

REVIEW

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Anti-tumor activities of probiotics in cervical cancer



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Abstract

Cervical cancer is considered as an important malignancy among women worldwide. Currently-used treatments of cervical cancer are reported to be cytotoxic for patients. Moreover, these therapies have shown some side effects which can negatively affect the lives of women suffering from this cancer. Therefore, there is need for anti-tumor agents that are less toxic than common therapeutic drugs. Besides, applying agents for preventing or reducing the side effects of cervical cancer therapies can be effective in improving the life quality of cervical cancer patients. Studies have shown that probiotics have several effects on biological processes. One of the most prominent aspects in which probiotics play a role is in the field of cancer. There are multiple studies which have focused on the functions of probiotics in diagnosis, prevention, or treatment of cancer. Besides their direct anti-tumor activities, probiotics can be used as an additional agent for enhancing or modulating other diagnostic and therapeutic methods. Herein, the effects of probiotics on cervical cancer cells are discussed, which may be useful in the prevention and treatment of this cancer. We review the studies concerned with the roles of probiotics in modulating and reducing the gastrointestinal adverse effects caused by cervical cancer therapies. Furthermore, we cover the investigations focusing on the combination of probiotics with other drugs for diagnosis or treatment of cervical cancer.

Keywords: Probiotics, Cervical cancer, Lactobacillus, Radiotherapy-induced diarrhea, Apoptosis

Background

There are thousands of bacterial species in the human body, which provide and maintain the health of their host [1, 2]. Nine percentage of microbial species are located in the urogenital tract. Thus, there should be a balancing connection between the immune system of host and microbiota that exist in urogenital tract [1, 3, 4]. Disruptions in this balance may lead to cervical cancer by allowing infectious agents to grow in this area. Currently-used chemotherapeutic drugs can result in

cytotoxic effects in patients suffering from cervical cancer. Besides, there are side effects caused by therapies which are unavoidable [5]. Therefore, there is need for anti-tumor agents that are non-toxic or cause less toxicity than other therapeutic agents. Also, applying drugs for preventing or reducing the side effects of cervical cancer treatment would be effective in enhancing the life quality of cervical cancer patients [6].

Herein, the effects of probiotics on cervical cancer cells which may be useful in the prevention and/or treatment of this cancer are discussed. We review the studies concerned with the roles of probiotics in modulating and reducing the gastrointestinal adverse effects caused by cervical cancer therapies. Furthermore, we cover the investigations focusing on the combination of probiotics

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with other drugs for diagnosis or treatment of cervical cancer.

Cervical cancer

Epidemiology

Cervical cancer is considered a global health concern since it is the fourth common malignancy among women worldwide [7]. Cervical cancer comprises 4% of all cancers that are diagnosed all around the world [8]. Based on morphological characteristics, there are three main subtypes of cervical cancer, including squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma. All of these subtypes have the same one-year net survival rate of 85% [9]. Adenocarcinoma and squamous cell carcinoma, the two most frequent subtypes, are responsible for nearly 25 and 70% of cervical cancer, respectively [10, 11]. In addition, there are metabolic disturbances in women with polycystic ovarian syndrome [12, 13], which may increase the risk of cervical cancer. Noteworthy, incidence rates and deaths of cervical cancer have been progressively reduced in the well-developed countries because of HPV vaccination and cancer screening programs [14, 15].

Risk factors

One of the well-studied risk factors of cervical cancer is HPV chronic infection. Besides, there are other factors implied to raise the risk of this cancer including smoking, co-infection with type 2 herpes simplex, co-infection with human immunodeficiency virus, high parity, and consumption of oral contraceptives for a long time [16, 17]. Some risk factors of cervical cancer are related to acquiring HPV infection or inefficient response of the immune system to HPV infection such as sexual debut at early ages, high-risk sexual partners, multiple sexual partners, immunosuppression, history of sexually transmitted infection (STI), and history of HPV-related vulvar or vaginal dysplasia [11].

