



## The Impact of Probiotics in Type 2 Diabetes Mellitus and Gut Brain Axis

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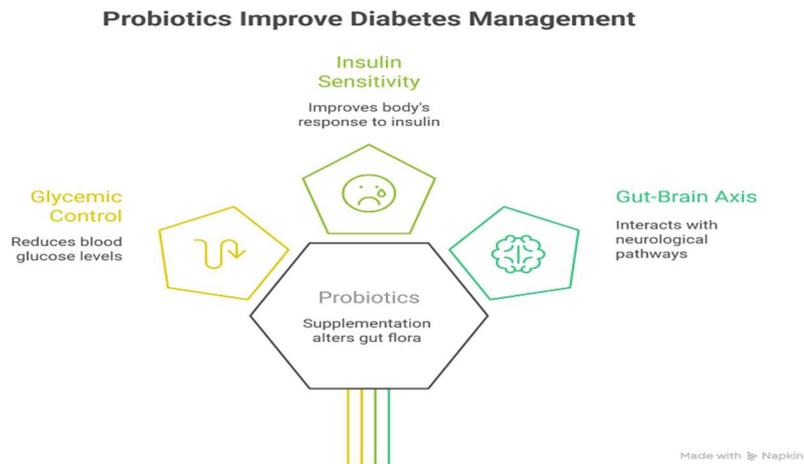
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### Keywords:

*Probiotic, Type 2 diabetes mellitus, microbiota, gut brain axis, Clinical trails*

### ABSTRACT

Type 2 diabetes mellitus (T2DM) is a major global health issue. Growing clinical trial (CT) evidence suggests that probiotic administration may foster a healthy gut microbiome in people with T2DM, potentially improving disease management. A review of randomized clinical trials revealed that taking probiotic supplements decreased fasting blood sugar levels, insulin resistance, and levels of haemoglobin A1c in type 2 diabetic patients. It has been established that probiotics alter the gut flora, resulting in improved glycaemic management and insulin sensitivity. In addition to their impact on metabolic management, probiotics have been linked to the gut-brain axis. The brain and the gut microbiome interact via neurological, endocrine, and immunological pathways, and probiotics have been demonstrated to interact with these pathways. In conclusion, probiotic supplementation improves glycaemic control in T2DM patients and may be a potential adjuvant therapy in the gut brain axis.

**GRAPHICAL ABSTRACT:****INTRODUCTION**

Diabetes mellitus can cause long-term damage in addition to organ failure and dysfunction. Diabetes mellitus can induce symptoms such as excessive urination, blurred vision, weight loss and increased thirst. In severe cases, it may also lead to stupor, coma, and, if left untreated, potentially result in death from ketoacidosis or a non-kenotic hyperosmolar condition<sup>1</sup>. Type 2 diabetes can manifest as either a relative insulin deficit with a primary insulin resistance or predominantly an insulin secretory dysfunction with insulin resistance. It is also known as non-insulin dependent diabetes, adult onset diabetes, or type 2 diabetes, this diabetes, which makes up 90–95% of cases, includes people who are having insulin resistance and typically have relative insulin shortage. Consequently, these individuals have reduced insulin secretion, which is inadequate to compensate for their insulin resistance. The likelihood of acquiring this kind of diabetes rises with age, weight, and inactivity<sup>2</sup>. Diabetes and hyperglycaemia brought on by drugs are widespread problems. Given that it raises the risk of infections, metabolic coma, micro vascular and macro vascular problems, and even mortality, it could be a major issue<sup>3</sup>. Lipid-modifying medications can potentially cause hyperglycaemia, and the diabetogenic impact of statins appears to vary depending on the kind and daily dosage used. Moreover, nicotinic acid may change glycaemic management. A higher incidence of steroid diabetes is linked to high glucocorticoid dosages<sup>4</sup>.

- **ETIOLOGY:**

A complete absence of insulin results from various pancreatic  $\beta$  cell disorders that constitute type 1 diabetes mellitus (T1DM). This is often explained by an autoimmune response that destroys pancreatic  $\beta$  cells (type 1A).

In certain individuals with type 1 diabetes who lack evidence of  $\beta$  cell autoimmunity, inherited defects in pancreatic  $\beta$  cell glucose sensing, along with other genetic or acquired factors, can contribute to problems with insulin production<sup>5</sup>.

