Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 12 [7] June 2023: 267-273

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

Dietary Synbiotic as a Supplemental Therapy to Reduce Cancer Symptoms: A Review

[1] Shashank V, [2] S Anu Kiruthika*, [3] Harish K R, [4] Pooja Pandey
[1-4] * Department of Microbiology, Indian Academy Degree College – Autonomous, Bengaluru, India.
*Email ID: kiruthika.anu@gmail.com

ABSTRACT
The significance of the human microbiome in the pathogenesis of cancer is becoming more widely recognized. Pre-, pro-, and synbiotics are some of the most well-studied ways to alter the microbiota for therapeutic purposes, and there is growing interest in their potential to be used in the diagnosis and treatment of cancer. In this review, we examine how these drugs may preserve the integrity of the intestinal barrier, regulate the immune system, regulate metabolism, and restrict the growth of host cells. We emphasize the epidemiological and trial-based evidence that pre-, pro-, and synbiotics play a role in cancer prevention. In the end, there is more evidence to support the use of these drugs as cancer treatment adjuncts. We go over their roles in enhancing the effectiveness of chemotherapy and radiation and/or reducing their side effects. The use of pre-, pro-, and synbiotics for clinical benefit in oncology patients has tremendous potential, but the discipline is still in its infancy, making it difficult for oncologists to provide their patients the right advice.
Keywords: *microbiome, oncology, probiotics, prebiotics, synbiotics.*

Received 09.05.2023 Revised 19.05.2023 Accepted 30.06.2023

INTRODUCTION

By specifically enhancing the growth and/or stimulating the metabolism of one or more numbers of health-promoting bacteria, a synbiotic product benefits the host by positively impacting the survival and implantation of live microbial dietary supplements in the gut. Because it suggests synergism. The word "synbiotics" should only be applied to products in which the prebiotic compound(s) benefit the probiotic organism(s). This review will examine the possible therapeutic uses of pre-, pro-, and syn -biotic concerning cancer. These agents now constitute the main treatments geared towards positive modification of the microbiota (as opposed to negative manipulation with antibiotics). As our grasp of science has evolved, pre- and probiotic classifications have undergone several changes. 'A substrate that is preferentially used by host microorganisms imparting a health advantage' is the definition of a prebiotic [1]. Numerous molecules fall under this category; the non-digestible oligosaccharides fructo-oligosaccharide (FOS, which may be found in foods like onions and garlic) and galacto-oligosaccharide have received the most research. These substances work by encouraging commensal bacteria to proliferate and/or operate in ways that are advantageous to the host. Probiotics, on the other hand, are "live microorganisms that, when administered in sufficient amounts, confer a health benefit on the host" [2].

Although many fermented foods (like kimchee, tempeh, kombucha, sauerkraut, probiotic yogurt or kefir) contain live organisms, the majority are not considered probiotics because the food itself confers the health benefit rather than the organisms, and they frequently do not contain enough organisms to be classified as probiotics. Synbiotics are a preparation that combines pre- and probiotics. Probiotics are a group of certain microorganisms that may be found in the *Lactobacilli* or *Bifidobacteria* genera and are available as single agents or multi-strain formulations. Probiotics are typically consumed orally and are made to survive transit to the lower gastrointestinal (GI) tract, whether they are consumed in the form of yogurt, freeze-dried live organisms taken as a powder, or in capsule form. [3] By competitive exclusion, direct antagonistic action, neutralization of pathogenic bacterial toxins, and preservation of intestinal barrier function, they may lessen the impact of pathogenic organisms on the host. Short-chain fatty acid (SCFA) generation, bile acid metabolism, vitamin biosynthesis, and carcinogen neutralization are only a few of the metabolic impacts of probiotics [4-6].

Probiotics may alter the immune response of the host to produce an oncosuppressive phenotype [7]. Finally, strains may alter stool consistency, gas production, and intestinal motility [8]. It is significant to remember that probiotics do not need to colonize the host to have positive effects because they are administered during intestinal transit [9]. Pre-, pro-, and synbiotics have been studied in both pre-clinical and clinical research in a variety of contexts relevant to patients with cancer. Mammalian microbiota's potential to influence cancer therapy toxicity and effectiveness as well as tumor genesis, cell growth, and metastasis is gaining more scientific support [10]. Before examining the data supporting the use of pre-, pro-, and synbiotics in the prevention and treatment of cancer, we will briefly explore the broad anticancer mechanisms of these symbiotic agents.

