia (All Types)	61,780	22,840
Liver and Intrahepatic Bile Duct	42,030	31,780
Lung Cancer (Including Bronchus)	228,150	142,670
Melanoma	96,480	7,230
Non-Hodgkin Lymphoma	74,200	19,970
Pancreatic	56,770	45,750
Prostate	174,650	31,620
Thyroid	52,070	2,170

BURDEN OF DISEASE :

The patients of colorectal cancer in India is lower than the western countries, and it is positioned as seventh leading cancer in India.[1]

Globo can, 2018 data

New cases: 27,605

Deaths: 19,548

Total number of patients living with the cancer disease may be estimated as 53,700 (5 years prevalence for all ages)

Mean age of rectal cancer (RC): around 40-45 yr. [7]

About 1,096,000 new cases of colon cancer are estimated to be diagnosed in 2018, while about 704,000 new cases of rectal cancer are expected. Together, these comprise 1.8 million new cases of CRC. CRC is the most diagnosed cancer

among men in 10 of the 191 countries worldwide. No country has CRC as the most diagnosed cancer among women [8].

The CRC is more incident among men than women and 3–4 times more common in developed than in developing nations. Age-standardized (world) incidence rates per 100,000 of CRC in both sexes is 19.7, in males is 23.6, and in females is 16.3 .While the age-standardized incidence rate among men is 30.1/100,000 in high-HDI (human development index) nations, it is 8.4 in low-HDI nations (the same statistics for women are 20.9 and 5.9, respectively) [8].

VARIOUS PROBIOTICS:

Probiotics available in some foods and dietary supplements are similar to the probiotics that exist naturally in our gut. Probiotics which are naturally present in our body are: Saccharomyces boulardii (a yeast) and bacteria in the Lactobacillus and bifobacterium families of microorganisms.[9]

The necessary strains you must explore for are: strains that exerted antitumor activities against human colon cancer cells included

1.Bacillus polyfermenticus

2.LGG/Bb12

3. LGG/Bifidobacterium animalis subsp. lactis .

4.Lactobacillus acidophilus (colonizes the little viscus to support nutrient absorption and digestion of dairy)

5.Bifidobacterium longum (integrity of the gut wall and scavenger of toxins)

6.Bifidobacterium bifidum (digestion of dairy farm, complicated carbohydrates, fat, and protein).[10]

MAINTENANCE:

Anything that affects our epithelial duct microbiota and gut barrier will result in dangerous gut health. Medication (especially antibiotics) will severely have an effect on the range and many of the microorganism that lives in our gut. Even associate degree unbalanced diet, like a carbohydrate-rich food or a high fat diet, will have an effect on our gut implements of war and permit infections, inflammation, hypersensitivity. It is necessary to take care of sensible gut health before the system breaks down. Take a healthy, diet that has high vegetable and fiber content guarantee an everyday intake of probiotics and prebiotics to assist support sensible gut health. Prebiotic was represented as "a non-digestible food ingredient that beneficially affects the host by selection stimulating the expansion and/or activity of 1 or a restricted range of microorganism within the colon, and so improves host health".[3] Some supplements known as Synbiotics contain a mixture of probiotics and prebiotics.

Worldwide Probiotic market and Dosage Forms :

The probiotic market is driven by the study demand for health-based product, among shoppers, particularly by the younger generations. Probiotics are a region of purposeful foods and beverages, and best-known for rising gut practicality, together with different advantages, as well as immunity boost then on. There is no clear demarcation for probiotics-based prescribed drugs and food merchandise, with variations across completely different countries. Thus, the complexness within the restrictive, legislative, and technological aspects is serving as a significant hurdle for the market growth. The scope of the market includes probiotics, such as functional food and drink (Dairy merchandise, hard

merchandise, Non-Alcoholic Beverages, Dietary Supplements, and others), dietary supplement and animal feed by sort. Probiotic dietary supplements don't seem to be used for the treatment or cure of any specific disorders, considerably. However, they function a mode of delivering bound ingredients within the body to enhance the diet. By channel, the market is classified as supermarkets/hypermarkets, pharmacies/health stores, convenience stores, and others.

