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REVIEW

Role of *Lactobacillus* in cervical cancer

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Abstract: Cervical cancer is a common malignant cancer among women worldwide. Changes in the vaginal microecological environment lead to multiple gynecological diseases, including cervical cancer. Recent research has shown that *Lactobacillus* may play an important role in the occurrence and development of cervical cancer. This review explores the role of *Lactobacillus* in cervical cancer. A total of 29 articles were included after identification and screening. The pertinent literature on *Lactobacillus* in cervical cancer from two perspectives, including clinical studies and experimental studies, was analyzed. An association network for the mechanism by which *Lactobacillus* induces cervical cancer was constructed. In addition, we provide direction and insight for further research on the role of *Lactobacillus* in cervical cancer.

Keywords: CIN, cervical cancer, *Lactobacillus*, microorganism

Introduction

Cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths among women worldwide.[1,2] Epidemiological investigations have shown that the number of new cases of cervical cancer per year is ~485,000, with 236,000 deaths occurring per year globally.[3] Patients with cervical cancer often exhibit no obvious symptoms and signs at early stages; thus, the disease tends to be ignored and is easily misdiagnosed. Cervical cytologic screening has generally been used to detect cervical cancer and premalignant lesions over the past decade, and early diagnosis and appropriate treatment reduce the risk of cancer-related death.[4]

Current research has shown that microorganisms may play an important role in the occurrence and development of cervical cancer.[5] Persistent infection with high-risk human papillomavirus (HR-HPV) is now believed to be a major causal factor in the development of the disease.[6] The bacteria in the vagina maintain a dynamic balance under physiological conditions, but the imbalance of vaginal flora leads to multiple gynecological diseases, such as coleitis, high-grade cervical intraepithelial neoplasia (CIN), and cervical cancer.[7] It has been confirmed that *Gardnerella* and *Monilia* are the main bacteria that induce coleitis.[8,9] Previous research has shown that the abundance of vaginal flora such as *Mycoplasma genitalium*,[10] aerobic lactobacilli, *Staphylococcus epidermidis*, Enterococci, *Escherichia coli*, and *Bacteriodes* species[11] in patients with cervical cancer is different from that in healthy controls. However, the relationship between vaginal flora and cervical cancer has not yet been elucidated.

Lactobacillus is a group of bacteria that can act as a catalyst to produce lactic acid during the process of glycolysis.[12] This group is the predominant bacteria in the healthy vagina and plays an important role in the protection of the female reproduction

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system.[13] Summarizing previous studies, *Lactobacillus* in the vagina exerts its protective functions mainly through the following four potential mechanisms: 1) By preventing pathogenic bacteria from adhering to the epithelial tissue: vaginal epithelial cells (VECs) of fertile woman encounter periodic changes including hyperplasia, peeling, and repair under the effect of estrogen and progestin. Free glycogen that is produced during this process supplies matter and energy for the growth of *Lactobacillus. Lactobacillus* is adsorbed and occupies the VECs, and these bacteria can prevent the conglutination of invasive pathogenic bacteria that induce malignant tumors.[14–16] 2) By secreting organic acid: *Lactobacillus* produces organic acid by decomposing glucogen to maintain the vaginal acidic environment,[17] which can inhibit the growth and resist the invasion of pathogenic bacteria. In addition, the vaginal acidic environment is beneficial to maintain the activity of bacteriocins and H_2O_2.[18] 3) By secreting various metabolites: exopolysaccharides (EPSs), phosphorylated polysaccharides, and peptidoglycans, which are secreted by *Lactobacillus*, can inhibit the proliferation of malignant tumors.[19,20] Bacteriocin and surface-active components can inhibit the production of tumorigenic substances and the growth of harmful microorganisms.[21] H_2O_2, which is also secreted by *Lactobacillus*, can directly kill harmful microorganisms or act in a bactericidal manner though the peroxidase-hydrogen peroxide-halide bactericidal system.[18] 4) By activating the immune system: *Lactobacillus* affects cellular and humoral immunity. On one hand, these bacteria can increase the proliferation and differentiation of thymus-derived cells (T cells).[22] On the other hand, *Lactobacillus*, as an immune sensitizer, can increase immunological recognition and proliferation of bone marrow-derived cell (B cells).[23] *Lactobacillus* also produces nitric oxide (NO) by stimulating macrophages and disrupting the energy metabolism of cancer cells.[24] Considering the importance of lactobacilli in cervical cancer, in this review, we comprehensively analyzed and classified the pertinent literature on lactobacilli in cervical cancer from two perspectives, clinical case investigations, and studies of molecular mechanisms. We also provide direction and insight for further research on intestinal flora in cervical cancer.