Prevention

HPV vaccination and screening of cervical cancer can be applied to prevent this disease. HPV, which is the most common STI globally, accounts for virtually all (99.7%) of the cervical cancer cases [18]. More than two-thirds of cervical cancers and precancerous lesions are caused by two HPV types that are type 16 and 18 [19, 20]. There are two approved vaccines for HPV, including bivalent vaccine and quadrivalent vaccine. The former one is against 16 and 18 types of HPV types and quadrivalent vaccine (against HPV types 6, 11, 16, and 18) [21]. Predictions show that the incidence of cervical cancer will decrease up to 83% by a 90% coverage of vaccine [22]. The pre-cancerous condition can be detected and treated by a secondary prevention method called cervical

cancer screening, which is helpful in malignancy prevention [23]. In high-resource countries, early diagnosis and treatment of precancerous lesions can prevent up to 80% of cervical cancer [24]. Cytology is the most frequent tool for cervical cancer screening which is used in developed countries [23]. In patients whose screening has shown premalignant cervical lesions such as cervical intraepithelial neoplasia, colposcopy is done to confirm the finding [25]. In low-resource countries, a feasible see-and treat method is visual inspection with acetic acid (VIA) or visual inspection with Lugol's iodine (VILI) [26]. However, coverage of screening programs is still low despite the increase in the availability of them [23].

Clinical presentation and diagnosis

Cervical cancer does not usually show any symptoms in its early stages [27]. Post-coital vaginal bleeding, abnormal vaginal bleeding, and malodorous vaginal discharge are symptoms of this cancer [28, 29]. Passages of urine and feces through the vagina are symptoms for an invasion of the bladder and rectum, respectively [30, 31]. A pelvic examination and cervical cytology, as well as visualization of the cervix and vaginal mucosa by a speculum, are needed when a woman presented with cervical cancer symptoms [11]. However, the cervix may look normal in observations when the cancer is micro-invasive or occurred in the endocervical canal [11]. There are possibly palpable swollen and hardened lymph nodes in inguinal and supraclavicular regions in patients with the advanced-stage disease [11]. In distant metastasis, positron emission tomography (PET)-computed tomography and fluoro-2-deoxy-D-glucose PET (FDG-PET) are two efficient methods for diagnosis [32].

Treatment

Currently, cervical cancer management is dependent on a multidisciplinary team approach [33]. In the early stages of the disease, there are multiple treating approaches that can be used, including surgery, radiation, neoadjuvant chemotherapy, and fertility preservation surgery [33]. The standard treatment for patients suffering from locally advanced cervical cancer is concurrent chemoradiation (CCRT) in which cisplatin is used alone or in combination with other drugs [33]. In nearly 30–40% of cases, there is a lack of complete response [33]. Bevacizumab is an inhibitor of vascular endothelial growth factor [34]. In the recurrent or metastatic form of the disease, bevacizumab administration along with chemotherapy has linked to enhanced survival [33]. Different treating options are available for managing metastatic patients who suffer from lung metastasis, bone metastasis, solitary brain metastasis, or multiple brain metastases. These treating approaches include chemotherapy and surgery, chemotherapy and bone

irradiation, craniotomy or stereotactic radiosurgery combined with radiotherapy, and chemotherapy and palliative brain radiation, respectively [32]. Moreover, CCRT followed by chemotherapy are helpful in lymph metastatic patients [32]. Investigations have provided promising findings of novel therapeutic methods such as inhibitors of the immune checkpoint, inhibitors of tyrosine kinase, and targeted therapy with anti-angiogenesis drugs [33].

Probiotics

What are probiotics?

Probiotic is a Latin-derived word with the meaning of “for life” [35]. Fermented products which include cheese, bread, wine, beer, and kefir were widely used for their nutritional and therapeutic benefits long before the identification of probiotics [35]. Living microorganisms that provide several beneficial impacts to their host in case of proper amounts are called probiotics [36, 37]. This broad definition comprises drugs containing probiotics, conventional foods, medical foods, dietary supplements, infant formula, animal feed, non-oral probiotics, and defined microbial consortia [38]. The focus of earlier studies were nutritional roles of probiotics which have been used as a food form or a dietary supplement [39]. However, recent probiotics research has concentrated on its functions in the medical and therapeutic fields [40]. The natural microbiota of intestine comprises the majority of probiotics, which are particularly lactic acid bacteria, including *Enterococcus*, *Vagococcus*, *Weisella*, *Leuconostoc*, *Lactococcus*, *Streptococcus*, *Tetragenococcus*, *Bifidobacterium*, *Carnobacterium*, *Oenococcus*, *Pedicoccus*, *Lactobacillus*, *Escherichia coli*, and *Saccharomyces* [41, 42]. Noteworthy, not all bacteria of the same species have the same characteristics and may have different effects on the organism. Besides, all strains are not probiotic [43].