Mechanisms of pre-, pro- and synbiotics as anticancer agents

Strong evidence suggests that the human microbiome participates in the development of cancer and is an important member of a trio of "interactomes" that also includes the host and the environment [11, 12]. A lot of research has been conducted on how the regulation of the microbiome by pre-, pro-, and synbiotics may help in the prevention and treatment of cancer because of this important role. There are possible pathways that may be roughly categorized into intestinal barrier function, immunomodulatory, metabolic, and anti-proliferative effects that support a non-carcinogenic impact of pre-, pro-, and synbiotics [13].

Intestinal barrier function

One of the fundamental principles of their symbiosis is the physical isolation of the microbiota from the host. One of the main causes of illness, including cancer, is recognized to be the disruption of the physical barriers between the microbiota and the host [12]. This barrier in the gut is made up of enterocytes, cell junction proteins, immune cells, secretory IgA, goblet cells, mucus, Paneth cells, and antimicrobial peptides (creating the "tight junction" between cells). The intricate and interconnected interaction between barrier failure, carcinogenesis, and inflammation is best shown by mucin 2 homozygous mutant mice, which spontaneously develop colorectal cancer (CRC) and lack the intestinal mucus needed to serve as a barrier. Additionally, patients with ulcerative colitis have impaired barrier function, which raises their risk of CRC [14, 15]. Probiotics have been shown to enhance the development of epithelial tight junctions and mucus production in preclinical studies using colonocyte cell lines and animal models [16, 17]. Studies on humans have also shown that probiotic therapy improves colonic epithelial integrity [18, 19]. Additionally, a synbiotic cocktail prevented the growth of CRC in a mouse model by up-regulating genes linked to the creation of tight junctions and the production of mucus [20].

Immunomodulation

The immune system's development and the activation of an anticancer response, both in the gut and at other places, depend on the microbiota. The main effectors for locating and eliminating damaged and possibly cancerous host cells are dendritic cells, natural killer (NK) cells, and T cells [21]. Toll-like receptors are cell-surface pattern recognition receptors that probiotics use to connect with dendritic cells, which in turn triggers responses from T cells and NK cells. In both rodent models [22] and human investigations [23, 24], formulations of probiotics and synbiotics containing *Lactobacillus casei* or *Bifidobacterium lactis* have been demonstrated to increase NK cell activity. Additionally, probiotic-induced NK cell activity has been found to inhibit cancer development in rodent models [25, 26]. Sivan et al. (2015) reported an especially intriguing case in which genetically comparable mice kept by several providers had varied development rates of subcutaneously implanted melanoma cells [27]. When compared to mice from Jackson Laboratory (JAX), Taconic Farms (TAC) animals showed considerably faster tumor growth. Prior to the injection of cancer cells into TAC mice, however, oral gavage of live, but not heat attenuated, Bifidobacterium spp. was able to limit tumor development to that observed in JAX animals. The researchers came to the conclusion that enhanced dendritic cell activity was responsible for this anticancer impact [27].

Metabolism

Numerous methods exist through which the metabolic activity of the microbiota might have a co-suppressive impact. The byproducts of bacterial non-digestible carbohydrate fermentation known as SCFAs, such as butyrate, acetate, and propionate, operate as a significant source of energy for colonocytes and have anti-inflammatory, anti-proliferative, and pro-apoptotic effects. Perhaps the most well-researched SCFA, butyrate causes NF-B downregulation and Treg cell induction [28]. Butyrogenic lactic acid bacteria can develop more quickly when prebiotics are present. Rats given prebiotics produced more SCFA had higher relative abundances of *Bifidobacteria* and were protected from CRC brought on by chemically induced colitis [29]. However, there have been conflicting findings about how pre-, pro-, or synbiotic treatment affects SCFA synthesis in humans. In one research, consuming resistant starch for three weeks (a prebiotic) was shown to raise feces SCFA [30], while in another, giving healthy human volunteers synbiotics failed to reveal any changes in fecal SCFA content or serum inflammatory markers

[31]. Because neither research had a sizable sample size (n = 17 at most), neither side can make definitive conclusions. Through the detoxification of pro-carcinogens, probiotics may also reduce the risk of cancer. Physiologically beneficial effects have not been seen in vivo investigations despite certain probiotic strains having cell-surface peptidoglycans that have been proven to bind mutagens in vitro [32]. Antioxidant characteristics in some probiotic strains can prevent carcinogenesis in mouse models [33]. Because they can produce carcinogens from substances found in the gut lumen, ß-glucuronidase and nitro reductase, for example, are involved in the development of cancer through their actions. Probiotics can lower the intestinal activity of these enzymes, according to several human investigations [34–36].

