ECRONICON OPEN ACCESS

EC NUTRITION
Review Article

Anti-Cancer Properties of Probiotics: A Natural Strategy for Cancer Prevention

Devaraja Gayathri* and Rashmi B S

Department of Studies and Research in Microbiology, Davangere University, Shivagangothri, Davanagere-577002, Karnataka, India

***Corresponding Author:** Devaraja Gayathri, Department of Studies and Research in Microbiology, Davangere University, Shivagangothri, Davanagere-577002, Karnataka, India.

Received: October 17, 2016; **Published:** November 02, 2016

Abstract

As a natural food, probiotics have proven their efficacy in preventing several types of cancer. Probiotics confer anti carcinogenic effect by excluding pathogenic microorganisms by competing for nutrients and receptors, producing antimicrobial metabolites and intern activating host immune system. Metabolites produced by probiotics confer protection against cancer, reducing mutagenicity, diminishing the genotoxicity of dietary carcinogens by mitigating xenobiotic metabolism, regulating apoptosis and suppressing tumor proliferation. In addition, probiotics alter food preference, influencing the physiology and mental health conferring the reduced risk of carcinogenesis. Therefore, probiotics would be considered safe adjuvant strategy to prevent cancer.

Keywords: *Probiotics; Prebiotics; Synbiotics; Carcinogenesis; Psychobionts; Apoptosis*

Introduction

The word cancer is startling and frightening the world. The cancer patients and their kin seem to be stranded because the rate of survival is very low, if survived, recovery is very challenging. As mentioned in the World Health Organization fact sheet (2014), cancer is a generic term for a large group of diseases that can affect any part of our body. It is one of the major leading causes of death worldwide and obviously has gained much attention of scientific community to develop and improve the cancer treatment with the intention to reduce the side effects of existing treatment and also to make the expensive drugs affordable to common man [1-2]. The primary goal of the scientific community involved in cancer research is to cure the disease or if not at least continuous efforts need to be make considerably to prolong the life of the patients by improving the quality of life. Intense research on cancer in recent years has increased the public awareness also. Publication of data from cancer research in the field of genomics, proteomics, and molecular pathology has also enhanced the knowledge about cancer and different promising treatments currently available [3-4]. Although, many drugs are in use to treat cancer, tolerance to their burden is really a challenging task. As it is well said that prevention is better than cure, an alternative to drugs in preventing cancer is the use of natural foods that confer anti carcinogenic effects. Therefore, in this article probiotics in combination with prebiotics as natural products to prevent different types of cancer has been discussed.

In recent years, dietary intervention to prevent cancer has received an incredible attention from clinical nutritionists, scientists and industrialists. In this context, foods with probiotics and prebiotics are in forefront as potential therapeutic agents in preventing cancer. The World Health Organization /Food and Agriculture Organization (2001) defined probiotics as live microorganisms which when administered in adequate amounts confer a health benefit on the host [5]. While Marcel Roberfroid who identified and named the prebiotics first in 1995 defined prebiotic as a selectively fermented ingredient that allows specific changes, both in the composition and/or activity

in the gastrointestinal microflora that confers benefits upon host well-being and health [6]. Probiotics provide health benefits to their host when supplied in appropriate amounts in viable form, enhancing digestion and absorption of nutrients, modulating mucosal and systemic immune responses, balancing the population of beneficial gut flora, excluding pathogens and producing essential vitamins and amino acids [7]. The mechanism of probiotic action primarily includes alteration in the composition of gut microbiota, maintaining epithelial barrier function, competition with harmful gut flora for nutrients and adhesion to the epithelium of the gastrointestinal tract. In addition, probiotics enhance the host immunity to pathogens by producing antibacterial substances that result in the suppression of specific pathogens. Hydrogen peroxide, bacteriocins, lactic and acetic acids are primarily responsible for non-specific inhibition of pathogens [8-10]. In addition to the above mentioned probiotic properties, certain species of intestinal microbiota particularly Lactic acid bacteria are proven to exhibit anti-carcinogenic action, anti-inflammatory effects and also take part in alleviating symptoms of lactose intolerance [11,12]. However, they are also characterized by anticholesterol activities. They reduce the cholesterol levels by producing lipase and also by assimilating fat in the body [11,13-14]. Many of these properties of probiotics directly or indirectly confer anti carcinogenic effects to hosts (Figure 1). In this context, present article throws light on different mechanism of action of probiotics in conferring anti carcinogenic effects in host.