Applications of probiotics

Probiotics applications in the prevention or treatment of various diseases have been studied in several investigations. Probiotics are involved in various processes of the digestive system such as digestion, metabolism, innate immunity of epithelial cells, eliminating pathogens, and communication between brain and gut through their adhesion to human intestines [44, 45]. Evidence has shown the beneficial effects of gut microorganisms producing nontoxic metabolites in different nutritional and clinical aspects [46–48]. Probiotics and fermented non-digestible food products, prebiotics, work together and have been shown to have several beneficial characteristics such as anti-pathogenic, anti-inflammation, antidiabetic, and anti-obesity [49, 50]. Probiotics are also involved in immune processes such as increasing antibody responses

and inhibiting the mononuclear cells proliferation [51, 52]. Probiotics have been used for a variety of gastrointestinal problems including irritable bowel syndrome, constipation, ulcerative colitis, and necrotizing enterocolitis [53–57]. Increasing anti-inflammatory cytokines such as interleukin-10 (IL-10) and IL-12 and reducing pro-inflammatory cytokines such as IL-1 β and IL-6 are anti-inflammatory activities of probiotics which have been investigated in different diseases [58, 59]. Studies indicated that probiotics can be helpful in autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis [58, 60–62]. Other findings have also revealed that probiotics are beneficial for high cholesterol levels in serum, allergy, vulvovaginal candidiasis, HIV, and cancer [63–66].

Safety and side effects of probiotics

In general, probiotics are safe [67]. Although, in patients who are immunocompromised or when someone is considered severely ill, precautions should be observed [67]. Rash, hiccups, nausea, constipation, and flatulence are some of the most common adverse effects of probiotics [67]. There are other probiotics side effects such as systemic infections, damaging metabolic activities, and transferring harmful genes such as resistance to antimicrobial agents [68]. In some rare cases, using *Lactobacillus* have led to the liver abscess, sepsis, and endocarditis [67]. There is evidence indicating that *Bacillus subtilis* can cause cholangitis, bacteremia, and sepsis [69]. Also, it is reported that *S. boulardii* may lead to fungal sepsis [70]. Altogether, probiotic-related risk of infection is the same as infection risk of commensal bacterial strains, and it seems that the advantages of probiotics outweigh its risks [71].

Probiotics and cancer

One of the most prominent aspects in which probiotics play a role is in the field of cancer. Probiotics act as a double-edged sword in this field. Accumulative investigations have revealed that microbiota can participate in the process of carcinogenesis of many types of cancers, including gynecological cancers. For instance in cervical cancer, dysbiosis is approved to have influences on both HPV infection by affecting HPV acquisition, clearance, and persistence and host immune response by affecting the levels of immune system proteins such as TGF β 1 [72]. Various studies have focused on the functions of probiotics in diagnosis, prevention, or treatment of cancer. Besides their direct involvement in the mentioned areas of cancers, probiotics can be used as an additional agent in enhancing or modulating other diagnostic and therapeutic methods. Kailaspathy et al. [73] have explained some underlying mechanisms by which probiotics may play their role as antitumor agents, such as

activating the immune system of the host, changing transit time and motility of the colon, suppressing pro-carcinogens and carcinogens, inhibiting bacteria that are involved in the transformation of pro-carcinogens to carcinogens, and reducing intestinal pH [73]. Findings demonstrate that probiotics make an impact on biological processes which are involved in cancer, including apoptosis, oxidative stress, proliferation, inflammation, and metastasis [74–77]. Long-time exposure to aflatoxins, especially aflatoxin B₁ has been related to a higher risk of liver cancer development [78]. It is suggested that probiotic supplements may be useful in preventing liver cancer due to their ability to reduce the aflatoxin exposure dose that is biologically effective [79]. Zonulin protein is involved in regulating intestinal permeability [80]. In colorectal cancer patients who undergo colectomy, findings indicate that administering probiotics perioperative results in a reduction in postoperative septicemia as well as zonulin concentrations in serum [80]. In breast cancer, long-term administration of probiotic strain *Lactobacillus plantarum* LS/07 has shown immunomodulatory effects such as reducing tumor necrosis factor (TNF)- α and increasing Cd4(+) T-cells [81]. One of the common side effects of systemic chemotherapy is diarrhea [82]. It has been revealed that probiotic *Clostridium butyricum* can reduce chemotherapy-induced diarrhea and systemic inflammatory responses in lung cancer patients [83]. Altogether, the role of probiotics in cancer is extensive and we will provide a more detailed description of their functions in cervical cancer.

