World Journal of Vaccines, 2017, 7, 43-75
http://www.scirp.org/journal/wjv
ISSN Online: 2160-5823
ISSN Print: 2160-5815

New Progress regarding the Use of Lactic Acid Bacteria as Live Delivery Vectors, Treatment of Diseases and Induction of Immune Responses in Different Host Species Focusing on *Lactobacillus* Species

Seria Masole Shonyela[1,2*], Guan Wang[2], Wentao Yang[2], Guilian Yang[1#], Chunfeng Wang[1†]

[1]College of Animal Science and Technology, Jilin Provincial Engineering Research Center of Animal Probiotics, Jilin Agricultural University, Changchun, China
[2]Ministry of Agriculture, Livestock and Fisheries, Dar es Salaam, Tanzania
Email: *henjemasole@yahoo.com, *seria.masole@sacidas.org, #yangguilian@jlau.edu.cn, †wangchunfeng@jlau.edu.cn

How to cite this paper: Shonyela, S.M., Wang, G., Yang, W.T., Yang, G.L. and Wang, C.F. (2017) New Progress regarding the Use of Lactic Acid Bacteria as Live Delivery Vectors, Treatment of Diseases and Induction of Immune Responses in Different Host Species Focusing on *Lactobacillus* Species. *World Journal of Vaccines*, **7**, 43-75.
https://doi.org/10.4236/wjv.2017.74004

Received: November 23, 2017
Accepted: November 27, 2017
Published: November 30, 2017

Abstract

Lactobacillus species are non-spore-forming, gram-positive bacteria and lactic acid producing bacteria (LAPB) that naturally inhabit the human and animal gastrointestinal and mouth organs. The aim of this review was to evaluate the new progress regarding the use of *Lactobacillus* species as live delivery vectors, prevention, and treatment of pathogenic and metabolic diseases. *Lactobacillus* strains of probiotics have been extensively studied and have confirmed that they can absolutely improve performance as live delivery vectors, a treatment option of various diseases such as: Hemorrhagic cecal coccidiosis in young poultry, hypertension, avian flu, obesity, diabetes, Derzsy's disease or parvovirus infection, human immunodeficiency virus infections, irritable bowel syndrome, gastrointestinal disorders, Fungal infections, vaginal eubiosis, fish and shellfish species diseases. We give you an idea about that *Lactobacillus* species have been proficient in preventing and treating both disorders in animal models and some are used for clinical trials. We present the most current studies on the use of *Lactobacillus* strains that had an impact on an effective immune response to a specific antigen because a variety of antigens have been expressed. Therefore *Lactobacillus* strains can be considered as good candidates because of its potential for diseases treatment and vaccine development as heterologous protein secretion to date.

Keywords

Lactobacilli, Probiotics, Lactic Acid, Live Delivery Vectors, Treatment, Immune Responses

1. Introduction

Lactic acid bacteria (LAB) are gram-positive bacteria and nonpathogenic. They are considered to be generally regarded as safe (GRAS) organisms [1] [2] and daily ingested by humans playing significant roles as health-promoting probiotics which is the most important point, to improve general health and protect from different kinds of illness [3] [4] [5] [6]. Also they are used for production of food and feed throughout the world [7] [8] [9] [10] [11] because of their wide use in the food industry for the production and the preservation of fermented products such as whole-grain sourdough bread or sourdough fermentation [12] [13]. Daily consumption of dairy yogurt having *Lactobacillus paracasei*, and heat-treated *Lactobacillus plantarum* possibly is successful alternative to improve immune function by enhancing IFN-γ concentration and NK cell function [14]. Probiotics can also survive on non-dairy foods under ambient storage conditions [15].

Recent studies present that *Lactobacillus* species have been used as Probiotics for the prevention or treatment of a range of diseases associated with diarrhea [16] [17] [18]. *Lactobacillus plantarum* assimilates cholesterol and modulates *ABCA*1, *CD*36, *NPC*1*L*1 and *SCARB*1 *in vitro* [19], immune function [20], inflammatory bowel disease [21] [22] [23], and respiratory viral infection [24]. In addition, probiotic bacteria in the *Lactobacillus* genera are capable to have therapeutic effects in the patients of psychological disorders, such as depression, anxiety, and memory [25] [26] [27].

The move towards for controlling the immune hyper-response in today's situation for the most part appoints the natural ways which assist the body to uphold the immune homeostasis and do not cause any side effects [28], such as use of probiotics in the company of combination of a non-digestible food ingredient that promotes the growth of beneficial microorganisms in the intestines. Quite a lot of research projects have used *Lactobacillus* strains as vectors including our laboratory (Jilin Provincial Engineering Research Center of Animal Probiotics) and other probiotics research projects in the world [29]-[35]. In addition *Lactobacillus* strains are well thought-out to be competent candidates for delivery systems of heterologous proteins and for the development of novel, safe production [36].

In this review, we evaluate the new progress regarding the use of *Lactobacillus* strains as live delivery vectors. An assortment of molecular tools has been developed to professionally express therapeutic molecules and antigens at different cellular localizations. We report systems developed to use *Lactobacillus* strains as a live vaccine, treatments and the effects of such an antigen presentation mode on both systemic and mucosal immune system.

2. Methods

The review search and writing were performed from March 8th 2017 until August 25th 2017.

2.1. The Inclusion Criteria Were as Follows

- The recent year's research studies from 2015 to 2017 published in English language regarding the use of newly developed technology and analytic methods of lactic acid bacteria as live delivery vectors, treatment of diseases, and immune responses vaccines in different host species focusing on *Lactobacillus* species.
- Included Clinical studies and Experimental studies, whether used animals model, human or patient in hospital and aquaculture focusing on *Lactobacillus* species.
- When the same groups of animal model or human and the same strain of *Lactobacillus* species were reported in multiple papers, only the most recent and complete paper was selected to avoid overlap.
- Some systemic reviews when needed in the introduction and discussion.

2.2. Exclusion Criteria

- Studies that met the following criteria were excluded: If comprising only conference abstracts were excluded due to the lack of sufficient data.
- If outcomes were presented in other ways such as figures without explanations of outcomes and if not meeting the inclusion criteria described above.

