Review

Surfacing role of probiotics in cancer prophylaxis and therapy: A systematic review

Subramanyam Dasari a, Chandrasekhar Kathera b, Avilala Janardhan c, Arthala Praveen Kumar d, Buddolla Viswanath e, *

a Department of Biomedical Sciences, University of Illinois, College of Medicine at Rockford, Rockford, IL 61107, USA
b College of Life Sciences, Jiangsu Key Laboratory for Molecular and Medical Biotechnology, Nanjing Normal University, Nanjing 210023, China
c Department of Plant Biotechnology and Genomics, Centre for Biotechnology and Plant Genomics (CBGP), Polytechnic University of Madrid (UPM), Madrid 28040, Spain
d Department of Virology, College of Sciences, Sri Venkateswara University, Tirupati 517502, India
e Department of Bionanotechnology, Gachon University, San 65, Bokjeong dong, Sujeong gu, Seongnam si, Gyeonggi do 461 701, Republic of Korea

ARTICLE INFO

Article history:
Received 4 August 2016
Accepted 21 November 2016

Keywords:
Probiotics
Molecular mechanism
Cancer
Therapy
Immune response

SUMMARY

Cancers figure among the most important causes of morbidity and mortality worldwide. Cancer and its associated infections are always complicated even when specific cancer regimens are available. It is well proved that Lactobacillus and other probiotic bacteria can modulate-ameliorate specific mechanisms against various infections including cancers. The present systematic review is intended to focus on the cellular and molecular mechanisms of probiotic bacteria in the prevention and treatment of various cancers. The clinical and experimental findings of various studies explain the mechanisms such as apoptosis, antioxidant activity, immune response and epigenetics and illustrate the role of probiotics in cancer management and prophylaxis. In addition, the present review also discusses the safety aspects of probiotics when they are used in therapeutic and nutritional diet management. However, further investigations are required to reveal the effectiveness of probiotics in cancer treatment in clinical settings.

1. Introduction

Uncontrolled proliferation of cells and their resistance to apoptosis are defining features of cancer cells. There is no single specific therapy for cancer because the exact causes of most cancer types are not understood; however, it is known that a range of physiological and metabolic disturbances in the cell lead to the development of cancer [1]. Each and every cancer has its unique significant targets such as apoptotic signals, immune regulatory signals, proteins and enzymes. Depending on these targets one can evaluate the therapeutic drugs which might prove effective in combating any particular cancer. Once the treatment has been given to the cancer cells, the efficacy of the cancer prophylaxis is based on the restoration sensitivity of transforming cells to their original state. Over prescription and misuse of chemotherapeutic antibiotics has led to resistance to antibiotic and chemotherapy/radiotherapy treatments and has become a problem in many cases [2]. The World Health Organization (WHO) has proposed that alternative disease control strategies in the prevention and treatment of certain infections may be required in the future [3]. The Association of Modifiable Health has established that at least one-half of all cancers may have dietary components, which indicates that nutritional factors play a major role in cancer treatment. Hence, many dietary components and natural health products have attracted the attention of scientists for the development of natural therapeutics. One such treatment is probiotics, non-pathogenic microorganisms (living in host), which protect and benefit the host against various infections including cancer [4].

According to the WHO nutritional guidelines, probiotics can be defined as “live microorganisms when administered in adequate quantities confer a health profit to the host cell” [5]. Probiotics have become a typical ingredient in many traditional foods and formulations hence the Food and Drug Administration (FDA) endorse probiotics for their virtually null safety issues [6]. Several attributes of probiotic bacteria have been used successfully in the treatment of acute diarrhoea, inflammatory bowel disease (IBD) and other intestinal disorders. In addition to the regulation of intestinal
epithelial homeostasis and immune responses, certain probiotics have been reported to have anticancer activity through different mechanisms [4].

