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Review Article

Anti-inflammatory and Immunostimulant Therapy with *Lactobacillus fermentum* and *Lactobacillus plantarum* in COVID-19: A Literature Review

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Abstract

Inflammatory diseases are diseases characterized by inflammatory symptoms. Acute inflammatory disease can cause dysregulation of the inflammatory immune response, thereby inhibiting the development of protective immunity against infection. Among the acute inflammatory disease is COVID-19. The initial viral infection causes the antigen-presenting cells to detect the virus through a phagocytosis mechanism in the form of macrophage and dendritic cells. *Lactobacillus fermentum* and *L. plantarum* are gram-positive bacteria potentially serving as immunomodulators caused by inflammation and immune system response. Short-chain fatty acids (SCFA) produced by *Lactobacillus* can induce immune response through tolerogenic dendritic cells. This probiotic bacterium can induce the production of different cytokines or chemokines. Following the results of *in vitro* and *in vivo* tests, *L. fermentum* and *L. plantarum* can induce IL-10 release to activate regulatory T-cell and inhibit tumor necrosis factor-α (TNF-α) binding activity of nuclear factor kappa B (NF-κB). Literature review showed that dysregulation of inflammatory immune response disorders due to inflammatory disease could be treated using probiotic bacteria *L. fermentum* and *L. plantarum*. Therefore, it is necessary to conduct further studies on the potential of indigenous Indonesian strains of these two bacteria as anti-inflammatory and immunostimulants.

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INTRODUCTION

Inflammation is a defense process of the body's system due to infections from bacteria and viruses and can also be caused by damage to body tissues[1]. Acute inflammation is the first line of defense due to infection. Coronavirus 2019 (COVID-19) is an acute inflammatory disease that can cause an impaired inflammatory immune response[2]. COVID-19 disease is a clinical syndrome caused by SARS-CoV-2. Originally discovered in China in December 2019, this disease has spread worldwide and was declared a pandemic by WHO on 11 March 2020. This disease causes human acute respiratory system like other betacoronavirus types such as human coronavirus 229E, NL63, OC43, HKU1, Middle-East respiratory syndrome (MERS), dan Severe Acute Respiratory Syndrome (SARS)[3-5].

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SARS-CoV-2 is transmissible through respiratory droplets, with a viral incubation period around 4-5 before initial symptoms emerge. About 97.5% of patients were reported to exhibit symptoms in 11.5 days[6]. The symptoms include fever, dry cough, breathing difficulty, muscle soreness, headache, and diarrhea. SARS-CoV-2 infections can turn into Acute Respiratory Distress Syndrome (ARDS) approximately 8-9 days after the first symptoms[7]. Severe ARDS in COVID-19 patients can be indicated by breathing difficulty and low blood oxygen level[8]. ARDS is known to cause respiratory failure leading to death in 70% of COVID-19 cases. Viral infection or secondary infection in patients is known to cause cytokine storm and sepsis symptoms, which result in death in 28% of the patients[9]. Uncontrolled inflammation in COVID-19 disease is reported to lead to multiorgan damage, eventually resulting in organ failure, especially heart, liver, and kidney failures[10]. However, this inflammation can be treated using probiotic bacteria.

Probiotic bacteria are the potential to treat diseases caused by inflammation and immune system responses[11]. Probiotic bacteria play roles in humoral immunity by interacting with intestinal epithelial cells and lamina propria-related cells through toll receptors. The probiotic bacteria are reported to lower cytokines that produce inflammatory cells and immune system decline through NF-KB transcription factor pathways[12]. Immune response and inflammation in the cell can be affected by NF-KB. In this regard, NF-KB has become the object of developing a treatment for diseases caused by inflammation[13]. Inflammatory response and immune system can be stimulated using *Lactobacillus* strain probiotic[14].

