Journal Bionature
p-ISSN 1411-4720
e-ISSN 2654-5160
Vol. 24. No. 2. Oktober 2023, p. 219-230
http://ojs.unm.ac.id/bionature

Mini Review: Controlling of Blood Glucose Levels Utilizing Lactic Acid Bacteria

Fatmawati Nur [1)], Hafsan [2) *], Faten Khudair[3)]

[1)2)]Universitas Islam Negeri Alauddin Makassar, Sulawesi Selatan, Indonesia.
[3)]Al-Manara College for Medical Sciences, Amarah, Iraq

Correspondence E-mail: hafsan.bio@uin-alauddin.ac.id

Received: 26 - 05 - 2023 Published: 20 - 10 - 2023

Abstract

Lactic acid bacteria (LAB) interest promises a prospective dietary approach for enhancing the management of blood sugar levels in individuals diagnosed with diabetic and those presenting with pre-diabetic conditions. This review article summarizes the available evidence on the role of LAB in blood sugar regulation, focusing on the mechanisms underlying its effects and relevant research results. LAB supplementation has been shown to improve glucose tolerance and insulin sensitivity in animal and human studies, as well as to reduce fasting blood glucose levels in individuals with type 2 diabetes. Potential mechanisms underlying the effects of LAB on blood glucose control include improving insulin sensitivity, reducing inflammation, and improving intestinal barrier function. However, further supporting studies are needed to fully understand the optimal strain and dose of LAB for blood glucose control and to elucidate the mechanisms by which they exert their effects. Despite promising results, the safety and potential side effects of LAB supplements should also be carefully considered. Overall, this review highlights the potential of LAB as a dietary strategy for blood sugar regulation in individuals with diabetic and pre-diabetic.

Keywords: Blood glucose control, Diabetic, *Lactic Acid Bacteria*, Insulin sensitivity.

INTRODUCTION

Type 2 diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose levels due to insulin resistance and impaired insulin secretion (Halawa et al., 2019; Kootte et al., 2012). According to the International Diabetes Federation, diabetes affects more than 463 million adults worldwide, and this number is expected to rise to 700 million by 2045 (International Diabetes Federation, 2019). Diabetes is associated with various complications, including cardiovascular disease, neuropathy, and nephropathy, and is a leading cause of morbidity and mortality worldwide (International Diabetes Federation, 2021).

Lifestyle modification encompassing dietary and physical activity interventions and pharmacological therapies constitute fundamental components in the comprehensive care of diabetic. However, there is growing interest in the potential for natural interventions, such as probiotics, to help control blood sugar levels and reduce the risk of diabetes complications (Kassaian et al., 2018).

Empirical evidence demonstrates the efficacy of probiotics in the regulation of blood glucose levels among individuals afflicted with diabetic and prediabetic conditions. (Cao et al., 2021; Kassaian et al., 2018). For example, a study published in the Journal of Food Science of Animal Resources found that rats fed fermented milk containing Pediococcus acidilactici strain BE and Pediococcus pentosaceus strain M103 had significantly lower blood glucose levels than control mice (Widodo et al., 2023). In another investigation, individuals diagnosed with type 2 diabetes, who were administered probiotics, exhibited notably reduced fasting blood glucose levels and enhanced insulin sensitivity in comparison to counterparts receiving a placebo. (Rezazadeh et al., 2019).

Probiotics are live microorganisms that provide health benefits to the host when consumed in adequate amounts (Ranjha et al., 2021). Lactic acid bacteria (LAB) are a type of probiotic commonly found in fermented foods such as yoghurt, kefir, and kimchi. Lactic acid bacteria have been shown to have a variety of health benefits, including improving gut health, improving immune function, and reducing the risk of infectious diarrhoea. In recent years, there has been increased interest in the potential of LAB to help control blood sugar levels in individuals with diabetic and prediabetic (Castro & Luchese, 2022; Ejtahed et al., 2012; Lazarenko et al., 2023).

The primary objective of this review is to succinctly outline the existing body of evidence concerning the application of lactic acid bacteria (LAB) for the regulation of blood glucose levels among individuals afflicted with prediabetic and diabetic conditions. This review will include mechanisms by which LABs can exert their beneficial effects on blood glucose control, evidence from human and animal studies, and the safety and side effects of L AB supplementation.

RESEARCH METHODS

The method used in writing this scientific article is the literature review method. We traced various literature relevant to the problem studied, namely the use of LAB in controlling blood sugar levels in individuals with prediabetic and diabetic with both test animals and humans. The collected data and information are selected so that the required scientific data and information are obtained and then compiled in a sub-subject, namely the mechanism of controlling blood glucose levels by Lactic Acid Bacteria.

RESULTS AND DISCUSSION

Lactic acid bacteria are a group of Gram-positive, non-sporulation bacteria commonly found in various food products such as yoghurt, kefir, and fermented vegetables. The beneficial effects of LABs on human health have been widely studied, including their potential to help control blood sugar levels in individuals with diabetic and pre-diabetic (Cao et al., 2021; Ejtahed et al., 2011; Jiang et al., 2022; Kassaian et al., 2018; Kijmanawat et al., 2019; Mu et al., 2023; Palacios et al., 2017); Sáez-Lara et al., 2016; Singh et al., 2017; Stefanaki et al., 2019; Sun & Buys, 2016; Wang et al., 2020; Yan et al., 2019; Zhang et al., 2016).

The potential of LAB to help control blood sugar levels in individuals with diabetic and pre-diabetic has been the subject of much research in recent years. LABs can exert their beneficial effects on blood glucose control through several mechanisms, including improving insulin sensitivity, improving intestinal barrier function, and reducing inflammation (Dai et al., 2022; Han et al., 2019; Mu et al., 2023; Noneng Nawangsih et al., 2022; Ostadrahimi et al., 2015; Rezazadeh et al., 2019; Singh et al., 2017; Yilmaz et al., 2022.

