













# Lactic acid bacteria fermented foods: Impact on immune system and consequences over type 2 diabetes mellitus

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## ABSTRACT

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease affecting millions worldwide. Recent studies suggest that dietary interventions may improve glycemic control and lower the risk of T2DM development. In this regard, lactic acid bacteria (LAB) fermented foods have gained attention due to their potential health benefits, including their ability to modulate the immune system and improve glucose metabolism. This review discusses probiotic LABs and their potential usefulness in treating metabolic disorders, focusing on diabetes mellitus (DM). The use of LAB in the fermentation mechanism of food can help in disease prevention and immunoregulation along with the benefits of preservation and escalated nutritional properties, and enhanced flavor of food. The probiotics and the metabolites produced during fermentation are involved in modifying the physiopathology and endocrine physiology or generating specific molecules for signaling pathways that may have these effects. Furthermore, this review discusses the effect, therapeutic approaches, and clinical trials of LAB and LAB fermented foods in different comorbidities, pediatric populations, gestational DM, and diabetic dietary supplements. However, there are still some roadblocks to their widespread use, such as ethical, cultural, and religious issues, which can be reduced with more real-life clinical studies. Additionally, further research into the bioinformatics of probiotic LAB strains is needed to collaborate with other researchers in this field.

## INTRODUCTION

Lactic acid bacteria (LAB), generally related to the order Lactobacillales (Pinu *et al.*, 2017), are heterogeneous, low pH-tolerant, Gram-positive, anaerobic-aerotolerant microbes acknowledged for their talent to ferment carbohydrates and yield lactic acid as an end or premier product (Dimidi *et al.*, 2019;

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Horak *et al.*, 2019; Singh *et al.*, 2017). LABs in a wide-ranging spectrum of fermented foodstuffs, such as fermented dairy (i.e., yogurt, cheese, fermented milk), cereal products, vegetables, fruit, fish, and meat, have shown remarkable health benefits and are considered in general to be safe (Li *et al.*, 2021a; Mokoena, 2017). They are part of the intestine's natural microbial ecosystem and appear essential in maintaining the gut microbiome's homeostasis and diversity (Bintsis, 2018).

Type 2 diabetes mellitus (T2DM) is a complicated, multifaceted, and most prevailing and widespread metabolic disorder associated with chronic hyperglycemia that is preceded by abnormal insulin sensitivity and synthesis (Wang *et al.*, 2021a). T2DM is considered by persistently raised blood glucose than physiological level preceded by an altered insulin quality and quantity. DM is the most prevalent long-standing endocrine non-communicable diseases (NCDs) and is of utmost concern for human health especially in low-middle-income countries and equally around the globe (Hajat and Stein, 2018; Khalequzzaman *et al.*, 2017; Rawal *et al.*, 2017). It is reported that DM, together with its complications, ranks among one of the top 10 mainsprings of departure of life. Consequently, DM and its complications remain the basis of death for over 1–1.6 million patients yearly (Abu *et al.*, 2019; Khan *et al.*, 2020; Lin *et al.*, 2020).

Additionally, it is estimated that 11.3% worldwide passed away because of DM alone. Moreover, 46.2% of these expiries are below 60 years (Saeedi *et al.*, 2020). Multiple studies reported that genetic influence exists for the snowballing of T2DM incidence because of genome dependability (Baig *et al.*, 2020; Irgam *et al.*, 2021). All diabetic-affiliated researchers believe environmental aspects contribute to DM development (Dendup *et al.*, 2018; Kolb and Martin, 2017). T2DM involves a series of immune responses and alleviated inflammation generated due to the disruption of inherent and acquired immune systems (Swain *et al.*, 2014). Furthermore, DM is associated with Interleukin-1 beta (IL-1 $\beta$ ) and Interleukin 6 (IL-6) mRNA levels in peripheral blood mononuclear cells, neutrophil function, and humoral immunity disorder, increasing susceptibility to infectious diseases such as pulmonary tuberculosis (TB) and pneumonia, urinary tract, skin, and soft tissue infections (Akbari *et al.*, 2018; Berbudi *et al.*, 2020).

Multiple studies have found a definite linkage allying the human host and the microbiota through various endocrines, neurological, and immune system pathways. The gastrointestinal microbiota (GM) regulates essential human physiologic systems such as digestion, energy metabolism, and the modulation of the inflammatory process (Al Bander *et al.*, 2020). The gut micro-flora maintains a symbiotic relationship and is pivotal in the individual or patient immune system's induction, training, and functioning. Several researchers suggested that the significant contribution of GM in T2DM and the constituent of the gut microbiome can affect the blooming of T2DM (Akissoé *et al.*, 2015; De Vuyst *et al.*, 2017; Setta *et al.*, 2020; Xia *et al.*, 2021). A stable, healthy, and diverse intestinal microbiota ends insulin resistance (IR) issues and decreases the possibility of T2DM (Acin-Albiac *et al.*, 2021).

Some earlier studies suggested that fermented food helps in reducing diabetic-associated health complications. The food that underwent fermentation, such as kimchi, kanji, soy milk, and kefir that are souring through LAB culture (*Saccharomyces*

*fragilis*, *Leuconostoc cremoris*, *L. casei*, *Streptococcus lactis*, *Streptococcus cremoris*, *Lactobacillus plantarum*, and *Streptococcus diacetylactis*) is reported to improve the antioxidant status of the host system and decrease anti-inflammatory machinery (Acin-Albiac *et al.*, 2021; Alihosseini *et al.*, 2017; de Almeida Souza *et al.*, 2020; Sivamaruthi *et al.*, 2018). Fermented foods, perchance described as those foods or sugar-sweetened beverages (SSBs) prepared by the regulated growth of microbes and enzymatic alterations of minor and major food constituents (Marco *et al.*, 2017). Other studies reported that fermented fruits, vegetables, and nuts significantly improve fasting glucose levels in T2DM patients (Lee *et al.*, 2016).

### Key Messages

- The fermentation of food by microorganisms that are typically members of the LAB family gives rise to bioactive components which have health benefits upon consumption.
- LAB produces several products during metabolism, including vitamins, short-chain fatty acids (SCFAs), bacteriocins, exopolysaccharides, and amines, which raise food's nutritional value and shelf life and reduce harmful substances in food.
- These bioactive compounds may directly modify endocrine physiology and pathophysiology, bringing about therapeutic benefits.
- LAB-fermented food includes pickles, fermented table olives, Indian bamboo tender shoots; sourdough bread and bread-like products; fermented salami, sausages; sauerkraut, Korean kimchi; fermented cereal yogurt; fermented milk-wheat mixtures; fish-shrimp mixtures; cheese and yogurts; Chinese soy sauce, Japanese miso and Indonesian Tempe.
- Probiotics have been found to improve blood glucose control in diabetes through suppression of  $\alpha$ -glucosidase and  $\alpha$ -amylase enzymes; production of d-amino acids and synthesizing B group vitamins, mainly riboflavin.
- They lower adherence of pathobiont, regulate lipid metabolism, improve gut epithelial integrity, suppress inflammatory response, improve insulin signaling, reduce cholesterol absorption and glucose intolerance.
- LAB strains also stimulate toll-like receptor 2 (TLR2)/toll-like receptor 6 (TLR6) and inflammasomes, which is linked with immune regulatory processes and infectious disease prevention.
- Fermented foods like soybean foods have several health benefits, that include "anti-carcinogenic, anti-diabetic, antioxidant, anti-inflammatory, and anti-hyperlipidemic."
- The utilization of LAB in the fermentation mechanism of food can help in disease prevention and immune-regulation along with the benefits of preservation and escalated nutritional properties and enhance flavor of food.

### OBJECTIVES OF THE STUDY

World Health Organization (WHO) defines NCDs as diseases of long duration resulting from a set of behavioral, physiological, environmental, and genetic factors. Most of NCDs are non-infectious in origin and cannot be transmitted directly from one individual to another. The principal categories of NCDs

are cardiovascular diseases (CVDs), chronic respiratory diseases, DM, and cancers (Fardet and Rock, 2018). In the present study, we aimed to investigate LAB-fermented foods and their impact on immune responses to T2DM. This comprehensive review will explore the types of LABs, LAB-fermented foods and their beneficial and therapeutic effects on T2DM and other metabolic disorders like gestational DM.

## MATERIALS AND METHODS

This narrative review was performed from August 2022 to November 2022. Electronic-based data were searched through several databases including Pubmed, Google Scholar, Google Search Engine, Science Direct, and Embase. The following search terms were used: “Lactobacillus,” “fermented food,” “Metabolic Syndrome,” “Inflammation and Diabetes Mellitus,” “Infections, Immunity, and Diabetes Mellitus,” “Molecular mechanism for Diabetes Mellitus,” “Lactobacillus, fermentation role in Inflammation,” “Gestational Diabetes Mellitus and fermented food,” “Role of Lactobacillus fermented food in Diabetes Mellitus,” “Lactobacillus fermented food and immune regulation,” “fermented food benefit in children.” Studies dated before 2000 and research material inaccessible in English were kept out of this desk-top research work. A hand-operated exploration of pertinent papers was performed, and studies deemed suitable were included in this research work.

## LAB DIVERSITY IN FERMENTED FOODS

Fermented foods are a superabundant provenance of microbes, which could be present as indigenous microbiota from natural sources or seed inoculum comprising utilitarian (advantageous and helpful) microorganisms that convert one food substance into edible food products biochemically or organoleptically to make the product palatable and acceptable to the consumers’ (Ashaolu and Reale, 2020; Furse *et al.*, 2019; Voidarou *et al.*, 2020). LAB is well known for synthesizing various metabolic end-product that benefit fermented foods’ nutritional properties. These groups of bacteria usually inhabit fermented food products (FFPs), vegetables, meats, the gastroenteric and urinogenital regions of human beings, domestic and animal life, soil, and water (Erdiansyah *et al.*, 2022).

LAB can synthesize a wide range of biotic acids (e.g., lactic acid) as their metabolic by-products using carbohydrates as the substrate source. The versatile metabolic potential of LAB is widely utilized in seed cultures, acidophilus or lactobacillus bacterium, and microbial cell blossoming laboratories (Kusumoto *et al.*, 2021; Zhao *et al.*, 2020). LAB constitutes a genetically and ecologically disparate category of Gram-positive, microaerophilic, non-motile, punctilious, low pH-compassionate, and rigorously fermentative microbes. They are designated into homofermentative and heterofermentative microbes, established on the products of fermented carbohydrates (Mokoena, 2017). *Firmicutes* comprising the genera/classes *Weissella*, *Lactobacillus*, *Vagococcus*, *Enterococcus*, *Leuconostoc oenococcus*, *Streptococcus*, *Tetragenococcus*, *Lactococcus*, *Carnobacterium*, *Pediococcus*, and *Leuconostoc*, etc. (Chakraborty *et al.*, 2019; Huang *et al.*, 2021; Silva *et al.*, 2018), and *Actinobacteria*, which includes the genus *Bifidobacterium* (Allwood *et al.*, 2021; Tamang *et al.*, 2026). *Lactobacillus* is mainly used as living microbes for

fermentation, known as starter cultures and probiotics, due to its antimicrobial effects and health benefits. Besides, *Lactococcus* and *Streptococcus* are used to some extent as starter cultures, whereas *Bifidobacterium* is used as a probiotic (Yerlikaya, 2019).

The genus *Lactobacillus* has reported a total of 154 species that could be categorized into 11 types established on their source of genesis (<http://www.bacterio.net/lactobacillus.html>). Most of the *Lactobacillus* species were in the alimentary canal of humans, animals, and their feces, followed by plant-based food and fermented by-products. *Bifidobacterium* and *Enterococcus* were reported from humans’ or animals’ intestines, feces, and skin (Kim *et al.*, 2021a). *Leuconostoc* genus is reported from chill-stored meats, clinical sources, fermented milk dairy products, namely yogurt, ymer, kefir, cultured buttermilk, filmj lk, cultured cream and koumiss, and plant materials (Leroy *et al.*, 2018). Species of the *Pediococcus* genus have been identified from spoiled food materials, dairy products, and fermenting cellars (Huang *et al.*, 2021; Wafula *et al.*, 2022). *Lactococcus* is principally related to milk products and plant materials (Di Stefano *et al.*, 2017; Trejo-Gonz lez and Guti rrez-Carrillo, 2022). *Propionibacterium* and *Bifidobacterium* species in fermented milk are usually observed as associated microbes (Simons *et al.*, 2020).

LAB associated with fermented food could be categorized into a primary starter and secondary cultures. Generally, *Lactococcus* spp., *Streptococcus thermophiles*, *Leuconostoc* spp., *Lactobacillus helveticus*, and *Lactobacillus delbrueckii* are the primary starters with a single function to produce lactic acid to ensure relevant conditions. Secondary cultures include *Lactobacillus*, *Carnobacterium*, *Enterococcus*, and *Pediococcus*, which convert the organoleptic characteristics of food (Hassan *et al.*, 2020).

Worldwide fermented foodstuffs are produced and marketed on a variety of raw materials used, such as fermented milk products, meat products (Mudadu *et al.*, 2022; Parlindungan *et al.*, 2021), cereals (Adesulu-Dahunsi *et al.*, 2018; Marga *et al.*, 2021; Menezes *et al.*, 2018; Voidarou *et al.*, 2020), vegetables (e.g., bamboo shoots) (Behera and Balaji, 2021; Kim *et al.*, 2016; Park *et al.*, 2014), legumes, dried, and smoked fish products, alcoholic beverages, etc. (Barons *et al.*, 2022; Tamang *et al.*, 2017). The primary starter in milk fermentation comprises *Lactococcus lactis* subsp. *lactis*, *Lactococcus lactis* subsp. *cremoris*, *Lactobacillus delbrueckii* subsp. *delbrueckii*, *Lactobacillus delbrueckii* subsp. *lactis*, *Lactobacillus helveticus*, *Streptococcus thermophilus*, and *Leuconostoc* spp. (Simons *et al.*, 2020). In the cheese-making process, the secondary cultures are *Brevibacterium linens*, *Debaryomyces hansenii*, *Geotrichum candidum*, *Penicillium camemberti*, *Propionibacterium freudenreichii*, and *Penicillium roqueforti* were utilized for the building up texture and flavor all the while of the cheese ripening procedure (Wu *et al.*, 2017). The secondary cultures in fermented milk comprised *Enterococcus durans*, *Enterococcus faecium*, *Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus salivarius*, and *Staphylococcus* spp. (Nehal *et al.*, 2019). LAB species found in cereal fermentation are predominant in *Pediococcus*, *Enterococcus*, *Weissella* *Lactococcus*, *Leuconostoc*, *Lactobacillus*, and *Streptococcus* (Wu *et al.*, 2022). The dominant species during vegetable fermentation are *Pediococcus* and *Lactobacillus*, followed by *Lactococcus*,

*Weissella*, *Tetragenococcus*, and *Leuconostoc* (Toe *et al.*, 2019). The LAB isolated from some FFPs from different regions (Agus *et al.*, 2018; Ashaolu and Reale, 2020; Carafa *et al.*, 2019; Kariyawasam *et al.*, 2021; Mikelsaar *et al.*, 2016; Tamang *et al.*, 2016). A list of diverse categories of LAB according to their source of origin throughout the globe is presented in Table 1 (Castellone *et al.*, 2021).

## FERMENTED FOODS AS THE SOURCE OF MICROBIAL METABOLITES

### Microbial metabolites

Microbial metabolites are low molecular weight chemical compounds needed for functioning the metabolic processes of microorganisms (Pinu *et al.*, 2017). These microbial metabolites per chance designated as “primary” and “secondary” constructed on their purpose and responsibility. Primary metabolites are essential for cellular growth, development, and reproduction (nucleotides, amino acids, and end products of fermentation like organic acid and ethanol); hence bacteria produce these continuously during their growth (Horak *et al.*, 2019; Singh *et al.*, 2017). Nonetheless, the secondary metabolites are not the growth requirements of bacteria. These are made when bacterial cells face nutrient deprivation and/or environmental stresses in the stagnant or static growth stage (Horak *et al.*, 2019). The secondary metabolites are antimicrobial, anti-parasitic, anti-tumor, enzyme inhibitors, and immune-suppressive (Singh *et al.*, 2017).

### Fermented foods

Fermented foods (foods and SSBs) are brought out through the conversion of food constituents due to the enzymatic actions of microorganisms during their growth. Since ancient times, fermented foods have been famous as traditional foods in different regions. In recent years, fermented foods are becoming more popular for their longer shelf life and beneficiary roles in human health (Dimidi *et al.*, 2019). Microorganisms produce fermented foods mainly by lactic, acetic, alcoholic, and alkaline fermentation processes. LAB has fermented dairy, meat, and vegetable products through lactic fermentation, while Kombucha, cocoa, and vinegar fermentation involves acetic acid bacteria by acetic fermentation. Yeasts carry alcoholic fermentations to produce beer, wine, and loaves of bread, and alkaline fermentations occur by various fungi during cheese, fermented meats, and soy products (Li *et al.*, 2021a). These fermentation processes form novel metabolites due to interacting with the food matrix and microbial enzymes. These metabolites have many benefits for human health (Li *et al.*, 2021b).

