Probiotics and Cancer: Boosting the Immune System

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Abstract

The concept of use of functional food/probiotics in the recent years as adjuvants for prevention and treatment of cancer has been on rise owing to their capabilities to restrain the host immune response and modulate the intestinal microflora. Numerous studies have proved that probiotics can be of potential use in the prevention and treatment of cancer through microbiota and immune modulation, condensed bacterial translocation, enhanced gut barrier function, anti-inflammatory, anti-pathogenic activity, reduced tumour formation, reduced metastasis, etc. Probiotics refer to live microbial incorporations available in a variety of food, mainly the fermented ones. Other than that, bacteria producing lactic acid, perceived to have useful properties such as resistance to pathogens, improving lactose digestion, etc. are also commonly referred as probiotics. The present chapter discusses the role of various probiotic strains in cancer and summarizes the important findings in relation to the probiotic mediated suppression of gastrointestinal and extra-intestinal cancers.

Keywords

Probiotics · Cancer · Immune system · Immunosurveillance · Lactobacilli

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3.1 Cancer: Role of Immune System

The human immune system is capable of specific obliteration of tumours without any toxicity to the normal tissues. In addition, the immune system can also preserve this memory for a long term and prevent the cancer reoccurrence via a process known as 'immunosurveillance'. The research in the immuno-oncology field has presented us with concrete substantiation that immunosurveillance can not only identify tumours but also stop and prevent reoccurrence of the same for a long term (Finn 2012). The idea of immunosurveillance was accredited in the 1990s when research involving knockout mice animal models corroborated the reality of the concept of cancer immunosurveillance in spontaneous and chemically induced tumours. Since then the dominant roles of the effector cells of the immune system such as natural killer T cells, B cells, perforin and interferons (IFN) (I and II) were elucidated in cancer immunosurveillance (Dunn et al. 2002, 2005; Kim et al. 2007). The target specificity of the immune response exists in the differentiation ability of the antigens of the tumour. Other than these, the viral proteins in tumour instigated by viruses, the self-expressed proteins from the tumour surface, and the mutated and the non-mutated proteins from the onco genes exhibit virtuous targets for immunosurveillance (Finn 2012). The cancer immunoexpurgation resulting from immunosurveillance generally follows three essential phases, i.e., elimination, equilibrium and escape (Dunn et al. 2002). The cancer cells are initially eliminated by the effector cells such as natural killer cells and IFN-γ from the innate response of the immune system. Eliminating the transformed cells can result in decreased immunogenicity thereby rendering the tumour resistant to effector cells of the immune system in the equilibrium phase. Ultimately, during the progression of the tumour when diagnostic methods are able to detect the size of the tumour, factors such as tumour-derived soluble factors can instigate various mechanisms in the tumour microenvironment for the escape from the attack of the immune system (Kim et al. 2006).

In the recent years, research has proved the role of probiotics in exalting the immune response for the fight of cancer (De Leblanc et al. 2007). Many strains of probiotic organisms have the potential to impact innate mechanisms of defence such as phagocytosis (Schiffrin et al. 1995, 1997; Pelto et al. 1998; Arunachalam et al. 2000). Perdigon et al. in 1988 proved the potential of *L. acidophilus* and *L. casei* in systemic immunostimulation by the increase in the phagocytosis capability of murine peritoneal macrophages (Perdigon et al. 1988). Similarly, probiotic organisms also help in regulating the activity of natural killer cells (Gill et al. 2001), enterocytes and cytokines production (Lammers et al. 2002). Probiotics also impact the adaptive immunity by stimulating the production of IgA (Link-Amster et al. 1994; Fukushima et al. 1998; Isolauri et al. 2000; Park et al. 2002), dendritic cells (DCs) and Treg cells (Christensen et al. 2002; Braat et al. 2004). In this chapter, we shall discuss the potential and use of probiotics for improving the immune system in cancer condition.

3.2 Probiotics: Improving Immunity

Probiotics exert several beneficial effects on the host immune system. These effects include blocking pathogenic bacterial effects by producing bactericidal substances and competing with pathogens and toxins for adherence to the intestinal epithelium. Probiotics have been found to improve the innate as well as adaptive immunity by modulation of DCs, macrophages, and T and B lymphocytes functions via toll-like receptor-regulated signalling pathways. DCs being the antigen presenting cells play an important role in both adaptive and innate immunity. They also possess the properties of activating naïve T cells and have an important role in guiding the helper T cells towards the regulatory pattern or Th1 and Th2 (Lammers et al. 2002). The Th1 responses of the immune system decisively rely on the proficiency of the DCs to produce interleukin (IL)-12. The same are characterized by the production of IFN-γ and IL-2. The Th2 immune responses generally involve humoral immunity and IL-4, IL-5, IL-6 and IL-13 (Link-Amster et al. 1994; De Leblanc et al. 2007). Some of the prominently studied mechanisms of immunity involve the production of the IFN-α or induction of indoleamine 2,3-dioxygenase, an immunoregulatory enzyme with prime role in the interaction between the T cells and the DCs (Fukushima et al. 1998; Park et al. 2002).

In a recent study, it was demonstrated that probiotics activate the innate immunity and trigger the adaptive immune responses. It was found that a mixture of probiotics including strains of *L. reuteri*, *L. acidophilus*, *B. bifidum*, *L. casei* and *Streptococcus thermophilus* stimulated regulatory DCs expressing elevated levels of (Transforming growth factor beta) TGFβ, (cyclooxygenase-2) COX2, IL10 and IFN-α, thereby promoting the generation of forkhead family transcription factor ($CD4^+Foxp3^+$) regulatory T cells and increasing the suppressor activity. Additionally, the aforementioned probiotic mixture induced T and B cell hypo-responsiveness and down-regulated the T helper cells without induction of apoptosis. It was also revealed in the in vivo studies that the aforementioned mixture supressed the intestinal inflammation, which involved association of $CD4^+Foxp3^+$ Tregs, induced by 2,4,6-trinitrobenzenesulfonic acid (Yan and Polk 2011).

3.2.1 Need of Probiotics in Cancer Therapy

Cancer is a cellular disorder in which a defective apoptotic pathway triggers uncontrolled cell growth. Normally, the cells grow and re-divide via mitosis, having control on the G_1 phase. The loss of control on the G_o pathway results in the condition called malignancy (Hamada et al. 2001). The advancements in medical science resulted in the development of new synthetic drugs against cancer. However, they have numerous side effects. With the advancement in the field of nutraceutical foods and nano-pharmacology, the first of its kind novel functional food to heal cancer is no far from the reality (Cencic and Chingwaru 2010).

Probiotics provide vital nutrients that impart health benefits and thus act as functional foods for dealing with many gastrointestinal disorders, and even cancer.

These are the class of microorganisms residing in the gastrointestinal tract and assisting the digestive and enzymatic function of the host (Ciorba et al. 2015). Humans receive IgA from the milk of the mother along with the inoculation cultures of the *Lactobacillus* (Soto et al. 2014). The journey of Lactobacillus is affected by the dysbiosis phenomenon between the pathogenic strains and probiotics microbial flora. It has been found that the concentration of these microbes falls in between the therapeutic window and has the potential to act as prophylactic and curative agents against different diseases of the host (Sandes et al. 2017).

3.2.1.1 Antioxidant Nature of the Probiotics for Prophylaxis Against Gastrointestinal Diseases and Cancer

Recently, it has been proven that these living non-pathogenic microbiota, after administration in appropriate doses act as antioxidant mediators thereby preventing and curing many diseases. They show different pharmacological and physiological activities that play a vital role in the human immune system (Wang et al. 2017). Chemicals released by the *Lactobacillus* strains e.g. SOD (superoxide dismutase) act as antioxidant mediators. These microbes also display the potential to chelate various metal ions during the digestion process e.g. *Lactobacillus casei* is proved to chelate Fe^{2+} or Cu^{2+}, due to its antioxidant nature (Amaretti et al. 2013).

