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RESEARCH ARTICLE

A COMPREHENSIVE REVIEW ON MANAGEMENT OF TYPE 2 DIABETES THROUGH PROBIOTICS

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Abstract

In the recent time, people are often biased to decide an appropriate medicine to recover a chronic disease. This critical biasness is occurred due to use of some commercial drugs, which have prominent side effects. Probiotics is a promising approach for the upcoming eras. Probiotics are the live microbial food additives which give health beneficiary effects beyond basic nutrition upon consumption in adequate amount. In the recent time, consumption of probiotics based foods are increased and probiotics based foods like yoghurt is one of the best stratagies to overcome diabetes. Yoghurt is a potential source of probiotic lactobacilli. Dahi is a home made variant of yogurt. Dahi has been considered as a functional food due to its several health benefits i.e. antidiabetic, antidiarreal, anticarcinogenic, cholesterol lowering and antiatherogenic properties. In this review management of type 2 diabetes through probiotics are critically discussed.

Introduction:-

Diabetes is a life threatening, complex, chronic disease and it's a condition when the pancreas does not produce enough insulin (a hormone that manages blood sugar, or glucose), or when the body cannot effectively use the insulin it produces. It generally requires continuous medical supervision with multifactorial risk-reduction programmes beyond glycemic control. Diabetes is a major public health problem, one of four priority non communicable diseases (NCDs) targeted for action by world leaders. Both the number of cases and the prevalence of diabetes have been steadily increasing day by day (WHO, 2016; WHO, 2019; ADA, 2019).

Globally, in 2014 an approximate 422 million adults were living with diabetes, compared to 108 million in 1980. The worldwide prevalence (age-standardized) of diabetes had almost doubled since 1980, rising from 4.7% to 8.5% in the adult population. This indicates an expand in associated risk factors such as being overweight or obese. In low- and middle-income countries, diabetes prevalence has risen faster than high-income countries. In 2012, diabetes generated 1.5 million deaths. An extra 2.2 million deaths is caused by higher-than-optimal blood glucose and for this the risks of cardiovascular and other diseases is increased over the past decades. 43 percent out of these 3.7 million deaths occur below the age of 70 years. In case of low- and middle-income countries, percentage of deaths due to diabetes occurs prior to age 70 is higher than in high-income countries. To distinguish between type 1 diabetes (which requires insulin injections for survival) and type 2 diabetes (where the body cannot properly use the insulin it produces), advanced laboratory tests is required. Type 2 diabetes affected patients are higher than Type 1 diabetes. Type 2 diabetes affected patients are more common in adult population but now a days it occurs in children too (WHO, 2016).

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Type 2 diabetes (non-insulin-dependent or adult-onset diabetes) occurs due to the body's ineffective use of insulin. Type 2 diabetes accounts for the huge majority of people with diabetes around the world. Signs may be similar to those of type 1 diabetes, but are often less marked or not present. If a type 2 diabetes patient is not checked by doctor for several years, different complications would be arised (WHO, 2016; WHO, 2019).

Quality of life and prevention of DM-related microvascular and macrovascular complications in diabetic patients is improved by managing blood glucose level. Nutritional therapy is a better option for the management of DM-related complications. In earlier times, before the discovery of insulin, nutritional therapy was a better option for the management of DM-related complications. In the present time, insulin and other oral/injectable hypoglycemic agents are being used for controlling Type 1 DM as well as Type 2 DM (T2DM). Due to the excessive cost of treatment and several side effects like as sudden hypoglycemia, lactic acidosis, multiple organ damage, and digestive discomfort, associated with the long time use of present-day antidiabetic drugs, safer and alternate methods for the management of DM is crying need for the type 2 diabetes patients (Sharma et al., 2016).

Probiotics are the live microbial food additives which give health benefiary effects beyond basic nutrition upon consumption in adequate amount (FAO/WHO, 2001). The effect of probiotic benefits have been investigated for improving immune function, lowering blood pressure, and improving lipids. There are different strains of lactic acid bacteria (LAB), such as Lactobacillus and Bifidobacterium are considered as important probiotics regimens. Fermented dairy products such as yogurt, containing adequate probiotic LAB, are well established for several health benefits (Reid et al., 2005).

There are several reports available which suggest the antidiabetic effect of LAB (Lactic acid bacteria). Administration of *Lactobacillus casei* by orally has a preventive effect on promotion of plasma glucose and depletion of plasma insulin levels by preventing immune mediated destruction of pancreatic b-cells in NOD and KK-Ay mice (Matsuzaki et al., 1997a, b & c). Oral administration of dahi containing *Lactobacillus acidophilus* & *Lactobacillus casei* detained the succession of streptozotocin induced diabetes in rats (15 gm/day/rat) for 28 days (Yadav et al ., 2008).

Several research reflects that diabetic patients have altered gut microbiota compared to non-diabetic counterparts and gut microbiota are involved in the occurrence of diabetes and metabolic disorders. So therefore gut microbiota of type 2 diabetic person would be changed by using probiotics and it's a recent field of interest to the researchers. Human clinical trials of probiotic capsules or yoghurt was conducted and yielded mixed results. Some studies indicate that probiotic yogurt ingestion for 6 weeks can significantly improve blood glucose level. (Ruan et al ., 2015). From this point of view, management of type 2 diabetes through probiotics are reviewed.

Definition of probiotics:

The term probiotic is come from the Greek language defining "for life"but the meaning of probiotics has evolved over time concurrently with the expanding interest in the use of live bacterial supplements and in relation to the progress made in understanding their mechanisms of action. Here the term was used to describe the stimulation of the growth of others microorganisms by substances produced by one microorganism and was later used to describe tissue extracts that stimulated microbial growth and animal feed supplements applying a beneficial effect on animals by contributing to their intestinal flora balance(Fuller et al .,1999). More updated definition of probiotics is "probiotics are live microbial feed supplements which beneficially affect the host animal by improving microbial balance" (Fuller et al .,1989). According to FAO, probiotics is defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host". (FAO/WHO, 2001).