Methods

The databases PubMed, Embase, and Cochrane were searched for literature published up to January 10, 2018. To achieve maximum sensitivity of the search strategy and identify all studies, the following terms were combined: ("cervix uterus" or "neck of uterus" or "uterine neck" or "cervical" or "cervix" or "uterine cervical" or "uterine cervix") and ("neoplasms" or "tumor" or "carcinoma" or "cancer" or "intraepithelial neoplasia" or "intraepithelial neoplasms") and ("lactic acid bacteria" or "lactobacillus" or "lactobacilli" or "vagina/vaginal flora" or "vagina/vaginal microflora" or "vagina/vaginal microorganism" or "vagina/vaginal microbiome" or "vagina/vaginal microbiota" or "vagina/vaginal microbe" or "vagina/vaginal microbiology" or "vagina/vaginal bacteria" or "vagina/vaginal bacterium"). All relevant abstracts were independently retrieved by two authors, and the articles with available information for the present systematic review were fully reviewed. A total of 29 articles were included after identification and screening. The detailed search strategy is presented in Figure 1.

Study selection

Studies adhering to the following criteria were considered for inclusion: 1) those published in English and 2) those involving *Lactobacillus* in CIN or cervical cancer in vivo or in vitro. The exclusion criteria were as follows: 1) letters, case reports, reviews, or conference reports; 2) the main studies not focused on the topic of vaginal *Lactobacillus* in CIN or cervical cancer; and 3) correlation clinical studies with a low quality score according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method.[25]

Results

CIN, which is considered to be a precancerous lesion of the cervix,[26] was included in the present study. After identification, screening, and validation, we identified a total of 29 pertinent studies related to *Lactobacillus* and several of its subgenera in cervical cancer and precancerous lesions of the cervix published in recent years. The 29 pertinent studies were divided into two groups that comprised 14 clinical studies in one group and 15 experimental studies in the other group. The clinical studies and experimental studies are shown in Tables 1 and 2, respectively.

As shown in Table 1, 16S rRNA gene sequencing was the main method used to detect microbial community structure and relative abundance. The presence of cervical cancer and precancerous lesions in women was associated with a high relative abundance of *Lactobacillus iners* and *Lactobacillus* sp and low relative abundance of *Lactobacillus jensenii* and *Lactobacillus crispatus.* Two investigations revealed that the abundance of *Lactobacillus* in women with human papillomavirus (HPV) infection was lower (panel numbers 6 and 10). A randomized, double-blind, placebo-controlled study