The most common groups of probiotic bacteria belong to the genera *Lactobacillus* (LAB) and *Bifidobacterium* (BFB), which are common indigenous microbiota of the human gastrointestinal tract [7]. The probiotic potentiality for management of intestinal and other inflammatory disorders of these two bacteria is well known. But there is a lack of well-documented mechanisms for these probiotics in inhibiting the initiation and progression of carcinogenesis. The present review will discuss emerging findings from both experimental and clinical studies, describing the anticancer activity of probiotics (*Lactobacillus*) through various mechanisms such as immunomodulatory effects, antioxidant activity, apoptosis, DNA damage prevention and epigenetic mechanisms (Fig. 1), thus paving the way for potential therapeutic intervention against various cancers [5,6].

1.1. An overview of probiotics in disease management

The probiotics LAB and BFB are an ecologically diverse group of microorganisms specified by the formation of lactic acid as the primary metabolite of sugar metabolism [8]. The beneficial activities of the probiotics were initially revealed by Metchnikoff (1845—1919), who proposed and meticulously documented the importance of fermented probiotic milk products in Balkan people [9]. Both LAB and BFB survive in the intestine and promote the recovery of normal gut microbiota [10]. Probiotic LAB could be significantly used in the management of diarrhoea both in adults and children [11]. Ozdemir [12], also reported that *Lactobacillus* GG effectively manages milk allergy in infants with increased production of IFN-ɣ. In another study, Del Carmen et al. [13] reported the potential application of probiotics in the prevention and treatment of inflammatory bowel disease. Recently it has been suggested that oral bacteriotherapy with probiotics might be useful in the management of atopic dermatitis (AD). A significant reduction of atopic eczema was demonstrated in children supplemented with probiotics with respect to the placebo group [14].

1.2. Probiotics in cancer treatment and management

It is well known that the development of many cancer types can be reduced by adopting certain lifestyle changes, for instance, smoking cessation and consuming a balanced nutritional diet which may counteract some causative factors, as suggested by the adoption of a nutritious and complete diet [15]. Much attention has been focused on decreasing cancer risk through diet variations, mainly the consumption of prebiotics (special form of dietary fibre that induces the growth of favourable bacteria) and probiotics. Recent reports demonstrated that there is an inverse association between cancer risk and cultured milk, yogurt and other fermented milk [16]. There exists encouraging evidence that specific probiotics (*Lactobacillus*) are valuable in the prevention and treatment of cancer through the increased production of cytokines (IL-2 and IL-12), antioxidants (SOD, CAT, GSH) and anti-angiogenic factors, in addition to decreasing DNA damage, inflammation, tumour size, cancer specific proteins, polyamine contents and pro carcinogenic enzymes (Fig. 2). To summarize the above discussed confirmation, probiotics aid in the suppression of cancer by multiple approaches at various stages of cancer with various degrees of treatment efficacy (Fig. 1).

Several experimental studies suggest the efficacy of probiotics in cancer prevention and treatment in humans and murine models [17—19]. Baldwin et al. [18] reported that *Lactobacillus acidophilus* and *Lactobacillus casei* were able to increase apoptosis induction in colorectal carcinoma cell line (LS 513), suggesting that these probiotic bacteria may possess anticancer activity. *Propionibacterium freudenreichii* was shown to induce the death of human colon and gastric cancer cell lines through the secretion of short chain fatty acids (SCFA) into the culture media. Both bacterial culture

---

Please cite this article in press as: Dasari S, et al., Surfacing role of probiotics in cancer prophylaxis and therapy: A systematic review, Clinical Nutrition (2016), http://dx.doi.org/10.1016/j.clnu.2016.11.017

