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Journal of Infectious Diseases & Travel Medicine
ISSN: 2640-2653

Role of Probiotics in Diabetes Mellitus

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Review Article

Volume 5 Issue 2

Received Date: September 20, 2021

Published Date: November 01, 2021

DOI: 10.23880/jidtm-16000154

Abstract

Diabetes mellitus has become a serious concern as it is a major public health issue. Due to the complications like diabetic nephropathy, diabetic cardiovascular complication, diabetic neuropathy, diabetic retinopathy and diabetic heapatopathy it has high despondence and lethality. Depending on the health conditions of diabetic patients the present study shows the effects of probiotic complements. This review summarizes that by restraining intestinal microbiota along with decreasing the inflammatory reactions and oxidative stress probiotics can increase insulin sensitivity and reduces autoimmune reactions. Recent evidences show that probiotics affects the host through restraining intestinal permeability and mucosal immune response, employing eating behaviors by appetite-regulating hormones and controlling endocannabinoid (eCB) system that is correlated with inflammation and diabetes. It is hypothesized experimentally and clinically that restraining the microbiota by probiotics could be impressive in anticipation and execution of diabetes. Literature ascertained that the complementation of probiotics can avert and boost the T1DM, T2DM and gestational DM. In culmination probiotics have a lot of favorable effects in health and disease reducing superficial annoyance, regulating the immune system and improving the body antioxidant defense.

Keywords: Probiotics; Diabetes Mellitus; Lactobacillus; Microbiota; Insulin

Introduction

Diabetes mellitus (DM), commonly known as hyper glycaemia is one of the most recurrent common metabolic disarray in the World, which occurs either due to decreased insulin secretion or insulin resistance [1]. In India since 1990 there was a radical increase in health loss due to diabetes which was reported in the Lancet Global health [2]. It is found that the prevalence of DM in US has also raised at an uncurbed rate, and it is assumed that by 2030 the number of Americans with DM might hike up to 55 million [3]. By the year 2035 it is assumed by the international "Diabetes mellitus federation" that 592 million people world-wide will suffer from diabetes mellitus which is the fifth major cause of mortality [4]. DM especially Type 2 diabetes (T2DM), the major causes of its despondence and lethality could induce diverse complications, such as diabetic nephropathy, diabetic cardiovascular complications, and neuropathy, eye and liver complications [4,5]. Therefore, it is the need of the hour to find impressive strategies for the anticipation and execution of DM and its complications [6].

The major cause of Type 2 DM (T2D) is by high blood glucose level, insulin deficiency and resistance whose prevalence is 90-95 % of DM [7]. In untreated cases of DM the quality of life is compromised and the risk of fatality increases. T2D patients face some psychological problems like stress, depression and anxiety which influence the psychological and social life [8]. The cause of T2DM is supposed to be by a chain of multiple risk factors like genetic liability, age,

overweight, or obesity and debilitated behavior. There are durable documentations that the intestinal microbiota affects the host by persuading bile and metabolism, body weight, pro-inflammatory status and insulin resistances, and modulating the gut hormones. Probiotics and antibiotics have favorable effect on glucose metabolism improvement and insulin resistance by modulating gut microbiota by consumption of probiotics. Current investigations showed that host microbiome play a crucial part in the prevalence and execution of DM, especially in T2D [9]. By promoting the glucose transporter 4 (GLUT-4) transcriptions in T2DM animal studies showed that probiotics can improve insulin binding potential, inhibit β- cells damages in the islets of Langerhans and additionally increase insulin sensitivity [9]. There was enhancement in at least one of the blood glucose markers in human and animal studies [10]. When consumed in requisite amounts Probiotics confirm a health benefit to the animals [11]. Probiotics have been identified for their several health-stimulating properties and alleviating the physiological and corporal hindrances and afflictions [12-16]. The favorable impact of probiotics are strain- specific, which is related to the host physiology as reported that Lactobacillus species bestow positive impact on host health. At present *Akkermansia muciniphila* contemplated as probable bacteria could be used to treat diabetic mice [17], but its use *in* human needs further elevations in the preparation of the therapeutic agent and detailed validation. Still there is an obligation to emphasize our expertise on the complicated bond between intestinal microbiota and diabetic hosts. This analysis gives an impact on preventing or improving diabetes by probiotics.

Gut Microbiota

The gut microflora plays an important role in managing and regulating different physiological processes. Different processes in the human body can be altered by the ecological structures of the microflora by the influence of internal and external factors [18] like antibiotics, prebiotics and probiotics. Gut microbiota is systematically a crucial factor in linking genes, environment and immune system [19]. Microbiome, the microbial organ of human genome is twice the size of the human nuclear genome and performs imperative metabolic and biological functions [19]. Bacteria like *Bacteriodetes* and *Firmicutes subjugate* the gut microbiota [20]. It are reported that in the infant gut it is generally very low [21]. During the course of development from infancy to old age the microbiota changes [22]. Depending upon transmission mode in diverse environments when babies are exposed to a vast of microbes they get colonized by chance [23]. The micrbiota in mother's vagina is associated with the infants born from vagina. Whereas, babies born by cassarean section have a microbiota distinctive to skin which predominantly consists of Staphylococcus and *Propionibacterium spp. Lactobacillus acidophilus* and *Lactobacillus casei* significantly delayed the advancement of high fructose-induced glucose in tolerance and especially *Lactbacillus casei* plasma levels by the oral administration of probiotics [24]. Inflation of Bifidobacterium species corresponds with improved glucose tolerance and insulin secretion [25]. The configuration of gut microbiome species in adult life changes by antibiotic therapy in early life, dietary pattern, luminal pH and osmolality and environmental factors [26]. However, in spite of extensive variations in the gut microbial composition and inter-individual variability, it has been suggested that most of the individuals harbor microbiota that can be classified in to one of these three dominant genera: *Bacteroides, Prevotella,* or *Ruminococcus* [27]. To vary the gut microbiota combination it is said that ingestion of probiotics-"live microorganisms which, when administered in sufficient amounts, present health benefits to the host" [28]. Various composition of probiotic culture is found in dairy products like fermented foods, yoghurts, and some cheese. Still it is unknown that at what level the food source changes the gut micro biota and gives a positive biological effect outside research [29].

Probiotics and Diabetes Mellitus

Diabetes, a multi- system chronic disease, with numerous complications involving several molecular mechanisms is associated with the intestinal micro biota [30]. The imminence for development of T2D are age above 40 years, overweight, family predisposition, chronic stress, lack of muscle activity and inappropriate diet which are considered to be the main stimulating factors [31]. It has been found that genetic factors are enforced in advancement of only 10-20 % of cases of diabetes whereas the way of subsistence and social behavior predominate [32].

Differentiating the positive effects of probiotics into following three major groups:

1. Transfiguration of the inherent as well as the acquired immune system of the host enforced in the prevention and therapy of infectious diseases but were also involved in the treatment of obstinate inflammation of the digestive tract. In dealing with neoplastic host cells probiotic activity could support the host immune system.
2. The prevention and therapy of infection depends on the governance and reclamation of the microbial serenity in the gut, interacting with other microoraganisms, synergism and /or pathogenism.
3. Deactivation of toxins and detoxification of toxins, xenobiotics, microbial products, endogenous products (e.g. bile salt) and food ingredients in the gut.

