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RESEARCH ARTICLE

PROBIOTIC AND ITS THERAPEUTIC APPROACH IN THE MANAGEMENT OF TYPE 2 DIABETES

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ABSTRACT

Human gut is home to trillions of microbes termed as gut microbiota which play a vital role in maintaining intestinal homeostasis. Evidences suggest that dysbiosis of gut microbiota is associated with pathogenesis of lifestyle diseases such as obesity and diabetes. During the last few decades the cases of type 2 diabetes is spreading worldwide affecting the health of an individual. Search for the novel therapeutic approached which is inexpensive and does not have side effects for the management of type 2 diabetes is required. The word "probiotic" comes from Greek language "pro bios" which means "for life" opposed to "antibiotics" and defined as those microbes which when ingested in certain amount gives beneficial health effect to the host.And the beneficial effects of probiotic on human health have been reported by various researchers. The cause of pathogenesis of diabetes is complex and it is caused by multiple risk factors. In this review the role of gut microbiota in the pathogenesis of diabetes and modulation of gut microbiota by probiotic for the management of type 2 diabetes have been discussed.

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INTRODUCTION

Today the world is facing the challenges of increasing rate of chronic metabolic diseases, diabetes and cardiovascular diseases which are the main causes of mortality. Since the last few decades, due to changes in dietary intake and sedentary lifestyle, there is increase in the prevalence of metabolic diseases worldwide and socio economic condition of the people is highly affected. According to the World Health Organization (WHO) at least 171 million people (2.8% of the world population) suffered from diabetes in year 2000 and the number will almost double by year 2030 (Wild *et al*., 2004). The global prevalence of prediabetes is also increasing enormously, with >470 million people estimated to suffer from prediabetes by 2030 (Tabak *et al*., 2012). The rise in diabetes prevalence is set to pose one of the most important challenges to healthcare systems over the coming years (Tonucci *et al*., 2015). One study estimates that losses in Gross Domestic Product (GDP) worldwide from 2011 to 2030, including both the direct and indirect costs of diabetes, will total US$ 1.7 trillion, comprising US$ 900 billion for high-income countries and US$ 800 billion for low- and middle-income countries (Bloom *et al*., 2011). The human body is inhibited by different types of microbes; human colon is heavily populated by trillions of bacteria which lived in harmony with the gut in a healthy individual. However disturbances of this balanced microbiota causes various types of diseases and diabetes is caused by the imbalanced of gut microbiota in the human body. Diabetes is a chronic metabolic disorder characterized by the insensitivity of insulin to glucose thereby causing high blood sugar. Over the last few decades, diabetes has been the cause of lethal cardiovascular events that have progressed the most, since a 62% increase has been quantified (Cani *et al*., 2009). There are basically two types of diabetes-type 1 andtype 2. Type 1 diabetes is hereditary in which body does not produce insulin and insulin need to be supplemented. Type1diabetes results from autoimmune destruction of pancreatic β cells in genetically predisposed individuals (Bluestone *et al*., 2010). Type2 diabetes is a metabolic disorder characterized by hyperglycemia, developinginsulin resistanceβ-cell dysfunction and impaired insulin secretion (Santaguida *et al*., 2005; Evans *et al*., 2002). Type 2 diabetes has become one of the most prevalent diseases worldwide and can lead to serious complications, such as cardiovascular disorders, renal failure and blindness (Inzucchi *et al*. 2012). One of the major goals of treating metabolic syndrome is to reduce the risk of heart disease by controlling hyperglycemia, for which several pharmacologic agents are being used. However, of particular concern is the tendency for most antihyperglycemic treatments to have side effects such as weight gain, hepatotoxicity, and cardiovascular disease (Cariou *et al*., 2012). At present, the treatment of diabetes are mainly focused on drugs and common oral antidiabetic drugs

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containing alpha-glucosidase inhibitors, sulfonylurea, meglitinides, biguanides and thiazolidinediones (Phun *et al*., 2012). These antidiabetic drugs have many side effects and expensive. Therefore alternative therapy which is inexpensive, effective and free of negative side effects is necessary. Since the root cause of diabetes is the dysbiosis of gut microbiota, restoration of the imbalanced gut microbiota by using novel therapeutic approached has gained considerable interest over the past few years. In this context, use of probiotic could be an effective method for prevention and treatment of diabetes. Use of probiotic has been suggested as one of the approaches towards modifying the colonal flora (Idzior Waluś and Waluś-Miarka, 2015).