### Fermented foods produced by LAB

The prominent role of LAB during fermentation is to bring out lactic acid through the fermentation of food carbohydrates. In addition, LAB also degrades proteins and lipids and produces abundant esters, aldehydes, sulfur compounds, alcohols, and acids that enhance the flavor of different FFPs. In addition to these, LAB’s metabolism results in the formation of vitamins, short-chain fatty acids, bacteriocins, exopolysaccharides, and amines. These products raise the nutritional value of food, increase food shelf life, and lower harmful substances (Bintsis, 2018; Wang *et al.*, 2021a). This microorganism is widely used

for food fermentation and preservation due to its beneficial characteristics. Examples of food fermented and preserved using LAB include fermented cucumber (pickles), fermented table olives, Indian bamboo tender shoots; sourdough bread and bread-like confection (Indian *idli*, Philippine *puto*); fermented meats (e.g., salami, sausages); fresh vegetables like cabbage (Korean kimchi, sauerkraut); fermented corn yogurt (Kenyan *Uji*, Benin Akpan, Nigerian *ogi*, etc.); fermented milk-wheat concoction [Egyptian *kishk* (*savory pudding*), Greek *trahanas*, etc.]; fish-shrimp blended food stuff (Philippine *burong dalag and balao balao*); and fermented milk (cheese and yogurts); the amino acid/peptide meat-aroma seasoning gravy and pasted made by cereal and legume fermentation (Chinese soy sauce, Japanese *miso*), and protein-rich vegetables met substitutes (Indonesian *Tempe*).

## Metabolites produced by LAB during fermentation process

### Organic acids

LAB produces varieties of organic acids during the lactic acid fermentation process, such as—lactic acid, acetate, propionate, 3-hydroxypropionate, formate, succinate, 2-ketoisocaproic acid, 2-hydroxyisocaproic acid, phenyl lactic acid, etc. These organic acids significantly produce fermented products’ flavor enhancers (Wang *et al.*, 2021a).

### Bacteriocins

LAB produces different bacteriocins such as lantibiotics containing lanthionine (e.g., Nisin), bacteriocins without lanthionine, and helveticin M and J; antibiotic diplococcin, which play the role as preservatives in fermented foods (Chakraborty *et al.*, 2019; Fuochi *et al.*, 2021; Hassan *et al.*, 2020; Silva *et al.*, 2018; Simons *et al.*, 2020; Wang *et al.*, 2021a).

### Vitamins

Several vitamins, like riboflavin, folic acid, nicotinic acid and nicotinamide, pyridoxine, cobalamine, vitamin C, Vitamin K<sub>2</sub>, etc., are formed by LAB. LAB is extensively consumed in the food business to churn out food by fermentation with specific vitamins for the targeted population (Wu *et al.*, 2017).

### Exopolysaccharides

LAB produces different types of EPS. EPS may be used as an additive in the food industry, increase food texture, exhibit excellent antioxidant and anticlotting properties, and show inhibitory effects on various pathogenic bacteria (Nehal *et al.*, 2019).

### Amino acids

Amino acids are essential taste enhancers of food (Christa *et al.*, 2022). LAB produces amino acids through proteolysis and amino acid catabolism (Toe *et al.*, 2019). Isoleucine, leucine, and valine are amino acids that contain prorated-string; phenylalanine tryptophan and tyrosine possess aromatic amino acids, and cysteine and methionine are sulfur-containing amino acids perform as the dominant amino acids to enhance the taste (Han *et al.*, 2019; Hernandez-Valdes *et al.*, 2020a, 2020b; Molfetta *et al.*, 2022; Moore *et al.*, 2021; Parthasarathy *et al.*, 2018; Yamazaki *et al.*, 2020). LAB also produces  $\gamma$ -aminobutyric acid (GABA) and ornithine. GABA and ornithine are both non-proteinogenic

Table 1. Diversity of LAB in fermented foods of different world regions.

Serial no.	Authors name	Journal name	Regions	LAB	Principal observations
1	Ashaolu and Reale, 2020	Microorganism. 2020; 8(8):1176.	European fermented foods	<i>L. alimentarius</i> , <i>L. acidophilus</i> , <i>L. casei</i> , <i>L. citreum</i> , <i>L. buchneri</i> , <i>L. brevis</i> , <i>L. delbrueckii</i> , <i>L. rossiae</i> , <i>L. sanfranciscensis</i> , <i>L. mindensis</i> , <i>L. anylvovorus</i> , <i>L. fermentum</i> , <i>L. farciminius</i> , <i>L. johnsonii</i> , <i>L. fructivorans</i> , <i>L. frumenti</i> , <i>L. paralimentarius</i> , <i>L. panis</i> , <i>L. plantarum</i> , <i>L. pontis</i> , <i>L. reuteri</i> , <i>L. mesenteroides</i> , <i>L. pseudomesenteroides</i> , <i>P. pentosaceus</i> , <i>W. confusa</i> , <i>W. korensis</i> , <i>W. cibaria</i>	In the manufacture of fermented vegetables and grains, the employment of various strains of bacteria, particularly LAB, can have positive socioeconomic impacts in addition to several other potential advantages.
2	Carafa <i>et al.</i> , 2019; Gao <i>et al.</i> , 2022	Food Res Int. 2019; 115:209–218. Foods. 2022;11(9):1344.	Fermented foods globally	<i>L. lactis</i> subsp. <i>lactis</i> , <i>Propionibacterium freudenreichii</i> , <i>Brevibacterium linens</i> , <i>L. plantarum</i> , <i>L. helveticus</i> , <i>L. delbrueckii</i> subsp. <i>delbrueckii</i> , <i>Staphylococcus</i> spp., <i>L. casei</i> , <i>L. lactis</i> subsp. <i>cremoris</i> , <i>L. delbrueckii</i> subsp. <i>lactis</i> , <i>L. salivarius</i> , <i>Leuconostoc</i> spp., <i>S. thermophilus</i> , <i>E. durans</i> , <i>E. Faecium</i>	Compared to the control, cheese was treated with the studied strains of <i>L. lactis</i> subsp. <i>lactis</i> , <i>S. thermophilus</i> , and <i>Lactobacillus rhamnosus</i> BT68 had a more consistent microbial composition over-ripening.
3	Kariyawasam <i>et al.</i> , 2021	Food Sci Technol. 2021;58(7):2467–2478. Nutrients. 2021;13(5):1516.	Asian fermented foods	<i>Streptococcus faecalis</i> , LAB <i>Lactobacillus plantarum</i> , <i>Leuconostoc mesenteroides</i> , <i>Torulopsis</i> , <i>L. casei</i> , <i>L. brevis</i> , <i>Lactobacillus bulgaricus</i> subsp. <i>Delbrueckii</i> ( <i>L. bulgaricus</i> ), <i>pullulans</i> , <i>Leuconostoc</i> , <i>L. cremoris</i> <i>lactis</i> , <i>Streptococcus thermophilus</i> , and <i>Propioni bacterium shermanii</i> <i>Lactobacilli</i> , namely <i>Lactobacillus helveticus</i> , <i>Lactobacillus plantarum</i> , <i>Lactobacillus kefir</i> , and <i>Lactobacillus casei</i>	The credibility of using milk products as carriers for unique probiotic bacteria.
4	Wang <i>et al.</i> , 2022	Crit Rev Food Sci Nutr. 2022;1–15.	Australian and American fermented foods	<i>Bifidobacterium</i> spp., <i>L. acidophilus</i> , <i>L. casei</i> , <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> , <i>L. gasserii</i> , <i>L. johnsonii</i> , <i>L. gasserii</i> , <i>L. rhamnosus</i> , and <i>S. thermophilus</i> .	The primary processes discussed by which the lactic acid bacillus dominant flavor is formed.
5	Wang <i>et al.</i> , 2022; Shahbazi <i>et al.</i> , 2021	Crit Rev Food Sci Nutr. 2022;1–15. Nutrients. 2021;13(5):1516.	African fermented foods	<i>Lactobacillus</i> sp., <i>L. lactis</i> subsp. <i>cremoris</i> , <i>L. lactis</i> subsp. <i>lactis</i> (dominating), <i>Enterococcus</i> , <i>Lactobacillus</i> , and <i>Leuconostoc</i> spp.	The importance of fermented plant foods on health, the anti-inflammatory and immunomodulatory qualities of specific fermented plant foods, and their effects on gut microbiota.

amino acids. GABA exists in nature abundantly and impairs neurotransmitters in the mammalian central nervous system (Wang *et al.*, 2021a). Ornithine performs multiple critical physiological functions: it works against obesity, stimulates growth hormones, promotes muscle growth, is anti-fatigue, treats cirrhosis, etc. (Lee *et al.*, 2021).

### Flavor compounds

The flavor elements synthesized by LAB encompass ketones, organic acids, ketones, alcohols, and esters through the metabolism of citric acid and amino acids. LAB has different metabolites such as diacetyl, acetoin, butanediol, erythritol, 2,3-butanedione, and 2,3-pentanedione as flavoring agents. In addition, LAB can synthesize sugar alcohols (polyols) used as stabilizers, thickeners, softeners, etc. Particular LABs can produce mannitol, which can be added as a sweetener to food for several health benefits for diabetic individuals. It does not significantly increase blood sugar levels (Lee *et al.*, 2021; Wang *et al.*, 2021a).

### Antioxidant substances

Many reports on LAB synthesizing antioxidant metabolites have recently been published. Some LAB can metabolize oxidized phenolic compounds and glutathione (Lee *et al.*, 2021).

## LABS AND METABOLIC HEALTH

### Metabolic syndrome (MetS)

MetS is also recognized as syndrome X or insulin resistance (IR) syndrome. It is a constellation of ailments leading to T2DM and cardiovascular diseases. Reaven originally described it in 1988 referring to a clustering factors related to hyperglycemia (Reaven, 1988), IR, systemic hypertension, obesity, and dyslipidemia (Saklayen, 2018). Several MetS definitions were proposed with slightly different cut-points and the cardinal components required to confirm the diagnosis. This led to confusion and a lack of consistency in the diagnostic criteria for MetS (Nilsson *et al.*, 2019). Recently, MetS has been defined as a group of comorbid illnesses that include obesity, hypertension, and unbalanced carbohydrate and lipid metabolism, with abnormal deposition of fats, IR, and prolonged low-grade inflammation, constitutes a significant health and social problem (Aguilar-Salinas *et al.*, 2019; Dobrowolski *et al.*, 2022). Multiple recent studies reported that adherence to guidelines improves MetS disease progression (Alefishat *et al.*, 2017; Sigit *et al.*, 2022; Standage-Beier *et al.*, 2022). A person would be qualified for the MetS if they have any three abnormal findings out of the succeeding five components: 1) upheaved waist perimeter, 2) uplifted triglycerides, 3) minimum high-density lipoprotein (HDL) cholesterol, 4) upraised blood pressure and 5) high-up fasting plasma glucose (FPG), based on the maximum ceiling points as outlined in Table 2.

The data collection on MetS remains particularly complex in apropos of the measurement, given the varying criteria used for its diagnosis; however, various epidemiological studies estimated that MetS prevalence varies between 20% and 45% (Ansarimoghaddam *et al.*, 2018; Engin, 2017; Herningtyas and Ng, 2019; Li *et al.*, 2018a). Over the past decades, several studies from multiple countries across the globe reported the trends of increasing MetS prevalence, including age-, gender-,

ethnicity- and other population-specific trends (Gao *et al.*, 2017; Hirode and Wong, 2020; Lee *et al.*, 2011; Li *et al.*, 2018b; Rojas-Martínez *et al.*, 2018). In the midst of the part and parcel of MetS, the pervasiveness of hypertriglyceridemia, impaired FPG, and abdominal obesity was significantly increased (Lee *et al.*, 2018b; Shin *et al.*, 2018).

Central (visceral) obesity has been considered the main initiating factor for developing all the MetS components. The uttermost time and time-again approved and acknowledged hypothesis for the underlying pathogenesis of MetS with IR results from inappropriate lipolysis and eventual rise in circulating free fatty acids associated with central obesity (Fahed *et al.*, 2022). Increased fatty acid production inhibits the antilipolytic effects of insulin, resulting in lipolysis and further production of free fatty acids (McCracken *et al.*, 2018). Additionally, the vicious cycle between IR and obesity is promoted by secondary hyperinsulinemia's weight gain effects of secondary hyperinsulinemia (Pennings *et al.*, 2018). The impact of obesity on insulin metabolism is multidirectional and interrelated, and they seem to be mediated via complex and multiple pathways (Barber *et al.*, 2021). Although the exact underlying pathogenic mechanisms of the development of obesity-related IR do not appear to be wholly understood, the current main theories suggest that they implicate chronic inflammation triggered by changes in adipokine and cytokine release (Amin *et al.*, 2019; Lauterbach and Wunderlich, 2017), gut microbial dysbiosis, which in its turn contributes to the inflammatory response (Jiao *et al.*, 2018), mitochondrial dysfunctions (Di Meo *et al.*, 2017), and remodeling of adipose extracellular matrix (ECM) (Lin *et al.*, 2016; Fig. 1).

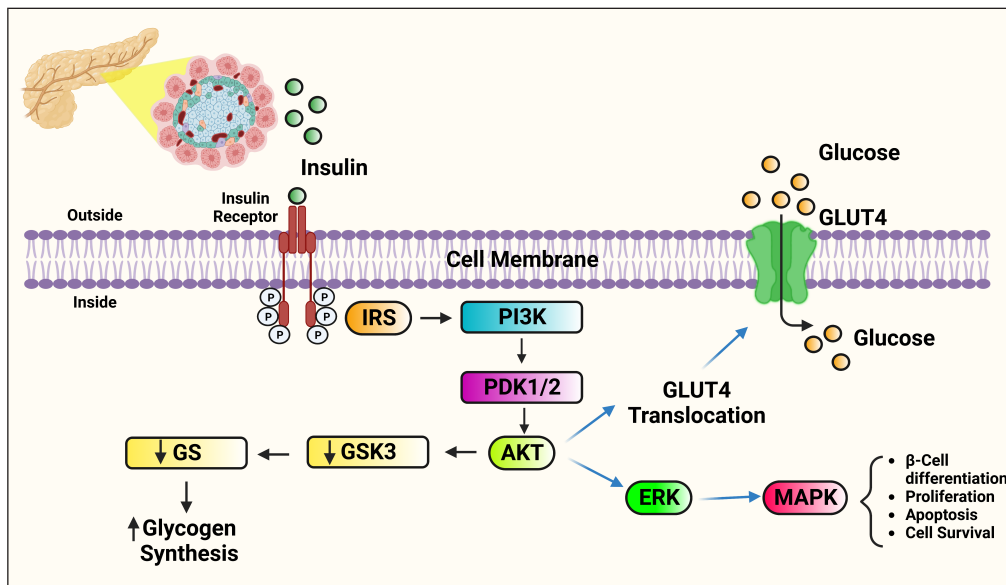
### Mechanisms of the health out-turn of fermented foods

Food fermentation changes biologically active and nutritional properties through microorganisms' growth and mitochondrial and biochemical processes in fresh and uncooked food (Dimidi *et al.*, 2019). The fermenting microorganisms can be found in the raw food or environment, such as in the kimchi or sauerkraut fermentation process, or added as starter cultures. For example, the bacterial genera commonly found in kombucha and kefir result from culture-dependent techniques (Rezac *et al.*, 2018).

Several putative modes of action have been suggested to describe the beneficial results of fermented food on human metabolism and health. Firstly, as food travels through the gastrointestinal tract (GIT), microorganisms from fermented food appear to be only transiently present in the gut. Nevertheless, these microorganisms may still provide a physiological benefit by leveraging the gut microbiota community and the consequent generation of by-products with potential immune-regulatory and other health effects (Şanlıer *et al.*, 2019). Secondly, some food compounds, such as flavonoids, may be converted to bioactive metabolites with high antioxidant activity. Such conversion occurs primarily due to acidification, the disintegration of the cell walls of food ingredients, and increased enzymatic activities that lead to bioactive antioxidant compound release (Adebo and Gabriela Medina-Meza, 2020). Thirdly, the fermenting bacteria dramatically increases the levels of bioactive molecules, such as biogenic peptides and polyamines, with likely repercussions on the immune and cardiovascular systems (Pessione and Cirrincione, 2016). Fourthly, the fermentation method helps reduce the extent

**Table 2.** Touchstone for clinical diagnosis of the “harmonized” MetS (adopted from Alberti *et al.*, 2009).

Measure	Categorical cut points	
	Men	Women
Blown up waist perimeter	From $\geq 85$ to 102 cm	From $\geq 80$ to 90 cm
Puffed-up triglycerides (drug treatment for escalated triglycerides is a substitute criterion)	$\geq 150$ mg/dl (1.7 mmol/l)	$\geq 150$ mg/dl (1.7 mmol/l)
Turn down HDL cholesterol (drug treatment to diminish HDL cholesterol is an alternative criterion)	$< 40$ mg/dl (1.0 mmol/l)	$< 50$ mg/dl (1.3 mmol/l)
Raised blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternative criterion)	Systolic $\geq 130$ and/or diastolic $\geq 85$ mmHg	Systolic $\geq 130$ and/or diastolic $\geq 85$ mmHg
Put up fasting glucose (drug treatment minimizing glucose is an alternative criterion)	$\geq 100$ mg/dl	$\geq 100$ mg/dl



**Figure 1.** Insulin signaling pathways. IRS: Insulin receptor substrate; PI3K: Phosphoinositide 3 kinase; PDK1: Phosphoinositide-dependent kinase-1; AKT: Protein kinase B; GSK3: Glycogen synthase kinase 3; GS: Glycogen synthase; ERK: Extracellular signal-regulated kinase; MAPK: Mitogen-activated protein kinase; GLUT4: Glucose transporter type 4. This figure has been developed by utilizing the premium version of BioRender (<https://biorender.com/>) with License No.:TC24TVFIRX. Image Credit: Susmita Sinha.

of certain anti-nutriments and toxins in food matrices. Sourdough ferment can significantly reduce osmotically active, non-digestible, and readily fermentable carbohydrates causing intolerance in patients with irritable bowel syndrome (Canesin and Cazarin, 2021). Enzymatic activities associated with the fermentation of soybeans help minimize phytic acid concentrations, a naturally occurring food toxin (Jacobsen *et al.*, 2018). Lastly, fermented food contains vitamins and prebiotics, which have multiple benefits to human health, like decreasing cancer risk, anti-inflammatory, and metabolic regulation (Cichońska and Ziarno, 2021; Tarvainen *et al.*, 2019).