Within the intestinal microbiota probiotics are convoluted in infection, defense, and prevention of cancer and maintain the physiological balance.

One of the circumstances for the pathogenesis of diabetes mellitus is oxidative stress. It is suppressed by Probiotics-containing food. *L acidophilus* (*Lactobacillus acidophilus)* and *L casei (Lactobacillus casei)* also attenuate oxidative stress and have anti diabetic effects. It has been reported that *Lactobacillus casei* decreases the oxidative stress and abolishes the effector functions of CD4+ T cells, companied by reducing the pro inflammatory molecules [33], thus having antioxidant, immune modulatory effects and diabetic effects.

It has been recommended that the remedial effects of probiotics on blood glucose may be associated with compositional alternation of the intestinal microbiota in diabetes [34]. Probiotic interventions in diabetes lead to growing interests in management and treatment (Table 1) [35-42]. Recent studies show that probiotic bacteria serve as anti-diabetic agents when given supplementation with probiotics to normalize glucose homeostasis in diabetic rats [43]. Some probable systems involved with T2D and insulin resistance are: within adipose cells there is an increase in breakdown of lipids, deficiency and resistance of insulin, blood glucose levels are high, kidneys have high retention of salt and water and inappropriate modulation by the central nervous system. For development of diabetes there should be an impairment of insulin secretion by pancreatic β-cells is therefore not all people with insulin resistance develop diabetes [18].

Diabetes Type	Study Group	Probiotic Strain	Dose & Duration	Results	Reference
	256 healthy pregnant women	*Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb 12	10^{10} CFU/d during pregnancy and over the 12 month`s postpartum period	Better glucose tolerance in the probiotics group was confirmed by a reduced risk of elevated glucose concentration	[35,36]
GDM	175 pregnant women	*Lactobacillus salivarius* UCC 118	Capsule contained 100 mg probiotic from 24 to28 week of gestation	Probiotic treatment of 4 wk during pregnancy did not influence maternal fasting glucose, the metabolic profile, or pregnancy outcomes	[37]
	64 pregnant women with GDM	*Lactobacillus acidophilus* LA-5, Bifidobacterium BB-12, *Streptococcus thermophiles* STY-31 and *Lactobacillus delbrueckiibulgaricus* LBY-27	For eight consecutive weeks	The weight gain in the probiotic group was significantly lower. Insulin resistance index in the probiotic group and 6.74 5 reduction over the study period.	[38]
T2DM	64 patients with type 2 diabetes	*Lactobacillus acidophilus* LA-5, *Bifidobacterium lactis* Bb-12	300 g/d of probiotic yogurt for 6 wk	Probiotic yogurt significantly decreased fasting blood glucose and hemoglobin	[39]
	60 overweight, healthy adults	VSL# 3	6 weeks	VSL #3 significantly improved insulin sensitivity	[40]
T1DM	44 patients with type 2 diabetes	*Lactobacillus acidophilus* La-5 and *Bifidobacterium lactis* Bb-12	300 g/d probiotic yogurt for 8 weeks	Consumption of probiotic yogurt caused significant decrease in HbA1c	[41]
	8676 newborns with T1DM-associated HLA genotypes	Probiotic infant formulas containing mixtures of various Lactobacillus and Bifidobacterium species	The species and amounts of microbes from probiotics were not studied	Early probiotic supplementation (at the age of 0-27 days) was associated with a risk of islet autoimmunity in children at the highest genetic risk T1DM	[42]

Table1: Studies about the effect of probiotics supplementation on diabetic subjects.

The probiotics usage is efficient in increasing the mucosal barrier to pathogens and antigen presentation.

Additionally, the effect of the probiotics on the stimulation and secretion of mucus in the intestine is directly correlated with the inhibitions of pathogenic *Escherichia coli* attachment and of damage to the intestinal tract. In the development of intestinal host defenses, as an adjuvant of immune responses or to strengthen the mucosal barrier different probiotics can function differently [44].

In humans or animals with Type 1 and Type 2 diabetes many researchers have proved that lactic acid bacteria and probiotic have distinct positive effect. It is shown in animal model that lactobacilli reduce the risk of developing T2D [24]. Studies in mice model show that by induction of high lipid diet obesity and diabetes, by providing probiotic supplements *Lactbacillus plantarum* DSM 15313 and *Lactobacillus gasseri* BNR 17 representing anti diabetes, leads to decrease in blood glucose level and improves glucose tolerance without influencing lipid and insulin levels [45].Proved clinically that in the progression, infection and development of complications in diabetes mellitus oxidative stress plays a crucial role [46]. The oxidative stress is suppressed by probiotic foods. In this review article highlights of the effects of probiotics on different types of diabetes will be discussed separately.

Gestational Diabetes Mellitus

One of the metabolic obstacles of pregnancy having incidence rate 3-25 % is gestational diabetes mellitus (GDM). In these patients probiotic supplementation may alleviate glycemic control [47]. GDM is a threat for short term and long term oppression of mothers and babies. It is believed that in short term, women with GDM undergo preeclampsia and deliver by caesarean section [48]. Moreover, GDM raises the risk of more adiposity, macrosomia (a birth weight of > 4000 gm), shoulder dystocia, admission to the neo natal intensive care unit and neo natal hypoglycemia in the infant [49]. It is also observed that both mother and baby in the long term GDM experience high risk of obesity in addition with metabolic and cardiovascular abnormalities [50,51]. The weight gaining process was effected when the supplementation of the probiotic capsule containing of four probiotic strain (*L . acidophilus* LA-5, *L. delbrueckiibularicus* LBY-27, *S. thermophiles* STY-31, and *Bifidobacterium* BB-12; 4 x 10^9 CFU in total) was administered for eight weeks as compared to the placebo group in recently diagnosed GDM patients after 6 weeks [52]. In short term complications though controlling blood glucose levels by existing therapies is effective it may not be appropriate for the longer term complications [53]. Subsequently, the averting of GDM would be better than treatment [54]. By change in metabolism by probiotics GDM can be prevented [55]. According to a preliminary study of probiotic supplementation in pregnant women having normal weight, with combined dietary/ probiotic supplementation showed a decrease in the rate of GDM from 34 % to 13 % (56). There was a better glucose response and HbA/c levels in pregnant women receiving nutritional counseling and probiotic supplement containing *B. lactis* Bb12 and *L. rhamnosus* GG when compared with the control groups receiving only healthy diet [56]. Laitinen, et al. proved that during pregnancy and up to 12 months after delivery, nutritional counseling along with probiotic supplementation, decreased blood glucose levels, helped in improving insulin sensitivity and also reduced insulin concentrations which were more effective than nutritional counseling [57]. The risk of GDM can be decreased by healthy diets before and during pregnancy [58,59]. During the last decade authors have proved that there was an increase of risk of developing gestational diabetes in mother`s diet during pregnancy, having high fat intake of carbohydrates, fiber and diet with high glycemic load [60,61].

Evidences show positive effects of dietary patterns with large intake of vegetarian foods (such as whole grains, fruits, vegetables, and brains) and fish, while the less intake of processed animal and fatty food is found in the presentation and treatment of gestational diabetes mellitus. This is a well-known dietary pattern of the Mediterranean diet (Med Diet) [62].There is a reduced incidence of gestational diabetes and increased glucose tolerance in diabetic pregnant women which is proved in many studies of a Med Diet [63].

