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Review Article

Interactions Between Gut Microbiota and Host Metabolism in Type 2 Diabetes: Pathophysiology and Treatment Prospects

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Abstract

The human colon is home to a diverse community of microorganisms collectively known as the gut microbiota. These microorganisms play an essential, though indirect, role in maintaining human health by supporting various physiological functions. The primary roles of the gut microbiota include reducing gut permeability, increasing the production of short-chain fatty acids, decreasing inflammation, and repairing leaky gut barriers. These microbes also produce several metabolites such as bile acids, butyric acid, branched-chain amino acids, trimethylamine-N-oxide, lipopolysaccharides, and short-chain fatty acids that influence the gut environment and can contribute to dysbiosis. This review explores the composition of the gut microbiota in healthy individuals compared to those with Type 2 Diabetes, with a particular focus on microbial metabolic activity that affects insulin sensitivity and resistance. It also examines diabetes-related physiological and pathological factors, including the effects of age, physical activity, obesity, diet, and antibiotic use, supported by clinical data. Furthermore, the review discusses various therapeutic approaches with promising potential for diabetes reversal. Overall, this work aims to provide valuable insights into gut dysbiosis and microbiota, contributing to future translational research.

Keywords: Type 2 Diabetes; Gut Microbiota; Metabolites; Insulin Sensitivity; Dysbiosis

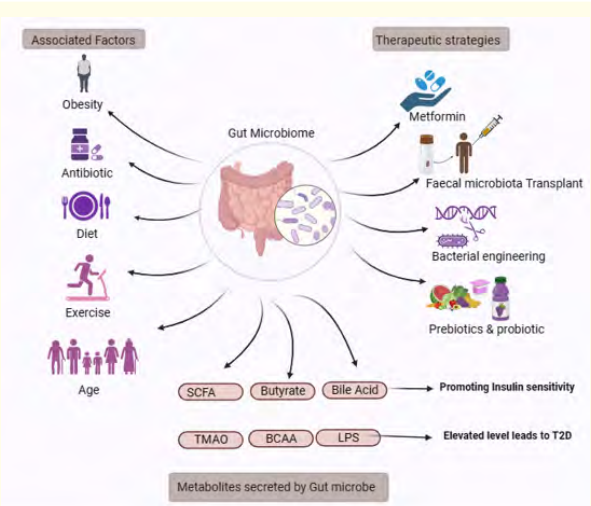

Figure 1: Graphical abstract.

Abbreviations

T2D: Type 2 Diabetes; GM: Gut Microbiota; FBG: Fasting Blood Glucose; GPR: G-Protein Coupled Receptor; TMAO: Tri Methyl Amine Oxidase; GLP: Glucagon Like Peptide; OUT: Operational Taxonomic Unit; HFD: High Fat Diet; FXR: Farnesoid X Receptor; GRAS: Generally Recognised as Safe; GEB: Genetically Engineered Bacteria; FMT: Faecal Microbiota Transplant.

Introduction

A chronic disease known as diabetes develops when insulin synthesis by the pancreas is inadequate or when the body is unable to utilise insulin efficiently it produces. Type 1 Diabetes (Diabetes Insipidus) is defined by a decrease in insulin secretion, which is known to control blood glucose levels, while Type 2 Diabetes

(Diabetes Mellitus) is characterised by an increase in insulin resistance. According to a WHO report in 2014, the incidence of diabetes among adults aged 18 years and older was 8.5%. The International Diabetes Federation stated that in 2021, prevalence was predicted to be greater in urban areas (12.1%) compared to rural areas (8.3%), and in more developed countries (11.1%) against less developed countries (5.5%) [1].

By 2045, the International Diabetes Federation predicts that 783 million individuals, or about 1 in 8 people will have diabetes, a 46% increase from today. Diabetes experienced a substantial relative increase (21.1%), with high-income individuals experiencing a 12.2% increase and low-income individuals experiencing an 11.9% increase in middle-income countries between 2021 and 2045 [2]. Growing evidence indicates that the body of human is colonised by a number of microorganisms. The gut flora consists mostly of commensals collectively known as gut microbiota. We have a whole world of them within us. The gut microbiota begins to change shortly after birth and continues to change until old-age [3]. Microbes inside gut are a complex ecosystem, which comprises of approx. 10^{13-14} species in the symbiosis of bacteria, fungi, archaea, and viruses [4]. Intestinal investigations have established a link between gut flora and Type 2 Diabetes. The close coevolution of microbes and mammalian hosts has led to a consistent symbiotic connection that regulates and supports several essential physiological processes. These include food digestion and nutrition, energy production and conservation, metabolic regulation of fat storage, maintenance of skin and mucosal barrier function, prevention of pathogen invasion, and differentiation of the immune system [5]. In a review, Cani., *et al.* [6] were the pioneers in discussing gut microbiota concerning Type 2 Diabetes. Research indicates that gut microbiota significantly impacts in energy balance, resulting in increased energy harvest, as well as influencing immunity, which can trigger inflammation and autoimmunity. These factors contribute to metabolic dysfunction, such as insulin resistance and deficiency. Studies involving humans have shown changes in microbiota signatures in individuals with diseases when compared to control groups, with some of these changes occurring before the onset of the disorders.

Most bacterial species, exist in the specific area of the colon, like *Akkermansia muciniphila, Bacteroides fragilis, Lactobacillus fermentum, Lactobacillus plantarum*, and *Lactobacillus casei,* reports that they play a protective role in lowering the incidence of Type 2 diabetes. These bacterial species not only maintain the integrity of the intestinal barrier but also reduce the expression of pro-inflammatory markers. This event can be attributed to the embrace of contemporary living practices. The shift in lifestyle has rendered the population susceptible to various metabolic diseases, including coronary heart disease, diabetes, and obesity. Dietary changes subsequently affect overall health by altering the balance between beneficial and opportunistic microbes. According to recent findings, GM can influence bile acid (BA) metabolism, including 'short chain fatty acids (SCFAs), lipopolysaccharide (LPS), and trimethylamine oxide (TMAO)', significantly impacting human metabolism [7]. This indicates they can be a promising novel approach for the T2D management.

A variety of gut-targeted therapies have been created to alter gut microbiota and to enhance glycaemic regulation in T2D. A possible strategy involves the utilisation of prebiotics, which positively influence metabolic markers by changing the composition of the microbiota. Another gut-targeted intervention is faecal microbiota transplant. Many of the observed physiological changes following FMT treatment exhibit anti-diabetic characteristics, such as improved glucose handling, enhanced basal metabolic rate, and reduced levels of systemic inflammation. However, metformin treatment has also demonstrated potential for enhancing both glycaemic control and insulin sensitivity in patients affected with T2D [8]. This review covers insights regarding the gut microbiota, gut profile in healthy and diseased individuals, their mode of action via metabolites, factors linked to their alteration, as well as some clinical evidence and therapeutic approaches, are discussed. The review summary has been elaborated, accompanying Figure 1, providing a clearer understanding of the discussed concepts and highlighting significant trends or outcomes.