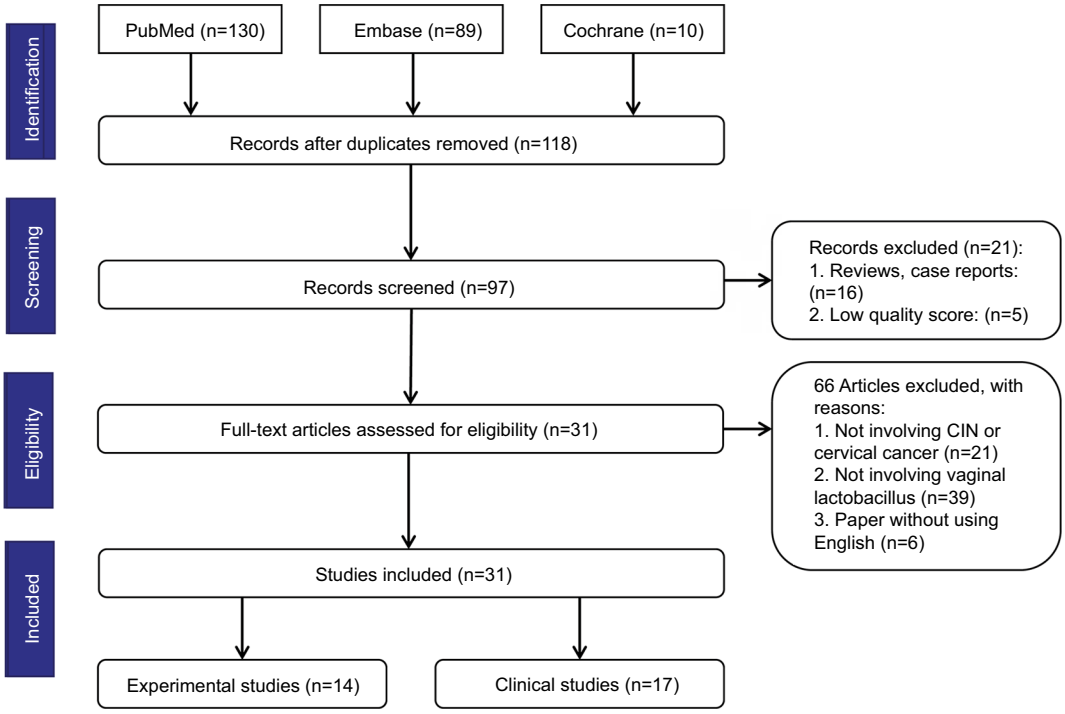

Figure 1 Literature search strategy.
Notes: Databases including PubMed, Embase, and Cochrane were searched for literature published up to January 10, 2018. A total of 29 studies including 17 clinical studies and 14 experimental studies were included after identification and screening.
Abbreviation: CIN, cervical intraepithelial neoplasia.

showed that an oral lactobacilli (panel number 11) and an HR-HPV E7-expressing *Lactobacillus*-based vaccine (panel number 8) were able to decrease the risk of CIN. Moreover, two randomized controlled trial studies (panel numbers 12 and 13) supported the hypothesis that LC9018 (a biological response modifier prepared from heat-killed *Lactobacillus casei* YTT9018) was able to protect patients from radiation-induced leukopenia with few side effects.

As shown in Table 2, cancer cell and animal models were used along with molecular biology techniques such as the cell counting kit-8 assay, Western blots, immunohistochemistry, polymerase chain reaction, and enzyme-linked immunosorbent assays to study the role of *Lactobacillus* and several subgenera in cervical cancer. The results showed that *Lactobacillus*, its subgenera, and their supernatants exhibited antimetastatic and antiproliferative activities in cervical cancer cell lines by regulating cancer-related genes and eliciting an immunological response. *Lactobacillus* inhibited the viability of cervical cancer cells through regulating HPV oncogenes (panel numbers 1 and 6), and HPV-type 16 E7 protein displayed on lactobacillus could protect against HPV-induced tumors through regulating cellular immunity (panel numbers 10–14). In particular, a negative result showed that *L. casei* extract was not able to inhibit the viability of cervical cancer cells in vitro (panel number 7).

As shown in Figure 2, a network of the mechanisms of *Lactobacillus* in cervical cancer was constructed to better visualize the theory behind the experimental studies.

Discussion

The vaginal microecological balance is dynamic and relative, and patients are able to recover from slight vaginal dysbacteriosis. The persistence of vaginal dysbacteriosis is thought to promote gynecological cancer.[7,27] A decline in the quantity and activity of *Lactobacillus* leads to an overgrowth of anaerobic bacteria.[28] Deleterious metabolites such as nitrous acid can be produced by these organisms, and the risk of HPV infection also increases.[29] Persistent infection of oncogenic HPV is a cause of cervical cancer.[6] The abundance of *Lactobacillus* in HPV infection is lower, and HPV oncogenes may be involved in regulation of the viability of cervical cancer cells inhibited by *Lactobacillus*. CIN, precancerous lesions of the cervix, is much more likely to occur with dysbacteriosis. Thus, the regulation and control of *Lactobacillus* may block the progression of cervical cancer.

The present study attempts to clarify the cross-talk between *Lactobacillus* and cervical cancer using both clinical and experimental studies by reviewing the pertinent literature. Experimental study can lay an important foundation for