Antiproliferative effects

Probiotic strains have been shown to be both pro-apoptotic and anti-proliferative. Cancer cell lines have been found to be affected by lactic acid bacteria, and comparable effects have been shown in mouse models [38, 39]. Different mechanisms have been put forth to explain these effects. Tumor Necrosis Factor and caspase-dependent apoptosis can be induced by altering cell signaling cascades (such as NF-B and MAPK), whilst SCFAs like butyrate can suppress cell proliferation by inhibiting histone deacetylase [40]. Probiotics have antigenotoxic characteristics in animals exposed to mutagens, and DNA damage is frequently both a cause and a driver of unchecked cancer cell growth [41]. Sadly, not much research has looked at how pre-, pro-, or synbiotics affect human cellular proliferation. According to Worthey et al [31], administering a synbiotic to human volunteers had no impact on the expression of the epithelial proliferation marker ki67 or the cellularity of the crypts in later rectal biopsies. Though O'Keefe et al did discover that moving from a low-fiber, high-animal fat diet to a high-fiber (resistant starch), low-animal fat diet decreased ki67 staining in intestinal mucosal biopsies in their well-conducted dietary swap trial [42]. It is impossible to attribute these changes explicitly to the fiber element given the nature of the dietary adjustment, but the findings are unquestionably intriguing.

Cancer prevention

Due to the colorectal cancers (CRC) widespread occurrence, the high density of microbiota in the colon (orders of magnitude greater than any other host niche), and the significant influence of environmental (rather than genetic) risk factors, probiotics' effects on CRC are among the topics of research that have received the most attention. Large-scale epidemiological studies have looked at the effects of yogurt and unpasteurized milk intake, which often include living microorganisms, even though no long-term prospective cohort investigations are looking at the effect of pre, pro, or synbiotic usage on CRC incidence. A prospective cohort study of 45,241 people found a significant relationship between higher versus lower yogurt consumption and a reduced risk of CRC (hazard ratio 0.65, 95% confidence interval (CI) 0.48–0.89) [43] while a study of 41,836 people found a relationship between unpasteurized milk consumption and a reduced risk of rectal (but not colon) cancer (relative risk (RR) 0.26, 95% CI 0.1–0.69) [44]. Consuming milk that has undergone fermentation or culture has also been linked to a reduced incidence of bladder cancer [45, 46]. However, a meta-analysis found no significant connection between CRC and milk or all dairy products alone [47], while milk and total dairy products were linked with a lower risk of CRC (RR 0.81, 95% CI 0.74-0.90). The evidence is intriguing but debatable, and there is a paucity of prospective data on pre-, pro-, and synbiotic usage in general as well as on primary cancer risk, as is the case with many epidemiological studies of dietary variables. A few studies have examined their function in reducing the risk of recurring cancer. Rafter et al [48] showed that various CRC indicators, including DNA damage and cellular proliferation, improved in the intervention group in a randomized controlled trial (RCT) comparing synbiotics to placebo in polypectomies or CRC patients. The secondary prevention of cancer recurrence in individuals with a history of CRC, however, was not found to be avoided by synbiotic treatment in a different study [49]. High dietary fiber consumption was found to be related to a decreased relative risk of eventual advancement to CRC (RR 0.72, 95% CI 0.63-0.83) in a meta-analysis involving approximately 11,000 participants with colorectal adenomas [50]. Interestingly, oral *Lactobacillus casei* Shirota treatment has shown more promise in preventing recurrent bladder cancer (after transurethral resection), with positive outcomes reported in two human studies as compared to placebo [49, 51].

Cancer treatment

It is not novel for bacterial agents to be employed in the therapy of cancer; since 1977, superficial bladder cancer has been effectively treated with Bacillus Calmette-Guérin implantation. Probiotics have been proven to have direct anticancer benefits in several mouse models (mentioned above), and researchers are looking at how bacteria may be genetically engineered for increased anticancer efficacy or employed as delivery systems for chemotherapeutics. The primary use of microbiome modifying treatment in treating human cancer, however, is now as an adjuvant therapy, enhancing the efficacy and/or reducing the side effects of chemotherapy, radiation, antibiotics, and surgery.