Gut microbiota composition

Every individual possesses a unique composition of gut microbiota. According to 16S rRNA gene sequence analysis, the major bacterial groups are classified into five phyla: 'Bacteroidetes, Firmicutes, Verrucomicrobia, Proteobacteria and Actinobacteria' with Bacteroidetes and Firmicutes being the most prevalent in the gut. The microbiota undergoes significant transformations over the course of our lives, influenced by a range of factors including diet, growth, lifestyle choices, nutritional status, illnesses, travel experiences, medical interventions, and the ageing process, all

of which have direct or indirect implications for human health. The healthy gut includes class Bacteroides of Genus *Bacteroides, Prevotella, Xylanibacter,* which help in degrading varieties of complex Glycan. Class Firmicutes of Genus *Ruminococcus, Clostridium, Lactobacillus, Roseburia, Eubacterium* and *Faecalibacterium,* which prominently act as butyrate producers and are useful in Probiotics. Class Actinobacteria of Genus *Collinsella* and *Bifidobacterium* also have role in probiotics. Class Proteobacteria of Genus *Escherichia* and *Desulfovibrio,* which are sulphate-reducing bacteria. Class Veruccomicrobia of genus *Akkermansia,* which inhabits in mucus layer of the large intestine and maintains intestinal integrity. Class Archaea of Genus *Methanobrevibacter* have an essential role in methanogenesis [8].

Research indicates that individuals with illness exhibit a decreased number of butyrate-synthesising bacteria, such as "*Faecalibacterium prausnitzii"* and "*Roseburia intestinalis"* in their gut flora. This aligns with the growing occurrence of sulfate-reducing (*Desulfovibrio*) and mucin-degrading ("*Akkermansia muciniphila"*, Lactobacillus species such as "*Lactobacillus gasseri"*, "*Streptococcus mutans"*, and "*Proteobacteria"*) species among individuals with type 2 diabetes. Certain studies indicate that butyrate could potentially influence diabetes in a beneficial way. In the following section, we will examine its importance. An imbalance in the microbiota may indicate impaired glucose tolerance and type 2 diabetes, characterised by a reduced presence of certain butyrate-producing bacteria (like "*Roseburia* and *F. prausnitzii"*) and an increased prevalence of opportunistic pathogens (such as "*Clostridium clostridioforme* and *E. coli"*) [9]. The microorganisms that inhabit mucus a number of investigations into the impacts of obesity and type 2 diabetes have concentrated on the microorganism *Akkermansia muciniphila*. This organism's rarity indicates its potential as a diagnostic tool for glucose intolerance. Individuals recently diagnosed with prediabetes and type 2 diabetes demonstrated decreased levels of *A. muciniphila.* In this manner, different gut microbial characteristics impact the physiology of the host. Figure 4 illustrates that a variety of beneficial microbes reside in healthy guts, contributing to insulin metabolism.

Occurrence of T2D in an individual

Metabolic dysfunction is characterised by the gut microbiota and the metabolites they produce. The mechanism of metabolites is the main factor that contributes to insulin resistance. The gut microbiota plays a crucial role in breaking down complex polysaccharides found in dietary fibre. This breaks them down into short-chain fatty acids (SCFAs) like acetic, propionic, and butyric acid, which can have a variety of effects on the host's metabolism. Incretins produced by intestinal L-cells, which include 'Glucagon-like Peptide-1 (GLP1)' and 'Glucose Dependent Insulinotropic Polypeptide (GIP)', regulate the balance of insulin and glucagon secretion, helps in glucose homeostasis. Unregulated glucagon production and insulin resistance-mediated hyperglycaemia are the outcomes of decreased incretin hormone activity, which occurs in pancreatic dysfunction and diabetes, as shown in Figure 1 [10]. The glucose transporter GLUT2 carries glucose from the capillaries to the beta cells of the pancreas along a concentration gradient. In the cytosol, glucose undergoes phosphorylation by glucokinase and hexokinase prior to its entry into the glycolytic pathway, resulting in ATP production. The immediate release pool (IRP) docked insulin granules in the plasma membrane exocytosed in response to this Ca^{+2} influx and elevated ATP levels. Energy metabolism and insulin sensitivity are just two of the many bodily functions affected by the gut microbiota.

It is possible to identify SCFA using the free fatty acid receptors FFAR2 and FFAR3. A longer carbon chain in an SCFA molecule has a negative correlation with the receptor's responsiveness; for instance, FFAR2 is more sensitive to acetate and propionate than butyrate, whereas FFAR3 is more sensitive to butyrate and propionate than acetate. As illustrated in Figure 1, Short Chain Fatty Acids serve as signal transduction molecules by interacting with and activating surface GPCRs, such as G-protein-coupled receptors 41 (GPR 41) and G-protein-coupled receptors 43 (GPR 43) [11]. Both receptors are found in colon tissue as well as in adipocytes, liver and skeletal muscle. As shown in Figure 1, this activation of GPR41 leads to increased production and secretion of the hormone peptide YY (PYY), which increases satiety by reducing gastrointestinal motility.

Metabolites produced by gut microbiota in Type 2 diabetes

It is well-established that microbial metabolites are connected with gut microbiota and influence host physiological processes. Long considered a "virtual organ" of human metabolic activity, the gut microbiota influences insulin resistance and diabetes through its metabolic activity. Diabetes mellitus (T2D) patients and

healthy controls have significantly different gut microbiota, and a metagenomic study found that impaired glucose metabolism might be attributable to a reduction in butyrate-synthesising bacteria [11].

Bile acids

Oral bile acid treatment altered the phylum levels and increased the Firmicutes to Bacteroidetes ratio in the intestinal microflora of rats, suggesting improved insulin sensitivity and glucose tolerance, according to a rat study [12]. Bile acid (BA) profiles are significantly influenced by gut microbiota remodelling. Primary BAs are transformed into secondary BAs, such as Lithocholic and Deoxycholic acid, which act as key signalling molecules via the Farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5) [13]. As illustrated in Figure 2, this signalling axis improves glucose tolerance by stimulating FGF19 and triggering GLP-1 secretion from L-cells. Mechanistically, FXR activation increases the ATP:ADP ratio in pancreatic β-cells, leading to KATP-channel closure and Ca^{2+} influx, which facilitates insulin release [14]. Clinical evidence supports this metabolic role; for instance, rectal taurocholate administration has been shown to improve insulin secretion and decrease serum glucose in diabetic patients [15]. A number of metabolic pathways, including insulin sensitivity, are controlled by these modified bile acids.