As there is an inadequacy of a universal standard to mention glucose tolerance during pregnancy conflict exists regarding the treatment of GDM [64]. Studies prove that with decisive monitoring of blood glucose levels nutritional inventions can be considered as a primary therapeutic option, and if diet alternations fail it will lead to control glucose levels with drug therapy. By changing the life style it is predicted that 70-80% of the cases could controlled [65]. The invulnerability of consumption of probiotics during pregnancy and early infancy is supported by the outcomes. For GDM prevention, high-risk overweight and obese pregnant women probiotics can be used as a safe method [66].

Type 1 Diabetes Mellitus (T1DM)

In Type 1 diabetes mellitus there is a progressive destruction of pancreatic β- cells and reduced or no insulin secretion [67], which accounts for 5-10 % diabetes mellitus [68]. Autoimmune destruction of pancreatic β- cells in genetically predisposed individuals leads to T1DM [69]. The destruction of β-cell involves innate and adaptive immune responses and when about 80% of β-cells are affected, and then the first signs of diabetes become illustrated [70]. Thus insulin therapy becomes necessary. Environmental factors are involved leading to either increase the initial

autoimmune response in genetically susceptible individuals, or may alter the destructive process at different levels along with the regular history [71,72].

The major site for pathogen invasion is intestinal mucosa: it acts as the first line of defense against antigens when intact. There is a layer of mucus, IgA- secreting cells, antimicrobial peptides and a complex system of epithelial barrier formed by adhesion and tight junctions in the intestinal wall [73]. The intestinal microbiota is efficient in attenuating the immune response and subsequently autoimmunity; the impact of intestinal bacteria in the pathogenesis of T1DM has been exhibited [74].

The gut microbiota is closely related with the immune system and helps in regulating the immune response in an extremely complex microenvironment [75]. In young T1DM prone rodents, islet autoimmunity and disease were protected by experimental micro biome intervention, showing the fact that microbial therapy can provide effective protection to individuals with high genetic imminence of T1DM. By early oral administration of VSL#3 diabetes development in NOD (non-obese diabetic) mice could be prevented which was proved by Calcinaro, et al. [76]. In protected mice the rate of beta cell destruction and insulitis was decreased. The improved expression and production of IL-10 in the pancreases lead to the prevention, where IL-10 positive iselet-infiltrating mononuclear cells were found.

To find out whether the ingestion of probiotics during the first 6 months of life reduces the emergence of T1Dm-associated autoantibodies in children with genetic risk of T1Dm a clinical trial was carried out. Furthermore an experimental study, having 200 subjects was designed to exhibit the safety and suitability of the need of probiotics during the first 6 months of life. This study showed that the concentration of autoantibodies at 6, 12, and 24 months of age was of predictable levels [77]. At the age of 12 months autoantibody was negative. If more than one autoantibody was present one subject was detected positive. With this it can be proved that the probiotics are capable of inhibiting the production of autoantibody against the pancreatic cell. The effectiveness of probiotics combination on pathogenesis and improvement of T1DM in animal studies or prospective clinical trials would be of help. Almost all the researchers in this field is carried out on animal model; so now there is a need for trials that will appraise the adequacy of probiotics in preventing or controlling autoimmune responses against β-cells which would be magnificent.

Probiotics which, when consumed in applicable amounts, may bestow health benefits to their host are a class of live microorganisms [78]. Intake of curd augmented with *Lactobacillus acidophilus* NCDC14 and *Lactobacillus casei* NCDC 19 has allegedly decreased lipid peroxidation, HbA1c and ameliorated intestinal transits in diabetic rat; however without collateral reduction of blood glucose levels [79]. Related study have shown preserved enzymatic activity of the antioxidant enzymes glutathione peroxidase, superoxide dismutase and catalase [80]. The intake of *Lactobacillus reuteri* GMNL-263 helps in reduction of glycaemia and HbA1c levels, which helps in preventing renal fibrosis [81]. Moreover, the efficacy of clinical trials administering probiotics may be definitive to a particular strain used and may not be deduced to another strains of other species [82].

Differentiation of Gut Microbiota in Presence and Absence of Diabetes:

The assortment of microorganisms in the digestive tract is called gut microbiota. In the distal colon of the human gut nearly 100 trillion gut flora, containing bacteria, archaea, viruses and eukaryotic microbes are present [83]. The microbiota and human health relationship is becoming increasingly known. The entire health of the host depends on a healthy gut flora. In host nutrient metabolism the normal gut flora has distinct functions, xenobiotic and drug metabolism, to maintain structural integrity of the gut mucosal barrier, immunomodulation and conservation against pathogens [84]. Many authors have published that the gut microbiota among adults with T_2DM and non-diabetic adults are variable [85]. A study proved that a distinctive imbalance in the composition and function of the intestinal bacteria resulted to insulin resistance which increased the risk of developing T_2DM [86]. Patients with T_2DM had gut microbial dysbiosis along with an enhancement in opportunistic pathogens and a reduction in butyrate producing bacteria. [87]. Kuang, et al. analyzed the microbiota composition among women with GDM and healthy pregnant women having 21 and 29 weeks of fecundation [88].

Mechanisms of Probiotics Action

Modulate Immune Differentiation

In mesenteric lymph nodes *Lactobacillus johsonii* induced T helper Th17 cell differentiation, hence imparted immunity to the development of T_1DM in diabetes liable rates. Th17 differentiation was not developed in a group treated with *Lactobacillus reuteri* but later on developed T_1DM [89]. It was found that daily probiotic treatment with *B. animails* for one month reduced the expression of pro-inflammatory cytokines like TNF-α,IL-1β, plasminogen activator inhibitor-1 and IL-6,in the mesenteric adipose tissue, liver and muscle (as obstinated by the concentration of coding messenger RNA) [90]. When probiotic supplementation was given for 4 weeks it failed to reduce makers of inflammation which was proved clinically in a study with patients of T_2DM [91].

Modulation of Inflammation and Oxidative Stress

Through improved inflammation probiotics help to improve insulin resistance and decrease the blood glucose levels [92-94]. Researches showed that ingestion of probiotic yogurt containing *Bifidobacterium animalis* subs. Lactis Bf 12 (DSM10140) and *Lactobacillus acidophilus* strain La % caused significant disease in HbA1c and TNF-α level in the intervention group [95]. Lactobacilli in an epithelial cell model reinforced the barrier function of epithelial cells by enhancing the levels of adhesion proteins, including beta-catenin and E-cadherin. They also accustomed the junctional E-cadherin/beta-catenin complex by enthralling protein kinase [96].

The pathogenesis of diabetes and obesity is due to chronic inflammation. Cytokines inflammation leads to leptin and insulin resistance. The appliances that link inflammation with insulin resistance are the activation of IkB kinase complex (inhibitor of kappa beta, a kinase which activates inflammation), extracellular signal-regulated protein kinases 1 and 2 (ERK ½), and c-jun N-terminal kinase. The changes lead to insulin resistance by reducing tyrosine phosphorylation of the insulin receptor substrate-1,GLUTH and PPAR-α which are afflicted by cytokines produced in the adipose tissue like tumor necrosis factor (TNF-α) or interleukin(IL)-1β [97].