Probiotics and cervical cancer

It was reported that probiotics can be efficient in different gynecological diseases [84]. Herein, we look into studies investigating how probiotics can be useful in the prevention, diagnosis, and treatment of cervical cancer.

Roles of probiotics on cervical cancer cells

Wang et al. [85] have shown that *Lactobacillus* supernatants (LS), *L. crispatus*, *L. jensenii*, and *L. gasseri*, inhibit the proliferation of Caski cells and cause some morphological alterations. Through incubating cells with LS, the number of S phase cells increased significantly; meanwhile, G2/M phase cells decreased [85]. E6 and E7 are two genes from eight genes that are encoded by HPV [86]. These two genes encode the proteins that are linked with p53 and pRB tumor suppressors and are required for conversion to malignancy [86]. LS treatment results in a reduction in the expression of CDK2, cyclin A, and HPV oncogenes (E6 and E7) [85]. Moreover, p21 expression was enhanced in LS-treated cells [85]. *Lactobacillus plantarum* bacteria, which were isolated from vaginal secretions of young adult and adolescent women,

are observed to have probiotic features and anticancer activities against HeLa cervical cancer line [87]. Another study on HeLa cell line revealed that human milk-isolated *Lactobacillus* strains (*Lactobacillus casei* SR1, *Lactobacillus casei* SR2, and *Lactobacillus paracasei* SR4) have remarkable probiotic activities, including antibiotic susceptibility, antioxidant roles, low pH resistance, and resistance to high levels of bile salts [88]. Furthermore, findings indicate that cell-free culture supernatants have anticancer activities, such as downregulating BCL-2 and upregulating apoptotic genes (caspase3, caspase8, caspase9, BAX, and BAD) [88]. Sungur et al. [89] reported that human vagina-isolated *L. gasseri* strains, G10 and H15, inhibits the HeLa cells proliferation. *Lactobacillus* exopolysaccharides exert cytotoxic effects on cancer cells and decrease their proliferation [90]. While lyophilized exopolysaccharides of *L. gasseri* strains led to apoptosis in HeLa cells, G10 apoptosis induction has related to Bax and Caspase3 upregulation [89]. Besides, strains of *L.gasseri* reduce TNF- α and increase IL-10, which leads to their anti-inflammatory effect on cervical cancer [89]. It is observed that treating HeLa cells with supernatants of *Lactobacillus rhamnosus* and *lactobacillus crispatus* reduces the expression of CASP3 gene as well as MMP2 and MMP9, which causes an inhibitory effect on metastasis [91]. Findings show that *Bifidobacterium adolescentis* SPM1005-A exerts an antiviral activity in SiHa cervical cell line, which express HPV type 16 and may prevent this cancer [92]. Treating cells with this bacterium has been shown to reduce the E6 and E7 oncogenes at mRNA and protein levels of E6 [92]. *L. gasseri* 3396 and *L. crispatus* 2743 are two probiotic strains [93]. It is observed that *L. crispatus* 2743 has an inhibitory effect on the expression of E6 and E7 at the mRNA level [93]. Meanwhile, *L. gasseri* 3396 has a smaller inhibitory impact on the E6 gene without any significant effect on the E7 gene [93] (Table 1).

Probiotics effects on gastrointestinal problems of cervical cancer patients

As we mentioned earlier, radiotherapy is an effective method for treating cervical cancer patients [94]. However, radiotherapy has multiple side effects causing an extra burden to patients such as nausea, vomiting, and diarrhea [95, 96]. Radiotherapy-induced diarrhea is one the most frequently occurred side effects, which can involve up to 80% of patients and may lead to severe complications [97, 98]. It is suggested that this side effect is the result of lactose and bile acids malabsorption [45]. Moreover, it may be due to the alterations in the intestinal flora and motility [45]. These events cause an impairment in immune roles of the gastrointestinal tract as well as its secretion and absorption [45].

