Indian Journal of Pathology and Oncology 2023;10(3):224–232

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Pathology and Oncology

Journal homepage: www.ijpo.co.in

Review Article

Role of *Lactobacillus* and calcium in colorectal cancer

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ARTICLE INFO

Article history:
Received 23-07-2023
Accepted 25-08-2023
Available online 27-09-2023

Keywords:
Probiotic
Calcium
Lactobacillus
Colorectal cancer
Wnt signaling pathway

ABSTRACT

Colorectal cancer (CRC) is the third most cancer which is prevalent globally. It is the second most leading cause of mortality worldwide. In Asia Colorectal cancer is most abundant type of cancer. Causative factors involved are genetic pattern, western lifestyle, alcohol, smoking, etc. The commonest therapy for colorectal cancer is the combination therapy of 5-fluorouracil with Leucovorin which is either co-administered with alkylating agent Oxaliplatin or with a topoisomerase inhibitor Irinotecan. There is still a need of therapeutic agent that increases the survival rate in colorectal cancer patients. Probiotics are well known to increase the proliferation of beneficial bacteria and recently they are widely researched for regression of carcinogenesis. *Lactobacillus* a commonly used probiotic, is observed to increase the expression of apoptotic ligand by modulating TNF action. *Lactobacillus* has also shown to represses cyclin D1 and inhibit the Wnt/β-catenin signaling thereby, not only prevent the proliferation of cancerous cells but also ensure the apoptosis of CRC cells. Calcium is a vital element in many biological pathways including cancer signaling pathway. A wide variety of research reflects the role of calcium in suppression of cancerous cells. Recently calcium has shown its role in inhibiting Wnt/-catenin signaling canonical pathway in colorectal cancer cells. The review focuses on the role of calcium and probiotic as a natural therapeutic option in the treatment of CRC.

1. Introduction

Cancer is considered as 2nd leading cause of death globally. Cancer treatment has grabbed attention in last years. Apart from breast and lung cancer, Colon cancer is third most diagnosed cancer in world. As per survey Asia has highest burden of Colon cancer. Around more than eighteen lakh new patients had CRC, with a mortality of around 880,792, as published in the GLOBOCAN (2018) data issued by WHO, Surprisingly among the above mentioned number for newly diagnosed CRC patients 50% belonged to Asiatic region.[1] The prevalence of colorectal cancer in both male and female is equal. Various therapeutic regimen is used in treatment of colorectal cancer like FOLFOX: leucovorin, 5-FU, and oxaliplatin, FOLFIRI: leucovorin, 5-FU, and irinotecan, CAPOX: capecitabine and oxaliplatin, etc.[2] There is still a need of therapeutic agent that increases the survival rate in colorectal cancer patients eventually by reducing the cytotoxic adverse effects of existing regimen.

Now-a-days anticancer agents used in the treatment and management of cancer differ in their structure and function out of which certain drugs act either by activation of pro apoptotic signal or by repression of pro survival signals. These agents are found to work mainly by modulating Ca^{2+} signaling pathways.[3] Calcium intake has shown evidences that directly link its role in the apoptosis of colorectal cancer cells. Probiotics are the healthy bacteria, which are administered to balance the healthy microflora in gut. Modulation of gut microflora with probiotic has established its beneficial role in treatment of several disease condition.

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https://doi.org/10.18231/j.ijpo.2023.051

Lactobacillus bacteria is abundant in gut and is commonly present in curd and other milk products. Since decades, *Lactobacillus* has been known for its role in diarrhea; recently it has shown suppression of carcinogenesis. It has found to have role in downregulating the proliferation of cancer cells. *Lactobacillus* has shown to modulate several cancers signaling pathways which enhances the apoptosis of cancer cells.[4]

Several medical studies have shown the role of calcium and probiotic in inhibiting the cancer cells. Calcium and probiotic therapy have shown to arrest proliferation and induce apoptosis of colorectal cancer cells.