MATERIALS AND METHODS

A search of systematic review of literature was done through electronic databases such as PubMed, and SciELO (The Scientific Electronic Library Online), Cochrane Library (via Wiley) and Google scholar. The search was performed using different combination of keywords such as "diabetes" or "gut microbiota"or "probiotic"or"India". The search was conducted in June 2017 and 488 publications were identified. However, 150 articles which met our criteria were selected and reviewed.

Diabetes

Diabetes is a chronic metabolic disorder causing epidemic worldwide. The socio-economic condition of the people is highly affected due to this chronic metabolic disease. It is projected that emerging economies, India and China alone will lose around US $0.5 trillion and $0.25 trillion, respectively, as a result of these chronic diseases in the next decade (Daar *et al*., 2007). The incidence of type 2 diabetes (T2D) reaches 4–5% in Europe, 8–10% in the USA andmore in South Asia (WHO, 2004). It is expected that more than 70% of total diabetic patients inthe world will be from developing countries by year 2030 (Azimi-Nezhad *et al*., 2008). Over the last few decades, due to urbanization there is change in lifestyle and diet of the people and are important risk factors of T2D. T2D is the most common form of diabetes and accounts for almost 90% of all diabetes in high-income group and may account for an even higher percentage in low-income and middle-income countries and put a huge burden on healthcare agencies and governments (Guariguata, 2011). Type 2 diabetes mellitus is a metabolic chronic diseases which is characterized by insulin resistance which consequently lead to high blood glucose level in the blood. T2D is due to insufficient insulin production from β-cells of pancreas. Diabetes mellitus has also been associated with an increased risk for developing premature atherosclerosis due to an increase in triglycerides (TG) and low-density lipoproteins (LDL), and decrease in high density lipoprotein levels (HDL) (Betteridge, 1994). Multiple metabolic disorders including impaired lipid and lipoprotein metabolism, oxidative stress (over production of free radicals and defect in endogenous antioxidant defense system), sub-clinical inflammation, vascular endothelial dysfunction and hypertension are commonly accompanied by type 2 diabetes (Spranger *et al*., 2003; Bekyarova 2007; Gadi and Samaha, 2007). The pathogenesis of diabetes mellitus is caused by multiple risk factors and dysbiosis of gut microbiota is one of the important risk factors.

Human gut microbiota and type 2diabetes

It is estimated that the human microbiota contains as many as 10^{14} bacterial cells, a number that is 10 times greater than the number of human cells present in our bodies (Ley *et al*., 2006; Savage, 1977; Whitman *et al*., 1998) consisting of 300 to 1000 different species in the intestines (Turnbaugh *et al*., 2007). It is estimated that these gut flora have around 100 times as many genes in aggregate as there are in the human genome, which leads to establishment of new term among the scientific community and it is called metagenome. The intestinal microbiota contributed many important functions for its host which includes maturation of the gut, nutrition of the host, resistance to pathogens and the maintenance of host health (Stecher and Hardt, 2008). Low bacterial counts are found in the stomach (10-1000/ml content), increasing in the small intestine and rising to 10^{12}/ml in the colon. The diversity of microbial numbers is determined by both intrinsic and extrinsic factors. Intrinsic factor includes GIT sections and the extrinsic factor includes diet, stress, drugs etc. Microbiotas are present in all the sections of the GIT. The majority of the gut microbiota is composed of strict anaerobes, which dominate the facultative anaerobes and aerobes by two to three orders of magnitude (Gordon and Dubos, 1970; Harris *et al*., 1976; Savage, 1970). The composition of microbiota in the GIT vary with different part of the mammalian gut becoming more richer and diverse, from 10^{1}-10^{3} bacteria per ml of content in the stomach reaches upto 10^{11}–10^{12} bacteria per ml of colonic content. The colon contains an extremely rich microflora of approximately 400–500 microorganisms species, out of which 99.9% are anaerobic bacteria. Such diversity is probably due to the decreased intestinal motility and the very low potential for oxy-reduction in this region (Berg, 1996; Bourlioux *et al*., 2003; Hart *et al*., 2002; Salminen *et al*., 1995).