Lactobacillus is a gram-positive, non-spore-forming, lactic acid bacteria. This bacterium generates lactic acid as its primary product through carbohydrate fermentation. Morphologically, *Lactobacillus* can be in the form of a non-shortening bar in the chain form. *Lactobacillus* is a part of microbiota colonizing the mouth and digestive tract[15]. *Lactobacillus* colony species commonly found in the digestive tract are *Lactobacillus plantarum* and *L. fermentum*[16]. *Lactobacillus plantarum* and *L. fermentum* exhibit high probiotic potentials and become potential anti-inflammatory and immune responses by modulating pro-inflammatory cytokines[17]. This paper reviews the anti-inflammatory and immunostimulant potentials of *L. plantarum* and *L. fermentum* reported *in vitro*, *in vivo*, and in clinical studies. This paper also provides information about the metabolite compounds of *L. plantarum* and *L. fermentum* as anti-inflammatory and immunostimulants in treating COVID-19.

INFLAMMATION AND IMMUNE RESPONSE

The virus is attached to the host through a receptor. Angiotensin 2 (ACE2) and TMPRSS2[18] are known to be the host receptor used by SARS-CoV-2 to infect the cell. This target receptor can be found in the respiratory tract, such as epithelial cells, alveolar epithelial cells, vascular endothelial cells, and macrophages in the lungs[19-21]. Viral replication and release may cause pyroptosis in the host cell and damage the associated molecular pattern, including ATP, nucleic acid, and ASC oligomer. The virus is recognized by epithelial cells, endothelial cells, and alveolar macrophages, triggering the formation of pro-inflammatory cytokine and chemokine (including IL-6, IP-10, macrophage inflammatory protein 1α (MIP1α), MIP1β, and MCP1). This protein attracts monocyte, macrophage, and T cell to the infected area and promotes further inflammation by adding interferon-γ (IFN-γ) produced by T cells.

The damaged immune response can cause further accumulation of immune cells in the lungs, leading to excessive pro-inflammatory cytokines and eventually damaging the lungs. The produced cytokine storm circulates to other organs, causing multiorgan damage. Bronchoalveolar fluid (BALF) patients with COVID-19 symptoms are reported to contain Chemokine CCL2 and CCL7. Both chemokines are responsible for recruiting Cc-chemokine receptor 2-positive (CCR2+)[22]. Several cytokine and chemokine monocytes are reported to play roles in the inflammatory process in COVID-19 patients[15,23-25]. The inflammation severity is indicated by the increase in cytokine and chemokine levels. Macrophage activation due to the viral infection can cause increased cytokine IL-6, IL-7, TNF-α, and inflammatory chemokine, including Cc-chemokine 2 (CCL2), CCL3, CXC-chemokine 10 (CXCL10), and IL2. The irregularity of mononuclear phagocyte activation may cause hyperinflammation in COVID-19 patients. Some hypotheses exist on the mechanism contributing to monocyte hyperactivity due to macrophage in COVID-19 patients[26,27].

The delayed type 1 interferon production leads to the increased cytopathic effect. The increased microbial threat may enhance the chemoattractant by alveolar epithelial cells, macrophages, and stromal cells, increasing the number of monocytes in the lungs. The monocytes then differentiate into pro-inflammatory macrophages through Janus-activated kinase (JAK)-signal transducer and activator of transcription (STAT). The T-cell will induce the monocyte-derived macrophages by producing granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF-α, and IFNγ.

Oxidized phospholipids (OxPLs) deposit in the lungs' infected area and activate monocyte-macrophage through Toll-like receptors 4 (TLR4), TRAF6, and NF-κB. The virus infection can trigger the TLR7 activation through single-stranded RNA virus recognition. The virus enters the macrophage cytoplasm through the type-1 interferon receptor. The virus activates the NLRP3 inflammasome and causes mature IL-1β and IL-18 secretions. The IL-1β cytokine can increase macrophage activation in autocrine or paracrine. It can also decrease interferon type I production in the infected lungs. Macrophage-activated monocyte contributes to the formation of cytokine storm of COVID-19 by releasing many pro-inflammatory cytokines[28].

SARS-CoV-2 hampers the body's normal immune response, causing immune system damage and uncontrolled inflammatory response in severe COVID-19 patients. COVID-19 patients are reported to exhibit lymphopenia, lymphocyte activation and dysfunction, granulocyte and monocyte disorder, high cytokine levels, increased immunoglobulin G (IgG), and a total of antibodies[29]. Immune response patterns in Covid-19 patients are depicted in **Figure 1**.

