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Effect of prebiotics, probiotics, and synbiotics on gut microbiome in diabetes among coastal communities

A. T. Rithi[1], Abhijit Mitra[2], Antara Banerjee[2], Divya Ilanchoorian[3], Francesco Marotta[4], Arun Kumar Radhakrishnan[1]*

[1]Department of Pharmacology, Chettinad Hospital and Research Institute (CHRI), Chettinad Academy of Research and Education (CARE), Chennai, India; [2]Medical Biotechnology lab, Faculty of Allied Health Sciences, Chettinad Academy of Research and Education (CARE), Chettinad Hospital and Research Institute (CHRI), Chennai, India; [3]Department of Community Medicine, Chettinad Hospital and Research Institute (CHRI), Chettinad Academy of Research and Education (CARE), Chennai, India; [4]ReGenera R&D International for Aging Intervention, Milan, Italy.

***Corresponding author**: Dr. Arun Kumar Radhakrishnan, Department of Pharmacology, Chettinad Hospital and Research Institute (CHRI), Chettinad Academy of Research and Education (CARE), Chennai, 603103, India.

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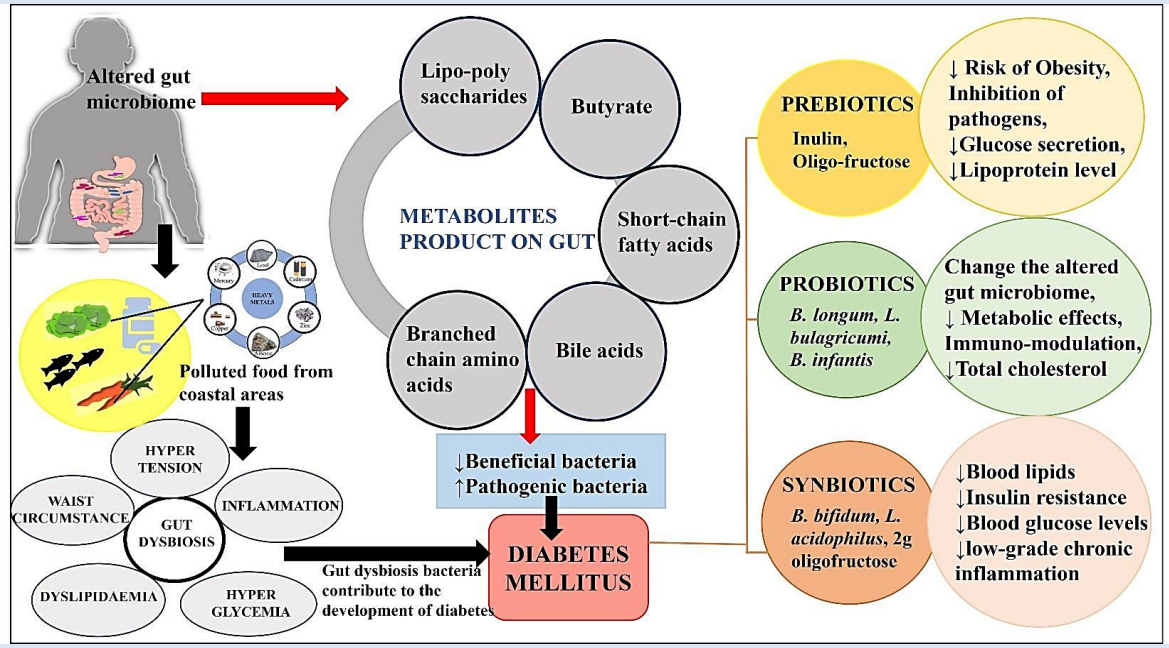
ABSTRACT

Cutting-edge research on oceans and human health is enhancing our comprehension of disease-causing organisms in coastal ecosystems. Coastal areas are affected by pollution resulting from the changes in hydrology and land utilization. In the coastal population, an elevated incidence of diabetes was observed. Diabetes mellitus is a prominent metabolic disease that is causing major burdens for patients as well as physicians. Diabetes is an intricate condition that encompasses several molecular pathways associated with the gut microbiome. The gut microbiome significantly influences the permeability of the gastrointestinal mucosa. Alterations in the wide range of gut microbiomes have been associated with various health issues including diabetes. The two major contributors to type 2 diabetes are insulin resistance and inflammation which may result in metabolic dysregulation due to dysbiosis. Due to gut dysbiosis, diabetes may show high prevalence in individuals living in coastal areas. The correlation between dysbiosis and diabetes can be made, especially considering probiotics have been demonstrated to have some impact in helping diabetic patients with their interrupted metabolism revert to normal. Probiotic intake has reportedly resulted in improved metabolic control among patients with type 2 diabetes. Prebiotics can be non-digestible carbohydrates that are naturally extracted or synthetically produced. Uses of synbiotics show a synergistic impact on type 2 diabetes by altering the gut environment. In coastal communities, the potential effects of probiotic, prebiotic, and synbiotic therapy on the gut microbiome of diabetic patients have been investigated. Although these therapies have demonstrated encouraging results in coastal areas, more research is needed to fully understand their implications for controlling diabetes in this setting. In this

review, we describe the role of the gut microbiome in diabetes patients residing in coastal regions and the underlying mechanisms that existed for analysing and predicting the function of the microbiome in diabetic people. The role of pre, pro, and synbiotics in type 1 and type 2 diabetes are precisely summarized.

