REVIEW ARTICLE

Immunomodulation in Lactic Acid Bacteria: Exploring Prospects for Adjunct Functional Food Therapy

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ABSTRACT
Probiotics have been extensively studied for their health benefits in humans and animals. A number of lactic acid bacteria (LAB) are classified as probiotics, and several studies showed their immunomodulatory effects in animal models and clinical trials. LAB are also involved in the gut microbiome cross talks by inhibiting pathogenic bacteria that induce inflammatory responses. Since an impaired gut microbial community has consequences in different organs such as the skin, brain, lungs, liver, and heart, immune responses in the gut have been associated with organ disorders. In this review paper, we discuss the beneficial effects of several LAB strains in human and animal immunity and related diseases. In addition, we explored the potential of local LAB strains and traditional functional foods in addressing human health.

Keywords: *lactic acid bacteria, immunomodulation, functional food, gut cross talk*

Introduction

Probiotics, defined by the World Health Organization as "live microorganisms, which when administered in adequate amounts, confer a health benefit on the host", are becoming popular as natural products that contribute to human health [1]. Probiotic microorganisms are generally part of the lactic acid bacteria (LAB), which are common commensals of the human gastrointestinal tract, and are important biological agents to food quality and safety [2]. Among LAB, the genera *Lactobacillus*, *Lactococcus*, *Pediococcus*, and *Streptococcus* are the most studied and utilized. Probiotics have been studied extensively for the maintenance of the gut microbiome by inhibiting pathogenic bacteria, improvement of intestinal health, and immunomodulation, which could lead to reduction of risks to certain diseases [3]. Several LAB strains affect the gut cross talk with other organs by modulating immunological parameters and intestinal permeability [4]. Thus, supplementation with probiotics promotes good health and well-being, reduces the risks and alleviates certain symptoms of various diseases [3,5,6].

Several LAB strains enhance both innate and adaptive immune response by inducing the maturation of and modulating the immunological functions of dendritic cells (DCs) [4,7]. The review paper by Tsai *et al*. [4] clearly discusses the role of LAB in the innate and mucosal immunity, highlighting the different immunomodulatory effects of different LAB strains in certain diseases. Although probiotics commonly promote good health, previous studies have shown that some LAB strains did not exert any therapeutic effects in atopic dermatitis [8,9]. Some strains caused bacteremia and complications in metabolic disorders [10,11]. These results show that the immunomodulatory and therapeutic effects of LAB are strain-specific.

Interestingly, several LAB strains isolated from functional foods showed potential in modulating the immune responses in healthy humans and in certain disorders, including obesity, inflammation, and allergies [13,14]. In the Philippines, local probiotic strains that showed promising benefits are usually isolated from traditional fermented foods [15-18]. These fermented foods vary among ethnic groups, and their diverse distribution in the archipelago provide more possibilities of discovering novel probiotics of importance. Medicinal and edible Philippine plants are also sources of local probiotic strains that exhibit industrial relevance and product development advantage [19]. The current probiotic research in the Philippines is geared towards the development of LAB-based functional foods [20]. However, there is a need to further explore the local LAB strains and their immunomodulatory properties. Moreover, the potential of local probiotic strains as starter cultures for new functional foods should be addressed.

In this review paper, we discussed the recent advancements in the immunomodulatory roles of LAB strains in certain diseases in human trials and animal models following the review paper of Tsai *et al.* [4]. Moreover, we explored the potential of local LAB strains and functional foods as adjunct therapy in addressing human health.

Immunomodulation: Microbiome Cross-Talks

The intestinal barrier serves as the first line of defense against pathogens and antigens in the gut that stimulate inflammatory responses (IR). The importance of the gut microbiota in maintaining the normal mucosal immune system has been highlighted in several studies [21-23]. The gut microbiota controls the development and functionality of gut-associated lymphoid tissues (GALT) and the activation of the innate immune system [24]. Therefore, a dysfunctional intestinal microbiota increases the intestinal permeability. With an impaired intestinal barrier, bacterial translocation and products trigger a hyperactive IR. Several organ disorders have been associated with gut inflammation, and inflammatory markers have been identified for every disease. In general, LAB modulates the intestinal immune system by stimulating cytokine responses, improving B cell functions, and inhibiting IRs, then further improving the gut cross talk with other organs (Figure 1A).