Lymphopenia is the primary marker of severe COVID-19 patients. Patients will likely exhibit declined CD4+ T, CD8+ T, and B cell levels[30]. T cell activation due to the virus infection may increase the IFN-γ, TNF-α, and IL-2 levels. In addition, lymphocytes are reported to release phenotypic programmed cell death protein-1 (PD1), T-cell immunoglobulin domain, mucin domain-3 (TIM3), and killer cell lectin-like receptor subfamily C member 1 (NKG2A). COVID-19 patients will likely exhibit increased neutrophil and decreased eosinophil, basophil, and monocyte. They also exhibit increased cytokine production, especially IL-1β, IL-6, dan IL-10. A higher IgG and total antibody titers are also observed in COVID-19 patients[29].

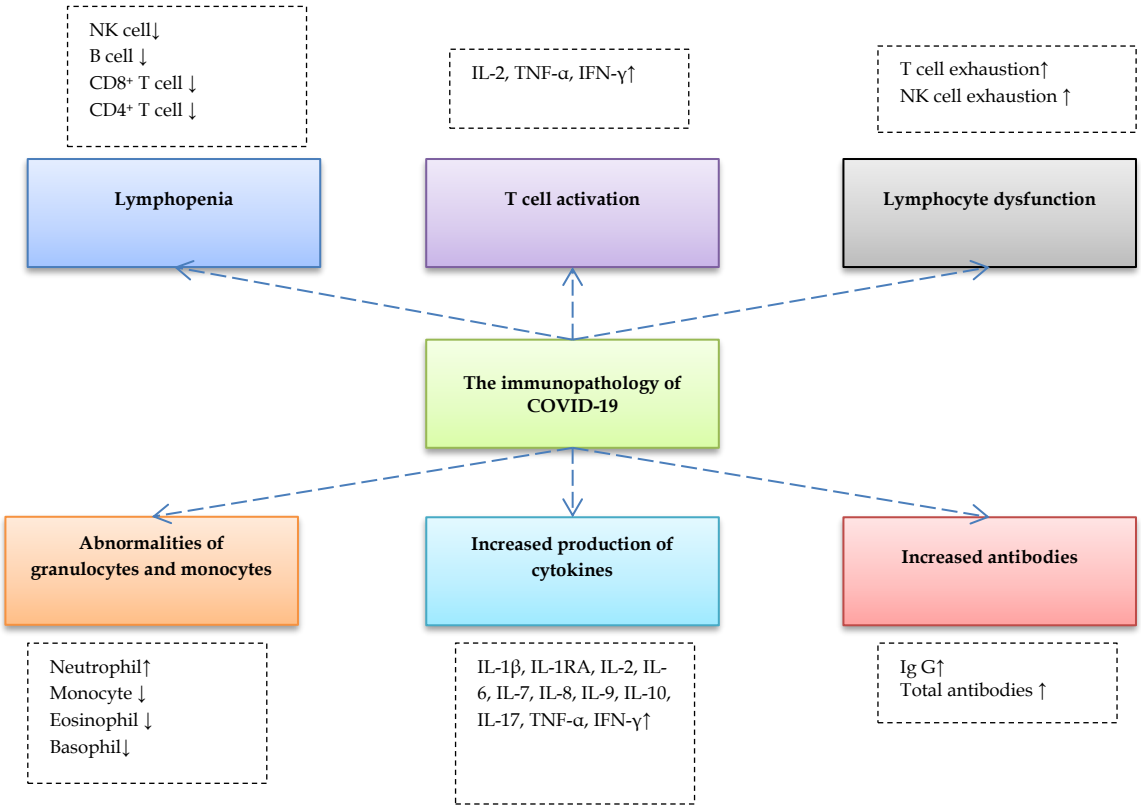

Figure 1. COVID-19 Immunopathological mechanism[29].

Lactobacillus METABOLITE COMPOUND

Lactobacillus produces intracellular and extracellular metabolism. The produced metabolite can provide information regarding the potential of bacteria on nutrition and its toxicity effect on the disease. Some metabolites are reported to be defrosting agents, antioxidants, antimicrobial agents, natural diet additives, and anti-inflammatory agents[31].