#### The after-effects of LAB-fermented food on metabolic health

The microbial collection of fermented foods is frequently comprised primarily of LAB, the most used microbes in food mass preparation. Many investigated probiotics originated in the LAB community. Hence regular consumption of LAB-fermented food has multiple effects on homeostasis and body functions (Castellone *et al.*, 2021). Russian-born biologist Élie Metchnikoff first presented a hypothesis about a link between eating LAB-

fermented food and health in 1907. He suggested that prolonging the expectation of life among Balkan people was credited to the substantial ingestion of Bulgarian yogurt and other curdled milk (Mowat, 2021). Since then, health benefits associated with lactic acid food fermentation, including metabolic health effects, have been explored in several studies (Castellone *et al.*, 2021; Cuevas-González *et al.*, 2020; De Filippis *et al.*, 2020; Mathur *et al.*, 2020), yet the exact mechanisms have not been elucidated clearly.

LAB-fermented food is recommended as a non-pharmacological approach to regulating hypertension (Castellone *et al.*, 2021; Eroğlu and Sanlier, 2022). The hypotensive effect is attributable to angiotensin-1-converting enzyme (ACE-1) inhibitors as among the leading observed clusters of bioactive peptides released due to fermenting process of the lactic acid process, specifically isoleucine, proline, proline (IPP) and valine, proline, proline (VPP) (Beltrán-Barrientos *et al.*, 2016; Huang *et al.*, 2021; Pujiastuti *et al.*, 2019). Cheddar cheeses containing probiotic *Lactobacillus acidophilus* and *L. helveticus* promote ACE-1 inhibitory activity. Thereby averting the alteration of Angiotensin-I into angiotensin-II and reducing raised blood

pressure through minimizing vasoconstriction (Ong and Shah, 2020; Qi *et al.*, 2020). Furthermore, improving human metabolism is linked to EPS formation by LABs. EPS are long sugars polymers with promising health effects, including immune modulation and antioxidant effect, and prebiotic properties such as producing organic acids and gasses inhibiting harmful gut bacteria (Lynch *et al.*, 2018). Recent studies revealed the competence of EPS to cut down cholesterol and glucose (Korcz *et al.*, 2018; Tiderencel *et al.*, 2020). Oral administration of LABs lowered inflammation cytokines through the significant renovation and advancement of epithelial protective power and regulated the expression of lipid and glucose metabolism genes (Tiderencel *et al.*, 2020).

### PROBIOTIC TRAITS OF LAB AS AN IMMUNE-REGULATOR/IMMUNE-MODULATOR

Probiotics are living bacteria and yeasts with beneficial health properties when ingested into the body or applied to it in appropriate doses. Probiotics are considered “good microorganisms,” and most are intestinal microbiota. The most widely used probiotics are the LAB because of their nutritional value. Ideally, a probiotic microbe should have the ability to: sustain within the digestive system while passing through it; adhere and colonize the epithelium of the intestine; remain viable in the GI environment; make use of the nutrients and substrates present in a host diet, and again, the organism should not cause disease nor is virulent (Żukiewicz-Sobczak *et al.*, 2014). Several methods have been used to assess ideal probiotics properties (Kim *et al.*, 2019a). These include the acid and bile salt forbearance test, which evaluates the capability of the organism to tolerate extremely low-pH and high-bile-salt congregation (Kim *et al.*, 2019a, 2019b); thermotolerance test, which is used to assess the organism’s ability to withstand temperature variations (Correa Deza *et al.*, 2017; Guo *et al.*, 2016); antibacterial assays to determine the antibacterial activities of the organism against bacterial enteropathogens (Kim *et al.*, 2019a, 2019b); cell adhesion test which assesses the capability of the microbe to bond to the walls of the gut (Kim *et al.*, 2019b; Xing *et al.*, 2014); lysosomal and proteolytic activity assay to evaluate the power of the microbe to resist hydrolytic lysosomal and proteolytic enzymes respectively (Kim *et al.*, 2019b).

Several reports have documented the health advantages of probiotics for humans (Collinson *et al.*, 2020; Hill *et al.*, 2014; King *et al.*, 2014; Piqué *et al.*, 2019). Probiotics can modify the microbiota of the digestive system to exert their beneficial effects (Tsai *et al.*, 2021). Probiotics are widely applied in several human endeavors, ranging from food products and agriculture to disease prevention and treatment and health maintenance, pre-operative and post-operative processes. They protect the host against pathogenic microbes and reinforce the immune system (Stavropoulou *et al.*, 2020).

Probiotics can control the activities of professional antigen-processing cells and the B- and T-cells via the invigoration of TLRs, thereby regulating their host’s innate and adaptive immune reprisal (Raheem *et al.*, 2021). These probiotics with immunoregulatory characteristics are referred to as immunobiotics. Recent studies have documented how probiotics, notably LAB, activate the immune system, some of which are outlined below.

### Dendritic cells (DCs) modulation by probiotics

DCs are well-known efficient and competent antigens-presenting cells and provide possible interaction between adaptive

and innate immunity. They process antigens and deliver the same to B- and T-cells of the immune system. They are scattered at different parts of the GIT and modulate interferon-gamma (IFN $\gamma$ ) production (the cytokines that stimulate proinflammatory responses that kill intracellular parasites and preserve autoimmune responses). This is called the Th1 response of the DCs upon activation. Th2-type responses of DCs involve the production of cytokines like ILs 4, 5, and 13, enhancing immunoglobulin (Ig) E and eosinophilic feedback during allergic diseases, and IL-10, which has more anti-inflammatory retribution (Azad *et al.*, 2018; Berraondo *et al.*, 2019). In the presence of *L. rhamnosus*, DCs can modulate the memory and naïve T cell and the free flow of ILs -2, 4, and 10 (Llewellyn and Foey, 2017). Also, oral application of *L. rhamnosus* was proclaimed to cause CD4+ to differentiate into Th1 and Th2 cells *in vivo* (Ludwig *et al.*, 2018). Specific probiotic strains regulate DC responses by stimulating various pathogen-sensing-signaling expressways like TLR2, TLR9, and Nucleotide-binding oligomerization domain-containing protein 2 (Llewellyn and Foey, 2017).

### Natural killer cells (NKs) modulation by probiotics

NKs play vital roles during tumor and viral immunologic responses. They can discriminate between normal and abnormal cells (Abel *et al.*, 2018). Upon strange cell recognition, NKs trigger the release of tumor necrosis factor-alpha (TNF $\alpha$ ) and IFN $\gamma$  or directly kill the infected or altered cells (Plaza-Diaz *et al.*, 2019). *Lactobacillus casei* Shirota (LcS) administration to sufferers with colonic polyps’ removal reportedly triggered IL-12 and TNF $\alpha$  proliferation, which was linked to NK activity (Plaza-Diaz *et al.*, 2019). LcS addition or abridgment also improves NK cell activity in lab animals due to the IL-12 expansion (Maekawa *et al.*, 2016).

### Neutrophils modulation by probiotics

Neutrophils are phagocytic natural immune cells primed to engulf pathogens. Probiotics modulate neutrophil effector responses by activating pathogen-sensing-signaling pathways specific to microbial strains (Wang *et al.*, 2020a). Probiotics induce neutrophils, causing cascades of hydrolytic enzyme activity linked to reactive oxygen species (ROS), the mobilization of chemokine-mediated phagocytosis, and the formation of Neutrophil extracellular trap (NET). Inflammatory cytokine production (Vong *et al.*, 2014) demonstrated that *L. rhamnosus* GG could prevent the formation of NETs, thereby reducing ROS that could damage tissues. However, the modulation of neutrophil signaling by probiotics is strain-specific and turn-on the biochemical transformation studied (Kovtun *et al.*, 2018).

### Probiotics regulate TLRs signaling pathways

TLRs are transmembrane proteins that play critical roles in innate immunity. They are single-spanning proteins (or bitopic protein) receptors. They derive their name (single spanning) because they span the lipid bilayer only once. They are expressed on non-professional antigen-presenting cells that identify structurally conserved molecules specific to microbes. Probiotics reportedly inhibited the inflammation in the intestinal environment by down-regulating TLR expression and release of metabolites that inhibit TNF $\alpha$  assessment into single-nucleus blood cells and prevent nuclear factor K-light-chain-enhancer of switch-on  $\beta$ -cells signaling in enterocytes (Llewellyn and Foey, 2017). LAB strains also



stimulated TLR2/TLR6, which is linked with immune regulatory processes and infectious disease prevention (Ren *et al.*, 2016).

### Probiotics modulate inflammasomes

Inflammasomes are large intracellular multiprotein innate immune system receptor complexes and sensors that stimulate caspase-1 and inflammation in a kickback or payoff to pathogens and molecules specific to host proteins (Schmitz *et al.*, 2015). Up on stimulus, they coordinate the maturation of IL-1 $\beta$  and -18 (Schmitz *et al.*, 2015), maintain intestinal homeostasis, and are implied in treating some metabolic diseases (like obesity, diabetes, and MetS) associated with dysregulation of the immune response or kickback (Fabersani *et al.*, 2017). LAB probiotics can modulate leptin levels and adipokine secretion and stimulate inflammasomes (Fabersani *et al.*, 2017).

### HYPERGLYCEMIA AND T2DM

The synthesis of glucose from perplexing carbohydrates must be regulated and is crucial for diabetes management. Even though medications like acarbose restrain  $\alpha$ -amylase and control glucose levels in T2DM, unwanted adverse effects (most notably diarrhea and flatulence) are common. As a result, there is a growing need for unconventional treatments with fewer or no side effects (Ujiroghene *et al.*, 2019). LAB is an essential part of the human gut flora and has various functions in the gastrointestinal system. As a result, gaining a better knowledge of the microflora in the intestine will aid in developing innovative techniques for the management and/or prevention of various disorders (de Almada *et al.*, 2015). Previous research has indicated that probiotic bacteria are vital in treating insulin-dependent diabetes. One study demonstrates that giving *L. casei* addition affects Sirtuin 1 and fetuin-A levels to a certain extent that renovates the glycemic index (GI) among T2DM cases through the probiotic mode of action (Khalili *et al.*, 2019a). Hyperglycemia is reduced when dairy products supplemented with probiotic bacteria, such as fermented milk, cheese, and yogurt, are consumed (Zepeda-Hernández *et al.*, 2021). Probiotics with properties such as LAB have recently been employed to inoculate natural products to improve their anti-diabetic properties. Diabetic patients may benefit from probiotic fermented products as a supplemental or adjuvant therapy (Ujiroghene *et al.*, 2019). The animal-model studies revealed that probiotic LAB's anti-diabetic effect stems from regulating glucose absorption from the gut, implying that certain LAB strains are critical for treating T2DM (Farida *et al.*, 2020). According to a human-randomized, double-blind, placebo-controlled experiment, probiotic bacteria promote favorable changes in gut microbiota, lower systemic inflammation by modifying systemic endotoxin magnitude, and diminish the systemic inflammatory reaction seen in T2DM patients (Rittiphairoj *et al.*, 2021).

### Hyperglycemia/T2DM and susceptibility to infection

DM is associated with multiple complications (Sapra and Bhandari, 2022). Apart from commonly known neutrophil-mediated ROS production complications, inflammatory cytokine synthesis alteration, aberrant neutrophil death, T cell response, and humoral immunity dysfunction (Berbudi *et al.*, 2020; Daryabor *et al.*, 2020; Doweiy *et al.*, 2021; Manosudprasit *et al.*, 2017). Therefore, there is increased susceptibility to infections in diabetic subjects like rhino-cerebral mucormycosis (Khanna *et al.*, 2021; Khanam *et al.*, 2023). Along with the negative effects of

infectivity, these infections may exacerbate DM symptoms such as ketoacidosis and hyperglycemia (Lizzo *et al.*, 2022).

Production of inflammatory cytokines in response to lipopolysaccharides (LPS) such as IL-1 and IL-6 is less in the case of diabetic subjects (Berbudi *et al.*, 2020; Doweiy *et al.*, 2021). Raised glycation in diabetes may result in reduced TNF $\alpha$  and IFN gamma formation by T lymphocytes and reduced secretion of IL-10 from myeloid cells. A decrease in class I central histocompatibility complex expression on the myeloid cell surface may result from glycation through the synthesis of the advanced glycation end product (AGEs) and impaired cellular immunity (Briceno *et al.*, 2022; Kitaura *et al.*, 2021). Hyperglycemia inhibits phagocytosis by decreasing complement binding with Igs. Complement-3 glycosylation inhibits attaching the addendum to pathogens' surfaces (Pavlou *et al.*, 2018; Zhou and Lansang, 2021).

In a hyperglycemic state, there is a reduction in polymorphonuclear migration, chemotaxis, and phagocytosis (Berbudi *et al.*, 2020; Subbaram *et al.*, 2022). Hyperglycemia also inhibits glucose-6-phosphate dehydrogenase (G6PD) activity, increases polymorphonuclear apoptosis, and decreases the migration of polymorphonuclear cells across the endothelium (Berbudi *et al.*, 2020; Chávez-Reyes *et al.*, 2021; Zhang *et al.*, 2020). G6PD has been observed in studies as an essential enzyme for the antioxidant defense mechanism against ROS toxic effect and in fighting against infection and proliferation of T lymphocytes (Dore *et al.*, 2021; Gnanaprakasam *et al.*, 2017). Chronic granulomatous diseases (CGD) (an immunodeficiency disorder that leads to patients suffering grave bacterial and fungal infections) are associated with a deficiency of G6PD (Sun *et al.*, 2022). Studies have observed a link between diabetes and G6PD deficiency (Ansari *et al.*, 2022; Karadsheh *et al.*, 2021). A survey with streptozotocin-induced diabetic rats observed phosphorylation of the G6PD enzyme by protein kinase A in the cortex of the experimental animals' kidneys. Comparable findings were also noted in the culture of endothelial cells of the aorta in the hyperglycemic state (Chávez-Reyes *et al.*, 2021; Zhang *et al.*, 2000). Also, protein glycosylation may be in hyperglycemic conditions that affect the enzyme's activity (Chávez-Reyes *et al.*, 2021; Reily *et al.*, 2019).

Increased susceptibility to oxidative stress may occur in hyperglycemic conditions due to reduced nicotinamide adenine dinucleotide phosphate (NADPH) levels needed for antioxidant activity in cells. Hyperglycemia increases the glucose level in cells that do not require insulin for glucose uptake. The excess glucose is metabolized using NADPH as a cofactor, thus creating NADPH deficiency (Hansen *et al.*, 2018).

A common complication in diabetic patients is diabetic ketoacidosis, which lowers venous blood pH (<7.3) (Duca *et al.*, 2017). Ketone bodies produced due to altered glucose metabolism lead to metabolic acidosis (Dhillon and Gupta, 2022). When pH is less than 6.5, leukocyte migration may delay due to the impairment of polymorphonuclear leukocyte mobility, inhibition of chemotaxis, and decrease in the formation of superoxides by neutrophils (Chávez-Reyes *et al.*, 2021; Fig. 2).

Also, it has been observed that tissue recuperation could be delayed in a hyperglycemic state through alterations in collagenase and growth factor secretion. Therefore, it may result in susceptibility to secondary infections in the tissue (Ayelign *et al.*, 2019; Chávez-Reyes *et al.*, 2021). AGEs may promote the activity

of inflammatory cells, which may result in a chronic imbalance in the immune system. This may lead to subclinical chronic inflammation and prevent optimum immune system functioning to overcome infections and promote the healing of wounds (Hu *et al.*, 2015).

T2DM is commonly related to infections related to the urinary tract and respiratory tract. *Mycobacterium TB* response in T2DM patients has been shown to decrease T lymphocyte function, antigen presentation, chemotaxis, and phagocytosis while promoting infection and disease development (Wang *et al.*, 2018). Other compromised tissues in subjects with diabetes are the GIT, skin, liver, bone marrow, and other organs/tissues (Daryabor *et al.*, 2020; Dryden *et al.*, 2015). Infection susceptibility may result in diabetic subjects' management complications like chronic periodontitis, emphysematous cholecystitis, sepsis, gangrenous cholecystitis, post-operative infection, pyelonephritis, rhino-cerebral mucormycosis, malignant external otitis and so on (Daryabor *et al.*, 2020; Dryden *et al.*, 2015; Kowalski *et al.*, 2022).