Various Dosage forms:

S.No.	Diseases	Probiotics
1	**Probiotics for Constipation**	1. Garden of life colon care 2. Lion heart pride probiotics 3. Nutrition essentials probiotics
2	**Probiotics for Diarrhea**	1.Garden of life raw probiotics 5-day max care 2. Florastor maximum strength probiotic 3. Bio sense probiotics
3	**For weight loss**	: 1. Garden of life raw probiotics: 2.VSL#3 3. Mega food megaflora
4	**For brain health:**	1. Garden of life dr. Formulated probiotic and mood supplement 2. Life extension florassist mood 3. Hyper biotics pro-15 probiotics
5	**Heart health:**	1. Innovix labs multi-strain probiotic 2. Nature's way primadophilus reuteri 3. Life extension florassist heart health probiotics
7	**General health**	**:** 1.GNC ultra 25 probiotic Complex 2. Foods probiotic-1
8	**Probiotics which may Improve IBS Symptoms:**	1.Renew Life Ultimate Flora Extra Care Probiotic 2.Jarrow Formulas Ideal Bowel Support 3.VSL#3

Reference : https://www.healthline.com/nutrition/best-probiotic-supplement#section6

Applications Of Probiotics :

Probiotics, Associate in Nursing example of a practical food, are the main focus of intense analysis activity in recent years and are outlined as "living microorganisms that upon activity in bound numbers exert health advantages on the far side inherent general nutrition."[11]

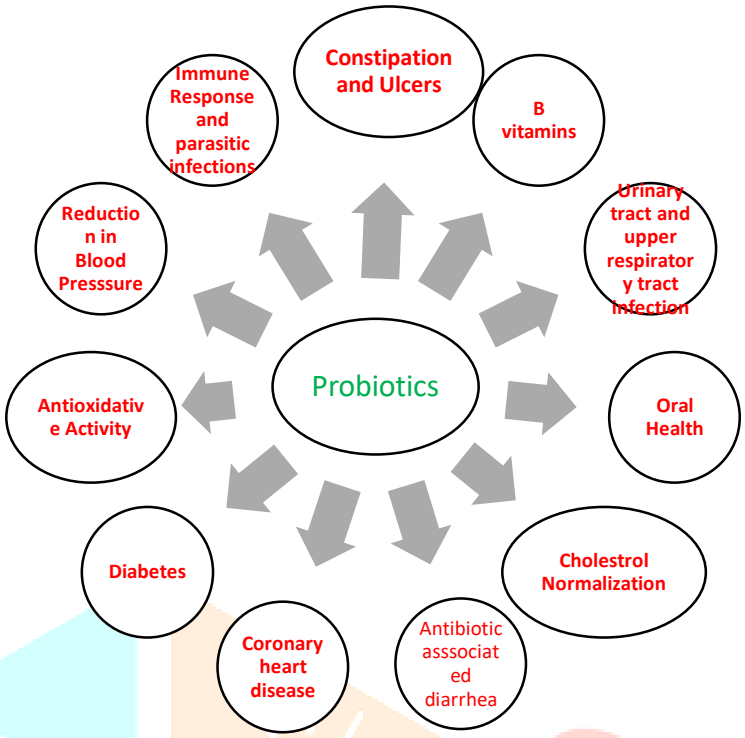
The list of useful effects attributed to probiotic bacterium is extensive[12] that has alleviation of inherited disease symptoms; bodily fluid steroid alcohol reduction; anti tumour effects assuaging constipation, relieving inflammation to call however some (joseph rafter) studies have shown that probiotic bacterium stop purported preneoplastic lesions or tumors elicited by carcinogens like one,2-dimethylhydrazine or azoxymethane.[9-10]

Several strains like *eubacteria rhamnosus* GG,[8,9] *eubacteria acidophilus*,[8,9*] eubacteria casei*, *Bifidobacterium longum*,[8,10] *Bifidobacterium infantis*, *Bifidobacterium adolescentis*, and *Bifidobacterium diacritical* mark showed vital suppression of colon growth incidence [Figure 5].[10]

Additionally, there's evidence for anticancer activities of science laboratory obtained in studies victimisation pre implanted growth cells in animal models.[11] anticancer activity found in peptidoglycans[12] isolated from *B.infantis* strain ATCC 15697[13] rumored anticancer polyose fractions originating from eubacteria cultures.