2.3. Article Search Strategy

Researchers performed searches of the electronic databases of:

- Elsevier (https://www.journals.elsevier.com/the-lancet-infectious-diseases/),
- PubMed (http://www.ncbi.nlm.nih.gov/pubmed/),
- Springer, Cochrane Library, Scopus, Ovid (Medline, EMBASE, PsycINFO), Orbis, and Web of Science

Data from 2015 to 25 August, 2017.

The following key words were used: "lactic acid bacteria," "*Lactobacillus*," "probiotics," as live delivery vectors, treatment of diseases, and immune responses vaccines in different host species." We also checked the references listed at the end of each publication to identify additional studies.

2.4. Data Collection

Whichever eligible studies with regard to the health-promoting effect of *Lactobacillus* species, as probiotics for companion animals, livestock, poultry and aquaculture were collected on a modified form and examined by the second and third authors. The form included study's author(s), publication date, *Lactobacillus Strain*, probiotic dosage, and treatment or vaccination outcomes. If the study data were unclear, such as if only abstract available but full text not easy to get to or if the outcome not saying anything on how long lasting immunity induced by the recombinant *Lactobacillus* strains we attempted to contact the corresponding author to obtain further information in detail.

2.5. Effectiveness Analysis

Treatment and vaccination outcomes were the major variables used to confirm currently the efficacy of *Lactobacillus* strains as probiotics in the treatment and vaccination of difference diseases.

3. Results

In the initial search we read about 182 articles about, Lactic acid bacteria were reviewed. But, no more than 168 Studies involving *Lactobacillus* species met the selection criteria since some data were unclear, incomplete, or too old to be included in this review.

4. *Lactobacillus* Strains as Health Promoting Probiotics

Lactobacillus species are non-spore-forming Gram-positive bacteria and lactic acid producing bacteria (LAPB) that naturally inhabits the human and animal gastrointestinal and mouth organs [37] [38] [39]. Many genetic tools have been developed and many of *L.* species its complete genome were recently sequenced [20] [37] [40] [41] [42]. *Lactobacillus* species have met the criteria necessary to consider them as probiotics and they also have nutritional and therapeutic effects, regarded as probiotics because they are able to survive and thrive throughout the gastrointestinal conditions and present their beneficial effects. It is therefore important to understand their mechanisms of action in order for them to be used both prophylactic and as treatment options for different diseases [41] [42] [43]. *Lactobacillus* species are an important part of normal intestinal microbiota of various mammalian species and is also the best characterized and widely commercialized probiotic because they provide an affordable means for prevention and treatment of various infectious, allergic and inflammatory conditions as demonstrated in numerous animal and human studies [44] [45]. The *in vitro* study by [46] about comparing Antibacterial activity of *Lactobacillus plantarum* Strains (Os13 and Kor14) showed strong antimicrobial activities against a wide range of potential pathogens especially *L. monocytogenes* since were active against potential pathogens and each *Lactobacillus plantarum* strains produced broad spectrum of antimicrobial agents. However, it is known that the health-promoting properties of *Lactobacillus* strains probiotics change extensively in response to their culture conditions. This is because may results in profound variability in probiotic functionality even when the strain remains unchanged, such as the IL-10 and IL-12 modulatory activity of *L. plantarum*

OLL2712 changes according to culture conditions [22] see **Table 1**.

4.1. Management of Gastrointestinal Disorders

In probiotic aspects, *Lactobacillus* species confirmed helpful roles in the commencement of the gut mucosal immune system [47] [48]. Supplementation with specific strains of *Lactobacillus* species as probiotics has been revealed to have modulatory effects on intestinal [1] [49] [50] [51] [52]. Efficient expression systems have already been developed for controlled and targeted production of the desired antigen for exposure to the gastrointestinal mucosal immune system [53] [54] [55] as have been shown to provide beneficial health effects to the host by replenishing natural gastrointestinal flora. *In vitro* studies have shown that *Lactobacillus* species supplementation protected the pigs against ETEC K88 infection by enhancing immune responses which attenuated intestinal damage, improved the performance and nutrient digestibility of pigs [43]. Also *Lactobacillus reuteri* I5007 strain modulated intestinal host defense peptides (HDP) expression and improved the gut health of neonatal piglets [56].

The study by Olek showed that there was no statistically significant differences between the *Lactobacillus plantarum* DSM 9843 (LP299V) and placebo groups in the prevention of antibiotic-associated gastrointestinal symptoms in children and reduced the incidence of diarrhea [57]. The study about the use of fermented dairy drink containing probiotic *Lactobacillus paracasei* CNCM I-1518

Table 1. Examples of *Lactobacillus* species as bacterial vaccine vectors or treatment against different pathogens or tumor.

Vector/attenuation or complementation	Antigen/target	Animal model/ Inoculation route	Detected immune response/indicator	References
Lactobacillus plantarum	H9N2 avian influenza virus (AIV)	Mouse/Oral	IgG, sIgA, CD4+, CD8+ T cell proliferation, IgA, and IFN-γ^+	[29] [78]
	Staphylococcus aureus	Mouse/Oral	sIgA, IFN-γ/IL-4	[45] [133]
	Listeria monocytogenes	Mouse/Oral	IgG, IL-10 and IL-12	[46]
	E. coli	Mouse/Oral	SIgA, IFN-, IL-12, TNF_, and IL-6	[91]
	Parvovirus	Mouse/Oral	CD11c$^+$, CD3$^+$CD4$^+$, CD3$^+$CD8$^+$, sIgA and IgG	[34]
Lactobacillus rhamnosus	*S. aureus*, *S. typhimurium*, and *E. coli*, inflammatory damage	Mouse/Oral	proinflammatory cytokines IL-8,TNF-α, IL-12p70, IL-6 and IL-1β, CD3$^+$CD4$^+$IFN-γ^+, and CD3$^+$CD4$^+$IL-10$^+$ T cells	[45] [98] [99]
	human rhinovirus	Gnotobiotic pigs/Oral	CD4$^+$T-bet$^+$IFNγ^+ T cells	[134]
Lactobacillus johnsonii	indigestion, abdominal pain	human	Th1 cells (CD45RO$^+$CD183$^+$CD196$^-$) and cytotoxic CD8$^+$ T cells	[109] [112]
Lactobacillus reuteri	food allergy	Mouse/Oral	IgE, Th 1 and 2, IFN-c and IL-4, IFN-c, GATA3 and T-bet IL-10, TGF-b and Foxp3, IL-10-CD11c+CD103+	[123]
Lactobacillus acidophilus	*Salmonella typhimurium*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*	Mouse/Oral	IgA, IL-12, IL-8, IL-6, and IL-1,	[94]

to prevent Antibiotic-associated diarrhea showed the importance of *Lactobacillus* strains in improving health [58]. Also older hospitalized patients treated with antibiotics lead to considerable cost savings, in addition to Infants hospitalized with rotavirus disease were treated with probiotics containing both *Bifidobacterium longum* BORI and *Lactobacillus acidophilus* AD031, Symptoms such as duration of fever, frequency of diarrhea, and frequency of vomiting tended to be ameliorated by the probiotic treatment [59].