The fingerprint analysis of metabolite compounds can be performed using gas chromatography to determine *Lactobacillus*'s intracellular and extracellular metabolite analysis[32]. Gas chromatography-Mass spectrometry (GC-MS) is a chromatography with high-resolution separation results and good sensitivity and specificity. This instrument can analyze metabolic products such as carbohydrates, fatty acids, organic acids, and amino acids[33]. The sample derivatization is necessary before performing GC-MS analysis[34]. Chaudary *et al*.[35] identified 40 metabolites and five bacteria isolations, including *L. plantarum* DB-2, *L. fermentum* J-1, *Pediococcus acidilactici* M-3, *L. plantarum* SK- 3 dan *P. pentosaceus* SM-234. Metabolite compounds generated by *Lactobacillus* are presented in **Table I**.

Table I. Identification of metabolite compounds of *L. plantarum* and *L. fermentum*[35]

***Lactobacillus plantarum* DB-2**	***Lactobacillus fermentum* J-1**	***Lactobacillus plantarum* SK-3**
2-ethoxyethylamine (PubChem ID: 66970)	2-propanol,1-hydrazino (PubChem ID: 236167)	2-propanol,1-hydrazino (PubChem ID: 236167)
2-hydrazino ethanol (PubChem ID: 8017)	(Z)-9-octadecenamide (PubChem ID: 5283387)	4-amino-1-butanol (PubChem ID: 25868)
2-propanol,1-hydrazino (PubChem ID: 236167)	2,4,dimethylbenzaldehyde (PubChem ID: 61814)	(Z)-9-octadecenamide (PubChem ID: 5283387)
(Z)-9-octadecenamide (PubChem ID: 5283387)	benzoic acid (PubChem ID: 243)	2,4-dimethylbenzaldehyde (PubChem ID: 61814)
acetic acid, acetic formic anhydride (PubChem ID: 75269)	decane (PubChem ID: 15600)	benzoic acid (PubChem ID: 243)
2,4-dimetilbenzaldehyde (PubChem ID: 61814)	dodecane (PubChem ID: 8182)	decane (PubChem ID: 15600)
benzoic acid (PubChem ID: 243)	dodecanoic acid (PubChem ID: 236167)	dodecane (PubChem ID: 8182)
decane (PubChem ID: 15600)	eicosanoid acid (PubChem ID: 10467)	dodecanoic acid (PubChem ID: 236167)
dl-2,3–butanediol (PubChem ID: 225936)	Isovaleric geraniol (PubChem ID: 5362830)	2-propoxy-ethanamine (PubChem ID: 111878)
dodecane dodecane (PubChem ID: 8182)	Hexadecane (PubChem ID: 11006)	2-(2-propenyloxy)- ethanol (PubChem ID: 8116)
dodecanoic acid (PubChem ID: 236167)	2,6,11,15-tetramethylhexadecane (PubChem ID: 136331)	isovaleric geraniol (PubChem ID: 5362830)
ethylamine (PubChem ID: 6341)	1-methylhexyl hydroperoxide (PubChem ID: 12981)	Hexadecane (PubChem ID: 11006)
formamide (PubChem ID: 713)	isopropyl alcohol (PubChem ID: 3776)	2,6,11,15-tetramethylhexadecane (PubChem ID: 136331)
isovaleric geraniol (PubChem ID: 5362830)	isopropyl myristate (PubChem ID: 8042)	pentyl hydroperoxide (PubChem ID: 135961)
hexadecane (PubChem ID: 11006)	lactic acid (PubChem ID: 107689)	isopropyl alcohol (PubChem ID: 3776)
2,6,11,15-tetramethylhexadecane (PubChem ID: 136331)	hexadecanoic acid (PubChem ID: 985)	isopropyl myristate (PubChem ID: 8042)
isopropyl alcohol (PubChem ID: 3776)	phenol,2,4-bis- (1,1dimethylethyl) (PubChem ID: 7311)	lactic acid (PubChem ID: 107689)
lactic acid (PubChem ID: 107689)	propinoic acid, 2-hydroxymethyl ester (PubChem ID: 126674963)	nitrosomethane (PubChem ID: 70075)
nitrosomethane (PubChem ID: 70075)	hexahydro-3-(2- methylpropyl) pirolo[1,2-a]pirazin-1,4-dion (PubChem ID: 102892)	hexadecanoic acid (PubChem ID: 985)
hexadecanoic acid (PubChem ID: 985)	tetracosane (PubChem ID: 12592)	phenol,2,4-bis- (1,1dimethylethyl) (PubChem ID: 7311)
phenol,2,4-bis- (1,1dimethylethyl) (PubChem ID: 7311)	tetradecane (PubChem ID: 12389)	propylene glicol (PubChem ID: 1030)
propylene glicol (PubChem ID: 1030)	tetradecanoic acid (PubChem ID: 11005)	hexahydro-3-(2- methylpropyl) pirolo[1,2-a]pirazin-1,4-dion (PubChem ID: 102892)
hexahydro-3-(2- methylpropyl) pirolo[1,2-a]pirazin-1,4-dion (PubChem ID: 102892)	undecane (PubChem ID: 14257)	(R)-1,2-propanediol (PubChem ID: 259994)
(R)-1,2-propanediol (PubChem ID: 259994)		tetradecane (PubChem ID: 12389)
tetracosane (PubChem ID: 12592)		undecane (PubChem ID: 14257)
tetradecane (PubChem ID: 12389)		
undecane (PubChem ID: 14257)		