---

**Fig. 1.** Probiotic bacterial strains and possible mechanisms against various cancers.
supernatants as well as pure SCFA induced emblematic signs of apoptosis such as generation of reactive oxygen species, loss of mitochondrial transmembrane potential, activation of caspase-3 and condensation of nuclear chromatin [19]. Probiotic *Lactobacillus* spp. induced selective cytotoxic, pro-apoptotic effects on leukemia and colon cancer cell lines, as well as anti-inflammatory effects on macrophage cells at the molecular level. Shyu et al. [20] reported that *Lactobacillus* spp. from dairy products secreted metabolites with cytotoxic and anti-inflammatory effects and they strongly suggest that the increased cytotoxicity for HT-29 and HCT116 cells may be associated with an upregulation of the early apoptosis gene markers *cfos* and *cjun*. Some probiotic strains have been reported to influence haematological cancers such as *Lactobacillus reuteri*, which enhanced TNF-induced apoptosis in human chronic myeloid leukaemia derived cells [21]. Le et al. [22] demonstrated that the symbiotic association between prebiotic and probiotic considerably assists the apoptotic response to a genotoxic carcinogen.

### 1.3. Probiotic induced immune response

The immune system plays a pivotal role in the prevention and control of tumour initiation and progression [23]. The interaction of numerous elements of the immune system such as antigen presenting cells (APC), different subsets of T-cells, B-cells, natural killer cells and dendritic cells are usually activated during invasion or mutation [5,24]. Experimental studies demonstrated that probiotics exert anticaner activity through immune-modulatory effects on cancer cells through macrophages, natural killer cells and T-cells [10]. A population-based case–control study showed an inverse association between beverages containing *L. casei Shirotia* (LcS) consumption and breast cancer occurrence [25]. The ingestion of LcS probiotics significantly prevents the recurrence of bladder cancer. Another multi-centred, prospective study demonstrated that the oral administration of LcS could enhance the efficacy of intravesical chemotherapy in patients who underwent transurethral resection for superficial bladder cancer [26]. Kanazawa et al. [27] demonstrated that the beneficiary activity of probiotics (LcS) against post-operative infectious complications in patients with biliary cancer.

Various mechanisms of the anticancer activity of probiotics such as augmentation of natural killer cell activity, modulation of host immune response through macrophages (induction of ILS) and restraint of the composition of indigenous microbiota and their metabolic activity are important. Natural killer cells are crucial for immune surveillance against cancer and infectious diseases, and higher natural killer cell activity has been reported to be associated with a lower risk of cancer development [10]. It has been demonstrated that an intravenous injection of *L. casei* LC 9018 amplified the NK cell activities of spleen cells in mice [28]. Previous studies also showed that the oral administration of LcS enhanced NK cell activity, leading to a delay of 3-methyl cholanthrene induced apoptosis.
carcinogenesis in mice [29]. In another study Gill et al. [30], also reported that the dietary consumption of milk supplemented with *Lactobacillus rhamnosus* and *Bifidobacterium lactis* enhanced the activity of NK cells in elderly people. The enhanced activity of NK cells was also observed in symbiotic association of probiotics with prebiotics (indigestible dietary fibre/carbohydrate) [31]. It has also been shown that oral administration of the probiotic bacteria in association with prebiotic bacteria effectively enhances the humoral immune response [31].

It was reported that a mechanism of increased NK cell activity by some strains of *Lactobacillus* (*Lactobacillus plantarum, L. rhamnosus* and *Lactobacillus paracasei*) activated peripheral blood mononuclear cells (PBMC) to induce IL-12 [32,33]. The major biological activities of IL-12 are directed towards T-cells and NK cells, which in turn leads to the enhanced production of cytokines [34]. Ogawa et al. [28] also reported that *L. casei* directly induced IL-12 production by human PBMC. In addition, they demonstrated that *L. casei* sp. *casei* as well as other *Lactobacillus* sp. induced IL-15 in the human intestinal epithelial cell line of colon cancer (Caco). Previously Ogawa et al. [35] reported that symbiotic association between probiotic *Lc* and its prebiotic dextran, exhibited immuno-modulatory activity in BALB/c mice. They also reported that IL-15 mediated the proliferation of Caco cells, while IL-12 induced by intestinal epithelial cells mediated the activation of intestinal intra epithelial NK cells [28]. Soltan Dalal et al. [36] suggest that the oral administration of *L. casei* significantly increases the production of IL-12, IFN-γ and the natural killer cells (NK) in mice bearing invasive ductal carcinoma. Together, these findings suggest that the cytokines induced by *L. casei* are associated with the activation of NK cells.