Microflora (gut microbiota) carries more than 3 million genes, which provides a broad range of functions and abilities for dynamical changes according to the factors of the environment (Burcelin *et al*., 2011). Human gut microbiotas are strongly involved in diverse metabolic, nutritional, physiological, and immunological processes, and changes in the composition of the gut microbiota directly influence the host's health (Kasubuchi *et al*., 2015; Tremaroli and Backhed, 2012). Recently, scientists and nutritionists have proposed that metabolic disorders might result from an alteration in gut microbiota composition (Kasubuchi *et al*., 2015; Nagatomo and Tang, 2015). Recent studies have manifested that gut microbiota is strongly associated with metabolic disorders (Delzenne *et al*., 2011; Greiner and Bäckhed, 2011). The proportions of the phylum Firmicutes and the class Clostridia are significantly reduced, whereas the class of the gram negative Betaproteobacteria is highly enriched in the faeces of type 2 diabetic hvcq1compared with non-diabetic individuals, and the proportion of Betaproteobacteria is positively correlated with plasma glucose levels (Larsen *et al*., 2010). High fat diets modify the intestinal microbiota, leading to increased intestinal permeability and susceptibility to microbial antigens, which ultimately correlates with the occurrence of metabolic endotoxemia and insulin resistance (Cani *et al*., 2007). It was studied that type 2 diabetes is associated with compositional changes in the intestinal microbiota with significantly lower relative abundance of *Firmicutes* whereas the proportion of *Bacteroidetes* and *Proteobacteria* is higher in diabetic patients compared to healthy controls (Larsen *et al*., 2010). Other studies have previously confirmed that reduction in *Bacteroides* and *Prevotella* is associated with noticeable decrease of metabolic endotoxemia and inflammation in type 2 diabetes mice (Cani *et al.,* 2009). Cani and co-workers hypothesized that the presence of gram negative bacteria in the

gut is connected with metabolic diseases, which is offering a likely explanation of the differences between the diabetic and nondiabetic microbiomes (Cani *et al*., 2009). The microbiome of type 2 diabetic patients are characterized by the depletion of several butyrate-producing bacteria, including Clostridium species, Eubacterium rectale, Faecalibacterium prausnitzii, Roseburia intestinalis and Roseburia inulinivorans (Qin *et al*., 2012, Karlsson *et al*., 2013). A recent study suggests that a higher blood glucose concentration may be predicted by a reduction in the proportion of anaerobes, particularly Bacteroides (Sepp *et al.,* 2014). Qin *et al*. (2012) have developed a protocol for a metagenome-wide association study based on deep shotgun sequencing of the gut microbial DNA extracted from fecal samples from Chinese T2D patients and nondiabetic controls. They identified 47 metagenomic linkage groups in the T2D-associated gene markers from the gut metagenome. Their results showed that patients with T2D had a moderate degree of gut microbial dysbiosis, a reduction in the abundance of some butyrate-producing bacteria, and an increase in various opportunistic pathogens.Short-chain fatty acids (SCFAs) such as butyrate, propionate and acetate are the metabolites produced by the gut microbiota which are investigated for its interference with host metabolism.These molecules are produced by the microbial fermentation of specific oligo- or polysaccharides (i.e. non-digestible carbohydrates) via distinct metabolic pathways(Reichardt *et al*., 2014). SCFAs bind to G protein coupled receptors (GPCRs) and exert various biological effects, including the regulation of glucagon-like peptide-1 (GLP1), which is associated with the improvement of insulin secretion and thus, lower glucose level (Tremaroli and Bäckhed, 2012).