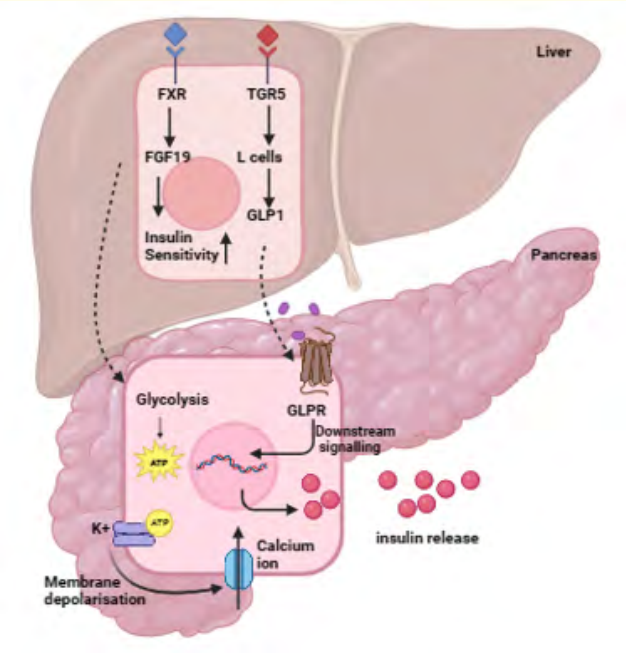

Figure 2: Role of bile acid in insulin metabolism in liver and pancreas.

For the FXR and TGR5 receptors, bile acid serves as a signal. In bile ducts, "sinusoidal endothelial cells, Kupffer cells, stellate cells, and biliary epithelial cells", all exhibit high levels of TGR5 expression. The activation of FGF19 by the FXR contributes to an improvement in insulin sensitivity increases the ATP: ADP ratio in pancreatic beta cells and drives glycolysis further. When this ratio increases, depolarization results from the ATP-sensitive potassium ion channels closing. The concentration of K+ rises as a result of K+ being unable to pass through the channel. The VDCC channel also allows Ca ions to enter the cell. When TGR5 receptor and secondary bile acid interact, L cells are activated and GLP1 is produced. When this GLP1 binds to the beta cell's GLPR receptor, it activates intracellular signalling proteins and produces insulin at the gene level, thus regulating glucose metabolism.

Branched chain amino acid

Research has linked BCAAs to an increase in insulin resistance, leading to their identification as a prognostic marker for type 2 diabetes. The term "branched chain amino acid" describes the trio of leucine, valine, and isoleucine. Hypothalamic leucine may serve as a nutritional signal that assists in reducing satiety by activating the mTOR (mammalian target of rapamycin) enzyme [16]. The neurological system is profoundly affected by leucine, an essential amino acid. In addition to its involvement in other critical cellular and developmental processes, the mTOR signalling network regulates cell proliferation, differentiation, survival, and metabolism. When insulin levels are high, mTOR is activated, which in turn activates ribosomal S6K1. S6K1 regulates translation initiation and elongation through phosphorylation. Activated S6K1 phosphorylates 26IRS-1, a protein that inhibits insulin signalling. At first, the Branched-Chain Amino Transferase (BCAT) can reversibly convert BCAA to their corresponding branched-chain α-ketoacids. Crucially, BCAT exists in two distinct forms, with one form encoded by the Bcat1 (cytosolic gene) and the other by the Bcat2 (mitochondrial gene). Leucine primarily forms a-KIC, isoleucine mostly forms a-KMIV, and valine primarily forms an AKMV. BCAT facilitates the transfer of amino groups from BCAAs to α-ketoglutarate, resulting in glutamate and the corresponding branched-chain α-keto acids (BCKA) [17]. But pertinent gene analysis can help with targeted treatment identification. Since the microbes in our gut have their own biosynthetic pathways for making BCAAs, it stands to reason that they may have some influence on the availability of these amino acids in our bodies. Because AA absorption occurs primarily in a small intestine, the ileal microbiota is the most important microbial source of AAs. An intestinal mechanism for the beneficial effects of BCAAs has been suggested by evidence indicating that dietary protein and BCAAs enhance glucagon-like peptide-1 (GLP-1) release while reducing the expression levels of certain genes, which is essential for fatty acid synthesis and absorption in a human intestinal cell line, NCI-H716 [18]. Research conducted by Weickert., *et al.* [19]. increased p70S6K levels in adipose tissue following a 6-week period of a high-protein diet rich in leucine and isoleucine cause insulin resistance. Taking a short-term BCAA supplement changed the composition of the gut flora and decreased insulin production after meals in type 2 diabetic patients, according to a recent study. The researchers also discovered that "*Prevotella copri* and *Bacteroides vulgatus*" are associated with BCAA synthesis in the gut. Taking into account the aforementioned benefits and drawbacks, it appears that there is a negative correlation between high BCAA and the risk of T2D, insulin resistance and obesity.

Short chain fatty acids

SCFAs are byproducts of dietary fibre fermentation that the microbiota in the intestines create. Butyrate, propionate, and acetate are the three primary short-chain fatty acids (SCFAs), and numerous studies have revealed that they influence both insulin sensitivity and glucose metabolism, potentially influencing the diabetic condition [20]. The levels and concentrations of SCFA are determined by the microbiota and the type of substrate (fibre) fed to GM. Based on stoichiometric equations, propionate is produced from fibre. However, with an adult average weight of 85 kg, its daily production of 29.5 mg/kg/day would contribute only a small fraction to the total glucose production (2.2 mg/kg/min), of which about half is due to gluconeogenesis [21]. Acetate, propionate, and butyrate are the main saturated fatty acids (SCFAs) that are produced by some species of gut bacteria that cannot be digested. This process involves four metabolic pathways, including acetyl-CoA, lactate, succinate, and propanediol. The pyruvate is converted into acetate through the acetyl-CoA pathway or Wood-Ljungdahl [22]. The condensation of two molecules of acetyl-CoA is one-way that butyrate is synthesised. Another way is by using lactate and acetate. The acrylate-succinate pathway can produce propionate from phosphoenolpyruvate, while the propanediol pathway can do the same from deoxyhexose sugars like rhamnose and fucose [7]. *Lactospira, Anaerotruncus*, *Clostridium* spp., *Parabacteroides*, and *Roseburia* are a few examples of bacterial species that produce acetate. Propanol and propionic acid can be produced from deoxy sugars by members of the Lachnospiraceae family, which includes "*Roseburia inulinivorans* and *Blautia* species, *Propionibacterium*, *Veillonella*, *Megasphaera"* etc. Additional amino acid pathways that can be utilized to produce butyric acid include the lysine, glutamate, and 4-aminobutyrate routes."*Fusobacterium spp*., *Peptostreptococcus asaccharolyticus*, *Clostridium sporosphaeroides*, *Acidaminococcus fermentans*, and *Clostridium symbiosum"* are among the Firmicutes that possess these pathways [23].