The identified metabolites, such as isopropyl alcohol, dodecane, hexadecane, tetradecane, hexahydro-3-(2-methyl propyl) pirolo[1,2-a], pyrazine-1,4-dion, 2,4-dimethyl benzaldehyde, isovaleric geraniol, phenol, 2,4 bis (1,1-dimethyl); 2,6,11,15-tetramethyl-hexadecanoic acid, (Z)-9-octadecenamide, are reported to be potential defrosting, antioxidant, antimicrobial, and anti-inflammatory agents[31]. In addition, short-chain fatty acids (SCFA) produced by probiotic bacteria, such as acetate,

butyrate, and propionate, play roles in decreasing nitric oxide (NO)[36,37]. Inflammation causes an immune response to activating cytokine in producing NO, resulting in increased NO. SCFA produced by Lactobacillus can induce immune response through tolerogenic dendritic cells (**Figure 2**). Fatty acid compounds can have an inhibitory effect on inflammation, especially omega-6 fatty acids. However, the interaction mechanism of omega-6 fatty acids and their lipid mediators in inflammation is still not well understood[38].

The tolerogenic process of dendritic cells makes the T-cell (CD4+) differentiate into T-cell regulators (Treg) and inhibits cytokine production by neutrophils and macrophages. Tolerogenic dendritic cells produce anti-inflammatory cytokines, interleukin-10 (IL-10), and transforming growth factor-β (TGF-β). A tolerogenic dendritic cell is a potential candidate for specific immunotherapy[37].