Chemotherapy and radiotherapy

It is important to draw attention to the specific circumstances in which probiotics may be advantageous [52]. The interaction between chemotherapeutic drugs and the microbiota has already been covered in great detail elsewhere in this special issue. The healthy gut microbiome has a varied microbial population as a vital component, and current research indicates that this community may also affect chemotherapy response and overall cancer survival. The role of the microbiota in chemotherapeutic drug anticancer activity has been emphasized in murine models [53, 54]. Low microbial diversity was separately linked to both a lack of clinical response to an immune checkpoint inhibitor in patients with advanced melanoma [56] and a decreased survival in patients following allogeneic hematopoietic stem cell transplantation [55].

Additionally, it has been demonstrated that chemotherapy itself substantially decreases microbial diversity [57]. As a way to preserve variety and enhance the efficiency of chemotherapy in this situation, pre- and probiotic treatment may be taken into consideration before and concurrently with chemotherapy. Although studies addressing this issue have not yet been published, it is an intriguing area for further research. Following pelvic radiation, which is frequently given to patients receiving treatment for urgynecological or rectal malignancies, changes in bowel function have been well-documented. The involvement of the microbiota in radiation-induced intestinal damage and the potential therapeutic use of probiotics are topics of considerable interest [58].

Following pelvic irradiation, dysbiosis has been linked to the emergence of postradiotherapy diarrhea [59], and several randomized trials have shown that probiotics can lessen the GI adverse effects of radiation [60]. Similar to GI mucositis, which can be dose- or treatment-limiting, is a frequent side effect of several chemotherapy drugs. Probiotics may interfere with the pathogenesis of mucositis on several levels, including triggering cytoprotective pathways, reducing reactive oxygen species, displacing pathogenic bacteria, and maintaining the integrity of the intestinal barrier. In 150 patients undergoing 5-fluorouracil-based chemotherapy for CRC, a randomized trial comparing probiotic supplements to placebo revealed substantially less grade 3/4 diarrhea in the intervention group (22 versus 37%, $p = 0.027$) [61]. Additionally, a meta-analysis has demonstrated that using probiotic supplements helped cancer patients experience less diarrhea (odds ratio antibiotics (OR): 0.52; 95% confidence interval (CI): 0.34-0.78) [62]. Expert recommendations have recently been published and encourage the use of probiotics including Lactobacillus in patients receiving chemotherapy or radiation for pelvic cancer in order to avoid diarrhea [63].

CONCLUSION

To sum up, pre-, pro-, or synbiotics have a lot of potential for preventing and treating cancer, but the science is still extremely young. Although there are well-established mechanisms through which probiotics may have positive benefits, clinical investigations tend to be scarce, small, heterogeneous, and frequently prone to bias [62]. It is difficult to infer that these treatments are more effective at preventing cancer than a balanced diet that is low in animal meat and rich in fiber, but many Westerners do not eat this way and have additional cancer risks factors, such as obesity and diabetes. The expenditures of long-term usage would not be small, but the hazards of taking pre- and probiotic supplements seem to be quite low. The most important research to determine any reduction in cancer risk is prospective longitudinal cohort studies. A stronger body of research supports the use of pre-, pro-, and synbiotics as adjuncts in the treatment of cancer. There is moderate evidence to support their usage, in particular, in the avoidance of infectious problems after surgery, antibiotic-associated diarrhea, and diarrhea linked to chemotherapy or radiation for pelvic cancer. Randomized interventional studies on people are crucial for understanding the possible advantages of co-administration with immunotherapy. However, for patients to gain the most from probiotics, we need to have a better understanding of the precise formulations that are effective in certain patient cohorts. Probiotic and prebiotic research is advancing at a fast rate, especially in the field of cancer where several promising therapeutic advantages are tantalizingly near. However, to achieve them, there must be a strong emphasis on performing high-quality, well-reported studies.