The evidence seems to be strong that the AMPK-dependent regulation of hepatic lipids and glucose homeostasis by acetate, propionate, and butyrate is dependent on the effects of peroxisome proliferator-activated receptor-gamma (PPARγ)

on gluconeogenesis and lipogenesis. Research has shown that acetate can slow down adipocyte lipolysis, which reduces the flow of free fatty acids (FFA) to the liver and helps fatty liver avoid worsening glucose homeostasis [24]. Consequently, butyrate is the primary focus of the studies presented here. Figure 3 shows the results of another study that indicated *Fecalibacterium prausnitzii* (butyrate-producing bacteria), decreased insulin resistance through a mechanism wherein the fatty acid receptor GPR43 mediates the secretion of the glucagon-like peptide-1 receptor (GLP-1) by colonic L cells [25]. Metabolite analysis was performed in Streptozotocin-induced diabetic mice by means of fermented sorghum as a source of butyrate. In addition to lowering insulin resistance and hyperglycaemia, FS supplementation also decreased the prevalence of opportunistic pathogenic bacteria, which are positively associated with type 2 diabetes. These bacteria include *Oscillibacter*, *Acetatifactor*, and *Acetivibrio*. Supplementing the diet with sorghum encourages the growth of opportunistic bacteria, such as *Muribaculum*, *Parabacteroides*, and *Phocaeicola* [26]. Dietary adjustments can regulate several beneficial microorganisms in the gut, and next-generation butyrate producers show great promise as probiotics.

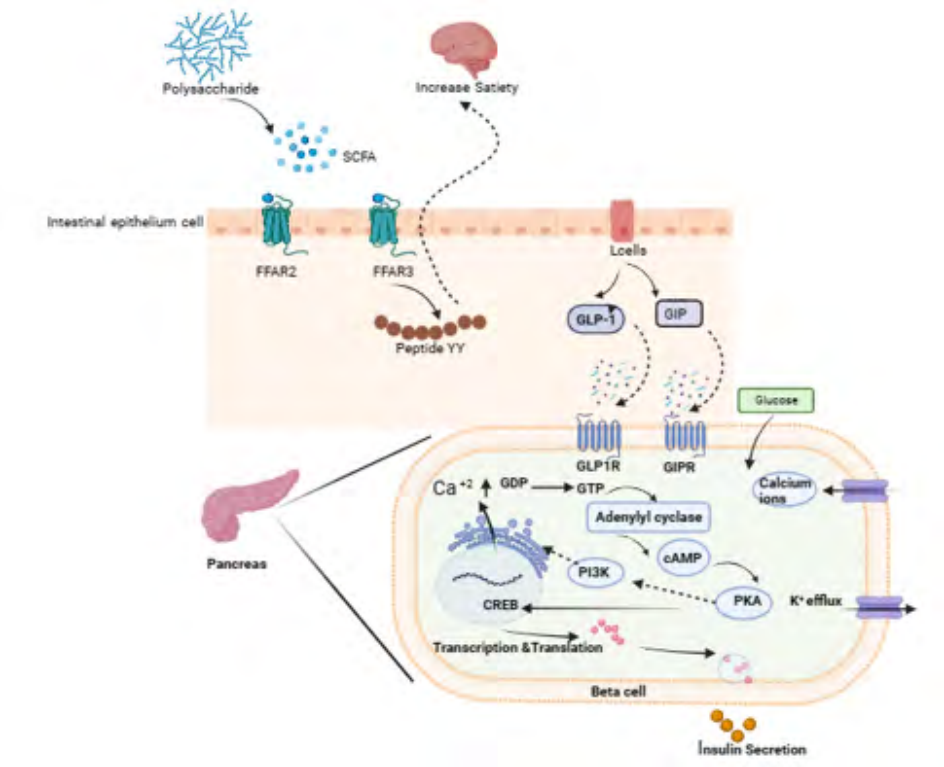

Figure 3: Mechanism of SCFA in insulin signalling.

Gut microbiota helps to digest complex polysaccharides and convert them into SCFA, which act as signal molecules for FFAR2 (more receptive to acetate and propionate and also called GPR41) and FFAR3 (butyrate and propionate) receptors present on intestinal epithelial cells. FFAR2 and FFAR3 are functionally related GPRs. Hormone peptide YY are secreted by the activation of this GPR41, which signals the feeling of satiety in the brain. Along with that, L cells are present throughout the gastrointestinal lining, which produce incretin hormones like GLP1 and GIP. These hormones cause the subunit of the pancreatic beta cell's GLP1 and GIP receptor to release GDP and change into GTP. This G subunit interacts to Adenylyl cyclase, which catalyses the conversion of ATP into cAMP, which then activates PKA, which in turn activates CREB, a transcription factor, to start transcription and translation of the genes necessary to make the insulin granules that are transported outside the beta cell for glucose metabolism.

TMAO

In the process of breaking down certain food substances, such as choline/phosphatidylcholine, l-carnitine, betaine, ergothioneine, and γ-butyrobetaine, the enzyme flavin monooxygenase (FMO3) converts trimethylamine N-oxide (TMAO) into trimethylamine (TMA), which is then absorbed into the bloodstream. The remaining TMAO is broken down into its component parts by the TMAO reductase enzymes found in the microbiota. The intestinal wall absorbs this converted form and sends it into the bloodstream, where it is oxidised into TMAO in the liver. While many different types of bacteria are capable of converting TMAO to TMA, the Enterobacteriaceae family has the greatest capability in this regard. Reduction of plasma TMAO occurs as a result of broad-spectrum antibiotic suppression of intestinal flora, which in turn influences bacterial recolonisation. Enzymes located in the endoplasmic reticulum (ER), called as "flavin adenine dinucleotide (FAD)" and "nicotinamide adenine dinucleotide phosphate (NADPH)", are integral to the process of oxidation of several neutrophilic substrates. The gut microbe's trimethylamine N-oxide demethylase (Tdm) anaerobically breaks down a tiny amount of TMAO in the diet into formaldehyde and dimethylamine (DMA) in equal proportions. This process is mainly carried out by methylotrophic bacteria and species of *Pseudomonas* and *Bacillus* [27].

Trimethylamine dehydrogenase converts the TMA produced by gut microbiota to dimethylamine (DMA), and dimethylamine dehydrogenase further breaks down DMA into methylamine (MA). Shih., *et al.* [28] in their experiment found a connection between TMAO and insulin resistance in the liver, since mice given a high-fat diet along with TMAO supplements had reduced glycogen synthesis, and FMO3 mutant mice had increased synthesis. One possible explanation is that insulin and glucagon both work together to directly inhibit FMO3 expression. Since FMO3 is required for FoxO1 expression and it is an important regulator of metabolism, repressing FoxO1 by reducing FMO3 expression in insulin-resistant mice can improve insulin sensitivity and restore glucose homeostasis [29]. This indicates that a high fibre and low-fat diet can assist in lowering TMAO levels.