Lactic Acid Bacteria Increase Insulin Sensitivity

The pivotal element in the management of blood glucose is insulin sensitivity, wherein insulin, a pancreatic hormone, regulates the metabolism of glucose. In individuals with insulin resistance, cells become less responsive to insulin, leading to increased blood glucose levels. Probiotics can ferment dietary fibre that is not digested by the human body. During this fermentation process, probiotics convert dietary fibre into short-chain fatty Acids (SCFAs), which are byproducts of bacterial metabolism. The three most common types of SCFAs produced by probiotics are acetate, propionate, and butyrate (Gao et al., 2009). Ilustrastion of potential biological effects of SCFAs in humans is described in Figure 1.

Types of SCFAs, especially propionate and butyrate, have been shown to have an important role in improving insulin sensitivity and regulating blood sugar. This mechanism involves the interaction of SCFAs with specific receptors on the body's cells, especially the GPR43 (also known as FFAR2) and GPR41 (also known as FFAR3) receptors (Tolhurst et al., 2012).

When SCFAs, such as propionate and butyrate, bind to GPR43 receptors located in pancreatic beta cells, the complex can stimulate insulin secretion. Insulin is a hormone that plays a role in regulating blood glucose levels. By increasing insulin secretion, the sensitivity of body cells to insulin can be improved, thereby facilitating glucose uptake into cells and regulation of blood sugar (Kimura et al., 2011; Tolhurst et al., 2012).

In addition, SCFAs can also affect glucose production by the liver. When SCFA binds to GPR41 receptors present in the liver, it can reduce glucose production by the liver through glycogen breakdown pathways and gluconeogenesis. Gluconeogenesis is the process by which the liver produces glucose from non-carbohydrate materials, such as amino acids and lactate. By reducing glucose production by the liver, blood glucose levels can be better controlled (Kimura et al., 2011).

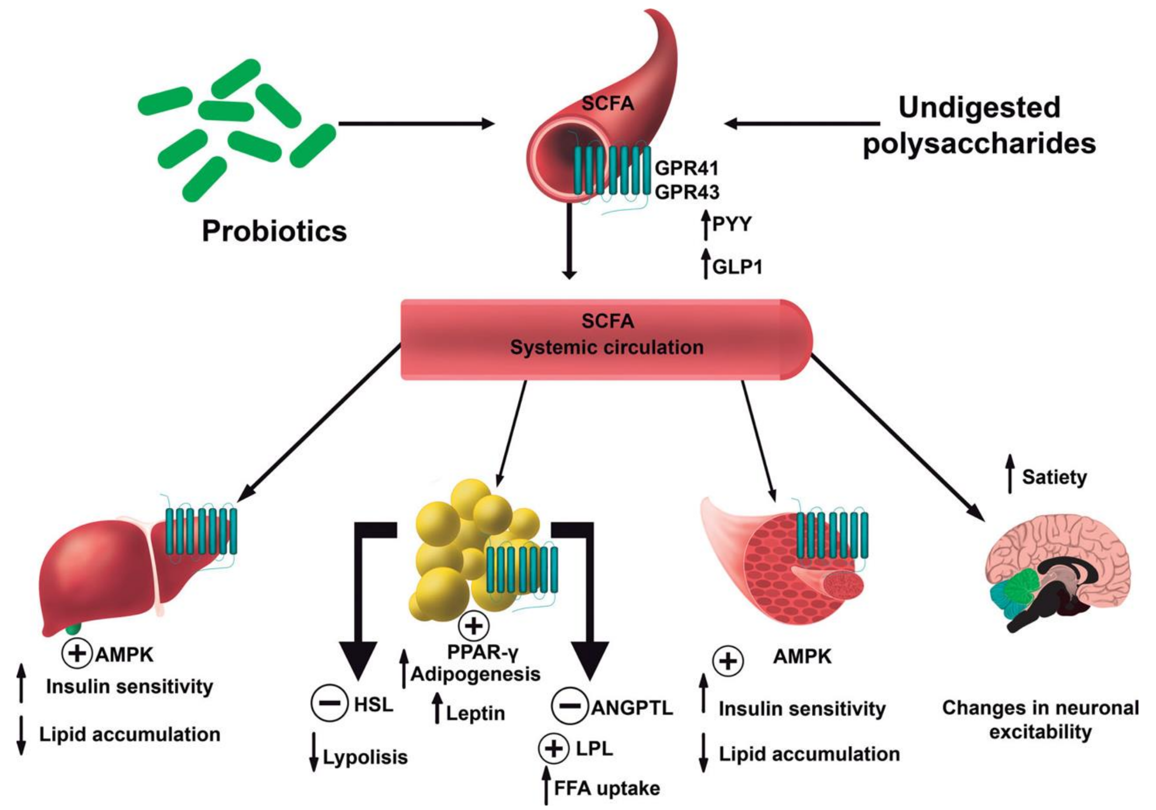

Figure 1. Potential biological effects of SCFAs in humans (Julio Plaza-Diaz et al., 2019)

Numerous investigations have ascertained that the supplementation of lactic acid bacteria (LAB) can enhance insulin sensitivity in both animal and human subjects. For example, a study published in the Journal Acta Diabetologist found that 120 prediabetic adults participated and were randomly allocated to receive probiotic or synbiotic supplements for 24 weeks, showing significantly improved quantitative insulin sensitivity compared to placebo (Kassaian et al., 2018).

Similarly, a study published in the Journal Renal Failure found that duration of intervention, probiotic dosing and probiotic consumption patterns positively impacted the modulation of function of vital organs including the pancreas as evidenced by an increase in the quantitative insulin sensitivity check index compared to those who received placebo (Dai et al., 2022).