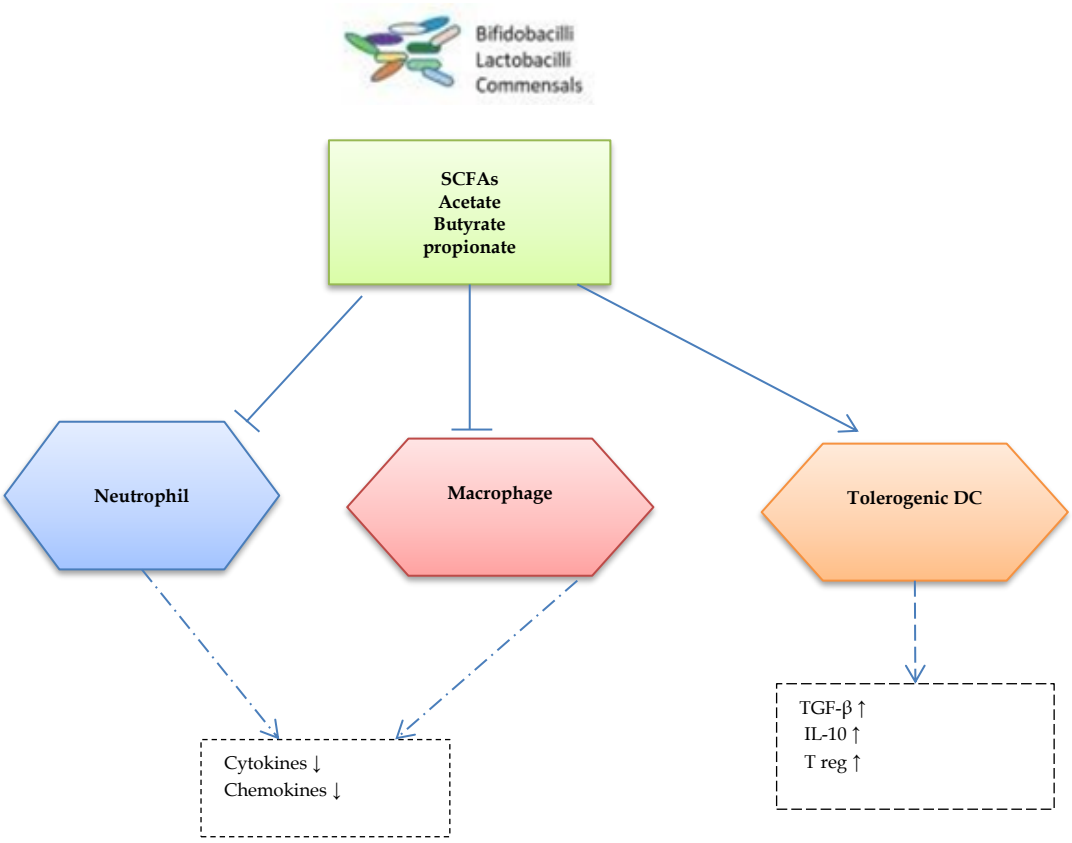

Figure 2. SCFA's work mechanism in decreasing inflammatory activities[37].

ANTI-INFLAMMATORY AND IMMUNOSTIMULANT ACTIVITIES OF *Lactobacillus*

Anti-inflammatory and immunostimulant activities of *Lactobacillus* have been widely studied through *in vitro* and *in vivo* research. **Table II** displays several studies on the anti-inflammatory and immunostimulant activities of *L. plantarum* with different strains. *Lactobacillus'* immunostimulant activities can occur through the increase in cytokine IL-10 production in mononuclear cells (macrophage and T-cell) in the intestine[39]. A study shows that *L. plantarum* CM can inhibit the binding activity of NF-κB in response to TNF-α. This response weakens the release of monocyte chemotactic protein 1 (MCP-1), pro-inflammatory chemokine, and NF-κB gene and inhibits the proteasome functions. *Lactobacillus plantarum* CM inhibits the activation of NF-κB from TNF through MyD88-dependent and MyD88-independent pathways. *Lactobacillus plantarum* can also inhibit TNF-α-induced MCP-1 production in Caco-2 cells and lower NF-κB, mitogen protein kinase, and production of TNF-α or IL-1β[40-42].

In vivo studies report that *L. plantarum* and *L. fermentum* possess inflammatory activities[43,44]. The effective dose of probiotic bacteria to treat inflammation is reported to be 1x10^8 – 10^9 CFU/mL[44,45]. *Lactobacillus fermentum* is reported to significantly lower malondialdehyde levels, TNF-α, IL-6, and resistin in mouse blood serum. *Lactobacillus* bacteria is also reported to increase catalase, superoxide dismutase, glutathione peroxidase, and adiponectin activities, suppressing the inflammation-inducing- oxidative stress. Most studies show that *L. plantarum* induces IL-10 secretion in splenocytes and mesenteric lymphocytes, blocking the expression of pro-inflammatory cytokines, IL-1β, IL-6, TNF-α, COX-2, forkhead box P3 (Foxp3), suppressor of cytokine signaling 3 (SOCS3). *In vivo* study shows a decline in mucose IL-12, IFN-γ, and immunoglobulin G2a in mice[46]. The treatment using L. plantarum Biocenol™ LP96 was reported to lower the expression of IL-1α, and IL-8 genes increase the IFN-γ and cytokine IL-10 secretion[47]. This paper reviewed *in vitro* and *in vivo* studies to show *Lactobacillus'* metabolite product potential in inhibiting inflammatory activities.

Table II. Results of *in vitro* and *in vivo* studies on anti-inflammatory and immunostimulant activities of *L. plantarum* and *L. fermentum*.