Although it is unclear whether DM increases all infection susceptibility, it has been observed that bacterial infections are more frequent, familiar, and severe (Chávez-Reyes *et al.*, 2021). Nevertheless, the most common and severe fungal diseases include aspergillosis (Ye *et al.*, 2020), coccidioidomycosis (Ellerbrook and Laks, 2015), and mucormycosis (Khanna *et al.*, 2021) among DM patients. Hyperglycemia increases susceptibility to infection through the induction of immune response impairment. Thus, glucose levels are a prerequisite to battling the disease in diabetic patients (Chávez-Reyes *et al.*, 2021).

### The immunological mode of action of susceptibility towards diabetics infections

Multiple effects on the human immune system are likely how diabetes increases infection vulnerability. The skin flora of diabetic people is changed, mainly *Staphylococcus aureus* colonization being more common (Balato *et al.*, 2019). Because of the influence of chronic hyperglycemia on peripheral nerves and vascular supplies, diabetic subjects are more likely to suffer from a breach of the integrity of the skin, which is a barrier to infections. Diabetic treatment and DM clout intestinal microbiota distribution and configuration (Daryabor *et al.*, 2020). It is now progressively apparent that the gut microbiome performs a critical role in immune response (innate and adaptive) by delivering immunomodulation molecules and pathogen recognition receptors' pathways (Gopalakrishnan *et al.*, 2018). Although the influence of moderate hyperglycemia on the infection vulnerability is uncertain, urinary tract infection is promoted by glycosuria.

Furthermore, hyperglycemia inhibits the activation of complements, phagocytosis, and degranulation of neutrophils, among other immunosuppressive effects (Hulme *et al.*, 2017). On the other hand, DM hyperglycemia increases susceptibility to TB and diseases headway towards latent TB infection to active pulmonary TB. Additionally, DM promotes more severe disease (Ngo *et al.*, 2021). Oxidative stress, chronic inflammation, and endothelium dysfunction are linked to diabetes (Ito *et al.*, 2019). This may encourage a change toward an overwhelming pro-inflammatory response in infections like dengue, leading to coagulopathy, cytokine storm, and vasculopathy characteristic of dengue in its severe form (Badawi *et al.*, 2018). Finally, hospital admission is more likely among diabetic subjects putting

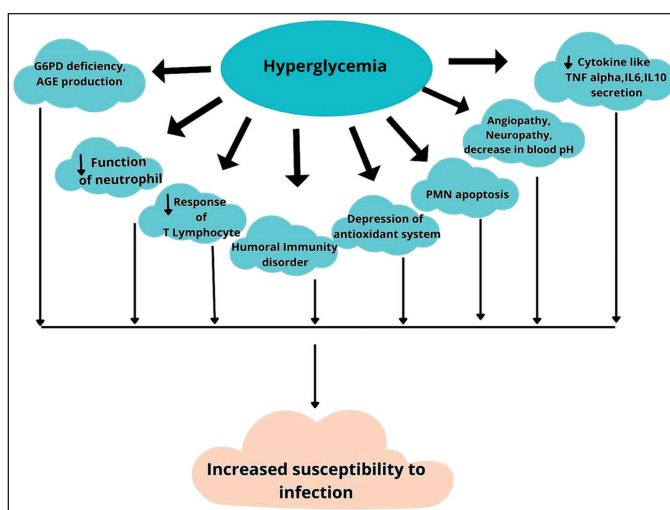
them at risk for hospital-acquired infections and especially with anti-microbial resistant pathogens (MacIntyre *et al.*, 2017). The conditions found in CGD, an inherited impairment in phagocytic function, and the pathogenic microbes that persons with DM have particularly heightened sensitivity to, such as *S. aureus* and invasive fungi, have some overlapping (Dinauer *et al.*, 2019). This points to a crucial mechanism of vulnerability in diabetes patients: impaired neutrophil and macrophage activity. Studies on the host retort to *Burkholderia pseudomallei* in persons with DM demonstrate that neutrophil migration, phagocytosis, and intracellular death are hindered (Luc *et al.*, 2019).

## METS, T2DM, AND MICROBIAL FLORA

### T2DM and microbiota

In modern society, people's dietary habits have changed. Excessive salt, sugar, and fat intake increase metabolic diseases (Fig. 3), such as obesity, IR, and T2DM. In addition, T2DM is a recognized dominant self-reliant hazardous component for several long-standing disease entities, such as coronary artery disease (Cho *et al.*, 2018). Several metabolism disorders are involved, marked by relative or absolute insulin secretion insufficiency and reduced insulin sensitivity in target organs and water, fat, electrolytes, protein, and other metabolism disorders (Einaron *et al.*, 2018). Studies showed the performance of inflammatory cytokines in DM and its aggravations (American Diabetes Association, 2013).

Also, hyperglycemia in IR can increase AGEs density which may raise the formation of IL 6, IL 1, and TNF $\alpha$  through raising oxidative stress and macrophage activation. Intermediates of inflammation leading to IR may also destroy  $\beta$  cells (Hasheminasabgorji *et al.*, 2021; Poznyak *et al.*, 2020; Yuan *et al.*, 2019). Whilst the cause and pathogenesis of T2DM are still elusive, its incidence is linked to inadequate secretion of insulin or IR, which is repeatedly related to obesity (Khodabandehloo *et al.*, 2016). It has been suggested by recent pharmacological research means that intestinal flora has a significant role in T2DM pathogenesis. A sedentary lifestyle and unhealthy eating habits



**Figure 2.** Showing pathophysiology of infection linked to hyperglycemia. Hyperglycemia leads to altered immune response, angiopathy, and depression of the antioxidant system, resulting in increased susceptibility to infection. PMN: Polymorphonuclear. Image Credit: Rahnuma Ahmad.

contribute to obesity development. Several metabolism pathways interact, leading to IR in obesity and T2DM (Jeon *et al.*, 2018; Song and Lee, 2018). Furthermore, muscle and adipose tissue become resistant to insulin due to a complex combined effect of the body's composition, genetic predisposition, and environmental and nutritional causes (DeFronzo *et al.*, 2015; Sinha and Haque, 2022).

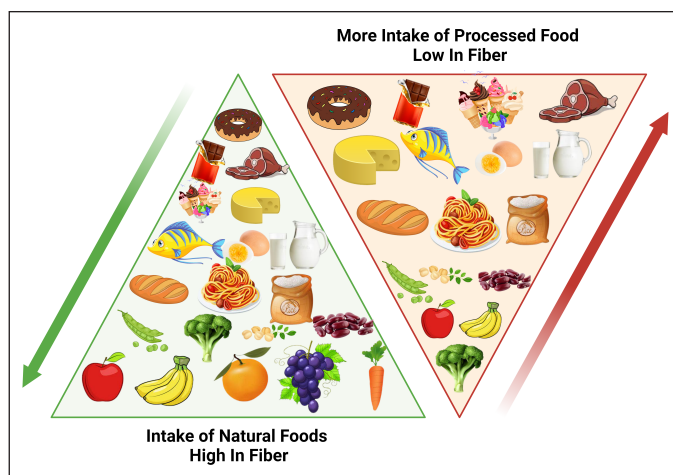
T2DM is characterized by resistance to insulin action in muscle and adipose tissue, caused by diverse aspects such as genetic predisposition, body configuration, and nutritional and environmental aspects (Galicía-García *et al.*, 2020). In addition, tissues become more IR observed when exposed to compensatory raised insulin levels (Freeman and Pennings, 2022). A crucial role is performed by diet in intestinal microbiota regulation. A polyunsaturated, saturated fatty acid diet, as well as a lack of oligosaccharides and phytochemicals, can all affect bacterial metabolism. Intestinal microbiota can be modified by a fat-rich diet directing to shoot up in the penetrability of the intestine and a rise in vulnerability to microbial antigens. This ultimately causes metabolic endotoxemia and IR (Merra *et al.*, 2020; Morita *et al.*, 2017; O'Keefe, 2016). Studies have shown that the intestinal flora

is a significant one among other factors of the environment, and its alterations can cause various metabolic diseases, including obesity and diabetes (Patterson *et al.*, 2016). Scientific evidence recommends that increased inflammatory stress is associated with molecular mechanisms leading to IR, and the intestinal microbiota interacts with environmental characteristics and vulnerable genetic elements, influencing the progress of DM (Galicía-García *et al.*, 2020).

Moreover, the intestinal microbiota arrangement is also allied to allergic reactions, inflammatory disease, cancer, diabetes, CVDs, and dyslipidemia (Cheng *et al.*, 2020; Han *et al.*, 2021; Iatcu *et al.*, 2022; Jia *et al.*, 2021; Rahman *et al.*, 2022; Zuo and Ng, 2018). However, probiotics can modify intestinal microbiota, which may be beneficial for managing several clinical conditions (Zhang *et al.*, 2015). In addition, probiotics possibly take part in maintaining healthy gut microbiota (Table 3) and can be used as an adjuvant in treating IR, which is effective (Kim *et al.*, 2019b; Sánchez *et al.*, 2017).

Consumption of probiotics would be an innovative approach to decreasing pro-inflammatory factors in humans suggested by several studies. Probiotics are live microorganisms that can colonize the human intestinal tract to upgrade the appropriate microbiological balance and alleviate DM and other metabolic diseases (Khalili *et al.*, 2019b; Zepeda-Hernández *et al.*, 2021). In a recent study, the investigation was done on 60 subjects (Razmpoosh *et al.*, 2019) to observe the effect produced by multi-strain probiotics on plasma insulin, lipid profile, and FPG. Similar observations were identified in multiple other studies (Bock *et al.*, 2021; Ding *et al.*, 2021; Kocsis *et al.*, 2020; Mohamadshahi *et al.*, 2014). Ingestion of fermented foods has resulted in several positive effects on physiologic health indicative factors. These advantageous health effects are enforced by combining the living microbes that the foods encompass. In addition, the biologically active ingredient is liberated into the foods as a spin-off of the fermentation procedure. Besides, fermentations characteristically involve utilizing compounds in the uncooked, fresh food substratum by microbes, for instance, LAB and yeasts.

Furthermore, on various occasions, the microorganisms involved in the fermenting procedure, and mostly in milk-originated fermented diets, co-occur with the lactic acid group of bacteria (Marco *et al.*, 2017). The LAB is a cluster of



**Figure 3.** Comparative view of natural foods and processed food we eat. This figure has been developed by utilizing the premium version of BioRender (<https://biorender.com/>) with License No.: PF24T9ZQ3D. Image Credit: Susmita Sinha.

**Table 3.** Classification of common intestinal flora (Gibson, 1999; Yang *et al.*, 2020).

Classification	Proportion	Common flora species	Function
Beneficial bacteria	30%	<i>Lactococcus</i> , <i>C. coccoides</i> , <i>Bifidobacterium</i> , <i>Lactobacillus</i> , <i>Enterococcus fecalis</i> , <i>Eubacterium</i> , <i>Rothia</i> , <i>Clostridium leptum</i> , <i>Clostridium butyricum</i> , <i>Enterococcus Faecium</i> , <i>B. vulgatus</i> , <i>Peptococcus</i>	It improves peristalsis of the intestine, protects against diarrhea and constipation, increases vitamin formation, excretes harmful substances, and prevents pathogen penetration.
Harmful bacteria	10%	<i>Escherichia coli</i> , <i>Peptostreptococcus</i> , <i>Clostridium Prazmowski</i> , <i>Clostridium tetani</i> , <i>Verillonella</i> , <i>Proteus</i> , <i>Fusobacterium</i> , <i>Streptococcus</i> , <i>Klebsiella</i> , <i>Clostridium</i> , <i>Prebotella</i> , <i>Veillonella</i> , <i>Atopobium</i> , <i>Staphylococcus</i> , <i>L. welshimer</i> , <i>Bacteroides</i>	It causes the production of toxic substances and raises the absorption of dangerous components through the intestine, making it susceptible to invading pathogens.
Conditional pathogenic bacteria	60%	<i>Rumenococcus</i> , <i>E. coli</i> , <i>Enterococcus</i> , <i>Bacteroides</i> , <i>Desulfovibrio</i> , <i>Pseudomonas aeruginosa</i> , <i>Proteus</i> , <i>Monilia albicans</i>	These invade and produce harmful effects on human health under some conditions.

microorganisms comprising genera/classes regularly detected in milk-fermented edibles (Lorenzo *et al.*, 2018). Apart from fermented dairy foods, LAB is present in meat, cereals, and fermented vegetables (Ashaolu *et al.*, 2020; Park *et al.*, 2014; Parlindungan *et al.*, 2021). Several studies have found a strong link between the consumption of fermented dairy products and weight maintenance (Mozaffarian, 2019; Mozaffarian *et al.*, 2011). Similarly, frequent yogurt consumers are less susceptible to T2DM and CVD and have a lower mortality risk (Eussen *et al.*, 2016; Schmid *et al.*, 2020). Investigations revealed that when LAB-fermented dairy like yogurt is consumed regularly, there is selective stimulation of healthy bacterial growth in the colon of humans. This may help protect from AGEs related pathology in those having risk of T2DM development (Feng *et al.*, 2021; Kellow *et al.*, 2014).

### Gastrointestinal barrier permeability

The mucosal lining of the intestine is a barrier of protection from unwanted substances that are likely to cause harm and is crucial in immune regulation (McDermott and Huffnagle, 2014). Host metabolic endotoxemia occurs in T2DM subjects as the gut permeability is markedly higher, which allows bacterial translocation through the epithelium of the gut and thus aggravates inflammation. These changes possibly lead to the destruction of  $\beta$ -cells and IR (Scheithauer *et al.*, 2020). *Limosilactobacillus fermentum*, *Lactobacillus acidophilus*, *L. rhamnosus*, and *L. gasseri* cause modification of gene encoding junction and adhesion proteins  $\beta$ -catenin and E cadherin and decrease protein kinase C  $\delta$  (PKC- $\delta$ ) expression (Hummel *et al.*, 2012). Adhesion junction interruption and increased intestinal permeability result from PKC- $\delta$  (Singh *et al.*, 2009). Enhanced permeability allows antigen absorption, aggravating  $\beta$ -cell injury within the pancreas and leading to an immune system response (Paray *et al.*, 2020). The innate immune response is activated by several parts and parcels of the microbial cell wall (Lemme-Dumit *et al.*, 2021). *Lactobacillus* fermented foods induce phosphorylation of  $\beta$  catenin. This strengthens the E cadherin/ $\beta$  catenin complex, promoting adhesion junction from the E cadherin binding site to the cytoskeleton (Syngai *et al.*, 2016). Antimicrobial proteins producing cells called Paneth cells, a component of the intestinal barrier, decrease the intestine's permeability (Lueschow and McElroy, 2020). Another study observed that when *Lactobacillus johnsonii* possesses the potential to reduce diabetes incidence, possibly by raising the expression of the claudin-1 gene and lowering oxidative stress (Gomes *et al.*, 2014). Another study reported that oral probiotics (*L. johnsonii*) shoot up gut antimicrobial activity and Paneth cells to reinforce the epithelial barrier against pathogenic microorganisms. This accomplishes or carries through one more crucial mode of action by employing probiotics to defend the host, by and large, against infective affliction (Cazorla *et al.*, 2018; Vazquez-Munoz *et al.*, 2022).

### Gut microbiota metabolites

#### Short-chain fatty acids

SCFAs, branched-chain amino acids (BCAAs), succinate, indole, and imidazole are all microbial metabolites formed at the time of anaerobic fermentation in the gut (Fan and Pedersen, 2021). After consuming complex carbohydrates,

colonic bacteria metabolize them to form oligosaccharides and monosaccharides, ferment to SCFAs and gases like methane, carbon dioxide, and hydrogen. There is the formation and release of chemokines, protective peptides, phagocytes, and cytokines resulting from SCFAs. These control glucose and lipid metabolism through energizing SCFAs' adipose tissue, brain cells, and hepatic and pancreas receptors. Furthermore, colonocytes and enterocytes use SCFAs as their primary energy source, which helps to keep the intestine free of inflammation and oxidative stress (Koh *et al.*, 2016; Oliveira *et al.*, 2019). Proteins, peptides, and dietary fibers that seepage the digestion in the upper intestine are metabolized by microbiota residing in the cecum and colon. Major SCFAs like butyric acid, acetic acid, and propionic acid biosynthesis are aided by the cecum and colon's microbiota by forming acetyl CoA and pyruvate from the glycolysis of glucose. SCFAs are then utilized for colonic mucosal epithelial cells or enter portal circulation (Ohira *et al.*, 2017). They act on G protein-coupled receptor (GPR) and thus stimulate glucagon-like peptide-1 (GLP-1) and GLP-2. They amplify insulin and adiponectin assertion, augment responsiveness, and cause the multiplication of pancreatic  $\beta$ -cells (Rosendo-Silva and Matafome, 2021).