The following sections describe the recent immunomodulatory effects and specific influence of LAB in human studies. Exploring the roles of LAB in addressing certain disorders will open the potential of LAB immunomodulation research in the Philippines. Table 1 summarizes the recent studies in LAB immunomodulation.

Gut Pathogen-Related Comorbidities

Pathogens in the gut can breach the intestinal lining and induce IR. Rotavirus and *Cryptosporidium* cause acute gastroenteritis, which impairs bowel movements and intestinal barrier function. *L. rhamnosus* GG increased the IgG response and improved the intestinal function of children with acute gastroenteritis caused by rotavirus or *Cryptosporidium* [25]. Moreover, subsequent diarrheal episodes were reduced during probiotic administration for 4 weeks [25].

Infection with Human Immunodeficiency Virus (HIV) strongly affects the integrity of the epithelial and the GALT, where approximately 60% of the CD4$^+$ T cells reside [26]. Characterized by immune cell dysfunction, HIV also causes intestinal disorder,

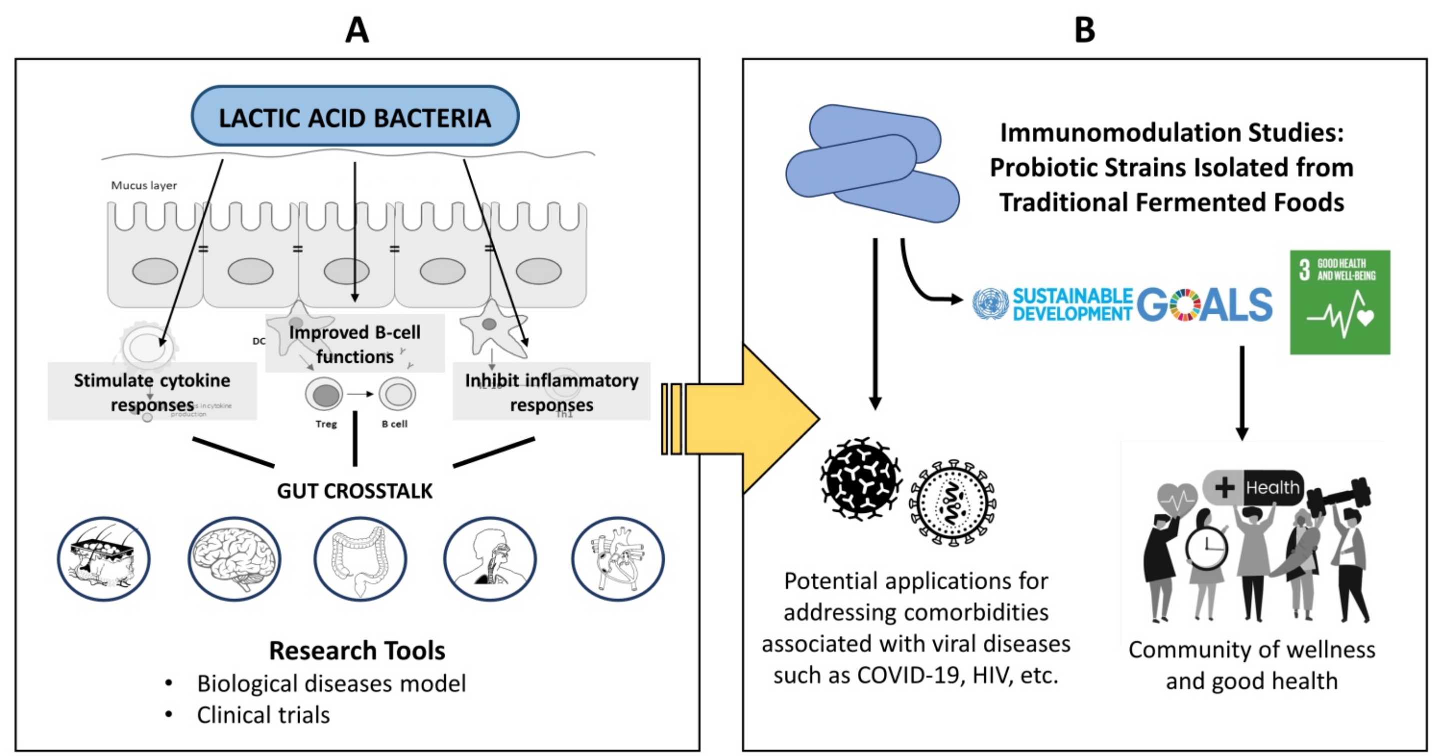

Figure 1. *Future directions of the study of lactic acid bacteria (LAB) immunomodulation in the Philippines: (A) the immunomodulatory role of LAB in different gut cross talk, and (B) using Philippine probiotic strains isolated from traditional fermented foods as resources and their future roles.*