REFERENCES

1. Gibson GR, Hutkins R, Sanders ME, *et al*. (2017). Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics, Nat Rev Gastroenterol Hepatol. 2017;14(8):491–502.
2. Hill C, Guarner F, Reid G, *et al*. (2014). Expert consensus document: The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic, Nat Rev Gastroenterol Hepatol. 2014;11(8):506–514. https://doi.org/10.1038/nrgastro.2014.66.

3. Oelschlaeger TA. (2010). Mechanisms of probiotic actions - A review, Int J Med Microbiol. 2010;300 (1):57–62. https://doi.org/10.1016/j.ijmm.2009.08.005
4. Orrhage K, Sillerstrom E, Gustafsson JA, *et al*. (1994). Binding of mutagenic heterocyclic amines by intestinal and lactic acid bacteria, Mutat Res. 1994;311(2):239–248. https://doi.org/10.1016/0027-5107(94)90182-1
5. Jones ML, Tomaro-Duchesneau C, Prakash S. (2014). The gut microbiome, probiotics, bile acids axis, and human health, Trends Microbiol. 2014;22(6):306–308. https://doi.org/10.1016/j.tim.2014.04.010
6. LeBlanc JG, Chain F, Martin R, *et al*. (2017). Beneficial effects on host energy metabolism of short-chain fatty acids and vitamins produced by commensal and probiotic bacteria, Microb Cell Fact. 2017; 16(1):79. https://doi.org/10.1186/s12934-017-0691-z
7. Commane D, Hughes R, Shortt C, *et al*. (2005). The potential mechanisms involved in the anti-carcinogenic action of probiotics, Mutat Res. 2005;591(1–2):276–289. https://doi.org/10.1016/j.mrfmmm.2005.02.027
8. Dimidi E, Christodoulides S, Scott SM, *et al*. (2017). Mechanisms of action of probiotics and the gastrointestinal microbiota on gut motility and constipation, Adv Nutr. 2017;8(3):484-494. https://doi.org/10.3945 /an.116.014407
9. Sanders ME. (2011). Impact of probiotics on colonizing microbiota of the gut, J Clin Gastroenterol. 2011; 45(Suppl): S115–S119. https://doi. org/10.1097/MCG.0b013e318227414a
10. Alexander J, Scott AJ, Pouncey AL, *et al*. (2018). Colorectal carcinogenesis: an archetype of gut microbiota–host interaction, Ecancermedicalscience. 2018; 12: 865. https://doi.org/10.3332/ecancer.2018.865.
11. Thomas RM, Jobin C. (2015). The microbiome and cancer: is the 'oncobiome' mirage real?, Trends Cancer. 2015;1(1):24–35. https:// doi.org/10.1016/j.trecan.2015.07.005
12. Schwabe RF, Jobin C. (2013). The microbiome and cancer, Nat Rev Cancer. 2013;13(11):800–812. https://doi.org/10.1038/nrc3610
13. Dos Reis SA, da Conceicao LL, Siqueira NP, *et al*. (2017). Review of the mechanisms of probiotic actions in the prevention of colorectal cancer, Nutr Res. 2017;37:1–19. https://doi.org/10.1016/j.nutres.2016.11.009
14. Caballero-Franco C, Keller K, De Simone C, *et al*. (2007). The VSL#3 probiotic formula induces mucin gene expression and secretion in colonic epithelial cells, Am J Physiol Gastrointest Liver Physiol. 2007; 292(1):G315–G322. https://doi.org/10.1152/ ajpgi.00265.2006
15. Anderson RC, Cookson AL, McNabb WC, *et al*. (2010). Lactobacillus plantarum MB452 enhances the function of the intestinal barrier by increasing the expression levels of genes involved in tight junction formation, BMC Microbiol. 2010;10:316. https://doi. org/10.1186/1471-2180-10-316