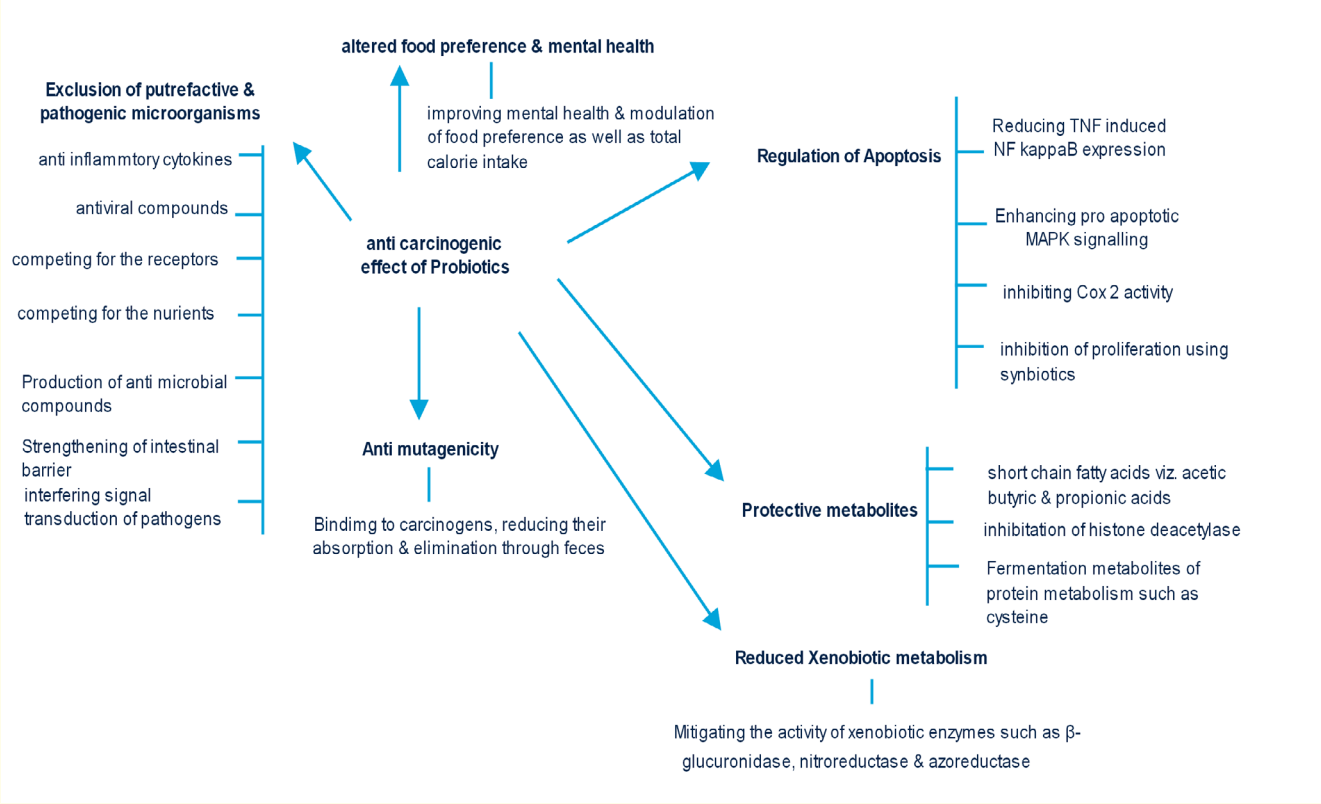

Figure 1: *Different strategies of probiotics in conferring anticancer property.*

Different strategies by which probiotics confer protection against carcinogenesis

Exclusion of pathogenic microorganisms

Several microbial infections are known to associate with the development of cancer and it has been reported that 17.8% of global cancer burden is due to infections. However, the exact mechanism is not yet clearly understood. Further, in developing countries the rate of infection associated cancer is 26.3% while in developed countries, 7.7% [15]. A growing body of literature showed that the bacterial and viral infections are of major threats compared to parasitic infections. Furthermore, 15.6% of worldwide incidence of cancer was ascribed to infection with bacterium *Helicobacter pylori* and viruses such as hepatitis B, hepatitis C, human papilloma viruses, human T cell lymphotrophic virus I (HTLV1) Epstein Barr virus, and HIV virus [16-17]. Epstein Barr virus has proven to cause Burkitt's lymphoma, nasopharyngeal carcinoma and many other types of lymphomas [18] while HTLV1 causes adult T-cell leukemia [19]. Whereas human papilloma virus causes bladder carcinoma [20] and parasites like liver fluke causes cancer of liver [21]. Therefore, elimination of pathogens would help in preventing cancer and thereby reduce the burden of infection associated cancer in humans.

On contrary, in several studies beneficial bacteria have proven to exclude pathogens by their mechanism of action and found useful in preventing infections. To consider, HIV is indirectly responsible for the development of many types of cancer due to immunodeficiency. Studies on HIV-1 infection and vaginal microbiota showed that beneficial microbiota helps in reducing the transmission rate of HIV- 1 in women. In women with normal vaginal microbiota, the frequency of HIV-1 was 14.5% while it is 26.7% in women with severe bacterial vaginosis [22]. In another study, probiotics such as *L. rhamnosus* found to eliminate herpes simplex virus type I by activating macrophages [23]. In addition, probiotics in the gut also helps to eradicate *H. pylori* mitigating the frequency of epigastric pain, vomiting, nausea and diarrhea [24-25]. The possible explanation for these findings may attribute to immunomodulatory properties of probiotics such as increased immune response by elevated levels of sIgA and anti-inflammatory cytokines, production of antiviral compounds that aids in restricting the pathogenesis. In addition, probiotics are known to exclude pathogens in the gut by inhibiting and displacing their adhesion by competing for the receptors on epithelial cells, nutrients, producing antimicrobial metabolites and strengthening the intestinal barrier. Moreover, probiotics also proven to inhibit the expression of genes for virulence and proteins by interfering signal transduction pathway of pathogens [22,26-27]. Prevention of the pathogens that are known to take part in carcinogenesis directly or indirectly would be one of the strategies to be considered in the prevention of initiation of cancer development. In this regard, perhaps probiotics serve as an effective tool in eliminating pathogens and protecting host from pathogen induced carcinogenesis.

Anti-mutagenic property of probiotics

Development of cancer is a multi-stage process that would initiate when mutations accumulate in the tumor suppressor and proto-oncogenes. The mutations may activate oncogenes or inactivate tumor suppressor genes or sometimes both [28]. Advanced molecular techniques facilitated the exploration of human genome at deeper level and documented a very high rate of mutations in cancer cells [29]. Cooking of fat and protein rich food such as meat at high temperature results in the release of mutagens such as acrylamide, heterocyclic amines, N- nitrosamines, polycyclic aromatic hydrocarbons, and other potent mutagens. In addition to cooking at high temperature, sometimes processing and preserving methods also contribute to the release of mutagens in the food [30-32]. In addition, certain species of intestinal microorganisms also sometimes produce genotoxic compounds and there by contribute to the increased risk of carcinogenesis. On the contrary, some of the beneficial intestinal bacteria found to mitigate the formation of mutagens and their effects. This can be explained better as follows; the intestinal microbial composition is directly related to the kind of food intake. Therefore, balanced diet helps in the establishment of good microbiota which is beneficial to the host while imbalanced food such as high protein and fat content with low fibres may increase the occurrence of harmful microorganisms in the intestine. For instance, Fecapentaenes, a class of dietary genotoxin produced in the colon by *Bacteroides* spp., has been frequently found in the feces of individual with high fat and protein rich diet [33]. In addition, anaerobic bacteria in the large intestine take part in enzymatic deconjugation and dehydroxylation of primary bile acids resulting in the formation of secondary bile acids which have been proven to exhibit tumor promoting ability in animal models [34]. In colon, *Eubacterium* and *Clostridium* sp. activate the cooked food mutagens namely 2-amino-3-methylimidazo/4, 5-f/qinoline (IQ) and

2-amino-3,4-dimethylimidazo/4,5-f/quinoline (MeIQ) to 7-hydroxy form which is directly mutagenic to *Salmonella*. In experimental animal models these heterocyclic amines proven to induce cancer in the liver and other organs. The formation of adducts with guanine would be one of the possible mechanism of heterocyclic amines in carcinogenesis [33,35]. Apart from this, the hydrogen sulfide produced by sulfate-reducing bacteria in the large intestine also shown to induce DNA damage in mammalian cells [36-37]. These findings may explain why food rich in protein and fat are more prone to cancer.