Table 1. *Immunomodulatory effects of probiotic intake in human clinical trials.*

Type of Disease	Probiotics	Outcome (Immunomodulatory Effect/Symptoms Improvement)	References
Gut Pathogen-Related Comorbidities			
Human Immunodeficiency Virus-1 (HIV-1)	*Bifidobacterium bifidum* with *Streptococcus thermophilus*	Increase $CD4^+$ count	[27]
	Lactobacillus rhamnosus HN001, *B. lactis* Bi-07, in combination with *Agave tequilana* Weber var. azul	Increase $CD4^+$ T-cell count Decrease IL-6 cytokine Modulation of the fecal microbiota	[26]
	L. casei Shirota	Increase levels of T lymphocytes and $CD56^+$, $CD4^+$ and Th17 Decrease in CD4/CD8 ratio Decrease in plasma HIV load	[29],[30]
	Vivomixx (L. plantarum DSM24730, *Bifidobacterium breve* DSM24732, *L. paracasei* DSM24733, *L. delbrueckii subsp. bulgaricus* DSM24734, *L. acidophilus* DSM24735, *B. longum* DSM24736, *B. infantis* DSM24737*)*	Modulation of interferon profiles Reduce T-cell activation in GALT and peripheral blood Improve the integrity of the gut epithelial barrier	[31],[32]
Acute gastroenteritis (caused by rotavirus and *Cryptosporidium*)	*L. rhamnosus* GG	Increase IgG response Improve intestinal function and reduced subsequent diarrheal episodes	[25]
Gut-Skin Axis and Hypersensitivities			
Allergic rhinitis	*L. casei* Shirota	Reduce IL-5, IL-6 and IFN-y production Modulation of specific IgG and IgE levels	[14]
	L. plantarum CBS125632	Modulation of cytokine responses	[13]
	L. paracasei ST11	Reduce interleukin levels (IL-5, IL-8, IL-10)	[45]
	NVP-1703 *(B. longum* IM55, *L. plantarum* IM76*)*	Increased IL-10 levels Improve clinical symptoms	[46]
Atopic dermatitis (eczema)	*L. paracasei* ssp. *paracasei* F19	Decrease Th0 and increase in Th1 and Th17 responses Promote adequate T helper response for protein antigens	[35]
	L. rhamnosus GG	Increase the proportion of memory B cells Decrease IgA- and IgM secreting cells Reduce the severity of maternal allergic disease	[37]
	L. reuteri	Lower secretion of Th2- and Th1-related cytokines, and IL-10 and Th2-associated CCL22 responses	[38]
	L. plantarum IS-10506	Lower levels of IL-4, IFN-y, IL-17 Improve clinical symptoms	[36]
Systemic sclerosis	*L. paracasei, L. rhamnosus, L. acidophilus, B. lactis*	Reduce Th17 levels	[43]
Gut-Brain Axis			
Multiple sclerosis	*L. acidophilus, L. casei, B. bifidum, L. fermentum*	Improve B cell function Decrease serum insulin concentration	[51]
	B. infantis, B. lactis, L. reuteri, L. casei, L. plantarum, L. fermentum	Decrease IL-6 and hs-CRP levels Increase IL-10 and NO levels Improve clinical symptoms and mental health scores	[49]
	Visbiome (eight strains from *Lactobacillus, Bifidobacterium, Streptococcus*)	Induce anti-inflammatory peripheral immune response Decrease the abundance of taxa associated with dysbiosis and enriched *Lactobacillus*	[50]
Schizophrenia	*L. rhamnosus* GG, *B. animalis* subsp. *lactis* Bb12	Modulate the immune function via IL-17-related immune responses Improve bowel function and reduced symptom severity	[57],[58]

Table 1. *Immunomodulatory effects of probiotic intake in human clinical trials. (continuation)*