16. Resta-Lenert SC, Barrett KE. (2009). Modulation of intestinal barrier properties by probiotics: role in reversing colitis, Ann N Y Acad Sci. 2009;1165:175–182. https://doi.org/10.1111/j.1749-6632.2009.04042.x
17. Lewis MC, Merrifield CA, Berger B, *et al*. (2017). Early intervention with *Bifidobacterium lactis* NCC2818 modulates the host- microbe interface independent of the sustained changes induced by the neonatal environment, Sci Rep. 2017;7(1):5310. https://doi. org/10.1038/s41598-017-05689-z
18. Liu Z, Qin H, Yang Z, *et al*. (2011). Randomized clinical trial: the effects of perioperative probiotic treatment on barrier function and post-operative infectious complications in colorectal cancer surgery - a double-blind study, Aliment Pharmacol Ther. 2011;33(1):50–63. https://doi.org/10.1111/j.1365-2036.2010.04492.x
19. Karczewski J, Troost FJ, Konings I, *et al*. (2010). Regulation of human epithelial tight junction proteins by Lactobacillus plantarum in vivo and protective effects on the epithelial barrier, Am J Physiol Gastrointest Liver Physiol. 2010; 298(6):G851–G859. https://doi.org/10.1152/ajpgi.00327.2009
20. Kuugbee ED, Shang X, Gamallat Y, *et al*. (2016). Structural change in microbiota by a probiotic cocktail enhances the gut bar- rier and reduces cancer via TLR2 signaling in a rat model of colon cancer, Dig Dis Sci. 2016;61(10):2908–2920. https://doi.org/10.1007/ s10620-016-4238-7
21. Fernandez NC, Lozier A, Flament C, *et al*. (1999). Dendritic cells directly trigger NK cell functions: cross-talk relevant in innate anti-tumor immune responses in vivo, Nat Med. 1999;5(4):405–411. https://doi.org/10.1038/7403
22. Ogawa T, Asai Y, Tamai R, *et al*. (2006). Natural killer cell activities of synbiotic *Lactobacillus casei* spp. casei in conjunction with dextran, Clin Exp Immunol. 2006;143(1):103–109. https://doi.org/10.1111/j.1365-2249.2005.02975.x
23. Gill HS, Rutherfurd KJ, Cross ML, *et al*. (2001). Enhancement of immunity in the elderly by dietary supplementation with the probiotic *Bifidobacterium lactis* HN019, Am J Clin Nutr. 2001;74(6):833–839. https://doi.org/10.1093/ajcn/74.6.833
24. Nagao F, Nakayama M, Muto T, *et al*. (2000). Effects of a fermented milk drink containing *Lactobacillus casei* strain Shirota on the immune system in healthy human subjects, Biosci Biotechnol Biochem. 2000;64(12):2706–2708. https://doi.org/10.1271/ bbb.64.2706
25. Lim BK, Mahendran R, Lee YK, *et al*. (2002). Chemopreventive effect of Lactobacillus rhamnosus on growth of a subcutaneously implanted bladder cancer cell line in the mouse. Jpn J Cancer Res. 2002;93(1):36–41. https://doi.org/10.1111/j.1349-7006.2002. tb01198.x
26. Takagi A, Matsuzaki T, Sato M, *et al*. (2001). Enhancement of natural killer cytotoxicity delayed murine carcinogenesis by a probiotic microorganism, Carcinogenesis. 2001;22(4):599–605. https://doi.org/10.1093/ carcin/22.4.599
27. Sivan A, Corrales L, Hubert N, *et al*. (2015). Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti- PD-L1 efficacy, Science. 2015;350(6264):1084–1089. https://doi.org/10.1126/science.aac4255