As mentioned above, certain groups of bacteria in the intestine are beneficial in preventing carcinogenesis. Probiotics mainly the species of lactobacilli and bifidobacteria have proven to stand first. It has been reported by *in vitro* and *in vivo* studies that lactobacilli can reduce mutagen induced chromosome aberrations by 80% [38]. The possible mechanism that confers antimutagenic or anticarcinogenic property involves the binding of mutagenic compounds such as heterocyclic amines to the bacteria, reducing their absorption in intestine, minimizing their retention time and eliminating through feces. In another study, lactic acid bacteria isolated from milk products showed characteristic antimutagenic effect against the mutagenicity of Trp-P2, a tryptophan pyrolysate for *Salmonella typhimurium* TA98 [39]. Live probiotics bound or inhibit the mutagens permanently, compared to killed bacteria indicating that the interaction with mutagens may influence the bacteria at genetic level to express the formation of some of the components, may be cell wall proteins to bind firmly or to inhibit by transforming the mutagens [40]. This is corroborated in a study, where the cell wall of bacteria isolated from *natto* a fermented food effectively bound hetero cyclic amines than the cytoplasmic contents, indicating the significance of cell wall components in reducing the effect of mutagenicity. Further, in an animal study, combination of *B. longum* and lactulose has been shown to confer protection against colon tumorogenesis in rats. Upon feeding of *B. longum* and lactulose the suppression of azoxymethane induced aberrant crypts foci was observed with an increased levels of colonic mucosal glutathione S-transferase, a phase II enzyme marker that participate in the detoxification of toxic metabolites and carcinogens [41].

Furthermore, the polysaccharide producing *B. longum* PS+ strain showed antimutagenicity against the mutagenecity of both 3-amino-1,4-dimethyl-5H-pyrido-[4,3-b] indole (Trp-P-1) and 3-amino-1-methyl-5H-pyrido[4,3-b] indole (Trp-p-2) in a related Ames test using *S. typhimurium* TA98 in dose dependent manner with increased fermentation period [42]. In addition, the glycoproteins of *L. plantarum* from kimchi- a kind of Korean fermented food also exhibited antimutagenic activity [43]. Further, the possibility of *Lactobacillus casei* DN 114001 to metabolize and adsorb heterocyclic amines was also reported [32]. Two strains of LAB, *B. longum* and *L. acidophilus* bound to two dietary carcinogens benzo[a]pyrene (B[a]P) and 3-amino-1-methyl-5H-pyrido[4,3-b] indole (Trp-p-2) more effectively and it has been also shown that the extent of binding of the heterocyclic amine carcinogens was pH dependent [44-45]. However, further research is required to corroborate these results in animal models and also to decipher the lactic acid bacterial mechanism in carcinogen binding at molecular level such that alternative strategies could be found to bind and eliminate the carcinogens more effectively, in reducing the risk of carcinogenesis.

Xenobiotic enzymes

The products and intermediates of xenobiotic metabolism also take part in the development of carcinogenesis. The enzymes responsible for the xenobiotic metabolism are generally referred as xenobiotic metabolic enzymes or xenobiotic enzymes. Some of the intestinal microorganisms produce these enzymes at higher levels which catalyze an array of reactions resulting in the formation of xenobiotic derived or transformed genotoxic and carcinogenic compounds [46]. To explain further, liver is the main site for metabolic transformations of xenobiotic and other endogenously produced compounds, where they would conjugate to molecules such as glucuronic acid and sulfate before excretion from the body. But for a high number of microbial species in the intestine, the final electron acceptors to carry out metabolic activities are other than oxygen due to less oxygenic environment. Therefore, the oxidized conjugated xenobiotic metabolites from the liver become final electron acceptors and are reduced by the intestinal microoganisms. In the intestine, particularly putrefactive bacteria *Eubacterium* spp., *Clostridium clostridiiforme*, *C. paraputrificum*, *C. nexile*, *Butyrivibrio* spp., and *Bacteroides* spp. produce higher levels of enzymes such as β-glucuronidase, nitroreductase, nitrate reductase and azoreductase that tend to deconjugate xenobiotic conjugates and release metabolites such as aglycones and other procarcinogenic substances in the intestine which further undergo reabsorp-

tion and recirculation thus extending their retention time in the body. As these metabolites are proven as potent carcinogens to humans and other animals it is evident that the presence of xenobiotic metabolizing enzymes increases the genotoxicity and carcinogenicity in the colon [47-50].