Research has shown that TMAO contributes to decreasing glucose tolerance, increasing insulin resistance and triggering inflammation. More specifically, TMAO levels are associated with a diet rich in animal products. This cascade includes the following genes: GLUT2, IRS2, PI3K, and RAC-serine/threonine-protein kinase (AKT) [30]. The identification of compounds that modulate the metabolism of trimethylamine N-oxide (TMAO) has the potential for new treatment approaches. It is possible to improve metabolic health and reduce risks by learning which chemicals affect TMAO levels and then developing therapeutic interventions based on that knowledge.

Lipopolysaccharide

Gram-negative bacteria are thought to be the ones that produce LPS. The intestinal mucosa and epithelial cells form a protective barrier [31]. An unbalanced gut microbiota is responsible for breakdown in the mucosal epithelial barrier, which in turn allows bacteria to translocate, as shown in Figure 4. Increased levels of peptidoglycan (PG) and lipopolysaccharide (LPS) and other microbe-associated molecular patterns (MAMPs) in the blood and tissues will help to prevent bacteria and other particles with toxic properties from entering the circulation through the intestinal lumen. Intestinal inflammation and increased tight junction permeability (TJP) are both facilitated by a TLR4-dependent process that is aided by the intestinal tight junction barrier, which is not functioning properly. The effect of high-dose LPS was studied in C57BL/6 TLR4−/− mice, which are deficient in TLR4, and it was found that the TLR4 signal transduction pathway also mediated the permeability increase in the intestine [32]. Making healthy food choices and taking care of other lifestyle factors that help the gut barrier function better can help reduce inflammation caused by LPS and strengthen the barrier itself.

Cross talk between insulin metabolism and gut permeability

When inflammation occurs in type 2 diabetes, intestinal permeability increases dramatically. LPS can enter the bloodstream via the portal system [33]. Restoring the gut barrier is possible in metabolic endotoxemia with the use of anti-inflammatory drugs, like 5-aminosalicylic acid. In certain metabolic syndromes, it prevents inflammation by lowering tissue microbiota dysbiosis. The mechanisms that disrupt and cause endotoxemia-induced

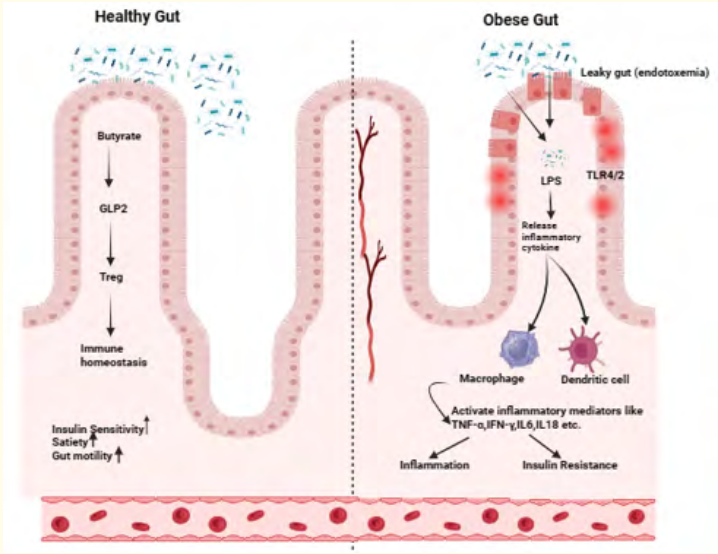

Figure 4: Mechanism of butyrate and LPS in healthy and obese gut respectively.

Left side showing a healthy gut of a high fibre diet, when butyrate (SCFA) is produced by gut microbiome, which produces GLP2 and activates Treg cells to maintain immunity and perform optimal functioning of a healthy gut, such as increasing satiety, insulin sensitivity and gut motility response to food intake, whereas right side shows an obese gut. When a person is taking a high fat diet, it leads to leaky gut or endotoxemia due to high level of LPS. These tight junctions on the cell lining become loose and allow gram-negative bacteria to pass through and enter into blood vessels causing inflammation by releasing inflammatory cytokines. This attracts macrophages and dendritic cell to produce inflammatory mediators like TNF-α,IFNγ,IL6 and IL18 and causing inflammation which is responsible for insulin resistance.

phenotypes have been investigated in conjunction with the decreased inflammatory markers. This is marked by persistently elevated levels of cytokines that promote inflammation in the bloodstream, including TNF-α, IL-6, IKKβ, and JNK. A negative impact on insulin signalling and, in certain instances, insulin resistance, can result from any of these molecules phosphorylating insulin receptor substrates (IRS) and converting them into serine. Mice given a high-fat diet have an increased risk of metabolic endotoxemia due to antibiotic exposure in their gut microbiota. This condition is associated with unregulated proinflammatory cytokines, increase in gut permeability, and a metabolic profile that is altered in diabetes and obesity [6]. Potential pathways for LPS translocation across intercellular channels include intestinal permeability (or "leaky gut"). It is possible that providing nutrients like SCFA to the epithelial cells helps the gut microbiota maintain a healthy gut lining, which protect mucous layer [4]. The proinflammatory cytokines IL6 and IL18 and the toll-like receptor 4 (TLR4) are both favoured by a leaky gut, which in turn promotes inflammation [34]. In mouse models, high-fat diets lead to various gastrointestinal issues, including altered gut microbiota, insulin resistance, inflammation, oxidative stress, intestinal permeability, increased plasma LPS, and glucose intolerance. Antibiotics or genetic engineering to eliminate the LPS receptor can partially or totally undo all of these alterations. Several studies were done on obese leptin (ob/ob) and leptin-receptor (db/db) mice which demonstrate heightened intestinal permeability, elevated portal LPS levels, and increased circulating inflammatory markers relative to lean, wild-type control mice [35]. Therefore, these microbes play an essential role in maintaining health.