Many signalling mechanisms at the cellular/molecular level assisted by the probiotic microbes involve multistep complex pathways (Table 3.1); Kelch-like erythroid cell-derived protein with CNC homology [ECH]-associated protein 1 (Nrf2-Keap1) deals with the transcriptional responses via exogenous sensitization (Smith et al. 2016) while the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) deals by excessive oxidative stress loading in host cells. The anabolic processes involved in the cell growth cycle and cell division are generally governed by (mitogen-activated protein kinase) MAPK. Whereas its subtypes, p38-MAPK and c-Jun N-terminal kinases (JNKs) are linked with the diverse stresses encountered by the cell affected by osmotic shock and irradiations. The following table provides the various signalling pathways associated with the probiotic microbes in different host cells (Mishra et al. 2015; Wang et al. 2017).

Probiotics show antioxidant activity by producing metabolites like folate and glutathione (GSH). The folate regulates the vital metabolism signalling pathways involved in DNA replication, methylation and maintenance of wear and tear of the host cells. Evidence-based studies have shown that *Bifidobacteria* induces the folate

Table 3.1 Signalling pathway regulated by the probiotics in relation to antioxidant activities

Probiotics	Host cells	Signalling pathways
Clostridium butyricum	Rats	Nrf2-Keap1
L. rhamnosus GG	Cell line Caco2	MAPK
Bacillus amyloliquefaciens	Cell line 'IPEC-1 cell line'	Nrf2-Keap1
Lactobacillus sp. *SC4*	Mice	Nrf2-Keap1
Lactobacillus sp. CM	Cell line YAMC	MAPK
Lactobacillus sp. FC255	Cell line mice	Nrf2-Keap1

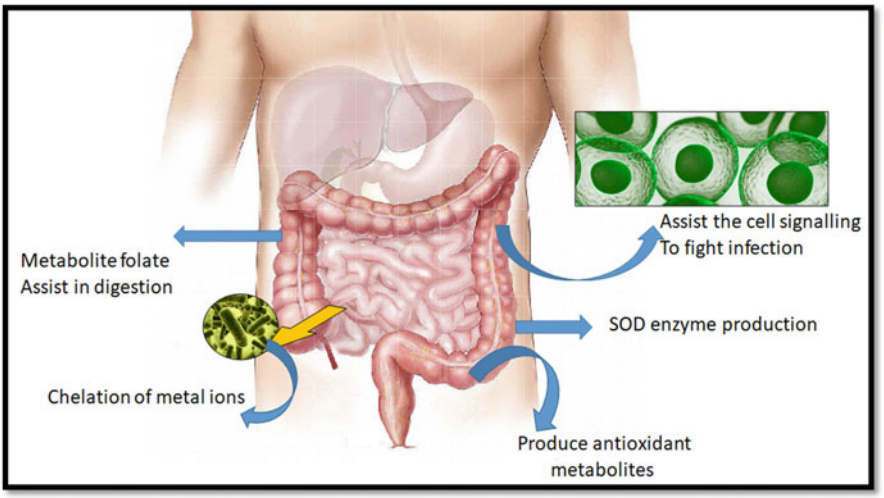

Fig. 3.1 Antioxidant activities exhibited by the probiotics involving various regulatory mechanisms

formation in animal models and human trials. Further investigations showed that the *L. fermentum* is capable of regulating the GSH system (Mikelsaar and Zilmer 2009; Wang et al. 2017). Thus, it can be concluded that probiotic treatments enhance the level of antioxidant metabolites.

Deficiency of vitamin B12 and folate promotes excessive oxidative stress in patients with type II diabetes. It has been shown that consumption of the yogurt, rich in *Lactobacillus* species, improves the level of the vitamin B12 along with the plasma folate relieving the oxidative damage in diabetes patients (Wang et al. 2017, Li et al. 2017a, p. 12). The detailed illustration of the antioxidant mechanism exhibited by the probiotics is given in Fig. 3.1.

3.2.1.2 Anticancer Nature of the Probiotics

Lactic acid bacteria also known as *Lactobacillus* are a genus from the probiotics group and are found to be useful in healing various common disorders and even cancer. The cancer healing abilities exhibited by the probiotics include various mechanisms, the most prominent being the suppression of cancer-causing mediators (Nami et al. 2014). This is regulated by preventing the carcinogenic metabolites from causing DNA alterations. Additionally, probiotics participate in the proper execution of the cell apoptosis, thereby preventing the cancer invasion by metastasis and growth of cancer stem cells (Motevaseli et al. 2017). The various mechanisms by which the probiotics act against cancer cells are illustrated in Fig. 3.2 and are discussed in detail in the following sections (Zhang et al. 2012; Yu and Li 2016; Motevaseli et al. 2017)

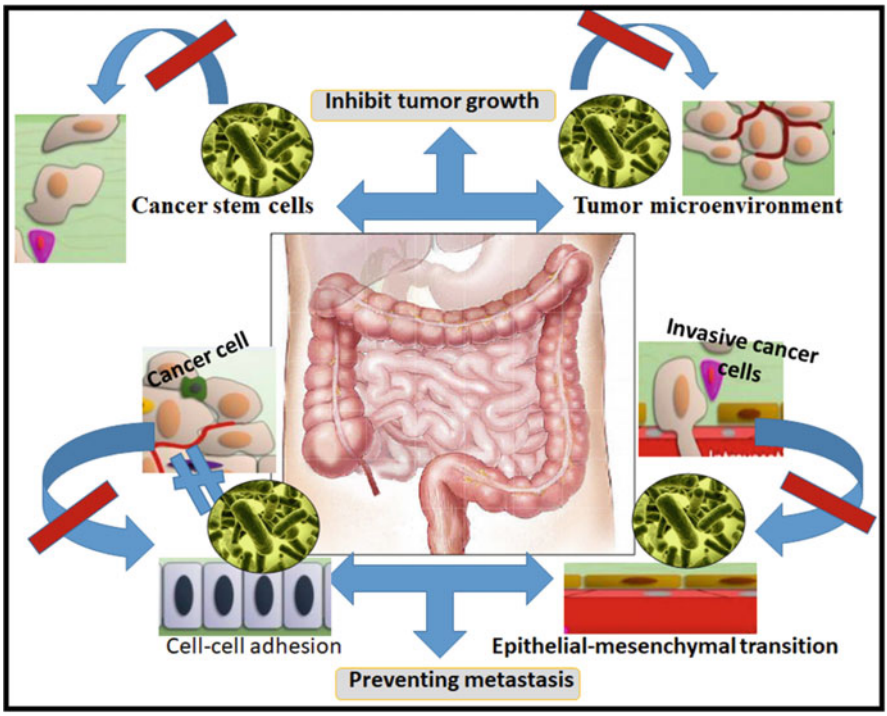

Fig. 3.2 Probiotic mechanisms inhibiting the infestation of the cancer

Protecting Host by Cell–Cell Adhesion

Normal physiology of the host tissue consists of tight junctions of the endothelial system showing cellular integrity. However, during the metastasis of cancer, these structures are weakened due to the damages in the scaffold proteins consisting of occludin and zonaoccludens-1 (ZO-1) (Motevaseli et al. 2017). Sometimes, the host cell membrane degrading agents such as matrix metalloproteinases assist the cancer cells to damage the structural integrity and invade other cellular structures and that is where probiotics play a role (Wan et al. 2014). The use of probiotics in a patient before surgery was found to enhance the liver barrier, thereby preventing the metastases (Eizaguirre et al. 2002; Dimitrov et al. 2014; Wang et al. 2017). *Lactobacillus* was found to be effective against cancer due to its cell adhesion mechanisms whereas *L. rhamnosus* decreased the overexpression of matrix metalloproteinase-2 in Caco2 cell line, thus maintaining cell–cell adhesion (Jan et al. 2002; von Ossowski et al. 2010; Motevaseli et al. 2017). Table 3.2 list cell–cell adhesion mechanism exhibited by probiotics.