Phagocytosis is the means of removing microorganisms from blood and tissue fluids and is mediated mainly by macrophages and polymorphonuclear neutrophils (PMN). It has been suggested that live *L. rhamnosus* HN001 exhibits dose-dependent effects on the phagocytic defense system of mice. LAB enhances natural and acquired immunity in healthy mice by increasing phagocytic activity of peripheral blood leukocytes and peritoneal macrophages as well as by production of cytokines [37]. Various immuno modulators can enhance the phagocytic activity in vitro, including probiotic bacteria. Dietary consumption of some strains of LAB has been shown to stimulate and enhance the cellular immune responses, including phagocytosis, proliferation of lymphocytes and cytokine production [38]. Probiotic bacteria interact with dendritic cells (DCs) through various surface molecules such as Lectin, TLR family members and co-receptors (CR) [39]. It has been suggested that the interactions between lipoteichoic acid (LTA)–Toll-like receptor 2 (TLR2), lipopolysaccharide (LPS)–TLR4 and flagellin–TLR5 induce the production of cytokines and co-stimulatory molecules for antigen presentation that can modulate T cell polarization. These interactions lead to phagocytosis and digestion in phagolysosomes, so that the interacting microorganism-associated molecular patterns (MAMPs) become available for recognition by pattern recognition receptors (PRR) [39]. Apart from whole bacteria probiotics, various components of LAB such as viable cells (VC), heat killed cells (HK), cell wall (CW) and exopolysaccharides (EPS) of LAB have been assayed for a macrophage–mediated immune response. Kim et al. [40] reported that whole cells, and enzymatically digested, *Bifidobacterium* sp. induced the release of cytokine (TNF–α) and nitric oxide (NO). Another study showed that viable cells of *L. paracasei* spp. *paracasei* NTU 101, significantly increased innate immunity and induced peyer’s patch mediated gut mucosal immunity [41]. Liu et al. [42] also reported the ability of *L. paracasei* spp. *paracasei* NTU 101 and 101EP, *L. plantarum* NTU 101EP and 102EP to induce IL-6, IL-1β and TNF–α production. They also observed that phagocytosis was induced by 101EP and 102EP. Hence, LAB enhances immunity by increasing phagocytic activity of leukocytes and macrophages.

*Lactobacilli* can draw out innate and adaptive immune responses in host cells by binding to PRR expressed on immune cells. PRR recognise conserved molecular structures known as pathogen associated molecular patterns (PAMPs) or MAMPs which leads to induction of cytokines, chemokines and other innate effectors [43]. These signal receptors can be divided into three families, namely TLR, retinoic acid inducible gene I (RIG-I) like receptors that recognise viral RNAs (RLRs) and nucleotide oligomerization domain (NOD) like receptors (NLRs). Of these three receptor families, TLRs are the most characterized, and approximately 10 types of TLRs have been identified in humans, and 12 in mice [44]. TLRs are a family of trans-membrane receptors that recognise repetitive patterns such as PAMPs present in various Gram positive and Gram negative bacteria [45]. TLRs are found in immune cells such as dendritic cells, macrophages, endothelial and mucosal epithelial cells, as well as cells from various organ systems [46].

Previously Meshkibaf et al. [47] documented the role of probiotics in the production of anti-inflammatory cytokines (IL-10) through TLR recognition both in murine and human models. In fact, the cell surface component (LTA) of *Lactobacillus acidophilus* strongly induces in vitro IL-10 from immune cells to fabricate inflammatory and regulatory cytokines [48,49]. The LTA can stimulate DCs through TLR-2 resulting in the release of cytokines by the oral vaccine vector *Streptococcus gordonii* [50]. Certain species of *Lactobacillus* can stimulate DCs to produce IL-12 and the anti-inflammatory cytokine (IL-10) [48,51]. However, disruption of LTA synthesis resulted in a *L. acidophilus* derivative that acts on increased production of IL-10 in DCs, and down regulated IL-12 levels [52]. Matsuguchi et al. [53] also reported that the purified LTA may be the better candidate than the whole bacteria for clinical usage to induce an immune response. Both peptidoglycan (PGN) and lipoteichoic acid have been demonstrated to activate macrophages in a CD14-dependent manner. Lipoteichoic acid from Gram positive bacteria (*Bifidobacteria, Strepotococcus*) also recognizes TLR-2, 6 and triggers the signalling cascade for the production of cytokines [54]. In light of the above findings it can be concluded that the probiotic *Lactobacillus* induces innate immunity in cancer cell lines.