IR is the foremost characteristic of T2DM. Obesity, MetS, and intestinal configuration changes with advanced lipopolysaccharide (LPS)-enriched Gram-negative bacteria are all associated with increased cellular penetrability. Furthermore, a microbial populace lacks that can produce helpful and advantageous SCFAs, which stabilize macrophages counter to inflammation and shield the gut endothelial barricade (Brar and Kohn, 2019). In high-fat diet conditions, metabolic endotoxemia is activated by gut dysbiosis. Gut dysbiosis increases intestinal permeability and decreases the synthesis of lipopolysaccharide (LPS) and peptidoglycan. This progression boosts the instigation of TLR-4 and additional inflammatory beckoning tracts, promoting IR and T2DM. Lowgrade systemic inflammation leads to obesity, T2DM, and ischemic stroke (Fuke *et al.*, 2019; Sonali *et al.*, 2022). So, deploying the gut microbiota with LAB-fermented foods could be a prospective interference to manage metabolic abnormalities such as T2DM, obesity, and IR (Le Barz *et al.*, 2015). When SCFAs (obtained from the fermenting process) combine with GPR41 and GPR43, enteroendocrine molecules produce, which promote the expression of the intestinal gluconeogenesis gene and appetite. Intriguingly these receptors, which take part in insulin secretion, are expressed by  $\beta$ -cells of the pancreas. A research study reported that the rodents having GPR41 knocked out had an alteration in the control of glucose employing GPR41 activated by SCFAs, which helps regulate insulin secretion by the pancreas (Veprik *et al.*, 2016). Such outcomes suggest that SCFAs-GPR signaling operates a condemnatory activity in glucose and insulin homeostasis.

#### Bile acids (BAs)

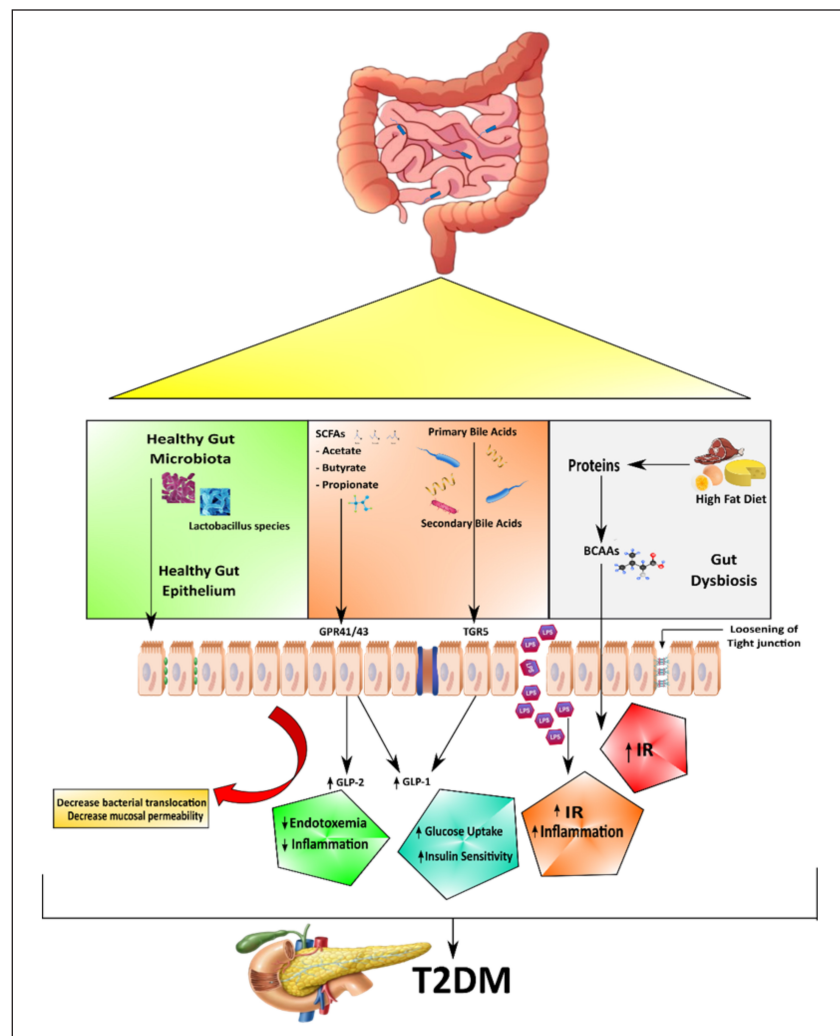
BAs are obtained from cholesterol through 7 $\alpha$  hydroxylase (rate-limiting enzyme) action. It then undergoes conjugation with taurine or glycine before being released in bile. Greater than 95% of it is reabsorbed in the colon and terminal of the ileum through enterohepatic circulation (Chen and Cassaro, 2022; Long *et al.*, 2017; Urdaneta and Casadesús, 2017).

In contrast, the secondary ones bind to the G protein-coupled BA receptor 1 (GPBAR 1/TGR5), promoting glucose homeostasis (Wahlström *et al.*, 2016). A recent study showed that patients with uncontrolled T2DM have increased BAs with elevated deoxycholic acid and less chenodeoxycholic acid (Delgado *et al.*, 2020). BAs can facilitate energy metabolism by combing and triggering nuclear transcription factors such as Farnesoid X Receptor (FXR) in the intestine and liver. Thus, using BAs to alter gut microbiota may benefit glycemic control and avert a cluster of metabolic changes for ahead-of-time T2DM subjects (Rajani and Jia, 2018). Therefore, TGR5 and FXR agonists via gut microbiota intonation may be a novel therapeutic ploy for treating T2DM (Fig. 4).

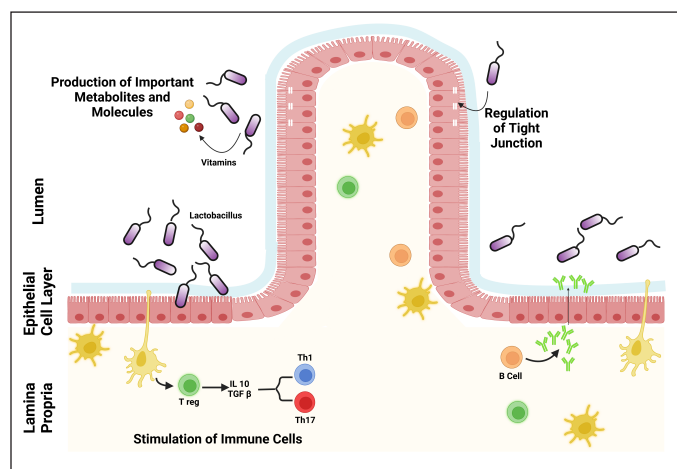
### Immune response

Immune-mediated pathogenesis, causing inflammation and autoimmunity, is a characteristic common for all types of diabetes (Cousminer *et al.*, 2018). A symbiotic association is favored by balancing gut microbiota, intestinal epithelium, and

the mucosal immune system (Hooper and Macpherson, 2010). An imbalance in the immune system is one of the processes involved in gut microbiota dysbiosis and T2DM (Yoo *et al.*, 2020). Gut microbiota and its metabolites preserve the equilibrium and role of intestinal T helper 17/regulatory T cell (Th17/Treg) (Takiishi *et al.*, 2017) (Fig. 5), and gut-associated lymphoid tissues, for instance, mesenteric lymph nodes, Peyer's patches, and isolated lymphoid follicles (Mörbe *et al.*, 2021; Rooks and Garrett, 2016). The Th17 and Treg cells are two CD4+ T helper cells; Th17 cells have been caught up in adipogenesis and glucose homeostasis control in obesity (Zhang *et al.*, 2021; Zhou and Liu, 2018). Gut microbiota is essential in selecting the immune system to differentiate the self from the non-self (Kriegel, 2015). It indorses innate hematology cells (ILC1, ILC2, and ILC3), noncytotoxic and cytotoxic cells, helper lymphoid cell synthesis, and NK cell formation (Moro and Koyasu, 2015; Panda and Colonna, 2019). Gut microbiota metabolites, for example, tryptophan and  $\alpha$ -galactosylceramide, augment immune organelles to produce IL-17, IL-12, and Ig A, which aid in averting the infiltration of



**Figure 4.** Comparative view of natural foods and processed food we eat. This figure has been developed by utilizing the premium version of BioRender (<https://biorender.com/>) with License No.: PF24T9ZQ3D. Image Credit: Susmita Sinha.



**Figure 5.** Interactions between *Lactobacillus* and intestinal epithelial cells result in the differentiation of immune cells and control of the barrier function of intestinal epithelial cells. This figure has been developed by utilizing the premium version of BioRender (<https://biorender.com/>) with License No.: UP24TBJUY. Image Credit: Susmita Sinha.

certain microorganisms into the bloodstream (Brown *et al.*, 2013; Honda and Littman, 2016). The ILCs are vibrant integrants of innate immunity that synthesize pro-inflammatory and regulatory cytokines to encourage immunity, inflammation, and tissue repair. A study showed that T2DM patients' greater adipose ILCs1 levels in tissue and circulation correlated with increased diabetes risk (Liu *et al.*, 2019). However, glucose homeostasis may be improved by ILC2s, leading to protection from IR onset and enhancement of recognized IR (Ali *et al.*, 2017). T helper 17 (T<sub>H</sub>17) cells possess well-defined relation with CD4<sup>+</sup> effector T cells. Hereby synthesizes the proinflammatory cytokine IL-17A, subsequently generating IL-17 and RORγ<sup>+</sup>, leading the way for chemokine making process and recruiting neutrophils to ensure autoimmune tissue damage (Crawford *et al.*, 2020; Valmori *et al.*, 2010). It has been further reported that insufficient IL17/RORγ<sup>+</sup> associated with CD4 T cells promotes T2DM and obesity (Garidou *et al.*, 2015). One more study reported that the alteration of gut microbiota is strongly related to the development of DM and its' grave consequences. This also suggested that preventive nutritional supplementations, especially with prebiotic and probiotics, possess properties to arrest the progression of DM diseases (Moffa *et al.*, 2019). This observation supports the role of the intestinal TH17 lineage in regulating insulin sensitivity. Researchers demonstrated LAB fermented foods inhibit trinitrobenzene sulfonic acid and, consequently, the inhibition of TNF-α gene expression (Ağagündüz *et al.*, 2021; Sevencan *et al.*, 2019).

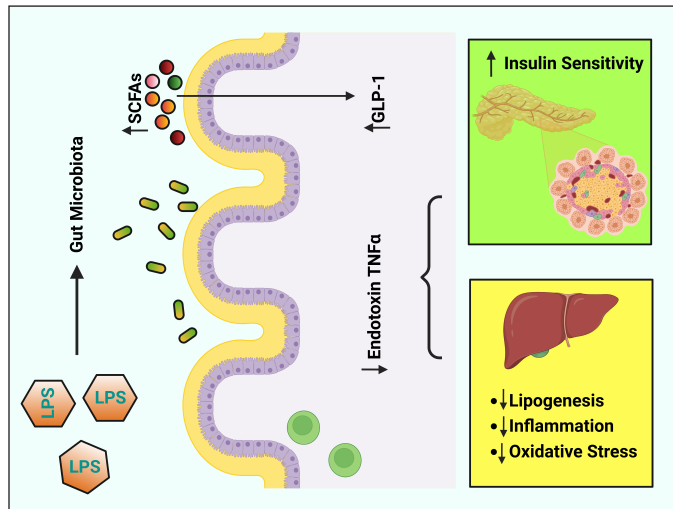
Moreover, soluble molecules formed by *Lactobacillus* species may decrease TNF-α production from activated macrophages. The intestinal *Lactobacilli* produce soluble proteins that bind with receptors on the cell surface, leading to TNFα secretion or synthesis prevention. This is independent of cell necrosis or proapoptotic effectors (Yun *et al.*, 2021a). The gut-diabetic partnership and the causal immunopathogenesis are fascinating. They include several commensal intestinal microbes that perform several homeostatic and metabolic functions, which

in dysbiosis situations, different products and metabolites can endorse and endure diabetes. In addition, the gut microbiota is essential in sustaining and modifying the equilibrium of the innate immune system responses in T2DM.

## PROTEOLYTIC BELONGINGS OF LAB IN DIABETIC PATIENTS

Extensive research has supported the hypothesis that LAB strains provide human health advantages with antidiabetic properties (Eviwie *et al.*, 2017). LAB has also been effective in treating diabetes in mice. In this rodent specie, the remission impact of nine LAB strains on the symptoms of a high-fat diet- and streptozotocin-induced T2DM and their mechanisms of action were investigated. Results revealed that the daily oral administration of *Bifidobacterium adolescentis*, *Bifidobacterium bifidum*, or *L. rhamnosus* to mice for more than 12 weeks lowered fasting postprandial blood sugar levels, enhanced glucose tolerance, and prevented pancreatic damage (Wang *et al.*, 2020b). Furthermore, it was observed that the hypoglycemic LAB strains contributed to reducing IR by increasing the generation of SCFA and decreasing inflammation. The LAB's ability to reduce inflammation was directly related to its ability to treat DM (Wang *et al.*, 2020b; Fig. 6).

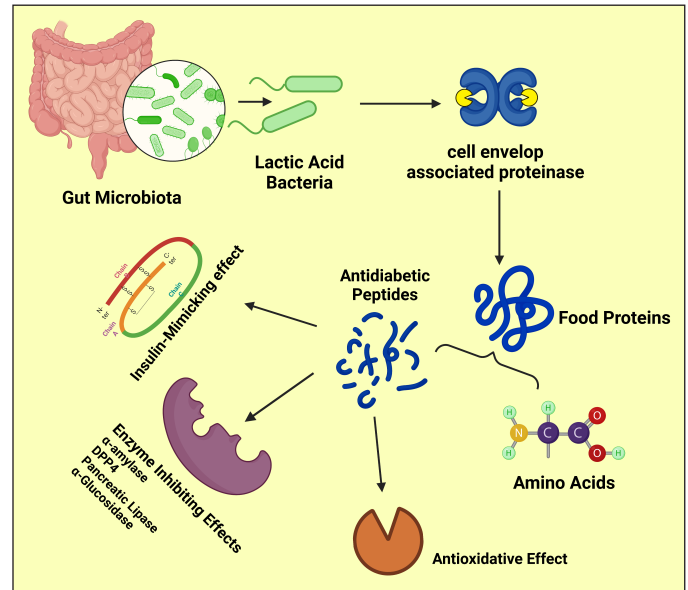
It is imperative to consider that T2DM is linked with hyperglycemia, oxidative stress, and defective proteolysis (Homma and Fujii, 2020). DM disrupts normal redox signaling (an essential regulator of wound healing), resulting in several pathogenic modes of action that change the balance between ROS formation and scavenging. Significantly, pathological oxidative stress can change the structure and function of the ECM, causing diabetes-related impaired wound healing (Kunkemoeller and Kyriakides, 2017). Oxidative stress also negatively affects the ubiquitin-proteasome system (UPS) and autophagy, two crucial intracellular proteolytic processes intimately linked. Indeed, both approaches are sensitive to oxidative alteration and could be prime ROS targets (Homma and Fujii, 2020). Recent research employing obese and hyperglycemic model mice found that both the UPS and autophagy systems are blocked. This suppression is followed by lipid buildup, IR, and tissue damage (Homma and Fujii, 2020). Defective proteolysis and oxidative stress cause increased IR, which is crucial in developing T2DM (Batista *et al.*, 2021). IR is enhanced by the misfolding and inefficient processing of proinsulin (Khilji *et al.*, 2020), IRS1/2 Ser/Thr phosphorylation, the gut microbiome, and other extrinsic factors such as circulating metabolites, fatty acid circulation, and inflammatory signals. The gut microbiota regulates the supply of circulating BCAAs, an excess linked to IR. The gut microbiota also regulates the generation of SCFAs and other metabolites, influencing systemic insulin sensitivity (Batista *et al.*, 2021). Empirical data has demonstrated that a non-dairy FFP produced gut microbiota changes in Zucker diabetic and fatty (ZDF) rats, improved glucose metabolism, and protected against the development of T2D (Cabello-Olmo *et al.*, 2019). LAB is a diverse collection of bacteria capable of fermenting carbohydrates into lactic acid (Kieliszek *et al.*, 2021). They synthesize peptides from their ribosomes (bacteriocins) and bioactive peptides via a complex proteolytic system that includes cell envelope-associated proteinases (CEP) (García-Cano *et al.*, 2019; Venegas-Ortega *et al.*, 2019).



**Figure 6.** Beneficial role of lactobacillus in T2DM. This figure has been developed by utilizing the premium version of BioRender (<https://biorender.com/>) with License No.: OC24TRHPW4. Image Credit: Susmita Sinha.

The enzymes ensure the success of the fermentation process by breaking down proteins to produce beneficial amino acids and bioactive peptides during milk fermentation (Brown *et al.*, 2017). The extracellular proteolytic activity of LAB isolated from various Malaysian fermented foods and their ability to synthesize amino acids extracellularly as feed additives have been studied. All 17 LAB isolates investigated are flexible extracellular protease producers with demonstrable proteolytic activities in acidic to alkaline medium (pH 5–8) (Lim *et al.*, 2019). The LAB uses the amino acid products of proteolysis to build cellular structures to enhance the gastrointestinal system's effective colonization and improve insulin signaling (Caricilli and Saad, 2013; García-Cano *et al.*, 2019). However, the peptides produced demonstrate their antidiabetic effects through an enzyme (pancreatic lipase,  $\alpha$ -amylase,  $\alpha$ -glucosidase, DDP4)-inhibiting, antioxidative, and insulin-mimicking activities (Elam *et al.*, 2021).