In line with the research, a study was also reported by Soleimani et al., (2017) who gave 60 diabetic patients a chance to take capsules containing probiotics Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum or placebo for 12 weeks. After 12 weeks, patients who received the bacterial supplement showed that they had a significant decrease in fasting plasma glucose and the quantitative insulin sensitivity test index improved significantly compared to placebo administration. This is in line with the Report by Cao et al., (2021) who collected various information and concluded that the quantitative insulin sensitivity check index in patients with abnormal glucose metabolism increased significantly with the administration of different probiotic formulations.

Exploration of the effects of probiotic administration on glucose metabolism has been proven in pregnant women with gestational diabetes mellitus (GDM). Compared to the placebo group, probiotics were associated with significant improvements in several indicators related to glycemic control including fasting plasma glucose and fasting serum insulin (Mu et al., 2023).

In the context of increased insulin sensitivity, the secretion of incretin hormones, especially glucagon-like peptide-1 (GLP-1), is also known to increase it through several mechanisms involving the regulation of various aspects of glucose metabolism (Drucker, 2018; Meier, 2012; Vilsbøll & Holst, 2004; Yabe & Seino, 2014). Following is an explanation of some of the mechanisms involved:

- Increased insulin secretion: One of the main effects of incretin hormones, such as GLP-1, is to stimulate insulin secretion from pancreatic beta cells. Insulin is an important hormone in regulating glucose metabolism by facilitating glucose uptake into cells and reducing glucose production by the liver. Increased insulin secretion in response to the hormone incretin can help increase the sensitivity of body cells to insulin (El Khamisy, 2010; He & Shi, 2017).
- Inhibition of glucagon release: The hormone incretin can also inhibit the release of the hormone glucagon from pancreatic alpha cells. Glucagon plays a role in increasing blood glucose levels by stimulating the breakdown of glycogen into glucose in the liver. By inhibiting the release of glucagon, the hormone incretin helps decrease glucose production by the liver, which in turn can improve insulin sensitivity (Drucker, 2018; Kim et al., 2018; Meier, 2012; Tolhurst et al., 2012; Zhao et al., 2022).
- Inhibition of gastric emptying: Incretin hormones, such as GLP-1, can slow gastric emptying after eating. This results in an increase in the contact time of food with the small intestine, slowing the absorption of glucose from the gastrointestinal tract into the bloodstream. By reducing the rate of glucose absorption, the hormone incretin helps control the increase in blood sugar after meals and reduces pressure on pancreatic beta cells to overproduce insulin (Drucker, 2018; Meier, 2012).
- Appetite regulation: In addition to its direct effects on blood sugar regulation, the hormone incretin may also play a role in appetite regulation. Research shows that GLP-1 can provide satiety signals to the brain, reduce food intake, and improve blood sugar control. By reducing overall food intake, the hormone incretin can help maintain a healthy weight and reduce the risk of insulin resistance (Drucker, 2018; Falcinelli et al., 2018; Hernández et al., 2019; Kim et al., 2018; Meier, 2012).

In general, the use of LAB in influencing insulin sensitivity is oriented towards a balanced composition of gut microbiota. The composition of gut microbiota will affect Glucose Metabolism. Some beneficial bacteria in the gut microbiota, such as Bacteroidetes, Ruminococcus, and Akkermansia, have been linked to improved insulin sensitivity.

The study reported by Everard et al. in 2013 utilizing mice demonstrated that alterations in the composition of gut microbiota, particularly an augmentation in Bacteroidetes bacteria population, can mitigate insulin resistance and enhance insulin sensitivity. Bacteroidetes bacteria can modulate glucose metabolism and stimulate the production of the hormone GLP-1 (glucagon-like peptide-1) which regulates blood sugar. Another study in mice by Caesar et al. in 2015 showed that increasing the number of Firmicutes bacteria in the gut microbiota can trigger inflammation and insulin resistance. Conversely, an increase in the number of Bacteroidetes bacteria can reduce inflammation and improve insulin sensitivity (Caesar et al., 2015; Everard et al., 2014).

Lactic Acid Bacteria improve intestinal barrier function

The barrier function of the intestine is also important in blood glucose control. The intestinal barrier helps prevent the entry of harmful substances, such as toxins and bacteria, from the intestines into the bloodstream, since the intestines have an important function as a physical barrier between the external environment and our body. The intestinal barrier function involves intestinal epithelium consisting of dense epithelial cells and channels between cells called associated junctions. The density and strength of the associated junctions are essential to prevent the entry of harmful microorganisms and molecules into the bloodstream. Imbalances in intestinal barrier function can lead to intestinal leakage or fragility in the intestinal barrier, which can lead to health problems such as intestinal inflammation, food allergies, and autoimmune disorders.

Probiotics, such as lactic acid bacteria, have been shown to have the ability to enhance intestinal barrier function by several mechanisms that include:

- Junction Reinforcement Related: Probiotics can influence the expression and activity of junction-related proteins, such as zonula occludens (ZO), occludin, and claudin, which play an important role in maintaining the strength and density of associated junctions. Research shows that probiotics, such as Lactobacillus plantarum, Lactobacillus acidophilus, and Bifidobacterium lactis, can increase the expression of associated junction proteins and reduce intestinal leakage in inflammatory conditions. A study by Anderson et al. in 2010 showed that supplementation of Lactobacillus plantarum can reduce intestinal permeability increases induced by zonulin, a protein that regulates intestinal leakage. This suggests that probiotics may affect intestinal barrier function through the regulation of associated junctions (Anderson et al., 2010).
- Production of Barrier Molecules: Probiotics may also increase the production of barrier molecules that are important in intestinal barrier function, such as mucus and immunoglobulin A (IgA). Mucus is a protective layer on the surface of the intestine that helps protect epithelial cells from damage and infection. IgA is an antibody primarily found in the gastrointestinal tract and plays a role in resisting pathogenic invasion (Mantis et al., 2011; Wells et al., 2017). Research by Mantis et al. in 2011 showed that some strains of Lactobacillus and Bifidobacterium can stimulate IgA production by intestinal plasma cells, which contributes to local defences against intestinal pathogens. In addition, probiotics can also stimulate mucus production by goblet cells, which helps protect the intestinal epithelium from damage and irritation.(Mantis et al., 2011; Wells et al., 2017;Mantis et al., 2011).