1.4. Anti-oxidant activity of probiotics

Oxidative DNA damage induction is a preliminary step during carcinogenesis of some drug induced cancers. It has been suggested that probiotics could be efficacious in the reduction of oxidative DNA damage caused by carcinogenic chemical agents in *vitro* and *in vivo* [55]. However, this treatment had not been effective in cancer prevention but the concept of antioxidant activity of probiotics was developed since both milk and milk containing LAB were shown to exert anticancer and antioxidant activity [56]. Data from experimental studies indicate that oral administration of certain types of LAB strains and their metabolic products reduced the risk of ROS accumulation and also degraded superoxide anions and hydrogen peroxides [42]. It was also reported that the exopolysaccharides (EPS) from *L. plantarum* C88 had an antioxidant effect which may involve scavenging of reactive oxygen species, enhanced regulation of enzymatic and non-enzymatic antioxidant activities and reduced lipid peroxidation. Recently, Zhang et al. [55] reported that *Lactobacillus Salivarious* REN inhibited the oxidative DNA damage in 4-nitroquinoline 1-oxide (4-NOO) induced oral cancer. Ramesh et al. [57] also reported that antioxidant activity was found to be strain specific and that these strains of *Lactobacillus* may be useful in developing functional foods to fight oxidative stress. Attention has been focused on extracellular polysaccharides from LAB against antioxidant activities [58]. Various *in vitro* studies
showed that LAB strains possess antioxidant properties and inhibit ROS through enzymatic mechanisms such as coupled NADH oxidase/peroxidase systems and catalase [59]. Heat killed cells and cytoplasmic fractions from the Lactobacillus strains L. paracasei NTU 101 and 102 also had inhibitory effects on cancer cell lines and antioxidant activities in vitro [60]. Lin et al. [61] also reported that the symbiotic association of Bifidobacterium longum and L. acidophilus display antioxidant activity by inhibiting linoleic acid peroxidation by 28–48%. Another study shows that the heat killed L. acidophilus 606 along with soluble polysaccharide components exhibited effective anti-oxidative activity [62]. In vitro studies postulated that LAB possess antioxidant properties and inactivate ROS through enzymatic (NADH oxidase/peroxidase system, superoxide dismutase and catalase) and non-enzymatic mechanisms such as scavenging by Mn [63].