Lactobacillus johnsonii could decrease intestinal *Campylobacter jejuni* burdens as offer valuable prophylaxis and treatment of *C. jejuni* induced intestinal, pro-inflammatory immune responses *in vivo* [60] and systemic immune responses in animal models and forms the basis for animal and human studies with vaccines [49] [50] [51] [61]. The study of *in vitro* and *in vivo* antagonistic activity of new probiotic culture against *Clostridium difficile* and *Clostridium perfringens*, exhibited immunomodulatory activity and among hospitalized adults, *Lactobacillus* probiotics reduced the risk of *clostridium difficile*-associated diarrhea when taken concomitantly with antibiotics, with no evident increase in adverse events [62] [63]. Although it shown that in elderly orthogeriet-ric patients on antibiotic do not support the use of Probiotic containing *Lactobacillus casei*, *Lactobacillus bulgaricus*, and *Streptococcus thermophiles* (ACTIMEL) for reducing the incidence of *Clostridium difficile* associated diarrhoea (CDAD). Regardless of these patients being at high risk for developing CDAD, failure to reveal a significant advantage makes this infection control strategy difficult to give good reason for [64]. Some studies have revealed that they give a helpful effect by production of antimicrobial molecules and promoting secretion of immunoglobulin IgA which are capable of inhibiting some intestinal pathogens [65] [66]. Evaluation of *Lactobacillus reuteri* L26 was concluded that has an antiviral effect on PCV2 in the intestine as immune response against porcine circovirus type 2 infections in germ-free mice significantly up-regulated gene expression of chemokines, interferon (IFN)-γ, IgA and PIgR in the ileum was accompanied by higher proportion of natural killer cells and higher proportion of CD19+ lymphocytes in the MLN [67].

4.2. Prevention and Management of Hypertension

Several animal and human studies have observed the association between the oral and gut microbiome with blood pressure [68]. The study confirmed a considerable reduction in microbial richness and multiplicity in the presence of hypertension. As well studies have confirmed a changed microbial composition and modified metabolite profiles, suggesting a role for microbial dysbiosis and microbial metabolites which including use of *Lactobacillus* species for hypertension treatment [66] [69] [70]. Some studies showed the effectiveness and safety of *Lactobacillus* species on the treatment of hypertension. As were observed in hypertensive patients increased myeloid inflammatory cells CD14+ cells, CD11b+ cells and Th17 cells, increased in CD4+ IL17+ cells. An increase in the Th17 cells was tremendously appropriate finding because demonstrated that levels of these cells were regulated by gut-intrinsic mechanisms that generate pro-inflammatory cytokines for instance TGF-β1, TNF-α, IL-1β and IL-6 [71] [72] [73].

Oral administration of recombinant *Lactobacillus plantarum* NC8 considerably decreased systolic blood pressure, increased level of nitric oxide, as well as decreased levels of endothelin and AngII in plasma, heart, and kidney, representing the potential application of recombinant *Lactobacillus plantarum* in the treatment of hypertension [69]. In additional; an oral, genetically-modified strain of the probiotic *Lactobacillus* was used to treat rats with high blood pressure in the lungs, which resulted in improved heart contractility, reduced blood pressure, and reduced heart wall thickness. Also researchers genetically engineered strains of *Lactobacillus* species, to express and secrete Ang-(1-7), tested in an animal study and was effectively treat pulmonary hypertension [69]. Fermented whey from bovine milk with several *Lactobacillus* species to free antihypertensive peptides from whey, and found that *Lactobacillus helvelticus* fermented whey hydrolysates contained peptides which showed strong angiotensin 1-converting enzyme inhibition. These peptides, at least in part, contributed to the ACE inhibitor effect of the fermentate. Whey fermented with *Lactobacillus brevis* also contained a potent ACE inhibitor peptide [74].

4.3. Prevention and Management of Respiratory Tract Disorders

The studies in the infant mice and immunocompromised-malnourished mice showed the improvement of the resistance to primary respiratory syncytial virus (RSV) infection, and secondary pneumococcal pneumonia. In relationship with the protection against RSV-pneumococcal superinfection, the study revealed that peptidoglycan from *Lactobacillus rhamnosus* CRL1505. Considerably enhanced lung $CD3^+CD4^+IFN\text{-}\gamma^+$, and $CD3^+CD4^+IL\text{-}10^+$ T cells plus $CD11c^+SiglecF^+IFN\text{-}\beta^+$ alveolar macrophages with the resulting of increases of IFN-γ, IL-10, and IFN-β in the respiratory tract [75] [76]. Nasal administration of *Lactobacillus rhamnosus* CRL1505 strain to malnourished mice under recovery reduced quantitative and qualitative alterations of $CD4^+$ T cells in the bone marrow, thymus, spleen and lung as well, CRL1505 treatment increased Th_2-cytokines; interleukin 10 and 4 in respiratory and systemic compartments [77]. The study of immunization with recombinant *Lactobacillus plantarum* expressing 3M2e-Fc demonstrated the markedly reduction of the viral load in the lung and protected against H1N1 influenza virus. As well as mouse-adapted H9N2 avian influenza virus (AIV) challenge in BALB/c mice, also provided effective protective immunity against infection with homologous and heterologous influenza viruses in a mouse mode and were seem to lower respiratory tract infections [29] [78] also see **Table 1**. The study of the effect of a probiotic supplement on the incidence of upper respiratory tract infections [61], and the metabolism of aromatic amino acids after exhaustive aerobic exercise in trained athletes daily supplementation with probiotics was found to be associated with a lower frequency of URTIs in athletes and seems to be beneficial in increasing training efficacy [79]. Respiratory viral infection via metabolic reprogramming and immune cell modulation *by Lactobacillus johnsonii* [24], *Avian Infuenza* infection [34] [80] [81]. In additional *Lactobacillus plantarum* GBLP2 isolated from Korean fermented vegetable exhibited preventive effect against the influenza virus infections in mice [82].