Keywords: Type 1 diabetes, gut microbiome, type 2 diabetes, coastal region, dysbiosis, prebiotics, synbiotics, probiotics.



INTRODUCTION

One of the major global causes of disease and death is diabetes mellitus [1]. The chronic metabolic disorder is epitomized by hyper-glycemia, which is an increase in blood glucose levels resulting from a malfunction in the production of insulin or its activity [2]. The incidence rate is growing. High blood glucose levels and an increase in insulin resistance are characteristics of the disease [3]. Obesity and genetic changes are among the extrinsic and intrinsic factors that are combined to form the risk factors for diabetes mellitus. Numerous illnesses such as hypertension, diabetes, and cancer are linked to increased levels of free radicals and oxidative stress [4].

The microbiota of the gut influences immunological response and dietary intake, which are critical factors in determining general health [5]. The gastrointestinal tract of humans normally has an enormous number of microorganisms, with an average of 10^{14} organisms per ml of luminal fluid. These microorganisms include more than 5,000 various types of bacteria. The gut microflora of healthy adults is primarily composed of six phyla: *Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria, Fusobacteria*, and *Verrucomicrobia* within the human intestinal tract [6]. Approximately 90% of these bacterial species may be divided into two major phyla, the *Firmicutes* and the *Bacteroidetes*, which are primarily composed of gram-positive and gram-negative bacteria. They play a crucial role in the nutritional absorption system and contribute to the reinforcement of the intestinal barrier [7]. Microbiome dysbiosis was a consistent phenomenon with diabetics, and it related to changes in the composition of the gut microbiome.

Reduced insulin sensitivity and inadequate glycemic control were caused by diabetes [8]. Several medical conditions, such as allergies, gastrointestinal inflammatory diseases, cancer, diabetes, cardiovascular diseases, and abnormalities in lipid metabolism, have been related to the gut microbiome composition.

Consequently, ocean and estuarine ecosystems play a significant role in influencing human exposure to a range of pathogenic microbes encompassing both indigenous marine pathogens and externally introduced microbial contaminants [9]. This also applies to industrial and agriculture pollutants of potential mutagenicity [10-12] and diabetogenic risk [13]. Ecosystems, functioning as primary reservoirs and influenced by terrestrial runoff, serve as protective barriers mitigating the impacts of surface activities on surrounding coastal environments and people communities [14]. Reductions in both the quantity and quality of crucial environments, sensitive to shifts in their surroundings, have consistently served as early indicators of widespread damage to coastal ecosystems [9]. While there are suggestions of a high prevalence of diabetes in coastal populations due to lifestyle factors, it is crucial to recognize the variations in reported prevalence in existing literature. Differences in screening criteria, age group composition, and the absence of lifestyle quantification demonstrated by Rao et al. (2010), highlight the complexity of this relationship [15]. Further research is needed to comprehensively explore the multifaceted factors influencing diabetes prevalence in coastal communities.

Probiotics may have a beneficial effect on gut flora, which could help with the treatment of a number of clinical disorders [16]. They have shown promise as supportive treatments for insulin resistance and contribute to a more balanced gut microbiome. Our understanding of the relationships between infections, coastal and marine habitats, and human health has greatly improved as a result of recent studies [9]. Prebiotics are a group of dietary substances that are categorized together based on their capacity to stimulate the growth and/or activity of particular healthy bacteria in genetically modified organisms, rather than always on similar structural affinity [17]. The word "synbiotics" indicates the mutually enhancing interaction that occurs between the beneficial intestinal bacteria and the specific substrates that help them grow once they migrate from the gut to the intestines, so they can establish their dominance [18]. A study on synbiotics has resulted in the availability of various synbiotic products for individuals. Numerous ailments, including a result of atopic dermatitis, gastrointestinal conditions, liver encephalopathy, inflammatory bowel disease, metabolic syndrome, and type 2 diabetes, can be effectively treated with various synbiotic mixtures [19]. In this review, we summarize an overview of the gut microbiota's involvement in diabetes residing in coastal regions, and strategies that leverage probiotics, prebiotics, and synbiotics to both prevent and treat individuals with diabetes.