1.5. Probiotics-induced apoptosis

Apoptosis is a process of programmed cell death, playing an important role in the regulation of cell proliferation as well as cell death [64]. An important event in many types of cancers is the reduced ability to trigger apoptosis associated with alterations in cell proliferation [65]. Most of the chemotherapeutic drugs against cancer used today exert their effects by inducing apoptosis [66]. Several studies showed that probiotic bacteria play a key role in the regulation of cell apoptosis through intrinsic and extrinsic pathways which are potentially critical mechanisms in the prevention of cancer. Chen et al. [67] demonstrated that the oral administration of L. acidophilus showed reduced severity of colorectal carcinoma and induced apoptosis in mice. Little is known about the mechanism of LAB-induced apoptosis via down regulation of the nuclear factor-kappa B (NF-kB)- dependent gene products which regulate cell proliferation (Cox-2, cycline D1) and survival (Bcl-2, Bcl-xl) [21]. In addition, L. reuteri suppresses the TNF-induced NF-kB activation, including the NF-kB dependent receptor gene, which is expressed in a dose and time dependent manner to slow down cancer cell growth [21]. Such characteristics of L. reuteri may be involved in the extrinsic pathway of apoptosis. Le et al. [22] demonstrated that a combination of probiotics (B. lactis) and prebiotics (starch) significantly facilitated the apoptotic response to a genotoxic carcinogen. Several probiotic strains have been reported to influence haematological cancers including L. reuteri-enhanced TNF-induced apoptosis in chronic myeloid leukemia human-derived cells by modulation of NF-kB and mitogen activated protein kinase signalling and condensed proteins that mediated cell proliferation (cycline D1 and Cox-2) or inhibited apoptosis (Bcl-2, Bcl-xl) [21]. Hwang et al. [68] also reported that LAB induced apoptosis in gastric cancer cells (KATO3) by inhibiting NF-kB and mTOR-mediated signalling. Cousin et al. [69] proposed another mechanism for probiotic induced apoptosis in their report of the pro-apoptotic potential of P. freudenreichii on HTG-1 gastric cancer cell lines. These probiotic bacteria induce chromatin condensation, apoptotic bodies, DNA fragmentation, accumulation of ROS, caspase activation, inactivation of mitochondrial trans-membrane potential and cell cycle arrest. Probiotic bacteria influence the intestinal microbiota and stimulate the intestine-associated immune cells, which is useful against intestinal inflammation and colon cancer. Specifically, the oral administration of fermented (probiotic yogurt) products induces cellular apoptosis by increasing cytokine (IL-10) secreting cells in mice [70]. Baldwin et al. [18] evaluated the anti-proliferative activity of L. acidophilus and L. casei against LS180 gastric cell lines through cellular apoptosis. The apoptotic potential of these two probiotic bacteria was increased in the presence of 5-fluorouracil (5-FU); this may be due to the faster activation of caspase-3 protein and down regulation of p21 protein levels.

HPV E6 and E7 proteins play a vital role in cervical carcinogenesis through inactivation of p53 and pRb tumour suppressor genes, which block apoptosis and reduce immune recognition [71]. Several attempts have been made to suppress these two genes by therapeutic drugs. Li et al. [60] reported down regulation of oncogenic genes which in turn increased the tumour suppressor genes and finally induced apoptosis in cervical cancer cells. Bifidobacterium adolescentis SPM1005-A showed antiviral activity through suppression of HPV E6 and E7 oncogene expression which indicated that the B. adolescentis SPM1005-A could potentially be used for prevention of HPV-associated cervical cancer [72].

1.6. Probiotics-induced cytotoxicity in cancer cells

In-vitro experimental evidence suggests that probiotics used for their anti-cancer activity operate via a process of cytotoxicity against tumour cells [42]. Recently, Nami et al. [73] also reported that the metabolites from L. acidophilus 36 YL exhibited the most potent cytotoxic effect against human cervical cancer cell lines (HeLa) and colorectal cancer cell lines (HT-29). Several other reports demonstrated that the anti-proliferative activity of LAB on growth of human cancer cell lines has its effects via cytotoxicity [74,75]. Liu et al. [42] explored the effects of different modalities of L. casei 01 cell free fractions (heat treated cells, crude cell wall, intra cellular extracts and exopolysaccharides) on 4-nitroquinoline N-oxide (4-NQO) induced genotoxicity and colon cancer cell line (HT-29), finding that EPS induced higher anti-proliferative activity against HT-29 cancer cell lines. Wang et al. [20] reported that whole peptidoglycan (WPG) of Bifidobacteria bifidum promoted the non-specific immunity through the secretion of IL-1, IL-6 and TNF-α from the peritoneal macrophages of nude mice. Recently, Chiba et al. [76] also reported that probiotic L. casei have the potential to induce IL-12 production and promote T17 cell development.