Characteristics of probiotics:

Probiotics is well characterized by their capability to survive for an unspecified time period in the upper digestive tract and to colonize in the intestinal lumen and colon. It is reported that functional foods containing probiotics are safe for the consumers and already no hazardous reports have found or production of any particular toxins by these strains(Von et al .,2000&Salminen et al ., 1998). It is also reported that antimicrobial substances like bacteriocins are produced by some probiotics. Temporarily the rate of mitosis in enterocytes is increased by some probiotic strains and they can reduce intestinal transit time, improve the quality of migrating motor complexes (Husebye et al .,2001). *Lactobacillus* and *Bifidobacterium* are the most common probiotics and in general most the probiotics are gram-positive, usually catalase-negative, rods with rounded ends, and occur in pairs, short, or long chains,non-flagellated, non-motile and non-spore-forming, and are intolerant to salt, optimum growth temperature is 37°C but

some strains such as *L. casei* prefer 30 °C and optimum pH for initial growth is 6.5-7.0(Von et al .,2000).*L. acidophilus*is microaerophilic,anaerobic and they have capability of aerobic growth. Bifidobacteriumare also anaerobic but some species are aero-tolerant. In according to probiotics fermentation capacity, they are either obligate homofermentative (*L. acidophilus, L. helvelicas*), obligate heterofermentative (*L. brevis, L. reuteri*), or facultative heterofermentative (*L. casei, L.plantarum)* (Barrangou et al., 2011). Various beneficial compounds are secreted by probiotics such as antimicrobials, lactic acid, hydrogen peroxide, and a variety of bacteriocins (Holzapfel et al., 2001&Gorbach et al.,2002) and it's very necessary for healty gut environment.Interaction with the host microflora and competitor for microbial pathogens (Gorbach et al .,2002).

Selection Criteria and Requirements for Probiotic Strains:
In accordance of the WHO, FAO, and EFSA (The European Food Safety Authority), probiotic strains must be fulfill both safety and functionality criteria and these criteria should also fulfill their technological usefulness. Some selection criteria of probiotic strains is given in table 1.

Table 1:- Selection criteria of probiotic strains (FAO guidelines 2002 and EFSA 2005).

Criterion	Required Properties
Safety	(a)Human or animal origin. (b)Isolated from the gastrointestinal tract of healthy individuals. (c)History of safe use. (d)Precise diagnostic identification (phenotype and genotype traits). (e) Absence of data regarding an association with infective disease. (f)Absence of the ability to cleave bile acid salts. (g)No adverse effects. (h)Absence of genes responsible for antibiotic resistance localised in non-stable elements.
Functionality	(a)Competitiveness with respect to the microbiota inhabiting the intestinal ecosystem. (b)Ability to survive and maintain the metabolic activity, and to grow in the target site. (c)Resistance to bile salts and enzymes. (d)Resistance to low pH in the stomach. (e)Competitiveness with respect to microbial species inhabiting the intestinal ecosystem (including closely related species). (f)Antagonistic activity towards pathogens (e.g., *H. pylori*, Salmonella sp., Listeria monocytogenes, *Clostridium difficile*). (g)Resistance to bacteriocins and acids produced by the endogenic intestinal microbiota. (h)Adherence and ability to colonise some particular sites within the host organism, and an appropriate survival rate in the gastrointestinal system.
Technological usability	(a)Easy production of high biomass amounts and high productivity of cultures. (b)Viability and stability of the desired properties of probiotic bacteria during the fixing process(freezing, freeze-drying), preparation, and distribution of probiotic products. (c)High storage survival rate in finished products (in aerobic and micro-aerophilic conditions). (d)Guarantee of desired sensory properties of finished products (in the case of the food industry). (e)Genetic stability. (f)Resistance to bacteriophages.

Probiotic Microorganisms:
To make a consumable probiotic fermented product selected microbial species and their strains are needed and such microorganisms are *Lactobacillus*, *Bifidobacterium*, and *Lactococus*,*Streptococcus*, *Enterococcus* etc. Bacillus and Saccharomyces strains are more commonly used to make a good Probiotic product. (Simon et al .,2005).

Usually one or mixed microbial strains are involvrd to make a probiotic product. *Lactobacillus, Bifidobacterium, and Lactococus,Streptococcus, Enterococcus* are known as human probiotic microorganisms.Beside these strains bacillus and some yeast strains belonging to the genus Saccharomyces are commonly used to make a good qualityful probiotic products(Simon et al .,2005).Some probiotic microorganisms used in human nutrition is given in Table 2.

Table 2:- Probiotic microorganisms used in human nutrition.

Type *Lactobacillus*	Type *Bifidobacterium*	Other Lactic Acid Bacteria	Other Microorganisms
L. acidophilus (a),* *L. amylovorus* (b),* *L. casei* (a),(b),* *L. gasseri* (a),* *L. helveticus* (a),* *L. johnsonii* (b),* *L. pentosus* (b),* *L. plantarum* (b),* *L. reuteri* (a),* *L. rhamnosus* (a),(b),*	*B. adolescentis* (a) *B. animalis* (a),* *B. bifidum* (a) *B. breve*(b) *B. infantis* (a) *B. longum* (a),*	*Enterococcus faecium* (a) *Lactococcuslactis* (b),* *Streptococcus thermophilus* (a),*	*Bacillus clausii* (a),* *Escherichia coli*Nissle 1917 (a) *Saccharomyces cerevisiae* (*boulardi*) (a),*

Legends: (a)Mostly as pharmaceutical products;(b) mostly as food additives; *QPS (Qualified Presumption of Safety) microorganisms.