2. *Lactobacillus* in Colorectal Cancer

Probiotics including Bifidobacterium, *Lactobacillus* and Clostridium butyricum are microbes with multiple health benefits to humans.[5] *Lactobacillus* bacteria present in gut is known to make certain antiangiogenesis factor which has beneficial role in cancer. *Lactobacillus* has also been found to produce glutathione (GSH), catalase (CAT) and superoxide dismutase (SOD) which are established for their antioxidant action.[6] This probiotic regulate immune response and is found to be effective in suppression of cancerous cells.[7]

3. *Lactobacillus* and Cancer Signaling Pathway

Balancing the gut flora by increasing the beneficial bacteria and suppressing the harmful bacteria is an established role of probiotics. However, the mechanism lies in suppression of pro-inflammatory cytokines, inhibition of pre neoplastic factors like NF-κB and STAT3 and repression of Wnt/β-catenin pathway. Improving the gut barrier function, regulating the immune response and increasing the apoptosis of neoplastic cells are few mechanisms through which various probiotics helps in management of CRC.[5]

Lactobacillus role in colorectal cancer is mainly via increase in the expression of apoptotic ligand by modulating TNF action. *Lactobacillus* has also shown to represses cyclin D1 /BIRC5a expression and inhibit the Wnt/β-catenin signaling[8] thereby, not only preventing the proliferation of cancerous cells but also ensuring the apoptosis of CRC cells.[9] Certain probiotics have shown action against carcinogens with SCFA (Short Chain Fatty Acid) production. SCFA influence both anti-inflammatory and antineoplastic action during cancer treatment.[10] Probiotic strains prevent CRC occurrence by inhibiting the expression or reducing the formation of cytokines which cause inflammation.[10] Probiotics hinder monocyte proliferation & stimulate antibody responses in the immune process. Probiotics also decrease proinflammatory cytokines such as interleukin-1β & interleukin-6, and increase anti-inflammatory cytokines, such as IL-10 and IL-12.[11] Elimination of early cancer cells by probiotics is done by activation of phagocytosis.[11] Mechanism like boosting macrophage activity, increasing TNF-α, INF-γ, IL-12, & NO, and stimulation of immune responses are the antitumor effects exerted by micro-ecological agents, especially probiotics.[12]

Inhibition of progression of CRC and cell cycle regulation is seen with *Lactobacillus* rhamnosus.[13] Maintenance of the balance of intestinal flora and inhibition of pathogenic bacteria was reported with *Lactobacillus* acidophilus. Polyphosphate derived from *Lactobacillus* is associated with apoptosis of CRC. *Lactobacillus* casei induces apoptosis by blocking the cell cycle. In a study, author observed that mutation caused by a chemical carcinogen N-methyl-N'-nitro-N-nitrosoguanidine and a food-derived carcinogen 2-amino-3,4-dimethyl-imidazo[4,5-f]-quinoxaline are inactivated by rhamnosus 231 and *Lactobacillus* rhamnosus Vc.[14] *Lactobacillus* rhamnosus Probio-m9 effects on CRC were reported in a study by suppression of p-signal transducer. Lactobacillus rhamnosus inhibited p-AKT and promoter of transcription-3. It has been shown to improve the gut bacteria balance especially Akkermansia, Bifififidobacterium, and Blautia.[15] A study, conducted using lactic acid bacteria Pediococcus pentosaceus exhibited reduction in tumor mass and inhibited the proliferation of CRC.[16] Increased SCFA like butyric acid through increased production by *Lactobacillus* fermentum NCIMB 5221 and Bifidobacterium lactis have shown to be successful in arresting the tumor cell growth and ensuring their apoptosis.[17] Several strains of Lactobacillus species including. L. delbrueckii, L. casei, L. plantarum are found to inhibit the mutagenic agents like DMH & MNNG chemically known as Dimethylhydrazine & methylnitronitrosoguanidine.

Several lactic acid bacteria have shown to regulate the levels of omega fatty acids by increasing the conjugated linoleic acid and decreasing the production of leukotrienes and prostaglandins in colon cells.[18]*Lactobacillus* fermentum NCIMB 5221 increase the synthesis of SCFAs (Short Chain Fatty Acids), and thus enhance the anti-proliferative function in CRC.[19]

4. Role of *Lactobacillus* in 5-fluorouracil (5-FU) Resistant CRC cells

In a Colorectal cell line containing 5-FU resistant cells, *Lactobacillus* plantarum (L.P) and 5-FU combination inhibited CRC cells, mainly through apoptotic induction and suppression of the Wnt/β-catenin signalling.[20] L. rhamnosus GG inhibit the uncontrolled multiplication of several CRC cell lines including HT-29, SW480 & Caco-2 by prompting apoptosis of neoplastic cells as well as by arresting them in cell cycle.[6]