Table 1 Clinical studies of *Lactobacillus* in cervical cancer

Number	Year	Authors	Number of women enrolled	Race or region	Subgenera of *Lactobacillus*	Methods	Diseases	Findings	Reference
1	2016	Piyathilake et al	Patients with CIN1 (n=90), CIN2 (n=208), and CIN3 (n=132)	Birmingham, AL, USA	*Lactobacillus reuteri* and several sub-genus level	16S rRNA sequencing	CIN	The cervical mucosal CT dominated by *L. iners* and unclassified *Lactobacillus* spp was associated with CIN2+ (OR =3.48; 95% CI, 1.27–9.55).	45
2	2016	Seo et al	Patients with CIN (n=65) and control (n=72)	South Korea	*L. crispatus* and *L. iners*	16S rRNA gene sequencing, a food-frequency questionnaire and multivariable logistic regression analysis	CIN	Diet characterized by *L. iners*-dominant type had a higher risk of CIN, compared with the *L. crispatus*-dominant type	46
3	2015	Mitra et al	Control (n=20), LSIL (n=52), HSIL (n=92), and cervical cancer (n=5).	Caucasian, Asian, and Black	*L. jensenii*	16S rRNA gene sequencing	LSIL, HSIL, and ICC	Increasing disease severity was associated with decreasing relative abundance of *Lactobacillus* spp. The vaginal microbiome in HSIL was characterized by lower levels of *L. jensenii* ($P<0.01$) compared to LSIL	47
4	2015	Oh et al	Women (n=70) and control (n=50)	South Korea	*L. iners* and *L. crispatus*	16S rRNA gene sequencing	CIN	A predominance of *L. iners* with a concomitant paucity of *L. crispatus* in the cervical microbiota was associated with CIN risk	48
5	2015	Mitra et al	Control (n=20), LSIL (n=52), HSIL (n=92), and cancer (n=5).	Caucasian, Asian, and Black.	*Lactobacillus*	16S rRNA gene sequencing	CIN	Women with CIN have a more diverse *Lactobacillus* depleted vaginal microbiome, compared to normal women	49
6	2015	Kwasniewski Wojciech et al	Women	European	*Lactobacillus*	16S rRNA gene sequencing	LSIL and HSIL	*Lactobacillus* spp are the predominant bacteria in the healthy cervix, HPV negative women but there is low abundance of lactobacillus in women with LSIL HPV (+)	50
7	2014	Silva et al	Patients with evolution (214) and without evolution (n=1970)	Brazilian; Gynecology and Obstetrics Department at a public tertiary-level university hospital between 1995 and 2000	*Lactobacillus* sp	Retrospective study and multivariable logistic regression analysis	Intraepithelial lesions; cervical cancer	*Lactobacillus* sp was risk factor associated with evolution from intraepithelial lesion and invasive neoplasia	51
8	2014	Kawana et al	Patients with CIN3 (n=17)	Japanese women; Japan	*Lactobacillus casei*	ELISPOT assay	CIN	Oral administration of an E7-expressing *Lactobacillus*-based vaccine can elicit E7-specific mucosal immunity in the cervix of CIN3 patients	52

9	2013	Rocha et al	Patients with preneoplastic and neoplastic cervical uterine lesions (n=625)	Public health care services in Divinopolis county, Minas Gerais state, Brazil	*Lactobacillus*	PCR	Preneoplastic and neoplastic cervical uterine lesions	*Lactobacillus* sp was the most frequent microorganism (65%) in the patients with preneoplastic and neoplastic cervical uterine lesions	53
10	2013	Dareng et al	Women (n=278)	Nigerian; Abuja, Nigeria	*Lactobacillus*	16S rDNA gene sequencing, Roche Linear Array(R) HPV genotyping test and logistic regression models	Women with or without HR-HPV infection	Low relative abundance of *Lactobacillus* spp is in 50% of HPV infection	54
11	2012	Ou et al	Women were randomized to oral lactobacilli (n=40) and oral placebo (n=40)	Chinese; Taiwan, China	Lactobacilli	HPV test, pap smear, and vaginal gram stain; randomized, double-blind, placebo-controlled study	High-risk HPV infection; CIN	Comparing with women in oral lactobacilli group, women in the placebo group had a significant higher percentage of subsequent CIN lesion during follow-up	55
12	1993	Okawa et al	Patients with stage IIIB cervical cancer (n=228)	Spanish; 50 institutions, Spain	*Lactobacillus casei*	Randomized controlled trial	Cervical cancer of stage IIIB	LC9018 (a biological response modifier prepared from heat-killed *Lactobacillus casei* YTT9018) could protect the patients from radiation-induced leukopenia during radiotherapy with few side effects	56
13	1989	Okawa et al	Patients with stage IIB or III cervical cancer (n=61)	Japanese; Department of Radiology, Tokyo Women's Medical College, Tokyo, Japan	*Lactobacillus casei*	Randomized controlled trial	Cervical cancer of stage IIB or III	LC9018 enhanced the therapeutic effect of the irradiation. LC9018 could protect the patients from leukopenia during radiotherapy	57
14	1978	Mead	Patients with invasive cervical cancer (n=21)	American; Department of Obstetrics and Gynecology at the University of Vermont College of Medicine, Burlington, VT, USA	Aerobic lactobacilli	Bacteria isolation and purification	Cervical cancer	Patients with cervical cancer have a decreased frequency of isolation of aerobic lactobacilli	11

Notes: Cervical cancer and precancerous lesions in women were associated with high relative abundance of *Lactobacillus* and several of its subgenera. Oral lactobacilli (panel number 11) and an E7-expressing *Lactobacillus*-based vaccine (panel number 8) were able to decrease the risk of CIN. LC9018 protected patients from radiation-induced leukopenia with few side effects.