4.4. Management of Chronic Constipation

Differentiations in the composition of the intestinal microbiota have been confirmed when constipated patients and healthy controls have been evaluated in different studies and have shown that *Lactobacillus* may play an essential role in the pathogenesis of chronic constipation [83]. *Lactobacillus* species as probiotics could reduce the migrating myoelectric complex (MMC) period and speed up small intestinal transit. Especially some of a good number studied strains such as *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, showed a significant role of reducing the level of intraluminal pH and promoting colonic peristalsis which is supportive for changing stool that could significantly increase the frequency of defecations and the softness of the stool [84] [85] [86]. The assessment of the effectiveness of *Lactobacillus casei rhamnosus* Lcr35 (Lcr35) in the management of functional constipation in children showed a significant increase in the frequency of defecation in both the placebo group and in the *Lactobacillus casei rhamnosus* Lcr35 group [87].

4.5. Prevention and Management of Hypercholesterolaemia

Recent studies have shown the potential use of *lactobacillus* species as part of the strategies in prevention and management of hypercholesterolaemia. Eating yogurt or taking capsules containing the *Lactobacillus* strain for example *Lactobacillus reuteri* NCIMB 30242 give the impression to decrease low-density lipoprotein cholesterol in adults with high cholesterol. Furthermore treatment of HT29 cells with *Lactobacillus plantaram* after prolonged exposure to cholesterol source it was demonstrated that was associated with up-regulation of *ABCA*1, restoration of *CD*36 to basal level and down-regulation of Neimann-Pick C1-Like 1 (*NPC*1*L*1). Also *Lactobacillus fermentum* NCIMB 5221 and *Lactobacillus fermentum* NCIMB 2797 have the potential via various modes of action to lower cholesterol [88] [89] [90].

4.6. Enhancement of Anti-Inflammatory Response

Lactobacillus plantarum L9 and *Lactobacillus acidophilus* LA were shown to some studies that have significant inhibition of *E. coli* adhesion and cell internalization to the enterocyte monolayer surface as shown in **Table 1**. Such as the study by [91] made known that *Lactobacillus plantarum* L9 and *Lactobacillus acidophilus* LA have good ability to adhere to Caco-2 cells. As well treatment with mixed lactic acid bacteria increased the anti-inflammatory factor and the secretion of sIgA in the intestine of mice infected with *Staphylococcus aureus* inhibited the inflammation [45] [92] [93] [94] [95]). *Lactobacillus fermentum* HY01 strain in some studies showed that had significant preventive effects in dextran sulfate sodium induced-colitis; at the same time, it can efficiently reduce edema, inflammatory cells infiltration, and colon mucosa injury. In addition to play a significant function in the down-regulation of concentrations of pro-inflammatory factors (IFN-, IL-12, TNF_, and IL-6) in particular shows a hopeful prevention for I_B_ degradation, decreases the protein levels of iNOS and COX-2 along with inhibition of NF-_B p65 phosphorylation cascades [17] [96] [97]. The outcome from some studies obtained from *Lactobacillus rhamnosus GG*, *Lactobacillus rhamnosus KLSD*, *Lactobacillus helveticus* IMAU70129, and *Lactobacillus casei* IMAU60214 demonstrated that strains induced early proinflammatory cytokines for example IL-8,TNF-α, IL-12p70, IL-6 and IL-1β. Phagocytosis and bactericidal activity of macrophages against various pathogens, such as *S. aureus*, *S. typhimurium*, *and E. coli*, were increased by pretreatment with *Lactobacillus* [45] [98] [99].

4.7. Management of Lactose and Glucose Intolerance

Population for whom lactose acts like an osmotic, non-digestible carbohydrate for the reason that they have a low amount of intestinal lactase; Lactose intolerance is a problem for a large part of the world. The predigestion of lactose could decrease the symptoms related with lactose intolerance in vulnerable persons. For the duration of fermentation of milk and yogurt having *Lactobacillus acidophilus*, generate lactase that hydrolyses lactose to galactose and glucose. *Lactobacillus* species probiotics have been revealed to improve lactose digestion and intolerance in some studies [100]. Glucose intolerance was to some extent prevented by supplementation of *Lactobacillus kefiri* treatment changed Bacteroidetes and Firmicutes profiles. It was demonstrated that the administration of *Lactobacillus kefiri* prevents the deleterious effects of fructose-rich diet intake, therefore improved metabolic disorders [101].

4.8. Prevention and Management of Cancer

Lactobacilli Strains play significant function in cancer etiology for the reason that they can manipulate several elements of the intestinal tract such as development, immune homeostasis, physiology and metabolism. Laboratory-based studies have demonstrated that *Lactobacilli* Strains contains strong anti-tumor effects [102]. Many studies of anti-tumor vaccines of *Lactobacillus* species using mouse models have been employed. *Lactobacillus* biotherapeutic for colorectal cancer (CRC), inhibited cancer-causing events, based on anti-CRC proliferative effect, immune modulation and metabolic activity, *in vitro* and *in vivo*, using a genetically-induced animal CRC model [103]. The study of inhibitory effects of probiotic *Lactobacillus* on the Growth of Human Colonic Carcinoma Cell Line

HT-29 showed that *Lactobacillus* can inhibit the growth of colonic carcinoma cells and may lead to apoptosis. Live *Lactobacillus acidophilus* and *Lactobacillus rhamnosus* GG, *Lactobacillus casei*, *Lactobacillus reuteri* has been confirmed to induce apoptotic cell death in both murine and human colon carcinoma cell lines as well as an experimental tumor model [104] [105] [106] [107] [108].