The progression of intestinal barrier function and reduction of the transmission of micro-organisms and their derivatives for example lipopolysaccharide (LPS) can be increased by probiotics [98], in the systemic circulation there by decreasing the allied release of pro-inflammatory cytokines through Toll-like receptor-4 (TLR-4) signaling [99]. The TLRs consists of a wide range of a family of cell membrane proteins present in variety of cells, which differentiate microbe-associated molecular patterns (MAMPs) during inflammatory responses. TLR-4 is present in insulin targeted tissues. By TLR-4 stimulation with activation of cytokine signaling cascades as well as raised concentration of reactive oxygen species (ROS) can be settled [100,101]. The main pathogenic factor of insulin resistance and diabetes is chronic low grade inflammation with high levels of pro-inflammatory cytokines [102,103]. Because of their immune-modulatory effects the anti-diabetic properties of probiotics may be the best in part. The bacterial metabolic activity can be modified by exuberance of nutrients like saturated and polyunsaturated fatty acids or shortage of oligosaccharides and phytochemicals [104].

Martino, et al. showed in a clinical trial that [105] the intake of 120g/day fermented milk supplemented with *Lactobacillus acidophilus* LA5 and *Bifidobacterium lactis* BB12 enhanced the glycemic control and interrupted a reduction in anti-inflammatory cytokines in T_2D. Consuming fermented milk having *L. casei* strain shiruta (FMLCS) for 16 weeks substantially changed the fecal microbiota and organic acid content. In T_2D patients the number of blood bacteria was remarkably reduced after the intake of FMLCS which also obstructed the bacterial translocation [106]. A report showed an increased enzymatic activity of the antioxidant enzymes glutathione peroxidase, super oxide dismutase and catalase [107]. A few strains of lactic acid bacteria consists of antioxidant properties by mechanisms that related to reactive oxygen species hunting, metal ion chelation, enzyme inhibition and inhibition of ascorbate autoxidation [108].

No positive Effects of Probiotic Supplementation Diabetic Conditions

Reports have shown that the potential of probiotic supplementation helps in the improvement of health among diabetic mellitus patients, also various studies showed negative results. It is also shown that the intake of a single strain probiotic (*L. salivarius* UCC 118) for six weeks had no substantial effect on the metabolic and glycemic status of GDM patients [109]. In pre-diabetic patients the consumption of symbiotic formula (*L. casei, L. acidophilus, L. bulgaricus, B. breve, B. longum, S. thermophiles* + FOS) had no positive impact on the lipid profile (TC, LDL, HDL, TG) [110]. After the supplementation of probiotic preparation (*L. acidophilus, L. bulgaricus, L. casei,* and *B. bifidum*) for six weeks it was found that there was insignificant change in the glycemic status of T2D patients [111].

Probiotics and Endocannabinoid System (eCB)

The endocannabinoid (eCB) system comprises of receptors, endogenous ligand and ligand metabolic enzymes. Tropically the eCB system illustrates a microcosm of psychoneuroimmunology or mind-body medicine [112]. The endocannabinoid (eCB) system is associated with inflammation and diabetes [113,114]. Through CB 1 receptor the intestinal microbiota stinulates gut eCB expression which modulates, gut permeability and plasma LPS levels [115]. In obese mice change in the microbiota decreases gut permeability. The CB 1 receptor`s in obese mice block the progress of gut barrier function by increasing the allocation and localization of tight junction proteins (ZO-1 and occluding). With the mentioned mechanism eCB system can inflect the gut permeability [116]. Cannabinoid receptor 2 (CB 2) is predominantly linked with cells which govern immune function, though it is expressed in the central nervous system [117,118]. Exhilarating of cannabinoid CB 2 receptor mitigates glucose tolerance in rats while CB 1 receptor

blockage mimes the effects of CB 2 receptor protogonist [119]. The facts prove that the inflection of glucose homeostasis by eCB system is because of the interaction of CB 1 and CB 2 receptors. The alternations in CB 2 receptor expression are positively associated with intestinal quantity of lactobacillus and negativity with counts of clostridium [120]. Overall the available evidence show that the host biological systems can be inflected by specific gut microbes which may lead to control of energy homeostasis, glucose metabolism and inflammation in obesity and T2DM [114].

Hormones Regulating Appetite and Behavior of Eating

To resist desires for high-sucrose and high fast food as part of their daily life is a challenge for many people. The main element for medical concern like obesity, diabetes heart disease, sleep apnea, and cancer is due to the unsound diet [121,122]. Many studies have shown that the gut microbiota since this is where the majority of the bacteria populating the human body are found and nutrition-related changes of taxa composition occur during obesity [123]. The eating behavior can be influenced by gut microbes to improve the fitness at the cost of host fitness. Other presumptions also projected that microbes may influence the eating behaviors, although not by competing for fitness but for evolutionary conflicts [124,125]. Metagenomic conflict between host microbes may be called as an extension of the genetic conflict context. The valgus nerve manages the microbial control; which may hinder with the physiological regulation which is organized by the valgus nerve. People facing cravings may have lower vagal tone. By blocking the valgus, food preferences can be altered by reducing microbial signaling through the valgus nerve [126,127]. Microbial communities having low alpha (intra-sample) diversity can over grow by one or more species having enhanced activity for production of behavior which alters hormones and neurochemicals. Nevertheless, in microbial communities any single microbial species having high alpha diversity has a tendency to transpire at lower abundance. The resistance to pathogenic invasions is more in highly diverse microbiota as compared to less diverse microbiota [128]. A physiologically diverse community will compete rather than manipulate the host and microbes will allocate source on competing and cooperating (e.g. via cross feeding). Similarly, probiotics that are known to increase microbiota diversity in humans are anticipated to decrease craving as compared to treatment control. Evidences show that gut microbiota plays a crucial role on energy homeostasis along the microbe-gut- brain axis [129]. It is seen that alteration in microbiota helps in alteration of entroendocrine signals which are sent to the Central Nervous System (CNS). The gut hormones like glucose-dependent insulin otropic peptide (GIP), glucagon-like peptide (GLP), peptide YY (PYY), can effect β-cell function, insulin secretion and regulate energy homeostasis through insulinotropic, satietogenic properties [130]. Batra, et al. showed that the sensitivity of insulin was enhanced by *Bifidobacterium adolescentis* [131] by increasing the manufacturing of glucagon-like peptide 1 (GLP-1). The glucose tolerance in GLP-1 is improved by various mechanisms which involve modulation of insulin secretion, pancreatic cell mass and food intake [132]. Break down the self-tolerance by immune cells by homeostatic mechanism recognized as non-self and produced autoantibodies in humans and other mammals. Against mammalian hormones the antibodies act as auto-antibodies; so that the microbes can handle human eating behavior (i) directly with peptide that are similar to satiety regulating hormones, or (ii) indirectly by motivating production of auto-antibodies interfering with appetite regulation [133]. The antibody responses affirm the interpretation that the regulation of eating behavior may be affected by combat between host and microbiota.