Pancreatic lipase inhibition and pancreatic protective activities are critical factors in averting and treating T2DM and obesity (Oluwagunwa *et al.*, 2021; Fig. 7). Pancreatic lipase inhibitors are antidiabetic agents, with the mechanism of action involving the breakdown of fat and the absorption of dietary triglycerides, the primary source of excess calories (Rajan *et al.*, 2020). A study discovered that skim milk fermented with different LAB strains has pancreatic lipase inhibitory activity. The results revealed that fermentates made with *Lactobacillus helveticus* strains at 42°C had the highest levels of pancreatic lipase inhibition, with strains SC8, SC44, and SC45 showing inhibition more significant than 49%, which was significantly higher than the activity of a milk control (Gil-Rodríguez and Beresford, 2019). It has also been demonstrated that the hydrolyzed proteins and peptides from oat bran obtained by LAB fermentation exhibited pancreatic lipase inhibitory properties. Specifically, in a computational model prediction, the peptide P3 (SPFWNINAH) interacted with residues Ser153, Asp177, and His264 of pancreatic lipase (Esfandi *et al.*, 2022). It has also been discovered that specific tripeptide scaffolds with a central arginine have shown



**Figure 7.** The proteolytic properties of LAB and their antidiabetic effects. This figure has been developed by utilizing the premium version of BioRender (<https://biorender.com/>) with License No.: ZU24U2K91F. Image Credit: Susmita Sinha.

significant, site-directed, *in-vitro* inhibitory activity in the binding pockets of pancreatic lipase (Stefanucci *et al.*, 2019).

Amylases hydrolyze starch molecules by cleaving to the glycosidic linkages to yield dextrans and oligosaccharides. T2DM is characterized by increased amylase activity and, consequently, increased postprandial hyperglycemia. Therefore, amylase inhibition is critical in treating T2DM (Proença *et al.*, 2022). The effect of sprouted quinoa yogurt beverages (QYB) fermented with antidiabetic LAB on  $\alpha$ -amylase was studied *in-vitro*. *In-vitro* investigations using swine pancreatic  $\alpha$ -amylase revealed that QYB fermented with *Lactobacillus casei* Zhang and *Lactobacillus casei* SY13 reduced the activities of  $\alpha$ -amylase in a dose-dependent manner, making them useful for the prevention of T2DM (Ujirohene *et al.*, 2019). The antidiabetic effect of fish sausages fermented with LAB isolates of *Enterococcus* spp. (*E. faecium*, *E. faecalis*, and *E. durans* strains) has been investigated. It was observed that compared with non-fermented control sausages, fermented sausages exhibited significant  $\alpha$ -amylase inhibition activities (AlKalbani *et al.*, 2019).

An antidiabetic inhibition activity of camel milk fermented was investigated in an *in-vitro* study using indigenous probiotic strains such as *Lactobacillus reuteri*-KX881777, *Lactobacillus plantarum*-KX881779, and a control strain *Lactobacillus plantarum* DSM2468 from bovine fermented milk. The results showed that the  $\alpha$ -amylase inhibition of the water-soluble extracts was greater than 34% in both milk types fermented with all strains during storage periods (Ayyash *et al.*, 2018). The hydrolyzed proteins and peptides from oat bran also exhibit  $\alpha$ -amylase inhibitory properties. Specifically, the peptide, P1 (YFDEQNEQFR), interacted with residues [Asp (Badawi *et al.*, 2018), Glu (Eussen *et al.*, 2016), and Asp (Stefanucci *et al.*, 2019)] of pancreatic of the active site of  $\alpha$ -amylase in a computational model prediction (Esfandi *et al.*, 2022).

$\alpha$ -glucosidase is an enzyme that enhances the digestion of dietary carbohydrates and starches to produce glucose to facilitate intestinal absorption and plays a critical role in developing T2DM (Kinariwala *et al.*, 2020). Cultures of *L. fermentum* (M2) and *L. fermentum* (M7) in fermented bovine milk exhibited anti-diabetic properties due to the presence of novel peptides with inhibitory activities against  $\alpha$ -glucosidase (Kinariwala *et al.*, 2020). Similarly, protein-derived peptides in yellow field peas (*Pisum sativum* L.) might be the reason for their antidiabetic properties (Liao *et al.*, 2022; Rungruangmaitree and Jiraungkoorskul, 2017). This is because the protein hydrolysates of the yellow field pea, which could be obtained by lactic acid fermentation, have exhibited in-vitro inhibitory properties against  $\alpha$ -glucosidase (Li *et al.*, 2017; Liao *et al.*, 2022). A study has also investigated the inhibiting activities of camel whey protein hydrolysates (CWPH) against  $\alpha$ -glucosidase. All 27 CWPH under investigation showed significant  $\alpha$ -glucosidase inhibitory activity as indicated by lowered IC<sub>50</sub> values (mg/ml) compared to intact whey proteins. Furthermore, 15 of the 196 peptides identified in the CWPH were selected as  $\alpha$ -glucosidase and  $\alpha$ -amylase inhibitors using an *in-silico* technique because of having many sites for the binding and robust affinity of binding to the enzymes of the target (Baba *et al.*, 2021).

DPP4 is an enzyme that affects glucose metabolism and whose inhibition elevates incretin levels (GLP-1 and GIP), which prevents glucagon release, boosts insulin secretion, reduces gastric emptying, and lowers blood glucose levels (Andersen *et al.*, 2018; Kuwata *et al.*, 2021). Peptides derived from the barbel muscle of *Barbus callensis* protein hydrolysate (BMPH) have nutritional and medicinal potential (Sila *et al.*, 2014). BMPH exhibits significant DPP4 inhibitory activity with an IC<sub>50</sub> value of 1.94 mg/ml (Sila *et al.*, 2016). Specifically, dipeptides that have a C-terminus Proline inhibit DPP4. Tri- and tetrapeptides with proline at the C-terminus may also be DPP4 inhibitors (Chakrabarti *et al.*, 2018; Nongonierma and FitzGerald, 2013).

There is a formidable research interest in producing naturally derived bioactive peptides with the potential to increase insulin sensitivity and reduce IR. The adipogenic and insulin-mimetic activity of milk-derived tripeptides such as IPP and VPP on cultured 3T3-F442A preadipocytes has been investigated. The results reveal that both peptides increased insulin signaling and helped prevent IR when exposed to TNF $\alpha$ . A factor that resulted in the prevention of IR is the suppression of NF- $\kappa$ B that forms in response to TNF $\alpha$ . VPP also increased the glucose transporter 4 (GLUT4) expression in adipocytes and improved glucose uptake in TNF- $\alpha$  -treated adipocytes (Beltrán-Barrientos *et al.*, 2016; Brown *et al.*, 2017; Chakrabarti *et al.*, 2018).

Bioactive peptides generated from milk proteins in fermented dairy foods by microbial proteolysis have also been shown to have antioxidant properties (Widyastuti *et al.*, 2021). For example, in a study, the bioactive peptides derived from Quinoa dough fermented with *Lactobacillus plantarum* T0A10 demonstrated antioxidant activity on human keratinocytes NCTC 2544 artificially subjected to oxidative stress, as measured by cell viability and radical scavenging activity (MTT and DCFH-DA assays, respectively) (Rizzello *et al.*, 2016). Overall, the amino acids and peptides obtained from the proteolytic activity of LAB on fermented foods make them of prophylactic or therapeutic significance in combating T2DM.

## CLINICAL IMPLICATIONS OF *LACTOBACILLUS* FOOD FERMENTATES IN DIABETIC PATIENTS

Diabetes is a common health problem worldwide. The incidence of T2DM has increased worldwide and has become a global pandemic (Knapp *et al.*, 2019; Pivari *et al.*, 2019). Persistent hyperglycemia or uncontrolled diabetes can also cause serious complications. Chronic hyperglycemia in diabetes results in dysfunction and damage of various organs, particularly the kidneys, heart, nerves, blood vessels, and eyes, in the long run (Chaudhury *et al.*, 2017; Knapp *et al.*, 2019). Natural therapies like herbal remedies, other natural methods, and lifestyle changes have recently been preferred for treating diabetes. Nutrition that includes more probiotics is considered a new approach to effectively treating various metabolic disorders (Li *et al.*, 2019; Şanlıer *et al.*, 2019; Yoo *et al.*, 2016). According to WHO, medicines derived from herbs are acknowledged widely and established as effective and safer, and national authorities may accept these medicines (WHO, 2016).

### Fermented yogurt and low fat-dairy foods

Fermentations typically involve utilizing microorganisms' compounds in the fresh or uncooked food substrate, such as LAB (Marco *et al.*, 2017; Melini *et al.*, 2019). The nutritional constituents of the food product are affected as the activity of microbes in food fermentation leads to the removal and/or addition of compounds (Voidarou *et al.*, 2020). Microorganisms act by the catabolic pathway to reduce the disaccharides (fructose, glucose, and sucrose) and monosaccharides found in meat, plant, and milk. This may also decrease the food's GI (Capurso and Capurso, 2020; Wolever, 2017). Consumption of fermented yogurts and low-fat-dairy foods can attenuate the likelihood of developing T2DM (Eussen *et al.*, 2016; Mathur *et al.*, 2020; Kok and Hutkins, 2018; Salas-Salvadó *et al.*, 2017) and is well established through several randomized controlled trials (Savaiano and Hutkins, 2021).

### Kefir

Several compounds (organic) like EPS, antibiotics, hydrogen peroxide, carbon dioxide, ethanol, peptides, amino acids, calcium, vitamins (B12, B1), and bioactive peptides are obtained through the fermentation of kefir beverages by microbes (Rosa *et al.*, 2017). When consumed regularly, kefir beverages may boost immunity, have anti-inflammatory and therapeutic effects, reduce cholesterol, and provide antioxidants to combat diabetes development (Rosa *et al.*, 2017; Wang *et al.*, 2020c). A study performed (Ostadrahimi *et al.*, 2015) on 60 subjects with diabetes found that kefir lowered hemoglobin A1c (HbA1c) and fasting blood glucose levels and suggested that it may aid in diabetes prevention as adjuvant or complementary therapeutics. In another study performed in Gaza, kefir was administered daily in newly diagnosed T2DM adult male subjects and found a rise in calcium levels and a reduction in fasting blood sugar (FBS), HbA1c, and phosphorus levels (Azizi *et al.*, 2021). However, some researchers have differed in their findings regarding the change in HbA1c (Salari *et al.*, 2021). Kefir has been reported to possess middle of the road GI and high insulinemic index food in a survey of incremental plasma glucose area under the curve using three kinds of kefir and thus pointed toward its suitability for diabetic subjects (Kong and Hendrich, 2012). Additionally, regular consumption of



kefir shows substantially lowers plasma triglycerides, liver lipids, liver triglycerides, IR, fasting glucose, fasting insulin, thoracic perimeter, central obesity abdominal, outcome of lipid oxidation, pro-inflammatory cytokine countenance (IL-1 $\beta$ ), and escalation of anti-inflammatory cytokine (IL-10) utterance (Rosa *et al.*, 2016). Kefir beverages, in general, are reported as an effective adjuvant or complementary therapy for preventing and treating diabetes and indicated its use in controlling blood glucose levels as part of a nutritional approach (Salari *et al.*, 2021).

#### Kimchi and Sauerkraut

The appropriate therapeutic intervention for obesity is essential in combating obesity-related metabolic disorders, including IR, DM, and CVDs, which increase the death rate (Lee *et al.*, 2018a). Lipid buildup and amplified systemic inflammation in obesity activate disproportionate energy homeostasis and atypical cellular physiological activity toward insulin, embarking on IR and T2DM (Ellulu *et al.*, 2017; Kojta *et al.*, 2020). Kimchi contains unique bioactive components and microorganisms that exhibit antiobesity properties (Kim *et al.*, 2021b) and antioxidants (Yun *et al.*, 2021b). They have been linked to improved immune response and anti-diabetic and anti-cancer effects (Lee *et al.*, 2018b). Vascular complications of diabetes include retinopathy, neuropathy, and atherosclerosis, which aggravate a rise in disease mortality and morbidity (Dal *et al.*, 2019). Cellular antioxidant activity reduces diabetic vascular complications (Babel and Dandekar, 2021; Shokri *et al.*, 2020). Thus, antioxidants protect against cellular damage from oxidative stress induced by DM-related hyperglycemia (Kanwugu *et al.*, 2022). Several studies have proved the antioxidant (Korus *et al.*, 2021; Meng and Oh, 2021) and antidiabetic (Shahbazi *et al.*, 2021) effects of kimchi. Animal studies have shown that kimchi protects against glucose-induced severe oxidative damage (Youn *et al.*, 2021), reduces IR and HbA1c, and improves glucose tolerance (Lee *et al.*, 2018b; Oh *et al.*, 2021). Similarly, Sauerkraut, the most traditional type of conserved cabbage initiated in the fourth pre-Christian era (Kusumoto *et al.*, 2021), have antioxidant, immunomodulatory, and anti-inflammatory properties (Castellone *et al.*, 2021; Dimidi *et al.*, 2019; Nielsen *et al.*, 2018; Skonberg *et al.*, 2021; Xu *et al.*, 2022a), and thus may help to attenuate the effects of diabetes. However, clinical trials have yet to be found.

#### Natto

Among the fermented soya products, equally in human and animal research have revealed that Natto has an antidiabetic effect (Nakai *et al.*, 2020) and prevents neuropathy due to diabetes by enhancing the status of antioxidants, suppressing renal tissue inflammation, and suppressing blood glucose elevations in the early phase after eating (Araki *et al.*, 2020).

#### Sourdough

Sourdough fermentation food improves postprandial glucose and insulin response (Gil-Cardoso *et al.*, 2021; Koistinen *et al.*, 2018; Stamataki *et al.*, 2017). Sourdough in baked bread can potentially intensify the impediment of  $\alpha$ -amylase harmful action (10%–90%) and, subsequently, reduce the speed starch digestive process. This suggests that sourdough bread suits people with diabetes (Darzi *et al.*, 2012).

#### Kombucha

Kombucha is a liquid refreshment drink that perhaps originated in Manchuria and was derived by undergoing microbial fermentation of tea (Villarreal-Soto *et al.*, 2018). Kombucha's health benefits are mostly limited to cellular analysis and animal studies (Marco *et al.*, 2017). Trials on animals have already proven the hypoglycemic effect of kombucha (Xu *et al.*, 2022b). The presence of organic acid-producing microorganisms has glucose metabolizing capacity, which may prevent diabetes (Kaashyap *et al.*, 2021; Lavasani *et al.*, 2019; Watawana *et al.*, 2016).

#### Miso

Soya-bean-originated food is rich in vegetable protein. It minimizes the serum concentrations of total cholesterol, low-density lipoproteins (LDLs), and triglycerides. Thereby often advocated as a dietary alternative for animal-origin protein. Fermented soy foods (tempeh, tofu, textured vegetable protein, and miso) are evidenced to have a positive impact on the impact of DM management, in addition to fermented soybean's lipid-lowering effects (Jayachandran and Xu, 2019; Kim *et al.*, 2021c; Zhu *et al.*, 2019), and reducing cardiovascular complications (Barańska *et al.*, 2021). More research revealed that soy protein has a broad spectrum of mechanisms to modify numerous cell-signaling alleyways for energy homeostasis and control inflammatory determinants related to DM pathophysiology (Das *et al.*, 2022). Miso, a fermented puree or mash of soybeans, has been customarily utilized for food flavoring among communities in Japan since the olden days. Miso contains protein and nitrogen, thereby highly nutritional (Sasaki *et al.*, 2020). Habitual consumption of miso is associated with a lower IR (Alkhalidy *et al.*, 2019; Takahashi *et al.*, 2021) and an antiobesity effect (Okouchi *et al.*, 2019). IR is a risk of sarcopenia (Mesinovic *et al.*, 2019), and sarcopenia is high in patients with T2DM (Takahashi *et al.*, 2020). Miso consumption was associated with a lower risk of sarcopenia in older women (Takahashi *et al.*, 2020). Interestingly, a study found that habitual miso consumption contributes to reasonable glycemic control in females but not males (Takahashi *et al.*, 2021).

#### Tempeh

Even though tempeh, a part of the traditional Indonesian cuisine, is a product of *Rhizopus oligosporus* fermented soybeans that are dehulled and boiled (Dimidi *et al.*, 2019), it also consists of LAB (Rezac *et al.*, 2018). *In vitro* relationship has been noted between tempeh and its higher ability to scavenge superoxides and free radicals compared to unfermented soybeans. However, randomized control trials have yet to be carried out to study the effect of consuming tempeh on human health (Dimidi *et al.*, 2019).