1.7. Other mechanisms induced by probiotics

In addition to the above discussed mechanisms, probiotic bacteria also induce other molecular mechanisms which lead to the death of cancer cells. Epigenetics involves alteration of the expression level of selected genes without any modifications in DNA sequence, such as DNA methylation, chromatic remodelling, and histone tail modifications [77]. Histone deacetylase inhibitors (HDACi) are epigenetic drugs used for their anti-proliferative activity against tumour cells [78]. Metabolites of probiotic bacteria, such as butyrate, a short chain fatty acid (SCFA), are important therapeutic compounds against cancer. Butyrate is one energy source for the colonocytes and has been used in the regulation of apoptotic cellular proliferation and differentiation [79]. Sodium butyrate induces anti-proliferative activity on many cancer cell types especially on colon cancer [80]. Archer & Hodin [81], hypothesised that butyrate affects gene expression in a process involving phosphorylation and acylation of histone proteins. In another study, Lightfoot et al. [82] reported that a mutant strain of L. acidophilus (LTA-deficient) induced epigenetic modifications and found increased expression of tumour suppressor genes in oral NCK 2025 cell lines. L. reuteri exhibited potent inhibition of colon cancer cell proliferation. The anti-proliferative activity of L. reuteri may be related to the production of SCFA metabolites in the colon, which may also decrease tumour growth and promote apoptosis [83]. Recent findings showed that LAB also induced anti-proliferative activities of colon cancer cells through synergistic action between cancer cells and SCFA metabolites [5]. Thirabunyanon et al. [84] reported that cell free supernatants of L. casei and L. rhamnosus decreased colon cancer cell invasion by inducing matrix metallo protein-9 and zonaducclen-1 thus acting to prevent colon cancer.

Please cite this article in press as: Dasari S, et al., Surfacing role of probiotics in cancer prophylaxis and therapy: A systematic review, Clinical Nutrition (2016), http://dx.doi.org/10.1016/j.clnu.2016.11.017
1.8. Role of probiotics in post-treatment cancer complications

Although both chemotherapy and radiotherapy are the gold standard for treatment of cancer, the severity of their associated complications continues to negatively impact patients’ quality of life. The chemotherapy-induced complications include mucositis (oral cavity and intestine) which is characterized by ulceration, diarrhoea and inflammation [85]. Diarrhoea is a frequently observed complication during pelvic radiotherapy in cervical, lymphoma, colon cancer, and pancreatic cancer [86]. Chemotherapy-induced mucositis and radiotherapy-induced diarrhoea are both associated with cytotoxic agents which damage the intestinal mucosal lining and alter water absorption capacity [87].

Regimen-induced complications are most widely treated by alterations in diet especially the introduction of probiotic food. Usage of probiotic nutritional intervention pre and post treatment may provide protection for healthy cells and tissues [86]. The protective role of probiotic bacteria against diarrhoea and mucositis may be due to the improved immune status of the gut [88]. Previous studies also explain that these probiotic bacteria may compete with pathogenic bacteria for binding on epithelial cells [86].

Saez-Lara et al. [89] reported that the probiotic compound VSL #3 (VSL pharma, Italy) prepared from highly concentrated freeze-dried living bacteria plays a major role in chemotherapy induced diarrhoea and mucositis. The protective role of VSL #3 is treatment specific which exerts good effects on the host organisms by improving the flora of indigenous microbiota in the intestine and reduces the growth of pathogens. Experimental and clinical studies of VSL #3 suggested the mechanism underlying the efficacy of probiotic VSL #3 to protect against diarrhoea. This mechanism is of great importance because of the targeting of an unregulated process of apoptosis which is the ultimate factor responsible for the radiation-induced injury of the intestinal epithelial cells [90].

Recently, Yamashiro & Nagata [91], reported that probiotics are used to ameliorate chemotherapy induced mucositis in paediatric malignancies.