Table 1 Studies investigating probiotics effects on cervical cancer cells

Probiotic	Cell line	Findings	References
supernatants of <i>L. crispatus</i> , <i>L. jensenii</i> , and <i>L. gasseri</i>	Caski	Inhibition of the viability by regulation of HPV oncogenes and cell cycle-related genes	[85]
Vagina-isolated <i>L. plantarum</i>	HeLa	Suppression of proliferation and induction of apoptosis	[87]
Milk-isolated <i>L. casei</i> and <i>L. paracasei</i>	HeLa	Induction of apoptosis	[88]
Vagina-isolated <i>L. gasseri</i>	HeLa	Inflammation and proliferation were reduced and apoptosis was increased	[89]
Supernatants of <i>L. rhamnosus</i> and <i>L. crispatus</i>	HeLa	Proliferation and metastasis were suppressed	[91]
<i>Bifidobacterium adolescentis</i> SPM1005-A	SiHa	Suppression of E6 and E7 oncogenes	[92]

There are some investigations concerned with the roles of probiotics in preventing or modulating the gastrointestinal problems which cervical cancer patients face due to cancer itself or the treatments. It is reported that administering a probiotic which contains live *Lactobacillus acidophilus* LA-5 plus *Bifidobacterium animalis* subsp. *lactis* BB-12 leads to reduced incidence of mild to moderate and severe diarrhea in cervical cancer patients who undergo beam pelvic radiotherapy [99]. In a study, a probiotic drink has been used for patients with cervical carcinoma who received radiotherapy and weekly cisplatin. Results showed that giving *Lactobacillus casei* DN-114001 as a probiotic has a significant effect on stool consistency. However, there was no reduction in the incidence of diarrhea in patients who received probiotic drink [100]. Another trial reported that fewer patients who were assigned to VSL#3 had radiation-induced diarrhea compared to the placebo group. A higher percentage of patients in the placebo group experienced grade 3 or 4 diarrhea compared to VSL#3 patients. Also, daily bowel movements were lower in patients who receive VSL#3 [101]. Therefore, probiotics can be considered as safe and effective agents for reducing radiotherapy-induced diarrhea in patients with cervical cancer. Symbiotics are products consisting of prebiotics and probiotics that include *Lactobacilli*, *Bacteroides*, *Bifidobacteria*, and *Eubacterium*. This product plays several beneficial roles including inactivating carcinogens, maintaining the integrity of intestine, immunomodulation, and anti-inflammatory activities [102, 103]. Findings demonstrated that patients who were given symbiotic showed lower levels of fecal calprotectin as well as less frequent and less intense vomiting [104]. Thus, symbiotic supplementation may be also helpful in reducing gastrointestinal adverse effects of cervical cancer patients (Table 2).

Probiotics provide a better diagnosis of cervical cancer

Bacteria can be used as a diagnostic device through engineering techniques that make the bacteria sense a specific molecule in the human body and consequently produce a signal [106]. For instance, Danino et al. [107] developed a probiotic-based diagnostic that is orally administered. They showed that using *Escherichia coli* Nissle 1917 is a non-invasive approach for producing signals that are detectable in urine; leading to the identification of liver metastasis. Danino et al. [107] showed that by programming, probiotics can be used for delivering gene circuits to unhealthy tissue microenvironment. *L. lactis* has been also used for detecting a molecule that is produced by *Vibrio cholera* [108]. Through developing a diagnostic circuit in this bacteria, the color of the host's feces changes when there is an infection, which provides an early alert of cholera [108]. Thus, engineering may make it possible to use probiotics as a diagnostic device in cervical cancer. *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 are two probiotic strains which have shown desirable effects on gynecological diseases [109, 110]. Evidence suggests that using *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 along with anti-infective agents leads to a reduction in false negative and false positive results of cervical malignancies; thus, cytological diagnoses are more reliable with this method [111]. Compared to when using anti-infective drugs alone, applying these probiotic strains provide a higher percentage of vaginal microflora normalization in patients who have vaginal infection [111]. A study investigated the impacts of probiotic strains on the quality of cervical smear and clearance of genital high-risk human papilloma virus [112]. It is observed that *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 significantly reduced the rates of unsatisfactory and mildly abnormal cervical smears. However, they did not affect the clearance of HPV [112].