I. health benefits & clinical uses of probiotics:

II. there are lot of benefits of probiotics.some health benefits and clinical uses of probiotics is given table 3.

Table 3:- Health benefits and clinical uses of probiotics.

Application	Description
01.Enhances lactose digestion	Bacterial micro flora resides in the small intestine enhances lactose digestion and it is possibly done possibly by increasing connection between lactose and lactase.(Shah, 2000)
02. Lowering blood glucose level in case of diabetes melitus	Probiotics are effective for the diabetic patients by balancing microbial gut flora. It is reported that Low-fat (2.5%) yoghurt containing probiotics *Lactobacillusacidophilus* and *Lactobacillus casei* was tested in rats against high fructose-induced type-2 diabetes and both of these bacteria proved beneficial effect in lowering blood glucose level by decreasing insulin resistance (Yadav et al.,2006). *Bifidobacteriumspp* is an important probiotics and it is reported that this bacteria delivers pharmaco nutritional support in treating insulin resistance. (Cani and Delzenne, 2011).
03. Hypocholestrolemic effects	Probiotics has hypocholestrolemic effects and it is found that that lactobacillus-fermented milk has hypocholestrolemic effects (Mann and Spoerry, 1974).
04. Management of colon cancer	Now a days management of colon cancer is a thinking issue. In case of animal studies it is proved the beneficial effects of LAB against colon cancer of rodents. In human trials it is also suggested that some types of LAB are anti-carcinogenic due to ability to lowering the activity of enzyme called β glucuronidase (which can generate cancer producing substances in the digestive system) (Brady et al., 2000).
05. Boosting up immune functions	Probiotics may boost up immune functions and they also inhibit the growth of harmful and bad gut bacteria. Immune cells like the IgA-producing cells, T lymphocytes and natural killer cells are boosted by some probiotics. The risk of urinary tract infections (UTIs) in women is reduced by *Lactobacillus crispatus* and it is reduced by 50%. Source:(https://www.healthline.com)
06.Reduction of liver diseases	Probiotics are very effective in the treatment of chronic liver diseases and they stop the entry of pathogenic microorganisms to blood flow and eventually to liver by increasing the strength of intestinal barrier (Cesaroet al.,2011).
07.Controlling the causes of dental caries	The number of mutant strain of *streptococci* (causal agent of dental caries) is reduced by using probiotics containing products. (Naseet al., 2001; Cildir et al.,2009;

	Haukioja, 2010).
08. Reduction of halitosis	For gut and mouth mediated halitosis ,using of probiotic product is a better option. (Delanghe et al., 1997).
09. Reduction of Oral candidiasis	*L. rhamnosus*strain is very effective in the reduction of the candida yeast count. (Haukioja, 2010).
10.Against viral infections	It is reported that the efficacy of antiinfluezal and anti herpetic effect of several *Thermophilus* species is high in guinea-pigs(Liaskovs et al., 2007).
11. Improvement of Digestive System	Probiotics are commonly found in fermented foods and they may help to balance the friendly bacteria in our digestive system. Source:(https://www.healthline.com/nutrition/)
12.Prevention of diarrhea	Probiotics used as a well known biotherapeutic agent in the prevention of diarrhea or reduce its severity.It is reported that probiotics reduced antibiotic-associated diarrhea by 42% and also reduced the risk of travelers' diarrhea by 8%.The most commonly associated with a reduced risk of diarrhea are *Lactobacillus rhamnosus*, *Lactobacillus casei* and the yeast *Saccharomyces boulardii* and the efficacy of reduction is dose dependent. Source:(https://www.healthline.com/nutrition/)
13. Improving Mental Health Conditions	Both experimental and clinical trials find that probiotic supplements can improve some mental health problems. It is reported that supplementing with *Bifidobacterium* and *Lactobacillus* strains for 1–2 months can improve anxiety, depression, autism, obsessive-compulsive disorder (OCD) and memory and it's a clinical trial findings. Source:(https://www.healthline.com/nutrition/)
14. Keeping heart healthy	Probiotics keeps our heart healthy. It is reported that certain lactic acid-producing bacteria may reduce cholesterol by breaking down bile in the gut.It is also reported that administration of a probiotic yogurt for 2–8 weeks reduced total cholesterol by 4% and LDL cholesterol by 5%. Source:(https://www.healthline.com/nutrition/)
15.Reduction of the Severity of Allergies and Eczema	In case of allergies and eczema the efficacy of probiotic strains is so high and some strains may reduce the severity of eczema in children and infants. It is reported that eczema symptoms improved for infants fed probiotic-supplemented milk, compared to infants fed milk without probiotics. Source:(https://www.healthline.com/nutrition/)
16.Reduction of the Symptoms of Certain Digestive Disorders	It is reported that *Bifidobacterium* and *Lactobacillus* strains have improved signs in people with mild ulcerative colitis. Source:(https://www.healthline.com/nutrition/)
17. Reduction of the belly fat& lead to weight gain	Several studies reported that, certain probiotics, such as *Lactobacillus acidophilus*, can even lead to weight gain. Another report suggested that, dieting women who took *Lactobacillus rhamnosus* for 3 months lost 50% more weight than women who didn't take a probiotic. Another study suggested that, intake of *Lactobacillus gasseri* for 12 weeks resulted in an 8.5% reduction of belly fat. Source:(https://www.healthline.com/nutrition/)

Diabetes mellitus:

Diabetes mellitus, generally people called it diabetes, is a chronic condition and it occurs when there are elevated levels of glucose in the blood because the body cannot produce any or enough of the hormone insulin or use insulin effectively(De Fronzo et al .,2015). A common effect of uncontrolled diabetes is elevation of higher blood glucose level over time and lead to serious damage to the heart, blood vessels, eyes, kidneys and nerves. It is reported that more than 400 million people live with diabetes(WHO, 2016). The number of people with diabetes worldwide and per region in 2017 and 2045 (20-79 years) is given in Figure 1(IDF Atlas).