Protecting Host by Inhibiting the Epithelial-Mesenchymal Transition (EMT)

The host's biological mechanism enables the epithelial cells to get polarized and develop affinity with the cell membrane. This results in the alteration of biochemical

Table 3.2 Cell–cell adhesion mechanism exhibited by the probiotics

Sr. no	Probiotics	Cell line/ host cell	Cell–cell adhesion mechanism
1	*L. acidophilus*	Human monocytes	Up-regulation of tissue inhibitors of metalloproteinases (TIMP)-1 as a tissue inhibitor
2	*L. rhamnosus* GG	Human monocytes	Up-regulation of metalloproteinases (TIMP)-9 as a tissue inhibitor
3	*L. rhamnosus* GG	MDA-MB-231 cells	Down-regulation of glucose transporter type 1 (*GLUT1)*
4	*L. acidophilus*	HT 29 cell line	Increase in intercellular adhesion molecule 5 (*ICAM5) expression*
5	*Lactobacillus species* (NCK2025)	HT 29 cell line	Up-regulation of TIMP-2
6	Kefir	4T1 cell line	Down-regulation of plasminogen activator urokinase
7	Kefir	Caco 2 cell line	Up-regulation of BCL2 associated X, apoptosis regulator (Bax)
8	Kefir	HT 29 cell line	Expression of tumour protein p53 (p53) independent of cyclin-dependent kinase inhibitor (p21) induction
9	*L. plantarum*	Caco 2 cell line	Translocation of zonula occludens-1 (ZO-1) in cell junction
10	*L. rhamnosus* GG	Caco 2 cell line	Up-regulation of Claudin-1 in cell junction

Table 3.3 EMT inhibition mechanism of the probiotics on the host cells

Sr. no	Probiotics	Cell line/host cell	EMT inhibition
1	*L. acidophilus*	CT 26 cell line	The up-regulation of the apoptosis TNF-factor based on ligand TNF-related apoptosis-inducing ligand (TRAIL)
2	*L. casei*	HT 29 cell line	Inhibition of TRAIL regulated metastasis
3	*L. casei*	CT 26 and HT29 cell line	Inhibiting the proinflammatory cytokines overexpression
4	*L. casei*	HT29 cell line	Inhibiting the microRNA 221 (miR-221) expression

processes affecting the migratory dimensions of the host cell against the invasion of cancerous cell. CXCŘ4 gene is found to be effective in enhancing the signalling pathway of EMT resulting in metastasis (Chen et al. 2012). The CXCŘ4 antibodies inhibit the adhesion to the cancerous cells preventing their migration. *L. acidophilus* is found to down-regulate the expression of CXCR4 and inhibit colon cancer in mice models (Chen et al. 2012; Motevaseli et al. 2017, 2018). Table 3.3 lists EMT inhibition mechanism of the probiotics on the host cell.

Inhibition of Tumour Microenvironment

The tumour microenvironment is developed by the communications that exist between the normal cells and tumour cells. The tumour-inducing cells in the microenvironment possess the ability to undergo various stages of tumour formation called tumourigenesis. These cells are non-malignant in nature and are related to the cells of the immune system and lymph nodal areas. A recent investigation carried out by the researchers demonstrated the anti-metastatic activities of *Lactobacillus* via alterations in the tumour microenvironment (Liu et al. 2015). Another study involving use of *L. casei* YIT018 in guinea pigs demonstrated their ability in suppressing the lymph node metastasis (Church and Galon 2015; Motevaseli et al. 2017). Table 3.4 lists mechanisms of tumour microenvironment inhibition by the proteins.

Inhibition of the Cancer Stem Cells

In the recent studies, it has been demonstrated that the 'cancer stem cells (CSC)' play an important role in haematological malignancies. Similar to normal stem cells, these cells possess abilities like self-renewal and prolonged survival and contribute to

Table 3.4 Mechanisms of tumour microenvironment inhibition by the probiotics (Orlando et al. 2009; Church and Galon 2015; Motevaseli et al. 2017)

Sr. no	Probiotics	Cell lines/ host cells	Tumour microenvironment inhibition pathways
1	*L. casei*	C47BL/6 mice	Suppresses tumour growth, protects against pulmonary metastasis
2	*L. casei*	C47BL/6 mice	Activation of natural killer cells as a cytolytic agent
3	*Lactobacilli species*	C47BL/6 mice	Suppression of metastasis
4	*Lactobacilli species YIT/9018*	Mice	Increase in IL-2 and IFN-γ level
5	*L. brevis*	BALB/c mice	Decreases the liver metastasis originated from the metastatic breast carcinoma
6	*L. brevis*	BALB/c mice	Increases the activity of the IFN-γ and IL-17 by activation of natural killer cells
7	*L. casei 431 CRL*	Wister rat	Antitumour activity linked to CD4+ and CD8+ lymphocytes
8	*L. casei* Shirota	HT29 cell line	Activation of natural killer cells
9	*L. rhamnosus* GG	HT29 cell line	Preventing the formation of free radicals with an enhancement of neutrophilic phagocytic activity
10	*L. casei* Shirota	Caco2cell line	Down-regulation of the angiogenic IL-1β factor
11	Kefir	Caco2cell line	Inhibiting the proangiogenic factor IL-6
12	*L. plantarum JDARSH*	HT 116 cell line	Preventing the formation of free radicals

Table 3.5 Cancer stem cells inhibition by the probiotics (Saxami et al. 2016; Motevaseli et al. 2017)

Sr. no	Probiotics	Cell line/ host cell	EMT inhibition pathways
1	*L. rhamnosus*	C47BL/6 mice	Inhibiting the (hypoxia-induced factor) HIF-1α signalling preventing metastasis
2	*Bifidobacterium breve*	C47BL/6 mice	Suppression of tumour cells by inhibition of inflammatory cytokine mediators
3	*L. plantarum*	HT 29 cell line	Activation of the natural killer cells by inhibition of inflammatory cytokine mediators
4	*L. crispatus*	HT 29 cell line	Down-regulation of HIF-1α signalling along with overexpression of *SFRP2*
5	*L. casei*	HT 29 cell line	Activation of the natural killer cells by inhibition of inflammatory cytokine mediators
6	*L. bulgaricus*	HT 29 cell line	Activation of the natural killer cells by inhibition of inflammatory cytokine mediators
7	*Bifidobacterium infants*	C47BL/6 mice	Suppression of tumour cells by inhibition of inflammatory cytokine mediators

cancer metastasis (Bui et al. 2015). These cells demonstrate heterogeneity in its functioning and show metastatic specificity to every organ system. The initiation and working of the CSC are due to the integral signalling pathways demonstrated by these cells against the host immune system (Llewellyn and Foey 2017). Alike stem cells, the self-transcriptional systems generated by CSC result in the induction of the hypoxic conditions in normal tissues. Further, this leads to regulations in signalling pathways involving multi-potent transcription factor Oct4, thereby initiating the migration of metastatic cells from one organ to the other. *L. rhamnosus* were observed to down-regulate the expression of hypoxia inducible factor-1α in breast cancer cell lines and colonic cancer cell lines (Bui et al. 2015; Motevaseli et al. 2017). Table 3.5 lists the pathways of cancer stem cell inhibition by the probiotics.

3.3 Probiotics and Cancer

The role of probiotics in cancer is recommended by several scientific indications and hypothesis that include upsurge in immune cell activation and suppression of the organisms converting procarcinogens. Below are some of the types of cancer and the study of probiotics associated with them.

3.3.1 Colon Cancer

Colorectal cancer is one of the leading cancers and nearly 862,000 deaths were reported in 2018 (Jan et al. 2002). The main reason behind the death owing to colorectal cancer is the leading dietary and behavioural risks taken by the patients which include obesity, low intake of fruits and vegetables, sluggish physical activity,

alcohol and tobacco consumption, etc. (Holscher 2017). Along with the diagnosis, the prognosis of the cancer is a critical issue. To cope up with these problems, few synthetic medicines have been discovered after several years of clinical trials. However, many have been discarded in the last phase of trials owing to host–drug incompatibility issues. Systemic administration is preferred rather than local for the treatment of colorectal cancer. This results in systemic toxicity and adverse effects on vital organs. Hence, there is the need for a drug that can be delivered by per-oral route, having local action, minimizing the systemic toxicity, controlling morbidity and preventing the mortality (Ohkawara et al. 2007).