### Type 2 Diabetes Mellitus:

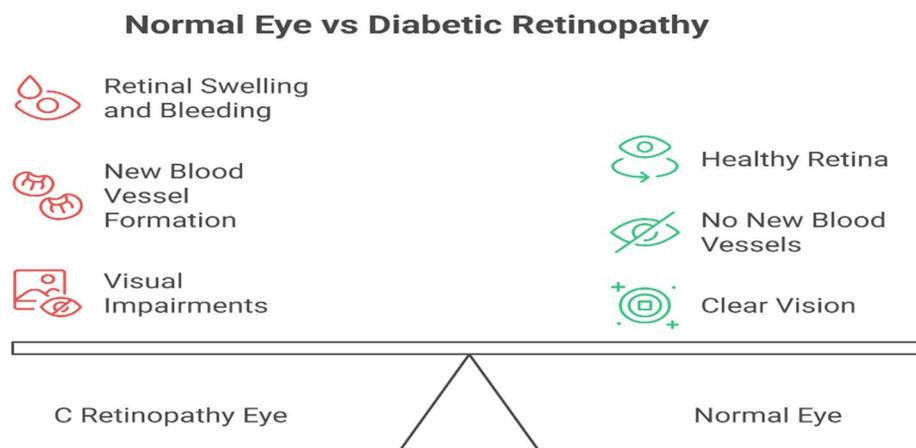
Type 2 diabetes mellitus (T2DM), the most prevalent type of diabetes, is distinguished by insulin resistance caused by changes in insulin's ability to work on its target tissues (muscle, liver, and fat). This issue is worsened by a varied and often gradual reduction in beta cells' insulin secretory ability. In the United States and Europe, most individuals with type 2 diabetes are either overweight or obese. However, in countries like China and India, a notable number of type 2 diabetes patients maintain a lean body mass index (BMI), even if they have greater amounts of visceral and hepatic fat<sup>6</sup>.

- **COMPLICATIONS :**

Diabetes leads to chronic damage to both large and small blood vessels, referred to as the macrovascular and microvascular systems. In type 2 diabetes, complications from elevated blood sugar often result in harm to major vessels, such as those in the heart and brain, which is a primary cause of death. Nonetheless, damage to smaller vessels in organs like the kidneys, eyes, and nerves is more widespread and greatly contributes to mortality<sup>7</sup>.

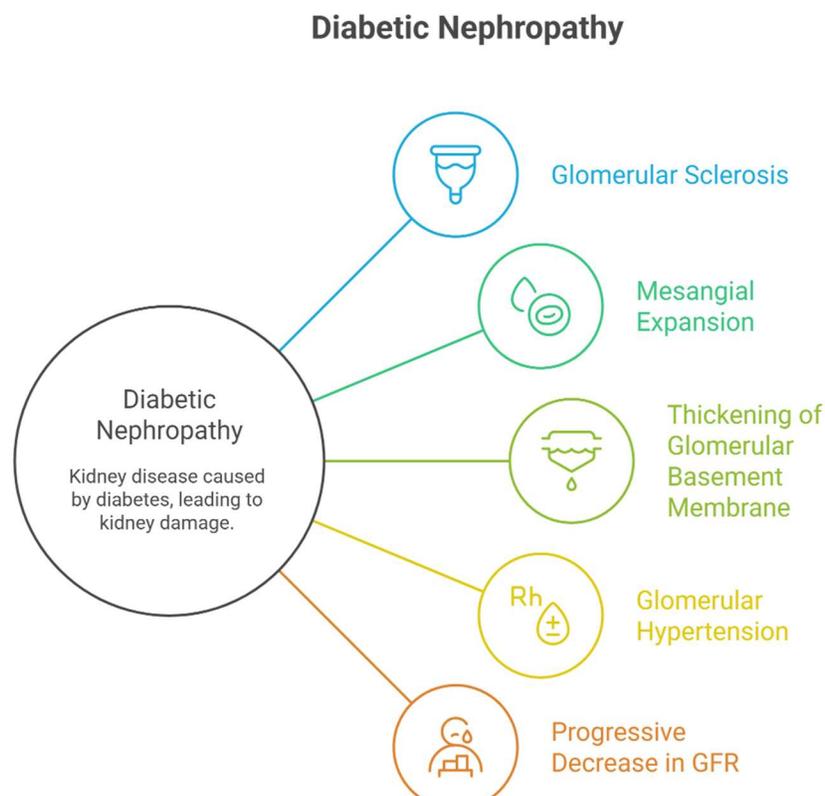
### 1.Diabetic Retinopathy

In the US, diabetic retinopathy is a prevalent cause of adult blindness. It is characterized by macular edema, as shown, proliferative retinopathy, or neovascularization, and background retinopathy, or retinal capillary microaneurysms, are its defining features<sup>8</sup>. in Fig . No : 1