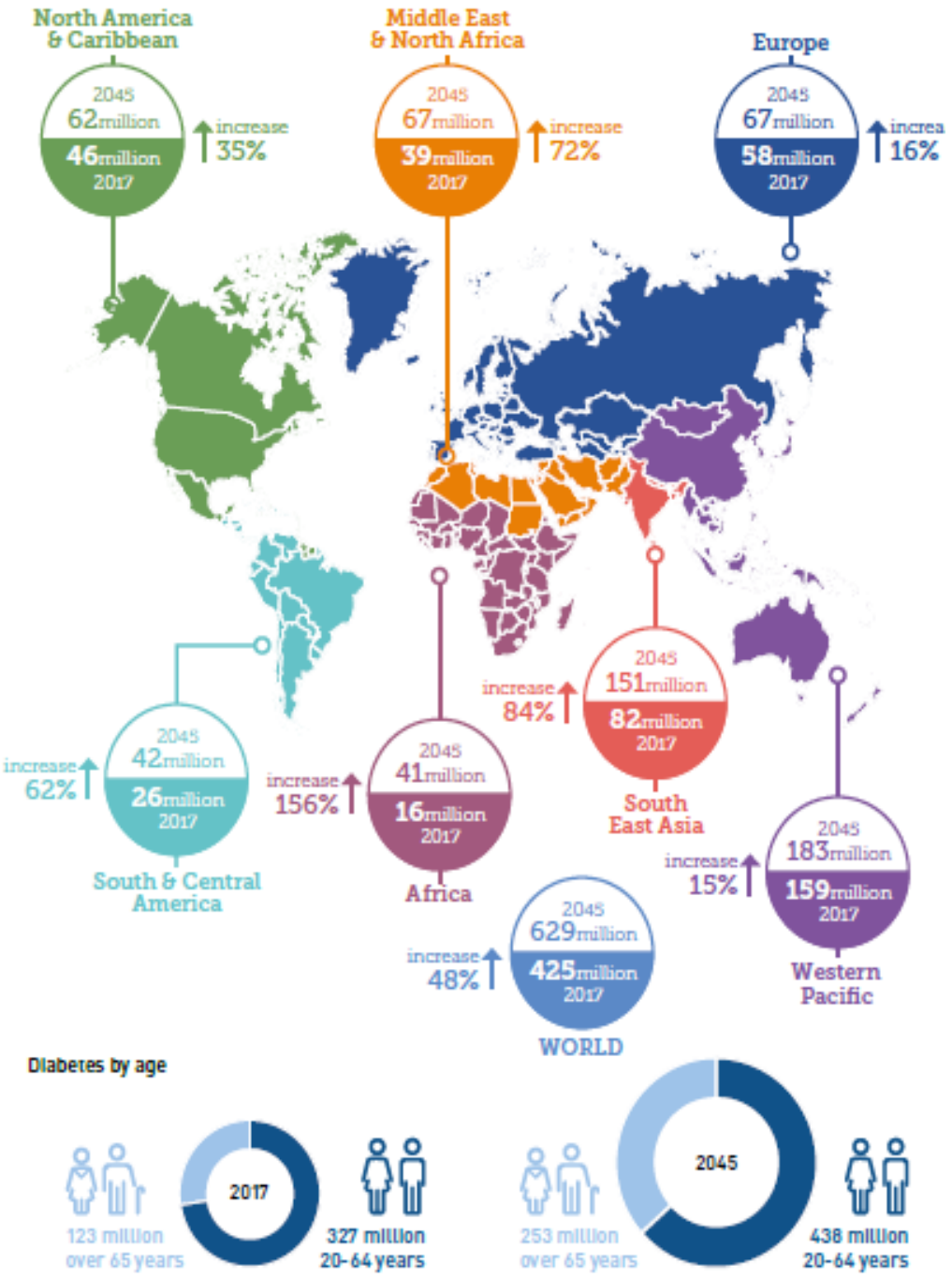

Fig 1:- Number of people with diabetes worldwide and per region in 2017 and 2045 (20-79 years).

Complications of diabetes:

All types of diabetes lead to many complications. It happens in many parts of the body and can enhances the overall risk of dying prematurely. Some major complications are heart attack, stroke, kidney failure, leg amputation, vision loss and nerve damage. In the time of pregnancy period, poorly controlled diabetes increases the risk of fetal death and other complications.(WHO, 2016).Some major complications of diabetes is given in Figure 2.