Many of the functional food and nutraceutical formulations are available commercially but are limited in curing minor diseases or disorders (Cencic and Chingwaru 2010; Patil et al. 2015, 2019a). In order to tackle this problem there is a need for novel nutraceutical formulations derived from natural origin (Patil et al. 2018, 2019b). These formulations should be able to control the manifestation of various types of cancer and the activity shall be consistent. Probiotic formulations are widely available in the market for the treatment of bowel disorders. *Lactobacillus* are generally derived and isolated from milk of different milking animals (Patil et al. 2019c). Furthermore, cultures of the *Lactobacillus* are also available as powder formulations possessing biological activities like mucoadhesion (Ouwehand et al. 2003) along with properties of hydrophobicity and autoaggregation. They also maintain proper bowel movements so as to prevent gastrointestinal tract disorders. Many reported functional foods have the ability to trigger and initiate the innate immune system of the host and biological properties, including antimicrobial properties, which combat the activities of pathogenic microorganisms (Campbell et al. 2000). The abilities possessed by some probiotic strains to scavenge the free radicals enable them as anticancer mediators. The prepared formulations are ideal if they mimic the natural antioxidant mediators having long shelf life. However, short shelf life of probiotics makes them less demanding in the existing market. Thus, the *Lactobacillus* formulations with longer shelf life along with the surplus biological activities like antimicrobial, antioxidant and anticancer activities can be beneficial. These microbes with antioxidant activity help in triggering the innate immunity system along with the release of certain chemicals (proteins) eventually killing the cancer cells. The preliminary investigation regarding the effect of probiotics is evaluated in cell line studies. The antiproliferative, antioxidant and anticancer nature of the probiotics have been demonstrated successfully on colonic cancer cell lines. The following Table 3.6 shows the anticancer model developed by using the different cell lines (Choi et al. 2006; Russo et al. 2007; Kim et al. 2008; Orlando et al. 2009, 2012; Motevaseli et al. 2013, 2017; Nami et al. 2014; Dimitrov et al. 2014; Ghoneum and Felo 2015; Yu and Li 2016; Saxami et al. 2016; Malik et al. 2018; Patil et al. 2020).

Table 3.6 In vitro cell line studies using different probiotics

Sr.no	Probiotic formulations	Colon cancer cell line
1	*L. reuteri*	HCT-116, DLD-1
2	*L. kefiri*	HT-29
3	*L. casei*	CT-26, HT-29, WiDr, DLD-1 and CX-1 cells
4	*B. adolescentis*	DN
5	*L. acidophilus*	HT-29, WiDr, DLD-1 and CX-1 cells
6	*L. bulgaricus*	DN
7	*L. fermentum*	CRL-1831, Caco-2
8	*L. salivarius*	DN
9	*B. adolescentis*	DN
10	*L. rhamnosus*	HGC-27, Caco-2 and HT-29
11	*L. plantarum A7*	Caco-2 and HT-29

Where DN indicates—Data not available

3.3.2 Cervical Cancer

Cervical cancer is another malignant form of cancer observed in women globally. Cervical cancer is ranked fourth in the major causes of cancerous death among women worldwide (Lv and Wang 2018). No signs or symptomatic conditions are observed among the patients with cervical cancer at early stages; however, it has been proven to be fatal at the later stages eventually leading to death (Musa et al. 2017). In general, the microecological environment of the vagina is very sensitive where minute chronic changes may precipitate cervical diseases. The current research has shown that certain microorganisms may alter the microecological environment of female genital tract resulting in the development of cervical cancer (Yang et al. 2018a). Infection by the human papillomavirus (HR-HPV) causes diseases like colitis, high-grade cervical intraepithelial neoplasia along with cervical diseases in women (Chase et al. 2015).

The vaginal microflora observed in the case of patients with cervical cancer showed different counts of pathogenic strains such as *Staphylococcus epidermidis*, *Escherichia coli*, *Mycoplasma genitalium* and Enterococci species as compared to the control (Yue et al. 2015; Grmek Košnik et al. 2016). However, the exact correlation between the different microflora in normal female genital tract and that of cervical cancer is not yet elucidated (Sierra et al. 2018).

Probiotics especially *Lactobacillus* have an important role in cervical disorders. The major potential mechanisms exhibited by the probiotics against cervical cancer include:

(a) The autoaggregation mechanism that prevents adhesion of pathogenic strains to vaginal epithelial cells (VECs) inhibiting the conditions such as hyperplasia and wear–tear, thus decreasing the chances of any diseases or disorders.

Table 3.7 In vitro cell line studies using different probiotics

Sr. no	Probiotic formulations	Cervical cancer cell line
1	*L. crispatus*	CaSki cells
2	*L. casei*	DN
3	*L. gasseri* strains	Women, cervical cancer cell and Caco 2 cell lines
4	*Lactobacillus rhamnosus* HN001 (L1)	Th17 cells and HeLa cell lines
5	*L. bulgaricus*	DN
6	*L. crispatus*	HeLa cells
7	*L. casei*	CaSki and HeLa cell lines
8	*B. adolescentis*	DN
9	*L. plantarum*	Women; HeLa cell lines and HUVEC normal cells
10	*L. gasseri* and *L. crispatus*	Human normal fibroblast-like cervical (normal cervical) and HeLa (cervical tumour) cells
11	*Lactococcus lactis* and *L. casei*	HeLa and U14 cell lines

Where DN indicates—Data not available

(b) The ability to produce organic acids, which maintain the acidic microenvironment of the vagina inhibiting the invasion and growth of pathogens (Medina-Colorado et al. 2017).
(c) Release of chemicals such as bacteriocin, hydrogen peroxide and surface-active components, which play a vital role in inhibiting tumourigenic substances due to pathogens (Zadravec et al. 2015; Homburg et al. 2017).
(d) An effective immune sensitizer, assisting the proliferation of B cells in the bone marrow (Yao et al. 2007; Lee et al. 2010).

Furthermore, *Lactobacillus* has been found effective in hampering the metabolic pathway of the cancerous cells by the release of nitric oxide (NO) (Sandes et al. 2017). Also they act as an effective humoral immunity modulator, which mediates the proliferation of T cells in the thymus gland of the infants (Sandes et al. 2017).

The preliminary investigation regarding the effect of probiotics is evaluated by cell line studies. The antiproliferative, antioxidant and anticancer nature of the probiotics has been demonstrated successfully on cervical cancer cell lines is presented in Table 3.7 (Ribelles et al. 2013; Nami et al. 2014; Kim et al. 2015; Motevaseli et al. 2016; Seo et al. 2016; Jang et al. 2017; Li et al. 2017b; Wang et al. 2018; Yang et al. 2018b).

3.4 Breast Cancer

The past few years have witnessed a reduction in mortality rate due to breast cancer. However, breast cancer still remains one of the common cancers prevalent among the female population of the world. The fraternity of science working in the area of

breast cancer prophylaxis and therapy has thus started taking interest in the therapies other than chemotherapy for breast cancer. In vitro studies have demonstrated that breast cancer proliferation was inhibited by the use of isolated probiotics strains or supernatant from the cultures. It was also studied that heat killed cells, their cytoplasmic fractions and the live cultures namely *Enterococcus faecalis* and *Staphylococcus hominis* isolated from the breast milk caused cytotoxicity by means of apoptosis induction and arrest of the cell in the G0/G1 phase. It was also reported that the probiotics inhibiting the growth of the breast cancer also exhibited anti-inflammatory properties, suggesting their oncolytic property via immunomodulation (Han et al. 2015; Lee et al. 2015b; Nami et al. 2015; Hassan et al. 2016). The daily consumption of the strain *Lactobacillus acidophilus was reported to* increase the production of immunomodulatory cytokine IL12 in splenocyte culture. The same was stimulated by the tumour antigens in breast tumour bearing BALB/c mice (Yazdi et al. 2010).

