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Anti-cancer and Biotherapeutic Potentials of Probiotic Bacteria

Zubaida Hassan*

Department of Microbiology, School of Life Sciences, Modibbo Adama University of Technology, Yola, Nigeria

Abstract

Current standard cancer drugs and various synthetic agents exhibit high toxic activities against cancer cells, but doubts have been raised as to their long term stability and safety. Generally, these synthetic agents are relatively expensive; this makes them not affordable to many people. Although most probiotic anticancer therapies are in preclinical development phase, due to their low efficacy and poor selectivity, gradual replacement of current cancer drugs and other synthetic agents with appropriate biotherapeutic substances is proposed to overcome the challenges associated with the use of these synthetic agents. These probiotics can have an effect on other aspects of human health and hence make life worth living during and after cancer treatment. At present, most anticancer research regarding probiotic microbes focuses on Lactobacillus and Bifidobacteria, but other probiotics are involved. This review describes the properties of probiotic bacteria as potential biotherapeutics to supplement current standard anti-cancer therapies. The reader will gain an overview of different probiotics tested so far with respective bioassays used in probiotic anti-cancer drug discovery. Note, Not all therapies used generated an effective response in all patients and that use of probiotic therapies provides negligible if any, detrimental side effects.

Keywords: Probiotics; Biotherapeutic agents; Cytotoxicity assays; Cancer

Introduction

Cancer is a deadly disease with high clinical significance and is mostly diagnosed at a late stage. It is defined as uncontrolled cell growth [1], and as a disease caused by a deficiency in DNA repair [2]. The mechanisms that initiate cancer remain unclear. To date, chemotherapeutics are the standard drugs used in the clinical treatment of cancer. However, these compounds are accompanied with considerable and complicated life-threatening side effects that most times gets worse than the tumour. As a protective alternative, recent research has focused on the biotherapeutic potentials of probiotic bacteria in cancer treatment. Supplementation with probiotics is proposed to improve quality of life during and after chemotherapy treatment. This is because these bacteria are generally regarded as safe, have long history of usage and affordable than chemotherapy.

For a long time, humans have relied on natural products and synthetic compounds as sources of medicine; these are mainly plant-based natural products [3-5]. Additionally, microbes and their derivatives possess pharmacological and/or biological ability that can enable them to be used in treating human diseases. Probiotic bacteria, for example, have been studied for their anticancer properties and have shown promising results [5-8]. Probiotics are defined as live microorganisms which, when taken in adequate amounts, can exert beneficial effects through their growth or other activities in the host.

The mechanisms by which cancer starts and develops remain unclear. Hence, while trying to fully understand its biology, it is necessary to find ways that can reduce the severity of the disease and improve patients' quality of life. Probiotic organisms prevent cancer through various mechanisms, among which are the secretion of soluble compounds during fermentation [9], triggering the immune response by natural killer cells [10], interfering with the synthesis of oestrogen in both normal and tumour-invaded breast tissues [11] and through competitive exclusion of pathogenic microbes in the intestine [12]. Others include reduced enterocyte apoptosis [13], modulation of inflammation [14], and maintenance of barrier function thus, suggesting that a probiotic-based therapy could be an effective therapeutic strategy [15].

Literature Review Criteria

Information for this review was compiled by searching the PubMed database for published articles using search terms "probiotic", "biotherapeutics" and "lactic acid bacteria" + the terms "cancer" or "oncology". Full articles were obtained, and references were checked for additional material where necessary.

According to Compare and Nardone [16], chronic bacterial infection can induce inflammatory processes, especially in the gastrointestinal tract. For example, *Helicobacter pylori* infection is associated with both gastric cancer and mucosa-associated lymphoid tissue lymphoma. However, probiotic microbes have the ability to inhibit a wide range of pathogens, thereby, preventing the initiation of infection with bacteria that may lead to development of tumour. The polysaccharide fraction of heat killed cells of these probiotics has been found to inhibit cancer cell proliferation while producing less cytotoxic effects on normal cells [6]. In addition to the heat killed fractions of probiotics, we previously reported anti-breast cancer effects from live as well as cytoplasmic fractions of *S. hominis* and *E. faecalis* [17]. This is an indication that heat soluble polysaccharides may play a significant role in the anticancer effects of these bacteria [6].