DIABETICS PEOPLE IN COASTAL REGIONS

In the coastal population, diabetes was found to be highly prevalent [15]. Kerala, a southern Indian state with a 20 percent type 2 diabetes frequency, is leading the nation in an epidemiological transformation and a predictor of the developments that will happen across the other parts of the country [20]. Type 1 diabetes also known as chronic autoimmune disease is caused by intricate interaction [21]. Based on epidemiological data, the prevalence of type 1 diabetes (T1D) ranges from 3% to 5% annually [22]. 8.2% of coastal people had diabetes, compared to 4.5% in the highlands ($p=0.03$) and 3.5% in the rainforest ($p<0.02$) region. An estimated 22.4% of the nation's population had impaired fasting glucose; it was more common in men than in women (28.3% vs. 19.1%; $p<0.001$), and it was more common in coastal areas (26.4%) than in the mountains (17.4%; $p=0.03$), but not in tropical areas (14.9%; $p=0.07$) [23]. A study prevalence

shows a total of 16% of people were found to have diabetes in the Karnataka coastal region. It was discovered that 18.8% of men and 14.4% of women had diabetes. 11.2% of participants self-reported having diabetes, and 4.8% of previously normal individuals had elevated fasting capillary blood glucose levels according to the screening criteria used in Karnataka coastal area [15]. Phenolic molecules are recognized as secondary metabolites that are necessary for defence responses, such as those involving antioxidant, anti-inflammatory, and antidiabetic properties [24].

In comparison to the non-coastal area, the coastal area's diabetes mortality shows a stronger relationship with environmental factors. The factors influencing diabetes in coastal and non-coastal areas are summarized in Table 1. The interplay between the innate immune system and intestinal microbiota in the gut is an epigenetic element that might affect the susceptibility to type 1 diabetes. The potential exists that an interaction with a food antigen may trigger the primary immune system reaction leading to pancreatic damage [25]. Additionally, various factors, encompassing both genetic and environmental influences, contribute to an individual's susceptibility to T1D. Furthermore, the incidence of T1D is consistent across genders [26]. Existing evidence indicates that an imbalance in the gut microbiome is linked to an increased predisposition to type 1 Diabetes [22].

Table 1. Factors influencing diabetes in coastal and non-coastal regions

Factors	Coastal	Non-coastal	Reference
Mortality	The coastal areas showed a higher correlation between environmental variables and diabetes mortality than the non-coastal areas.		Zheng et al., 2023 [27]
Dietary pattern	Seafood is more easily accessible in coastal areas and can be a good source of lean protein and omega-3 fatty acids.	They depend on different sources of protein and the development and treatment of diabetes can be influenced by dietary habits.	Ssewanyana et al., 2018 [28]
Physical activity	Individuals living in coastal areas can get involved in water-based activities.	Lifestyle choices can impact the levels of physical activity, and non-coastal areas might offer different leisure opportunities.	Ssewanyana et al., 2018 [28]
Climate	Their climates might be milder, which would promote outdoor activities during the entire year.	More severe temperatures could impact individual outdoor activities and fitness routines.	Zheng et al., 2023 [27]
Socio-economic	Economic activities in the coastal region, such as fishing and tourism, can have an impact on socioeconomic variables and way of life.	Individual's different economic pursuits may have an effect on their ability to obtain medical treatment, dietary habits, and overall health.	Aswathy et al., 2017 [20]

Dysbiosis due to the interaction of gut microbiome, the environment, and genetic variations, may result in impaired mucosal immune response and higher intestinal permeability in people with type 2 diabetes. These

factors could be associated with the development or aggravation of type 2 diabetes mellitus (T2DM) [29]. Some clinical research has demonstrated a link between lipopolysaccharides and the onset of type 2 diabetes. Simultaneously, the movement of viable bacteria from the intestinal barrier into the bloodstream seems to be associated with the progression of type 2 diabetes. A comprehensive human metagenome-wide association study has revealed noteworthy correlations between specific gut microbes, bacterial genes, and metabolic pathways in patients with type 2 diabetes (T2D) [25]. Administering appropriate doses of quercetin for protection against oxidative stress can be crucial in diabetes mellitus linked to the acidification of the internal environment observed in certain types of cancer [30]. One of the studies demonstrated the different parts of Kerala, India's southern state, have varying prevalence rates of type 2 diabetes; Kerala is going through an advanced phase of epidemiology transformation. Diabetes demonstrates similarities across communities [20].

Gut microbiome in coastal diabetic people: Coastal communities may be exposed to environmental factors, including pollutants or changes in coastal ecosystems that could influence the gut microbiome and inflammatory responses. The human gut microbiome can be negatively impacted by microplastic pollution in coastal areas [31] and is capable of causing IBD, IBS, obesity, and type 2 diabetes [32]. Low levels of *Bifidobacterium* and *Faecalibacterium prausnitzii*, two gram-positive bacteria with anti-inflammatory activities, are seen in diabetics [33]. The human host's gut microbiome directly as well as indirectly promotes a number of crucial functions, such as the formation of the immune cells, the digestive breakdown of foods, the synthesis of vitamins, and the extraction of energy from inedible carbs [34]. A variety of metabolites such as short-chain fatty acids are produced from starch that is resistant to the gut microbiome and influences various pathways of signalling that are important for maintaining human health [35]. Dysbiosis is the alteration of the balance of the microbiota as a result of multiple factors such as inflammation in the gut, antibiotic consumption, menopause, stress, and contaminants [36]. Insulin resistance and other pre-diabetes disorders are influenced by gut microbiome composition [37]. The gut microbiota profiles of diabetics remain inconsistent and varied [25].