Nowadays, food isn't any longer thought-about by customers solely in terms of style, immediate nutrition wants however conjointly in terms of their ability to produce specific health advantages on the far side their basic nutrition price. the biggest phase of the practical market is dominated by healthy food product targeted toward up the balance activity of the internal organ microflora in recent years.[14] The probiotics square measure suppressed the harmful bacterium by dominant pH of the massive bowel through the assembly of potable, carboxylic acid acids.[15] Microbial-based medical care of cancer is one in all the rising cancer treatment modalities. Vital advancements are created to review develop live bacterium or microorganism product like proteins, enzymes, immunotoxins secondary metabolites of bacterium fungi that specifically target cancer cells cause growth regression through growth inhibition,

cell cycle arrests or necrobiosis induction.[16]



PROBIOTIC MECHANISM FOR INHIBITON OF COLON CANCER:

Probiotic microorganism have recently become the main focus of analysis due to their anti-cancer properties.

Probiotics have been shown to change the expression of different genes participating in cell death and apoptosis [10], invasion and metastasis [11], cancer stem cell maintenance [12] as well as cell cycle control [1].

Some epidemiological studies have indicated that consumption of large quantities of fermented milk products containing lactobacillus or bifidobacterial are associated with a lower incidence of colon cancer [8], although, different studies have instructed that intake of fermented dairy products imparts very little, or almost no protection [16].

The mechanisms by which probiotics may inhibit colon cancer are not yet fully distinguished. Although, there is evidence for: Alteration of the metabolic activities of intestinal microflora, alteration of physicochemical conditions in the colon, binding of potential carcinogens, short chain fatty acid production, production of anti-tumor properties or anti-mutagenic properties containing compounds, elevating the hosts' immune reaction and changing the hosts' physiology.

Lactic acid bacteria shrinked the certain activities of fecal enzymes in human volunteer studies [17]. After considering the outcome of feeding L. acidophilus strains NCFM and N-2 on the activity of three bacterial enzymes (β -glucuronidase, nitro reductase and azo reductase) in 21 healthy volunteers[18]. Both strains had close outcomes and caused a notable reduction in the specific activity of the three enzymes in all subjects after 10 d of feeding. A swing of the effect was perceived within 10-30 d of stopping Lactobacillus feeding; recommending that uninterrupted consumption of these bacteria was obligatory to continue the outcome. Human studies have revealed that the dimensions for probiotics to lessen the activity of bacterial enzymes is strain determined. To this end, L. plantarum 299V, L. rhamnosus DR20 and L. acidophilus A1 were not able to lower β -glucuronidase affects in healthy cases[17,18,19], while L. casei Shirota and L. acidophilus notably decreased enzymatic activity[15,16]. Reports issued to date do not always find reductions in the same enzymes, whereas findings with β -glucuronidase and nitro reductase are most

persistently practical. Even we do not have any knowledge about how or whether a decrease in these enzymetic activities affect cancer rates in man.

It has been advocated that large bowel cancer could be guided straight by minimizing intestinal pH[20], hence averting the extension of putrefactive bacteria. In rats given inulin accommodating diets with or without B. longum, an increase in caecal weight and β -glucosidase and a decrease in faecal pH were observed[18], though some other studies did not detect a significant change in intestinal pH[20].

One contension about colon carcinogenesis demands a cytotoxic effect on the colonic epithelium, deploy by bile acids in the aqueous phase of faeces, escorted by an increased proliferation of cells in the intestine[20]. Dietary fat has also been evaluated a risk factor for colon cancer. This event may be intervened by increased levels of secondary bile acids in the colon, produced by the action of bacterial 7a-dehydroxylase on primary bile acids. It has been exhibited that a 6-wk administration of L . acsidophilus fermented milk supplements to colon cancer patients arises in lower concentrations of soluble bile acids in faeces[21]. In a spare investigation, patients with colonic adenomas participated in a 3-mo study, where L. acidophilus was regulated jointly with B. bifidum[22]. During this era, the faecal hydrogen ion concentration was reduced considerably, and patients having a maximum proliferative actions within the upper colonic crypts than that calculated for subjects at low risk for colon carcinoma showed a big decrease after therapy by the lactic acid bacteria.