Type of Disease	Probiotics	Outcome (Immunomodulatory Effect/Symptoms Improvement)	References
Acute stress	*L. plantarum* HEAL9	Low plasma levels of inflammatory markers (fractalkine and CD163)	[52]
Stress and anxiety	*L. plantarum* P8	Reduce levels of pro-inflammatory cytokines Reduce stress, enhanced memory and cognitive traits	[54]
	L. plantarum DR7	Reduce levels of IFN-y and TGF-a Increase levels of IL-10 Reduce stress, improved cognitive traits and memory function	[55]
Gut-Liver Axis			
Liver cirrhosis	VSL#3 *(L. casei, L. plantarum, L. acidophilus, L. delbrueckii subsp. bulgaricus, B. longum, B. breve, B. infantis, S. salivarius* subsp. *thermophilus*	Modulate cytokine level Improve liver function	[64]
Alcoholic hepatitis	*L. subtilis* *S. faecium*	Decrease TNF-a levels	[67]
	L. casei Shirota	Modulate IL-10 and TLR4 expression	[68]
Nonalcoholic fatty liver disease	*L. casei, L. rhamnosus, S. thermophilus, B. breve, L. acidophilus, B. longum, L. bulgaricus, fructooligosaccharide*	Modulate TNF-a and NF-kB levels	[70]
Gut-Heart Axis and Metabolic-Related Comorbidities			
Crohn's Disease	*B. bifidum*	Induce CD80 and CD86 expression	[72]
Diabetes mellitus type 2 with chronic heart disease	*L. acidophilus, L. casei, B. bifidum, inulin*	Decrease HOMA-B cell function Improve insulin metabolism	[71]
Ulcerative colitis	*L. salivarius* ATCC11741	Increase TGF-B production in a dose-dependent manner	[72]

leading to diarrhea as one of the clinical manifestations of HIV progression [27]. Recent studies on probiotics as adjuvant HIV therapy focus on the immunomodulatory effects of LAB strains. For instance, the combination of *Bifobacterium bifidum* and *Streptococcus thermophilus* increased the CD4+ count and slightly improved stool consistency in HIV-infected children [27]. *L. rhamnosus* HN001 and *B. lactis* Bi-07, together with *Agave tequilana* Weber var. azul, increased the CD4 count in HIV-infected patients [26]. Moreover, this synbiotic modulated the fecal microbiota and decreased the concentration of IL-6, which is an immune marker for cardiovascular risk and mortality in HIV-infected patients [26,28]. *L. casei* Shirota(LcS)-fermented milk drink increased T lymphocytes and $CD56^+$ cells, decreased TGF-β, IL-10, IL-12, and IL-1β expression ' . The improvement in the immunological status of HIV-infected patients with probiotics is a promising alternative for antiretroviral therapy (ART), which can be very limited in other countries. Interestingly, increased $CD4^+$ cell and decreased regulatory T-cell counts were observed in LcS-fed HIV-infected children who had received ART [30]. Likewise, lyophilized multi-strain probiotic Vivomixx® modulated the interferon profiles (IFN-α subtypes, IFN-β, IFN-γ), reduced T-cell activation in GALT and peripheral blood, and improved the integrity of the gut epithelial barrier of ART-treated HIV-infected patients [31,32]. The oral administration of LcS and Vivomixx® improved the recovery of $CD4^+$ T cells and the integrity of the gut mucosal barrier that remains to be impaired even during ART [33].

Gut-Skin Axis and Hypersensitivities

An impaired gut microbiome has been associated with integumentary health by modulating the systemic immune response [34]. A defective adaptive Th1 development has been observed in individuals with atopic dermatitis (AD), a chronic inflammatory skin disorder [35]. Moreover, strong expression of Th2 was observed in patients with AD [36]. Recent adjunct therapeutic approaches to AD involve the use of probiotics [37]. Feeding *L. paracasei* ssp. *paracasei* F19 in healthy infants increased the IFN-γ/IL-2 and IL17A/IL-2 ratios, as well as the Th1 and Th17 responses, which could prevent the development of allergic disease [35]. *L. rhamnosus* GG might have strengthened the gut barrier in infants with AD by decreasing IgG-secreting cells and increasing memory B cells [37]. Pre- and post-natal freeze-dried *L. reuteri* supplementation decreased the prevalence of IgE-associated eczema [38]. Moreover, *L. reuteri* decreased the allergen responsiveness by lowering the secretion of Th2- and Th1-related cytokines during infancy, as well as the IL-10 and Th-2 associated CCL22 responses [39]. Microencapsulated *L. plantarum* IS-10506 lowered the IL-4, IFN-γ, and IL-17 levels and improved the clinical symptoms of children with AD [36]. These results show that LAB supplementation modulates the immune response and alleviate symptoms of AD.