A decreased butyrate-producing bacteria (particularly Roseburia intestinalis and Faecalibacterium prausnitzii); moderate dysbiosis; pro-inflammatory ecology with a greater number of microbiota genes associated with oxidative stress, decreased activity of genes engaged in the synthesisation of vitamin, and an elevated LPS concentration in serum are the main features of the microbiome of T2DM patients. In addition, there is an increase in the accessibility of the gastrointestinal tract [38].

Effect of metabolites on the gut and development of diabetes in coastal communities: In over a decade, numerous kinds of studies have examined various forms of expression between the gut microbiome and their hosts. The impact of metabolites on the gut microbiome concurring to cause diabetes is illustrated in Figure 1.

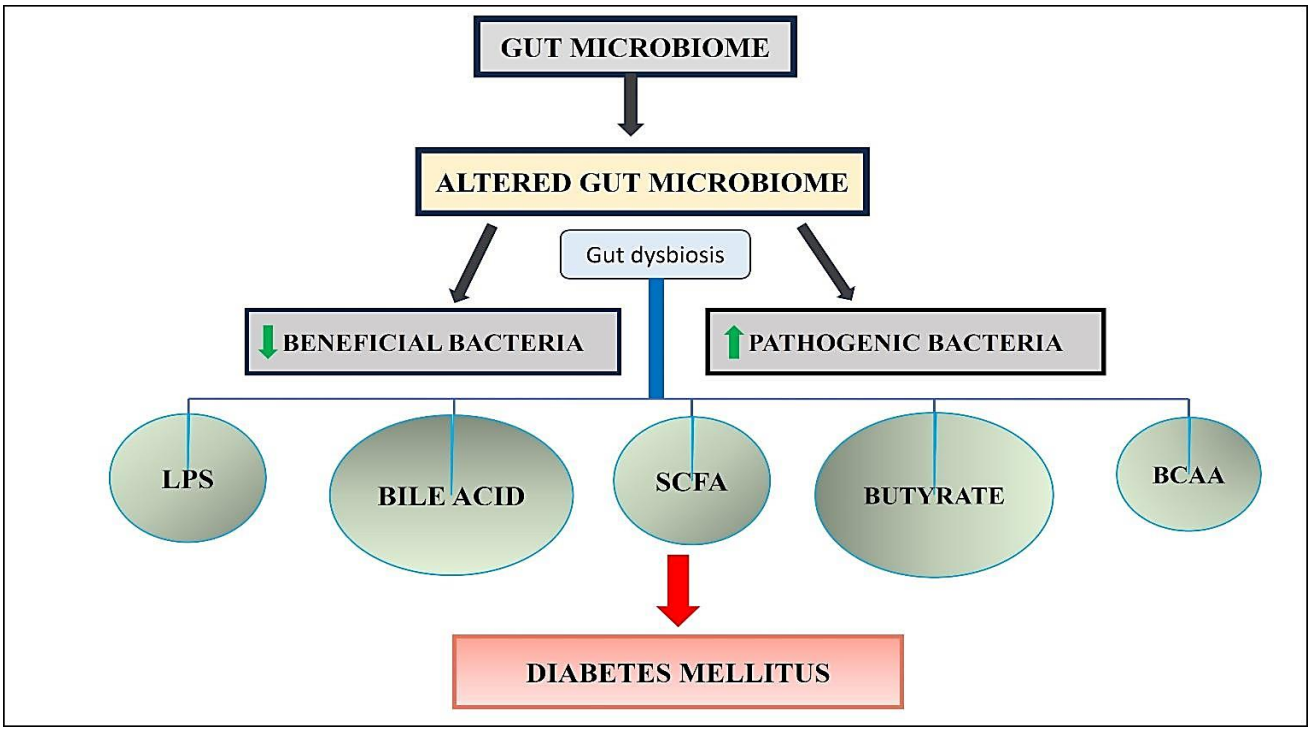


Figure 1. Impact of metabolites on gut microbiome causing diabetes

These investigations have explored the mechanisms, analysing and predicting the function of the microbiome in the inhibition of resistance to insulin, with a focus on components such as lipopolysaccharides (LPS) and short-chain fatty acids (SCFAs) [39]. Most of this research has focused on the activation of diabetes indicators, namely an immunological response and a low-grade inflammatory response, where gut microbiota and their metabolites play a key role [40]. Interestingly, it has been shown that by following healthy guidelines for diabetes, an indirect beneficial array of protective mechanisms against cancer may also arise [41].

Lipopolysaccharides (LPS): LPS originates from the cell wall of gram-negative bacteria [42]. Low-grade inflammation has been found to originate from LPS-promoting immune cells' and adipocytes' release of inflammatory cytokines. On the other hand, butyrate or acetic acid can alter the way of immune cells function [39]. Studies have shown that by stimulating the TLR4 signalling pathway, saturated fatty acids can cause low-grade inflammation and insulin resistance [43]. Various studies have demonstrated the involvement of TLR2 in the inflammatory response when the signalling cascade activated by LPS-LBP-TLR4 is initiated [44]. The progression of type 2 diabetes appears to be significantly influenced by the strength of the intestinal wall. The primary role of the intestinal epithelium, which functions as a barrier, is to restrict the interplay throughout the primary specific immunity, the gut microbiome, and other body organs [45]. Investigations performed on animals have demonstrated that lipopolysaccharide (LPS) has a role in the control of diabetes-associated pathways, which are distinguished by the elevated inflammatory response [46].