Conclusion

Probiotics are effective in diseases like infective diarrhea, chronic inflammatory bowel disease, lactose in tolerance and allergy, and their role in diabetes is well known. Due to this an association among pathogenic bacteria and chronic low grade inflammation is entrenched. The glycemic parameters predicted by clinical studies improve by modulating the gut microbiota. The probiotics used in clinical studies are Lactobacillus and Bifidobacterium species [134]. Probiotics claimed to have favorable effects on improving several metabolic disorders like non-alcoholic fatty liver disease [135], hyperlipidemia and diabetes along with other complications such as cancer and immune related diseases [136]. The glycemic and inflammatory status of GDM patients was controlled by the probiotic supplements [137]. The mechanisms involved for probiotics was increase in fasting insulin concentrations for reduction of FPG, increase in HDL, and decrease in TC, TG, LDL, to improve the lipid profile, decrease the systolic and diastolic blood pressure to maintain the normal blood pressure. Further there is a need of more research to be accomplished for choosing the exact strain, therapeutic dose, period of study and its optimum effects. Also further research has to be carried out to know the effects of various probiotic strains for preventing and improving T1DM, T2DM, and GDM.

Conflict of Interest: There is no conflict of interest among the authors.

References

1. Aassoc AD (2014) Diagnosis and classification of diabetes mellitus. Diabetes Care 37 suppl 1: S81-S90.

2. India State-level Disease Burden Initiative diabetes collaborators (2018) The increasing burden of diabetes and variations among the states of India: the Global Burden of Disease Study 1990-2016. Lancet Global Health 6(12): E1352-E1362.

3. Rowley WR, Bezold C, Arikan Y, Byrne E, Krohe S (2017) Diabetes 2030; insights from yesterday, today, and future trends. Population Health Management 20(1): 6-12.

4. Guariguta L, Whiting DR, Hambleton I, Beagley J, Linnekamp U, et al. (2014) Global estimates of diabetes prevalence for 2013 and projections for2035. Diabetes Res Clin Pract 103(2): 137-149.

5. Du WH, Peng SM, Liu ZH, Shi L, Tan LF, et al. (2012) Hypoglycemic effect of water extract of Pu-erh tea. J Agric Food Chem 60(40): 10126-10132.

6. Li Y, Wang C, Huai Q, Guo F, Liu L, et al. (2016) Effects of tea or tea extract on metabolic profiles in patients with type 2 diabetes mellitus: A meta-analysis of ten randomized controlled trials. Diabetes Metab Res Rev 32(1): 2-10.

7. Cannon A, Handelsman M, Heile M, Shannon M (2018) Burden of illness in type 2 diabetes mellitus. J Manag Care Spec Pharm 24(9): S5-S13.

8. Peyrot M, Rubin RR, Lauritzen T, Snoek FJ, Mathews DR, et al. (2005) Psycosocial problems and barriers to improved diabetes management: results of the cross-national diabetes attitudes, wishes and needs (DAWN) study. Diabetic Medicine 22(10): 1379-1385.

9. Vallianou NG, Stratigou T, Tsagarakis S (2018) Microbiome and diabetes: where we are now ? Diabetes Res Clin Pract 146: 111-118.

10. Razmpoosh E, Javadi M, Ejtahed HS, Mirmiran P (2016) Probiotics as beneficial agents in the management of diabetes mellitus: a systematic review. Diabetes Metab Res Rev 32(2): 143-168.

11. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, et al. (2014) Expert consensus document: the international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. Natr Rev Gastro & Heapatology 11(8): 506-514.

12. Shivamaruthi BS (2018) A comprehensive review on clinical outcome of probiotic and symbiotic therapy for inflammatory bowel disease. Asian Pacific J of Trop Biomedicine 8(3): 179-186.

13. Sivamurathi BS, Kesika P, Chaiyasut C (2018) Probiotic based therapy for atopic dermatitis: outcomes of clinical studies-AA mini review. Asian Pacific J of Trop Biomedicine 8(6): 328-332.

14. Sivamurathi BS, Kesika P, Chaiyasut C (2018) Influence of probiotic supplementation on climacteric symptoms in menopausal women- A mini review. Inter J of Applied Pharma 10(6): 43-46.

15. Sivamurathi BS, Kesika P, Chaiyasut C (2018) A review on anti-aging properties of probiotics. Inter J of Applied Pharma 10(5): 23-27.

16. Sivamurathi BS, Prashanth MI, Kesika P, Chaiyasut C (2019) Role of probiotics in human mental health and diseases. Tropi J of Pharmace Res (In press).

17. Cuesta-Zuluaga J de la, Mueller NT, Agudelo VC, Velásquez-Mejía EP, Carmona JA, et al. (2017) Metformin is associated with higher relative abundance of mucin-degrading Akkermansia muciniphila and several short chain fatty acid-producing microbiota in the gut . Diabetes Care 40(1): 54-62.

18. Naydenov K, Anastasov A, Avramova M, Mindov Iv, Tacheva T, et al. (2012) Probiotics and Diabetes Mellitus. Trakia J of Sci 10(1): 300-306.

19. Musso G, Gambino R, Cassader M(2010) Obesity, diabetes, and gut microbiota the hygiene hypothesis expanded? Diabetes care 33(10): 2277-2284.

20. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, et al. (2006) An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 444: 1027-131.

21. Adlerberth I, Wold AE (2009) Establishment of the gut microbiota in Western infants. Acta Paediatr 98(2): 229-238.

22. Clemente JC, Ursell LK, Parfrey LW, Knight R (2012) The impact of the gut microbiota on human health: an integrative view. Cell 148(6): 1258-1270.

23. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, et al. (2010) Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci 107(26): 11971-11975.

24. Andersson U, Branning C, Ahrne S, Molin G, Alenfall J, et al. (2010) Probiotics lower plasma glucose in the high-fat fed C57BL/6J mouse. Benef Microbes 1(2): 189-196.

25. Yin YN, Yu QF, Fu N, Liu XW, Lu FG (2010) Effects of four Bifidobacteria on obesity in high-fat diet induced rats.

World J Gastroenterol 16(27): 3394-3401.

26. Blaser M (2011) Antibiotic overuse: stop the killing of beneficial bacteria. Nature 476(7361): 393-394.

27. Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, et al. (2011) Enterotypes of the human gut microbiome. Nature 473(7346): 174-180.

28. Homayouni A (2009) Letter to the editor Food Chem 114: 1073.

29. Allen SJ, Jordan S, Storey M, Thornton CA, Gravenor M, et al. (2010) Dietary supplementation with lactobacilli and bifidobacteria is well tolerated and not associated with adverse events during late pregnancy and early infancy. J Nut 140(3): 483-488.

30. Gomes AC, Bueno AA, de Souza RGM, Mota JF (2014) Gut microbiota, probiotics and diabetes. Nutrition 13: 60.

31. Stefanov TS, Vekova AM, Kurktschiev DP, Temelkova-Kurktschiev TS (2011) Relationship of physical activity and eating behavior with obesity and type 2 diabetes mellitus Sofia Lifestyle (SLS) study. Folia Med 53(1): 11-18.

32. Villarini M, Caldini G, Moretti M, , Trotta F, Pasquini R, et al. (2008) Modulatory activity of a lactobacillus casei strain on 1, 2-dimethylhydrazine-induced genotoxicity in rats. Environ Mol Mutagen 49(3): 192-199.

33. So JS, Kwon HK, Lee CG, Yi HJ, Park JA, et al. (2008) Lactobacillus casei suppresses experimental arthritis by down- regulating T helper 1 effector functions. Mol Immunol 45(9): 2690-2699.

34. Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, et al. (2010) Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PloS one 5(2): e9085.

35. Yadav H, Jain S, Yadav M (2012) Probiotics and diabetes/ obesity. Bioactive Food as Dietary Interventions for Diabetes: Bioactive Foods in Chronic Disease States 307-317.