On contrary, certain species of probiotics inhibit or mitigate the activity of xenobiotic enzymes. For example, probiotic bacteria such as *Lactobacillus acidophilus* hindered the conversion of exogenously administered aromatic nitro azo and amine glucuronide compounds to free amines [51]. When viable *Lactobacillus acidophilus* of dose 106/ml of milk was fed continuously for 4 weeks, 2 - to 4 - fold reductions in the activities of β-glucuronidase, nitroreductase and azoreductase was observed. Supplementation of *Lactobacillus acidophilus* in omnivorous diet has also significantly decreased the fecal bacterial β-glucuronidase and nitroreductase activity. However, withdrawal of probiotic from feed reversed the condition suggesting that continuous feeding of probiotic may mitigate the chances of development of dietary aromatic and amine compounds induced carcinogenesis in the colon by influencing the metabolic activity of intestinal microflora. While, ingestion of a fermented dairy product containing *L acidophilus*, *Bifidobacterium bifidum*, *Streptococcus lactis* and *S cremoris* did not affect the activities of β-glucuronidase and azoreductase, but decreased the activity of nitroreductase [52]. Whereas *Lactobacillus casei* strain Shirota, *L. fermentum* and *L. plantarum* decreased β-glucuronidase activity [12,52-55]. From these studies, it can be understood that although bacterial xenobiotic enzyme activity is strain specific, the duration and dose of probiotic intake are also other considering factors in reducing the effects of xenobiotics. Therefore, further extensive research is required to work out which strain of probiotics is effective against which type of xenobiotic enzymes and also the size of the dose needs to be determined, such that the consortium of probiotic strains which are proven effective can be used in preventing xenobiotic metabolism induced carcinogenesis.

Production of protective metabolites

Probiotics produce a wide range of metabolites that confer health benefits to the host. The metabolites of probiotic bacteria such as arginine, glutamine, Short Chain Fatty Acids (SCFAs), bacteriocins and hydrogen peroxide are protective to the intestine [56]. Acetate, butyrate and propionate are the most significant primary SCFAs produced by the probiotics in the intestine during fermentation of prebiotics. Among the organic acids produced by probiotic lactobacilli and bifidobacteria which were assayed for their antimutagenic activity against the mutagens according to Ames TA-100 assay using a mutant of *Salmonella typhimurium*, butyric acid showed highest inhibition of mutagens compared to acetic acid, while lactic and pyruvic acids failed to inhibit at appreciable levels [40]. Further, milk fermented by *Propionibacterium freudenreichii* induced apoptosis features such as DNA laddering, chromatin condensation, cell cycle arrest, accumulation of reactive oxygen species, disruption of mitochondrial transmembrane potential, formation of apoptotic bodies, caspase activation and release of cytochrome C in HGT-1 human gastric cancer cells indicating that the fermented metabolites are capable of inducing apoptosis, a mechanism of programmed cell death thought to be promising strategy in controlling tumorogenesis [57].

Further, the following discussion could help to give possible explanation for the mechanism of protective role of metabolites such as short chain fatty acids produced by probiotics in preventing or treating cancer. Butyrate nourishes the colonic mucosa and meantime it has also been proven to promote the apoptosis of transformed colonocytes. In addition, it has also been reported to inhibit histone deacetylase enzyme which together with histone acetyltransferases determines the acetylation status of histones and thereby affect the regulation of gene expression [58-59]. By altering the transcription of small number of genes responsible for cell differentiation, arrest of cell growth and apoptosis in tumour cells, butyrate has proven its efficiency in the prevention and management of cancer. In another study, butyrate and propionate induced apoptosis and necrosis in Kato III human gastric carcinoma cell line has also been reported. The butyrate effects were comparatively greater than propionate [60]. This was also corroborated in another study where the combination of butyrate and propionate effectively induced apoptosis compared to propionate alone in Caco-2 human colon cancer cell line [61]. While in another study, propionate and acetate from propionibacteria along with other metabolites in the culture supernatants induced apoptosis by loss of mitochondrial transmembrane potential, caspase-3 processing, nuclear chromatin condensation and generation of reactive oxygen species [62]. These studies evidence the therapeutic property of SCFAs, mainly acetate, butyrate, and propionate for cancer.

Further, the acetone extracts of freeze dried yogurt containing palmitic and iso palmitic acids produced during lipolysis of milk showed significant dose dependent anti N-methyl-N'-Nitro-N-nitroguanidine (MNNG) activity in the Ames test and it has also been proven that anti mutagenic activity of the yogurt is associated with bacterial growth [63-64]. These studies evidenced and suggested that the inclusion of the short chain fatty acids or the administration of synbiotics with high potential to produce SCFAs can be used for the prevention of carcinogenesis. Apart from fatty acids, other metabolites of fermented milk and milk products are proven to confer anti carcinogenic effect. To consider, in an *in vivo* assay with yogurt isolate *L. bulgaricus* 191R, Dimethylhydrazine (DMH) induced DNA damage was prevented while *Streptococcus thermophilus* failed. However, *St. thermophilus* CH3 and *L. bulgaricus* 191R was shown to produce antigenotoxic metabolites that can deactivate MNNG *in vitro*. The possible explanation for the underlying mechanism may be attributed to the fermentation metabolite such as thiol group containing cysteine produced during protein metabolism inactivated MNNG and reduced MNNG induced DNA damage in rat colon cells as determined by comet assay [65]. Probiotics produce wide range of metabolites that are beneficial to host and many of which are not yet characterized. Screening and characterization of these metabolites with the help of structural, functional and comparative genomics may help in exploring the significant properties for the betterment of human health. Once the expression of genes that code for these metabolites are located in the sequenced genome, production of metabolites can be enhanced, improving the strains of probiotics through biotechnological approach.

Anti-proliferative activity and regulation of apoptosis

Apoptosis is a process of programmed cell death that occurs in physiological and pathological conditions. It depletes the cancer cells and constitutes a target for anti-cancer chemotherapy. Both morphological as well as physiological changes can be observed during apoptosis. Morphological changes in nucleus mainly involve the chromatin condensation, nuclear fragmentation while cytoplasmic changes involves rounding up of the cell, pyknosis and retraction of pseudopodes. The physiological changes involve activation of caspases, breakdown of DNA and proteins, and changes in the membrane and recognition by phagocytic cells [59-62]. During oncogenesis, removal of genetically unstable cells through apoptosis is helpful in the down regulation of proliferative tumor cells to treat cancer. However, malignant cells resist apoptosis signals and do not undergo apoptosis easily. Furthermore, recent studies deciphered the potentiality of probiotics in regulation of apoptosis. For example, in a study, *L. ruteri* quelled TNF induced NF kappaB and has also been shown to reduce the expression of NF kappa B dependent gene products that intercede cell survival and cell proliferation. The study also reported that *L. ruteri* may regulate cell proliferation by facilitating apoptosis of activated immune cells via inhibition of Ikappa Balpha ubiquitination and enhancing pro apoptotic MAPK signaling [66].