Table 2 Studies concerned with the roles of probiotics in preventing or reducing the adverse effects of cervical cancer therapies on gastrointestinal tract

Type of probiotics	Dosage	Duration of probiotic consumption	Results	References
L. acidophilus LA-5 plus Bifidobacterium animalissubsp. Lactis BB-12	One capsule containing 1.75 billion lyophilized live bacteria t.i.d.	From the first day until the end of radiotherapy	Severity and incidence of radiotherapy-induced diarrhea were reduced	[99]
L. acidophilus plus bifidobacterium bifidum	2 × 10 ⁹ units of a L. acidophilus plus bifidobacterium bifidum b.i.d.	Beginning 7 days before starting radiotherapy and continuing every day during radiotherapy	Stool consistency was improved and need for anti-diarrheal medication was reduced	[105]
L. casei DN-114001	96 mL of a liquid yogurt containing approximately 108 CFU/g of L. casei DN-114001 t.i.d.	Beginning 7 days before starting radiotherapy and continuing every day during radiotherapy	Stool consistency was improved but there was no reduction in the incidence of radiotherapy-induced diarrhea	[100]
VSL#3	one sachet containing 450 billion/g of bacteria, including four strains of lactobacilli, three strains of bifidobacteria, and one strain of <i>Streptococcus salivarius</i> t.i.d.	From the first day of radiation therapy until the end of the scheduled cycles of radiotherapy	Daily bowel movements and incidence of radiotherapy-induced diarrhea were reduced	[101]
Symbiotic	symbiotic containing 1 × 10 ⁷ (CFU)/g biogel of L. acidophilus NCFM, Bifidobacterium lactis Bi-07 1 × 10 ⁶ CFU/g biogel, and blue agave inulin t.i.d.	Seven weeks	Fecal calprotectin and frequency and intensity of vomiting were reduced	[104]

Colony-forming unit, CFU; b.i.d., twice a day; t.i.d., three times a day

Combination of probiotics with other cervical cancer therapies

Cisplatin has been one of the most important chemotherapeutics in patients with advanced cervical cancer [113]. It is reported that cisplatin pro-apoptotic and anti-growth effects are enhanced by co-treatment with Lactobacillus bacteria in mouse models with lung cancer [114]. Co-treatment with Lactobacillus led to the upregulation of IFN-γ, PRF1, and GZMB; resulting in a better anti-tumor response to cisplatin [114]. PD-L1 blockade has shown a better anti-tumor activity in mice harbouring unfavorable gut microbiota by orally administrating Bifidobacterium probiotic. Also, it is observed that this combined treatment prevented tumor growth [115]. A study of 228 patients with cervical cancer at stage IIIB demonstrated that combining LC9018, a response modifier that is derived from heat-killed Lactobacillus casei YIT9018, with radiation therapy would improve the outcomes [116]. Okawa et al. concluded that patients who received LC9018 as an adjuvant agent had a longer survival and relapse-free interval than patients who received radiation therapy alone. Moreover, these patients showed less severe radiation-induced leukopenia [116]. In a recent study, Negi et al. [117] provided a drug delivery approach in which probiotic strains were applied. They concluded that the pessaries which contain cisplatin and probiotic biomass can be a better therapeutic method for cervical cancer since probiotic strains showed favorable effects such as scavenging free radicals [117]. In contrast, Kim et al. [118] reported that the

extract of L. casei showed no synergistic effects with anti-cancer drugs to suppress the Hela and Caski cancer cells growth. Although there are many studies on the role of probiotics in cervical cancer, little is known about their synergistic effect with other drugs of this cancer. However, probiotics may be potential agents that can increase the antitumor effects of other drugs [119].

Effects of probiotics on the therapeutic targets of cervical cancer

While the majority of articles focus on the direct role of probiotics on cervical cancer cells or their role in reducing the side effects of other treatments, evidence from other cancer types suggests that probiotics may affect other drug targets of this cancer. However, studies in this area are limited and more research is needed.