Effects of probiotic species on cancer *in vitro*

With increase in cancer incidences coupled with adverse side effect of current therapies, researchers are focusing more on the use of probiotic bacteria as anticancer and antioxidant agents to be protective adjuncts against human diseases [5-8,17]. Although various synthetic agents exhibit even higher cytotoxic activities on most cancer than probiotics, people are concerned about the stability and safety of these

***Corresponding author:** Zubaida Hassan, Department of Microbiology, School of Life Sciences, Modibbo Adama University of Technology, Yola, Nigeria, Tel: +2347029273726; E-mail: zubaidahassan@mautech.edu.ng

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synthetic substances in the long term. Generally, these synthetic agents are relatively more expensive [6]. Nami [5] reported that *Enterococcus faecalis* strains exert anti-proliferative effects on a breast cancer cell line, resulting in 41.27% viability, while having little effect on the viability (94.02%) of normal human umbilical vein endothelial cells (HUVEC). Similarly, in our previous study, it was shown that *E. faecalis* and *S. hominis* inhibit up to 66.99% 31.09% viabilities in MCF-7 cells after co-culture for 24 h with negligible effects of >90% viabilities on their non-malignant control, MCF-10 cells [17].

Lactobacillus acidophilus and *Lactobacillus casei* excrete anti-tumour substances which have been suggested to be components of the bacterial cell wall [18]. Freeze dried *Lactobacillus acidophilus* La-05 and *Lactobacillus casei spp. paracasei* Lc-01 showed anti-proliferative effects against a breast cancer cell line (MCF7), even in the absence of live organisms. The secretion of soluble compounds during fermentation was thought to be responsible for these beneficial effects [9]. Hirayama and Rafter [19] also reported the growth inhibition of MCF7 cells by compounds produced by *L. acidophilus* and *L. casei*. In addition, *Lactobacillus acidophilus* 606 also inhibits human pancreatic cancer cell line (PANC-1) proliferation by the production of soluble polysaccharides.

Effects of probiotic species on cancer and inflammation *in vivo*

Various experimental animal models have been used to evaluate the anti-cancer properties of different probiotics. *Lactobacillus acidophilus* for example, has been shown to induce IL-12 production in BALB/c mice; this interleukin can then trigger immune responses by natural killer cells [6]. *Lactobacillus casei spp. casei* ATCC 39392 was administered orally to 6-8-week-old female BALB/c mice for two weeks before transplanting tumour cells, after which the probiotic bacteria were continually administered for three weeks with three-day intervals between the weeks. The results from this study showed an increase in IL-12, IFN-γ and natural killer cells [20]. It is well-known that IL-12, IFN-γ and natural killer cells are modulators of the immune system, vital players in both innate and adaptive immune responses. With this, it can be proposed that probiotics therapy can be long live through generation of memory cells from adaptive immunity.

Lactobacilli were shown to delay the development of tumours in both normal and tumour-invaded breast tissues. De Moreno De LeBlanc [11] reported that *Lactobacillus helveticus* R389 is able to delay the development of tumours. This was related to peptide production by this organism, which decreased the expression of IL-6 and increased the expression of IL-10, and also induced apoptosis in tumour cells. IL-6 is a cytokine that stimulates aromatase activity, an enzyme involved in the synthesis of oestrogen in both normal and tumour-invaded breast tissue. Oestrogen is hypothesized to influence breast cancer mediated through estrogen receptor α as well as estradiol, but the mechanism is poorly understood [21]. IL-10 on the other hand, is a pleiotropic anti-inflammatory cytokine [22]. Although increase expression of IL10 is not a favourable prognostic value due to its immunosuppressive nature, but its antiangiogenic functions [23] is vital in checking tumour growth. IL-10 inhibits tumorigenesis *via* down-regulation of VEGF, IL-1b, TNF-α, IL-6, and MMP-9 through translocation of NF-κB pathway [23]. Breast cancer susceptibility may be attributed to IL-10 gene polymorphisms.