It has also been reported that probiotic isolates, *L. rhamnosus* and *Bifidobacterium lactis* induced apoptosis through mitochondrial pathway in Caco-2 cells [67]. In addition, cell bound exopolysachcharide (cb-EPS) has also been shown to inhibit colon cancer cell line by directly affecting cell morphology [68]. In another *in vitro* study, the soluble polysaccharide from *L. acidophilus* showed anticancer activity by inducing apoptosis in the HT cell line [69]. Similarly, exopolysaccharides obtained from *L. casei* 1 also exhibited antiproliferative activity against HT-29 cells suggesting that the exopolysaccharides of lactobacilli have the potentiality in controlling the development of tumors [70]. The synbiotic combination of *Bifidobacterium lactis* and resistant starch promoted the apoptotic deletion of carcinogen damaged cells in the rat colon [71]. The combination of *B. breve, L. lactis* and oligoalternan a glucooligosaccharide inhibited the proliferation of HT-29 cells [72]. Similarly, in another study, feeding of lyophilized *B. longum* to rats resulted in the significant suppression of colon tumor incidence, tumor multiplicity and also reduced the tumor volume [73]. However, administration of *L. plantarum* and *L. fermentum* with vincristine significantly decreased the aberrant crypts per focus in 1, 2 Dimethylhydrazine (DMH) treated mice [12]. These findings suggest the use of synbiotics in combination with other therapeutics for the prevention of cancer effectively.

The expression of Cyclooxygenase 2 (Cox 2) was found more in colon cancer tissues [74] and over expression of prostaglandin endoperoxide synthase-2 or Cox 2 found to induce phenotypic changes in intestinal epithelial cells (IEC) which could intensify their tumorogenic potentiality and it has also been proven to increase resistance to apoptosis [75]. However, distinct strains of probiotics proven to

suppress the expression of Cox 2 in IEC [76]. The probiotics that confer inhibitory activity to Cox 2 could be useful in designing future probiotic regimes for the prevention of carcinogenesis. Another strategy to prevent carcinogenesis is the inhibition of ornithine decarboxylase (ODC) and spermidine/spermine N1 acetyltransferase (SSAT). ODC and SSAT are the rate limiting enzymes in polyamine biosynthesis and catabolism respectively. Polyamines cause cell proliferation and are expressed at higher levels in cancer tissues [77]. Dietary administration of *Lactobacillus rhamnosus* GG reduced both ODC mRNA and the activity as well as polyamine content and neoplastic proliferation in HGC-27 human gastric cancer cells [78]. Dietary administration of lyophilized cultures of *Bifidobacterium longum* significantly suppressed the azoxymethane induced colon carcinogenesis in rats which was associated with a decrease in colonic mucosal cell proliferation, colonic mucosal and tumor ODC, and ras-p21 oncoprotein activities [79-80]. Down regulation or arresting of uncontrolled proliferation of tumor cells is of prime significance in treating cancer. In this regard probiotics with antiproliferative and apoptosis regulatory properties could be a promising strategy along with the combination of other therapies to treat cancer at early stages.

Probiotics for altered food preference and mental health

Several studies on gut microbiota and its host provided evidence that both human and microbiota in the gut are mutually regulated by each other. This can be related and described as follows: the human behavior, mainly the food habit i.e. the kind of food ingested, frequency and quantity greatly determines the gut microbial composition and diversity of an individual. On the other hand, it has been well studied that gut microbiota influence the host physiology to a greater extent, therefore, the kind of microbial diversity in the gut determines the health of an individual [81]. In addition, several studies have also reported that gut microflora influences the mental health and also to some extent take part in the function of brain. Norris., *et al*. (2013) hypothesized that "bacteria control host appetite" [82]. As above mentioned, the fat and protein rich diet is mainly associated with the increased risk of carcinogenesis; to overcome this one has to adapt to change the food habit, preferring a balanced diet not containing high fat and protein which upon overcooking release dietary amines and other genotoxins. Further, the infusion of intestinal long chain fatty acids such as linolenic and linoleic acids modulated food preference as well as total calorie intake via the vagal nerve and midbrain hypothalamic neural pathways [34-35,83].

In addition, the pharmabiotics such as gamma amino butyric acid (GABA), acetylcholine, serotonin, catecholamines etc., produced by probiotics and other commensal gut microbiota may modulate neural signaling with enteric nervous system when they release into intestinal lumen [84-85]. Acetylcholine the principal vagal neurotransmitter significantly attenuated the release of cytokines TNF, interlukin-1beta, Il-6 and IL-18 [86]. However, the exact mechanism is yet to be elucidated, additionally several studies also showed that TNF blocking in anti-cancer therapy [87-88].

Since several beneficial aspects of probiotics on health are evident, probiotics can be also used to improve the physical and mental health status of cancer survivors. Psychobiotics, a class of probiotics produces a health benefit in patients suffering from psychiatric illness. These bacteria are capable of producing and transferring neuro active substances such as GABA and serotonin which acts on gut brain axis [89]. Furthermore, *L. rhamnosus* (JB-1) induced region-dependent alterations in GABAB1b mRNA in the brain which increases in cortical regions and accompanying reductions in the expression of hippocampus, amygdala, and locus coeruleus regions, in comparison with control-fed mice and also reduced stress induced carticosterone and anxiety, depression related behavior. In an another study, *B. longum*, decreased excitability of enteric neurons, conferring anxiolytic effect by activating vagal pathways in mice [90]. Balancing gut microflora, producing health benefiting pharmacobionts, influencing mental health, altering food preferences probiotics definitely would aid in keeping away the cancer, perhaps help to restore the health status in cancer survivors in addition to management.

Conclusion

Probiotics and prebiotics selectively modulates the gut microbiota, eliminating pathogens, reducing mutagenecity and genotoxicity of dietary carcinogens, suppressing xenobiotic enzyme activity, preventing the release and reabsorption of procarcinogenic substances, producing metabolites with anticancer properties, regulating apoptosis, and modulating immunity, confer protection against carcinogenesis

to the host. In addition, a healthy balanced diet can aid in reducing the risk of carcinogenesis. Accordingly, probiotics also proven to alter the food preference and helps an individual to adopt healthy food, thereby conferring protection against cancer. Therefore, probiotics perhaps a promising and safe natural product for the prevention and management of cancer.