**FIGURE NO 1 : DIABETIC RETINOPATHY****2. Diabetic Nephropathy :**

Diabetic nephropathy, which is typified by sclerosis of glomerulus, mesangial enlargement, and glomerular basement membrane thickening is one of the primary causes of chronic kidney disease in the US. These abnormalities result in glomerular hypertension and a progressive decrease in glomerular filtration rate (GFR). Systemic hypertension might speed up the progression. Most often the condition is asymptomatic until renal failure or nephrotic syndrome appear as depicted<sup>9</sup>.in Fig No: 2

**FIGURE NO 2 : DIABETIC NEPHROPATHY****3. Diabetic Neuropathy :**

Diabetic neuropathy develops due to metabolic changes within cells that impair nerve function, the direct impact of high blood sugar on nerve cells, and reduced blood flow to nerves caused by microvascular complications. It can present in several types, including<sup>10</sup>.

- Autonomic neuropathy

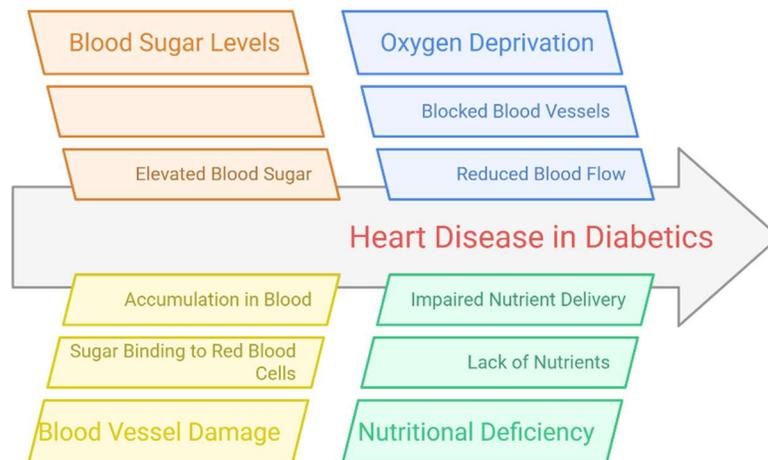


- Systemic polyneuropathy
- Cranial neuropathy
- Mononeuropathy
- Radiculopathy<sup>11</sup>.

**Heart Disease :**

Heart disease is among the most common effects of diabetes. Heart disease is among the most common effects of diabetes. Over time, even slightly raised blood sugar levels might harm your blood arteries, leading to potentially fatal heart issues. Because your body cannot consume all of the sugar, more of it adheres to red blood cells and accumulates in the bloodstream, which can damage or block the blood vessels that deliver oxygen and nutrients to the heart<sup>12</sup>. Keeping your HbA1c level as close to your target as possible is important for protecting your heart and blood vessels. Over time, even a little increase in blood sugar increases your risk.

**Understanding Diabetes-Related Heart Disease**



**FIGURE NO 3 : HEART DISEASES**

**ROLE OF PROBIOTICS :**



Live bacteria or probiotics and yeasts, are beneficial for health, particularly for digestive system. We usually think about them in relation to harmful microbes. But your body is full with both harmful and beneficial microorganisms. Probiotics are sometimes referred to as "good" or "helpful" bacteria since they promote intestinal health. Eating more beneficial microorganisms to improve health has been spoken about since the early 1900s. "Probiotics" is a relatively recent phrase. It combines the Greek word for "life" with the Latin word for "for"<sup>13</sup>.

- **Types of Probiotics :**

Probiotics are a broad category of microbes. Although they all provide unique advantages, the most belong to two categories.

A) **Lactobacillus:** Possibly the most well-known probiotic. It's the kind found in fermented foods like yogurt. Diverse strains have the potential to alleviate diarrhea and aid individuals who are lactose intolerant. This kind of bacteria generates lactic acid, which aids in regulating the growth of pathogenic germs, and the enzyme lactase, which breakdown lactose, or milk sugar. Additionally, it functions as muscle fuel and enhances the body's absorption of nutrients. The mouth, small intestine, and vagina naturally contain lactobacillus bacteria<sup>14</sup>.