Bacterial Strain	Method	Animal/cell	Dose	Inhibitory effect	Reference
L. plantarum APsulloc 331261	*in vitro*	THP1 cell	-	Inducing the expression of macrophage cytokine, IL-1β, inflammatory cytokine, and IL- 10,	48
L. plantarum L15	*in vitro*	Caco- 2	-	Lowering the expression of TLR4 and MyD88 genes and genes associated with NF-κB signalling pathways.	49
L. plantarum M2 and *L. plantarum* KO9	*in vitro*	Caco- 2	-	Inhibiting TNF-α production	50
L. plantarum MYL26	*in vitro*	Caco- 2	-	Inhibiting NF- κB, MAPK, TOLLIP, SOCS1, SOCS3, and IκBα expression	51
L. plantarum Lp62	*in vitro*	Intestinal epithelial cell HT-29, macrophage J774	-	Inhibiting production of IL-8, TNF-α, IL1-β, and IL-17.	52
L. plantarum CAU1055	*in vitro*	RAW264.7 cells	-	Inhibiting production NO, TNF-α, IL-6.	53
L. plantarum K8	*in vitro*	Intestinal epithelial cell HT-29	-	Inhibiting NF- κB and MAPK,	41
L. plantarum A41 and *L. fermentum* SRK414	*in vitro*	Intestinal epithelial cell HT-29	-	Decreasing the regulation of mRNA expression from proinflammatory cytokine TNF- α, IL1β, and IL-8 and enhancing intestinal barrier integrity by increasing protein ZO-1 expression	17
L. plantarum K8	*in vitro*	Monocytic THP-1 cell human	-	Inhibiting TNF- α , IL-1, NF-κB Increasing MAPK, Inhibiting NOD2 production	42
L. fermentum MCC 2760	*in vitro*	Caco- 2, intestinal epithelial cell HT-29	-	Increasing cytokine IL-10 production and inhibiting IL-6 production	54
L. fermentum CECT5716	*in vitro*	RAW 264.7 cells	-	Decreasing the proinflammatory cytokine TNF- α, IL1β, and IL-6	55
L. plantarum CGMCC1258	*in vivo*	Mouse without IL- 10	10^9 CFU/mL	Decreasing IFN-γ, TNF-α, and MPO production	56
L. plantarum Lp91	*in vivo*	Mouse without IL- 10	10^9 CFU/mL	Reducing expression of TNF-α and COX-2, Increasing the production of IL-10	57
L. plantarum OLL2712	*in vivo*	obese and type 2 diabetic KKAy mice	-	Increasing cytokine IL-10, suppressed proinflammatory cytokine level	58
L. fermentum DALI02	*in vivo*	Mouse hyperlipidemia	10^9 CFU/mL	Decreasing expression of TNF-α, IL- 6, and resistin and significantly increase APPN level	43
L. fermentum SNR1	*in vivo*	Wistar Albino Rats	10^8 CFU/mL	Increasing IL- 10, IL-6	59
L. fermentum and *L. salivarius*	*in vivo*	DSS mouse colitis	5×10^8 CFU/mL	Improving the colonic expression of markers in immune response	60
L. fermentum KBL374 and *L. fermentum* KBL375	*in vivo*	Female mouse C57BL/6N	10^9 CFU/mL	Increasing cytokine level associated with Th1, Th2-, and Th17, Increasing IL- 10, and increasing CD4+CD25+Foxp3 +Treg	61
L. plantarum LP-Onlly	*in vivo*	Mouse without IL- 10	10^9 CFU/mL	Lowering the inflammation and histological injury value; increasing the number of bifidobacteria and lactobacili	62