4.9. Management of Diabetes and Obesity

Current review study revealed that construction of a recombinant strain of *Lactobacillus gasseri*, *Lactobacillus paracasei* elicits various health benefits through its antimicrobial activity, bacteriocin production, and immunomodulation of the innate and adaptive systems therefore had significantly reduced blood glucose levels and increased insulin levels [109] [110] [111]. Also *Lactobacillus* species such as: *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus bulgaricus* have been known to improve obesity-associated metabolic problems. Researchers said this may be attributed to interactions with obesity-promoting bacteria in the gut and direct modulation of host immunity and gut barrier function. Administration of *Lactobacillus johnsonii* N6.2 considerably decreases the happening of indigestion, abdominal pain, and cephalic syndromes were observed. Additionally, some studies demonstrated that monocytes and natural killer cell numbers were increased significantly and an increase of circulating effector Th1 cells ($CD45RO^+CD183^+CD196^-$) and cytotoxic $CD8^+$ T cells subset was observed in the *Lactobacillus johnsonii* N6.2 group [109] [112].

4.10. Management of Irritable Bowel Syndrome

The thoroughly assessment and a meta-analysis studies of the effect of *Lactobacillus* in treating the irritable bowel syndrome was found to be more effective with a significantly higher rate without any side effects. The researchers noted that abdominal distension was significantly reduced by probiotics containing, *Lactobacillus casei*, or *Lactobacillus plantarum and* flatulence, pain and bloating caused by IBS were significantly reduced *by Lactobacillus acidophilus*, have concluded that some *Lactobacillus* are beneficial in improving symptoms and reducing the risk of persistent symptoms in some patients with Irritable bowel syndrome, even though the overall effect is modest [113] [114] [115].

4.11. Prevention and Management of Fungus

Lactobacillus acidophilus DDS-1, *Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus salivarius*, *Lactobacillus rhamnosus*, and *Lactobacillus brevis* are acknowledged to inhibit the growth of *Candida albicans* by enhancing the immune system, reduce the candida overgrowth and by taking repeatedly prevents the reappearance of yeast infections in future [58].

4.12. Prevention and Management of Vaginal Infections

Lactobacillus species are thought to be a valuable biomarker and agents that can promote various aspects of vaginal health such as *Lactobacillus crispatus*, *Lactobacillus jensenii*, *Lactobacillus iners* and *Lactobacillus gasseri* [116] [117] [118]. Many types of pathogens for vaginal infections such as; candidal vaginitis, vaginal eubiosis prevention by killing dysbiotic microbes with acidic lactic acid is one of the claims often made specifically for *lactobacillus* strains probiotics, formulated with multiple or single strains. Such as (*Lactobacillus plantarum*, *Lactobacillus fermentum*, *Lactobacillus rhamnosus* GR-1, *Lactobacillus reuteri* RC-14, *Lactobacillus acidophilus*, *L. brevis*, *L. gasseri*, *L. crispatus*,) such as establishment of vaginal eubiosis by killing dysbiotic microbes, and many types of pathogens, with acidic lactic acid, have been evaluated in several randomized clinical trials that it can prevent vaginal infections, alone or as adjuncts to antibiotic therapy, and for the prevention of bacterial vaginosis [119] [120] [121] [122].

4.13. Prevention and Management of Nematodes

One study assessed some aspect of the currently characterization of *Lactobacillus* strains belonging to *Lactobacillus delbrueckii* sub species *bulgaricus* and *lactis* demonstrated that *L. delbrueckii* subsp. *bulgaricus* in diet exerted advantageous effects on nematodes, both *L. delbrueckii* subsp. *lactis* strains affected lifespan and larval development of nematodes, galactose metabolic capabilities and *L. delbrueckii* subspecies *bulgaricus* strain confirmed promising probiotic features [52]. Treatment with *Lactobacillus rhamnosus* JB-1 strain significantly enhanced worm expulsion in resistant C57BL/6 mice, and this was associated with increases in goblet cell numbers, IL-10 levels, and epithelial cell proliferation [52].

4.14. Prevention and Management of Allergy

One study assessed some aspect of the consequence of *Lactobacillus reuteri* in opposition to food allergy was examined in ovalbumin (OVA)-sensitized BALB/c mice study. It was demonstrated that *Lactobacillus reuteri* possesses anti-allergic activities by means of promoting tolerogenic immune responses, modulating enteric flora, as a result worsen profile of enteric flora, and attenuated allergic diarrhea was re-established by *Lactobacillus reuteri* also supplementing infant with *Lactobacillus rhamnosus* GG offered as management of cow milk allergy [123].

5. *Lactobacillus* species as Recombinant Strain, Elicit Specific Mucosal and Systemic Immune Responses

Recombinant probiotics can act as a vaccine arming the host immune system to deal with pathogens. To develop a safe, effective, and convenient vaccine for the prevention of pathogenic, and metabolic problem require to construct recombinant lactic acid bacteria such as *lactobacillus* strains that can express the foreign virus protein, bacteria or cell antigen hence trigger the mucosal and systemic immune responses. Many experimental and clinical studies of *Lactobacillus* strains as probiotic have reported that had an impact on an effective immune response to a specific antigen because a variety of antigens have been expressed in *Lactobacillus* strains, summarized in **Table 1**.

Recombinant *Lactobacillus* strains are known to elicit specific mucosal and systemic immune responses against antigens recent studies demonstrated that lactic acid is a major antimicrobial factor produced by *Lactobacillus* species such as: Recombinant *Lactobacillus plantaram* studies The study by [124] about assessment of recombinant *Lactobacillus plantarum* expressing SO7 of *Eimeria tenella* fusion DC-targeting peptide were significantly reduce pathological damage in cecum in broiler chickens, that means could become a hopeful oral vaccine candidate against *E. tenella* infection. [22] [35] [125] [126].

The study of Immunogenicity in mice showed higher numbers of $CD11c^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, and interferon gamma- and tumor necrosis factor alpha-expressing spleen lymphocytes in mice immunize with recombinant *Lactobacillus Plantarum* NC8 Expressing Goose Parvovirus VP2 Gene than those in the control groups [32]. A recombinant *Lactobacillus plantarum* NC8 strain expressing NP-M1-DCpep from H9N2 AIV has been studied in a mouse model and exhibited significantly increased T cell-mediated immune responses and mucosal sIgA and IgG levels, which provided protection against H9N2 AIV challenge, in additional intranasal administration induced stronger immune responses and provided effective protection against challenge with the H9N2 virus and *L. plantarum* vaccine vector expressing hemagglutinin provided protection against H9N2 challenge infection [34].