- Interaction with Epithelial Cells: Probiotics can interact directly with intestinal epithelial cells through recognition molecules called pattern recognition receptors (PRR). PRR detects the presence of pathogens and molecules derived from microorganisms to activate the defence response (Anderson et al., 2010; Pessione, 2012; Wang et al., 2019; Yan et al., 2007). Studies by Ivanov et al. in 2009 showed that Lactobacillus reuteri interacts with intestinal epithelial cells via PRR, such as Toll-like receptor 2 (TLR2), to stimulate the production of antimicrobial peptides that fight pathogens. These interactions help strengthen local defence responses and improve the integrity of intestinal barrier function(Ivanov et al., 2009).
- Modulating the Immune Response: Probiotics can also modulate the immune response in the gut by regulating the balance between pro-inflammatory and anti-inflammatory immune responses. In inflammatory bowel conditions, an exaggerated immune response can impair intestinal barrier function (Castro & Luchese, 2022; (Everard et al., 2014); Kang et al., 2022;Wells et al., 2017). Research by Wells et al. in 2017 showed that supplementation of Bifidobacterium lactis and Lactobacillus acidophilus in mice with colitis reduced intestinal inflammation and epithelial damage. It is associated with the suppression of the pro-inflammatory immune response and increased anti-inflammatory immune response. (Castro & Luchese, 2022; Everard et al., 2014; Kang et al., 2022; Wells et al., 2017).

In individuals with type 2 diabetes, intestinal barrier function can be compromised, leading to increased inflammation and insulin resistance. Inflammation is a key factor in the development of insulin resistance and type 2 diabetes. Chronic, low-grade inflammation is common in individuals with type 2 diabetes and is associated with increased insulin resistance and a higher risk of complications. Probiotics may help reduce inflammation by modulating the immune system and reducing levels of pro-inflammatory cytokines. For example, a study published in the journal Nutrition Research Reviews found that supplementation with probiotics and prebiotics reduced levels of pro-inflammatory cytokines via the NF-κB pathway reduced intestinal permeability, and decreased oxidative stress in individuals with type 2 diabetes (Kim et al., 2018).

Lactic acid bacteria can help improve intestinal barrier function by promoting the growth of beneficial bacteria and reducing levels of harmful bacteria in the gut. For example, a study published in the journal Diabetes found that supplementation with Lactobacillus acidophilus was found to reduce intestinal permeability and inflammation and reduce weight, and fat mass in mice fed a high-fat diet. Moreover, It proved that L. acidophilus was also able to reverse high-fat diet-induced intestinal dysbiosis, as indicated by a decrease in the ratio of Firmicutes-to-Bacteroidetes and levels of endotoxin-containing Gram-negative bacteria (Kang et al., 2022).

Lactic Acid Bacteria suppress inflammation

Inflammation is the body's natural response to injury or infection, but chronic inflammation can lead to long-term health problems such as inflammatory bowel disease, arthritis, and cardiovascular disease. Probiotics, such as lactic acid bacteria, have been shown to have anti-inflammatory effects by several mechanisms that include:

- Inhibition of Immune Response: Probiotics can inhibit the excessive immune response that causes chronic inflammation. This mechanism involves interactions between probiotics and immune cells in the gut. Probiotics can affect the production of cytokines, molecules that play a role in stimulating or inhibiting inflammation. A study by (Mohamadzadeh et al., in 2011 it was shown that Lactobacillus reuteri can reduce intestinal inflammation in mice with colitis through suppression of the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α). Probiotics may also stimulate the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10), which help inhibit inflammation.(Mohamadzadeh et al., 2011)

- Regulation of Cellular Immune Response: Probiotics can modulate cellular immune responses, especially Th1 and Th17 responses involved in inflammation. The Th1 response involves the production of pro-inflammatory cytokines, whereas the Th17 response is related to chronic inflammation. Research by Tang et al. in 2008 showed that Lactobacillus casei can inhibit Th1 and Th17 cell activation, as well as reduce inflammation in mice with ulcerative colitis. It is associated with decreased production of pro-inflammatory cytokines, such as interferon-gamma (IFN-γ) and interleukin-17 (IL-17) (Tang et al., 2017).
- Inhibition of Mast Cell Activation: Mast cells are a type of immune cell that plays a role in responding to allergens and infections. Excessive activation of mast cells can cause inflammation and allergic responses. Studies by Plaza-Diaz et al. in 2012 showed that some strains of Lactobacillus and Bifidobacterium can inhibit mast cell activation and release of inflammatory mediators, such as histamine. This inhibition of mast cell activation helps reduce inflammation in allergic conditions and inflammatory diseases (Plaza-Diaz et al., 2019).
- Influence on Transcription Factors: Probiotics may also influence the activity of transcription factors involved in inflammation regulation, such as nuclear kappa factor B (NF-κB) and peroxisome proliferator-activated receptor gamma (PPAR-γ). NF-κB is a transcription factor that regulates the production of pro-inflammatory cytokines, while PPAR-γ plays a role in inhibiting inflammation. Research by Yan et al. in 2017 showed that Lactobacillus acidophilus can inhibit NF-κB activation and stimulate PPAR-γ expression in immune cells. This results in decreased production of pro-inflammatory cytokines and reduced inflammation in inflammatory bowel disease conditions (Yan et al., 2007).