36. Laitinen K, Poussa T, Isolauri E (2009) Probiotics and dietary counselling contribute to glucose regulation during and after pregnancy: a randomised controlled trial. Br J Nutr 101(11): 1679-1687.

37. Lindsay KL, Kennelly M, Culliton M, Smith T, Maguire OC, et al. (2014) Probiotics in obese pregnancy do not reduce maternal fasting glucose: a double-blind, placebo-controlled, randomized trial (Probiotics in Pregnancy Study). Am J Clin Nutr 99(6): 1432-1439.

38. Dolatkhah N, Hajifaraji M, Abbasalizadeh F, Aghamohammadzadeh N, Mehrabi Y, et al. (2015) Is there a value for probiotic supplements in gestational diabetes mellitus? A randomized clinical trial. J Health Popul Nutr 33:25.

39. Ejtahed HS, Mohtadi-Nia J, Homayouni-Rad A, Niafar M, Asghari-Jafarabadi M, et al. (2012) Probiotic yogurt improves antioxidant status in type 2 diabetic patients. Nutrition 28(5): 539-543.

40. Rajkumar H, Mahmood N, Kumar M, Varikuti SR, Challa HR, et al. (2014) Effect of probiotic (VSL# 3) and omega-3 on lipid profile, insulin sensitivity, inflammatory markers, and gut colonization in overweight adults: a randomized, controlled trial. Mediators Inflamm 2014: 348959.

41. Mohamadshahi M, Veissi M, Haidari F, Javid AZ, Mohammadi F, et al. (2014) Effects of probiotic yogurt consumption on lipid profile in type 2 diabetic patients: A randomized controlled clinical trial. J Res Med Sci 19(6): 531-536.

42. Uusitalo U, Liu X, Yang J, Aronsson CA, Hummel S, et al. (2016) Association of early exposure of probiotics and islet autoimmunity in the TEDDY study. JAMA Pediatr 170(1): 20-28.

43. Yadav H, Jain S, Sinha P (2008) The effect of probiotic Dahi containing Lactobacillus acidophilus and Lactobacillus casei on gastropathic consequences in diabetic rats. J Med Food 11(1): 62-68.

44. Walker WA (2008) Mechanisms of action of probiotics. Clin Infect Dis 1: 144-151.

45. Yun SI, Park HO, Kang JH (2009) Effect of Lactobacillus gasseri BNR 17 on blood glucose levels and body weight in a mouse model of type 2 diabetes. J Appl Microbiol 107(5): 1681-1686.

46. Ceriello A, Motz E (2004) Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. Arterioscler Thromb Vasc Biol 24(5): 816-823.

47. Dallanora, S, Medeiros de Souza Y, Deon RG, Tracey CA, Freitas-Vilela AA, et al. (2018) Do probiotics effectively ameliorate glycemic control during gestational diabetes? A systemic review. Archives of Gynec & Obeste 298(3): 477-485.

48. Dempsey JC, Ashiny Z, Qiu C-F, Miller RS, Sorensen TK, et al. (2005) Maternal pre-pregnancy overweight status and obesity as risk factors for cesarean delivery. J Matern

Fetal Neonatal Med 17(3): 179-185.

49. Wendland EM, Torloni MR, Falavigna M, Trujillo J, Dode MA, et al. (2012) Gestational diabetes and pregnancy outcomes-a systematic review of the World Health Organization (WHO) and the International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria. BMC Pregnancy Childbirth 12: 23.

50. Kim C (2010) Gestational diabetes mellitus and risk of future maternal cardiovascular disease. Expert Rev Cardiovasc Ther 89120: 1639-1641.

51. Crume T, Ogden L, West N, Vehik K, Scherzinger A, et al. (2011) Association of exposure to diabetes in utero with adiposity and fat distribution in a multiethnic population of youth: the Exploring Perinatal Outcomes among Children (EPOCH) Study. Diabetologia 54(1): 87-92.

52. Kesika P, Sivamaruthi BS, Chaiyasut C (2019) Do probiotics improve the health status of individuals with diabetes mellitus/ A review on outcomes of clinical trials. Bio Med Res Inter 48: 1-11.

53. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, et al. (2005) Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 352(24): 2477-2486.

54. Nitert MD, Barrett HL, Foxcroft K, Tremellen A, Wilkinson S, et al. (2013) SPRING: an RCT study of probiotics in the prevention of gestational diabetes mellitus in overweight and obese women. BMC Pregnancy Childbirth 13: 50.

55. Barrett HL, Dekker Nitert M, Conwell LS, Callaway LK (2014) Probiotics for preventing gestational diabetes. Cochrane Database Syst Rev 9: 2-9.

56. Luoto R, Laitinen K, Nermes M, Isolauri E (2010) Impact of maternal probiotic-supplemented dietary counseling on pregnancy outcome and prenatal and postnatal growth: a double-blind, placebo-controlled study. Br J Nutr 103(12): 1792-1799.

57. Laitinen K, Poussa T, Isolauri E. Nutrition, Allergy, Mucosal Immunology and Intestinal Microbiota Group (2009) Probiotics and dietary counselling contribute to glucose regulation during and after pregnancy: a randomised controlled trial. Br J Nutr 101(11): 1679-1687.

58. Kinnunen TI, Puhkala J, Raitanen J, Ahonen S, Aittasalo M, et al. (2014) Effects of dietary counseling von food habits and dietary intake of Finnish pregnant women at increased risk for gestational diabetes-a secondary analysis of a cluster-randomized controlled trial. Matern Child Nutr 10(2): 184-197.

59. Guelinckx I, Devlieger R, Mullie P, Vansant G (2010) Effect of lifestyle intervention on dietary habits, physical activity, and gestational weight gain in obese pregnant women: a random controlled trial . Am J clin Nutr 91(2): 373-380.

60. Saldana TM, Siega-Riz AM, Adair LS (2004) Effect of macronutrient intake on the development of glucose intolerance during pregnancy. Am J Clin Nutr 79(3): 479-486.

61. Zhang C, Liu S, Solomon CG, Hu CY (2006) Dietary fiber intake, dietary glycemic load, and the risk for gestational diabetes mellitus. Diabetes care 29(10): 2223- 2230.

62. KIarmanos B, Thanopoulou A, Anastasiou E, Assaadkhalil S, Albache N, et al. (2014) Relation of the Mediterranean diet with incidence of gastetational diabetes. Eur J Clin Nutr 68(1): 8-13.

63. Shen J, Obin MS, Zhao L (2013) The gut microbiota, obesity and insulin resistance. Mol Aspects Med 34(1): 39-58.

64. Poolsup N, Suksomboon N, Amin M (2014) Effect of treatment of gestational diabetes mellitus: a systemic review and meta-analysis. Plos one 9(3): e92485.

65. Brown J, Alwan Na, West J, Brown S, Mckinlay CJ, et al. (2017) Lifestyle interventions for the gestational diabetes. Cochrane database of systemic reviews 5(5): CD011970.

66. Nitert MD, Barrett HL, Foxcroft K, Tremellen A, Wilkinson S, et al. (2013) SPRING: an RCT study of probiotics in the prevention of gestational diabetes mellitus in overweight and obese women. BMC Pregnancy Childbirth13: 50.