Recombinant *L. plantarum* expressing 3M2e-Fc elicited Peyer's patch (PP) DC activation, improved the number of gamma interferon (IFN-γ)-producing T cells and increased the frequency of $CD8^+$IFN-γ^+ cells in the mesenteric lymph nodes and enhanced specific sIgA secretion [34].

Recombinant *Lactobacillus plantarum* with surface displayed hemagglutinin subunit 2 (HA2) alone or together with heat-labile toxin B subunit (LTB) from enterotoxigenic *Escherichia coli* in Balb/c mice increased the percentages of $B220^+$ IgA^+ B cells in peyer patch, in consistent with elevated production of mucosal SIgA antibody determined by ELISA [31]. Other *Lactobacillus* species that have been studied for recombinant are: Recombinant *Lactobacillus plantarum* ULAG11 strain was transformed with pLuc2 in millet seed [127], Recombinant *Lactobacillus rhamnosus* and *Lactobacillus fermentum* [128] [129].

Administration of recombinant *Lactobacillus casei* expressing F4 (K88) fimbrial adhesin FaeG in conjunction with a heat-labile enterotoxin A (LTAK63) and heat-labile enterotoxin B (LTB) of enterotoxigenic *Escherichia coli* as an oral adjuvant in mice showed significantly higher levels of FaeG-specific serum IgG and mucosal sIgA, as well as the proliferation of lymphocytes [130] [131] [132].

6. *Lactobacillus* species as Mucosal Delivery Vectors for DNA Vaccines and Therapeutic Proteins

The approach of using live bacterial cells as means of transportations to deliver recombinant antigens has appeared in excess of the past two decades as an interesting option for the improvement of new vaccines. *Lactobacillus* species are known to influence the immune response in a strain-dependent manner; therefore, they are good candidates for developing innovative oral vectors, comprising good options to reduce the strength of pathogens, meant for mucosal delivery approaches [124] [130]. Lately, ever-increasing confirmation supported that *Lactobacillus* strains expression systems, through expression and delivery of antigens/adjuvant, are hopeful oral vaccine vectors, due to their: efficient delivery of immunogens to the mucosal inductive locations, exceptional safety, reduced antigen degradation and prevention of protein purification.

On the use of *Lactobacillus* species as mucosal delivery vectors for therapeutic proteins and DNA vaccines such as expression signals and host strains, for the heterologous expression of therapeutic proteins such as antigens, cytokines and enzymes [135] [136]. Resulting recombinant *Lactobacillus* strains have been tested successfully for their prophylactic and therapeutic effects in different animal models: especially, anti-oxidative *Lactobacillus casei*, *Lactobacillus plantaram* and *Lactobacillus reuteri* strains were constructed and tested in different study models as delivery vehicles for presentation to the mucosa of compounds with pharmaceutical attention, mainly vaccines [35] [124] [130] [137]. The viability of shuttle vector for heterologous protein expression in *Lactobacillus casei* TISTR1341 was determined that is able to modulate the host response through cloning in pRCEID-LC7.6, the gene encoding the nucleocapsid protein (NP), from the influenza A virus under the control of the homologous promoter from the lactate dehydrogenase gene. *Lactobacillus casei* strains carrying this recombinant plasmid was made known to productively express the NP protein [135]. The study by Lin *et al* showed that, recombinant *Lactobacillus acidophilus* (LA-ET) was safe in a cell model and excluded EHEC O157:H7 from LoVo cells at rates of nearly 94 in exclusion and 60% in competition assays. *Lactobacillus acidophilus* induced higher levels of specific mucosal and systemic antibody responses and improved interferon-γ and interleukin-4 and -10 productions, which was coupled with assorted helper T (Th1/Th2) cell responses, and protected against EHEC O157:H7 colonization and infection in mice [136].

This review gave you knowledge to understand the immune system and recent developments in cloning and expression techniques as demonstrating and support the concern of using *Lactobacillus* strains, to develop novel therapeutic protein mucosal delivery vectors which should be tested now in human clinical trials.

7. Safety Concerns of *Lactobacillus* Strains

Our study was confirmed that there were no significant adverse events have been demonstrated in the experimental, clinical studies and other controlled trials of *Lactobacillus* species strains because are not expected to degrade host tissue components for example *Lactobacillus rhamnosus* GG; it has been administered to children with chronic inflammatory disease, to adults with inflammatory bowel disease, and to patients with HIV. The administration of *Lactobacillus johnsonii* N6.2 did not modify the Comprehensive metabolic panel (CMP) or complete blood count (CBC) of participants this also important common safety [112]. Combinations of *Lactobacillus rhamnosus* or *Lactobacillus paracasei* with *Bifidobacterium longum* has been used safely from 2 months before delivery until the breastfed infant was 2 months and study of *Lactobacillus Fermentum* CECT5716 as prevention of mastitis in breastfeeding women [138] [139]. It is safe when taken by mouth appropriately many studies were orally administered; *Lactobacillus* is also likely safe for women to use inside the vagina [122]. To prevent the reproduction of *Lactobacillus* species in the environment recombinant plasmids and chromosomally-modified bacterial strains can be controlled by the use of auxotrophic mutants. *Lactobacillus* has rarely caused disease in people with weakened immune systems and side effects are usually mild and mainly frequently include intestinal gas.

For these reasons, *Lactobacillus* species has been proven safe both invitro and invivo and are considered as suitable mucosal delivery vectors for heterologous antigens and can be used in clinical trials.

8. Discussion

Lactobacillus strains as probiotic activate the mucosal immune system through the stimulation of gut antigen presenting cells to promote protection. Different probiotic strains of *Lactobacillus* genera acquire significant and widely acknowledged immunomodulatory properties and health-promoting [35] [140]. The approaches leading to the efficient targetness engages the natural ways which do not cause any side effects and assist the body to uphold the immune homeostasis such as the use of probiotics are the ways forward. Different studies have looked into the prospective mechanisms of action by which *Lactobacillus* strains as probiotics might play a role as primary immune response against pathogens.