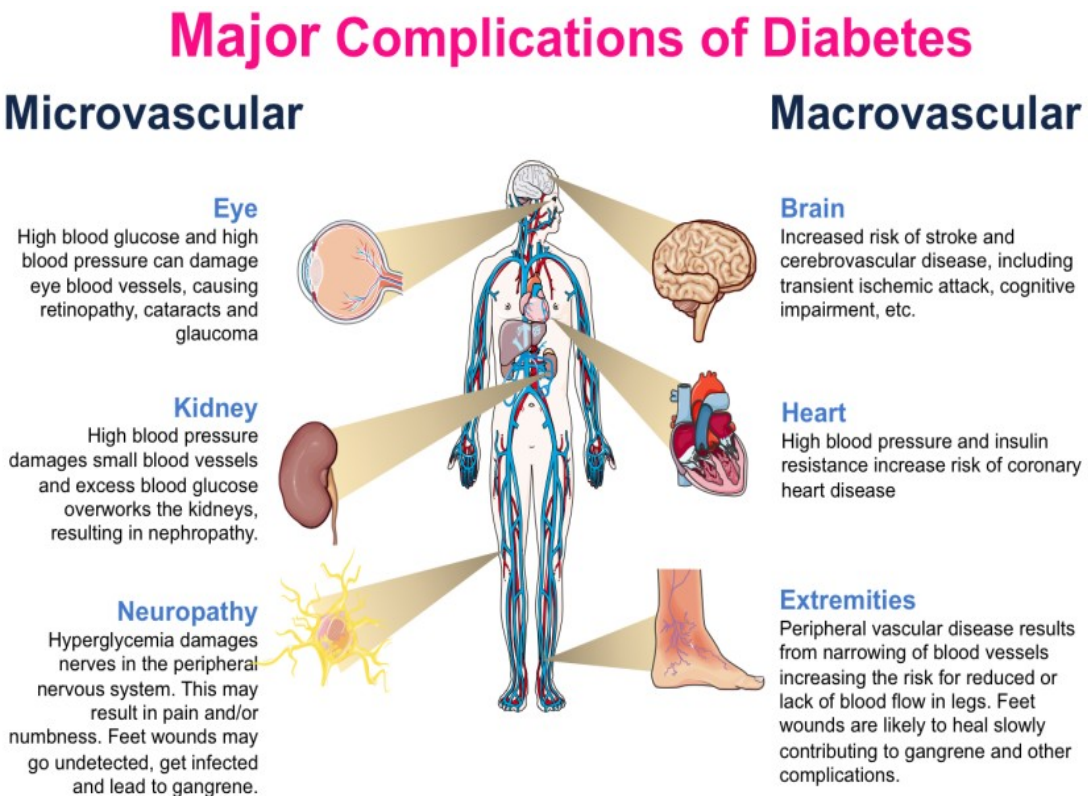

Fig 2:- Major microvascular and macrovascular complications associated with diabetes mellitus.

Classification of Diabetes mellitus:

Type 1 diabetes:

Type 1 diabetes (previously known as insulin-dependent, juvenile or childhood-onset diabetes) is identified by lack of insulin production in the body. Routinely administration of insulin is crying need for type 1 diabetes patients to control the amount of glucose in their blood. It is very risk to survive a type 1 diabetes patients without the uptaking of insulin in their body externally. Causes of type 1 diabetes is not known and still it is currently not preventable. Signs of type 1 diabetes are excessive urination and thirst, constant hunger, weight loss, vision changes and fatigue.(WHO, 2016). There are lot of symptoms around type 1 diabetes patients. Some are given in Figure 3.

Fig 3:- Symptoms around type 1 diabetes patients. (IDF atlas).

Type 2 diabetes:
Type 2 diabetes (formerly called non-insulin-dependent or adult onset diabetes) is more common than type 1 diabetes and it results from the body's ineffective use of insulin. Around the world, majority of people who has diabetes are type 2(World Health Organization; 2016.). Symptoms are alike to type 1 diabetes, but are often less marked or absent. If a patient who has type 2 diabetes but still undiagnosed for several years, then he would be in massive trouble or complications. It is more common in adults but in the recent time it also found in children. There are lot of symptoms around type 1 diabetes patients .Some are given in Figure 4.

Fig 4:- Symptoms around type 2 diabetes patients. (IDF Atlas).

Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG):
Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are in-between state in the transition between normal blood glucose levels and diabetes (especially type 2), though the transition is not inevitable. People who has this situation ,they are at increased risk of heart attacks and strokes.
d) Gestational diabetes (GDM)

Gestational diabetes (GDM) is occurs in pregnancy and it's a non permanent condition and also bear a long term risk of type 2 diabetes (Bellamy et al .,2009).The condition is present when blood glucose values are over normal but still under those diagnostic of diabetes. During pregnancy and delivery, women with gestational diabetes are at increased risk of some complications as are their infants. By prenatal screening gestational diabetes is diagnosed, rather than reported symptoms.

Gut Microbiota:
Gut is an important organ in human body. Medical literature refers, the gut microbiota as an 'exteriorized organ'(Zhu et al .,2010).A human body is host to 100 trillion bacteria and it is more higher than human cells in our body(Ramakrishna et al .,2007). Microbiome is a collective name and it is the total the genetic material of the intestinal microbes and it already exceeds the magnitude of the human genome(Fig 5) over 100 times (Eckburg et al .,2005, Gill et al .,2006, Palmer et al ., 2007 and Zhu et al .,2010).

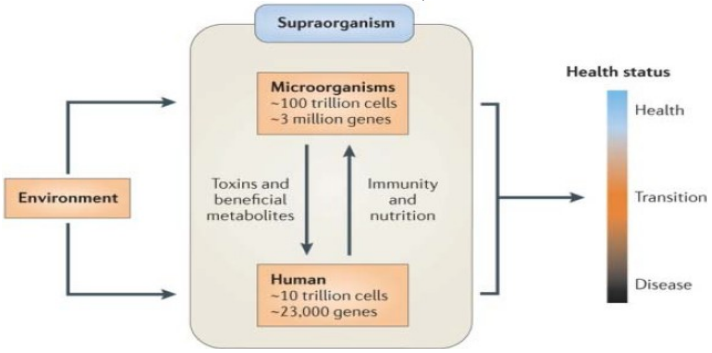

Fig 5:- Amount of cells in humans and microorganisms resides in intestinal microflora.

Microbiome. Gram negative Bacteroides, Proteobacteria and Verrucomicrobia as well as gram positive Firmicutes and Actinobacteria are the phyla that account for the vast majority of all gutmicrobes (Eckburg et al .,2005, Zhu et al .,2010 Arumugam et al ., 2011 and Zoetendal et al .,2008). From stomach to small intestine,the microbial population of the gut increase in density. In the stomach, microbial population of the gut is very sparse and it is due to luminal acidity and vigorous peristalsis. From duodenum to jejunum to ileum, microbial population is also increases in density. In duodenum the population is 10^1-10^3 organisms/ml, In jejunum 10^4-10^6 organisms/ml) and in ileum it is 10^5-10^7 organisms/ml (Fig 6).