3.5 Liver Cancer

The microbiome in the gut has been allied with the progression of liver disorders namely liver fibrosis (De Minicis et al. 2014), fatty liver disease (Raman et al. 2013; Wong et al. 2013) and in the recent years, liver cancer (Yoshimoto et al. 2013). In a recent study it was found that probiotics could inhibit the progression of the hepatocellular carcinoma in mice (Li et al. 2016). It was seen that upon feeding probiotics mixture to the mice with liver tumours, there was a shift in the gut microbiota, leading to the reduction of the tumour size in the liver of the mice. In addition to the above, it was also evident that there was a down-regulation in the angiogenic factors. Also, the level of the Th17 cells in gut and employment of Th17 to the tumour site were seen to be on the lower side in the mice treated with probiotics. The anticancer effect of the given probiotics was believed to have associated with the SCFAs-related pathway.

3.6 Other Cancers

Apart from the above-mentioned cancers, other types of cancers such as leukaemia, melanoma, lung cancer were also shown to have inhibited by the treatment of probiotics both in vivo and in vitro (Gui et al. 2015; Han et al. 2015; Lee et al. 2015a). Tuo et al. in their study demonstrated the antiproliferative activity of eight different strains of lactobacillus strains on leukaemia cells (Tuo et al. 2015). Similarly, Sivan et al. studied gut microbiota and immunotherapy on melanoma by the use of bifidobacterium species. It was found that the administration of the same caused reduction in the tumour volume of melanoma bearing mice (Sivan et al. 2015).

3.7 The Fate of Probiotics in the Animal and Clinical Studies

The anticancer effects of probiotics were determined by using various animal models such as rats and mice, the positive results of which lead to clinical trials on human volunteers (Fiala 1977; Chester et al. 1986; Foo et al. 2011; Asha and Gayathri 2012; Byelinska et al. 2015; El-Khadragy et al. 2018). Many studies were recently carried out using *L. acidophilus*, *L. amylovorus*, *L. brevis*, *L. bulgaricus*, *L. casei immunitas*, *L. casei*, *L. crispatus*, *L. delbrueckii*, *L. fermentum*, *L. gallinarum*, *L. helveticus*, *L. johnsonii*, *L. johnsonii LC-1*, *L. lactis*, *L. plantarum*, *L. reuteri*, *L. rhamnosus*, *L. salivarius*, *L. sporogenes* for analysing their anticancer activity using different animal models (Byelinska et al. 2015).

Mostly, probiotics have been employed as complementary synergistic mediators to manage intestinal disorders during chemotherapy and radiotherapy of cancer patients (Liu et al. 2011). *L. casei DN-114001* was investigated for its progression in the host body by the stool consistency studies and bowel movements physiology in patients undergoing radiation (Merenstein et al. 2010). Many researchers reported that the combination of *L. acidophilus* and *B. bifidum* minimize radiation-induced diarrhoea (Hickson 2011). It has also been reported that chemotherapy changes the human gut microbiota inviting the pathogenic strains such as *Clostridium difficile* in the gut of the patients suffering from colorectal cancer (Nakanishi et al. 2003; Shinnoh et al. 2013). The enteral administration of *bifidobacterium* and *Lactobacillus* not only improved the patient's intestinal environment but also minimized the side effects of radiotherapy (Walrand et al. 2012). Many studies showed that the administration of the probiotic formulations reduced post-operative trauma and intestinal infections (Liu et al. 2011; Zhang et al. 2012). Administration of probiotics also decreased the chances of tumour formations induced by aflatoxins, which are used as a marker for liver cancer (Kumar et al. 2012; Huang et al. 2017). The current research showed that the inclusion of probiotics as a nutraceutical agent reduces the risk of breast cancer in women after menopause. The consumption of these probiotics did not affect the level of the hormone in these women during their reproductive phase of the life (Bonorden et al. 2004). Probiotics were also found to be effective against the atypia form of colorectal tumours in patients consuming the *L. casei* for a period of 4 years (Gianotti 2010; Zhang et al. 2012).

3.8 Future Perspective and Conclusion

Cancer development is a progressive and protracted process involving complicated factors leading to metastasis. Epidemiological studies provide basis that probiotics have the potential to improve the lifestyle of the cancer patients and alter carcinogenesis. Research also shows that a number of probiotics have the potential of preventing cancer. These probiotics along with multiple health benefits possess anti-mutagenic and anti-carcinogenic properties. Such convincing research provides a strong basis for the acceptance of probiotics as chemo-supportive and chemo-preventive agents. However, the combination of the conventional treatment

approaches and probiotics have been known to play a critical role in the variance of the clinical results in the trials. Owing to the promising results, the future of probiotics seems bright and probiotic therapy is now being preferred in cancer. The effectiveness however is dependent on the species and strain of probiotics exerting its actions via multiple pathways in cancer treatment/prevention. This opens several possibilities in the area of genetically modified/engineered probiotic strains. Research is being conducted on engineered strains of organisms not only for therapy but detection too and the results seem convincing. Undoubtedly, the research investigations in the field of probiotics for cancer is in its infancy; however, the same has reassuring future in preventive therapy.

References

Amaretti A, di Nunzio M, Pompei A et al (2013) Antioxidant properties of potentially probiotic bacteria: in vitro and in vivo activities. Appl Microbiol Biotechnol 97:809–817. https://doi.org/10.1007/s00253-012-4241-7

Arunachalam K, Gill H, Chandra R (2000) Enhancement of natural immune function by dietary consumption of Bifidobacterium lactis (HN019). Eur J Clin Nutr 54:263–267

Asha A, Gayathri D (2012) Synergistic impact of Lactobacillus fermentum, Lactobacillus plantarum and vincristine on 1, 2-dimethylhydrazine-induced colorectal carcinogenesis in mice. Exp Ther Med 3:1049–1054

Bonorden MJL, Greany KA, Wangen KE et al (2004) Consumption of Lactobacillus acidophilus and Bifidobacterium longum do not alter urinary equol excretion and plasma reproductive hormones in premenopausal women. Eur J Clin Nutr 58:1635–1642. https://doi.org/10.1038/sj.ejcn.1602020

Braat H, van den Brande J, van Tol E et al (2004) Lactobacillus rhamnosus induces peripheral hyporesponsiveness in stimulated CD4+ T cells via modulation of dendritic cell function. Am J Clin Nutr 80:1618–1625

Bui VT, Tseng H-C, Kozlowska A et al (2015) Augmented IFN-γ and TNF-α induced by probiotic bacteria in NK cells mediate differentiation of stem-like tumors leading to inhibition of tumor growth and reduction in inflammatory cytokine release; regulation by IL-10. Front Immunol 6:1–15. https://doi.org/10.3389/fimmu.2015.00576

Byelinska I, Lynchak O, Rybalchenko T et al (2015) Morphofunctional parameters of blood cells of a rat with 1, 2-dimethylhydrazine-induced colon carcinogenesis. Cytol Genet 49:158–164

Campbell CG, Chew BP, Luedecke LO, Shultz TD (2000) Yogurt consumption does not enhance immune function in healthy premenopausal women. Nutr Cancer 37:27–35. https://doi.org/10.1207/S15327914NC3701_3

Cencic A, Chingwaru W (2010) The role of functional foods, nutraceuticals, and food supplements in intestinal health. Nutrients 2:611–625. https://doi.org/10.3390/nu2060611

Chase D, Goulder A, Zenhausern F et al (2015) The vaginal and gastrointestinal microbiomes in gynecologic cancers: a review of applications in etiology, symptoms and treatment. Gynecol Oncol 138:190–200. https://doi.org/10.1016/j.ygyno.2015.04.036

Chen C-C, Lin W-C, Kong M-S 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 107:1623–1634. https://doi.org/10.1017/S0007114511004934

Chester JF, Gaissert HA, Ross JS et al (1986) Augmentation of 1, 2-dimethylhydrazine-lnduced colon cancer by experimental colitis in mice: role of dietary vitamin E. J Natl Cancer Inst 76:939–942

Choi SS, Kim Y, Han KS et al (2006) Effects of lactobacillus strains on cancer cell proliferation and oxidative stress in vitro. Lett Appl Microbiol 42:452–458. https://doi.org/10.1111/j.1472-765X.2006.01913.x