Continuing with regards to the capacity of lactic acid bacteria (LAB) to attenuate inflammation, an additional investigation delineated the impact of incorporating nine lactic acid bacteria strains on alleviating symptoms associated with type 2 diabetes induced by a high-fat diet and streptozotocin in mice. Furthermore, the study expounded upon the underlying mechanism of action. Oral administration of Bifidobacterium teenis, B. bifidum or Lactobacillus rhamnosus to rats daily for more than 12 weeks showed that individual strains can reduce fasting and postprandial blood sugar levels, improve glucose tolerance and prevent pancreatic damage. Bacterial strains that exhibit hypoglycemic effects play a beneficial role in reducing insulin resistance by contributing to the production of short-chain fatty acids and the reduction of inflammation. The ability of lactic acid bacteria to reduce inflammation was found to be closely related to their ability to relieve diabetes mellitus (G. Wang et al., 2020).

Safety and Side Effects of Lactic Acid Bacteria

Not all probiotic supplements are created equal, and the quality and purity of probiotics can vary greatly between products. The use of probiotic supplements should be discussed with a healthcare professional, especially in individuals with medical conditions with compromised immune systems, such as those with HIV/AIDS or undergoing chemotherapy, who should avoid taking probiotics or who use drugs that may negatively react with probiotics.

The use of lactic acid bacteria as an antidiabetic therapy has attracted attention in recent years. However, as with any therapy, it is important to consider the safety and potential side effects that may be associated with LAB use. Some things related to the safety of using LAB as an antidiabetic and some side effects that may occur are as follows:

- Safety of LAB Use: Most studies and clinical trials that have been conducted on LAB to date indicate that LAB is generally safe to use as an antidiabetic therapy. LAB is a microorganism that naturally exists in the human body and has long been consumed in various forms of fermented foods, such as yoghurt and probiotic dairy products. As a result, LAB has been regarded as safe for consumption. A study by Delzenne & Reid in 2016 concluded that (Delzenne & Reid, 2009) LAB use is generally considered safe, with fewer incidences of adverse events reported in the literature. Reported side effects are generally mild and temporary, such as mild indigestion.

- Indigestion: One of the possible side effects associated with the use of LAB is mild indigestion. These include symptoms such as flatulence, diarrhoea, gas, or digestive discomfort. However, studies show that these side effects are generally temporary and may disappear on their own over time. A study by Rabot et al. in 2010 evaluated the side effects of (Rabot et al., 2010) LAB use in humans and found that the reported gastrointestinal side effects were generally mild and temporary. Nonetheless, it is important to note that these side effects can vary between individuals.
- Risk of Infection: As microorganisms, there is potential concern about the risk of infection associated with the use of LAB. However, the LAB used in antidiabetic therapy is usually a standardized strain that has gone through a rigorous purification process. A study by Doron et al. in 2018 evaluated the risk of infection associated with the use of LAB in the context of probiotic therapy. They concluded that well-standardized LAB rarely causes infection in healthy individuals. However, the risk of infection may be higher in individuals with compromised immune systems or serious medical conditions (Doron et al., 2005).
- Potential Drug Interactions: Drug interactions are an important factor to consider in the use of LAB as an antidiabetic therapy. Conventional therapy for diabetes involves the use of drugs such as metformin or sulfonylureas. Before using LAB as an adjunct therapy, it is important to consult a medical professional to check for potential drug interactions that may occur (Ihekweazu & Versalovic,2018). A study by J. Plaza-Diaz et al. in 2019 investigated the interaction between LAB and conventional antidiabetic drugs. They found that most LAB did not show significant interactions with antidiabetic drugs, but some LAB strains might affect the absorption or metabolism of certain drugs. Therefore, proper medical monitoring and supervision are required when using LAB along with conventional antidiabetic therapy.(Ihekweazu & Versalovic, 2018;Plaza-Diaz et al., 2019).

The use of Lactic Acid Bacteria (LAB) as an antidiabetic is generally considered safe with few reported side effects. Possible side effects, such as mild indigestion, are generally temporary and may disappear on their own. The risk of infection is rare, especially in healthy individuals. However, drug interactions are possible, and consultation with a medical professional is important before using LAB along with conventional antidiabetic therapy.

CONCLUSION

Lactic acid bacteria have shown promise as a natural and safe intervention for controlling blood sugar levels in individuals with prediabetic and diabetic. LAB can improve insulin sensitivity, increase glucose uptake by body cells, and modulate gut microbiota, leading to lower blood glucose levels and reducing the risk of diabetes complications. Evidence from human and animal studies suggests that supplementation of probiotics with LAB may be a valuable addition to current diabetes management strategies. More research is needed to determine the optimal dose and duration of LAB supplementation and to identify the specific strain of LAB that is most effective in controlling blood sugar levels.

ACKNOWLEDGEMENT

We would like to thank all those who have helped and contributed to this research.

REFERENCES

Anderson, R. C., Cookson, A. L., McNabb, W. C., Park, Z., McCann, M. J., Kelly, W. J., & Roy, N. C. (2010). Lactobacillus plantarum MB452 enhances the function of the intestinal barrier by increasing the expression levels of genes involved in tight junction formation. *BMC Microbiology*, *10*(1), 316.

Caesar, R., Tremaroli, V., Kovatcheva-Datchary, P., Cani, P. D., & Bäckhed, F. (2015). Crosstalk between Gut Microbiota and Dietary Lipids Aggravates WAT Inflammation through TLR Signaling. *Cell Metabolism*, *22*(4), 658–668.

Cao, D. X., Wong, E. Y., Vela, M. N., & Le, Q. T. (2021). Effect of Probiotic Supplementation on Glycemic Outcomes in Patients with Abnormal Glucose Metabolism: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Annals of Nutrition and Metabolism*, *77*(5), 251–261.