Abbreviations: CCK-8, cell counting kit-8; CIN, cervical intraepithelial neoplasia; CT, community type; HPV, human papillomavirus; HR-HPV, high-risk HPV; HSIL, high-grade squamous intraepithelial lesion; ICC, invasive cervical cancer; *L. crispatus*, *Lactobacillus crispatus*; *L. iners*, *Lactobacillus iners*; *L. jensenii*, *Lactobacillus jensenii*; LSIL, low-grade squamous intraepithelial lesion; PCR, polymerase chain reaction.

Table 2 Experimental studies of *Lactobacillus* in cervical cancer

Number	Year	Authors	Experimental animal and cell model	Subgenera of *Lactobacillus*	Methods	Diseases	Findings	Reference
1	2017	Wang et al	CaSki cells	*L. crispatus*, *L. jensenii*, and *L. gasseri*	MTT assay, flow cytometry, and PCR	Cervical cancer	Supernatants of *L. crispatus*, *L. jensenii*, and *L. gasseri* have inhibitory effects on the viability of cervical cancer cells via regulation of HPV oncogenes and cell cycle-related genes	43
2	2017	Li et al	HeLa and U14 cell lines and Xenograft mouse	Lactobacilli	CCK-8, Western blot, and immunohistochemistry	Cervical cancer	Lactobacilli inhibit the migratory ability of cervical cancer cell lines and the upregulation of E-cadherin may be involved in the molecule mechanism	58
3	2017	Sungur et al	Women, cervical cancer cell and Caco-2 cell lines	*L. gasseri* strains	HPLC, WST-1 cell proliferation assay, ELISA, and PCR	Cervical cancer	EPSs of *L. gasseri* strains isolated from human vagina induce apoptosis in HeLa cells by associating with an upregulation of Bax and Caspase 3	44
4	2017	Jang et al	Th17 cells and HeLa cell lines	*Lactobacillus rhamnosus* HN001 (L1) and *Lactobacillus acidophilus* La-14 (L2)	Enzyme-linked immunospot assay, immunoblotting, PCR, and flow cytometry	Cervical cancer	*Lactobacillus rhamnosus* HN001 (L1) and *Lactobacillus acidophilus* La-14 (L2) inhibited the adherence of *Gardnerella vaginalis* to cervical cancer cells	59
5	2016	Nouri et al	HeLa cell lines	LRS and LCS	MTT assay and PCR	Cervical cancer	LRS and LCS have antimetastatic and antiproliferative activities on HeLa cell lines	60
6	2016	Motevaseli et al	HeLa cells	*L. crispatus* and *Lactobacillus rhamnosus*	PCR	Cervical cancer	*L. crispatus* and *Lactobacillus rhamnosus* culture supernatants can decrease the expression of ATG14 and BECN1 as well as the HPV E6 oncogene in HeLa cells	61
7	2015	Kim et al	CaSki and HeLa cell lines	*Lactobacillus casei*	Flow cytometry	Cervical cancer	*Lactobacillus casei* extract cannot inhibit the viability of cervical cancer cells or the growth of cancer cells in the presence of anticancer drugs in vitro	62
8	2014	Nami et al	Women; HeLa cell lines and HUVEC normal cells	*Lactobacillus plantarum*	16S rDNA gene sequencing, disk diffusion antibiotic susceptibility test, MTT assay, DAPI staining method, and flow cytometry	Cervical cancer	*Lactobacillus plantarum* 5BL, which is isolated from vaginal secretions of adolescent and young adult women, exhibits desirable probiotic properties and remarkable anticancer activity against the HeLa cell lines with no significant cytotoxic effects on HUVEC normal cells	63
9	2013	Motevaseli et al	Human normal fibroblast-like cervical (normal cervical) and HeLa (cervical tumor) cells	*L. gasseri* and *L. crispatus*	MTT assay, Trypan blue staining, lactate dehydrogenase assay, colorimetric caspase-3 activity assay, and PCR	Cervical cancer	*L. gasseri* and *L. crispatus* exert cytotoxic effects on cervical tumor cells and this cytotoxicity is independent of pH and lactate	64
10	2013	Ribelles et al	Mice, inbred C57BL	*Lactococcus lactis* and *L. casei*	Cell surface display techniques	Cervical cancer	E7-expressing LAB, as a mucosal live vaccine, protects against HPV-type 16-induced tumors in mice	65
11	2010	Lee et al	Mice	*L. casei*	Enzyme-linked immunospot assay	Cervical cancer	Oral *L. casei* bearing the surface-displayed E6 protein induces T-cell-mediated cellular immunity and antitumor effects in mice	22