Acknowledgements

The authors sincerely acknowledge the funding support by Department of Biotechnology, Government of India, India, for funding support in sponsoring the R&D project No.BT/PR7089/FNS/20/734/2013.

Bibliography

1. Jemal A., *et al*. "Global cancer statistics". *A Cancer Journal for Clinicians* 61.2 (2011): 69-90.
2. Siddiqui M., *et al*. "The High Cost of Cancer Drugs and What We Can Do About It". *Mayo Clinic Proceedings* 87.10 (2012):935-943.
3. Ludwig JA., et al. "Biomarkers in cancer staging, prognosis and treatment selection". Nature Reviews Cancer 5.11 (2005): 845-856.
4. Ewing JC., *et al*. "The wave of the future: genetic profiling in treatment selection". *Clinical Journal of Oncology Nursing* 18.6 (2014): 717-718.
5. "Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria". World Health Organization /Food and Agriculture Organization (2001).
6. Gibson GR., *et al*. "Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics". *Journal of Nutrition* 125.6 (1995): 1401–1412.
7. Siciliano RA., *et al*. "Molecular mechanisms of probiotic action: a proteomic perspective". *Current Opinion in Microbiology* 15.3 (2012): 390-396.
8. Bielecka M., *et al*. "Interaction of *Bifidobacterium* and *Salmonella* during associated growth. Resistance of Bifidobacterium to gastrointestinal conditions". *International Journal of Food Microbiology* 45 (1998): 151-155.
9. Gill HS., *et al*. "Stimulation of the immune system by lactic cultures". *International Dairy Journal* 8.5-6 (1998): 535-544.
10. Asha., *et al*. "Antagonistic Potential of Lactobacillus against Enteropathogenic Bacteria; Purification and Characterization of their Bacteriocins". *Advance Journal of Food Science and Technology* 4.5 (2012): 265-269. https://doaj.org/toc/2042-4876.
11. Fooks LJ., *et al*. "Prebiotics, probiotics and human gut". *International Journal of Dairy Science* 9.1 (1999): 53-61.
12. Asha., *et al*. "Synergistic impact of Lactobacillus fermentum, Lactobacillus plantarum and vincristine on 1, 2-dimethylhydrazine-induced colorectal carcinogenesis in mice". *Experimental and Therapeutic Medicine* 3.6 (2012): 1049-1054.
13. McNaught CE., *et al*. "Probiotics in clinical practice: a critical review of the evidence". *Journal of Nutrition Research* 21.1-2 (2001): 343-353.
14. Rashmi BS, *et al*. "Partial Purification, Characterization of Lactobacillus sp G5 Lipase and their Probiotic Potential". *International Food Research Journal* 21.5 (2014): 1737-1743.
15. Parkin DM., *et al*. "The global health burden of infection-associated cancers in the year 2002". *International Journal of Cancer* 118.12 (2006): 3030-3044.
16. Pisani P., *et al*. "Cancer and infection: estimates of the attributable fraction in 1990". Cancer Epidemiology, Biomarkers & Prevention 6.6 (1997): 387-400.

17. Thompson MP., *et al*. "Epstein-BarrVirus and Cancer". Clinical Cancer Research 10.3 (2004): 803-821.

18. Gonçalves DU., *et al.* "Epidemiology, Treatment, and Prevention of Human T-Cell Leukemia Virus Type 1-Associated Diseases". *Clinical Microbiology Reviews* 23.3 (2010): 577-589.

19. Cooper K., *et al*. "Human papillomavirus and schistosomiasis associated bladder cancer". *Molecular Pathology* 50.3 (1997): 145-148.

20. Sripa B., *et al*. "Liver Fluke Induces Cholangiocarcinoma". *PLOS Medicine* 4.7 (2007): e201.

21. Petrova MI., *et al*. "Vaginal microbiota and its role in HIV transmission and infection". *FEMS Microbiology Reviews* 37.5 (2013): 762-792.

22. Khani S., *et al*. "*In vitro* study of the effect of a probiotic bacterium Lactobacillus rhamnosus against herpes simplex virus type 1". *Brazilian Journal of Infectious Diseases* 16.2 (2012): 129-135.

23. Tolone S., *et al*. "Evaluation of Helicobacter pylori eradication in pediatric patients by triple therapy plus lactoferrin and probiotics compared to triple therapy alone". *Italian Journal of Pediatrics* 38 (2012):63.

24. Khodadad AMD., *et al*. "Probiotics for the Treatment of Pediatric Helicobacter pylori Infection: A Randomized Double Blind Clinical Trial". *Iranian Journal of Pediatrics* 23.1 (2013): 79-84.

25. Collado MC., *et al*. "Role of commercial probiotic strains against human pathogen adhesion to intestinal mucus". *Letters in Applied Microbiology* 45.4 (2007): 454-460.

26. Corr SC., *et al*. "Understanding the mechanisms by which probiotics inhibit gastrointestinal pathogens". *Advances in Food and Nutrition Research* 56 (2009): 1-15.

27. Ferguson LR. *et al*. "Role of dietary mutagens in cancer and atherosclerosis". *Current Opinion in Clinical Nutrition & Metabolic Care* 12.4 (2009): 343-349.

28. Loeb KR., *et al*. "Significance of multiple mutations in cancer". *Carcinogenesis* 21.3 (2000): 379-385.

29. Cross AJ., *et al*. "Meat-related mutagens/carcinogens in the etiology of colorectal cancer". *Environmental and Molecular Mutagenesis* 44.1 (2004): 44-55.

30. Jägerstad M., *et al*. "Genotoxicity of heat-processed foods". *Mutation Research* 574.1-2 (2005): 156-172.

31. Nowak A., *et al*. "Ability of probiotic Lactobacillus casei DN 114001 to bind or/and metabolise heterocyclic aromatic amines *in vitro*". *European Journal of Nutrition* 48.7 (2009): 419-427.