5. Dietary Habits Interlinked to Gut flora and Colorectal cancer (CRC)

A High fat, refined sugar and low fibre, negatively affects the Gut flora. High fat and low fibre diet supports the growth of toxic bacteria like Fusobacterium nucleatum and Bacteroides fragilis. These toxic bacteria trigger an inflammatory response, increase the oncomirs and decrease tumor suppressor miRNAs. Oncomir promotes cell multiplication and arrests cell death, ultimately causing CRC. However, fibre rich diet with minimal fat positively supports growth of *Lactobacillus* and Bifidobacterium. These healthy bacteria enrich the gut flora and hence inhibit an inflammatory response, decrease the oncomirs and increase tumor suppressor miRNAs. Decrease in oncomir arrests multiplication of cells and increase in tumor suppressor miRNAs promote apoptosis of tumorous cells. Similar to healthy diet a probiotic supplement maintains a healthy gut flora contributing in prevention of CRC.[20]

Table 1: Different *Lactobacillus* showed an anti-tumor activity against colorectal cancer[17]

Bacteria	Mode of anti-cancer activity
L. plantarum, L. casei, L. acidophilus, L. delbrueckii,	They are found to inhibit the mutagenic agents like DMH (1,2 Dimethylhydrazine) and N-methyl-N′-nitro-N-nitrosoguanidine (MNNG). Lactobacillus have shown to regulate the levels of omega fatty acids by increasing the conjugated linoleic acid and decreasing the production of leukotrienes and prostaglandins in colon cells
L. rhamnosus, L. reuteri	Cancer is linked to loss of Tight junctions TJ in Epithelial cells. L. rhamnosus, L. reuteri increase TJ protein
L. rhamnosus	Induces apoptosis through the activation of p53 & inhibition of NF-kB
L. reuteri	Inhibited TNF-induced NF-kB activation and induced apoptosis of activated immune cells
Lactobacillus	Induce maturation of dendritic cells (DCs) and enhance cytolytic potential of NK cells through production of interferon gamma (IFN-γ)
Lactobacillus casei	Ferrichrome of *Lactobacillus* case inhibits the growth of colon cancer by inducing apoptosis through the -Jun N-terminal kinase pathway
L. fermentum, B. lactis	Enhance SCFA production which successfully arrest the tumor cell growth and ensuring their apoptosis

6. Research progress in *Lactobacillus*

6.1. Clinical evidences

In a study, when *Lactobacillus* rhamnosus was given in combination with 5-fluorouracil (5-FU) in colon cancer patients, it helped to improve the oral mucosa and alleviate diarrhea.[21] In colon cancer patient administration of combination of Inulin with L. rhamnosus GG (LGG) and B. lactis Bb12 improved the immune response.[22] In a trial, patients with moderate to severe atypical cellular hyperplasia were administered either wheat bran or *Lactobacillus* casei or *Lactobacillus* shirota. It was observed that the tumor generation was less with probiotic intake.[20] 380 subjects with at least 2 colorectal tumors removed were assigned to the wheat bran (n=95), L. casei (n=96), both (n=96) and no treatment (n=93) groups, respectively. As compared to control group, the multivariate adjusted ORs for occurrence of tumors were 0.76 (0.50-1.15) and 1.31 (95% CI 0.87-1.98) for the L. casei group and wheat bran group, respectively. L. casei group had significantly lower rate of occurrence of neoplasm having moderately abnormal cell structure.[23] In both case controlled studies conducted using yoghurt and cultured milk consumption were shown be inversely associated with colon cancer.[24] Intake of milk and milk products, in high amount has shown to reduce the incidence of CRC in Finland than in other countries, despite a high-fat intake as per epidemiological study data.[25,26] In a clinical study where the intake of fried minced beef showed urinary mutagenicity. Administration of *Lactobacillus* casei demonstrated a marked suppressive effect on urinary mutagenicity.[27] In another study, a short term (3 days) intake of L. acidophilus has showed lower fecal mutagenicity in population consuming fried meat as against fried meat diet and ordinary fermented milk.[28] *Lactobacillus* consumption demonstrated a marked suppressive effect on the urinary mutagenicity arising from ingestion of fried ground beef in humans.[27] The mutagenicity of urine and faeces associated with the ingestion of carcinogens in cooked meat is shown to be reduced due to the consumption of lactobacilli in a study on healthy volunteers.[24] The atypia of colorectal tumours in patients who had undergone resection was suppressed by intake of live L. casei Shirota (LcS).[29]