It is reported that miR-29a and miR-21 are the most common downregulated and upregulated miRNAs, respectively, involved in the progression of invasive cervical cancer [120]. There some other dysregulated miRNAs in cervical cancer, including miR-10a, miR-20b, miR-106, miR-16 and miR-9 [120]. Moreover, exfoliated cells of the cervix that are associated with cancer progression present dysregulated miR-375, miR-125, and miR-34a [120]. It is found that vaginal-isolated Lactobacillus lactis leads to the downregulation of TLR-4, miR-200b, and miR-21, which is associated with apoptosis induction [121]. Also, it is observed that the probiotic *Escherichia coli* Nissle 1917 restores the expression levels of some miRNAs, including miR-143, miR-155,

and miR-375 [122]. MiR-21 is reported to have a significantly higher level in the human umbilical vein endothelial cell that were cultured in different conditions of *Lactobacillus acidophilus* such as water extract, culture media, culture-filtered and unfiltered supernatants. Furthermore, cells treated with *L. acidophilus* culture media have shown the highest miR-21 level compared to cells treated with other conditions of *L. acidophilus*. Conversely, *Escherichia coli* lipopolysaccharide resulted in a decrease in miR-21 levels compared to the control group [123].

HPV infection triggers the activation of NF-κB that affects both innate and adaptive immune responses. The virus eliminates the inhibitory effects of the immune system by downregulating NF-κB; resulting in a persistent status of infection [124]. Then, NF-κB reactivates during the transformation to cervical cancer. NF-κB leads to the transcriptions of genes that are involved in proliferation and metastasis as well as cell immortality and VEGF-dependent angiogenesis [124]. Probiotics are capable of inhibiting the inflammation through suppressing different signaling pathways such as the nuclear factor-κB (NF-κB) pathway. Besides, lipopolysaccharides binding to the CD14 receptor can be inhibited by probiotics; leading to a decrease in overall NF-κB activation as well as the production of pro-inflammatory cytokines [125]. Findings show that anti-inflammatory *Lactobacillus plantarum* NK3 and *Bifidobacterium longum* NK49 suppress the activation of NF-κB and the expression of

TNF-α in the mice vagina and uterus [126]. *Lactobacillus johnsonii*, *Bifidobacterium longum*, *Lactobacillus plantarum*, *Lactobacillus delbruekii*, and *Lactobacillus fermentum* are also observed to inhibit NF-κB activation [127–129].

Findings indicate that STAT3 has a potential role in the development of cervical cancer [130, 131]. HPV positive cervical cancer cells have a higher level of constitutively activate STAT3 compared to HPV-negative cells [132]. Moreover, Shukla et al. reported that STAT3 is associated with the conversion of precancerous cervical lesions to cancer [132]. It is observed that pro-inflammatory cytokine IL-6 mediate the autocrine activation of STAT3 in HPV+ cervical cells [133]. Phosphorylation of STAT3 increases with both conditioned media from HPV+ cervical cells and recombinant IL-6 [133]. Probiotic agent VSL#3 has chemopreventive roles against the colitis-associated carcinogenesis. Evidence has revealed that VSL#3 exerts its function through the suppression of IL-6/STAT3 [134]. Zhou et al. [135] also reported that exopolysaccharides from *Lactobacillus plantarum* NCU116 promote the binding of STAT3 to the promoter of occluding and ZO-1. Besides, treatment with this exopolysaccharide results in STAT3 knockdown; leading to a reduction in the expressions of occludin and ZO-1 [135]. On the other hand, it is reported that *Lactobacillus* enhances the generation of intestinal stem cells by activating STAT3 signaling pathway [136].