Castro, V. M. R., & Luchese, R. H. (2022). Antidiabetogenic mechanisms of probiotic action in food matrices: A review. *PharmaNutrition*, *21*, 100302.

Dai, Y., Quan, J., Xiong, L., Luo, Y., & Yi, B. (2022). Probiotics improve renal function, glucose, lipids, inflammation and oxidative stress in diabetic kidney disease: a systematic review and meta-analysis. *Renal Failure*, *44*(1), 862–880.

Delzenne, N., & Reid, G. (2009). No causal link between obesity and probiotics. *Nature Reviews Microbiology*, *7*(12), 901–901.

Doron, S., Snydman, D. R., & Gorbach, S. L. (2005). Lactobacillus GG: Bacteriology and Clinical Applications. *Gastroenterology Clinics of North America*, *34*(3), 483–498.

Drucker, D. J. (2018). Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. *Cell Metabolism*, *27*(4), 740–756.

Ejtahed, H. S., Mohtadi-Nia, J., Homayouni-Rad, A., Niafar, M., Asghari-Jafarabadi, M., & Mofid, V. (2012). Probiotic yogurt improves antioxidant status in type 2 diabetic patients. *Nutrition*, *28*(5), 539–543.

Ejtahed, H. S., Mohtadi-Nia, J., Homayouni-Rad, A., Niafar, M., Asghari-Jafarabadi, M., Mofid, V., & Akbarian-Moghari, A. (2011). Effect of probiotic yogurt containing Lactobacillus acidophilus and Bifidobacterium lactis on lipid profile in individuals with type 2 diabetes mellitus. *Journal of Dairy Science*, *94*(7), 3288–3294.

El Khamisy, A. E. S. (2010). Effect of Bifidobacterium and Lactobacillus acidophilus in diabetic rats The 5 th Arab and 2 nd. *International Annual Scientific Conference. Le*.

Everard, A., Lazarevic, V., Gaïa, N., Johansson, M., Ståhlman, M., Backhed, F., Delzenne, N. M., Schrenzel, J., François, P., & Cani, P. D. (2014). Microbiome of prebiotic-treated mice reveals novel targets involved in host response during obesity. *The ISME Journal*, *8*(10), 2116–2130.

Falcinelli, S., Rodiles, A., Hatef, A., Picchietti, S., Cossignani, L., Merrifield, D. L., Unniappan, S., & Carnevali, O. (2018). Influence of Probiotics Administration on Gut Microbiota Core. *Journal of Clinical Gastroenterology*, *52*(Supplement 1), S50–S56.

Gao, Z., Yin, J., Zhang, J., Ward, R. E., Martin, R. J., Lefevre, M., Cefalu, W. T., & Ye, J. (2009). Butyrate Improves Insulin Sensitivity and Increases Energy Expenditure in Mice. *Diabetes*, *58*(7), 1509–1517.

Halawa, M. R., El-Salam, M. A., Mostafa, B. M., & Sallout, S. S. (2019). The Gut Microbiome, Lactobacillus acidophilus; Relation with Type 2 Diabetes Mellitus. *Current Diabetes Reviews*, *15*(6), 480–485.

Han, M.-M., Sun, J.-F., Su, X.-H., Peng, Y.-F., Goyal, H., Wu, C.-H., Zhu, X.-Y., & Li, L. (2019). Probiotics improve glucose and lipid metabolism in pregnant women: a meta-analysis. *Annals of Translational Medicine*, *7*(5), 99–99.

He, M., & Shi, B. (2017). Gut microbiota as a potential target of metabolic syndrome: the role of probiotics and prebiotics. *Cell & Bioscience*, *7*(1), 54.

Hernández, Canfora, Jocken, & Blaak. (2019). The Short-Chain Fatty Acid Acetate in Body Weight Control and Insulin Sensitivity. *Nutrients*, *11*(8), 1943.

Ihekweazu, F. D., & Versalovic, J. (2018). Development of the Pediatric Gut Microbiome: Impact on Health and Disease. *The American Journal of the Medical Sciences*, *356*(5), 413–423.

International Diabetes Federation. (2019). IDF diabetes atlas 9th edition 2019. *In International Diabetes Federation*. https://www.diabetesatlas.org.

International Diabetes Federation. (2021). IDF Diabetes Atlas 2021. *In International Diabetes Federation*. In International Diabetes Federation.

Ivanov, I. I., Atarashi, K., Manel, N., Brodie, E. L., Shima, T., Karaoz, U., Wei, D., Goldfarb, K. C., Santee, C. A., Lynch, S. V., Tanoue, T., Imaoka, A., Itoh, K., Takeda, K., Umesaki, Y., Honda, K., & Littman, D. R. (2009). Induction of Intestinal Th17 Cells by Segmented Filamentous Bacteria. *Cell*, *139*(3), 485–498.

Jiang, H., Cai, M., Shen, B., Wang, Q., Zhang, T., & Zhou, X. (2022). Synbiotics and Gut Microbiota: New Perspectives in the Treatment of Type 2 Diabetes Mellitus. *Foods*, *11*(16), 2438.

Kang, Y., Kang, X., Yang, H., Liu, H., Yang, X., Liu, Q., Tian, H., Xue, Y., Ren, P., Kuang, X., Cai, Y., Tong, M., Li, L., & Fan, W. (2022). Lactobacillus acidophilus ameliorates obesity in mice through modulation of gut microbiota dysbiosis and intestinal permeability. Pharmacological Research, 175(1).

Kassaian, N., Feizi, A., Aminorroaya, A., Jafari, P., Ebrahimi, M. T., & Amini, M. (2018). The effects of probiotics and synbiotic supplementation on glucose and insulin metabolism in adults with prediabetes: a double-blind randomized clinical trial. *Acta Diabetologica*, *55*(10), 1019–1028.