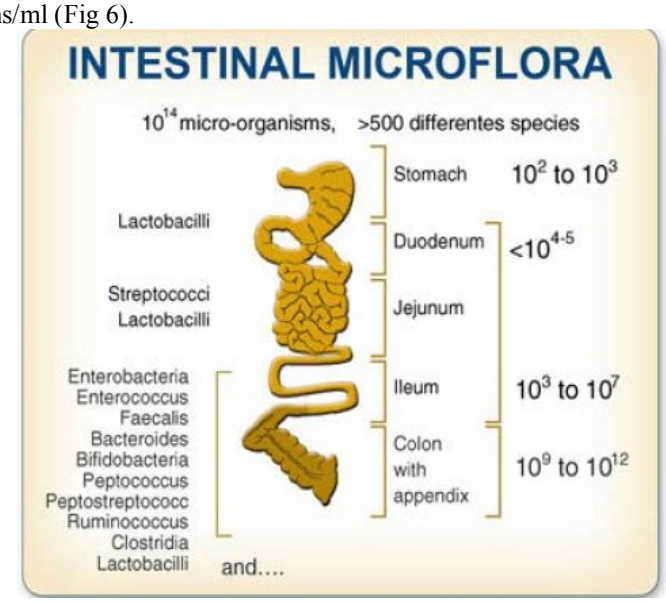

Fig 6:- Amount of microorganisms in intestinal microflora.

In the large intestine, microbial population is 10^{11}-10^{12} organisms/g of stool (Ramakrishna et al .,2007).

Probiotics and type 2 diabetes preventing mechanism:

Probiotics are live microorganisms and they show several health benefits.Some probiotics i.e. *Lactobacillus*, *Bifidobacteria* has effect on type 2 diabetes. These bacteria uses some mechanism collaborately and in a specialized way they lowered blood glucose level.They show satinogenic and insulionotropic effect and they also secrete gut hormone like GLP1,GLP2 etc. and these way lowered blood glucose level in type 2 diabetes patients(Fig 7).

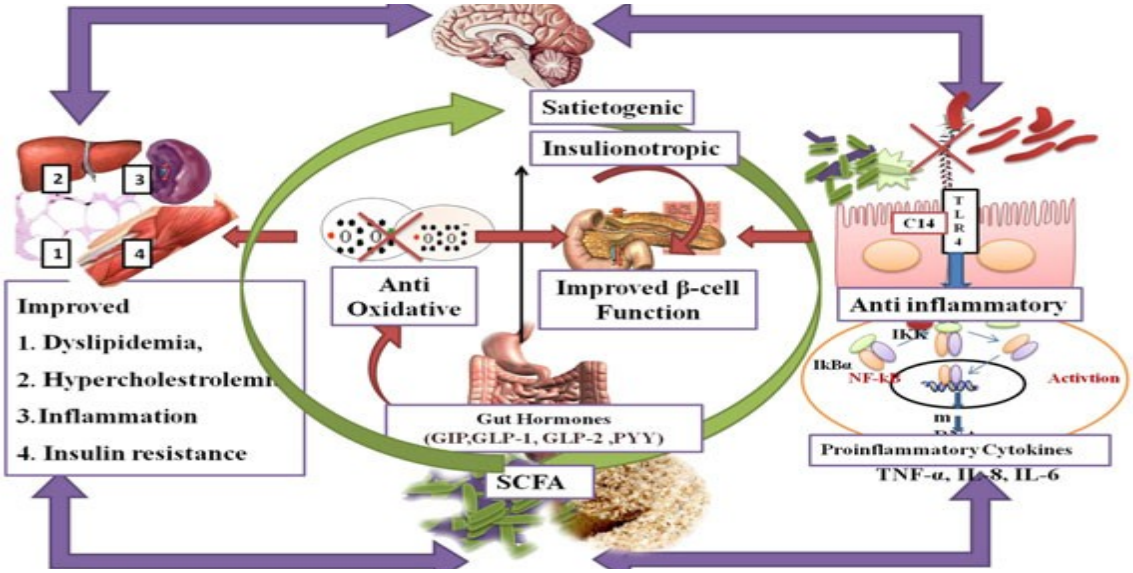

Fig 7:- Probable mechanisms of probiotics action in the management of type 2 diabetes

Some Potential mechanisms linking probiotics to diabetes is given Table 4.

Table 4:- Potential mechanisms linking probiotics to diabetes.

Study	Study design, animals or participants	Probiotic strain	Mechanisms suggested
01.Tian et al.	Experimental study. High fat diet and streptozotocin-induced type 2 diabetic rats	*Lactobacillus paracasei*subsp. *paracasei* G15 and *Lactobacillus casei*Q14	• reducing the intestinal mucosal permeability and improving the epithelial barrier function through modification of the gut microbiota and preventing translocation of bacterial lipopolysaccharides into systemic circulation
02.Duan et al.	Experimental study. Diabetic rats	Human *lactobacilli* engineered to secrete GLP-1(1-37)	• reprograming intestinal cells into glucose-responsive insulin secreting cells
03.Holowacz et al.	Experimental study. High-fat-diet C57/BL6J mice	Multispecies *Lactobacillus*-and*Bifidobacterium*-containing probiotic mixture	• reducing expression of the gene encoding CCL-2 • preventing macrophage infiltration of adipose tissue and insulin resistance
04.Le et al.	Experimental study. C57BL/6J mice with streptozotocin (STZ)-induced diabetes	*Bifidobacterium*species(spp.)	• increasing the levels of proteins related to innate immune responses • reducing transcription of target genes such as those of pro- inflammatory cytokines • inducing differentiation of adipocytes into a cell type capable of inducing insulin sensitivity in diabetic mice
05.Park et al.	Experimental study. C57BL/KsJ-db/db (db/db) mice Experimental study	*Lactobacillus rhamnosus*GG	• reducing infiltration and activation of macrophage in white adipose tissues