				good bacteria, decreasing the number of pathogenic bacteria of eterococci and *Clostridium perfringens*	
L. plantarum LP3457	*in vivo*	Mouse ZDF	10^8 CFU/mL	Decreasing IL-1β, IL-6, and CRP expression, Increasing IL-10 level	63
L. plantarum K8	*in vivo*	Healthy mouse	10^9 CFU/mL	Reducing expression of TNF-α and IL-6	64
L. plantarum ZS2058 (ZS2058) and *L. rhamnosus GG*	*in vivo*	Specific pathogen-free mice	5×10^9 CFU/mL	Changing in the levels of tissue necrosis factor (TNF)-α, IL-10 and myeloperoxidase (MPO)	65
L. fermentum XY18	*in vivo*	Gastric injury model group mice	1×10^9 CFU/kg	Reducing expression of TNF-α, IL-12 and IL-6	66
L. fermentum MCC2760	*in vivo*	Hypercholesterolemic C57BL6 Mice	0.95 log CFU/mL	Increasing cytokine IL-10, suppressed proinflammatory cytokine level TNF-α, IL-12 and IL-6	67
L. fermentum DALI02	*in vivo*	Hyperlipidemic mouse	10^9 CFU/mL	Reducing expression of TNF-α and IL-6	43
L. fermentum CQPC07	*in vivo*	Obessed mouse	10^9 CFU/kg	Decreasing the number of inflammatory cytokine interleukin (IL)-1β, tumor necrosis factor-α (TNF-α), IL-6, and interferon- γ (IFN-γ), and increasing the production of cytokine IL- 10 and IL-4.	45

Lactobacillus IN THE TREATMENT OF COVID-19

Probiotics have an essential role in the eubiosis of the human microbiota[68]. Patients with COVID-19 symptoms had lower intestinal bacteria counts than normal patients[69]. These gut bacteria can enhance the immune response[70]. Probiotics and their metabolites can be used as a complementary strategy other than vaccines that can inhibit COVID-19[71]. *Lactobacillus* can inhibit the development of viruses through various mechanisms, direct interaction between probiotics and viruses; stimulation of the immune system; and virus-inhibiting metabolites[72]. The metabolites produced by lactic acid bacteria can inhibit the development of pathogenic bacteria and viruses[73]. These metabolites include amino acid derivatives (indolelactic acid, phenyllactic acid 2-hydroxy-4-,2-hydroxy-4-methylpentanoic acid, and 2-hydroxy-4-methylthio butanoic acid), fatty acids (3-hydroxy-5-cis-dodecanoic acid and 3-hydroxydodecanoic acid), organic compounds (acetic acid, lactic acid, propionic acid, succinic acid, and benzoate acid), cyclic peptides (cyclo(L-Phe-L-Pro) reutericyclin), and other groups of chemical compounds (δ-dodecalactone)[74].

Clinical trials showed that 75.61% of patients treated with probiotic bacteria had a shorter treatment time than those not treated with probiotics. These bacteria can reduce secondary infections and moderate the patient's immune system based on the analytical parameters of IL-6, CRP, total T lymphocytes, NK cells, B lymphocytes, CD4 + T cells, CD8 + T cells, and CD4/CD8 ratio[75]. In another study, patients receiving probiotic bacteria *L. plantarum* (KABP022, KABP023, and KAPB033) with a combination of *P. acidilactici* KABP021 for 30 days showed inhibition against the COVID-19 virus[76]. *In silico* studies have also carried molecular docking on the metabolite *L. plantarum* Probio-88 to the SARS-CoV-2 helicase. The high binding affinity and hydrogen bonding suggests that the association of PlnE and PlnF on the helicase of SARS-COV-2 may inhibit virus replication[77].

Indonesia abounds in biodiversity, including microorganisms. *Lactobacillus plantarum* and *L. fermentum* indigenous strains of Indonesian have potential as anti-inflammatory and immunostimulant. Our preliminary research showed that the superior candidate bacteria from the two strains had antibacterial activity and could withstand acidic conditions and high temperatures. Therefore, further study is needed to determine the anti-inflammatory and immunostimulant activities to be used as an immunomodulator for COVID-19.

CONCLUSION

Based on the results of experimental and clinical research data, *L. plantarum* and *L. fermentum* have activities as anti-inflammatory and immunostimulants in COVID-19 patients. *Lactobacillus* can reduce the activity of inflammatory cytokines IL-1β, IL-6, TNF-, COX-2, Foxp3, SOCS3 suppressor, and increase IL-10. Patients treated with probiotics had a faster recovery time than those not treated with *Lactobacillus*. *Lactobacillus* can reduce secondary infection and increase immune response in COVID-19 patients. Bioactive compounds from these bacteria can also cause anti-inflammatory and immunostimulant activities.

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AUTHORS' CONTRIBUTION

All authors are the main contributors in carrying out the research and writing this review article.

DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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