Christensen HR, Frøkiær H, Pestka JJ (2002) Lactobacilli differentially modulate expression of cytokines and maturation surface markers in murine dendritic cells. J Immunol 168:171–178

Church SE, Galon J (2015) Tumor microenvironment and immunotherapy: the whole picture is better than a glimpse. Immunity 43:631–633. https://doi.org/10.1016/j.immuni.2015.10.004

Ciorba MA, Hallemeier CL, Stenson WF, Parikh PJ (2015) Probiotics to prevent gastrointestinal toxicity from cancer therapy: an interpretive review and call to action. Curr Opin Support Palliat Care 9:157–162. https://doi.org/10.1097/SPC.0000000000000134

De Leblanc ADM, Matar C, Perdigón G (2007) The application of probiotics in cancer. Br J Nutr 98:S105–S110

De Minicis S, Rychlicki C, Agostinelli L et al (2014) Dysbiosis contributes to fibrogenesis in the course of chronic liver injury in mice. Hepatology 59:1738–1749

Dimitrov Z, Gotova I, Chorbadjiyska E (2014) *In vitro* characterization of the adhesive factors of selected probiotics to Caco-2 epithelium cell line. Biotechnol Biotechnol Equip 28:1079–1083. https://doi.org/10.1080/13102818.2014.969948

Dunn GP, Bruce AT, Ikeda H et al (2002) Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol 3:991

Dunn GP, Bruce AT, Sheehan KC et al (2005) A critical function for type I interferons in cancer immunoediting. Nat Immunol 6:722–729

Eizaguirre I, Urkia NG, Asensio AB et al (2002) Probiotic supplementation reduces the risk of bacterial translocation in experimental short bowel syndrome. J Pediatr Surg 37:699–702. https://doi.org/10.1053/jpsu.2002.32256

El-Khadragy MF, Nabil HM, Hassan BN et al (2018) Bone marrow cell therapy on 1, 2-dimethylhydrazine (DMH)-induced colon cancer in rats. Cell Physiol Biochem 45:1072–1083

Fiala ES (1977) Investigations into the metabolism and mode of action of the colon carcinogens 1, 2-dimethylhydrazine and azoxymethane. Cancer 40:2436–2445

Finn O (2012) Immuno-oncology: understanding the function and dysfunction of the immune system in cancer. Ann Oncol 23:viii6–viii9

Foo N-P, Ou Yang H, Chiu H-H et al (2011) Probiotics prevent the development of 1, 2-dimethylhydrazine (DMH)-induced colonic tumorigenesis through suppressed colonic mucosa cellular proliferation and increased stimulation of macrophages. J Agric Food Chem 59:13337–13345

Fukushima Y, Kawata Y, Hara H et al (1998) Effect of a probiotic formula on intestinal immunoglobulin a production in healthy children. Int J Food Microbiol 42:39–44

Ghoneum M, Felo N (2015) Selective induction of apoptosis in human gastric cancer cells by Lactobacillus kefiri (PFT), a novel kefir product. Oncol Rep 34:1659–1666. https://doi.org/10.3892/or.2015.4180

Gianotti L (2010) A randomized double-blind trial on perioperative administration of probiotics in colorectal cancer patients. World J Gastroenterol 16:167. https://doi.org/10.3748/wjg.v16.i2.167

Gill H, Rutherfurd K, Cross M (2001) Dietary probiotic supplementation enhances natural killer cell activity in the elderly: an investigation of age-related immunological changes. J Clin Immunol 21:264–271

Grmek Košnik I, Dermota U, Golle A (2016) Frequency of detection of Gardnerella vaginalis in vaginal smears in the Upper Carniola region. Acta Dermatovenerol Alp Pannonica Adriat 25:31–33

Gui Q, Lu H, Zhang C et al (2015) Well-balanced commensal microbiota contributes to anti-cancer response in a lung cancer mouse model. Genet Mol Res 14:5642–5651

Hamada S, Sutou S, Morita T et al (2001) Evaluation of the rodent micronucleus assay by a 28-day treatment protocol: summary of the 13th Collaborative Study by the Collaborative Study Group

for the Micronucleus Test (CSGMT)/Environmental Mutagen Society of Japan (JEMS)–Mammalian Mutagenicity Study Group (MMS). Environ Mol Mutagen 37:93–110. https://doi.org/10.1002/em.1017

Han KJ, Lee N-K, Park H, Paik H-D (2015) Anticancer and anti-inflammatory activity of probiotic Lactococcus lactis NK34. J Microbiol Biotechnol 25:1697–1701

Hassan Z, Mustafa S, Rahim RA, Isa NM (2016) Anti-breast cancer effects of live, heat-killed and cytoplasmic fractions of Enterococcus faecalis and Staphylococcus hominis isolated from human breast milk. In Vitro Cell Develop Biol Anim 52:337–348

Hickson M (2011) Probiotics in the prevention of antibiotic-associated diarrhoea and Clostridium difficile infection. Ther Adv Gastroenterol 4:185–197. https://doi.org/10.1177/1756283X11399115

Holscher HD (2017) Dietary fiber and prebiotics and the gastrointestinal microbiota. Gut Microbes 8:172–184. https://doi.org/10.1080/19490976.2017.1290756

Homburg C, Bommer M, Wuttge S et al (2017) Inducer exclusion in Firmicutes: insights into the regulation of a carbohydrate ATP binding cassette transporter from Lactobacillus casei BL23 by the signal transducing protein P-Ser46-HPr. Mol Microbiol 105:25–45. https://doi.org/10.1111/mmi.13680

Huang L, Duan C, Zhao Y et al (2017) Reduction of aflatoxin B1 toxicity by Lactobacillus plantarum C88: a potential probiotic strain isolated from Chinese traditional fermented food "Tofu". PLoS One 12:1–16

Isolauri E, Arvola T, Sütas Y et al (2000) Probiotics in the management of atopic eczema. Clin Exp Allergy 30:1605–1610

Jan G, Belzacq AS, Haouzi D et al (2002) Propionibacteria induce apoptosis of colorectal carcinoma cells via short-chain fatty acids acting on mitochondria. Cell Death Differ 9:179

Jang S-E, Jeong J-J, Choi S-Y et al (2017) Lactobacillus rhamnosus HN001 and Lactobacillus acidophilus La-14 attenuate Gardnerella vaginalis-infected bacterial vaginosis in mice. Nutrients 9(6):531. https://doi.org/10.3390/nu9060531

Kim R, Emi M, Tanabe K, Arihiro K (2006) Tumor-driven evolution of immunosuppressive networks during malignant progression. Cancer Res 66:5527–5536

Kim R, Emi M, Tanabe K (2007) Cancer immunoediting from immune surveillance to immune escape. Immunology 121:1–14. https://doi.org/10.1111/j.1365-2567.2007.02587.x

Kim Y, Lee D, Kim D et al (2008) Inhibition of proliferation in colon cancer cell lines and harmful enzyme activity of colon bacteria by Bifidobacterium adolescentis SPM0212. Arch Pharm Res 31:468–473. https://doi.org/10.1007/s12272-001-1180-y

Kim S-N, Lee WM, Park KS et al (2015) The effect of Lactobacillus casei extract on cervical cancer cell lines. Contemp Oncol (Pozn) 19:306–312. https://doi.org/10.5114/wo.2014.45292

Kumar M, Verma V, Nagpal R et al (2012) Anticarcinogenic effect of probiotic fermented milk and chlorophyllin on aflatoxin-B1-induced liver carcinogenesis in rats. Br J Nutr 107:1006–1016. https://doi.org/10.1017/S0007114511003953

Lammers K, Helwig U, Swennen E et al (2002) Effect of probiotic strains on interleukin 8 production by HT29/19A cells. Am J Gastroenterol 97:1182–1186

Lee T-Y, Kim Y-H, Lee K-S et al (2010) Human papillomavirus type 16 E6-specific antitumor immunity is induced by oral administration of HPV16 E6-expressing Lactobacillus casei in C57BL/6 mice. Cancer Immunol Immunother 59:1727–1737. https://doi.org/10.1007/s00262-010-0903-4