12	2010	Adachi et al	C57BL/6 mice	*L. casei*	Flow cytometry	Cervical cancer	*L. casei*-PgsA-E7 (HPV-type 16 E7 protein displayed on lactobacillus) can improve T cells with specific mucosal E7-type I immune responses and induce mucosal cytotoxic cellular immune responses	66
13	2006	Poo et al	Mice	*L. casei*	Western blot, flow cytometry, and immunofluorescence microscopy	Cervical cancer	Oral administration of *L. casei*-PgsA-E7(HPV-type 16 E7 protein displayed on lactobacillus) induces E7-specific antitumor effects in C57/BL6 mice	67
14	2006	Aires et al	Mice	*L. casei*	Western blotting, electron microscopy analysis, immunofluorescence, immunosorbent assay, and enzyme-linked immunosorbent assay	Cervical cancer	HPV-type 16 L1 virus-like particles by recombinant *L. casei* cells are the promising vaccine against HPV-16 infection	68
15	1999	McNicol et al	CaSki carcinoma cell line	*Lactobacillus acidophilus*	PCR and quantitative culture	CIN; HPV 16 infection	Isolation of *Lactobacillus* sp (P=0.05) is associated with low-grade CIN or normal histology	69

Notes: Cancer cell and animal models and molecular biology techniques were used to study the role of *Lactobacillus* and several of its subgenera in cervical cancer. *Lactobacillus*, several subgenera, and their supernatants had antimetastatic and antiproliferative effects in cervical cancer cell lines by regulating cancer-related genes and eliciting an immunological response.

Abbreviations: DAPI, 14′,6-diamidino-2-phenylindole; ELISA, enzyme-linked immunosorbent assay; EPSs, exopolysaccharides; HPV, human papillomavirus; *L. casei*, *Lactobacillus casei*; *L. crispatus*, *Lactobacillus crispatus*; *L. gasseri*, *Lactobacillus gasseri*; *L. jensenii*, *Lactobacillus jensenii*; LAB, lactic acid bacteria; LCS, *L. crispatus* supernatant; LRS, *Lactobacillus rhamnosus* supernatant.

further clinical study, and clinical study can be the reliable test of experimental study. *Lactobacillus* as a probiotic is characterized by fewer side effects and can be used as oral preparation. The signal peptide of S-layer on monolayer cell membrane of *Lactobacillus* is easy to combine with the exogenous target protein. These characteristics determine the *Lactobacillus* as a desired vector for recombinant protein vaccine and, moreover, *Lactobacillus* in vaginal flora as protection against HPV-related disease. Thus, the use of *Lactobacillus* as a vector to construct the HPV-related protein vaccine can achieve admirable antitumor effects in clinical practice.

Many clinical studies found that a decline in the quantity and activity of *Lactobacillus* was involved in the initiation and progression of cervical cancer, which provides a novel insight into the use of probiotics to prevent cervical cancer.[47,54,58] Some experimental studies found that *Lactobacillus* and its metabolites inhibit the proliferation of cervical cancer cells by regulating cancer-related genes or through an immunological mechanism. These studies provide a theoretical basis for further clinical application of *Lactobacillus* in cervical cancer.