More recent studies developed a recombinant *Lactobacillus* strains harbouring proteins or antigens in order to control infections [30] [32] [34] [35] [40] [125] [126]. *Lactobacillus* species based vaccines can regulate immunostimulatory responses and make active antigen presenting cells (APCs), such as macrophages T cells, dendritic cells (DCs) and epithelial cells. DCs are seen as professional APCs that elicit a primary immune response against pathogens challenge [80]. However, several current studies have point out that immunostimulatory function showed tissue-specific differences among DCs in terms of inducing T helper (Th) cell responses [35] [130] [131] [132] and recommended that *Lactobacillus* species are actively concerned in the improvement of adaptive immune responses by programming many aspects of CD4+ T cell differentiation [80]. In additional many *Lactobacillus* species are microbe-associated molecular pattern (MAMPs) is capable of interacting with epithelial pattern recognition receptors, mainly the Toll-like receptor-2 (TLR2), TLR6 and nod-like receptors which leads to an up-regulation of signaling pathways to modulate the host's immune response [141] [142].

In recent years, studies using newly developed technology and analytic methods suggests that *Lactobacillus* species may enhance host defenses and improve vaccine response as a result of the influence of bacteria on host immunity and intestinal integrity against enteric parasites and that *Lactobacillus* strains as probiotics have been extensively studied as a treatment option of various diseases such as: Viral infections in animals and humans, probiotics modulate mucosal immunity, reduced rotavirus binding and infection, and produced antimicrobial peptides with anti-viral activity against rotavirus [33] [143] [144], cancer [106] [145] [146], Haemorrhagic cecal Coccidiosis [124], Hypertension [69], obesity [147], diabetes [148], human immunodeficiency virus infection [20], Irritable bowel syndrome [44], fish and shellfish species diseases [149], Fungal infections [150], vaginal health [151].

The administration of microbial metabolites for the prevention and treatment of aberrant immune response is also gaining importance [106] [152]. The market size of probiotics has to the highest degree increased consumer anxiety concerning health-promoting effect of nutraceuticals [38] [140] [153].

Researchers have discovered more specific functions of *Lactobacillus* species in mediating host immunity and immunologic diseases, such as have been revealed to directly down regulate T effector-mediated inflammatory responses as upregulating anti-inflammatory T regulatory cell expression in mice [45] [93]. Similarly Wang and colleagues found that, pretreatment with *Lactobacillus plantarum* L9 to prevent tumour necrosis factor (TNF-α) induced transcellular bacterial translocation and IL-8 production in Caco-2 cells, the researcher demonstrated that it showed the potential to protect enterocytes from an acute inflammatory response and concluded as good potential prophylactic agents in counteracting bacterial translocation, as well in the mixed *Lactobacillus plantarum* group IFN-/IL-4 decreased significantly from infection to convalescence but there was significantly higher secretion of sIgA in the intestine of mice [91].

Wen and colleagues' 2015 study of *Lactobacillus GG* (LGG) when supplemented in gnotobiotic pigs, with an oral attenuated human rhinovirus(HRV) vaccine found significant strong adjuvant effect and increased mucosal populations of HRV-specific IFN-gamma producing T lymphocytes and oral administration of LGG attenuates an *S. Infantis*-induced increase in the level of serum IL-22, excessive Th1 immune responses and induces the expansion of $CD4^{+}$T-bet^{+}IFNγ^{+} T cells in peripheral blood, which helps in the eradication of intracellular pathogens [134].

The current studies by Rocha-Ramirez and colleagues' 2017 and 2016 found that nuclear translocation NF-κB pp65 and TLR2-dependent signaling were increased by treatment with the *Lactobacillus* species (*L. rhamnosus GG*, L. *rhamnosus KLSD*, *L. helveticus* IMAU70129, and *L. casei* IMAU60214). This demonstrates that probiotic strains of *Lactobacillus* exert early immunostimulatory effects that may be directly linked to the initial inflammation of the response of human macrophages [98] [154]. *Lactobacillus* species such as *Lactobacillus plantarum*, and *Lactobacillu scasei* have been shown to increase the expression of proteins involved in tight junction barrier function which induces several protective mechanisms that restore tissue damage, such as modulation of the stability of tight junctions of the gastrointestinal lining because when become compromised and permeability increases, it allows toxins and other forms of waste to leak into the bloodstream then endotoxins trigger immune activation through Toll-like receptor 4 (TLR4) [94] [155].

Live *Lactobacillus rhamnosus GG* and UV-inactivated showed that are equally effective in decreasing IL-8 in the intestinal epithelium [98]. Live and heat-killed *Lactobacillus rhamnosus GG* confirmed that are competent to exert comparable effects on the secretion of pro- and anti-inflammatory cytokines and chemokines when included in the diet of infant rats and have reported that these bacteria had an impact on the phagocytic activity of macrophages against extracellular pathogens such as *Lactobacillus acidophilus* ADDIN EN.CITE [156].

Recently, Albarracin, Clua, Kolling, Zelayaand colleagues took a different approach studies about *Lactobacillus rhamnosus* and found that induces cytokines which are involved in the immunomodulatory protective effect of HK1505 and PG1505 in the respiratory superinfection: IL-10, IFN-β, and IFN-γ, pointed out that IL-10 involved in the protection against inflammatory damage, while IFN-γ participated in the reduction of pneumococcal growth in the lungs. As well *L. rhamnosus* CRL1505 improved the numbers of $CD3^{+}CD4^{+}IFN\text{-}\gamma^{+}$, and $CD3^{+}CD4^{+}IL\text{-}10^{+}$ T cells in the lungs of infant mice and IFN-β involved in the protection against lung tissue injury [75] [157] [158] [159].

Studies by Ren, wan, Kemgang, Jung and colleagues found that *Lactobacillus* strains induces Th1 mediates cellular immunity and secretion of IFN-γ cytokines, a Th2 response to humoral immunity, and IL-4 secretion which are able to capture intracellular bacteria, viruses, and cancer. *Lactobacillus* strains increase Th1 type IFN-γ cytokine secretion in spleen cells of mice infected with *S. aureus* while reducing the secretion of Th2 type IL-4 cytokines, also revealed that, serum IFN-γ levels were higher in the mice infected with *Lactobacillus* strains compared to mice infected with the control. Some studies have shown that IL-4 is the key to the survival and proliferation of T cells, as IL-4 promotes the production of Th2 cells and excessive IL-4 inhibits the production of IFN-γ. The level of sIgA which inhibits allergenic and pathogenic microorganisms in the intestinal contents of mice treated with *Lactobacillus* strains were significantly higher [45] [160] [161] [162].