Lee N-K, Han KJ, Son S-H et al (2015a) Multifunctional effect of probiotic Lactococcus lactis KC24 isolated from kimchi. LWT Food Sci Technol 64:1036–1041

Lee N-K, Son S-H, Jeon EB et al (2015b) The prophylactic effect of probiotic Bacillus polyfermenticus KU3 against cancer cells. J Funct Foods 14:513–518

Li J, Sung CYJ, Lee N et al (2016) Probiotics modulated gut microbiota suppresses hepatocellular carcinoma growth in mice. Proc Natl Acad Sci 113:E1306–E1315

Li P, Gu Q, Yang L et al (2017a) Characterization of extracellular vitamin B 12 producing Lactobacillus plantarum strains and assessment of the probiotic potentials. Food Chem 234:494–501. https://doi.org/10.1016/j.foodchem.2017.05.037

Li X, Wang H, Du X et al (2017b) Lactobacilli inhibit cervical cancer cell migration in vitro and reduce tumor burden in vivo through upregulation of E-cadherin. Oncol Rep 38:1561–1568. https://doi.org/10.3892/or.2017.5791

Link-Amster H, Rochat F, Saudan K et al (1994) Modulation of a specific humoral immune response and changes in intestinal flora mediated through fermented milk intake. FEMS Immunol Med Microbiol 10:55–63

Liu Z, Qin H, Yang Z et al (2011) Randomised clinical trial: the effects of perioperative probiotic treatment on barrier function and post-operative infectious complications in colorectal cancer surgery - a double-blind study: randomised clinical trial: perioperative probiotics on colon cancer. Aliment Pharmacol Ther 33:50–63. https://doi.org/10.1111/j.1365-2036.2010.04492.x

Liu Z, Li C, Huang M et al (2015) Positive regulatory effects of perioperative probiotic treatment on postoperative liver complications after colorectal liver metastases surgery: a double-center and double-blind randomized clinical trial. BMC Gastroenterol 15:34. https://doi.org/10.1186/s12876-015-0260-z

Llewellyn A, Foey A (2017) Probiotic modulation of innate cell pathogen sensing and signaling events. Nutrients 9:1–31. https://doi.org/10.3390/nu9101156

Lv L, Wang X (2018) MicroRNA-296 targets specificity protein 1 to suppress cell proliferation and invasion in cervical cancer. Oncol Res 26:775–783. https://doi.org/10.3727/096504017X15132494420120

Malik SS, Saeed A, Baig M et al (2018) Anticarcinogenecity of microbiota and probiotics in breast cancer. Int J Food Prop 21:655–666. https://doi.org/10.1080/10942912.2018.1448994

Medina-Colorado AA, Vincent KL, Miller AL et al (2017) Vaginal ecosystem modeling of growth patterns of anaerobic bacteria in microaerophilic conditions. Anaerobe 45:10–18. https://doi.org/10.1016/j.anaerobe.2017.04.014

Merenstein D, Murphy M, Fokar A et al (2010) Use of a fermented dairy probiotic drink containing Lactobacillus casei (DN-114 001) to decrease the rate of illness in kids: the DRINK study a patient-oriented, double-blind, cluster-randomized, placebo-controlled, clinical trial. Eur J Clin Nutr 64:669–677

Mikelsaar M, Zilmer M (2009) Lactobacillus fermentum ME-3 – an antimicrobial and antioxidative probiotic. Microb Ecol Health Dis 21:1–27. https://doi.org/10.1080/08910600902815561

Mishra V, Shah C, Mokashe N et al (2015) Probiotics as potential antioxidants: a systematic review. J Agric Food Chem 63:3615–3626. https://doi.org/10.1021/jf506326t

Motevaseli E, Shirzad M, Raoofian R et al (2013) Differences in vaginal lactobacilli composition of Iranian healthy and bacterial vaginosis infected women: a comparative analysis of their cytotoxic effects with commercial vaginal probiotics. Iran Red Crescent Med J 15:199–206. https://doi.org/10.5812/ircmj.3533

Motevaseli E, Azam R, Akrami SM et al (2016) The effect of Lactobacillus crispatus and Lactobacillus rhamnosus culture supernatants on expression of autophagy genes and HPV E6 and E7 oncogenes in the HeLa cell line. Cell J 17:601–607

Motevaseli E, Dianatpour A, Ghafouri-Fard S (2017) The role of probiotics in cancer treatment: emphasis on their in vivo and in vitro anti-metastatic effects. Int J Mol Cell Med 6:66

Motevaseli E, Khorramizadeh MR, Hadjati J et al (2018) Investigation of antitumor effects of *Lactobacillus crispatus* in experimental model of breast cancer in BALB/c mice. Immunotherapy 10:119–129. https://doi.org/10.2217/imt-2017-0088

Musa J, Achenbach CJ, O'Dwyer LC et al (2017) Effect of cervical cancer education and provider recommendation for screening on screening rates: a systematic review and meta-analysis. PLoS One 12:e0183924. https://doi.org/10.1371/journal.pone.0183924

Nakanishi S, Kataoka K, Kuwahara T, Ohnishi Y (2003) Effects of high amylose maize starch and Clostridium butyricum on metabolism in colonic microbiota and formation of azoxymethane-induced aberrant crypt foci in the rat colon. Microbiol Immunol 47:951–958

Nami Y, Abdullah N, Haghshenas B et al (2014) Assessment of probiotic potential and anticancer activity of newly isolated vaginal bacterium *Lactobacillus plantarum* 5BL: cancer microbial biotherapy. Microbiol Immunol 58:492–502. https://doi.org/10.1111/1348-0421.12175

Nami Y, Haghshenas B, Haghshenas M et al (2015) The prophylactic effect of probiotic Enterococcus lactis IW5 against different human cancer cells. Front Microbiol 6:1317

Ohkawara S, Furuya H, Nagashima K et al (2007) Effect of oral administration of *Butyrivibrio fibrisolvens* MDT-1, a gastrointestinal bacterium, on 3-methylcholanthrene-induced tumor in mice. Nutr Cancer 59:92–98. https://doi.org/10.1080/01635580701397608

Orlando A, Messa C, Linsalata M et al (2009) Effects of *Lactobacillus rhamnosus* GG on proliferation and polyamine metabolism in HGC-27 human gastric and DLD-1 colonic cancer cell lines. Immunopharmacol Immunotoxicol 31:108–116. https://doi.org/10.1080/08923970802443631

Orlando A, Refolo MG, Messa C et al (2012) Antiproliferative and proapoptotic effects of viable or heat-killed *Lactobacillus paracasei* IMPC2.1 and *Lactobacillus rhamnosus* GG in HGC-27 gastric and DLD-1 colon cell lines. Nutr Cancer 64:1103–1111. https://doi.org/10.1080/01635581.2012.717676

Ouwehand AC, Salminen S, Roberts PJ et al (2003) Disease-dependent adhesion of lactic acid bacteria to the human intestinal mucosa. Clin Vaccine Immunol 10:643–646. https://doi.org/10.1128/CDLI.10.4.643-646.2003

Park J-H, Um J-I, Lee B-J et al (2002) Encapsulated Bifidobacterium bifidum potentiates intestinal IgA production. Cell Immunol 219:22–27

Patil AR, Shinde SS, Kakade PS, D'souza JI (2015) Lactobacillus model moiety a new era dosage form as nutraceuticals and therapeutic mediator. In: Biotechnology and bioforensics. Springer, Singapore, pp 11–21

Patil A, Disouza J, Pawar S (2018) Granules of unistrain Lactobacillus as nutraceutical antioxidant agent. Int J Pharm Sci Res 9(4):1594–1599

Patil A, Disouza J, Pawar S (2019a) Shelf life stability of encapsulated lactic acid bacteria isolated from Sheep milk thrived in different milk as natural media. Small Rumin 170:19–25

Patil A, Disouza J, Pawar S (2019b) Evaluation of Lactobacillus plantarum growth in milk of Indian buffalo breeds based on its physico-chemical content. Buffalo Bull 38(2):345–352