B) **Bifidobacterium** - It is present in a few dairy products. It could lessen the signs and symptoms of a few different illnesses, including irritable bowel syndrome (IBS). This species of bacteria is frequently found in dietary supplements and meals. They are believed to Boost immunity, facilitate the transformation of lactose into nutrients that the body can use, prevent the formation of the dangerous bacteria in gut. A yeast called *Saccharomyces boulardii* is present in probiotics. It seems to aid in the battle against diarrhea and other digestive issues<sup>15</sup>.

Common species of probiotics :

- Genus genetic subtypes are probiotic species. The effects of each probiotic species on the body vary. Labels for foods or supplements will provide the probiotic species names along with the genus name. For instance, the genus names of *Lactobacillus* and *Bifidobacterium* are frequently shortened to B. or L. and coupled with the name of the specific species, such as *acidophilus*. You now have the probiotic *Lactobacillus acidophilus*. The name on food or supplement labels will look like this<sup>16</sup>.

These are the six probiotic species that are frequently listed on food and supplement labels.



- a) *B. Animalis*: Dannon uses this species as a component in its Activia yogurt. It helps against food-borne germs and facilitate digestion. It may also strengthen your immune system.
- b) *B. breve*: This species inhabits the vagina and the digestive system. It combats yeast or bacteria that cause infections in both locations. It ferments carbohydrates to aid in your body's absorption of nutrients. In order to make plant fiber palatable, it is also broken down<sup>17</sup>.
- c) *B. lactis*: Made from unpasteurized milk. It is a component in Nestle's Good Start Natural Cultures probiotic baby formula. It can also be used as a precursor to: Cottage cheese, buttermilk, and other cheeses
- d) *B. longum*: The gastrointestinal tract is home to this species. In addition to being an antioxidant, it aids in the breakdown of carbohydrates<sup>18</sup>.
- e) *L. acidophilus*: This species inhabits the vagina and the small intestine. Along with aiding with digestion, it may also help against vaginal bacteria. Yogurt and fermented soy products like miso contain it.
- f) *L. reuteri*: The mouth and intestines are home to this species. It reduced the oral germs that cause tooth decay, according to one research. It is also believed to support the digestive tract<sup>19</sup>.

### **GUT BRAIN AXIS DEFINITION AND COMPONENTS :**

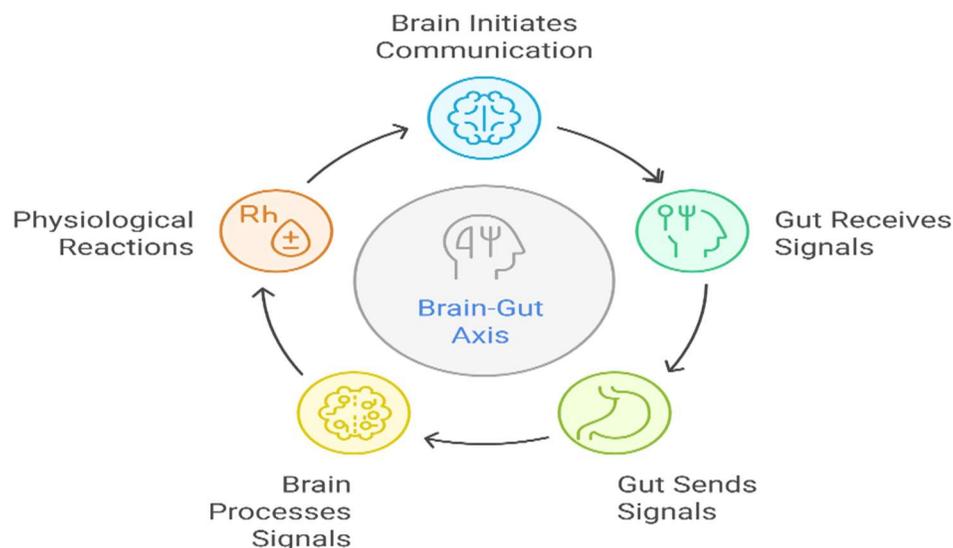
The gut-brain axis is an two-way hormonal and neurological signalling mechanism that connects the stomach and brain<sup>20</sup>. The nervous system and stomach are connected by a number of mechanisms that control metabolic balance. We will give a summary of the gut brain axis's function in maintaining metabolic homeostasis in this review, highlighting a number of novel theories about how the two brain regions interact. Additionally, this traditional route of nutrient-induced neuronal and hormonal communication in the gut-brain connection does not consider the important point of gut microbiota in shaping gut-derived claim. It is now clear that the gut microbiota may affect the regulation of glucose and energy by means of a number of pathways, such as its effect on host- gut brain connection and direct transmission to the brain through metabolites generated by microorganisms<sup>21</sup>. The abundance of bacterial cells and genes is the reason behind this. The function of gastrointestinal peptides in controlling sensations of fullness has been the subject of numerous research. Additionally, gut peptides are important for controlling insulin sensitivity and secretion. According to recent research, bone metabolism is also impacted by the hormone peptide YY, which is generated in the gastrointestinal tract. There is a growing