Lactobacillus strains have reported to activate Toll-like receptors (TLR) signaling which induces an increase in the production of proinflammatory cytokines for instance TNF-α, IL-12, and IL-8 which damage the host beyond the defense against invading pathogens, also increases in the secretion of anti-inflammatory cytokines such as IL-10.*Lactobacillus* strains probiotics and several TLR antagonists have revealed constructive results in the treatment of obesity and other related diseases including diabetes mellitus. [57] [64] [163].

It was also shown that mixed *Lactobacillus plantarum* used as inhibition of *Staphylococcus aureus* by crude and fractionated extract from lactic acid bacteria IFN-γ/IL-4 ratio decreased appreciably from infection to recovery. The secretion of sIgA in the intestine of mice was significantly higher in the mixed *Lactobacillus plantarum* group than in the single lactic acid bacteria group. Treatment with mixed *Lactobacillus* strains increased the anti-inflammatory factor and the secretion of sIgA in the intestine of mice infected with *Staphylococcus aureus* and inhibited inflammation [45] [133]. Evaluation of *Lactobacillus coryniformis* CECT5711 strain as a coadjuvant in a vaccination process [16].

Lactobacillus rhamnosus JB-1 strain modulates goblet cell biology and endorses parasite removal via an IL-10-mediated pathway and gives narrative approaching into probiotic effects on innate defense in nematode infection [52]. It was suggested that *Lactobacillus reuteri* as a functional probiotic against food allergy in allergic mice there were production of serum IgE, activation of mast cell, signature T helper (Th) 1 and 2 cytokines; IFN-c and IL-4. Further it was made known that the intestinal expression of IL-4, IFN-c, GATA3 and T-bet was down-regulated, improved the expression of IL-10, TGF-b and Foxp3, and the number of IL-10-secreting CD11c+CD103+ mesenteric lymph node (MLN) cells and heat killed *Lactobacillus reuteri* attenuated OVA-induced cell proliferation and IL-2 secretion by MLN cells [123]. Also *Lactobacillus* strains can improve health in the course of many mechanisms/means, to protect the host against potentially pathogenic species that populate the GIT of animals and humans. *Lactobacilli* strains, such as *Lactobacillus acidophilus* LA1, are able to prevent the colonization of the intestine by pathogenic bacteria, such as *Salmonella typhimurium*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, by antagonistic elimination. *Lactobacillus* strains may protect the host from pathogen invasion by increasing the intestinal epithelial barrier. Some LAB microbe-associated molecular patterns (MAMPs) are able of working together with the Toll-like receptor-2 (TLR2), TLR6 and nod-like receptors [94]. Moreover *Lactobacillus salivarius* JTB07 and *Lactobacillus reuteri* JTB07 have been reported to upregulate the expression of IL-12, IL-8, IL-6, and IL-1, while *Lactobacillus acidophilus* JTB05 to upregulate the interferon-gamma expression level of their host cells [45] [159] [164]. *Lactobacillus salivarius* UCC 118 and *Lactobacillus johnsonii* LJ-1 were reported to enhance the IgA response and phagocytic activity in head-kidney leucocytes [165].

Many of published research reports have indicated the significance of producing interferon-gamma (IFN-γ), interleukin as well as IgA for treatment of diseases because were repeatedly observed. Development of immunity by *Lactobacillus* strains could associated with lymphoid tissues that regulate the immune response of their hosts for example *Lactobacillus helveticus* R389, *Lactobacillus rhamnosus* HN001 and *Lactobacillus acidophilus* HN017 [97] [166] [167] [168] have been reported to have the ability to improve the immune system of their host. The mechanism of this improvement is thought to be caused by the consequence of the *Lactobacillus* strains because of the: total serum protein, globulin, interferon-gamma, prostaglandin E production, albumin, tumor necrosis factor, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-6 (IL-6), and lymphocytes proliferation.

9. Conclusion and Recommendation

This review has tried to study experimental and clinical studies that are providing a clear understanding of the beneficial *Lactobacillus* strains which have been applied from the year 2015 to 2017. Collectively, the review results support *Lactobacillus* species as probiotics because various *Lactobacillus* strains have proved to be effective and powerful tools for use in human and animal health as antimicrobial against a wide range of potential pathogens and management of metabolic disorders, Vectors expression systems, and immunization strategies have gradually increased the potential use of *Lactobacillus* strains. For this reason, *Lactobacillus* species are considered as a potential replacement of traditional, frequently pathogenic, attenuated microbial transporters. A favorable point of using *Lactobacillus* strains probiotics is the ability to use the mucosal administration, particularly via the universal oral route, which presents several advantages: simplifies vaccine administration, promotes a special type of local immunity and is attractive from the immunological and practical approach, especially for mass vaccination programs in contrast to systemic inoculation. This review sum up and sort out the available information on the application of *Lactobacillus* species as live oral vaccine vectors for induction of immune responses and treatment of pathogenic and metabolic diseases. It constitutes an important source of general information for researchers interested in mucosal vaccine development and constructing *Lactobacillus* strains with vaccine potential. About the safety of *Lactobacillus* strains, the combining of the high immunogenicity vectors with low risk is a proper level of safety, efficacy and providing proper biological control of the recombinant microorganism. Therefore *Lactobacillus* strains can be considered as good candidates for diseases treatment and vaccine development as heterologous protein secretion to date.

Acknowledgements

The financial support by Chinese Government through a grant from the Chinese Government (CSC) (Grant number 201508330278) is highly acknowledged**.** Also we are thankful to the Jilin Agricultural University for the internet to download Data for this review.

Funding

This study was funded by Chinese Government (CSC) Grant number 201508330278.

Availability of Data and Materials

Not applicable.

Conflict of Interest

Author1 declares that she has no conflict of interest.
Author 2 declares that he has no conflict of interest.
Author 3 declares that she has no conflict of interest.
Author 4 declares that she has no conflict of interest.
Author 5 declares that she has no conflict of interest.

Consent for Publication

Not applicable.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors."

Authors' Contributions

Author 1 searching data and writing first draft.
Author 2 writing second draft.
Author 3 references writing.
Author 4 and Author 5 Supervisions and editing last draft of the manuscript.
"All authors read and approved the final version of the manuscript".

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