Probiotics as biotherapeutic of type 2 diabetis

The existence of concept of probiotics took place around 1900, when Nobel Prize-winning Eli Metchnikoff in 1908 at the Pasteur Institute suggested that "the dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes" (Metchnikoff, 1908). According to the expertpanel of Food and Agriculture Organization of the UnitedNations (FAO) and the World Health Organization (WHO), (FAO/WHO, 2002) defined probiotic as "live microorganisms which when administered in adequate amounts confer a health benefit on the host". Most commonly used microbes as probiotics are lactobacilli and bifidobacteria. The health benefits derived by the consumption of foods containing probiotic bacteria are well documented and more than 90 probiotic products are available worldwide (Shah, 2000). Probiotics play an important role to improve the health of the host by restoration of the disturbed gut microbiota. Products containing probiotic bacteria have been increasingly applied to prevent or treat numerous disorders such as irritable bowel syndrome, inflammatory bowel disease, chronic idiopathic constipation, obesity, allergic and pulmonary diseases, and various types of diarrhea (Floch, 2014) A growing body of evidence suggests that favorable associations exist between probiotic consumption and metabolic profile among diabetes subjects (Kasińska and Drzewoski, 2015; Dolpady *et al*., 2016). In an animal study, researchers observed that a fermented milk product containing probiotic bacteria significantly delayed the onset of glucose intolerance, hyperglycemia, and hyperinsulinemia in diabetic rats induced by high fructose concentration (Yadav *et al*., 2007). In elderly T2D patients who consumed a daily dose of 200 mL of a symbiotic drink containing 108 CFU/mL *Lactobacillusacidophilus*, 108 CFU/mL *Bifidobacterium bifidum* and 2 g oligofructose over over 30 d, there was a significant increase in high-density lipoprotein cholesterol and a significant reduction in fasting glycemia (Moroti *et al*., 2012). In another investigation, patients with T2DM who consumed 300 g/d of probiotic yogurt containing *L. acidophilus* La5 and *Bifidobacteriumlactis* Bb12 for 6 wk had a significant reduction in fasting glycemia and hemoglobin (Ejtahed *et al*., 2012). Probiotic yogurt containing multiple Bifidobacterium strains has been studied to augment fasting blood glucose, plasma insulin and triglyceride levels in high-fructose-fedrats (Yin *et al*., 2010). Therapeutic probiotics that can manipulate the gut microbiota may also prevent some of the risk factors underlying the development of metabolic syndrome, including dyslipidaemia, increased fasting glucose levels and insulin resistance (Kootte *et al*., 2012).

Shubat, a type of camel milk fermented with lactic acid bacteria, had significant hypoglycaemic potentials and modulated lipid metabolism and protected renal function in rats with T2D (Manaer *et al*., 2015). VSL#3, a commercially available mixture of probiotics containing 3 × 1011 CFU/g of *Bifidobacterium longum, B. infantis* and *B. breve*, has been shown to improve insulin signalling and reduce inflammation in the adipose tissue of ApoE−/− rats (Mencarelli *et al*., 2012).In previous studies, oral administration of probiotics in T2D mice reduced blood glucose levels, improved antioxidant status, regulated disorders of lipid metabolism and controlled inflammation (Tabuchi *et al*., 2003; Calcinaro *et al.,* 2005; Manaer *et al*., 2015).Hulston *et al*., 2015 reported probiotics consumption to have a positive influence on blood glucose concentration and insulin sensitivity in healthy subjects fed with an obesogenic diet. *Lactobacillus plantarum* CCFM0236 has potential hypoglycaemic ability by ameliorating insulin resistance, antioxidant capacity and systemic inflammation in mice (X Li *et al*., 2016). It has been shown that *Lactobacillus acidophilus, L.fermentum, L. gasseri* and *L. rhamnosus* modulate the expression of genes encoding junction and adhesion proteins E-cadherin and β-catenin, and reduce the expression of protein kinase C-δ (PKC-δ) (Hummel *et al*., 2012). It has been suggested that probiotics may increase GLP-1 secretion fromenteroendocrine L-cells to improve carbohydrate metabolism, decrease glucotoxicity andincrease insulin sensitivity of target cells (Tremaroli and Bäckhed, 2012).

Conclusion

Homoeostasis of gut microbiota is vital for good health. Dysbiosis of human gut microbiota is associated with the occurrence of type 2 diabetes. The concept of probiotic for the management of T2D has good prospects since it is inexpensive and no side effects. Evidences from clinical trials reported that there is positive potential of probiotic in management of T2D.However, more well conducted clinical trial are required in future to prove its efficacy and safety for its acceptance by the consumer. In order to fully utilize the biotherapeutic potential of probiotic, its mechanism of action should be investigated at molecular level.

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