06.Stenman et al.	Male C57Bl/6J mice	*Bifidobacteriumanimalis*s sp.*lactis*420 (B420)	• increasing the ileum GLP-1 concentration and increasing the amount of insulin released from pancreatic beta cells.
07.Wei et al.	Experimental study. Streptozotocin-induced type 1 diabetic mice	*Lactobacillus kefiranofaciens*M and *Lactobacillus kefiri* K	• modulating the gut microbiota by increasing the number of Gram-positive and decreasing the number of Gram-negative bacteria • inhibiting the pro-inflammatory and inflammatory cytokines, and elevating the production of IL-10.
08.Everard et al.	Experimental study. Type 2 diabetic db/db mice	*Saccharomyces boulardii*	• changing the gut microbiota composition
09.Kim et al.	Experimental study. Rat L6 skeletal muscle cells and KK-AY mouse NIDDM model	*Bifidobacteriumlactis*HY8101	• increasing the mRNA expressions of pp-1, GLUT4, and PPAR-γ, and decreasing the mRNA expressions of GSK-3β, and G6PC (all involved in glucose metabolism and insulin sensitivity)
10.Zhang et al.	Experimental study. HFS diet-induced pre-insulin resistance and a low dose-STZ HFS rats	*Lactobacillus casei*	• microbiota-based bile acid-chloride exchange mechanism: decrease in the number of bile acid 7α-dehydroxylating activity possessing bacteria, bile acid elimination, upregulating of chloride ion-dependent genes (ClC1-7, GlyRa1, SLC26A3, SLC26A6, GABAAa1, bestrophin-3 and CFTR) and prevention of chloride ion loss.
11.Li et al.	Experimental	*Lactobacillus plantarum*	• increasing short-

	study. Type 2 diabetes in rats	NCU116	chain fatty acids (SCFA) such as butyric acid in colon which leads to the growth of *lactobacilli* and *bifidobacteria* and in lowering intestinal pH and to increased GLP-1 secretion • mRNAupregulation of glucose transporter-4 (GLUT-4) and regulation of the expression of PPAR-α and PPAR-γ
15.Bejar et al	Experimental study. Alloxan-induced diabetes in rats	*Lactobacillus plantarum* TN627	• decreasing serum α-amylase activity, thus limiting the process of carbohydrate hydrolysis and absorption
12.Hsieh et al.	Experimental study. High fructose-fed diabetic rats	*Lactobacillus reuteri* GMNL-263	• stimulating GLP-1 secretion
13.Okubo et al.	Experimental study. KK/ Ta mice	*Lactobacillus plantarum* strain No. 14	• reducing the accumulation of visceral fat and preventing low grade inflammation and production of pro-inflammatory adipokines
14.Yadav et al.	Experimental study. C57J/B6 male mice	Probiotic VSL#3	• increasing the levels of butyrate, thus stimulating release of GLP-1 from intestinal L-cells
15.Amar et al	Experimental study.HFD-fed WT mice	*Bifidobacteriumanimalis*subsp. lactis 420 (B420)	• preventing mucosal bacterial adherence and translocation of live bacteria from the intestine towards adipose tissue and blood
16.Lau et al.	Experimental study.	*Lactobacillus johnsonii*N6.2	• mediating a TH17 bias within the mesenteric

	Bio-breeding diabetes- prone rats		lymph node and retention of the TH17 differentiation state without conversion to Th1 state
17.Zarfeshani et al.	Experimental study. Streptozotocin-induced diabetic rats	*Lactobacillus casei*	• reducing the onset of inflammation by lowering blood levels of IL6 and CRP and neutrophils
18.Aumeunier et al.	Experimental study. NOD mice	VSL#3 containing *Bifidobacterium, Lactobacillus* and *Streptococcus*	• stimulating toll-like receptors (TLRs) with immunoregulatory effects on anti-inflammatory cytokines such as interleukin-10 (IL10) and transforming growth factor beta (TGF-β)
19.Yadav et al.	Experimental study. Rats	Dahi containing probiotic *Lactobacillus acidophilus* and *Lactobacillus casei*	• inhibiting the lipid peroxidation and preserving the activity of antioxidant enzymes including SOD, GPx and catalase
20.Yadav et al.	Experimental study. Rats	Dahi containing *Lactobacillus acidophilus* and *Lactobacillus casei*	• inhibiting the elevation of thiobarbituric acid- reactive substances and decreasing reduced glutathione in the liver and pancreatic tissue
21.Calcinaro et al.	Experimental study. Female NOD mice	VSL#3 containing bifidobacteria, lactobacilli and *Streptococcus salivariussubsp. thermophilus*	• inducing a change in the cytokine secretion pattern from a pro-inflammatory to an anti-inflammatory profile by means of gut-associated lymphoid tissue (GALT)
22.Tabuchi et al.	Experimental study. Streptozotocin-induced diabetic rats	*Lactobacillus* GG	• using glucose as a source of nutrition or by controlling the intestinal flora balance and through similar activity such as indigestible fiber, thus affecting glucose absorption. • suppressing oxidative

			stress.
23.Matsuzaki et al.	Experimental study. Alloxan-induced diabetic mice	*Lactobacillus casei*	• preventing nitric oxide production (free radical) and ß-cell destruction in islets of Langerhans
24.Matsuzaki et al.	Experimental study. KK-Ay NIDDM model mice	*Lactobacillus casei*	• improving the disordered post immune responses via inhibition of the production of IL2 and interferon gamma (INF-γ) and reducing the increase of CD3+ and CD4+ T cells
25 .Ejtahed et al.	Randomized, double-blind, controlledclinical trial with type 2 diabetic patients, 30 to 60 years old	Probiotic yogurt containing *Lactobacillus acidophilus* La5 and *Bifidobacteriumlactis* Bb12	• increasing erythrocyte superoxide dismutase (SOD) and glutathione peroxidase (GPx) activity and total antioxidant status (TAS)

Effects of probiotic administration on diabetes mellitus in experimental studies:
Several *in vivo* study was conducted by several group of person and some experimental studies is given in Table 5.