Systemic sclerosis (SSc) is an autoimmune disorder of the connective tissue clinically manifested as fibrosis in the skin and internal organs [40]. Patients with SSc were observed to have increased cytokines required for Th17 cell expansion [41]. As of writing, studies on the effect of probiotics in SSc patients are very limited. *B. infantis*, *L. rhamnosus* GG and *L. casei* improved the clinical symptoms of SSc patients [41,42]. On the other hand, the combination of *L. paracasei*, *L. rhamnosus*, and *B. lactis* decreased the proportion of Th17 cells, but no significant changes in clinical symptoms were observed [43]. Further studies should be done to understand the effect of LAB in improving the symptoms of Ssc.

For the past few decades, allergic diseases have become a major public health issue. Allergic diseases are characterized by an impaired Th2 cell response to an allergen, which then stimulates the secretion of cytokines and production of IgE [5]. the development of allergies may also be attributed to the disturbance in the gastrointestinal tract and changes in the gut microbiota composition. LAB were observed to stimulate the immune system in allergic rhinitis (AR) and asthma in humans. The oral supplementation of *B. longum* and *L. acidophilus* showed potential in reducing clinical symptoms of AR and asthma [44]. *L. paracasei* ST11 downregulated IL-5, IL-8, and IL-10 in adults with AR [45]. Ingestion of the milk drink with live LcS reduced IL-5, IL-6, and IFN-γ levels and modulated IgG and IgE levels in individuals suffering from seasonal AR [14]. Likewise, a yogurt drink with *L. plantarum* CBS125632 modulated the cytokine responses and decreased the IgE levels in seasonal AR [13]. The probiotic NVP-1703, which contained *B. longum* IM55 and *L. plantarum* IM76, improved AR symptoms and increased serum IL-10 levels in adults [46]. Meanwhile, the immunomodulatory effects of LAB against asthma remain unclear as contradicting results were observed in several studies. However, the positive effects of some LAB strains on asthmatic individuals show that the effect is strain-specific. *L. reuteri* DSM 17938, with addition of vitamin D3, increased IL-10 levels in asthmatic children while reducing bronchial inflammation [47]. Serum IgE levels were increased in asthmatic children after oral intervention with *L. paracasei* GMNL-133 and *L. fermentum* GM-090 [48]. Although these LAB had immunomodulatory effects on AR, alleviation of allergic symptoms should be addressed further in future clinical studies.

Gut-Brain Axis

The gut-brain axis involves the bidirectional communication between the intestinal environment and central nervous system. Similar to other gut cross talks, regulation of immune responses is influenced by the activity of intestinal microbes. Multiple sclerosis (MS) is an autoimmune and inflammatory neurological disease, and susceptibility to MS increases with an impaired gut microbiota composition [49,50]. Administration of the multi-strain probiotic Visbiome, which consisted of eight LAB strains, decreased the frequency of inflammatory monocytes in MS patients [50]. In addition, the multi-strain probiotic decreased the abundance of *Akkermansia* and *Blautia* (dysbiosis-associated taxa) and enriched *Lactobacillus* in the gut [50]. These results suggest that intake of probiotic capsule containing *L. acidophilus*, *B. bifidum*, *L. casei*, and *L. fermentum* improved the mental health of MS patients, decreased serum insulin, and improved B cell function [51]. Recently, the intake of probiotic capsule containing *B. infantis*, *B. lactis*, *L. reuteri*, *L. casei*, *L. plantarum*, and *L. fermentum* modulated the IL-6 and IL-10 levels and improved the disease severity and mental health of MS patients [49]. These studies suggest that the use of multi-strain probiotics may efficiently improve and control MS severity.

Oral administration of probiotics is also known to have effect on psychiatric disorders. Individuals with acute and chronic stress were observed to have elevated plasma and salivary IL-1β, IL-10, IL-6 and TNF-α levels [52,53]. Low plasma levels of inflammatory markers (fractalkine and soluble CD163) were observed in patients with chronic stress administered with encapsulated *Lactiplantibacillus plantarum* HEAL9 [52]. As compared to placebo, administration of *L. plantarum* P8 reduced IFN-γ and TNF-α, and these pro-inflammatory cytokines were observed to be positively correlated with psychological traits in stressed adults [54]. *L. plantarum* DR7 modulated inflammatory cytokines (IFN-γ, TGF-α, IL-10), reduced stress and anxiety levels, and improved cognitive traits and memory in stressed adults [55]. Interestingly, DR7 affected the serotonin pathway by favoring the expression of tryptophan hydroxylase, which converts tryptophan to serotonin. Decreased levels of serotonin have been associated with inflammation and anxiety [56].