CRC patients shows abundance of colon cancer associated microbes such as Fusobacterium, Selenomonas, and Peptostreptococcus. In an intervention study of CRC patients who received probiotics containing L. acidophilus and Bifidobacterium animalis versus the CRC patients who were not receiving probiotic were compared. It was observed that patients receiving the probiotic combination has 77% excess of butyric acid (SCFA) producing bacteria including Clostridiales spp. and the phylum Firmicutes, especially Faecalibacterium as compared to 63% in CRC patients who did not receive probiotics.[30] Colon cancer patients receiving probiotic combination were associated with decrease in CRC-associated bacteria like Fusobacterium and Bacteroides.[31,32] Several species of *Lactobacillus* and Bifidobacterium had shown to decrease the multiplication and growth of colon cancer cells including *Lactobacillus* plantarum, *Lactobacillus* casei, *Lactobacillus* rhamnosus, *Lactobacillus* acidophilus, *Lactobacillus* paracasei, Bifidobacterium lactis and Bifidobacterium longum

Probiotic supplementation also reduced the inflammation in patients with colon cancer. In the patients who underwent surgery for colon cancer probiotics had shown to increase the number of beneficial bacteria and reduced the number of pathogenic bacteria in feces. These probiotics are found to stimulate the immunity, which eventually halt the metastasis of the colon cancer cells. *Lactobacillus casei* regressed atypical colorectal tumors, while on the other hand *Lactobacillus* rhamnosus effectively alleviated abdominal pain caused by chemotherapeutic regimen of 5-FU.[6]

6.2. *Preclinical evidences*

Probiotics was shown to reduce the proliferation of tumor cells, tumor count, and reduced the expression of NF-κB, in an inflammation induced colon cancer in a mouse model.[33] *Lactobacillus helveticus* inhibited proliferation and tumor formation, and reduced the TH17 cell count involved in production of IL17, in a mice with colon cancer.[33] *Lactobacillus casei* strain Shirota (LcS) by inhibiting IL-6 and downregulating inflammation has been shown to have protective properties against CRC in a mice study.[34] In various animal studies where colorectal cancer inducers like Azoxymethane, Methyl nitrosourea, DMH and Dextran sodium sulfate were administered to either rat or mice, probiotics have been reported to reduce the activity of β-glucosidase & β-glucuronidase, ammonia concentration, aberrant crypt foci count, effects of cytotoxic and genotoxic, chronic inflammation, oxidative stress, development of dysplasia and carcinoma, and colitis; and increase butyrate and histone-acetylation levels, apoptosis, tumor suppressor miRNAs, and CXCR2 signaling.[6] In a study, there was a significant suppression of the in vitro neoplastic proliferation as well as reduction in the mortality rate in the mice who were administered tumor cells by injection. This study specifically used the cytoplasmic fraction of *Lactobacillus acidophilus*, *Lactobacillus casei* YIT9029, and *Bifidobacteriumlongum* HY8001 in treatment group.[35] An in vivo study demonstrated, dose-dependent growth reduction CRC cells (CT26) in BALB/c (Bagg Albino) mice due to peptidoglycan from a *lactobacillus species*.[36] *L. bulgaricus* and *B. longum* fed rats showed a reduced incidence and number of induced colonic tumors.[37] In a study, yogurt containing 6 x 10^9 CFU of *L. bulgaricus* and *S. thermophilus* showed inhibition of tumor progression and promotion in a DMH dihydrochloride induced colorectal cancer in mice.[38] *Lacticaseibacillus rhamnosus* GG is found to arrest the initial progressive phase of dimethyl hydrazine induced colon tumors, especially in animals fed a high-fat diet.[39] Author Goldin and Gorbach, observed reduced incidence of DMH-induced colon carcinogenesis and increased latency period in rats on dietary supplementation of L. acidophilus.[40]