evidence that the gut- brain axis's functions are influenced by afferent gastrointestinal nerves, particularly the vagus nerve<sup>22</sup>.

### GUT- BRAIN AXIS COMPONENTS AND PRINCIPLE :

- The gut and brain translate with each other in both directions. The hypothalamic pituitary-adrenal (HPA) axis, the autonomic (parasympathetic and sympathetic) nerve systems and the facilitate brain-to-gut communication, which controls a number of physiological reactions, including digestion and stomach motility as depicted<sup>23</sup>. in Fig No 3.
- The gastrointestinal system is regarded as a major sensory organ and has the biggest surface area of the body visible to the outside world. Entero endocrine cells (EECs), When nutrients are present, the intestinal epithelium's specialized chemosensory cells are among the first sentinels to become active<sup>24</sup>. They emit signaling peptides that are recognized by nearby sensory cells, immunological cells, the brain, and neurons in the Enteric nervous system (ENS) in addition to being carried by the blood. Probiotic consumption increases the number of gut microorganisms, which improves the pace of absorption in the gut by activating the neurons that cause glucose to be turned into glycogen right away. Thus, glucose levels are kept constant<sup>25</sup>.

### Brain-Gut Communication Cycle



**FIGURE NO 5 : ELEMENTS OF GUT BRAIN AXIS**

- **Role in metabolic regulation and homeostasis:**



Metabolic illnesses are influenced by and treated by the gastrointestinal tract. The gut gives the brain vital information about entering nutrients throughout a meal, enabling the right managing of ATP and glucose maintained<sup>26 27</sup>.

Moreover commonly used drug for type 2 diabetes, metformin, lowers blood sugar in part through the stomach by altering bile acid signaling and gut microbiota or by reducing hepatic glucose production through gut-brain-liver communication pathways. simultaneously, these results highlight the GI tract's function as a therapeutic target and show how it contributes to the maintenance of metabolic disorders. The supreme brain regions, such as the arcuate nucleus (ARC), can receive signals from vagal afferent neurons and relay them to the Nucleus Tractus Solitaries (NTS). The enteric nervous system can also activate vagal afferent neurons by releasing gut-derived neurotransmitters that detect intestine marks, such as 5-HT from ECs and Intra Ganglionic Laminar Endings (IGLEs).

### **Neuronal gut–brain connection :**

Signaling from the gut- brain axis is a two-way channel. The main routes by which signals from the brain reach the stomach to regulate a range of physiological processes are the hypothalamic- pituitary axis and the autonomic nervous system. But vagal and spinal afferent neurons mediate neural communication from the stomach to the brain. Although spinal afferent innervate the gut it appears that they have little effect on energy and glucose homeostasis. However, a more recent study found that spinal afferents may have a role in mediating intestinal glucose sensing. Furthermore, the Enteric nervous system is known as “second brain” that controls several gastrointestinal processes apart from central nervous system activity, can serve as a mediator in transmitting information from the gut to the brain.

### **Vagus nerve :**

Because of its lengthy extensions that start in the brainstem and innervate several visceral organs, the tenth cranial nerve (vagus nerve) is also called as the "wanderer nerve." Vagal afferent terminals are dispersed throughout the gut in various layers, with many of them innervating the GI tract's lamina propria close to EECs. There are two primary ways that the gut can activate VANs: chemoreception and mechanic stimulation. Specifically, Signals from the gut can excited Anorexigenic neurons that are controlled by amphetamine, pro-opiomelanocortin/cocaine, agouti-related peptide/neuropeptide Y, and other substances. These neurons are a subset of the arcuate nucleus's (ARC) specialized neurons, which maintains glucose and energy balance. Importantly, the left and right vagal nerve both branches have different and asymmetrical innervations inside the GI and terminations in the hindbrain<sup>28</sup>.Brain uses