In experimental dog models of cyclophosphamide-induced neutropenia, the duration of the condition was shortened and augmentation of leukocyte reconstituting capacity was enhanced after the administration of a heat killed strain *E. faecalis* [24]. In another study, milk fermented with *B. lactis*, *L. lactis*, *S. thermophilus*, and *L. bulgaricus* was found to improve inflammation in a mouse model of colitis, increase butyrate-producing bacteria, and decrease the number of *Enterobacteriaceae* strains which are capable of inducing colonic inflammation [25]. It has been shown that *Lactobacilli* and *Bifidobacteria* are able to increase the probiotic concentration and significantly decrease putrefactive microorganisms such as coliforms in the faeces of animals [26,27]. These putrefactive microorganisms are associated with the synthesis of putative carcinogens in the colon [28,29] and such microbes are linked to decrease in tumorigenesis in the IL-10 knockout mice model [29].

Beyond animal studies, few researchers have discussed the biotherapeutic effects of probiotics in humans. The consumption of probiotic fermented dairy products has a long history in cancer research. In the year 1977, an epidemiological study conducted by Malhotra, in Finland revealed that, despite a high fat intake, the incidence of colon cancer was low compared to other countries [30]. A reduction in procarcinogenic elements such as mutagens found in a western, meat-rich diet was observed in the urine and faeces of healthy volunteers who consumed *Lactobacilli*. In most cases, mutagens excreted in the urine and faces are inversely proportional to the lactobacilli secreted [31]. Therefore, it was hypothesised that the *Lactobacilli* consumed were responsible for this effect.

In a case control study by Veer [32] conducted in the Netherlands, a country that has a high incidence of breast cancer, suggested the protective ability of fermented milk and Gouda cheese on the risk of this cancer. However, no statistically significant relationship was found between the consumption of non-fermented milk and breast cancer. According to Toi [33], daily consumption of *Lactobacillus casei* Shirota has a significant, inverse association with the early occurrence of breast cancer, irrespective of menopausal status. In population-based case-control studies, an inverse association has been documented for colorectal cancer and the consumption of yoghurt or other cultured milk products [34,35]. An inverse relationship has also been demonstrated between breast cancer in women and the consumption of yoghurt and other fermented milk products [16].

Comparing the stool bacteria of colorectal cancer patients and that of healthy individuals, there was a significant decrease in *Bifidobacteria* and *Ruminococcus bromii* [12,36]. These bacteria were found in the mucosa-adherent microbiota in the cancer patients at a lower rate than in healthy individuals [37]. Similarly, a randomised, double-blind and placebocontrolled trial with 26 healthy adults conducted by Johansson [38] demonstrated that the consumption of *Lactobacillus plantarum* fermented rose-hip drink for a period of three weeks significantly increased faecal probiotics and decreased pathogenic sulphite-reducing clostridia. As in animal studies, human studies have also shown that *Lactobacillus acidophilus* is capable of decreasing faecal putrefactive flora while increasing commensal lactobacilli [39]. These putrefactive microorganisms are associated with the synthesis of putative carcinogens in the colon [28,29].

Effects of cell free probiotic supernatants on cancer

Live probiotic microbes as well as their heat killed cells, secreted metabolites and cytoplasmic fractions exert anticancer properties. Lactoglobulin and α-lactalbumin have been reported to be the two major proteins that play important roles in the anticancer effects of lactobacillus. Lactoglobulin is a good source of sulphur amino acids and has immune modulatory effects, while α-lactalbumin forms complexes

with oleic acid, which are lethal to tumour cells [40]. Biotherapeutic efficacy assessments of *E. faecalis* secreted metabolites revealed apoptotic effects on human breast, colon, cervical, and gastric cancer cell lines while producing negligible cytotoxic effects on HUVEC (normal cell line). This selective effect is mainly associated with their ability to recognise proteins secreted by different cancer cells [5].

Heat killed cells and cytoplasmic fractions of eight different species of *Lactobacillus* and four species of *Bifidobacteria* were studied by Liu and Pan [8] against breast and colon cancer cell lines. They reported strong anti-proliferative and antioxidant effects of these microbes. Heat killed cells of these bacteria were able to reduce the viability of human breast adenocarcinoma cells to 46.3% with no inhibitory effects on the intestinal 407 cell line. We also observed similar effect when breast cancer cells (MCF-7) were cocultured with cytoplasmic fractions of bacteria in for 24 h, we recorded 31.09% viabilities with negligible effects of >90% viabilities on their non-malignant control, MCF-10 cells [17].