Short chain fatty acids (SCFAs): SCFAs are generated when non-digestible dietary fibers mostly acetate, propionate, and butyrate are fermented by bacteria in the intestinal tract [4, 39]. The range of bacteria in various sediment layers in coastal areas is identified by the concentration of saturated carbon filler (SCFA), butyrate indicating the impact on bacterial growth and composition of bacterial community [47]. Studies done in

mice have demonstrated that SCFA dietary supplementation enhances insulin sensitivity, rectifies dyslipidemia, prevents weight gain, and enhances energy expenditure in diet-induced obese mice [48]. In clinical investigations, it has been observed that dietary fiber promotes the production of SCFAs by the gut microbiome, whereas many other potential producers are comparatively diminished in individuals with type 2 diabetes [49]. According to a metagenomic study, individuals with type 2 diabetes who have not been treated with metformin may exhibit a reduction in the abundance of butyrate-producing genera, such as *Roseburia* spp and *Subdoligranulum* spp [50]. Moreover, the number of butyrate-producing bacteria is lesser in prediabetic persons than in healthy individuals, indicating that a lack of these types of bacteria may be one of the progenitors of diabetes [51].

Role of bile acids signalling: The liver synthesizes bile acids, which undergo enzymatic metabolism by gut microbiota to transform into secondary bile acids [52]. The bile acids generated by the gut microbiota may affect human glucose and lipid metabolism by modulating signaling via bile acid receptors [49]. Furthermore, it has been shown that obese T2DM people have elevated circulation levels of bile acids [53], and these levels have been demonstrated to correlate with BMI [54]. Furthermore, it highlights the importance of bile acids in improving glucose balance during RYGB (Roux-en-Y Gastric Bypass), since FXR mutant mice's metabolism does not improve following vertical sleeve gastrectomy (VSG) [55].

Branched chain amino acids (BCAA): Branched-chain amino acids (BCAA) are regarded as predicting markers for T2D and may be associated with an increased chance of developing T2D [56]. The substantial correlation between BCAA and diabetes, along with the possible role of amino acid metabolism in the initial stages of diabetes, was also shown by extensive research [57]. Investigation carried out on rats has indicated that insulin resistance is also induced by high-fat nutritional supplementation with BCAA [58]. The finding that including more branched-chain amino acids in one's diet raises the risk of type 2 diabetes and insulin resistance has been confirmed through human research [59]. Phosphatidylinositol 3-kinase (PI3K) activation and increased oxidation of free fatty acids are considered to be the mechanisms behind BCAA-induced insulin resistance [60]. The specific mechanism is still unknown, though, and needs further investigation.

Role of butyrate: *Faecalibacterium prausnitzii*, also known as *F. prausnitzii*, has been identified as the most prevalent butyrate-producing bacterium by analysis of human fecal samples. The intestinal microflora of type 2 diabetes patients has less *F. prausnitzii* and *Roseburia* than the intestinal microflora of healthy people, according to extensive metagenomic association studies conducted across a range of populations [61]. Furthermore, studies suggest that elevated *F. prausnitzii* levels help reduce insulin resistance and inflammatory symptoms [39]. *Roseburia* spp, another butyrate-producing microbe is essential for immune system function and intestinal health maintenance because it controls T cell balance constantly by creating butyric acid [62]. Moreover, prediabetic subjects have fewer butyrate-producing bacteria in their bodies than healthy subjects [51].

Biotics role in diabetics of coastal areas: The role of probiotics, prebiotics, and synbiotics in individuals with diabetes, including those in coastal communities, is an area of research interest. These interventions aim to modulate the composition and activity of the gut microbiome, potentially influencing metabolic health. Multiple investigations have discovered that probiotics, prebiotics, and synbiotics enhance gut microbiome homeostasis, maintaining the gut barrier integrity, and changing the immune responses. These compounds also

have a positive impact on host health by reducing the risk of infections from pathogens, and conditions related to obesity, type 2 diabetes, IBD, colon cancer, etc [63-64]. The role of pro, pre, and synbiotics in the gut microbiome of diabetes is shown in Figure 2.