Kijmanawat, A., Panburana, P., Reutrakul, S., & Tangshewinsirikul, C. (2019). Effects of probiotic supplements on insulin resistance in gestational diabetes mellitus: A double-blind randomized controlled trial. *Journal of Diabetes Investigation*, *10*(1), 163–170.

Kimura, I., Inoue, D., Maeda, T., Hara, T., Ichimura, A., Miyauchi, S., Kobayashi, M., Hirasawa, A., & Tsujimoto, G. (2011). Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). *Proceedings of the National Academy of Sciences*, *108*(19), 8030–8035.

Kim, Y. A., Keogh, J. B., & Clifton, P. M. (2018). Probiotics, prebiotics, synbiotics and insulin sensitivity. *Nutrition Research Reviews*, *31*(1), 35–51.

Kootte, R. S., Vrieze, A., Holleman, F., Dallinga-Thie, G. M., Zoetendal, E. G., de Vos, W. M., Groen, A. K., Hoekstra, J. B. L., Stroes, E. S., & Nieuwdorp, M. (2012). The therapeutic potential of manipulating gut microbiota in obesity and type 2 diabetes mellitus. *Diabetes, Obesity and Metabolism*, *14*(2), 112–120.

Lazarenko, L., Melnykova, O., Babenko, L., Bubnov, R., Beregova, T., Falalyeyeva, T., & Spivak, M. (2023). *Probiotic Concepts of Predictive, Preventive, and Personalized Medical Approach for Obesity: Lactic Acid Bacteria and Bifidobacteria Probiotic Strains Improve Glycemic and Inflammation Profiles* (pp. 371–390).

Mantis, N. J., Rol, N., & Corthésy, B. (2011). Secretory IgA's complex roles in immunity and mucosal homeostasis in the gut. *Mucosal Immunology*, *4*(6), 603–611.

Meier, J. J. (2012). GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nature Reviews Endocrinology*, *8*(12), 728–742.

Mohamadzadeh, M. , Olson, S., Kalina, W. V., Ruthel, G., Demmin, G. L., Warfield, K. L., & Klaenhammer, T. R. (2011). Lactobacilli activate human dendritic cells that skew T cells toward T helper 1 polarization. *The National Academy of Sciences*, 2880–2885.

Mu, J., Guo, X., Zhou, Y., & Cao, G. (2023). The Effects of Probiotics/Synbiotics on Glucose and Lipid Metabolism in Women with Gestational Diabetes Mellitus: A Meta-Analysis of Randomized Controlled Trials. *Nutrients*, *15*(6), 1375.

Noneng Nawangsih, E., Juan Salma Tugi, R., & Siti Fasihah, I. (2022). Effect of Soyghurt Lactobacillus Acidohillus on Blood Glucose Levels in Alloxan-Induced Diabetic Rats. *KnE Medicine*.

Ostadrahimi, A., Taghizadeh, A., Mobasseri, M., Farrin, N., Payahoo, L., Beyramalipoor, G. Z., & Vahedjabbari, M. (2015). ffect of probiotic fermented milk (Kefir) on glycemic control and lipid profile in type 2 diabetic patients: A randomized double-blind placebo-controlled clinical trial. *Iranian Journal of Public Health*, *44*(2), 228–237.

Palacios, T., Vitetta, L., Coulson, S., Madigan, C. D., Denyer, G. S., & Caterson, I. D. (2017). The effect of a novel probiotic on metabolic biomarkers in adults with prediabetes and recently diagnosed type 2 diabetes mellitus: study protocol for a randomized controlled trial. *Trials*, *18*(1), 7.

Pessione, E. (2012). Lactic acid bacteria contribution to gut microbiota complexity: lights and shadows. *Frontiers in Cellular and Infection Microbiology, 2*.

Plaza-Diaz, J., Ruiz-Ojeda, F. J., Vilchez-Padial, L. M., Gil, A., & Galvez, J. (2019). Gut microbiota and the human microbiome in the context of metabolic disorders. Clinical Microbiology Reviews, 32(2), e00055-18.

Plaza-Diaz, J., Ruiz-Ojeda, F. J., Gil-Campos, M., & Gil, A. (2019). Mechanisms of Action of Probiotics. *Advances in Nutrition*, *10*, S49–S66.

Rabot, S., Membrez, M., Bruneau, A., Gérard, P., Harach, T., Moser, M., Raymond, F., Mansourian, R., & Chou, C. J. (2010). Germ-free C57BL/6J mice are resistant to high-fat-diet-induced insulin resistance and have altered cholesterol metabolism. *The FASEB Journal*, *24*(12), 4948–4959.

Ranjha, M. M. A. N., Shafique, B., Batool, M., Kowalczewski, P. Ł., Shehzad, Q., Usman, M., Manzoor, M. F., Zahra, S. M., Yaqub, S., & Aadil, R. M. (2021). Nutritional and Health Potential of Probiotics: A Review. *Applied Sciences*, *11*(23), 11204.

Rezazadeh, L., Gargari, B. P., Jafarabadi, M. A., & Alipour, B. (2019). Effects of probiotic yogurt on glycemic indexes and endothelial dysfunction markers in patients with metabolic syndrome. *Nutrition*, *62*, 162–168.

Sáez-Lara, M., Robles-Sanchez, C., Ruiz-Ojeda, F., Plaza-Diaz, J., & Gil, A. (2016). Effects of Probiotics and Synbiotics on Obesity, Insulin Resistance Syndrome, Type 2 Diabetes and Non-Alcoholic Fatty Liver Disease: A Review of Human Clinical Trials. *International Journal of Molecular Sciences*, *17*(6), 928.