6.3. *Calcium citrate in colorectal cancer*

Calcium is an essential mineral required for growth and development of bones.[41] Ingestion of dietary Ca^{+2} from various sources like fruits and vegetables is inversely relate to the risk of CRC has been reported from various data.[42,43] Data suggest that vitamin D in the form of cholecalciferol & Calcium duo can potentially arrest the uncontrolled cell proliferation. Cell proliferation have been shown to decrease in the presence of elevated vitamin D and Calcium levels in various cell culture studies.[44] Cholecalciferol, a form of vitamin D & calcium intake has shown to be beneficial in preventing several types of cancer. This has been reported through various epidemiological and preclinical studies. Vitamin D in the form of Cholecalciferol & calcium have the strongest effect in prevention of colorectal cancer (CRC) as observed in studies.[45] Cholecalciferol which is a vitamin D & calcium duo is found to be effective in arresting metastatic progression by several mechanism including stimulation of differentiation, apoptotic pathway and enhancing adhesion. This combination also inhibits multiplication of cancer cells and suppress inflammatory markers.[46]

Calcium is found to reduce the risk for colon cancer which is supported by two hypotheses, either by the bile acid sequestration or by the regulation the cell cycle.[47] High consumption of calcium through diet or supplements, results in binding of calcium to toxic bile acids & fatty acids which are produced as a result of fat digestion. The above action of calcium halts the inflammatory trigger of toxic bile acids & fatty acids which act as mutagens and mitogens.[47]

6.4. *CaSR (Calcium Sensing Receptor) mediated inhibition of the Wnt/-catenin pathway*

The calcium sensing receptors, CaSR are present in the epithelial layer of colon which modulate the inflammatory responses and gut barrier function.[48] CaSR regulate a balance between crypt cell division and apoptosis. In an intestinal-specific CaSR knockout mouse, it was observed that proliferation was upregulated in the crypt cells and apoptosis was downregulated leading to expansion of proliferative zone.[49] Intake of rich calcium diet interact with CaSR present on the colonic epithelium and further activate intracellular anti mitotic pathways.[50]

6.5. *Role of CaSR in cell cycle control in colon carcinoma*

Initially activated CaSR inhibit the activity of PLA2. PLA2 inhibition in turn downregulates the arachidonic acid and eicosanoids availability required for proliferation of cells. Later on, these cells are inhibited in the G1/S-phase transition due to suppression of c-myc proto-oncogene. Furthermore, suppression of cyclin D1 and stimulation of cyclin-dependent kinase inhibitor p21 occurs. CaSR directly

inhibit the Wnt signaling pathway in intestinal crypt cells by suppressing T-cell transcription factor (TCF)-4 and inducing the E-cadherin protein which is responsible for tumor suppression.[51]

6.6. Calcium has anti-inflammatory effect

CaSR increases claudin-2 tight junction expression and hence maintains the gut barrier function. Claudin-2 suppress release of inflammatory mediators thereby exerting anti-inflammatory action.[52]

6.7. Calcium induces apoptosis

High calcium consumption triggers the G protein coupled receptors called CaSR which increases intracellular IP3 levels, this cascade of secondary message induces the release of stored calcium from endoplasmic reticulum, which raises cytosolic calcium concentrations. High cytosolic calcium is a triggering factor for apoptotic pathway thereby causing apoptosis of cancerous cells. This calcium stimulated neoplastic cell apoptosis is mainly mediated by caspases, certain apoptotic proteins and death causing receptors. Another cause for apoptosis of colon cancerous cell is mitochondrial calcium overload which results in mitochondrial malfunction.[53]

The pathogenesis of several chronic diseases is linked to low calcium intake. Low calcium intake is directly proportional to total cancer incidence.[51,54] Various research have suggested the role of extracellular Ca^{+2}in halting colon cancer cell proliferation and on the other hand enhancing differentiation of cells (via upregulating signaling pathways).[55] In CRC pathology the early phase dysregulation in cell functioning pathway like APC/Wnt/CTNNB1 (Catenin Beta 1) beta Catenin pathway is commonly seen.[56,57] Several studies have reported positive results with calcium administration in early phase of colon cancer which mainly emphasize on action of extracellular calcium on colon neoplastic cells[58] & normal colon cells[59] where calcium downregulates the CTNNB1 transcription.