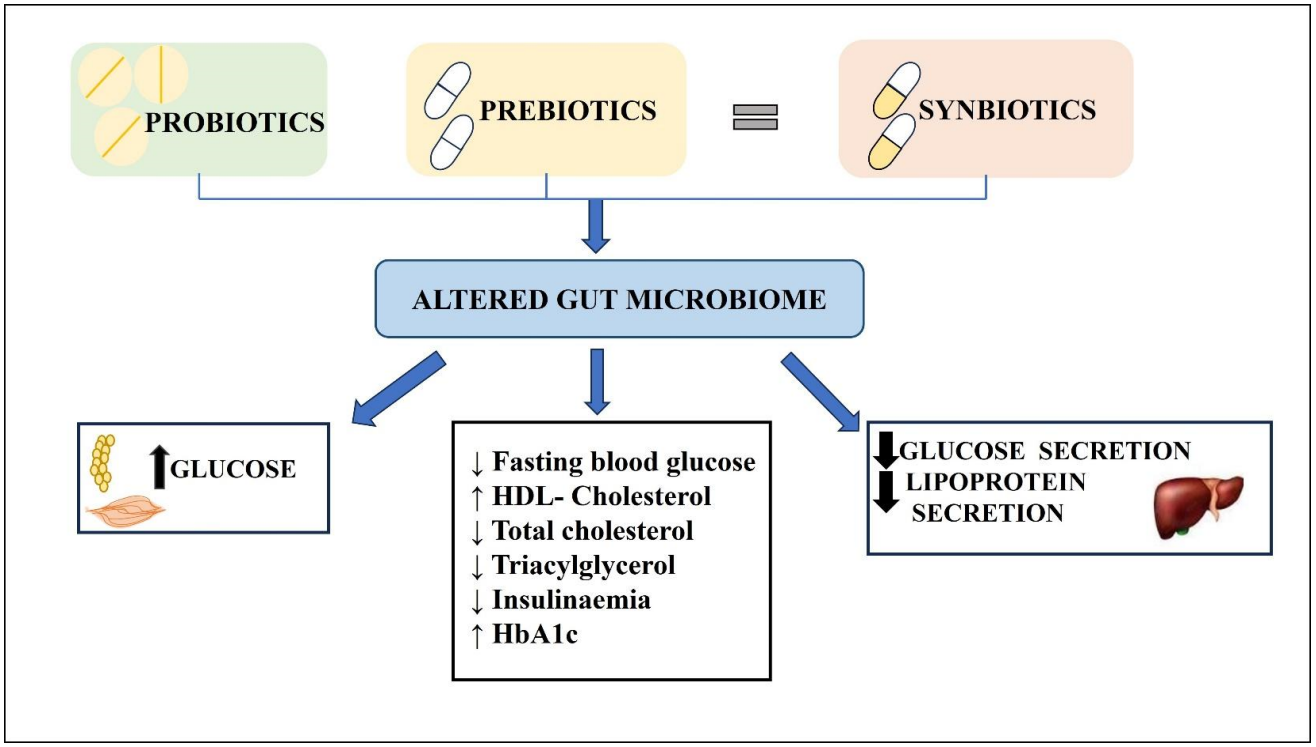


Figure 2. Role of probiotics, prebiotics, and synbiotics in diabetes

Probiotic: Probiotics are live microorganisms, mainly bacteria and yeast, which confer health benefits to the host when consumed in adequate amounts [65]. Probiotics can assist in reducing weight through enhancing the number and diversity of the microbiome, controlling immune responses, and boosting metabolic rates [66]. Probiotics can be found naturally in certain fermented foods like kefir, yogurt, sauerkraut, kimchi, and miso [67-68]. Coastal communities with unique dietary patterns, such as a high intake of seafood or specific local foods, may have distinct microbial profiles. Probiotics could potentially contribute to maintaining or restoring a healthy gut microbiota in these populations. Additionally, they are available as dietary supplements in the form of capsules, tablets, and powders [69]. Many species belonging to the genera *Lactobacillus* and *Bifidobacterium* shows an essential benefit in maintaining a healthy gut microbiota and an exciting intestinal habitat. Furthermore, probiotics customized to a particular strain also promote good health outcomes, such as immune system maintenance [70-71]. Probiotic components linked to beneficial outcomes encompass a range of cellular components, including but not limited to peptidoglycan, teichoic acids, polysaccharides, fimbrial/pili contents, and bacteriocins [72]. *Lactobacillus* (Firmicutes phylum) and *Bifidobacterium* (Actinobacteria phylum) are the probiotic strains that have been found to have the most beneficial effects on human glucose metabolism [73-76]. Probiotics, particularly *Lactobacillus* spp, have been scientifically shown in two recent reviews [32, 77] to have beneficial impacts on the management and prevention of T1D and T2D.

According to Ziegler et al. (2021), treating dysbiosis at an early age may promote immunological tolerance and inhibit the development of β-cell autoimmunity [78]. From 7 days to 12 months of age, they advised giving

Bifidobacterium infantis to infants who had an increased genetic risk of type 1 diabetes (T1D) in order to test the hypothesis. The main goal of the study was to determine if this intervention could reduce the overall level of β-cell autoantibodies in children [78]. Wang et al. (2022) [79] demonstrated that the randomized controlled trials (RCT) of 59 type 1 diabetes patients aged from 6 to 18 underwent insulin injection therapy and probiotics of three strains such as *L. salivarius* subsp. *Salicinius* AP-32 and *L. johnsonii* MH-68 isolated from human gut and *Bifidobacterium animalis* subsp. *Lactis* CP-9 from breast milk. Results of this study showed that probiotics play a major role in reducing the glucose level and immune-inflammatory cytokines were inhibited [79]. Numerous studies show the beneficial effects of probiotics to prevent and cure diabetes are illustrated in Table 2.