1.9. Safety aspects of probiotics in cancer treatment

Probiotics and their safety aspects have been important for evaluation of the therapeutic role of probiotics against infections and cancer. A properly assessed probiotic (diet) consumption/treatment plays a key role in the management of disease [3]. Evaluation of safety aspects of probiotic consumption is a complex but very important task when this is used as a therapeutic agent. The safety aspects include viability in delivery vehicles (diet), acid and bile resistance, adherence to gut epithelial tissue, effect of antimicrobial substances, and stimulation of host immune responses [92]. Experimental and clinical studies on the therapeutic efficacy of probiotics depend on purity, dosage and stability of those probiotic products [3]. Lactobacillus and Bifidobacteria are members of the indigenous microbiota of the human oro-gastro intestinal tract and they occasionally cause opportunistic infections. Both probiotics have been associated with certain infections such as bacteremia, dental infections, food allergies and endocarditis. These infections are associated with an imbalance of intestinal microbiota and increased gut permeability [92].

Well-established data are available for the safety assessment of probiotics through several approaches, including intrinsic properties, and pharmacokinetics along with the host—probiotic interactions [93]. The data explain the survival of the probiotics within the gastrointestinal tract, their colonization, translocation and the fate of active components which are important for evaluation of probiotic ingestion. The pharmacokinetics of probiotics have been studied using perfusion and biopsy techniques [94]. In vitro studies of probiotic bacteria have reported the deconjugation of bile salts producing free bile acids, which are more inhibitory to susceptible bacteria than the deconjugated form, and degradation of mucus membranes [95,96]. Other in vitro parameters being studied include platelet aggregation properties, binding of human intestinal mucosa and the production of unwanted metabolites [3]. Strains of Lactobacilli species that are intrinsically resistant to antibiotic (vacomycin) have a good and a long history of safety and these resistant strains could not transfer the resistance to other bacteria. Probiotics and their products have been safely consumed in large quantities for a long time in Europe and Japan. However, the proven and presumptive findings indicate that sporadic localized infections may occur in immunocompromised patients and show that no zero risk has been attributed to consumption of living probiotics [3].

Chemotherapy induced diarrhea is one of the most common cancer associated toxicities which lead to the chemotherapy regime being stopped or reduced [97]. Diarrhoea is unpleasant for the cancer patient and may reduce the response to radiotherapy and chemotherapy; they may also require further treatment to prevent associated morbidity and mortality [88]. As infections are common in immunocompromised patients, the microflora plays a role in immunity [97], and probiotics should be evaluated both for efficacy in preventing infection and for safety, and it is particularly important to investigate whether probiotics may cause infection themselves [99]. Beckerson et al. [100] advise against the use of products containing probiotics for neutropenic cancer patients. However, Gibson et al. [101] suggest that consumption of probiotics (Lactobacillus species) may help prevent diarrhoea during chemotherapy or radiotherapy in patients with pelvic malignancies. A systematic review demonstrated that the administration of probiotics reduces the average frequency of daily bowel movements and may reduce the need for anti-diarrhoeal medication but mentions that they may be a rare cause of sepsis [97].

2. Conclusion

It is clear that in vitro, in vivo and clinical findings attest to the fact that the probiotic-based therapeutics and diet play an important role in suppressing various infections and dysplastic conditions. Insights into cellular and molecular mechanisms such as immune responses, apoptosis, anti-oxidant and epigenetic mechanisms bring novel approaches for the development of probiotic-based therapeutics. Supplementation of dietary constituents is an emerging and safe strategy in cancer prevention. Situated at the interface of supplemented nutrition and health, probiotics play a pivotal role in allaying many cancers. As stated earlier, many pre-clinical and clinical studies of probiotics in the treatment and prophylaxis of various cancers have illustrated their efficiency, the benefits often being species and strain specific. In future, the possibility of genetically modified probiotic microorganisms may provide new opportunities for their prophylactic and therapeutic use. Therefore, constructive research on genetic manipulation is required to improve the existing probiotic characteristics of particular strains, as well as to prepare novel probiotic organisms with specific properties for treatment and prophylaxis of various cancers.

Conflicts of interests

The authors declare no relevant competing financial interests to disclose.
Acknowledgements

The authors wish to thank Prof. Chris Anthony for his help in drafting this manuscript. The authors are indebted to all the researchers whom we cited in this review for their significant and valuable research. No funding was received to perform this review.

References