67. Ramadan G, El-beih NM, El- Ghffar EAA (2009) Modulatory effects of black v. green tea aqueous extract on hyperglacaemia, hyperlipidaemia and liver dysfunction in diabetic and obese rat models. Br. J Nutr 102(11): 1611-1619.

68. Nunes AR, Alves MG, Moreira PI, Oliveira PF, Silva BM (2014) Can tea consumption be a safe and effective therapy against diabetes mellitus-induced neurodegeneration? Curr Neuropharmacol 12(6): 475-489.

69. Young Is, Torney JJ, Trimble ER (1992) The effect of ascorbate supplementation on oxidative stress in the streptozotocin diabetic rat. Free Radic Biol Med 13(1): 41-46.

70. Yessoufou A, Ategbo JM, Girard A, Prost J, Dramane Kl, et al. (2006) Cassava-enriched diet is not diabetogenic rather it aggravates diabetes in rats .Fundam Clin Pharmacol 20(6): 579-586.

71. Lin C-H, Lin C-C, Shibu MA, Liu C-S, Kuo C-H, et al. (2014) Oral Lactobacillus reuteri GMN-32 treatment reduces blood glucose concentrations and promotes cardiac function in rats with streptozotocin-induced diabetes mellitus. Br J Nutr 111(4): 598-605.

72. Trucco M (2009) Gene-environment interaction in type 1 diabetes mellitus. Endocrinol Nutr 56: 56-59.

73. Lavie CJ, Milani RV, Ventura HO (2009) Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol 53(21): 1925-1932.

74. Nazmi M, Hajifaraji M, Abd Mishani M (2013) The effect of adipokines secreted from adipose tissue on immune function in obese subjects. Iranian J of Nutr Sci & Food Technology 7(5):887-896.

75. Atkinson MA, Eisenbarth GS (2001) Type 1 diabetes: new perspectives on disease pathogenesis and treatment. Lancet 358(9277): 221-229.

76. Calcinaro F, Dionisi S, Marinaro M, Candeloro P, Bonato V, et al. (2005) Oral probiotic administration induces interleukin-10 production and prevents spontaneous autoimmune diabetes in the non-obese diabetic mouse. Diabetologia 48(8): 1565-1575.

77. Ljungberg M, Korpela R, Ilonen J, Ludvigsson J, Vaarala O (2006) Probiotics for the prevention of beta cell autoimmunity in children at genetic risk of type 1 diabetes-the PRODIA study. Ann N Y Acad Sci 1079: 360-364.

78. WHO (2001) Evaluation of Health and Nutritional properties of Probiotics in Food including Power Milk with Live Lactic Acid Bacteria. Joint WHO/FAQ Expert Consultation on Geneva, World Health Organization, Cordoba, Argentina.

79. Yadav H, Jain S, Sinha RR (2008) The effect of probiotic Dahi containing Lactobacillus acidophilus and Lactobacillus casei on gastropathic consequences in diabetic rats. J Med Food 11(1): 62-68.

80. Yadav H, Jain S, Sinha PR (2008) Oral administration of Dahi containing probiotic Lactobacillus acidophilus and Lactobacillus casei delayed the progression of streptozotocin-induced diabetes in rats. J Dairy Res 75(2): 189-195.

81. Lu YC, Yin LT, Chang WT, Huang JS (2010) Effect of Lactobacillus reuteri GMNL-263 treatment on renal fibrosis in diabetic rats. J of Biosci Bioeng 110(6): 709-715.

82. Marik EP (2012) Colonic flora, probiotics, obesity and diabetes. Front Endocirnol 3: 87.

83. Hasain Z, Norfilza MM, Kamaruddin NA, Ismail NAM, Gnanou JV, et al. (2020) Gut microbiota and gestational diabetic mellitus: A review of host-gut microbiota interactions and their therapeutic potential. Frontier in Cellular and Infect Microbiol 10: 188.

84. Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala H, et al. (2015) Role of the normal gut microbiota. World J Gastroenterol 21(29): 8787-8803.

85. Li C, Li X, Han H, Cui H, Peng M, Wang G, et al. (2016) Effect of probiotics on metabolic profiles in type 2 diabetes mellitus: A meta-analysis of randomized controlled trials. Medicine (Baltimore) 95(26): e4088.

86. Pedersen HK, Gudmundsdottir V, Nielsen HB, Hyotylainen T, Nielsen T, et al. (2016) Human gut microbes impact host serum metabolome and insulin sensitivity. Nature 535(7612): 376-381.

87. Qin J, Li Y, Cai Z, Li S, Zhu J, et al. (2012) A meta genome –wide association study of gut micribiota in type 2 diabetes. Natur 490(7418): 55-60.

88. Kuang YS, Lu JH, Li SH, Li JH, Yuan MY, et al. (2017) Connections between the human gut microbiome and gestational diabetes mellitus. Giga Science 6(8): 1-12.

89. Lau K, Benitez P, Ardissone A, Wilson TD, Collins EL, et al. (2011) Inhibition of type 1 diabetes correlated to a *Lactobacillus johnsonil* N6.2-mediated Th17 bias. J Immunol 86(6): 3538-3546.

90. Amar J, Chabo C, Waget A, Klopp P, Vachoux C, Bermúdez-Humarán LG, et al. (2013) Intestinal mucosal adherence and translocation of commensal bacteria at the early onset of type 2 diabetes: Molecular mechanisms and probiotic treatment. EMBO Mol Med 3(9): 559-572.

91. Andrasen AS, Larsen N, Skovsgaard TP, Berg RMG, Møller K, et al. (2010) Effects of Lactobacillus acidophilus NCFM on insulin sensitivity and systemic inflammatory response in human subjects. Br J Nutr 104(12): 1831-1838.

92. Al-Salami H, Butt G, Fawcett JP, Tucker IG, Golocorbin-Kon S, et al. (2008) Probiotic treatment reduces blood glucose levels and increases systemic absorption of gliclazide in diabetic rats. Eur J Drug Metab Pharmacokinet 33(2): 101-106.

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

94. Ma X, Hua J, Li Z (2008) Probiotics improve high fat diet-induced hepatic steatosis and insulin resistance by increasing hepatic NKT cells. J Hepatol 49(5): 821-830.

95. Mohamadshahi M, Veissi M, Haidari F, Shahbazian H, Kaydani G-A, et al. (2013) Effects of probiotic yogurt consumption on inflammatory biomarkers in patients with type 2 diabetes. Bioimpacts 4(2): 83-88.

96. Hummel S, Veltman K, Cichon C, Sonnenborn U, Schmidt MA (2012) Differential targeting of the E-cadherin/β-catenin complex by gram-positive probiotic lactobacilli improves epithelial barrier function. Appl Environ Microbiol 78(4): 1140-1147.

97. Boulange CL, Neves AL, Chilloux J, Nicholson JK, Dumas ME (2016) Impact of gut microbiota on inflammation, obesity and metabolic disease. Genome Med 8(1): 42.

98. Cani PD, Neyrinck AM, Fava F, Knauf C, Burcelin RG, et al. (2007) Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. Diabetologia 50(11): 2374-2383.