Mutagenic compounds, frequently set up in the western meat-rich diet, can be hurdle to the intestinal and lactic acid bacteria in vitro and binding has been set up to be suited well with the trimmed in the mutagenicity perceived after exposure to the bacterial strains. In an investigation, the potential of 22 strains of intestinal bacteria to hold together the mutagenic pyrolyzates was investigated and contrasted their capability to that of some dietary fibres[23]. Some indoles, including 3-amino1-methyl-5H-pyrido (4, 3-β) indole (Trp-P-2) were productively hurdled to all gram-positive and some gram negative bacterial cells, maize bran, and apple pulp and soybean fiber. The mutagenicity of Trp-P-2 for Salmonella typhimurium TA98 within the presence of S9 combinatin was strangled by the addition of L.casei to the reaction mixture, indicating that Trp-P-2 is not causing any mutation under the assay conditions. A further current study signifies a declined intake of Trp-P-2 and its metabolites in various tissues of mice enlarged with dietary lactic acid bacteria[24]. furthermore, the dissipation of lactobacilli by human volunteers has been shown to reduce the mutagenicity of urine and feces associated with the ingestion of carcinogens in cooked meat[25]. It is practicable that the lactic acid bacteria companion are regulating the intake and excretion of mutagens by simply binding them in the intestine. Lactobacilli have also been shown to degrade nitrosamines[26]. Nitrosamines have been manifested to be carcinogenic in animal models and these compounds have been noticed in human faeces.

Probiotics in Cancer Therapy : In last few years, probiotics uses are increasing day by day as a part of combination therapy with conventional treatment of cancer. An previous case, controlled and comparative study performed on 223 patients results in 1993 shows that combination therapy including radiation and treatment with heat-killed L. casei strains (LC9018) and improved the induction of immune response mechanisms against cancer cells thereby enhancing tumor regression in patients with carcinoma of the uterine cervix [27]. Research on azoxymethane-induced CRC mice model treated by the probiotic mix composed of seven different strains of lactobacilli, bifidobacterial , and streptococcus demonstrated suppression of colon carcinogenesis due to modulation of mucosal CD4+ T polarization and changes in the gene expression [28]. Moreover, current experiment explored the effects of B. infantis administration in CRC rat model demonstrated a considerable attenuation of chemotherapy-induced intestinal mucositis correlated with decreased level on proinflammatory cytokines (IL-6, IL-1β, TNF-α) and increased CD4+ CD25+ Foxp3+ T regulatory cell response [29]. As a result of these findings, probiotic bacteria have been gaining traction as a crucial component in successful cancer immunotherapy [35,38-40].

Latest experiments:

The most latest experiments performed on mice have shown the key role of gut microbiota (Bacteroides and Bifidobacterium) in anti-PD-L1 (Programmed death-ligand 1) and anti-CTLA-4 (cytotoxic T lymphocyte-associated protein 4) therapies [34,35]. Immuno modulatory result was exhibited in intense activation of nerve fibre cells and also the advancement of antitumor lymph cells response. Essentially, Sivan et al. [35] observed a similar improvement of tumor control as a result of Bifidobacterium treatment alone compared to anti–PD-L1 therapy, whereas combination of both strategies was sufficient to nearly eliminate tumor outgrowth. These groundbreaking results indicate that administration of probiotics appears to be a promising strategy in maximizing the efficiency of cancer immunotherapy.[41]

Various Types of Cancers, probiotics strains and their therapeutic impacts:

Types of Cancer	Probiotic Strain	Therapeutic Impacts Of Probiotics	Reference
Head and Neck Cancer	L. *brevis* L. *acidophilus*	Probiotic reduces the incidences of ulcerative inflammations of oral mucous membranes in the treated patients. Release of free radicals and Ca2? from cancer cells	Sharma.et al[43] Shi et al[44]
Skin	L. *rhamnosus* GG	Higher production of IFN-c, T-helper, CTL Increase IgA? and activated dendritic cells	Weill et al [45] Yazdi et al [46]
Breast	L. *acidophilus*	Higher production of IL-12 Decrease in tumor growth	Maroof et al [47]
Liver, gall bladder	L. *rhamnosus* P. *freudenreichii*	Decrease the amount of cancer proteins viz. c-myc, bcl-2, cyclin D1 and rasp-21 Enhancement in the levels of GSH, SOD, CAT Reduce inflammation and infection	Kumar et al[48] Kanazawa et al [49] Sugawara et al [50]