Lactobacillus and its metabolites, which are used as treatments as well as prophylactic agents, have unique advantages. *Lactobacillus* as a vaginal parasitical bacterium has a lower toxicity and fewer side effects compared to other bacteria. It acts mainly by regulating the microecological environment and, compared to other bacteria, is less susceptible to resistance.[30] *Lactobacillus* and its metabolites are efficacious and superior in clinical applications for the prevention of cervical cancer.[31]

In addition to cervical cancer, *Lactobacillus* is associated with the proliferation and regulation of cells of other cancer types, such as breast cancer,[32] colorectal cancer,[33] gastric cancer,[34] and oral cancer.[35,36] Observations in these other cancers may offer insights into the study of *Lactobacillus* in cervical cancer. The main observations regarding *Lactobacillus* in cancers are as follows: 1) *Lactobacillus* can activate and strengthen the antitumor effects of immunocytes such as thymus-derived cells (T cells), natural killer (NK) cells, dendritic cells (DCs), and macrophages and immunological factors produced by immunocytes;[37–39] 2) a large amount of unmethylated dinucleotide repeat sequences present in the nuclei of *Lactobacillus* can activate the innate immune response by binding to a specific receptor that exists on the surface of human cells;[40] 3) *Lactobacillus* that is suitable for reproduction and growth in an anaerobic environment can selectively accumulate in the hypoxic zones of solid cancers;[41]