Singh, S., Sharma, R. K., Malhotra, S., Pothuraju, R., & Shandilya, U. K. (2017). *Lactobacillus rhamnosus* NCDC17 ameliorates type-2 diabetes by improving gut function, oxidative stress and inflammation in high-fat-diet fed and streptozotocintreated rats. *Beneficial Microbes*, *8*(2), 243–255.

Soleimani, A., Zarrati Mojarrad, M., Bahmani, F., Taghizadeh, M., Ramezani, M., Tajabadi-Ebrahimi, M., Jafari, P., Esmaillzadeh, A., & Asemi, Z. (2017). Probiotic supplementation in diabetic hemodialysis patients has beneficial metabolic effects. *Kidney International*, *91*(2), 435–442.

Stefanaki, C., Michos, A., Mastorakos, G., Mantzou, A., Landis, G., Zosi, P., & Bacopoulou, F. (2019). Probiotics in Adolescent Prediabetes: A Pilot RCT on Glycemic Control and Intestinal Bacteriome. *Journal of Clinical Medicine*, *8*(10), 1743.

Sun, J., & Buys, N. J. (2016). Glucose- and glycaemic factor-lowering effects of probiotics on diabetes: a meta-analysis of randomised placebo-controlled trials. *British Journal of Nutrition*, *115*(7), 1167–1177.

Tang, Y., Wu, Y., Huang, Z., Dong, W., Deng, Y., Wang, F., Li, M., & Yuan, J. (2017). Administration of probiotic mixture DM#1 ameliorated 5-fluorouracil–induced intestinal mucositis and dysbiosis in rats. *Nutrition*, *33*, 96–104.

Tolhurst, G., Heffron, H., Lam, Y. S., Parker, H. E., Habib, A. M., Diakogiannaki, E., Cameron, J., Grosse, J., Reimann, F., & Gribble, F. M. (2012). Short-Chain Fatty Acids Stimulate Glucagon-Like Peptide-1 Secretion via the G-Protein–Coupled Receptor FFAR2. *Diabetes*, *61*(2), 364–371.

Vilsbøll, T., & Holst, J. J. (2004). Incretins, insulin secretion and Type 2 diabetes mellitus. *Diabetologia*, *47*(3), 357–366.

Wang, G., Si, Q., Yang, S., Jiao, T., Zhu, H., Tian, P., Wang, L., Li, X., Gong, L., Zhao, J., Zhang, H., & Chen, W. (2020). Lactic acid bacteria reduce diabetes symptoms in mice by alleviating gut microbiota dysbiosis and inflammation in different manners. *Food & Function*, *11*(7), 5898–5914.

Wang, Y., Dilidaxi, D., Wu, Y., Sailike, J., Sun, X., & Nabi, X. (2020). Composite probiotics alleviate type 2 diabetes by regulating intestinal microbiota and inducing GLP-1 secretion in db/db mice. *Biomedicine & Pharmacotherapy*, *125*, 109914.

Wang, Y., Yin, Y., Chen, X., Zhao, Y., Wu, Y., Li, Y., Wang, X., Chen, H., & Xiang, C. (2019). Induction of Intestinal Th17 Cells by Flagellins From Segmented Filamentous Bacteria. *Frontiers in Immunology*, *10*.

Wells, J. M., Brummer, R. J., Derrien, M., MacDonald, T. T., Troost, F., Cani, P. D., Theodorou, V., Dekker, J., Méheust, A., de Vos, W. M., Mercenier, A., Nauta, A., & Garcia-Rodenas, C. L. (2017). Homeostasis of the gut barrier and potential biomarkers. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, *312*(3), G171–G193.

Widodo, W., Kusumaningrum, H. R. P., Wihadmadyatami, H., & Wicaksana, A. L. (2023). Milk Fermented with Pediococcus acidilactici Strain BE Improves High Blood Glucose Levels and Pancreatic Beta-Cell Function in Diabetic Rats. *Food Science of Animal Resources*, *43*(1), 170–183.

Yabe, D., & Seino, Y. (2014). Defining the role of GLP-1 receptor agonists for individualized treatment of Type 2 diabetes. *Expert Review of Endocrinology & Metabolism*, *9*(6), 659–670.

Yan, F., Cao, H., Cover, T. L., Whitehead, R., Washington, M. K., & Polk, D. B. (2007). Soluble Proteins Produced by Probiotic Bacteria Regulate Intestinal Epithelial Cell Survival and Growth. *Gastroenterology*, *132*(2), 562–575.

Yan, F., Li, N., Shi, J., Li, H., Yue, Y., Jiao, W., Wang, N., Song, Y., Huo, G., & Li, B. (2019). *Lactobacillus acidophilus* alleviates type 2 diabetes by regulating hepatic glucose, lipid metabolism and gut microbiota in mice. *Food & Function*, *10*(9), 5804–5815.

Yang, G., Zhang, L., Wang, C., Zhao, Y. J., Zhao, Z. J., Gao, L., Cui, W. D., & Li, S. Y. (2020). Screening and Evaluation of Lactobacillus Strains for Improving Metabolic Syndrome. Modern Food Science and Technology, 36(11), 54–60.

Yilmaz, B., Elibol, E., Shangpliang, H. N. J., Ozogul, F., & Tamang, J. P. (2022). Microbial Communities in Home-Made and Commercial Kefir and Their Hypoglycemic Properties. *Fermentation*, *8*(11), 590.

Zhang, Q., Wu, Y., & Fei, X. (2016). Effect of probiotics on glucose metabolism in patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials. *Medicina*, *52*(1), 28–34.

Zhao, Y., Shu, Y., Zhao, N., Zhou, Z., Jia, X., Jian, C., & Jin, S. (2022). Insulin resistance induced by long-term sleep deprivation in rhesus macaques can be attenuated by *Bifidobacterium*. *American Journal of Physiology-Endocrinology and Metabolism*, *322*(2), E165–E172.