28. Vinolo MA, Rodrigues HG, Nachbar RT, *et al*. (2011). Regulation of inflammation by short chain fatty acids, Nutrients. 2011;3(10):858–876. https://doi.org/10.3390/nu3100858
29. Hu Y, Le Leu RK, Christophersen CT, *et al*. (2016). Manipulation of the gut microbiota using resistant starch is associated with protection against colitis-associated colorectal cancer in rats, Carcinogenesis. 2016;37(4):366–375. https://doi.org/10.1093/carcin/ bgw019
30. Phillips J, Muir JG, Birkett A, *et al.* (1995). Effect of resistant starch on fecal bulk and fermentation-dependent events in humans, Am J Clin Nutr. 1995;62(1):121–130. https://doi.org/10.1093/ajcn/62.1.121
31. Worthley DL, Le Leu RK, Whitehall VL, *et al*. (2009). A human, double-blind, placebo-controlled, crossover trial of prebiotic, probiotic, and synbiotic supplementation: effects on luminal, inflammatory, epigenetic, and epithelial biomarkers of colorectal cancer, Am J Clin Nutr. 2009;90(3):578–586. https://doi.org/10.3945/ajcn.2009.28106
32. Bolognani F, Rumney CJ, Rowland IR. (1997). Influence of carcinogen binding by lactic acid-producing bacteria on tissue distribution and in vivo mutagenicity of dietary carcinogens, Food Chem Toxicol. 1997;35(6):535–545. https://doi.org/10.1016/ S0278-6915(97)00029-X.
33. Kumar RS, Kanmani P, Yuvaraj N, *et al*. (2012). Lactobacillus plantarum AS1 isolated from south Indian fermented food Kallappam suppress 1,2-dimethyl hydrazine (DMH)-induced colorectal cancer in male Wistar rats, Appl Biochem Biotechnol. 2012;166(3):620–631. https://doi.org/10.1007/s12010-011-9453-2
34. Bouhnik Y, Flourie B, Andrieux C, *et al*. (1996). Effects of *Bifidobacterium* sp fermented milk ingested with or without inulin on colonic bifidobacteria and enzymatic activities in healthy humans, Eur J Clin Nutr. 1996; 50(4):269–273.
35. Ling WH, Hanninen O, Mykkanen H, *et al*. (1992). Colonization and fecal enzyme activities after oral *Lactobacillus* GG administration in elderly nursing home residents, Ann Nutr Metab. 1992;36(3):162–166. https://doi.org/10.1159/000177712
36. Marteau P, Pochart P, Flourie B, *et al*. (1990). Effect of chronic ingestion of a fermented dairy product containing *Lactobacillus acidophilus* and *Bifidobacterium bifidum* on metabolic activities of the colonic flora in humans, Am J Clin Nutr. 1990;52(4):685–688. https://doi.org/10.1093/ajcn/52.4.685
37. Iyer C, Kosters A, Sethi G, *et al*. (2008). Probiotic Lactobacillus reuteri promotes TNF-induced apoptosis in human myeloid leukemia-derived cells by modulation of NF-kappaB and MAPK signalling, Cell Microbiol. 2008;10(7):1442–1452. https://doi.org/10.1111/ j.1462-5822.2008.01137.x
38. Chen CC, Lin WC, Kong MS, *et al*. (2012). Oral inoculation of probiotics *Lactobacillus acidophilus* NCFM suppresses tumour growth both in segmental orthotopic colon cancer and extra-intestinal tissue, Br J Nutr. 2012;107(11):1623–1634. https://doi. org/10.1017/S0007114511004934
39. Le Leu RK, Brown IL, Hu Y, *et al*. (2005). A synbiotic combination of resistant starch and *Bifidobacterium lactis* facilitates apoptotic deletion of carcinogen-damaged cells in rat colon, J Nutr. 2005;135(5):996–1001. https://doi.org/10.1093/jn/135.5.996
40. Berni Canani R, Di Costanzo M, Leone L. (2012). The epigenetic effects of butyrate: potential therapeutic implications for clinical practice, Clin Epigenetics. 2012;4(1):4. https://doi.org/10.1186/1868-7083-4-4
41. Pool-Zobel BL, Bertram B, Knoll M, *et al*. (1993). Antigenotoxic properties of lactic acid bacteria in vivo in the gastrointestinal tract of rats, Nutr Cancer. 1993;20(3):271–281. https://doi.org/10.1080/01635589309514295
42. O'Keefe SJ, Li JV, Lahti L, *et al*. (2015). Fat, fibre and cancer risk in African Americans and rural Africans, Nat Commun. 2015;6:6342. https://doi.org/10.1038/ncomms7342
43. Pala V, Sieri S, Berrino F, et al. (2011). Yogurt consumption and risk of colorectal cancer in the Italian European prospective investigation into cancer and nutrition, cohort Int J Cancer. 2011;129(11):2712–2719. https://doi.org/10.1002/ijc.26193
44. Sellers TA, Vierkant RA, Djeu J, *et al*. (2008). Unpasteurized milk consumption and subsequent risk of cancer, Cancer Causes Control. 2008;19(8):805–811. https://doi.org/10.1007/s10552-008-9143-8
45. Ohashi Y, Nakai S, Tsukamoto T, *et al*. (2002). Habitual intake of lactic acid bacteria and risk reduction of bladder cancer, Urol Int. 2002;68(4):273–280. https://doi.org/10.1159/000058450
46. Larsson SC, Andersson SO, Johansson JE, *et al*. (2008). Cultured milk, yogurt, and dairy intake in relation to bladder cancer risk in a prospective study of Swedish women and men, Am J Clin Nutr. 2008;88(4):1083–1087. https://doi.org/10.1093/ajcn/88.4.1083
47. Aune D, Lau R, Chan DS, et al. (2012). Dairy products and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, Ann Oncol. 2012;23(1):37–45. https://doi.org/10.1093/annonc/mdr269
48. Rafter J, Bennett M, Caderni G, *et al*. (2007). Dietary synbiotics reduce cancer risk factors in polypectomized and colon cancer patients, Am J Clin Nutr. 2007;85(2):488–496. https://doi.org/10.1093/ajcn/85.2.488
49. Ishikawa H, Akedo I, Otani T, *et al.* (2005). Randomized trial of dietary fiber and *Lactobacillus casei* administration for prevention of colorectal tumors, Int J Cancer. 2005;116(5):762–767. https://doi.org/10.1002/ijc.21115
50. Ben Q, Sun Y, Chai R, *et al*. (2014). Dietary fiber intake reduces risk for colorectal adenoma: a meta-analysis, Gastroenterology. 2014; 146(3):689–699.e6. https://doi.org/10.1053/j.gastro.2013.11.003
51. Aso Y, Akaza H, Kotake T, *et al*. (1995). Preventive effect of a *Lactobacillus casei* preparation on the recurrence of superficial bladder cancer in a double-blind trial, The BLP Study Group Eur Urol. 1995; 27(2):104–109. https://doi.org/10.1159/000475138
52. Pouncey A (2018). Gut microbiota, chemotherapy, and the host: the influence of the gut microbiota on cancer treatment, Ecancermedicalscience.2018; 5;12:868. https://doi.org/10.3332/ecancer.2018.868