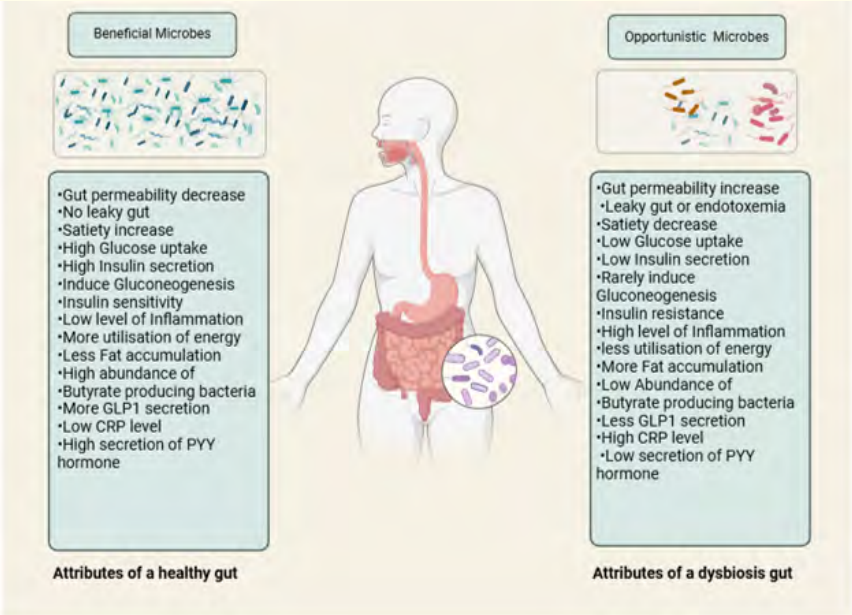

Figure 5: Comparative attributes of healthy and dysbiosis gut.

Multiple aspects of the gut microbiota have several impact on host physiology. Healthy guts have an abundance of beneficial microbes that aid in insulin metabolism. The gut microorganisms maintains the permeability of cell lining while strengthening barrier integrity, preventing leaky gut. Beneficial microbes are helpful for increasing satiety by sending signals to the brain. High fibre or Mediterranean diets aids in inducing glucose uptake by GLUT2 transporter. Additionally, if bacteria are favourable, they reduce event of gluconeogenesis, increase butyrate synthesis, increase GLP-1 secretion, and result in lower levels of inflammation and CRP. While microbial dysregulation impact opportunistic pathogen which impaired gut barrier by loosening the tight junction. This triggers the release of inflammatory cytokines, leading to high levels of inflammation and, consequently, elevated serum CRP levels. Low levels of good bacteria cause low GLP1 secretion, which reduces GPCR signalling and lowers insulin production, causing insulin resistance and gut dysbiosis.

Alteration in microflora associated with different factors

Diabetes in different age

Patients with newly diagnosed type 2 diabetes who were given metformin alone were the subjects of a study. The participants, who ranged in age from middle-aged to elderly, were given a GLP-1 receptor agonist formulation once weekly for a total of eight weeks. Some improvements were observed in HbA1c, islet β-cell function index, and FBG. The hypoglycaemic effect of GLP-1 on vascular endothelial functions, which decreases intestinal inflammation, is well-indicated by this [36]. The prevalence of firmicutes is higher in children older than four years old compared to those younger than that age. People over the age of 70 have a higher prevalence of *Proteobacteria*. Low grade inflammation, caused by an imbalance of gut microbes, is more common in the elders by the increased abundance of *Enterobacteriaceae* [37]. A Mexican study examined gut profile in children and adolescents with the MetS and Type 2 Diabetes conditions, the numbers of bacteria belonging to the groups *Streptococcaceae*, *Lachnospiraceae*, *Peptostreptococcaceae*, *Eggertellaceae*, *Erysipelotrichaceae*, and *Bifidobacteriaceae* decreased, while those of the groups *Prevotellaceae*, *Ruminoccocaceae*, *Enterobacteriaceae*, and *Coriobacteriaceae* rose. Loss of gut microbial diversity may be indicated by the genus-level such as "*Streptococcus*, *Ruminococcus*, *Odoribacter*, *Mediterraneibacter*, *Lachnoclostridium*, *Klebsiella*, *Flavonifractor*, and *Enterocloster*" in the MetS and Type 2 Diabetes groups when compared to the healthy condition [7]. For optimal

health throughout life, it is essential to keep the gut microbiota diverse and balanced. Nevertheless, it is important to investigate the ways in which gut microbes is impacted by aging within the larger framework of the changes in genetics and lifestyle that occur with aging.

Influence of exercise

An increase in the diversity of beneficial bacteria may be a result of regular physical activity over the long term. While cells are at rest, insulin plays an essential role in glucose absorption. There seems to be a relationship between the intensity and duration of exercise and increased glucose absorption and utilisation during exercise. Glucose metabolism increases in direct proportion to the intensity of exercise. Consequently, exercise helps lower blood sugar levels. When comparing the gut microbes of mice given a regular diet and those given a high-fat diet, both with and without exercise, exercise not only counteracted the influence of the high-fat diet on the microbiome but also prompted large-scale changes in the phyla 'Tenericutes, Bacteroidetes, and Firmicutes', mirroring the effects of the diet itself. During physical activity, both healthy and diabetic mice showed changes in '*Bacteroides/Prevotella* spp., *Methanobrevibacter* spp., and Clostridium cluster I'. However, an abundance of Bifidobacterium spp. was found in non-diabetic mice, suggesting that diabetes mitigated this effect [38]. Exercise seems to significantly influence the gut microbiome diversity in older adults, as evidenced by a notable mean difference of 0.266, in contrast to 0.034 for middle-aged individuals and 0.081 for younger individuals, based on the age-based analysis of the Shannon Index [36]. Distinct variations in the gut flora are caused in large part by factors such as urbanization and sedentary lifestyle. Using 16S rRNA high-throughput sequencing, researchers in eastern China examined faecal samples from students. *Faecali bacterium* levels were higher in adolescents whose exercise sessions lasted longer compared to those whose sessions were shorter (LDA = 4.303, p = 0.04). The percentages of Bacteroides were significantly higher in urban adolescents (p = 0.001, FDR = 0.004) compared to their rural and town counterparts, while the percentages of 'Prevotella' and 'Bifidobacterium' were slightly lower (p = 0.05, FDR = 0.019). Nevertheless, the study also took into account factors like food and amount of sleep [39]. These specific microorganisms are responsible for metabolising muscle-derived lactic acid and producing short-chain fatty acids, which have a beneficial role in the intestinal cell lining and thus induce intestinal resistance.

Impact of obesity in diabetes

An environment is present in the lives of Asian Indian children which tends to obesity. Obesity around the middle and a high body fat percentage are traits that run-in their family. Insulin resistance was found to be highly prevalent among children with adverse truncal body fat patterning, excess body fat and abdominal adiposity according to a population-based epidemiological study that included 250 healthy urban post pubertal children (155 males and 95 females) [38]. Epigenetic modifications like DNA methylation, its intermediates, histone acetylation/methylation state, and non-coding RNA are impacted by metabolites produced by the gut microbiota. For example, in people who are predisposed to obesity and cardiovascular disease, new research has shown that *Ruminococcus*-related genes are less prevalent. *Ruminococcus* levels were linked to one BMI-related differentially methylated region (DMR), which was situated between the MACROD2 and SEL1L2 genes. A lower risk of cardiovascular disease was related with obesity and a higher relative abundance of *Ruminococcus*, in contrast to the results in normal-weight individuals [39]. Obese people are more exposed for metabolic abnormalities; understanding these microbial differences can help develop strategies to prevent them. Researchers looked at the effects of metformin in a mouse model that was induced to eat diet containing high fat. All HFD-groups prior to metformin treatment had high levels of the following taxa: 'Muribaculaceae, Lactobacillus, Parabacteroides, Mucispirillum, and Dorea'. The relative abundance of Bacteroides increased in all groups that were given a high-fat diet following the treatment, while the relative abundance of Lachnospiraceae decreased. The high-fat diet group reveals the most common bacteria were Lactococcus, Lachnospiraceae, and Bacteroides [40].