Individuals with schizophrenia were observed to have impaired immune responses, wherein Type 17 immune response is downregulated [57]. The oral administration of adjunct probiotic containing *L. rhamnosus* GG and *B. animalis* subsp. *lactis* BB12 (Ferrosan) increased the levels of cytokines related to IL-17 and improved the bowel movement of patients [57,58]. Interestingly, decreased the levels of acute-phase reactant von Willebrand factor (vWF), which is a marker of cardiovascular risk in schizophrenia, was observed. However, the combination of *L. rhamnosus* GG and *B. animalis* subsp. *lactis* BB12 did not reduce the psychotic symptoms. As of writing, limited references are available on the efficacy of LAB on schizophrenia. Further studies should be conducted to validate the use of probiotics as treatment.

Gut-Liver Axis

The gut-liver axis have a symbiotic relationship that is primarily attributed through a portal circulation [59]. Interestingly, the liver has a number of innate immune cells including NK cells and macrophages that become activated when the intestinal barrier is damaged [60]. However, the liver becomes excessively exposed to toxic factors caused by the dysbiosis and bacterial dislocation, compromising the health of the host. Several studies have shown the potential of probiotics and synbiotics in liver diseases, but these studies were mostly performed in animal models [61-63]. Only few LAB strains used in clinical trials were observed to have immunomodulatory effect on liver diseases. The probiotic VSL#3 decreased the levels of TNF-α, IL-1β, and IL-6, and improved the liver function of patients with cirrhosis [64]. Liver cirrhosis is characterized by the reduction of liver cells and scarring of the liver accelerated by the gut dysbiosis, which increases the systemic IR [65]. Alcohol abuse can develop cirrhosis and hepatic carcinoma. A study by Kirpich *et al*. [66] showed that the combination of *B. bifidum* and *L. plantarum* 8PA3 altered the gut microbiota and improved lipid enzyme levels such as aspartate transaminase and alanine aminotransferase in alcoholic hepatitis (AH) patients. Similar observations were observed when combination of *L. subtilis* and *S. faecium* was administered in AH patients [67]. Interestingly, the probiotic decreased TNF-α levels in AH patients [67]. LcS also showed potential against alcoholic cirrhosis by modulating IL-10 secretion and TLR4 expression, possibly restoring the neutrophil phagocytic function [68]. Meanwhile, a recent meta-analysis evaluated the role of probiotic and synbiotic in nonalcoholic fatty liver disease (NAFLD) [69]. Generally, probiotic and synbiotic therapies improved aminotransaminase levels and reduced high-sensitivity C-reactive protein (hs-CRP) in NAFLD patients [69]. Mofidi *et al.* [70] observed that the synbiotic supplement containing seven LAB strains and fructooligosaccharides reduced the TNF-α and NF-κB levels in lean NAFLD patients. These studies suggest that LAB-based therapy show great promise for clinical improvements of liver diseases.

Gut-Heart Axis and Metabolic-Related Comorbidities

Inflammatory-induced metabolic syndromes are risk factors for cardiovascular diseases, including atherosclerosis, chronic heart disease, and heart failure. There have been studies linking the risks of having cardiovascular diseases (CVD) in obesity, diabetes mellitus (DM), and inflammatory bowel disease patients (IBD). The combination of *L. acidophilus*, *L. casei*, *B. bifidum*, and inulin decreased the HOMA-B cell function and improved the insulin metabolism in DM-type 2 patients with chronic heart disease [71]. Improving serum insulin levels reduces the risk of having CVD of DM-type 2 patients [71]. Meanwhile, increased expression of co-stimulatory molecules from DCs were observed after probiotic supplementation in IBD patients. Particularly, *B. bifidum* induced CD80 and CD86 expression in patients with Crohn's disease, while *L. salivarius* ATCC11741 increased the production of TGF-β in individuals with ulcerative colitis [72]. Meanwhile, consumption of pentasa combined with Bifico, a probiotic capsule containing LAB strains, reduced the level of CRP in IBD patients [73]. Elevated serum CRP levels has been associated with the increased risk of developing CVD [74]. The systematic review and meta-anlysis of Mazidi *et al*. also highlighted the significant role of probiotics in preventing CVD by reducing CRP levels. Although limited, these clinical studies suggest that probiotics targeting the impaired IRs in metabolic disorders and IBD shows potential in preventing cardiovascular risks.