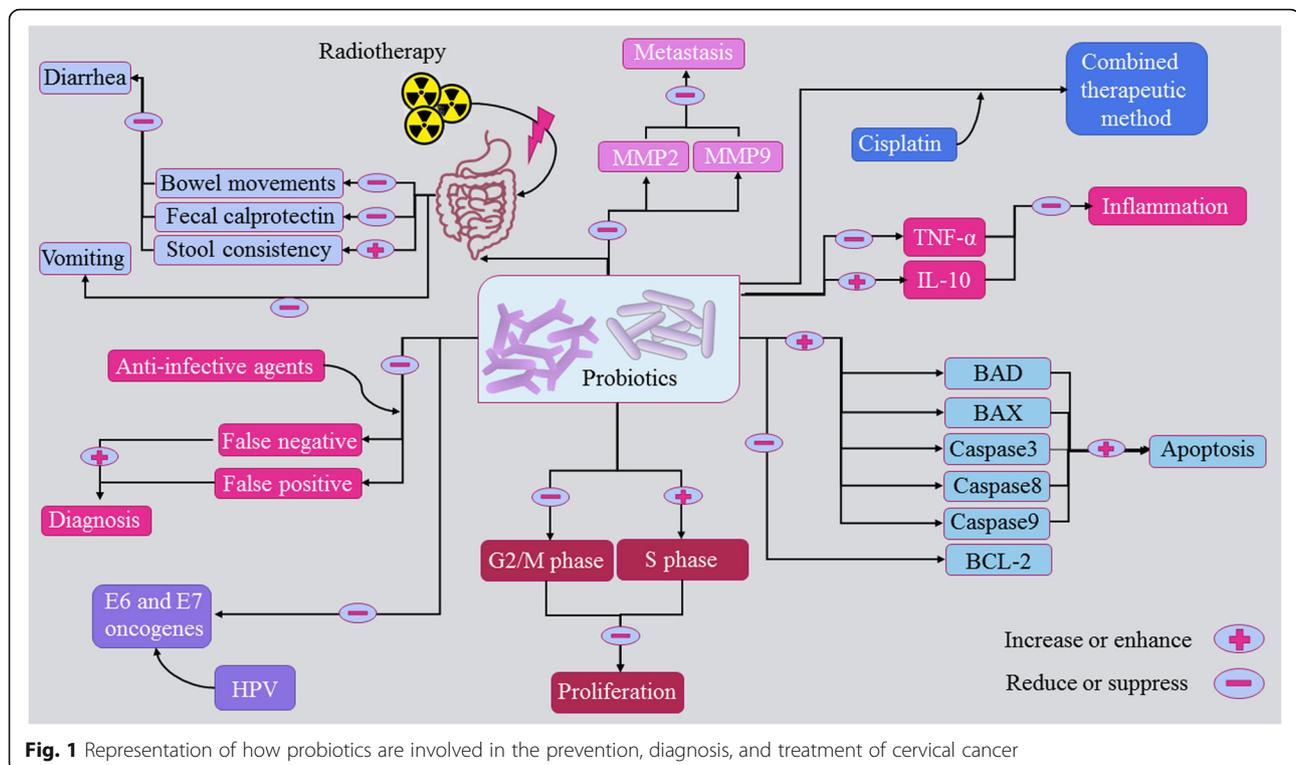


Fig. 1 Representation of how probiotics are involved in the prevention, diagnosis, and treatment of cervical cancer

Conclusions

Cervical cancer is one of the most important cancers among women. Probiotics are beneficial in different cancers. Some studies have been focused on the effects of the probiotic on cervical cancer (Fig. 1). Findings have shown that probiotics have remarkable abilities which may lead to the prevention or treatment of cervical cancer including induction of apoptosis, inhibiting proliferation, reducing inflammation, and suppressing metastasis. Evidence suggests that concurrent use of probiotics with other therapeutic drugs results in an improvement in treatments. When combined with anti-infective drugs, probiotics have been shown to provide a better diagnostic method for cervical cancer patients. Besides, clinical trials are indicating that administering probiotics have a significant impact on gastrointestinal side effects which are caused by cervical cancer therapies. However, more research, especially clinical trials, should be done to understand the precise effects of these anti-tumor agents. Besides, the side effects of probiotics in cervical cancer patients should also be carefully investigated. Overall, probiotics appear to be potential anticancer agents which can be used in the prevention and treatment of cervical cancer.

Abbreviations

HPV: Human papillomavirus; VIA: Visual inspection with acetic acid; VILI: Visual inspection with Lugol's iodine; TNF: Tumor necrosis factor; STI: Sexually transmitted infection; PET: Positron emission tomography; LS: Lactobacillus supernatants; CCRT: Concurrent chemo-radiation; IL: Interleukin

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