Influence of diet

A person's diet is thought to play a major role in shaping their gut flora. A vegetarian diet may differ from a non-vegetarian one. Protein sources in cereals, such as pulses and legumes, and meat have different effects on a person's microbiota. Because city dwellers eat more processed foods, sugar, fat, and fresh produce, their microbiota is different from that of rural residents. The gut microbes and microbe-associated metabolites may also be impacted by fermented foods, such as fermented soybean foods. The variety of gut microbes is enhanced by a diet high in fermented

foods. Yogurt, kefir, kimchi, and other fermented veggie eaters fared better in terms of health [41]. Interactions between the observed gut microbiota (fruit/vegetable microbiota index) and their associated faecal metabolites with T2D risk were investigated in a Chinese study on middle-aged elderly adults. The study also looked at relationships between three categories: fruits only, vegetables only, and fruits and vegetables. The 31 organisms that were found to be associated with fruit consumption belonged to the following families: *Enterobacteriaceae*, *Ruminococcaceae*, *Acidaminococcus*, *P. stercorea*, *Prevotella copri*, *Fusobacterium*, and *A. muciniphila.* Eating a lot of fruit may have detrimental effects on human wellbeing, such as increasing the production of short-chain fatty acids, protecting the intestinal mucosa, making insulin more sensitive, and reducing inflammation. SCFAs generated through DF fermentation improve the functionality of the intestinal barrier by boosting the proliferation and differentiation of cells in the intestinal mucosa [13].

Probiotic bacteria are able to digest inulin, a well-known prebiotic that humans cannot. Oral administration of inulin and 16S rRNA gene 454 pyrosequencing were found to be effective in treating diabetes in Streptozotocin-induced mice. The diabetic group that took inulin had a much lower abundance of Desulfovibrio, the bacteria responsible for making lipopolysaccharide, but a much higher abundance of *Lactobacillus* and SCFA-producing bacteria like '*Lachnospiraceae*, *Phascolarcto bacterium*, and *Bacteroides*'. Treatment with inulin raises serum GLP-1 levels, which suppress hepatic gluconeogenesis, decrease IL-6 production, and inhibit inflammation [42]. The results of this study show that the prebiotic inulin can reduce insulin resistance. Intestinal microbiota and food consumption were analysed through correlation, and the results showed that dairy consumption was positively correlated with the phylum Actinobacteria, beans and grains were negatively correlated with Patescibacteria, and white meat was positively correlated with Firmicutes. The relative abundance of Fusobacteria is positively correlated with an animal-based diet, while the phylum Actinobacteria, is positively correlated with a vegetarian diet [43]. The key to long-term stability in microbiota configurations and consistent eating habits is adaptability, not dietary interventions because they are only implemented for a short time.

Influence of antibiotics

Antibiotics lessen the activity of bacteria in the stomach, including commensal bacteria. Several findings shows that antibiotic can have ability to induce changes in microbial community in the gut and may have a role in the occurrence of diabetes according to given studies. It is well-documented that antibiotics alter the host's native microbiota, favouring the growth of resistant bacteria that can cause opportunistic infections. According to Korpela., *et al.* [44] changes in the gut microbiota were observed as a result of oral antibiotic therapy with macrolides, specifically Bacteroides and Bifidobacterium. As an example, erythromycin decreases the populations of Streptococci, Enterococci, and Enterobacteria while increasing the populations of Staphylococci, and streptomycin increases the expansion of Bacteroideceae and decreases Ruminococcaceae [45]. Also, at neonatal stage, the neonate is seeded with its first microorganisms, which helps it quickly form its own unique microbial ecosystem. The prevalence of Bifidobacterium species was lower in the neonates given antibiotics, while *Klebsiella* and *Enterococcus* species were higher, according to a randomised trial on neonates given intravenous antibiotic combinations. Amoxicillin + cefotaxime influences the antimicrobial resistance gene composition more than penicillin + gentamicin [46]. To completely comprehend antibiotic effect on the microbiota and whether or not these alterations are linked to diabetes, larger-scale population-based investigations are required.

Therapeutic strategies based on gut microbiota

Metformin intervention

An insulin hormone regulator, metformin increases GLP-1 concentration and facilitates glucose extraction in the intestines, among its many intestinal effects. Achieving glycaemic control is made easier with this. Metformin was administered three times to healthy non-diabetic patients and twice to diabetic patients in a study that collected stool samples for shotgun metagenomic taxonomic profiles. In contrast to the Responders' baseline enrichment of '*Enterococcus faecium*, *Lactococcus lactis*, *Odoribacter*, and *Dialister*,' the non-Responders subgroup had a higher prevalence of '*Prevotella copri*' (FDR = 0.01). Metformin altered the composition of the microbiota in large intestine, leading to an upregulation of SGLT-1 gene expression, as explored by Bauer., *et al.* [47]. The release of GLP-1 can occur via this SGLT-1.

In addition, rodents whose diets were high in fat had their SGLT-1 expression levels restored when given metformin. The beneficial role of gut was demonstrated in these studies, which showed that oral metformin administration was therapeutically superior to intravenous metformin administration in type 2 diabetic patients. Quantification of genomic information was performed on 22 type 2 diabetic patients who had not yet begun treatment. Firmicutes and Bacteroidetes were the patient groups identified through observation prior to the start of metformin treatment (M0). The microbiota showed *Prevotella* and *Firmicutes* enterotypes after a 4-month metformin treatment (M4). The species '*Akkermansia muciniphila'*, destroys host glycans and mucans, multiplies significantly following metformin use [48]. Metformin, on the other hand, can be thought of as a treatment for patients who have been diagnosed with the disease.