Metabolites extracted from *Lactobacillus* sp. used in yoghurt fermentation have been shown to have potential roles in the inhibition of growth and induction of apoptosis in human tongue squamous carcinoma (CAL-27) cells *in vitro* [40]. The metabolites, from *Lactobacillus* sp., contain a number of peptides, amino acids, short chain fatty acids, lactic acid, butyric acid, and certain other chemicals, which may play important roles in its anticancer activities. These metabolites induced cytotoxic effects in CAL-27 cells of early apoptotic by 12.8%, while the percentage of the late cells was up to 69.48% [40]. Heat killed cells of *Lactobacillus casei* ATCC 393 and Lactobacillus acidophilus 606 have been reported to have inhibitory effects against cancer cells [6] by the production of soluble polysaccharides, which inhibit the proliferation of HT29 and HeLa cancer cells.

Effects of probiotic species on side effects of cancer chemotherapy

It is well-known that chemotherapy is at present is the standard treatment for cancer. However, it may not be the ideal therapy as it is associated with complicated side effects on patients. These side effects include chemotherapy-induced fatigue, gastrointestinal toxicity, haematological toxicity, alopecia, as well as cell and organ toxicity [41]. Chemotherapy is also associated with peripheral neuropathy and dysphonic syndrome [42]. In most cases, the side effects associated with these drugs are often of more concern than the progression of the tumour. For example, oxaliplatin is a promising drug routinely used in the treatment of human cancers such as colorectal, breast, ovarian, genitourinary, head/neck and gastroesophageal. However, it is associated with peripheral neuropathy [42].

Another widely used chemotherapy drug in treating variety of cancers is 5-fluorouracil (5-FU). Its administration also results in severe side effects such as arrhythmias, silent myocardial ischemia, angina, congestive heart failure, myocardial infarction, cardiogenic shock, and sudden death [43], intestinal and oral mucositis [15]. Those diagnosed with intestinal mucositis may suffer from nausea, vomiting, dyspepsia, dysphagia, and diarrhea [44]. These often leads to infection and malnourishment [45]. In many cases, the treatment must be ceased until the patient recovers from these severe effects [15]. While 5-FU compromise individual's immune system through these side effects, probiotics reduce risk of infection thus, renders them ideal for use in a disorder such as mucositis [15].

Currently, some probiotics are successful in the treatment of mucositis induced by 5-FU. For example, *Lactobacillus fermentum* BR11 and *Streptococcus thermophilus* TH-4 improved the histological deficits caused by 5-FU [46,47]. *Lactobacillus acidophilus* combat 5-FU-induced changes in gastrointestinal motility, enhancing intestinal transit and gastric emptying and decreasing retention in the distal bowel segment thus normalizes bowel function by reducing inflammation associated with the chemotherapy [48].

Lactobacillus acidophilus is used for the treatment and prevention of gastrointestinal disorders associated with diarrhea of varying etiology [49] such as intestinal mucositis caused by the cytotoxicity of chemotherapy and radiotherapy used in cancer treatment [48]. In a clinical trial, *Lactobacillus acidophilus* associated with *B. bifidum* was satisfactory for diarrhea prophylaxis during pelvic radiation therapy with concomitant cisplatin. Acute inflammatory changes might play an important role in the pathogenesis of these symptoms [50].

Although, many probiotic anticancer therapies are yet to be tested in clinical trials, because of their low efficacy, they are associated with long-term stability and safety. Biotherapeutics may decrease the risk and severity of chemotherapy-related toxicity and side effects associated with treatment, as these organisms have the ability to enhance homeostasis in patients. Probiotics have been used for the prevention and treatment of chemotherapy-induced side effects such as infectious complications and diarrhoea [51]. The development of bowel problems often leads to infections in cancer patients; the use of antibiotics is such cases can lead to the dissemination of antibiotic resistance due to immunosuppression from chemotherapy. Thus, probiotics have been used in preventing bowel colonisation by pathogenic microorganisms through competitive inhibition [51].

While anticancer chemotherapeutics such as 5-FU cause diarrhoea in patients due to incomplete absorption of the drugs or the overuse of antibiotics [51], biotherapeutics are known to prevent this effect [47,52] and so the use of probiotics is recommended in cancer chemotherapeutic treatment. Many of the current cancer therapeutic agents are limited in their use due of their toxic effects on normal cells and tissues, thus biotherapeutics may be an ideal supplementation with cancer chemotherapy and future alternative in cancer treatment and prevention.