#### Overview of lactobacillus food fermentates in different comorbidities

One meta-analysis has emphasized that eating or drinking LAB-fermented foods positively impacted overweight and obesity (Mozaffarian *et al.*, 2011). In contrast, independent research has revealed that regular consumption of fermented yogurts and dairy foods can decrease the probability of emerging CVDs and T2DM (Buziau *et al.*, 2019; Drouin-Chartier *et al.*, 2019; Eussen *et al.*, 2016; Tapsell, 2015). It has been observed that the complex issues

of glucose metabolism make easy by fermented milk. It also minimizes muscle pain related to resistance exercise (Iwasa *et al.*, 2013). Other fermented foods like kimchi have been verified to possess antiobesity and antidiabetic therapeutic benefits (Lee *et al.*, 2015; Song *et al.*, 2019; Yun *et al.*, 2021b). Some LAB strains possess the potential to synthesize EPS through the fermentation process (Deepak *et al.*, 2016). Multiple studies verified that EPS contains antidiabetic cholesterol-reducing, antioxidant, and immunomodulatory pharmacotherapeutics efficacy (Angelin and Kavitha, 2020; Jurášková *et al.*, 2022; Prete *et al.*, 2021; Tan *et al.*, 2020).

Trillions ( $10^{14}$  microbes) of nonpathogenic microorganisms coexist with humans, ensuring numerous health benefits (Altveş *et al.*, 2020; Brunkwall and Orho-Melander, 2017; Velmurugan *et al.*, 2017). These non-pathogenic beneficial microbial and ecological communities, known as the microbiome and the human gut, act as an eclectic basin (Berg *et al.*, 2020) and are thought an organ since GM performs critical metabolic and defensive accomplishments (Villanueva-Millán *et al.*, 2015). Dysbiosis is any disturbance of these ecological and symbiotic communities (Blandino *et al.*, 2016). Such troubles in the microbiome often promote multiple NCDs by altering our normal physiology (Agus *et al.*, 2018; Schippa and Conte, 2014). Explicitly, DM is documented as related to the dysbiotic intestinal background (Adeshirlarijany and Gewirtz, 2020; Li *et al.*, 2017; Schippa and Conte, 2014), and multiple studies reported a positive relation between altered GM and T2DM (Cunningham *et al.*, 2021; Gurung *et al.*, 2020; Hersoug *et al.*, 2016).

Recently, animal and plant-derived organic substances have been synthesized with an antidiabetic pharmacological potential (Khalivulla *et al.*, 2021; Tran *et al.*, 2020). Multiple studies revealed that traditional fermented foods positively impact the management of DM (Cuamatzin-García *et al.*, 2022; de Almeida Souza *et al.*, 2020; Sivamaruthi *et al.*, 2018). Kefir is a therapeutically efficacious food preference for the diabetic population to regulate blood glucose (Azizi *et al.*, 2021; Farag *et al.*, 2020). China and Japan are two nations recognized as the leading countries for the origin of fermented soy foods, including fermented black soybean and red tofu (Dimidi *et al.*, 2019; Jang *et al.*, 2021). Several soybean-fermented foods originated from Asia, including “tempeh, natto, miso, tofu, douche, soy sauce, and doenjang” (Dimidi *et al.*, 2019). Fermented soybean foods possess several health benefits, including “anti-carcinogenic, antidiabetic antioxidant, anti-inflammatory, and anti-hyperlipidaemic” (Dimidi *et al.*, 2019). In contrast, multiple studies reported that the prevailing documentation regarding health benefits raises the question of whether the studies are conducted in cell culture models or on animals (Jayachandran and Xu, 2019; Kapp *et al.*, 2019; Marco *et al.*, 2021).

### Lactobacillus fermented foods among pediatric population

As the prevalence of obesity in children rises, T2DM also increases alarmingly in the pediatric age group (Astudillo *et al.*, 2021; Valaiyapathi *et al.*, 2020). The prognosis of these children is worse than adult diabetic patients as it advances rapidly (Barrett *et al.*, 2020; Grøndahl *et al.*, 2021). The challenges and complications are not often met adequately by present therapeutic protocols in this group (Grøndahl *et al.*, 2021; Shah *et al.*, 2022). Prevention should be our prime target for at-risk children (Astudillo *et al.*,

2021; Fornari *et al.*, 2021). Another review article; recommended that disturbance in the constitution of microbiota contributes to the development of T2DM in childhood (Brar and Kohn, 2019), and the remedial alternatives that stabilize this dysbiosis should be sought. There is no evidence-based guidance for childhood dietary interventions for type 2 DM (Parkinson *et al.*, 2018; Valaiyapathi *et al.*, 2020). Researchers showed that dietary intervention, including yogurt intake, helps control blood glucose levels in T1DM (Ahola *et al.*, 2016). Animal studies have also supported this (Abdelazez *et al.*, 2018), but no such studies regarding T2DM in children were found as per the methodology applied in this study. Given the evidence of the beneficial effects of fermented food on adult diabetic patients, trials in the pediatric age group are time-demanding.

Multiple research projects reported that LAB-fermented foods improve the host’s defensive action at mucosal sites, including the gut, through synthesizing pathogen-specific or non-specific antibodies for resisting pathogenic microorganisms, thereby preventing gastrointestinal diseases (Asama *et al.*, 2017; Ghoneum *et al.*, 2021; Kotani *et al.*, 2014; Olayanju *et al.*, 2022; Plaza-Diaz *et al.*, 2019). Other studies revealed *Pediococcus acidilactici* strain K15 promotes the synthesis of IFN- $\beta$  by human BDCA1+ DCs and produces enormous quantities of IgA by human B cells by stimulating BDCA1+ DCs. Thereby, it is expected that K15 to employ the repressive effects against viral respiratory tract infections in pediatric cases (Hishiki *et al.*, 2020; Kawashima *et al.*, 2018a, 2018b). Furthermore, it has been reported that pediatric coeliac disease patients had archetypal total serum IgA when they took 200 g/day of sweet baked products made from fermented wheat flour (Rizzello *et al.*, 2016).

### IMPLICATIONS OF LAB FERMENTATES IN GDM

GDM is a transient state of glucose intolerance diagnosed during pregnancy’s second or third trimester (Choudhury and Devi Rajeswari, 2021; Melchior *et al.*, 2017). A pregnant mother with GDM gradually becomes resistant to insulin, mainly due to the production of diabetogenic hormones like progesterone, estrogen, cortisol, placental growth hormone, placental lactogen, and leptin (Behboudi-Gandevani *et al.*, 2019; Plows *et al.*, 2018). GDM may affect up to a quarter of global pregnancies depending on age, obesity, ethnicity, history of GDM, and family history of diabetes and may predispose some women to develop T2DM in the future (Choudhury and Devi Rajeswari, 2021; Kim *et al.*, 2021d; Zhu and Zhang, 2016). GDM may also cause gestational hypertension, pre-eclampsia, and eclampsia, increasing the risk of excessive fetal growth, recurrent abortions, and stillbirths (Goldstein *et al.*, 2017; Sharma *et al.*, 2022; Su *et al.*, 2021b; Szmuiłowicz *et al.*, 2019). Recent metagenomics studies and some systemic reviews on GDM indicate the relationship between intestinal microbiota and GDM. Women with GDM show enrichment of organisms with amino- and nucleotide-sugar metabolism and insulin signaling (Su *et al.*, 2021b). Dysbiosis can contribute to obesity, low-grade inflammation, IR, and high blood sugar concentration (Hasain *et al.*, 2020; Su *et al.*, 2021b). Management of GDM generally depends on lifestyle changes, regular blood sugar monitoring, and pharmacological interventions; however, each method has its shortcomings.

Additionally, heterogeneity in the hyperglycemic condition, physical and mental status, and lack of DM

self-management education among different women render the management processes difficult (Martis *et al.*, 2018; Oskovi-Kaplan and Ozgu-Erdinc, 2021). Historically, like probiotics, LAB and their fermented products are famous for providing superior health benefits and maintaining a healthy gastrointestinal system (Rezac *et al.*, 2018). Interestingly, modification of gut microbiota using different LAB-containing probiotics has been shown to control high blood sugar in adults with T2DM and women with GDM (Łagowska *et al.*, 2020; Lloyd-Price *et al.*, 2016). Probiotic supplements have been shown to alleviate the pathology of GDM through amino acids and BA metabolism in an animal model (Zheng *et al.*, 2022). While formulating a probiotic, it is essential to select the species carefully as a single strain of *Lactobacillus* species might not improve the gut microbiota; however, multi-strain probiotics can be more effective against a wide range of endpoints (Halkjær *et al.*, 2020; Nabhani *et al.*, 2018; Reuben *et al.*, 2022). The earlier study also reported several health benefits of using multi-strain probiotics containing *Lactobacillus* and *Bifidobacterium* species in women with GDM (Hasain *et al.*, 2020). They alleviated various GDM-related pathophysiologic conditions by reducing pathobiont adherence, regulating lipid metabolism, improving the integrity of gut epithelia, suppressing multiple inflammatory responses, improving insulin signaling, reducing glucose tolerance, and reducing glucose tolerance, and reducing cholesterol absorption (Hajat and Stein, 2018). However, the selection of multi-strain probiotics should be based on evidence-based efficacy trials rather than the number of strains in the product (Ouweland *et al.*, 2017). Additionally, it is vital to understand the duration and optimum dose of the supplementation.

LAB performs a substantial capacity in a diverse of fermentation processes worldwide. Many of these fermented foods have proven benefits in controlling blood sugar. Studies have reported the effectiveness of consuming probiotic yogurt during pregnancy in reducing the risk of GDM and the development of IR (Okesene-Gafa *et al.*, 2020; Wickens *et al.*, 2017). Likewise, the intake of soybean-based fermented foods like miso and natto before and during early pregnancy may minimize the incidence of GDM (Dong *et al.*, 2021; Wang *et al.*, 2021b). Another soybean-fermented product, “tempeh,” has benefited from abnormal carbohydrate metabolism in experimental animals with induced T2DM (Huang *et al.*, 2018). Tempeh also showed promising results in decreasing levels of HbA1c and triglyceride in human subjects (Su *et al.*, 2021b).

Similarly, kefir milk has reduced the fasting blood glucose and HbA1c levels in human subjects (Ostadrahimi *et al.*, 2015). The impact of tempeh and kefir on women with GDM has not been studied yet; however, it can be expected to reduce blood sugar, given that similar kinds of LAB are involved in their fermentation process. Therefore, to avert glucose intolerance in women with GDM and reduce the risk of the development of T2DM in these women, it is vital to add a probiotic supplement containing suitable LAB alongside a clinically proven lifestyle modification program.

### IMPACTS OF LAB ON DIABETIC DIETARY SUPPLEMENTS

Despite the availability of several conventional medicines, diabetic patients are increasingly turning to “complementary and alternative medicine” (CAM) to assist their

health. Such CAM options include but are not limited to dietary supplements, which may consist of “vitamins, minerals, herbs, and other botanicals and substances such as enzymes (Cross and Thomas, 2021). While some dietary supplements are abused by diabetic patients (Hannon and Fairfield, 2020), recent debates have targeted microbes’ fermentation effects.

The two types of food fermentation include: aerobic (fungal and alkaline) and anaerobic (alcohol and lactic acid), respectively (Şanlıer *et al.*, 2019). Lactic acids (produced from pyruvate, formed through glycolysis (degradation of monosaccharides) are one of the primary organic acids formed in fermented foods propagated by acetic acid bacteria and both homofermentative and heterofermentative LAB, which produce acetic acid, mannitol, ethanol, lactic acid, and CO<sub>2</sub> from hexoses (Cross and Thomas, 2021; Wang *et al.*, 2021a).

*Lactobacillus* can carry out food fermentation by-products of LAB, *Lactococcus*, *Streptococcus*, and *Leuconostoc* species (Bintsis, 2018), classified as probiotics, bacteriocins, bio-preservatives, and EPS (Raj *et al.*, 2021). To guard against harmful microorganisms and enhance the immune system, probiotics produced by lactic acid-producing bacteria are essential. The Food and Agriculture Organization and the WHO both suggest using LAB recognized from the human GIT as probiotics in humans (Zielinska and Kolożyn-Krajewska, 2018). Probiotics have also been shown to enhance glucose control in diabetic nephropathy (DN) patients, increasing their therapeutic potential in clinical practice (Jiang *et al.*, 2021). Additionally, EPS generated by *Lactobacillus plantarum* C70 and *Lactobacillus plantarum* RJF4 strains of disparate origins show an antidiabetic action by suppressing  $\alpha$ -glucosidase and  $\alpha$ -amylase enzymes *in vitro* (Angelin and Kavitha, 2020).

Based on the literature, a repeatedly well-studied dietary supplement used by diabetic patients includes; water-soluble vitamins (vitamin C, folate/folic acid, vitamin B12, vitamin B6, biotin, and niacin), Fat-soluble vitamins (Vitamin E), Minerals (chromium, potassium, selenium, sodium, and zinc), amino acids (leucine, seventeen on taurine, and one on Beta-Alanine), fiber, macronutrients, yogurt, and caffeine (Chan *et al.*, 2020).

Consuming green vegetables, dairy products, eggs, and meat supplements diabetic patients with water-soluble vitamins like riboflavin, reducing the consequences of IR and MetS development (Mazur-Bialy and Pocheć, 2017). LAB can synthesize B group vitamins, mainly riboflavin, from food fermentation, resulting in fermented bio-enriched food for diabetes patients. Thakur *et al.* (2016) noted that riboflavin production in *Lactobacillus fermentum* KTLF1 and *L. plantarum* in MRS medium could be up to 2.36 and 2.13 mg, respectively.

Dairy fermentations also include protein degradation by LAB to yield a range of small molecule peptides or free amino acids valuable in managing T2DM (Wang *et al.*, 2021a). Among the several amino acids found in foods, lactic acid fermentative foods have been shown to contain a high concentration of d-amino acids. The effects of d-amino acids in diabetic management cannot be overstated; for example, d- Aspartic acid in horny cell layers serves to prevent cells from oxidation, and d-Serine mitigates nephropathy (Kobayashi, 2019) and as well plays a crucial role in recognition of DN in patients go through renal biopsy and improve the clinical outcomes (Iwata *et al.*, 2021).

**Table 4.** Lists of different LAB isolated from various sources and their functions.

Serial No.	LAB	Therapeutic metabolites	Source	Functions	Reference
1.	<i>Pediococcus pentosaceus</i> M41	EPS	Dried marine fish with a low water activity ( $a_w$ )	Antioxidant, antimicrobial, antitumor activity, $\alpha$ -glucosidase, and $\alpha$ -amylase inhibitions	Ayyash <i>et al.</i> , 2020
2.	<i>Lactobacillus plantarum</i> HY	EPS	Sichuan pickle made at home	$\alpha$ -amylase inhibitory and antioxidant activity	Kim <i>et al.</i> , 2018
3.	<i>Lactobacillus plantarum</i> H31	EPS	Pickled cabbage	Overexpression of GLUT-4, AMPK, and AKT-2 gene $\alpha$ -amylase activity and decreased activity of $\alpha$ -amylase in IR HepG2 cells that are resistant to insulin Enhanced phagocytic action of macrophages and the secretion of NO.	Huang <i>et al.</i> , 2020
4.	<i>Lactobacillus plantarum</i> JLK0142	EPS-0142	fermented dairy tofu	The expanded immunomodulatory pharmacological action in the cyclophosphamide-persuaded immunosuppressed experimental animal.	Wang <i>et al.</i> , 2018
5.	<i>Lactobacillus rhamnosus</i> LB11ac10	EPS1-1	Yogurt and fermented milk	Inhibition of the $\alpha$ -glucosidase activity	Wang <i>et al.</i> , 2022
6.	<i>L. fermentum</i> , <i>L. casei</i> and <i>L. rhamnosus</i>	Culture supernatant	Human infant gut	and $\beta$ -glucosidase inhibitory activities and in vivo reduction of blood glucose responses	Sharma <i>et al.</i> , 2017; Evivie <i>et al.</i> , 2017
7.	<i>Lactobacillus agilis</i>	Culture supernatant	Rhizosphere soil of <i>Ocimum tenuiflorum</i> , <i>Azadirachta indica</i> , <i>Ficus carica</i> .	$\alpha$ -amylase inhibition, antidiabetic effect	Khan <i>et al.</i> , 2021
8.	<i>Lactobacillus fermentum</i> 21828	Culture supernatant	Apple juice	$\alpha$ -Glucosidase inhibition	Wang <i>et al.</i> , 2021a
9.	<i>Lactobacillus plantarum</i> 152 and <i>Pediococcus acidilactici</i> 004	Culture supernatant	Sichuan pickles Kimchi	Functional strain with prospective antidiabetic possessions	Cai <i>et al.</i> , 2019
10.	<i>Lactobacillus plantarum</i> RJF4	Hetero- EPS (Glucose, mannose)	Rotten jack fruit	$\alpha$ -amylase inhibition	Beltrán-Barrientos <i>et al.</i> , 2016; Angelin and Kavitha, 2020.
11.	<i>Lactobacillus gasseri</i> ATCC 33323	Inactive full-length form of GLP-1(1-37)	Recombinant strains	Reprogramming intestinal non- $\beta$ -cells into cells with insulin-secreting property	Mays and Nair, 2018; Hwang and Chang, 2020; Miraghajani <i>et al.</i> , 2017.
12.	<i>Enterococcus faecium</i>	Bacteriocin-related antimicrobial	Isolates from Nile lechwe and Grant's zebra feces	Antioxidant agents in the making by bacteriocin architects	Daba <i>et al.</i> , 2021.
13.	<i>Enterococcus faecalis</i>		Milk fermentates	Diminish synthesis of ACE and $\alpha$ -glucosidase Stimulates DCs to produce inflammatory cytokines IL-12 and regulatory IL-10,	Graham <i>et al.</i> , 2019
14.	<i>Lactobacillus acidophilus</i> <i>L. casei</i> and <i>Bifidobacterium longum</i>			Induces IL-10 in DCs, cut-back synthesis of IL-12 levels. Intensified the total numbers of T cells, NK cells, MHC class II+ cells, and CD4-CD8+ T cells. Over the production of TNF- $\alpha$ .	Del Carmen <i>et al.</i> , 2017; Jacouton <i>et al.</i> , 2017; Rahbar <i>et al.</i> , 2019.