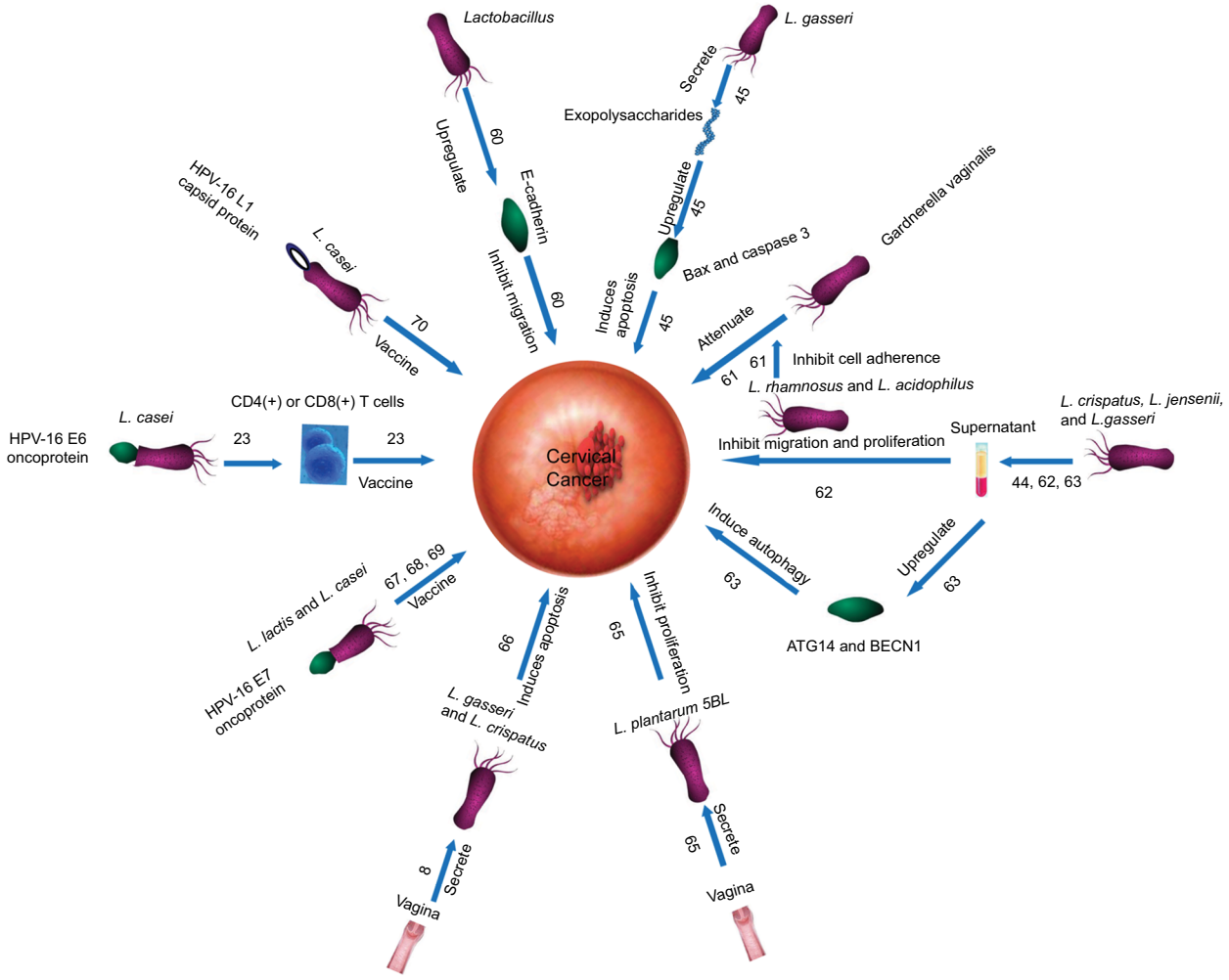

Figure 2 Network illustrating the effects of *Lactobacillus* in cervical cancer.
Note: An association network for *Lactobacillus* in cervical cancer was constructed based on the analysis of experimental studies and allows improved visualization of these studies.
Abbreviations: HPV, human papillomavirus; *L. acidophilus*, *Lactobacillus acidophilus*; *L. casei*, *Lactobacillus casei*; *L. crispatus*, *Lactobacillus crispatus*; *L. gasseri*, *Lactobacillus gasseri*; *L. jensenii*, *Lactobacillus jensenii*; *L. lactis*, *Lactobacillus lactis*; *L. plantarum*, *Lactobacillus plantarum*; *L. rhamnosus*, *Lactobacillus rhamnosus*.

and 4) *Lactobacillus* can selectively locate to solid cancers and can be used as a vector for gene therapy and targeted therapies.[35]

The diagnosis and treatment of cervical cancer have been advanced considerably in recent years, but there is still a long way to go in regard to cancer prevention. This review cannot include some unpublished research or ongoing studies. There is also a lack of large-scale multicenter clinical trials and clinical prospective cohort studies in the literature. A perfect theory cannot be constructed for the mechanism of action of *Lactobacillus* in cervical cancer. Vaginal *Lactobacillus* and its metabolites may provide a novel insight into the prevention of cervical cancer. Thus, we put forth some future directions for further study.

Future directions

Elucidate the role of vaginal *Lactobacillus* in cervical cancer

Lactobacillus is the dominant bacteria in the vagina and affects the growth of other bacteria.[42] There appears to be a complex relationship between cervical cancer and vaginal *Lactobacillus*. However, many problems deserve further consideration. How do the community structure and diversity of *Lactobacillus* vary with differences in race, region, lifestyle, and diet? How does *Lactobacillus* drive the occurrence and development of cervical cancer? What is the role of *Lactobacillus* metabolites in balancing vaginal microecology and the development of cervical cancer?

Elucidate the immunological functions mediated by vaginal *Lactobacillus* in cervical cancer

Immunotherapy provides a broad perspective for the treatment of cancers. Vaginal *Lactobacillus* and its metabolites do affect the immune system in cervical cancer.[22] Though much effort has been made into understanding the mechanisms of this effect, many bottlenecks must be addressed before stepping from the imbalanced vaginal microecological system to the immune system to cervical cancer genesis and development. *Lactobacillus* is an easily available probiotic that is safe and has no side effects or toxicity. The envelope of *Lactobacillus* is often used as a carrier to express an alternative antigen for vaccines, which may provide a novel idea for the primary prevention of cervical cancer. A cervical cancer vaccine based on *Lactobacillus* with an HPV vaccine promises to be a new method for the prevention of cervical cancer. Prospective studies on cervical cancer incidence after intervention with the *Lactobacillus* vaccine should be performed.

Elucidate the molecular mechanism by which *Lactobacillus* inhibits cervical cancer

Lactobacillus inhibits the proliferation of cells from multiple cancer types. Most studies have focused on the relationship between *Lactobacillus* and cancer, but the mechanisms underlying this relationship have yet to be clarified. Many enzymes and peptides and the lactic acid secreted by *Lactobacillus* are involved in activating and regulating important signaling molecules and pathways in cervical cancer.[43,44] It is necessary to elucidate the specific molecular mechanism or construct the molecular regulatory network in future research. *Lactobacillus* acts as a valuable cloning vector and is currently mainly used as a plasmid vector for the experimental research of cancer in vitro. This use may suggest additional therapeutic use as a carrier to express antioncogenes or encapsulated anticarcinogens in the future.

In light of the importance of *Lactobacillus* in cervical cancer, much attention has been paid to the study of vaginal microecology in recent years. *Lactobacillus* has shown tremendous promise for the prevention and treatment of cervical cancer. However, knowledge of vaginal microecology and *Lactobacillus* is far from complete. More research will be required before clinical application of *Lactobacillus* in cervical cancer is achieved.

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Disclosure

The authors report no conflicts of interest in this work.

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