Potential mechanisms of probiotic action in cancer

High degree of strain specificity is associated with mechanisms of probiotic action on cancer. The mechanisms by which probiotics reduce cancer may include the modulation of the immune response. This can differ according to the site where the tumour is present. Unlike in colon cancer, which is the most studied type of cancer where the consumption of fermented food product changes gut-associated immune cells and peritoneal macrophages, in the breast, immune cells changes are observed only when the target cell affects the mammary gland [11]. Probiotics also act by potentiation of natural killer which mediates antitumor activity of a cell [53].

Lactic acid bacteria have been shown to prevent many types of cancer through the hydrolysis of glucuronides by β-glucoronidase, thereby liberating carcinogens [19], i.e., reducing glucuronidase, azoreductase, and nitroreductase, which can convert procarcinogens to carcinogens in the intestine [54,55]. These organisms prevent colon cancer by their production of azoxymethane, enhancing O^6-methylguanine in colon mucosal DNA, and binding to and digesting free bioavailable toxins in the colon [54]. In addition, these organisms reduce DNA damage caused by chemical carcinogens [28]. Lactobacillus rhamnosus GG

has demonstrated preventive ability on intestinal cells, preventing transepithelial electrical resistance (TEER) reduction and maintaining ZO-2 levels in Caco-2 cells treated with proinflammatory interferon-δ [56] through the inhibition of proinflammatory tumor necrosis factor (TNF)-α expression, a cytokine which is also involved in the development of intestinal mucositis [57].

Anticancer probiotics also induce host innate defence mechanisms such as macrophage activation [58]. These microbes recognise and ligate pathogen-associated molecular patterns, dimerise tumour recognition receptors, especially toll-like receptors, and interfere with the transmission of intracellular signals of inflammation and tissue regeneration adaptor proteins [18]. Toll-like receptors are likely candidates to mediate the effects of the innate immune response on tumorigenesis [16]. The molecular mechanisms often associated with the anticancer effects of probiotics includes cytochrome P450 blockade, a reduction in carcinogen generation, downregulation of Ras-p21 expression, increased cell differentiation, inhibition of COX-2 upregulation, inhibition of nitric oxide synthase, increased short-chain fatty acid production, and a reduction in intestinal pH which inhibits putrefactive bacteria [58]. These genes are crucial in the initiation and development of cancer.

As a mechanism of cancer death induced by *Glossogyne tenuifolia* [4], *E. faecalis* and *S. hominis* inhibit MCF-7 cells proliferation by altering G0/G1 cell cycle phase [17]. Cytoplasmic fractions of *Lactococcus lactis spp.* were used to treat a colon cancer cell line by attacking G0/G1 cell cycle growth phase [1]. This phenomenon may simply be related to the ability of the bacteria to cause the overexpression of cyclin A and under expression of cyclin E proteins [1]. Progression of the cell cycle from G_1 to S phase in eukaryotic cells is controlled by cyclins A, D, and E. These proteins are responsible for the activation of different G_1 phase kinases (CDK4/6 and CDK2) [59].

Overexpression of cyclin D1 can lead to shortening of the G_1 phase of the cell cycle and subsequently lead to phenotypic changes. Transcription of cyclin D1 is promoted by the kinase cascade *via* the Ras signalling pathway [60]. In the nucleus, cyclin D1 is phosphorylated and activated by cyclin activating kinase (CAK) to form cyclin D/CAK4 complexes. The main function of cyclin D/CAK4 in the G_1 phase is to inactivate growth suppressor proteins such as retinoblastoma protein (pRB). Phosphorylated pRB is capable of driving quiescent cells into S phase [60].

Discussion and Conclusion

Following the toxicity concern of current cancer chemotherapy and uncertainly in terms of long-term stability and safety of other synthetic compounds, probiotics are becoming relevant in the fight against cancer. These organisms have been shown to delay tumour formation, inhibit cancer cells proliferation, burst healthy growth in normal cells, enhance homeostasis and thus help prevent life-threatening side effects that accompany current cancer treatment. In addition, long-term stability and safety of probiotics in human consumption have been documented. These effects were also represented in animal models. Although, most of the *in vivo* trials have had small sample sizes, and thus there is a substantial risk of bias. It is strongly recommended that large, properly designed clinical trials to be carried out to establish proper evidences of biotherapeutic properties of these organisms as anticancer treatments. Finally, the emerging relationship between probiotics and cancer opens an interesting field in cancer prevention and treatment.

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