Faecal microbiota transplantation (FMT)

By introducing beneficial bacteria from healthy donors, faecal microbiota transplantation (FMT) helps patients restore the balance and function of their gut microbiota. When it comes to recurrent *C. diff*, FMT is the gold standard treatment. These recommendations for the administration of FMT '*Clostridium difficle'* infection were drafted by the 'Infectious Diseases Society of America' (IDSA) and the 'Society for Healthcare Epidemiology of America' (SHEA) [49]. Patients with type 2 diabetes reported a marked improvement in their symptoms after receiving FMT; however, there was a statistically significant difference between the pre- and post-treatment levels of fasting blood sugar and haemoglobin A1c among the patients. There may be individual variation in the response to FMT. Donor screening is critical for reducing the risk of infection and ensuring safe practices. Diabetic patients who had positive results from FMT had considerably higher concentrations of the *Rikenellaceae* family in their faeces before treatment [50]. It seems that this microbial change is linked to better clinical outcomes. One trial looked at the effects of adjunct FMT (with metformin). Firmicutes outpaced Bacteroidetes in post-intervention growth in both the FMT-only and FMT+metformin groups. This shows that it can be a feasible option for reversing diabetes [9]. Research and exploration into the long-term effects of this transplantation (FMT) remain an area of ongoing research. It would be challenging to inject faeces without transmitting disease, even though previous research has demonstrated that faecal microbiota transplantation has a highly favourable outcome.

Probiotics and prebiotics in diets

Unlike probiotics which are live organisms prebiotics generally oligosaccharides are fermented by bacteria. The perfect balance of gut flora can be maintained with the aid of probiotics and the interactions between their metabolites. Animal studies and clinical trials have shown that probiotics lower cholesterol and lipid levels in the blood. These days, the majority of research focuses on fructans and galactose, specifically inulin, fructooligosaccharides (FOSs), and galactose (GOSs), which are prebiotics. There has also been research on other oligosaccharides, including sodium oligomannose, low xylose, arabinoxylan, pectin, resistant starch, and oligosaccharides found in human milk and other dairy products [41]. Through a cooperative relationship with their microbial metabolites, probiotics promote a healthy intestinal flora balance. Synbiotics are a catch-all term for both prebiotics and probiotics. By feeding and controlling the gut flora, synbiotics improve human health in the most basic and apparent way. Synbiotics have many medical uses, including protecting the liver, regulating blood lipids, preventing tumour growth, and treating vaginitis and UTIs [51]. The effectiveness of the synbiotics combination on type 2 diabetes was confirmed in a study using a diseased mouse model. Thanks to the synbiotics combination of 'lactulose', 'arabinose', and '*Lactobacillus plantarum'*, the experimental treatment group of mice exhibited marked improvements in glucose and lipid metabolism, marked reductions in blood glucose and lipid levels, and marked reductions in body weight when compared to the model control group [52]. A comprehensive review of clinical trials evaluating prebiotic, probiotic, and synbiotics treatments looked at hepatic biomarkers for type 2 diabetes. After the intervention, the levels of various hepatic biomarkers, including alkaline phosphatase, bilirubin, total protein, and aspartame transaminase, were found to be significantly reduced [43]. To achieve specific health objectives, individualized synbiotics formulations can be developed using data from each person's microbiota analysis, which reveals particular microbial imbalances.

Genetically modified bacteria as potent therapeutic

In probiotic engineering, beneficial bacteria are engineered to colonize the gastrointestinal tract and produce therapeutic compounds locally [53]. Because of its importance for cellular and humoral activities, such as reducing inflammation or improving the adaptive immune response, '*Lactococcus lactis'* has the Generally Recognised As Safe (GRAS) designation and is thus a promising

candidate for therapeutic approaches [54]. Gene synthesis, DNA/RNA sequencing, DNA transfection, Large DNA fragment cloning, Clustered regularly interspaced short palindromic repeats-cas9 (CRISPR-cas9) [55,56], and other gene transfer methods are available for use in bacterial modification. The development of engineered bacteria that can synthesize a wide-range of proteins and molecular compounds originally from wild microbes is largely attributable to these methods [57]. Researchers Hu., *et al.* [58]. engineered a new strain of '*Lactobacillus plantarum*' (*L. plantarum*) pMG36e-GLP-1 and used artificial insemination to introduce it into mice. Relieved diabetic symptoms, reduced inflammatory reaction, and promoted islet βcell proliferation were all outcomes of this study. It is possible for genetically modified organisms to exhibit consistent behaviour across various human microbiotas. Liu., *et al.* found that recombinant Lactobacillus expressing heat shock protein 65 and IA2P2 (a 23 amino acid peptide) effectively decreased pancreatitis symptoms and improved diabetes by balancing Th17/Tregs and Th1/Th2 cells and preventing T cells in T1D from proliferating in response to antigens [56]. One way to look at the advantages of Genetically Engineered Bacteria is this: Enhanced production efficiency leads to lower healthcare costs; GEBs have long-term effects on colonization sites; side effects are reduced, especially when taken orally; and compounds with structural instability or environmental sensitivity no longer require drug purification or low-temperature storage. In contrast to the need for multiple medications to attain synergistic therapy, GEBs can produce a wide range of foreign proteins or substances in a single strain [59]. Reactions to altered bacteria by the immune system are possible. Immune responses and possible side effects need to be evaluated by researchers. It is necessary to ascertain whether the genetically engineered bits (GEBs) can transpose into the DNA of different types of bacteria or cells from mammals. Additional translational research into various beneficial strains related to Type 2 diabetes is required, but this biotherapeutic clinical application shows promise for disease management.

Conclusion

This review addresses the link between microbial diversity and host health. Metagenomic sequencing holds great promise in assessing the diversity within us while pinpointing the underlying mechanisms of dysbiosis. Gut microbiota has tremendous potential for treatment of Diabetes. Furthermore, this knowledge will be useful for personalised therapy because each individual has their own signature microbiota, which might vary depending on characteristics such as age, gender, exercise, diet, obesity, and other chronic diseases. It might or might not be necessary for bacteria isolated from the western population to successfully colonize the gut of Indians. In order to simplify the Indian gut profile, a comparative investigation with many correlated factors should be necessary. To obtain novel insights, the vast microbial diversity found in the human gut must be explored in order to establish a firm link between insulin resistance and many aspects related with it. To achieve these long-term goals, a large cohort study including different intrinsic components and their interactions, as well as microbial abundance, must be conducted. Due to the low prevalence of FMT in India, it is vital that its effectiveness be researched in Asian populations along with the success rate of bacterial suspension from healthy faecal samples of western populations in Indian gut. For greater efficacy, combined therapies such FMT with probiotics, prebiotics, or metformin can be investigated further. It is feasible that this combination will produce superior diabetic recovery outcomes. The comparison of tribal, urbanized, and ruralized societies should be considered because tribal communities pioneered microbial diversity and conserved vital knowledge regarding gut flora.

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Conceptualization : AT. Software: RS. Validation: AT and RS. Formal analysis: AT and RS. Writing – Original Draft: AT and RC. Writing – Review and Editing: AT, RC, RS. Supervision: AT.

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Competing Interest

The corresponding author declares that there is no conflict of interest about any financial/commercial problem on behalf of all authors.

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Data Availability

No data sets were generated during the current study.

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