Fibers, macronutrients, and caffeine are diabetic dietary supplements that benefit fasting glucose, HbA1c, insulin concentrations, body weight, and microbial diversity (Hannon and Fairfield, 2020; Lenoir-Wijnkoop *et al.*, 2016). There exists a void in the literature on studies relating to the pharmacological action of LAB on dietary fiber and diabetic nutrients. In an *in-vitro* experiment done on rats to see the effect of an extract of natto-red beans that was fermented by *Bacillus subtilis*, it was observed that FBS and DN are prevented through boosting antioxidant status and reducing inflammation in renal tissue at NRBE, 200 mg/kg BW (Chan *et al.*, 2020). Multiple studies (Bruno *et al.*, 2021; Lenoir-Wijnkoop *et al.*, 2016; Scrafford *et al.*, 2019, 2020) suggested that increasing intake in the adult population by 100 g per day of some LAB fermented products like yogurt could generate substantial cost savings and significant patient benefits by minimizing the incidence of T2DM. The impact of LAB-fermented food cannot be overstated in a nutshell. It has been noted to improve diabetic health and patients' economic status.

#### THERAPEUTIC APPROACHES TO LAB FERMENTATES INDUCED IMMUNOPATHOLOGY IN T2DM

Several health benefits to the host can be attributed to LAB, such as regulating glucose and fat metabolism and boosting the host's response to oxidative stress and inflammation. Nonetheless, a number of studies have uncovered the anti-diabetic mechanism of probiotics by revealing a significant increase in the epithelial barrier performance, hence downregulating inflammatory cytokines such as TNF-, IL-1, and IL-8 in the colon tissue and liver (Bezirtzoglou *et al.*, 2021; Slattery *et al.*, 2019; Wang *et al.*, 2020d). Expression of glucose and lipid metabolism genes like glycogen synthase kinase 3 $\beta$  (GSK-3 $\beta$ ), fatty acid synthase, and sterol regulatory element-binding transcription factor 1c have been reported to be upregulated upon oral treatment *Lactobacillus acidophilus* (Tiderencel *et al.*, 2020). Besides these, upregulation of protein kinase B (Akt), reshaping gut microbiota with the rising formation of short-chain-fatty-acid producing microbes, has been

depicted as antiobesity therapy using *L. acidophilus* (Duan *et al.*, 2021; Mazloom *et al.*, 2019).

LAB discharges extracellular macromolecules known as EPS as a firmly bonded capsule or a loosely connected slime layer. They substantially protect against dehydration, phage attack, cell recognition, toxic or antibiotic chemicals, osmotic stress, and phagocytosis (Angelin and Kavitha, 2020). Multiple research has revealed the EPS-mediated anti-inflammatory, antidiabetic, and antioxidant potential of several reported LAB species of LABs. Besides, culture supernatant of LAB, out of the way from rhizosphere soil, fermented kimchi, pickles, etc., have also been shown to potentiate alpha-amylase inhibition exerting antidiabetic effects (Khan *et al.*, 2021; Tiderencel *et al.*, 2020; Wang *et al.*, 2021a). Table 4 illustrates the significant metabolites from various reported LABs with their functions resisting T2DM.

Inflammation-derived obesity-associated IR is a significant characteristic of T2DM (Kumar *et al.*, 2018). IL-10 is an anti-inflammatory cytokine with diminished circulating levels in obese, lipid-induced, and IR subjects, preventable with acute IL-10 treatment (Kawai *et al.*, 2021). Novel findings from several studies demonstrated that IL-10 promotes sensitivity to insulin and protects skeletal muscle against obesity-induced macrophage infiltration responsible for the rise in inflammatory cytokines and causing harm to glucose and insulin signaling metabolism. T2DM-related pathogenic insulin-signaling phenotypes can be attenuated by IL-10 produced in skeletal muscle, which may be advantageous in developing future therapeutics for the illness (Ellulu *et al.*, 2017; McLaughlin *et al.*, 2017; Wu and Ballantyne, 2017). However, LAB isolates have also been demonstrated to influence the gene expression of proinflammatory and anti-inflammatory cytokines, along with anti-apoptotic protein kinase activation and downrate of TNF- $\alpha$  and IL-6 (Kanmani and Kim, 2018; Lee *et al.*, 2022). Also, epithelial expression of IL-10 has been revealed in a study employing oral supplementation with a commixture of *Lactobacillus* and *Bifidobacterium* strains in a mice model (Azad *et al.*, 2018; De Marco *et al.*, 2018; Yousefi *et al.*, 2019). Table 5 illustrates a comprehensive list of cytokines reported to be influenced by various isolates of LABs.

Table 5. Cytokines affected by various LAB.

Serial No.	LAB	Cytokines and their functions	Ref.
1	<i>Lactobacillus sakei</i>	IL-1 $\beta$ , IL-6, and TNF- $\alpha$	Jang and Min, 2020
2	<i>L. johnsonii</i>	TGF- $\beta$	Azad <i>et al.</i> , 2018; Diez-Ozaeta and Astiazaran, 2022; Yousefi <i>et al.</i> , 2019.
3	<i>Lactobacillus salivarius</i> and <i>Bifidobacterium infantis</i>	Curtailed of INF- $\gamma$ and TNF- $\alpha$ by Peyer's patch lymphocytes and proinflammatory cytokine production by spleen cells	Jeong <i>et al.</i> , 2022; Raheem <i>et al.</i> , 2021, Cristofori <i>et al.</i> , 2021.
4	<i>L. paracasei</i> and <i>L. reuteri</i>	Depletion in mucosal proinflammatory cytokines. Therefore, it minimizes the colitis forming in the presence of <i>Helicobacter hepaticus</i> infection	Mohseni <i>et al.</i> , 2021; Capurso, 2019.
5	<i>Lactobacillus rhamnosus</i> GG	Activation of anti-apoptotic Akt/protein kinase B and impediment of proapoptotic factors by way of the p38 MAPK pathway	Rohith and Halami, 2021.
6	Mixture of <i>Lactobacillus</i> and <i>Bifidobacterium</i> species	Expressed IL-10 (an anti-inflammatory cytokine) and suppresses response to a stimulus of TNF- $\alpha$ and IL-6 (proinflammatory cytokines)	
7	<i>Lactobacillus</i> and <i>Bifidobacterium</i> strains	Stimulate the immunoglobulin production (IgA) spark epithelial cell expression of IL-10, TGF- $\beta$ , and IL-6	

## CLINICAL TRIALS WITH LAB FERMENTED FOODS DEPICTED

**Table 6.** Recent clinical trials of fermented foods indexed in PubMed.

Fermented food	Author's and journal details	Type of research	Principal findings
KAT diet (includes Kimchi and fermented soybean)	Kim <i>et al.</i> Alleviation of dyslipidemia via a traditional balanced Korean diet represented by a low glycemic and low cholesterol diet in obese women in a randomized controlled trial. <i>Nutrients</i> . 2022a;14(2):235. doi: 10.3390/nu14020235	Randomized controlled trial	KDT substantially minimizes anthropometric and biochemical variables than those having a control diet. Serum total cholesterol, non-HDL cholesterol, and triglyceride levels statistically significantly decreased among the KDT group compared to the control group. The waist circumference ( $p = 0.108$ ) and IR index ( $p = 0.089$ ) cottoning to be lower among the KAT folk than in the control class.  Hansik, have a favorable pay-off on MetS than those having western food consumers. High-Hansik consumers had a 0.87-time lower risk of MetS.
Kimchi, pickles	Kim <i>et al.</i> Inverse association of a traditional Korean diet composed of a multigrain rice-containing meal with fruits and nuts with MetS risk: The KoGES. <i>Front Nutr</i> . 2022b; 9:1051637. doi: 10.3389/fnut.2022.1051637.	Clinical trial	Hansik consumers had a reverse relationship with the body mass index, waist circumference, and fat mass. Nonetheless, a positive relation was observed with the skeletal muscle mass. Furthermore, a high-hansik consumer had better blood pressure and serum LDL and triglyceride control.  Efficient kefir intake improves the anthropometrical parameters, GI, and lipid profile and controls hypertension and inflammatory status in patients with MetS.  Kefir consumers demonstrated low LDL-C and apolipoprotein B levels than milk drinkers ( $p > 0.05$ ). Additionally, milk and kefir drinkers are related to controls both systolic and diastolic blood pressure when equated with the baseline ( $p < 0.05$ ).
Probiotic Kefir	Bellikci-Koyu E, <i>et al.</i> Probiotic kefir consumption improves serum apolipoprotein A1 levels in MetS patients: a randomized controlled clinical trial. <i>Nutr Res</i> . 2022; 102:59–70. doi: 10.1016/j.nutres.2022.02.006.	Randomized controlled clinical trial	Additionally, regular intake of kefir for 3 months was associated with minimizing administration and decreased serum TNF- $\alpha$ , IL-6, IL-6, IFN $\gamma$ , and homocysteine concentrations significantly ( $p < 0.05$ ).
Fermented <i>Carica papaya</i> and <i>Morinda citrifolia</i>	Kharaeva Z, <i>et al.</i> Fermented <i>Carica papaya</i> and <i>Morinda citrifolia</i> as perspective food supplements for the treatment of post-COVID symptoms: randomized placebo-controlled clinical laboratory study. <i>Nutrients</i> . 2022;14(11):2203. doi: 10.3390/nu14112203.	Randomized placebo-controlled clinical laboratory study.	Fermented <i>Carica papaya</i> and <i>Morinda citrifolia</i> possess immune modulating, redox balancing, and anti-inflammatory properties that are well demonstrated than conventional therapeutic interventions.
Iranian traditional foods, fermented food	Salehi <i>et al.</i> Effects of traditional Iranian fermented food consumption on blood glucose, blood pressure, and lipid profile in type 2 diabetes: a randomized controlled clinical trial. <i>Eur J Nutr</i> . 2022 Oct;61(7):3367–3375. doi: 10.1007/s00394-022-02867-2.	Randomized controlled clinical trial	This study revealed that Ash-Kardeh consumers had statistically significantly reduced levels of fasting blood glucose ( $p = 0.003$ ), total cholesterol ( $p = 0.025$ ), triglyceride ( $p = 0.003$ ), SBP ( $p < 0.001$ ), and DBP ( $p = 0.014$ ) than the control group. Additionally, the Ash-Kardeh treated group had statistically significantly ( $p = 0.048$ ) higher level HDL than the non-intervened group.
Fermented <i>Rhus verniciflua</i> stokes	Kwak <i>et al.</i> Effect of fermented <i>Rhus verniciflua</i> stokes extracts on liver function parameters in healthy Korean adults: a double-blind, randomized controlled trial. <i>Trials</i> . 2021;22(1):830. doi: 10.1186/s13063-021-05656-0.	Randomized double-blind randomized controlled trial	This study did not detect any statistically significant ( $p > 0.05$ ) difference observed regarding the values of liver disease-related parameters and serum lipid profiles between treated and untreated groups.

*Continued*

Fermented food	Author's and journal details	Type of research	Principal findings
Pickle juice	Tapper <i>et al.</i> Pickle juice intervention for cirrhotic cramps reduction: the PICCLES randomized controlled trial. <i>Am J Gastroenterol.</i> 2022;117(6):895–901. doi: 10.14309/ajg.0000000000001781.	Randomized controlled trial	This study reported that pickle juice reduces the visual analog scale for cramps (VAS-cramps) statistically significantly ( $p = 0.03$ ) than control arms (tap water). Additionally, the proportion of VAS-cramps reduces significantly ( $p = 0.2$ ).
Fermented Panax ginseng	Fukami <i>et al.</i> Pharmacokinetic study of compound K in Japanese subjects after ingestion of Panax ginseng fermented by <i>Lactobacillus paracasei</i> A221 reveals significant increase of absorption into blood. <i>J Med Food.</i> 2019;22(3):257–263. doi: 10.1089/jmf.2018.4271.	Randomized, crossover, single-dose, two-period, open-label research.	This study revealed that 58.3 and 17.5-fold were more remarkable in the FG group than in the NFG folk. Furthermore, the FG group's mean testosterone concentration substantially increased 24 hours after administration. These results demonstrated that the principal ginsenoside metabolite of ginseng, CK, synthesized by <i>L. paracasei</i> A221, has an inherent advantage in health preservation in healthy middle-aged and old Japanese adults.
Fermented soybean-lettuce powder	Han <i>et al.</i> Evaluation of the effectiveness of fermented soybean-lettuce powder for improving menopausal symptoms. <i>Nutrients.</i> 2022;14(14):2878. doi: 10.3390/nu14142878.	Randomized, double-blind clinical trial	This study reported a significant decrease in the Kupperman index after being treated with Fermented Soybean-Lettuce. Nonetheless, no significant change was observed in the control group. Soybean lettuce extract relieves post-menopausal syndrome without any adverse effects. It has been explained as soybean has been known to alleviate menopausal difficulties. Lettuce possesses antidiabetic and anti-inflammatory potential and enhances the quality of sleep. Natural NO metabolites are synthesized through fermentation, which augments the persuasiveness of the functional molecules.
Red ginseng extract with LAB	Jeon <i>et al.</i> Concomitant administration of red ginseng extract with LAB increases the plasma concentration of deglycosylated ginsenosides in healthy human subjects. <i>Biomolecules.</i> 2022;12(12):1896. doi: 10.3390/biom12121896.	Clinical Trials	LAB supplementation raises the plasma levels of deglycosylated ginsenosides, such as GRh2, CK, PPD, and PPT, by facilitating the deglycosylation metabolism of ginsenosides in the intestine.
Red ginseng extract	Kim <i>et al.</i> Pharmacokinetics of ginsenoside Rb1, Rg3, Rk1, Rg5, F2, and compound K from red ginseng extract in healthy Korean volunteers. <i>Evid Based Complement Alternat Med.</i> 2022c; 2022:8427519. doi: 10.1155/2022/8427519.	Clinical trials	BRG had a higher absorption rate of bioactive ginsenosides, which enhanced the therapeutically efficacious with the increased pharmacological commotion of ginseng.

Hansik = A traditional Korean fermented food; Korean traditional diet = KDT; Metabolic Syndrome = MetS; Low-density lipoprotein cholesterol = LDL-C; Tumor necrosis factor- $\alpha$  = TNF-), Interleukin 6 = IL-6, Interleukin 10 = IL-10, Interferon-gamma = Interferon- $\gamma$ ; Ash-Kardeh = One of the few fermented foods without a dairy base of Iran; systolic blood pressure = SBP; diastolic blood pressure = DBP; high-density lipoprotein cholesterol = HDL; Cytotoxic T lymphocytes = CD3+CD16+CD56; Fermented ginseng = FG; Nonfermented ginseng =NF; Red ginseng = RG; Fermented red ginseng = FRG; Lactic acid bacteria = LAB; compound K = CK, ginsenoside Rh2 = GRh2; protopanaxadiol = PPD, protopanaxatriol = PPT; bioconverted red ginseng extract = BRG, Nitric oxide = NO.

## CONCLUSION

The use of probiotic LABs and related fact-finding has garnered significant inquisitiveness for several years, leading to the creation of various food items with multiple health advantages (Table 6). This study has pointed up some of the applications of these valuable microbial strains, hence raising the likelihood of their adoption shortly. Several of the evaluated research shows that LABs possess strong antidiabetic properties by generating bioactive compounds, triggering suppression of inflammatory responses, leading to severe health damages from T2DM. Shortly, their usage as functional starting cultures in dairy products such as yogurt and ice cream will provide encouraging results. More real-life clinical studies may substantially reduce ethical, cultural, and religious roadblocks to probiotic LAB research. To expand the use of probiotic LABs, leading government, and academic institutions examine the processes behind their ameliorative benefits. Delivering strategies

such as microencapsulation must be further refined to maximize the survival of many viable probiotic LAB cells. Bioinformatics of probiotic LABs strains also need more research. This new study area provides an excellent opportunity for researchers, physicians, biotechnologists, and food professionals to collaborate on applying LAB-derived bioactive molecules as innovative therapeutic possibilities for treating illnesses such as DM.

## RECOMMENDATION

More real-life clinical research studies must be carried out to recognize and realize the beneficial aspect of LAB on human health. Also, governments and academic institutions need to play an active role in incorporating LAB use for human health. Further refinement of delivery means to ensure LAB cells' survival needs to be done. Researchers should further investigate and use probiotics as therapeutics for various illnesses in the best possible ways.

## AUTHORS' CONTRIBUTION

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## CONFLICT OF INTEREST

The authors declare no conflicting interest.

## ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

## DATA AVAILABILITY

This is a narrative review paper. All data utilized are from open sources.

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