Table 5:- Effects of probiotic administration on diabetes mellitus in case of experimental studies.

References	Probiotics	Type of cell/animal model	Quantity	Study period	Results
01. Amar et al .,2011	*Bifidobacteriumanimalis* subsp. lactis 420	C57BL/6, ob/ob, CD14−/−, ob/obxCD14−/−, Myd88−/−, Nod1−/−or Nod2−/−mice fed a high fat diet	10^9 CFU/day	6 weeks	Decreased TNF-α, IL-1β, PAI-1 and IL-6 Increased insulin sensitivity
02. Ivanov et al .,2008	*Lactobacillus johnsonii* N6.2 and *Lactobacillus reuteri* TD1	BB rats, NOD mice, and C57BL/6 mice	1×10^8 CFU/day	140 days	Positive TH17 phenotype modulation
03. Yadav et al .,2007	*L. acidophilus, L. casei,* and *L. lactis*	Male Wistar rats fed a high fructose diet	diet supplemented with 15% of dahi ad libitum	8 weeks	Decreased blood glucose, HbA1c, glucose intolerance, plasma insulin, liver glycogen, plasma total cholesterol, triacylglycerol, low-density lipoprotein cholesterol, very low-density

					lipoprotein cholesterol, and blood free fatty acids
04. Andersson et al.,2010	*L. plantarum* DSM 15313	Female C57BL/6 J mice fed a high fat diet	25×10^8 CFU/day	20 weeks	Decreased blood glucose
05. Mencarelli et al.,2012	VSL#3 (*L. acidophilus* MB 443,*L.delbrueckii* subsp. *bulgaricus* MB 453, *L. casei* MB 451, *L. plantarum*MB 452, *B. longum* Y10, *B. infantis* Y1, *B. breve* Y8, and *S. salivarius* subsp. *thermophilus* MB 455)	ApoE−/−C57BL6 male mice	25×10^8 CFU/day	12 weeks	Decreased Insulin; Decreased Glucose tolerance, Increased insulin signaling Decreased TNF-α and RANTES; Increased IL-10
06. Ma et al., 2008	VSL#3(*L. acidophilus* MB 443,*L.delbrueckii* subsp. *bulgaricus* MB 453, *L. casei* MB 451, *L. plantarum*MB 452, *B. longum* Y10, *B. infantis* Y1, *B. breve*Y8, and *S. salivarius* subsp. *thermophilus*MB 455)	NOD mice	1.5×10^9 CFU/day	12 weeks	Decreased Hepatic NKT cell depletion; Decreased IKKβ activity Decreased NF-κB binding activity Increased insulin signaling
07. Calcinaro et al., 2005	VSL#3(*L. acidophilus* MB 443,*L.delbrueckii* subsp. *bulgaricus* MB 453, *L. casei* MB 451, *L. plantarum*MB 452, *B. longum* Y10, *B. infantis* Y1, *B. breve*Y8, and *S. salivarius* subsp. *thermophilus*MB 455)	Female NOD mice	9 mg/week	70 weeks	Decreased incidence of auto-immune diabetes;Increased insulitis and decreased rate of β-cell destruction; Increased IL-10
08. Yadav et al., 2008	*Lactococcuslactis* ssp. *diacetylactis*NCDC 60, *L. acidophilus* NCDC 14, and *L. casei* NCDC 19	Male Wistar diabetic rats	15 g/day (8,83 CFU/g lactobacilli and 7,89 log CFU/g lactococci)	15 weeks	Increased gastric emptying dahi probiotic feeding did not change blood glucose levels; Decreased Thiobarbituric acid-reactive species in intestinal tissues; Decreased HbA1c
09. Lu et al., 2010	*L.reuteri* GMNL-263	Male Sprague–Dawley diabetic rats	1×10^9 CFU/day	4 weeks	Decreased HbA1c and blood glucose; Decreased JAK2 and STAT1 phosphorylation; Decreased PAI-1
10. Chen et al., 2012	*Bifidobacteriumadolescentis*	Male Wistar rats fed a high fat diet		12 weeks	Increased insulin sensitivity

Legends: HbA1c: Glycated hemoglobin; NF-kB: nuclear factor kappa B; LPS: Lipopolysaccharides; IκBα: inhibitory kappa B alpha; TNF-α: tumor necrosis factor alpha; IL-1β: interleukin-1 beta; PAI-1: plasminogen activator inhibitor-1; IL-6:interleukin-6; JAK2: Janus kinase 2; STAT1: signal transducer and activator of

transcription 1; IL-10: interleukin-10; IKKβ: inhibitors of kappa beta kinase beta; NKT: natural killer T cells; RANTES: regulated upon activation, normalT-cell expressed and secreted; Th17: T helper 17; T1D: type 1 diabetes.

Conclusion:-

In the recent time, a significant number of people suffer with type 2 diabetes. In developing countries a number of diabetic patients live below the poverty line. They could not meet up their daily nutritional requirement and a substantial population remains malnourished. As probiotic bacteria have potential therapeutic or prophylactic effects, so development of numerous probiotic products such as fermented milk drinks, yoghurt, cheese, icecream, sausages, probiotic juice and drinking water etc. with defined culture are badly required. These products would be able to confer health benefits and lowering blood glucose level of type 2 diabetes patients. Incoporation of probiotics live microorganisms (isolated from indigenous yoghurt) in market yoghurts can positively enhance health status of larger segment of type 2 diabetic peoples. Therefore probiotic yoghurt and other probiotic based food and feed can be used as a biotherapeutic agent for type 2 diabetes patient.

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