Table 2. Positive effects of probiotics strains in diabetes

DIABETES TYPE	PROBIOTICS STRAINS	OUTCOME	REFERENCE
Type 1 Diabetes mellitus	*Bifidobacterium infantis* to infants	↑Immune tolerance ↓development of β-cell autoimmunity	Ziegler et al., 2021 [78]
	L. salivarius subsp. *Salicinius* AP-32, *L. johnsonii* MH-68, *Bifidobacterium animalis* subsp. *Lactis* CP-9	↓Immune inflammatory cytokines ↓synthesis of glucose	Wang et al., 2022 [79]
	Bifidobacterium longum, Lactobacterium bulagricumi, Streptococcus thermophilus	↑ FBG ↑ Low-density lipoprotein cholesterol ↑HbA1c ↑MSG	Zhang et al., 2023 [80]
Type 2 Diabetes mellitus	*L. acidophilus* La-5, *B. animalis* subsp *lactis* BB-12	↑Glycaemic control ↑synthesis of acetic acid ↓Inflammatory cytokines (TNF-α, resistin)	Tonucci et al., 2017 [81]
	L. acidophilus La-5, *B. lactis* Bb12, *L. bulgaricus*	↑ Fasting blood glucose ↑Antioxidant	Ejtahed et al., 2012 [82]
	L. plantarum A7, *Bifidobacterium*	↑ HbA1c ↑Fasting insulin	Firouzi et al., 2016 [83]
	Lactobacillus acidophilus, *L. casei,* *L. rhamnosus,* *L. bulgaricus, Bifidobacterium breve,* *B. longum,* *Streptococcus thermophilus*	↑ Plasma total GSH ↑Fasting plasma glucose ↓Serum hs-CRP	Asemi et al., 2013 [84]

Probiotics exhibit potential in curing Type 2 Diabetes Mellitus (T2DM), and several potential pathways have been identified [85]. Probiotic ingestion frequently improves the symptoms of Type 2 diabetes mellitus (T2DM), such as elevated peripheral insulin sensitivity, reduced endoplasmic reticulum stress,

lowered systemic LPS levels, as also shown in advanced liver disease [86], and enhanced intestinal integrity [86]. In an animal model, probiotics such as *L. rhamnosus, L. acidophilus*, and *B. bifidum* treatment decreased *Firmicutes* and increased *Bacteroidetes* abundance [87]. Fifteen randomized controlled trials (RCTs) including nine hundred and two individuals were examined in the systematic review of probiotic therapies to treat Type 2 diabetes mellitus (T2DM). The results of the meta-analysis showed that among those with type 2 diabetes, probiotic therapy was linked with reduced levels of insulin resistance, fasting blood glucose levels (FBG), and HbA1c [88]. According to a meta-analysis that examined their Probiotics effects on type 2 diabetes. The results show that probiotics significantly reduce systolic and diastolic blood pressure, total cholesterol, triglyceride levels, C-reactive protein (CRP), HbA1c, fasting insulin levels, and fasting plasma glucose. Probiotic intake did not significantly affect levels of low-density lipoprotein (LDL) or body mass index (BMI), but it was associated with higher levels of high-density lipoprotein (HDL) [65].

Prebiotic: Non-digestible carbohydrates, referred to as prebiotics, have an impact on the gut microbiome and immune system. Prebiotics exist in numerous forms that can be divided into many different groups [89]. High amylose maize starch (HAMS) is a prebiotic and dietary fibre that provides a unique way to modify the gut microbiota to mitigate diabetes [90]. Fructans low-calorie content and prebiotic activity constitute its beneficial components. One form of non-digestible fibre with prebiotic properties is referred to as galactooligosaccharides [91]. Women took an insulin supplement for 19 days. The results showed a significant increase in *Bifidobacteria*, which are useful through fermentation, and a decrease in Enterococci and *Enterobacteriaceae*, but no statistically significant changes in *Bacteroides, Clostridium*, or *Faecalibacterium prausnitzii* [17]. This type of interaction has a role in developing autoimmune diseases, such as type 1 diabetes [92]. Substrates known as prebiotics are those that host bacteria specifically use for nutritional benefits [17]. To maintain the host's gut microbiota in a healthy state, they promote the development as well as enzymatic activation of intestinal microbes [93]. Wang et al. (2019) study shows that the effect of inulin-type fructans by using a meta-analysis of 33 Randomised controlled trials of 1346 participants significantly showed the decreasing level of fasting blood glucose, glycosylated hemoglobin (HbA1c), fasting insulin (FINS), and homeostasis model assessment-insulin resistance (HOMA-IR) in type 2 diabetic patients [94]. Some clinical investigations are illustrated in Table 3.

Synbiotic: A product that has both probiotics and prebiotics is referred to as a synbiotic. Prebiotics and probiotics work in harmony to benefit the host in an effective manner [100]. The use of synbiotics may be considered in coastal populations with diabetes to enhance the effectiveness of probiotic interventions and promote a balanced gut microbiota. Synbiotics help the host by either triggering microbial metabolic processes that support human health or specifically encouraging the growth of probiotics [101]. This increases the ability to survive the process of probiotics in the digestive tract and improves the environmental conditions of the gut. Multiple investigations demonstrate the digestive and urinary tract health benefits of synbiotics, as well as their potential anticancer and antiaging properties [18].