32. Tassell VRL., *et al*. "Metabolism of dietary genotoxins by the human colonic microflora; the fecapentaenes and heterocyclic amines". *Mutation Research* 238.3 (1990): 209-221.

33. Nagengast FM., *et al*. "Role of bile acids in colorectal carcinogenesis". *European Journal of Cancer* 31.7-8 (1995): 1067-1070.

34. Wakabayashi K., *et al*. "Food-derived mutagens and carcinogens". *Cancer Research* 52.7 (1992): 2092s-2098s.

35. Attene-Ramos MS., *et al*. "Hydrogen sulfide induces direct radical-associated DNA damage". Molecular Cancer Research 5.5 (2007): 455-459.

36. Attene-Ramos MS., *et al*. "DNA damage and toxicogenomic analyses of hydrogen sulfide in human intestinal epithelial FHs 74 Int cells". *Environmental and Molecular Mutagenesis* 51.4 (2010): 304-314.

37. Renner HW., *et al*. "The possible role of probiotics as dietary antimutagens". *Mutation Research* 262.4 (1991): 239-245.

38. Hosoda M., *et al*. "Studies on antimutagenic effect of milk cultured with lactic acid bacteria on the Trp-P2-induced mutagenicity to TA98 strain of Salmonella typhimurium". *Journal of Dairy Research* 59.4 (1992): 543-549.

39. Lankaputhra WE., *et al*. "Antimutagenic properties of probiotic bacteria and of organic acids". *Mutation Research* 397.2 (1998): 169-182.

40. Challa A., *et al*. "Bifidobacterium longum and lactulose suppress azoxymethane-induced colonic aberrant crypt foci in rats". Carcinogenesis 18 (1997): 517-521.

41. Sreekumar O., *et al*. "The antimutagenic properties of a polysaccharide produced by Bifidobacterium longum and its cultured milk against some heterocyclic amines". *Canadian Journal of Microbiology* 44.11 (1998): 1029-1036.

42. Rhee CH., *et al*. "Three glycoproteins with antimutagenic activity identified in Lactobacillus plantarum KLAB21". *Applied and Environmental Microbiology* 67.8 (2001): 3445-3449.

43. Orrhage K., *et al*. "Binding of mutagenic heterocyclic amines by intestinal and lactic acid bacteria". *Mutation Research* 311.2 (1994): 239-248.

44. Bolognani F., *et al*. "Influence of carcinogen binding by lactic acid-producing bacteria on tissue distribution and in vivo mutagenicity of dietary carcinogens". *Food and Chemical Toxicology* 35.6 (1997): 535-545.

45. Lang M., *et al*. "Metabolism of xenobiotics and chemical carcinogenesis". *IARC Scientific Publications* 148 (1999): 13-22.

46. Hentges DJ. "Human intestinal microflora in health and disease". *Academic Press, New York* (1983): 1-568.

47. Rafii F., *et al*. "Azoreductase activity of anaerobic bacteria isolated from human intestinal microflora". *Applied and Environmental Microbiology* 56.7 (1990): 2146-2151.

48. Rowland IR. "Toxicology of the colon - role of the intestinal microflora". In Macfarlane, G. T. and Gibson, G. (Eds). Human Colonic Bacteria, Role in Nutrition, Physiology and Pathology, CRC Press Boca Raton (1995): 155-174.

49. Humblot C., *et al*. "β-Glucuronidase in human intestinal microbiota is necessary for the colonic genotoxicity of the food-borne carcinogen 2-amino-3-methylimidazo[4,5-f] quinoline in rats". *Carcinogenesis* 28.11 (2007): 2419-2425.

50. Goldin BR., *et al.* "Alterations of the intestinal microflora by diet, oral antibiotics, and Lactobacillus: decreased production of free amines from aromatic nitro compounds, azo dyes, and glucuronides". *Journal of the National Cancer Institute* 73 (1984): 689-695.

51. Marteau P., *et al*. "Effect of chronic ingestion of a fermented dairy product containing Lactobacillus acidophilus and Bifidobacterium bifidum on metabolic activities of the colonic flora in humans". *American Journal of Clinical Nutrition* 52 (1990): 685-688.

52. Goldin BR., *et al*. "Effect of diet and Lactobacillus acidophilus supplements on human fecal bacterial enzymes". *Journal of the National Cancer Institute* 64 (1980): 255-261.

53. Goldin, BR., *et al*. "The effect of milk and Lactobacillus feeding on human intestinal bacterial enzyme activity". *American Journal of Clinical Nutrition* 39.5 (1984): 756-761.

54. Spanhaak S., *et al*. "The effect of consumption of milk fermented by Lactobacillus casei strain Shirota on the intestinal microflora and immune parameters in humans". *European Journal of Clinical Nutrition* 52.12 (1998): 899-907.

55. De Keersmaecker SC., *et al*. "Strong antimicrobial activity of Lactobacillus rhamnosus GG against Salmonella typhimurium is due to accumulation of lactic acid". *FEMS Microbiology Letters* 259.1 (2006): 89-96.

56. Cousin FJ., *et al*. "Milk fermented by Propionibacterium freudenreichii induces apoptosis of HGT-1 human gastric cancer cells". *PLoS One* 7.3 (2012): e31892.

57. Marks P., *et al*. "Histone deacetylases and cancer: causes and therapies". *Nature Reviews Cancer* 1.3 (2001): 194-202.

58. Wong JM., *et al*. "Colonic health: fermentation and short chain fatty acids". *Journal of Clinical Gastroenterology* 40.3 (2006): 235-243.

59. Matthews GM., *et al*. "Short-chain fatty acid modulation of apoptosis in the Kato III human gastric carcinoma cell line". *Cancer Biology & Therapy* 6.7 (2007): 1051-1057.

60. Matthews GM., *et al*. "Short-chain fatty acids induce apoptosis in colon cancer cells associated with changes to intracellular redox state and glucose metabolism". *Chemotherapy* 58.2 (2012): 102-109.