53. Iida N, Dzutsev A, Stewart CA, *et al*. (2013). Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment, Science. 2013;342(6161):967–970. https://doi.org/10.1126/science.1240527
54. Viaud S, Saccheri F, Mignot G, *et al*. (2013). The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide, Science. 2013;342(6161):971–976. https://doi.org/10.1126/science.1240537
55. Taur Y, Jenq RR, Perales MA, *et al*. (2014). The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic stem cell transplantation, Blood. 2014;124(7):1174–1182. https://doi.org/10.1182/blood-2014-02-554725
56. Gopalakrishnan V, Spencer CN, Nezi L, *et al*. (2018). Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients, Science. 2018;359(6371):97–103. https://doi.org/10.1126/science.aan4236
57. Montassier E, Gastinne T, Vangay P, *et al*. (2015). Chemotherapy-driven dysbiosis in the intestinal microbiome, Aliment Pharmacol Ther. 2015;42(5):515–528. https://doi.org/10.1111/apt.13302
58. Ferreira MR, Muls A, Dearnaley DP, *et al*. (2014). Microbiota and radiation-induced bowel toxicity: lessons from inflammatory bowel disease for the radiation oncologist, Lancet Oncol. 2014;15(3):e139–e147. https://doi.org/10.1016 /S1470-2045(13)70504-7
59. Manichanh C, Varela E, Martinez C, *et al*. (2008). The gut microbiota predispose to the pathophysiology of acute postradiotherapy diarrhea, Am J Gastroenterol. 2008;103(7):1754–1761. https://doi.org/10.1111/j.1572-0241.2008.01868.x
60. Delia P, Sansotta G, Donato V, *et al*. (2007). Use of probiotics for prevention of radiation-induced diarrhea, Tumori. 2007;93(2):S1–S6.
61. Osterlund P, Ruotsalainen T, Korpela R, *et al*. (2007). *Lactobacillus* supplementation for diarrhoea related to chemotherapy of colorectal cancer: a randomised study, Br J Cancer. 2007;97(8):1028–1034. https://doi.org/10.1038/sj.bjc.6603990
62. Hassan H, Rompola M, Glaser AW, *et al*. (2018). Systematic review and meta-analysis investigating the efficacy and safety of probiotics in people with cancer, Support Care Cancer. 2018;26(8):2503–2509. https://doi.org/10.1007 /s00520-018-4216-z

CITATION OF THIS ARTICLE

Anup Kumar Sarkar and Sanjoy Sadhukhan. Impact of Salinity on Growth and Development of Plants with the central focus on Glycophytes: an overview. Bull. Env. Pharmacol. Life Sci., Vol 12 [7] June 2023: 267-273