99. Guha M, Mackman N (2001) LPS induction of gene expression in human monocytes. Cell Signal 13(2): 85-94.

100. Cristofaro P, Opal SM (2006) Role of Toll-like receptors in infection and immunity. Drugs 66(1): 15-29.

101. Medzhitov R (2001) Toll-like receptors and innate immunity. Nat Rev Immunol 1(2): 135-145.

102. Pickup JC (2004) Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. Diabetes Care 27(3): 813-823.103.

103. Shoelson SE, Lee J, Goldfine AB (2006) Inflammation and insulin resistance. J Clin Invest 116(7): 1793-17801.

104. de La Serre CB, Ellis CL, Lee J, Hartman AL, Rutledge JC, et al. (2016) Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation. Am J Physiol Gastrointest Liver Physiol 299(2): G440-G8.

105. Martino H, Tonucci L, Santos K, Oliveira L, Ribeiro S (2015) Effects of Probiotics on Glycemic Control and Inflammation in Type 2 Diabetes Mellitus: A Randomized, Double-Blind, Placebo-controlled Study. FASEB J 29: 922.6.

106. Sato J, Kanazawa A, Azuma K, Ikeda F, Goto H, et al. (2017) Probiotic reduces bacterial translocation in type 2 diabetes mellitus. Scientific Reports 7(1): 12115.

107. Diamond S, Millstein E (1988) Current concepts of migraine therapy. J Clin Pharmacol 28(3): 193-199.

108. Milind P, Jyoti M (2014) Curd: A sedative with a bonus bowl of useful side effect. Int Res J Pharm 5: 131-135.

109. Lindsay KL, Brennan L, Kennelly MA, Maguire OC, Smith T, et al. (2015) Impact of probiotics in women with gestational diabetes mellitus on metabolic health. American J of Obster and Gyne 212(4): 496e1- 496e11.

110. Mahboobi S, Iraj B, Maghsoudi Z, Feizi A, Ghiasvand R, et al. (2014) The effect of probiotic supplementation on markers of blood lipids, and blood pressure in patients with prediabetes. Inter J of Prevent Med 5(10): 1239-1246.

111. Mazloom Z, Yousefinejad A, Dabbaghmanesh MH (2013) Effect of probiotics on lipid profile, glycemic control, insulin action, oxidative stress, and inflammatory markers in patients with ype 2 diabetes. Iranian J of Med Sceinces 38(1): 38-43.

112. McPartland JM, Guy GW, Di Marzo V (2014) Care and feeding of the endocannabinoid system: A sysremic review Of potential clinical interventions that upregulate the endocannabinoid system. Plos One 9(3): e89566.

113. Scherer T, Buettner C (2009) The dysregulation of the endocannabinoid system in diabesity—a tricky problem. J Mol Med 87(7): 663-668.

114. Cani PD, Geurts L, Matamoros S, Plovier H, Duparc T (2014) Glucose metabolism: Focus on gut microbiota, the endocannabinoid system and beyond. Diabetes Metab 40(4): 246-257.

115. Muccioli GG, Naslain D, Bäckhed F, Reigstad CS, Lambert DM, Delzenne NM, et al. (2010) The endocannabinoid system links gut microbiota to adipogenesis. Mol Syst Biol 6: 392.

116. Cani PD, Osto M, Geurts L, Everard A (2012) Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes associated with obesity. Gut Microbes 3(4): 279-288.

117. Onaivi ES (2011) Commentary: functional neuronal CB2 cannabinoid receptors in the CNS. Curr Neuropharmcology 9(1): 205-208.

118. Atwood BK, Mackie K (2010) CB2: a cannabinoid receptor with an identy crisis. British J of Pharmcology 160: 467-479.

119. Bermudez-Silva FJ, Sanchez-Vera I, Suárez J, Serrano A, Fuentes E, et al. (2007) Role of cannabinoid CB 2 receptors in glucose homeostasis in rats. Eur J Pharmacol 565(1-3): 207-211.

120. Aguilera M, Vergara P, Martínez V (2013) Stress and antibiotics alter luminal and wall-adhered microbiota and enhance the local expression of visceral sensory-related systems in mice. Neurogastroenterol Motil 25(8): e515-e529.

121. Calle EE, Kaaks R (2004) Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 4(8): 579-591.

122. Anderson JW, Kendall CW, Jenkins DJ (2003) Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. J Am Coll Nutr 22(5): 331-339.

123. Forte N, Fernandez-Rilo AC, Palomba L, Marzo VD, Cristino L (2020) Obesity affects the microbiota-gut-brain axis and regulation thereof by endocannabinoids and related mediators. Int j Mol Sci 21(5): 1554-1579.

124. Rhee SH, Pothoulakis C, Mayer EA (2009) Principles and clinical implications of the brain–gut–enteric microbiota axis. Nat Rev Gastroenterol Hepatol 6(5): 306-314.

125. Lyte M (2011) Probiotics function mechanistically as delivery vehicles for neuroactive compounds: microbial endocrinology in the design and use of probiotics. Bioessays 33(8): 574-581.

126. Camilleri M, Toouli J, Herrera M, Kulseng B, Kow L, et al. (2008) Intra-abdominal vagal blocking (VBLOC therapy): clinical results with a new implantable medical device. Surgery 143(6): 723-731.

127. Sarr MG, Billington CJ, Brancatisano R, Brancatisano A, Toouli J, et al. (2012) The EMPOWER study: randomized, prospective, double-blind, multicenter trial of vagal blockade to induce weight loss in morbid obesity. Obes Surg 22(11): 1771-1782.

128. Ursell LK, Treuren WV, Metcalf JL, Pirrung M, Gewirtz A, et al. (2013) Replenishing our defensive microbes. Bioessays 35(9): 810-817.

129. Patel AK, Singhania RR, Pandey A, Chincholkar SB (2010) Probiotic bile salt hydrolase:current developments band prospectives. Appl Biochem Biotechnol 162(1): 166-180.

130. Panwar H, Rashmi HM, Batish VK, Grover S (2013) Probiotics as potential biotherapeutics in the managemenof type 2 diabetes-prospects and perspectives. Diabetes Metab Res Rev 29(2): 103-112.

131. Batra P, Das SK, Salinardi T, Robinson L, Saltzman E, et al. (2013) Relationship of cravings with weight loss and hunger. Results from a 6month worksite weight loss intervention. Appetite 69: 1-7.

132. Ramirez I (1990) Why do sugars taste good? Neurosci Biobehav Rev 14(2): 125-134.

133. Duca FA, Swartz TD, Sakar Y, Covasa M (2012) Increased oral detection, but decreased intestinal signaling for fats in mice lacking gut microbiota. PLoS One 7(6): e39748.

134. Shah NJ, Swami OC (2017) Role of probiotics in diabetes:aA review of their rationale and efficacy. EMJ Diabet 5(1): 104-110.

135. Nabavi S, Rafraf M, Somi M, Rad AH , Jafarabadi MA (2014) Effects of probiotic yogrut consumption on metabolic factors in individuals with nonalcoholic fatty liver disease. J of Dairy Sci 97(12): 7386-7393.

136. Homayouni RA, Torab R, Mortazavian AM, Mehrabany EV, Mehrabany LV (2013) Can probiotics prevent or improve common cold and influenza? Mutr 29(5): 805-806.

137. Dallanora S, de Souza YM, Deon RG, Tracey CA, Freitas-Vilela AA, et al. (2018) Do probiotics effectively ameliorate glycemic control during gestational diabetes? Archives of Gyn and Obstetrics 298(3): 477-485.