61. Jan G., *et al*. "Propionibacteria induce apoptosis of colorectal carcinoma cells via short-chain fatty acids acting on mitochondria". *Cell Death & Differentiation* 9.2 (2002): 179-188.

62. Nadathur SR., *et al*. "Antimutagenicity of an acetone extract of yogurt". *Mutation Research* 334(2) (1995): 213-224.

63. Nadathur SR., *et al*. "Palmitic acid is the major fatty acid responsible for significant anti-N-methyl-N'-nitro-N-nitroguanidine (MNNG) activity in yogurt". *Mutation Research* 359.3 (1996): 179-189.

64. Wollowski I., *et al*. "Bacteria Used for the Production of Yogurt Inactivate Carcinogens and Prevent DNA Damage in the Colon of Rats". *Journal of Nutrition* 129 (1999): 77-82.

65. Iyer C., *et al*. "Probiotic Lactobacillus reuteri promotes TNF-induced apoptosis in human myeloid leukemia-derived cells by modulation of NF-kappaB and MAPK signalling". *Cell Microbiology* 10 (2008): 1442-1452. https://www.ncbi.nlm.nih.gov/pubmed/18331465.

66. Altonsy MO., *et al*. "Differential induction of apoptosis in human colonic carcinoma cells (Caco-2) by Atopobium, and commensal, probiotic and enteropathogenic bacteria: mediation by the mitochondrial pathway". *International Journal of Food Microbiology* 137. (2-3) (2010): 190-203.

67. Kim Y., *et al.* "Cell-bound exopolysaccharide from probiotic bacteria induces autophagic cell death of tumour cells". *Letters in Applied Microbiology* 51.2 (2010): 123-130.

68. Choi SS., *et al.* "Effects of Lactobacillus strains on cancer cell proliferation and oxidative stress in vitro". *Letters in Applied Microbiology* 42.5 (2006): 452-8.

69. Liu CT., *et al.* "Antiproliferative and anticytotoxic effects of cell fractions and exopolysaccharides from Lactobacillus casei 01". *Mutation Research* 721.2 (2011): 157-62.

70. Leu LRK., *et al.* "A synbiotic combination of resistant starch and Bifidobacterium lactis facilitates apoptotic deletion of carcinogen-damaged cells in rat colon". *Journal of Nutrition* 135. 5 (2005): 996-1001.

71. Grimoud J., *et al.* "In vitro screening of probiotics and synbiotics according to anti-inflammatory and anti-proliferative effects". *International Journal of Food Microbiology* 144.1 (2010): 42-50.

72. Singh J., *et al.* "Bifidobacterium longum, a lactic acid-producing intestinal bacterium inhibits colon cancer and modulates the intermediate biomarkers of colon carcinogenesis". *Carcinogenesis* 18.4 (1997): 833-841.

73. Sano H., *et al.* "Expression of cyclooxygenase-1 and -2 in human colorectal cancer". *Cancer Research* 55.17 (1995): 3785-3789.

74. Tsujii M., *et al.* "Alterations in cellular adhesion and apoptosis in epithelial cells overexpressing prostaglandin endoperoxide synthase 2". *Cell* 83.3 (1995): 493-501.

75. Otte JM., *et al.* "Probiotics regulate the expression of COX-2 in intestinal epithelial cells". Nutrition *Cancer* 61.1 (2009): 103-113.

76. Deng W., *et al.* "Role of ornithine decarboxylase in breast cancer". *Acta Biochimica et Biophysica Sinica* 40.3 (2008): 235-243.

77. Linsalata M., *et al.* "Lactobacillus rhamnosus GG influences polyamine metabolism in HGC-27 gastric cancer cell line: a strategy toward nutritional approach to chemoprevention of gastric cancer". *Current Pharmaceutical Design* 16.7 (2010): 847-53.

78. Reddy BS., *et al.* "Prevention of colon cancer by pre- and probiotics: evidence from laboratory studies". *British Journal of Nutrition* 80.4 (1998): S219-S223.

79. Femia AP., *et al.* "Antitumorigenic activity of the prebiotic inulin enriched with oligofructose in combination with the probiotics Lactobacillus rhamnosus and Bifidobacterium lactis on azoxymethane-induced colon carcinogenesis in rats". *Carcinogenesis* 23.11 (2002): 1953-1960.

80. Bäckhed F. "Programming of host metabolism by the gut microbiota". *Annals of Nutrition and Metabolism* 58.2 (2011): 44-52.

81. Norris V., *et al*. "Hypothesis: Bacteria Control Host Appetites". *Journal of Bacteriology* 195.3 (2013): 411-416.

82. Ogawa N., *et al*. "Intestinal fatty acid infusion modulates food preference as well as calorie intake via the vagal nerve and midbrain-hypothalamic neural pathways in rats". *Metabolism* 61.9 (2012): 1312-1320.

83. Wall R., *et al*. "Bacterial neuroactive compounds produced by psychobiotics". *Advances in* E*xperimental Medicine and Biology* 817 (2014): 221-239.

84. Patterson E., *et al*. "Gut microbiota, the pharmabiotics they produce and host health". *Proceedings of the Nutrition Society* 73.4 (2014): 477-489.

85. Borovikova LV., *et al*. "Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin". *Nature* 405.6785 (2000): 458-462.

86. Moore RJ., *et al*. "Mice deficient in tumor necrosis factor-alpha are resistant to skin carcinogenesis". *Nature Medicine* 5.7 (1999): 828-831.

87. Popivanova BK., *et al*. "Blocking TNF-alpha in mice reduces colorectal carcinogenesis associated with chronic colitis". *Journal of Clinical Investigation* 118.2 (2008): 560-570.

88. Dinan TG., *et al*. "Psychobiotics: a novel class of psychotropic". *Biological Psychiatry* 74.10 (2013): 720-726.

89. Bercik P., *et al*. "The anxiolytic effect of Bifidobacterium longum NCC3001 involves vagal pathways for gut-brain communication". *Neurogastroenterology & Motility* 23.12 (2011): 1132-1139.

90. World Health Organization fact sheet (2014).

Volume 5 Issue 4 November 2016