7. Research Progress in Calcium

7.1. Clinical evidences

In a study, patients with adenomas were given 1200 mg of calcium in combination with 400 IU of Vitamin D. In these patients' half of the polyps were transected and remaining were marked & left in situ, the combination was effective in reducing the proliferative index in polyps as well as in flat mucosa. Mucin 5AC levels (a marker of malignancy) were negatively impacted with supplementation of Calcium and Vitamin D.[60]

A meta-analysis was conducted to see the relationship of high dietary Calcium & Magnesium with incidences of CRC. The analysis showed an inverse relationship of high dietary Calcium and Magnesium and colon cancer, since the HR was found to be 0.76 (95% CI 0.72, 0.80) & 0.80 (95% CI 0.73, 0.87) respectively. Another meta-analysis including case studies also showed that intake of food rich in Ca^{+2}, Mg^{+2}, and K^{+} was inversely correlated to incidence of colorectal cancer, since the OR was found to be 0.36 (95% Confidence interval 0.32, 0.40), 0.80 (95% Confidence interval 0.63, 0.98) & 0.97 (95% Confidence interval 0.74, 1.21) respectively.[61]

Another meta-analysis including randomized trials concluded that high calcium intake prevents the relapse of adenomas (RR, 0.88 [95% Confidence interval 0.79 to 0.99]). In addition to this subgroup analyses successfully showed that high dose calcium (≥1600mg/day) effectively offers better protection in terms of adenoma relapse (Relative risk, 0.74 [95% Confidence interval 0.56–0.97]).[62]

In a systemic review and meta-analysis, calcium supplementation was moderately effective in preventing adenomas (Relative Risk = 0.89, 95% Confidence interval: 0.82-0.96 for fixed effect; and Relative Risk = 0.87, 95% Confidence Interval: 0.77-0.98 for random effects) in participants who had undergone follow-up colonoscopies. The NNT (Number Needed to Treat) was 20 (95% Confidence Interval: 12-61) in order to halt a single colorectal adenoma relapse in a time period of 3-5 years.[63]

Twenty-nine studies (9 cohort, 20 case-control) examined the association between calcium intake and colorectal cancer. A data from twenty-two studies revealed a moderate protection of calcium supplementation in CRC patients. Few trials highlighted that high dose of calcium supplementation reduces CRC risk. It negates the CRC risk by 28 - 69%.[64] Around 88000 women & 44000 men were included in the Nurses' Health Study & Health Professionals Follow-Up Study. These subjects were assessed and followed up for a duration of 4 years for their calcium intake. Around 3,078 incident CRC cases were documented. A statistically reliable reduction in CRC risk (multivariable RR: 0.78, 95%Confidence Interval: 0.65–0.95) was seen with total calcium intake (≥1400 vs. <600 mg/d). However, enhanced risk reduction was observed on distal colon cancer (0.65, 0.43–0.99.[65]

In a meta-analysis including fifteen studies with a total of 12,305 subjects, consuming calcium ranging from 250–1,900 mg/day were followed for 4-16 years. It was observed that every 300 mg/day incremental dose of total calcium effectively reduced 8% risk of colorectal cancer. The risk decreased less steeply in higher range of total calcium intake.[66]

A Meta-analysis conducted in patients with adenomas receiving 1200 - 2000mg/d of calcium supplementation showed reduction of recurrence of adenomas (Relative Risk = 0.80 [95% Confidence Interval, 0.69–0.94], P = 0.006).[67]

A meta-analysis of 26,335 CRC patients with calcium supplementation showed a moderate risk reduction. The

difference between relative risk of highest and lowest calcium consumption was found to be 0.76 for colon (10 cohort) with 95% Confidence Interval: 0.69–0.84, p value for heterogeneity = 0.70 and 0.72 for rectum (7 cohort) with 95% Confidence Interval: 0.60–0.86, p value for heterogeneity = 0.92.[68]

A study was conducted to corelate the link between intake of calcium along with vitamin D & prevalence of colorectal cancer. The study included large patient population with 85,903 males & 105,108 females. The results showed a negative correlation between risk of cancer and calcium consumption [Males (Relative Risk 0.70; 95% Confidence Interval 0.52-0.93; p for trend <0.05); Females (Relative Risk 0.64; 95% Confidence Interval 0.50-0.83; p for trend less than 0.05)] & dairy products [Males (Relative Risk 0.77; 95% Confidence Interval 0.59-1.01; p for trend less than 0.05); Females (Relative Risk 0.66; 95% Confidence Interval: 0.49- 0.89; p for trend <0.05).[69] Another study called Calcium Polyp Prevention Study was conducted in 913 subjects to estimate the role of calcium supplementation on relapse rate of CRC adenoma. Calcium supplementation moderately curtailed the relapse risk of CRC adenomas (Relative Risk = 0.76, 95% CI: 0.60–0.96). Subjects were supplemented with either 1200 mg calcium carbonate regularly or placebo.[69] Further analysis on advanced stage adenomas reflected better outcome with calcium consumption (Relative Risk of 0.65, 95% Confidence Interval: 0.46–0.93).[70] A 5-year study showed a highly negative correlation between calcium intake and risk of adenoma. As compared to placebo the risk curtailment was high in calcium receiving subjects (Relative Risk of 0.63, 95% Confidence Interval of 0.46 to 0.87).[71] An inverse relationship between calcium intake and CRC risk was observed in Males (highest vs. lowest quintile, Relative Risk of 0.70, 95% Confidence Interval: 0.52– 0.93) as well as in Females (Relative Risk of 0.64, 95% Confidence Interval: 0.50–0.83) based on the results from multiethnic Cohort.[72]