While it is known that gut dysbiosis contributes to the development of obesity and diabetes, the lifestyle and diet of healthy individuals also contribute to their susceptibility to cardiovascular diseases. However, human clinical trials are very limited as of writing. Recently, Malik *et al.* [75] observed that *L. plantarum* 299v improved the vasodilation of the brachial artery of patients with coronary artery disease. Moreover, *L. plantarum* 299v modulated the levels of inflammatory cytokines involved in vascular endothelial dysfunction leading to the development of CVD. The same strain modulated IRs and improved the blood pressure of smokers, reducing their risk of having cardiovascular diseases [76]. The importance of LAB supplementation on the prevention of coronary heart disease in healthy individuals should be elucidated in the future.

Potential of LAB-based Adjunct Functional Food Therapy

Nowadays, foods are not only prepared for the mere intention of satisfying hunger but also to improve the health and well-being of individuals. Interestingly, there has been an increasing consumer demand for naturally-processed food products. Functional foods are ordinary foods added with components and ingredients to confer a specific health benefit other than their own nutritional value [2]. Most functional foods are being recognized because they deliver probiotic microorganisms, while LAB contribute to the enhanced health benefit of functional foods [77]. Linares *et al.* [2] listed some lactobacilli and bifidobacteria that increased the vitamin levels, enriched gamma-aminobutyric acid, and synthesized bacteriocins in fermented products. Consumption of LAB-fermented foods also showed potential in improving the health and alleviating metabolic diseases in individuals [6]. The development of functional foods targets to improve immune function, as functional foods are practical and realistic options in addressing certain complications in human health. Interestingly, some LAB-fermented functional foods showed immunomodulatory characteristics *in vitro* and *in vivo*. For instance, *L. delbrueckii* ssp. *bulgaricus* LB340-fermented skim milk showed antioxidant activity and had a positive effect on the proliferation of murine spleen lymphocyte [78]. Plant-based paste fermented by several *Lactobacillus* and *Pediococcus* strains, with yeast, was found to have anti-inflammatory and anti-allergy activities *in vitro* [79]. Mice fed with the commercial fermented food Xeniji were found to have improved antioxidant activity and higher serum levels of IL-12, IL-18, and IFN-γ [80].These results suggest the huge impact of functional foods as adjunct therapy. However, further studies are needed to assess the immunomodulatory effects of functional foods in humans.

The Philippines has a wide-range of fermented foods, and each fermented food is traditionally unique per community. Elegado *et al*. [81] listed the different fermented foods geographically distributed in the archipelago. LAB isolated from different fermented food preparations showed antimicrobial activity against pathogens and bacteriocinogenic properties [16-18,20].Strains isolated from traditional fermented foods (*L. plantarum* BS and *P. acidilactici*) improved the safety, nutritional, and sensory properties of *pindang damulag* (fermented carabeef) [82]. This study suggests that local LAB strains can be used as starter cultures for the development of functional foods. Moreover, *L. fermentum* 4B1 isolated from *Balao-balao* (fermented shrimp) showed promising anti-obesity activity in mice comparable to commonly prescribed weight-loss drug [18]. This study highlights the importance of exploring 4B1 for developing local functional foods addressing certain health complications relevant in the country. Although preliminary studies (listed in the review of Banaay *et al.* [20]) showed the beneficial effects of local fermented foods, research on the immunomodulatory properties of the local LAB strains as well as fermented foods is limited as of writing. The previous section addressing the immunomodulatory effects of certain LAB strains emphasizes the need to explore further our existing probiotic strains. Tapping local probiotic strains and developing the current local functional foods into potential adjunct therapies should be given importance (Figure 1B).

On Animal Models to Study Immunomodulation in the Philippines

Many studies have shown the immunomodulatory effects of LAB in swine and mice models (Table 2). The growing list of studies on probiotics that modulate immune responses in certain disorders firstly utilizes animal models to confirm potential adjunct therapies in succeeding trials. The potential of LAB strains not yet studied in clinical trials is being explored in mice models. A recent study presented the potential of *Pediococcus acidilactici* in improving the clinical symptoms of AD [83]. Protection against H. pylori infection was induced by *L. fermentum* UCO-979C [84]. The impact of LAB in neurodegenerative diseases are also being studied first in mice, as there is still limited information in the communication between the gut and brain [85,86].