signals from the vagus nerve to control glucose and energy balance after a meal. In fact, when carbs, proteins, or fatty acids are entered into the small intestine, vagal afferent activity increases, indicating that VANs react to nutrients perceived in the gut. One study claims that the overexpression of potassium-containing channels in the nodose ganglia, which intensifies the hyperpolarization of VANs, is the reason for the reduction in vagal transmission observed with HFD eating. One study contends that the decrease in vagal signaling associated with HFD feeding is due to the increased levels of K<sup>+</sup> channels in the nodose ganglia, which causes the hyperpolarization of VANs. However, other studies have connected changes in the microbiota of the gut to vagal afferent communication and the reduction during HFD feeding (refer to the “Gut microbiota–brain connection” section). For a more thorough analysis of the gastrointestinal signaling impairment associated with obesity<sup>29</sup>.

#### Enteric nerve system:

Innervating the whole GI tract, the ENS is a self-contained neural system made up of two bundles of ganglia: the myenteric plexus, which lies in the sphincter muscle layer of the gut, and the sub mucosal plexus, which lies beneath the gut’s epithelium layer. Mechanoreceptor and excitation of the skeletal muscle surrounding the gut, which enables independent regulation of GI transit and motility, is one of the primary functions of the ENS. It’s interesting to note that GLP-1 non susceptibility during high-fat diet providing decreases enteric excitation and Nitric oxide generation, which is caused by changes in the gut microbiome (see to the to the section on the “Gut microbiota–brain connection”). This, in turn, sends a signal to the hypothalamus, increasing the release of NO from the hypothalamus and increasing the body’s use of glucose. When considered collectively, the data point to the possibility is the ENS mediates gut–brain communication they controls metabolic homeostasis.

The digestive system is in charge of breaking down food and absorbing nutrients. Additionally, it functions in immunological, neurological, and endocrine pathways. Furthermore, signal transmission and communication in between the enteric and central neural systems are initiated by the gut flora. The Enteric nerve system, the central nerve system, and the parasympathetic, sympathetic neurons involved in signal neurons transmission between the brain and gut -brain make up the gut- brain axis. Normal digestion, absorption, ATP generation, and consequent managing of glucose homeostasis are all ensured by a gut-brain axis that is properly controlled. We might prevent and treat metabolic diseases including diabetes, obesity, and hypertension more effectively if we understood the basic monitoring mechanisms of the gut brain axis of involves in glucose homeostasis. <sup>30</sup>.



AUTHOR NAME	INTERVENTION	REFER ENCE
<b>01 . Ashrafian et al, Wang et al, Kim et al, Tarrah et al, and Sun et al. Yan et al</b>	Effects on glucose homeostasis and cholesterol metabolism: In the latter study in mice, <i>Lactobacillus acidophilus</i> SJLH001 had a statistically significant effect on the regulation of transcription genes, essential for glucose transport and cholesterol metabolism.	14
<b>02 . Hongyu Wang and Liang Li</b>	The hypoglycemic ability ( $\alpha$ -amylase, $\alpha$ -glucosidase and dipeptidyl peptidase 4), probiotic property and antioxidant activity of lactic acid bacteria were comprehensively evaluated by a principal component analysis (PCA) and analytic hierarchy process (AHP).	1
<b>03. Alharbi YM, Sakr SS, Albarrak SM, Almundarij TI, Barakat H, Hassan MF.</b>	Systematic review and meta-analysis were performed to evaluate the effect of probiotics on serum high sensitivity-C reactive protein (hs-CRP) and oxidative stress biomarkers among patients with Diabetic Nephropathy (DN).	2
<b>04. Bohlouli J, Namjoo I, Borzoo-Isfahani M, Kermani MA, Zehi ZB, Moravejolahkami AR.</b>	Using a Wistar rat burn injury model, they assessed the effect of oral glutamine (Gln) with probiotics on burn-induced intestinal inflammation and oxidative stress.	3
<b>05 . Patel F, Parwani K, Patel D, Mandal P.</b>	In rats with streptozotocin-induced diabetes, the antioxidant, antidiabetic, and hypolipidemic effects of probiotic-enriched processed camel milk (FCM) in combination with <i>Salvia officinalis</i> .	4