Patil A, Disouza J, Pawar S (2019c) Lactobacillus rhamnosus ARJD as a functional food with potential antioxidant and antibacterial abilities. Acta Sci Pharm Sci 3(8):63–70

Patil A, Dubey A, Malla M, Disouza J, Pawar S, Alqarawi A, Abd-Allah E, Kumar A (2020) Complete genome sequence of Lactobacillus plantarum strain JDARSH, isolated from sheep milk. Microbiol Resour Announc 9(2):e01199–e01119

Pelto L, Isolauri E, Lilius E et al (1998) Probiotic bacteria down-regulate the milk-induced inflammatory response in milk-hypersensitive subjects but have an immunostimulatory effect in healthy subjects. Clin Exp Allergy 28:1474–1479

Perdigon G, De Macias M, Alvarez S et al (1988) Systemic augmentation of the immune response in mice by feeding fermented milks with Lactobacillus casei and Lactobacillus acidophilus. Immunology 63:17

Raman M, Ahmed I, Gillevet PM et al (2013) Fecal microbiome and volatile organic compound metabolome in obese humans with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 11:868–875

Ribelles P, Benbouziane B, Langella P et al (2013) Protection against human papillomavirus type 16-induced tumors in mice using non-genetically modified lactic acid bacteria displaying E7 antigen at its surface. Appl Microbiol Biotechnol 97:1231–1239. https://doi.org/10.1007/s00253-012-4575-1

Russo F, Orlando A, Linsalata M et al (2007) Effects of *Lactobacillus rhamnosus GG* on the cell growth and polyamine metabolism in HGC-27 human gastric cancer cells. Nutr Cancer 59:106–114. https://doi.org/10.1080/01635580701365084

Sandes S, Alvim L, Silva B et al (2017) Selection of new lactic acid bacteria strains bearing probiotic features from mucosal microbiota of healthy calves: looking for immunobiotics

through in vitro and in vivo approaches for immunoprophylaxis applications. Microbiol Res 200:1–13. https://doi.org/10.1016/j.micres.2017.03.008
Saxami G, Karapetsas A, Lamprianidou E et al (2016) Two potential probiotic lactobacillus strains isolated from olive microbiota exhibit adhesion and anti-proliferative effects in cancer cell lines. J Funct Foods 24:461–471. https://doi.org/10.1016/j.jff.2016.04.036
Schiffrin E, Rochat F, Link-Amster H et al (1995) Immunomodulation of human blood cells following the ingestion of lactic acid bacteria. J Dairy Sci 78:491–497
Schiffrin EJ, Brassart D, Servin AL et al (1997) Immune modulation of blood leukocytes in humans by lactic acid bacteria: criteria for strain selection. Am J Clin Nutr 66:515S–520S
Seo S-S, Oh HY, Lee J-K et al (2016) Combined effect of diet and cervical microbiome on the risk of cervical intraepithelial neoplasia. Clin Nutr 35:1434–1441. https://doi.org/10.1016/j.clnu.2016.03.019
Shinnoh M, Horinaka M, Yasuda T et al (2013) Clostridium butyricum MIYAIRI 588 shows antitumor effects by enhancing the release of TRAIL from neutrophils through MMP-8. Int J Oncol 42:903–911. https://doi.org/10.3892/ijo.2013.1790
Sierra L-J, Brown AG, Barilá GO et al (2018) Colonization of the cervicovaginal space with Gardnerella vaginalis leads to local inflammation and cervical remodeling in pregnant mice. PLoS One 13:e0191524. https://doi.org/10.1371/journal.pone.0191524
Sivan A, Corrales L, Hubert N et al (2015) Commensal Bifidobacterium promotes antitumor immunity and facilitates anti–PD-L1 efficacy. Science 350:1084–1089
Smith RE, Tran K, Smith CC et al (2016) The role of the Nrf2/ARE antioxidant system in preventing cardiovascular diseases. Diseases 4:1–20. https://doi.org/10.3390/diseases4040034
Soto A, Martín V, Jiménez E et al (2014) Lactobacilli and bifidobacteria in human breast Milk: influence of antibiotherapy and other host and clinical factors. J Pediatr Gastroenterol Nutr 59:78–88. https://doi.org/10.1097/MPG.0000000000000347
Tuo Y, Jiang S, Qian F et al (2015) Antiproliferative effect of 8 different Lactobacillus strains on K562 cells. J Dairy Sci 98:106–110
von Ossowski I, Reunanen J, Satokari R et al (2010) Mucosal adhesion properties of the probiotic Lactobacillus rhamnosus GG SpaCBA and SpaFED pilin subunits. Appl Environ Microbiol 76:2049–2057. https://doi.org/10.1128/AEM.01958-09
Walrand S, Lhommel R, Goffette P et al (2012) Hemoglobin level significantly impacts the tumor cell survival fraction in humans after internal radiotherapy. EJNMMI Res 2:20. https://doi.org/10.1186/2191-219X-2-20
Wan Y, Xin Y, Zhang C et al (2014) Fermentation supernatants of Lactobacillus delbrueckii inhibit growth of human colon cancer cells and induce apoptosis through a caspase 3-dependent pathway. Oncol Lett 7:1738–1742. https://doi.org/10.3892/ol.2014.1959
Wang Y, Wu Y, Wang Y et al (2017) Antioxidant properties of probiotic bacteria. Nutrients 9 (5):521. https://doi.org/10.3390/nu9050521
Wang K-D, Xu D-J, Wang B-Y et al (2018) Inhibitory effect of vaginal lactobacillus supernatants on cervical cancer cells. Probiotics Antimicrob Proteins 10:236–242. https://doi.org/10.1007/s12602-017-9339-x
Wong VW-S, Tse C-H, Lam TT-Y et al (2013) Molecular characterization of the fecal microbiota in patients with nonalcoholic steatohepatitis–a longitudinal study. PLoS One 8(4):e62885
Yan F, Polk D (2011) Probiotics and immune health. Curr Opin Gastroenterol 27:496–501
Yang J, Nolte FS, Chajewski OS et al (2018a) Cytology and high risk HPV testing in cervical cancer screening program: outcome of 3-year follow-up in an academic institute. Diagn Cytopathol 46:22–27. https://doi.org/10.1002/dc.23843
Yang X, Da M, Zhang W et al (2018b) Role of Lactobacillus in cervical cancer. Cancer Manag Res 10:1219–1229. https://doi.org/10.2147/CMAR.S165228
Yao X-Y, Yuan M-M, Li D-J (2007) Molecular adjuvant C3d3 improved the anti-hCGbeta humoral immune response in vaginal inoculation with live recombinant Lactobacillus expressing hCGbeta-C3d3 fusion protein. Vaccine 25:6129–6139. https://doi.org/10.1016/j.vaccine.2007.04.090

Yazdi MH, Dallal MMS, Hassan ZM et al (2010) Oral administration of Lactobacillus acidophilus induces IL-12 production in spleen cell culture of BALB/c mice bearing transplanted breast tumour. Br J Nutr 104:227–232

Yoshimoto S, Loo TM, Atarashi K et al (2013) Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. Nature 499:97–101

Yu A-Q, Li L (2016) The potential role of probiotics in cancer prevention and treatment. Nutr Cancer 68:535–544. https://doi.org/10.1080/01635581.2016.1158300

Yue X-A, Chen P, Tang Y et al (2015) The dynamic changes of vaginal microecosystem in patients with recurrent vulvovaginal candidiasis: a retrospective study of 800 patients. Arch Gynecol Obstet 292:1285–1294. https://doi.org/10.1007/s00404-015-3774-2

Zadravec P, Štrukelj B, Berlec A (2015) Improvement of LysM-mediated surface display of designed ankyrin repeat proteins (DARPins) in recombinant and nonrecombinant strains of Lactococcus lactis and Lactobacillus species. Appl Environ Microbiol 81:2098–2106. https://doi.org/10.1128/AEM.03694-14

Zhang J-W, Du P, Yang B-R et al (2012) Preoperative probiotics decrease postoperative infectious complications of colorectal cancer. Am J Med Sci 343:199–205