Table 3. Various clinical studies showing the beneficial role of prebiotics and synbiotics in type 2 diabetes

DIABETIC TYPE	PREBIOTICS	OUTCOME	REFERENCE
Type 2 diabetes mellitus	Inulin-type Fructans	↓ Fasting blood glucose ↓HbA1c ↓Fasting insulins ↓HOMA-IR	Wang et al., 2019 [94]
	Inulin	↑Fasting blood glucose ↑HOMA-IR ↑HbA1c	Zhang et al., 2022 [95]
DIABETIC TYPE	**SYNBIOTIC STRAINS**	**OUTCOME**	**REFERENCE**
Type 2 diabetes	*B. bifidum*, *L. acidophilus*, 2g oligofructose	↓ Fasting glycemia ↑ HDL-C	Moroti et al., 2012 [96]
	Lactobacillus acidophilus, Bifidobacter bifidum, Bifidobacter lactis, and *Bifidobacter longum,* 6g inulin	↑ HDL-C ↑ (LDL)/HDL	Kassaian et al., 2017 [97]
	Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum and 0.8g inulin	↓ blood glucose ↓ insulin levels ↓ insulin resistance ↑ insulin sensitivity	Soleimani et al., 2018 [98]
	Bacillus Coagulans, Lactobacillus rhamnosus, Lactobacillus acidophilus and fructooligosaccharide	↓ Insulin level ↓ HOMA-IR CRP ↓ HOMA-β levels	Velayati et al., 2021 [99]

Positive effects of synbiotics on T2DM control have been demonstrated through various research, which is encouraging for T2DM patients. Insulin resistance and glucose metabolism in the host may be improved by using synbiotics to alter the gut microbiota [102]. Using the meta-analysis, they investigated the impacts of probiotics and synbiotics on biochemical variables among individuals with prediabetes and type 2 diabetes, such as fasting insulin levels, FPG, HbA1c, HOMA-IR, and OGTT. Despite an important variation in glucose levels following OGTT, probiotic and synbiotic consumption enhanced QUICKI and lowered FPG, HbA1c, fasting insulin, and HOMA-IR [103]. Some clinical investigations are illustrated in Table 3. The effects of probiotics, prebiotics, and synbiotics in type 1 Diabetes mellitus patients were investigated by systemic review and meta-analysis shows the insulin demands, C-peptide, and serum HbA1c did not significantly improve. Supplementing with probiotics may be an additional therapeutic approach for type 1 diabetes [104].

CONCLUSION

Compared to non-coastal regions, coastal regions have a high prevalence of diabetes attributed to the lifestyle

manners and dietary patterns of the coastal communities. Fatal incidence in diabetes are more strongly correlated with pollution exposure in coastal areas. It became known that co-morbid conditions including hypertension and hypercholesterolemia could independently predict an increased risk of diabetes. Several antigens isolated from the gut microbiome may play a role in the regulation of immunological disorders. Functional disruptions could be a factor in the autoimmune death of β-cells in the pancreas that results in T1D, and elevated inflammatory cytokine expression could be linked to resistance to insulin and T2D. Research on diabetic people and gut microbiome has evolved progressively, transitioning from initial studies, which established a robust association, to delving into causality and potential underlying mechanisms such as the role of butyrate, bile acids, lipopolysaccharides, short-chain fatty acids, and Branched-chain amino acids. In this review, we summarized the concept that probiotics, prebiotics, and synbiotics might be beneficial for managing and preventing Type 1 and Type 2 diabetes by altering the gut microbiota which has been confirmed. The data from the clinical trials and experimental research shows the beneficial effects of probiotics, prebiotics, and synbiotics in type 1 and type 2 diabetic people with either increased or decreased in FBG, HbA1c, immune tolerance, levels of plasma glucose, and fasting insulin were also discussed. Along with biotics, some organic compounds like squalene also prevent type 2 diabetes [105]. A profound, evidence-based approach, taking care of qualitative aspects of functional foods and bioactive compounds, as well as their extraction and testing methodologies represent a mandatory path to follow, as envisaged in the Functional Food Center consensus [106].

Abbreviations: DM: Diabetes mellitus, T2DM: type 2 diabetes mellitus, FBG: fasting blood glucose, CRP: c-reactive protein, SCFA: short-chain fatty acids, BCAA: branched-chain amino acids, LPS: lipopolysaccharides, BMI: body mass index, VSG: vertical sleeve gastrectomy, RYGB: Roux-en-Y gastric bypass, PI3k: phosphatidylinositol 3-kinase, RCT: Randomised control trials, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, MSG: mean sensor glucose, TNF-α: Tumor necrosis factor alpha, GSH- glutathione, LBP-lipopolysaccharide-binding protein, FXR- Farnesoid X receptor, FPG: fasting plasma glucose.

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