Esophagus, stomach	L. *rhamnosus* strain GG L. *casei* P. *freudenreichii*	Increase the amountof total organic acid and acetic acid Decrease infection and inflammation Resist gastric pH and inhibit the growth of H. pylori Reduce ornithine decarboxylase mRNA and activity, polyamine content and neoplastic proliferation Inactivate NF-jB promoter activity and inhibit mTOR-mediated signaling Activate caspase and release cytochrome c Strengthen the toxicity of drug Reduce insulin resistance	Tanaka et al [51] Brunser et al [52] Linsalata et al [53] Hwang et al [54] Cousin et al [55] Shao et al [56] Hakannson et al [57]
Colon, rectum	P. *freudenreichii* L. *casei* L. *rhamnosus* B.*polyfermenticus* L. *acidophilus* B. *longum* L. *gasseri*	Cause cancer inhibition by necrosis Decrease MMP-9 and increase the tight junction protein, increasing IL-10 secreting cells, cellular apoptosis and Diminished the pro carcinogenic enzymes Suppress the ErbB2 and ErbB3 receptors Potentiate 5-fluorouracil Prevent high-grade dysplasia or tissue damage Increase the antiangiogenic factor angiostatin, VDR expression and alkaline sphingomyelinase Inhibition of aberrant crypt foci Activation of PPARc	Lan et al [58] Escamilla et al [59] De Moreno et al [60] Ma et al [61] Baldwin et al [62] Foo et al [63] Dubey [64] Asha And Gayatri [65]
Cervix	B. *adolescentis* L. *acidophilus* B. *bifidum*	Suppress cancer precursors Improve stool consistency in irradiated patients	Verohoeven et al [66]
Bladder, prostrate	L. *casei* L. *rhamnosus*	Potentiate drug Enhance the activity of dendritic cells Activate neutrophils and induce DC maturation TRAIL production facilitated NK activity	Naito et al[67] Seow et al [68] Feyisetan et al[69] Kandasamy et al [70] Horinaka et al [71]
Blood	L. *kefiranofaciens* L. *kefiri*	Down-regulate TGF-a and up-regulate TGF-b1 mRNA expression	Maalouf et al [72]

	S. turicensis L. *reuteri* L. *gasseri*	Reduce the expression of atrophy markers Decrease inflammatory cytokines	 Tavil et al [73] Bindels et al [74]

Conclusion:

Comprehensive, analysis in vitro systems and in a very broad scope of animal models lay out substantial perceptible that probiotics exert anti-neoplastic effects. Their dissipation will be favorable in averting the onset of cancer, however conjointly within the treatment of existing tumors. though, proof from human investigations remains finite. several researchers have known the necessity for fastidiously designed human clinical trials. what is more, analysis is needed to spot the probiotic, prebiotic or syn biotic union that may be additional effectual for humans. It's probable that there'll not be a supreme remedy for all cases, however the remedy can rely upon the individuals' distinctive microorganism composition. New choices square measure given through the genetic manipulation of probiotics, planned to act as a delivery system for anti-neoplastic factors within the colon. whereas this field of study is favorable and thrilling, this enthusiasm ought to be modulated by the actual fact that we have a tendency to square measure seemingly a few years removed from deciding the way to use these negotiators and their ultimate role could endure quite restricted. though, its secure to add up that probiotics clutch vital prospective as a replacement set up of action for the hindrance and treatment of large intestine cancer. Probiotics are the live safety microorganism and these microbes generally provide a healthy environment for gut system. All the specified scientific evidences and various invitro and in vivo based studies indicates that the use of probiotics may prevent the risk of colon cancer. But most of the studies related to prevention of colon cancer by using probiotics are unclear, further confirmation studies are needed and the observed effects cannot be generalised. Future research needs in terms of the underlying mechanism of action involved in each of the observed effects.

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