Subjects from France (Relative Risk = 0.72, 95% Confidence Interval: 0.47 to 1.10)[73] & China (Relative Risk = 0.6, 95% Confidence Interval: 0.3 to1.0)[74] were shown to have a lower risk of CRC as their intake of calcium was high. Another observation was made in Japan Public Health center, where a prospective study was done on population of Swedish Males (Relative Risk = 0.68, 95% Confidence Interval : 0.51–0.91);[75,76] as well as in the Cancer Prevention Study II Nutrition Cohort[77] of both males and females (Relative Risk = 0.87, 95% Confidence Interval: 0.67 to 1.12). All the above studies concluded a negative correlation of CRC with calcium supplementation.

Inverse relationship was seen in dietary calcium and CRC risk in males (highest vs. lowest quintile, Odds Ratio of 0.6, 95% Confidence Interval: 0.5 to 0.9) & females (Odds Ratio of 0.6, 95% Confidence Interval : 0.4 to 0.9), where total 1993 colon cancer cases were compared against 2410 controls.[41] Similar inverse association was observed in a study conducted in Italy where 1953 patients of CRC receiving calcium from diet reflected reduced colon cancer risk (1495 vs. <1013 mg/d, Odds Ratio of 0.72, 95% Confidence Interval: 0.6–0.9).[78]

A long-term trial was conducted in patients receiving calcium (1200 mg/ day) for over a period of 4 years. A strong improvement was observed in pathology of advanced stage neoplastic cells (Relative Risk of 0.65, 95% Confidence Interval 0.46 to 0.93),[70] proving the role of calcium in downregulating the proliferation of adenomatous cells which eventually leads to cancer.

A placebo-controlled trial was conducted in women's consuming diet rich in calcium (1400–1500 mg) & vitamin D (1100 IU).[79] A high calcium and vitamin D diet for half year time has downregulated the development of polyps in adenomatous polyposis patients.[46] The consumption of high levels of calcium and dairy products including milk was negatively correlated to CRC incidence in a data pooled from 10 cohort studies.[80] In the European Cancer Prevention Organization Intervention Study including 665 patients a downfall in relapse of adenoma (Relative Risk of 0.66, 95% Confidence Interval 0.38 to 1.17) was seen in a group receiving 2000mg of calcium as against placebo.[81] An approximate 25% reductions CRC risk was reported in 45,354 subjects consuming both high dietary and supplemental calcium intake who were followed for 8.5 years.[82]

7.2. *Preclinical evidences*

High fat diet was given to C57Bl/6 mice for a period of 24 months leading to formation of tumors in colorectal region, in colon cancer model. The colon tumor incidence and multiplicity both reduced significantly when the diet was supplemented with calcium and vitamin D.[83] In mice bearing the Apc1638N+/− mutation and fed with the High fat diet, colonic tumor formation was prevented by high Calcium and vitamin D intake.[84]

8. Conclusion

Cancer is known to be a leading cause of morbidity and mortality worldwide. Overall cost of chemotherapeutic agents imposes heavy economic burden to the patients seeking anticancer therapy. Probiotics are found to exert antineoplastic action by several ways including chelation of carcinogens, halting the absorption of mutagenic agents via intestine and boosting the host immune function. Calcium has been known to arrest proliferation of cancer cells by several mechanism. Calcium supplementation along with probiotics can be considered as good therapeutic option for Colorectal cancer.

9. Source of Funding

None

10. Conflict of Interest

There is no conflict of interest.

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Cite this article: Une HD, Kumavat MY, Shirsat AB. Role of *Lactobacillus* and calcium in colorectal cancer. *Indian J Pathol Oncol* 2023;10(3):224-232.