**Table No 1 :**  
 Author  
 Contributions and  
 Probiotics-Focused  
 Work in the  
 Review of  
 Probiotic  
 Modulation of the  
 Gut-Brain Axis in  
 Type 2 Diabetes  
 Mellitus  
**CONCLUSION:**

<b>06. Bohlouli J, Namjoo I, Borzoo-Isfahani M, Kermani MA, Zehi ZB, Moravejolahkami AR.</b>	Probiotics were tested for their impact on oxidative stress biomarkers and serum high sensitivity-C reactive protein (hs-CRP) in patients with diabetic nephropathy (DN) using a systematic review and meta-analysis methodology.
<b>07. Li G, Feng H, Mao XL, Deng YJ, Wang XB, Zhang Q, Guo Y, Xiao SM</b>	A total of thirty RCTs with 1,827 T2MD patients were found. The current research provided evidence that probiotic supplements improved T2DM patients' glycemic control. For T2DM patients, it could be a viable adjuvant treatment.
<b>08 . Palacios T, Vitetta L, Coulson S, Madigan CD, Denyer GS, Catterson ID.</b>	Since metformin is frequently recommended early in type 2 diabetes mellitus and has been proven to affect the microbiota, this choice also meant adding patients who were taking the medication .

The studies mentioned above indicate a decrease in diabetes mellitus and associated consequences. Probiotics are used to draw it, as they can aid in the regulation and management of the metabolic process and expedite the conversion of glucose to glycogen. Probiotics have been shown in several studies to effectively manage diabetes mellitus by preserving or regulating gut health<sup>31</sup>.

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**Table No 1 : Past carried work of the assessment in the action of probiotics**

AUTHOR NAME	INTERVENTION	REFERENCE
<b>01. Ashrafian et al, Kim et al, Sun et al, Wang et al, Tarrah et al, and Yan et al.</b>	In a recent study conducted on mice, <i>Lactobacillus acidophilus</i> SJLH001 demonstrated a notable impact on the expression of key transcriptional genes involved in glucose transport and cholesterol metabolism, with results showing statistical significance.	14
<b>02 . Hongyu Wang and Liang Li</b>	The hypoglycemic potential (involving $\alpha$ -amylase, $\alpha$ -glucosidase, and dipeptidyl peptidase-4), probiotic characteristics, and antioxidant activity of lactic acid bacteria were thoroughly assessed using principal component analysis (PCA) and the analytic hierarchy process (AHP).	1
<b>03. Alharbi YM, Albarrak SM, Barakat H, Hassan MF, Sakr SS, Almundarji TI.</b>	A systematic review and meta-analysis examined the influence of probiotics on serum high-sensitivity C-reactive protein (hs-CRP) and oxidative stress markers in individuals with diabetic nephropathy (DN).	2
<b>04. Bohlouli J, Borzoo-Isfahani M, Zehi ZB, Moravejolahkami AR, Namjoo I, Kermani MA.</b>	The effect of oral glutamine (Gln) combined with probiotics on burn-induced intestinal inflammation and oxidative stress was evaluated using a Wistar rat burn injury model.	3
<b>05 .Patel F, Parwani K, Mandal P,</b>	The antioxidant, antidiabetic, and hypolipidemic	4



<b>Patel D.</b>	effects of probiotic-enriched processed camel milk (FCM) combined with <i>Salvia officinalis</i> were studied in rats with streptozotocin-induced diabetes.	
<b>06. Bohlouli J, Namjoo I, Kermani MA, Moravejolahkami AR, Borzoo-Isfahani M, Zehi ZB.</b>	The effects of probiotics on oxidative stress biomarkers and serum high-sensitivity C-reactive protein (hs-CRP) in patients with diabetic nephropathy (DN) were analyzed through a systematic review and meta-analysis.	5
<b>07. Li G, Feng H, Deng YJ, Wang XB, Guo Y, Xiao SM, Mao XL, Zhang Q.</b>	A review of thirty randomized controlled trials (RCTs) involving 1,827 patients with type 2 diabetes mellitus (T2DM) revealed that probiotic supplementation significantly improved glycemic control. This suggests that probiotics could serve as an effective adjuvant therapy for T2DM management.	9.1
<b>08 . Palacios T, Vitetta L, Madigan CD, Caterson ID, Coulson S, Denyer GS.</b>	As metformin is commonly prescribed early in the treatment of type 2 diabetes mellitus and has been shown to influence the microbiota, the study also included patients who were using this medication.	2