Mice are great models for different immunomodulation studies, and there are specific strains of mice for different diseases. These models can be easily reproduced in the lab, and they share similar biological processes with humans. However, there is an increasing interest of using LAB as probiotics in swine because its genome is closer to humans as compared with mice [87]. A review paper highlighted that supplementation of different lactobacilli strains in pig feeds

Table 2. *Immunomodulatory effects of different LAB strains on swine and mouse models.*

Probiotics	Animal model	Immunomodulatory Effect	Symptoms improvement	References
Vivomixx	TMEV-IDD mice model	Reduce the Breg cell production in CNS Promote IL-10 expression	Improvement of motor disability Modulation of beneficial gut microbes in MS	[85]
Pediococcus acidilactici	NC/Nga mice	Reduce relative mRNA expression of PAR-2, TNF-a, IL-4 and IL-13 Reduce serum IgE and TNF-a in dorsal skin	Improve the clinical symptoms of atopic dermatitis Modulation of the gut microflora	[83]
L. fermentum UCO-979C	Balb/c mice	Increase the production of intestinal IFN-y and the number of Peyer's patches $CD4^+$ T-cells Stimulate intestinal and peritoneal macrophages *in vivo*	Protection against *H. pylori* infection	[84]
L. rhamnosus Lcr35	Female Wistar rats	Decrease in IL-23 secretion	Attenuate visceral hypersensitivity and acute psychological stress	[86]
L. reuteri LR1	Weaned pigs (Duroc x Landrace x Yorkshire)	Increase intestinal cytokines (TGF-B, IL-22) Improve intestinal barrier function (ZO-1 and occluding transcripts)	Improve growth performance	[89]
L. acidophilus	Weaned pigs (Landrace x Yorkshire)	Decrease the expression of TRL4 and NF-kB and number of immune cells including $CD4^+$ and CD8+ after LPS challenge	Improve ADWG and ADFI	[90]
L. rhamnosus GG	Piglets (Duroc x Landrace x Large White)	Increase expression of tight junction proteins Reduce serum TNF-a expression	Alleviate gut inflammation	[92]
	Neonatal gnotobiotic pigs with doses of human rotavirus vaccinem	Enhance rotavirus-specific serum IgA response, rotavirus-specific effector/memory T-cell	Improve mucosal barrier	[93]
L. rhamnosus GG, *B. animalis* subsp. *lactis* Bb12	Neonatal gnotobiotic pigs	Modulate B-cell responses to rotavirus vaccine	Reduce virus shedding	[91]

improved growth performance and carcass quality, and prevented gastrointestinal infection [88]. Recent studies elaborated the immunomodulatory effects of different LAB strains on swine: modulation of cytokine levels, increase expression of tight junction proteins, and stimulating B cell responses [89,90]. Interestingly, gnotobiotic piglets were used as animal models for assessing the impact of probiotics on rotavirus infection or vaccination. *L. rhamnosus* GG and *B. animalis* subsp. *lactis* Bb12 modulated B cell responses to rotavirus vaccine, enhanced serum IgA response, and reduced virus shedding in piglets [91-93]. Neonatal piglets have similar immune responses, gut physiology, and milk diet with infants [91]. These results suggest the potential of swine as good model system for application to humans, and it should be elucidated further. Pigs have been utilized broadly in research, providing abundant information to explore these animals as models of LAB immunomodulation studies. In the Philippines, pig production has intensified that changes in their diet are needed to improve health and reproduction. These changes can also be easily patterned to the biology of human health and disease because of the similar response of pig and humans in several varieties of drugs [94]. Besides the physiologic similarities with humans, the use of swine in immunomodulation studies can be cost-effective because of the increased pig production efficiency in the Philippines. Thus, local pigs can be tapped as animal models for future immunomodulation studies in the country.

Conclusion

Dietary supplementation of lactic acid bacteria modulates the immune responses by enhancing the mucosal immunity. Through this, the gut cross talks with other organs are improved, possibly reducing inflammatory markers and improving clinical symptoms in humans. By adapting the methods used in biological diseases model and clinical trials, there will be a promising application of probiotic strains isolated from traditional fermented foods (Figure 1B). Utilizing local probiotics for immunomodulation studies in the Philippines will highlight the importance of these strains in developing functional food products available for all and creating a community of wellness and good health.

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