



PROBIOTICS AND DIABETES MELLITUS

K. Naydenov¹, A. Anastasov², M. Avramova¹, Iv. Mindov^{1*}, T. Tacheva²,
A. Tolekova³, T. Vlaykova²

¹Undergraduate student in Medicine, Medical Faculty, Trakia University, Stara Zagora, Bulgaria

²Dept. of Chemistry and Biochemistry, Medical Faculty, Trakia University, Stara Zagora, Bulgaria

³Dept. of Physiology, Pathophysiology and Pharmacology, Medical Faculty, Trakia University, Stara Zagora, Bulgaria

ABSTRACT

The term probiotics derived from the Latin prefix *pro* which means *for* and the Greek noun *βίος* (*bios*) which means "life". Probiotics have been defined as "live microorganisms which, when administrated in adequate amounts, confer a health benefit on the host". Probiotics are commonly consumed as part of fermented foods with specially added active live cultures; such as in yogurt, soy yogurt, or as dietary supplements which causes numerous positive effects to host organisms. The pathogenesis of diabetes mellitus is complex and some of the factors implemented in it are oxidative stress and inflammation. Some probiotics have been reported to decrease the oxidative stress and to suppress the effector functions of CD4+ T cells, accompanied by reducing the pro-inflammatory molecules [1], thus having antioxidant, immune-modulatory effects and antidiabetic effects. In addition probiotics may be able to improve the lipid profile, which is the main risk factor for cardiovascular diseases (CVD) and can improve insulin sensitivity by attenuating systemic inflammation.

The current review summarizes findings in the scientific literature suggesting that yogurt is a functional food that may exert antidiabetic and antioxidant properties. Interest in human microflora has only recently been emerged and it has been shown that human microflora probably has a major role in maintaining the homeostasis of human metabolism and application of probiotics is an useful approach for modulation of human microbiota.

In conclusion probiotics have a lot of beneficial effects in health and disease, reducing extrinsic nuisances, modulating the immune system and improving the body antioxidant defense.

Key words: probiotics, diabetes, metabolic syndrome, prevention

INTRODUCTION

The term probiotics derived from the Latin prefix *pro* which means *for* and the Greek noun *βίος* (*bios*) which means "life" [2]. According to the currently adopted definition by FAO/WHO, probiotics are: "Live microorganisms which when administered in adequate amounts confer a health benefit on the host" [3-5]. *Lactic acid* bacteria (LAB) from the genera *Lactobacillus*, *Streptococcus*, *Enterococcus*, the genus *Bifidobacterium* some yeasts and non-pathogenic strains *Escherichia coli* are the most common types of microbes proved to be probiotics [6]. Probiotics are

commonly consumed as part of fermented foods with specially added active live cultures; such as in yogurt, soy yogurt, or as dietary supplements which causes numerous positive effects to host organisms.

Gut flora consists of microorganisms that live in the digestive tracts of animals and is the largest reservoir of human flora with concentration of 10^{14} cells/ml and approximate weight of 1.5 kg. In this context, gut is synonymous with intestinal tract, and flora with microbiota and microflora. The human body, consisting of about 10 trillion cells, carries about ten times ($100 \cdot 10^9$) as many microorganisms from 300 to 1000 different species in the intestines [7]. In result our gut microflora (gut microbiom) carries more than 3 million genes, which provides a broad range of functions and abilities for dynamical changes

*Correspondence to: Ivan Mindov, Undergraduate student in medicine, Medical Faculty, Trakia University, 11 Armeiska Str, Stara Zagora, Bulgaria, E-mail: i.mindov@hotmail.com

according to the factors of the environment [8]. The metabolic activities performed by these microorganisms resemble those of an organ, leading some to liken gut bacteria to a "forgotten" organ [9]. 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 metagenome includes genomes of all microorganisms which humans are hosts for, as they can live in various organs such as skin, lungs, vagina, mouth and intestinal tract [10].

Main part of the gut flora consists of *Bacteria* which make up to 60% of the dry mass of feces. However, it is probable that 99% of the bacteria come from about 30 or 40 species. *Fungi* and *Protozoa* also make up a part of the gut flora, but little is known about their activities.

It is shown that the Gram-negative *Bacteroidetes* and the Gram-positive *Firmicutes* account for more than 90% of all phylotypes of gut Bacteria [11]. Other phyla that are found as part of the gut microbes include the Gram-negative *Proteobacteria* and *Verrucomicrobia* as well as the Gram-positive *Actinobacteria* [6]. More than 90% of the bacterial population are obligate anaerobes (*Bacteroides*, *Eubacterium*, *Bifidobacterium*, *Fusobacterium*, *Peptostreptococcus*) [11].

The gut microflora has its importance in controlling and regulating of different physiological processes. Once it is set, the gut microflora can be influenced by various internal or external factors, which can modify its ecological structure. Such factors are antibiotics, prebiotics and probiotics and thus variety of processes in human body can be altered. Considering this, the gut microbiota is a key organ in nutritional metabolism and possibly its imbalance contributes to the development of obesity [12] and diabetes [13, 14]. These morbidnesses are associated with considerable changes in the constitution and the metabolic functions of the gut microbiom [6]. It has been proved that oral administration of probiotics which contains *Lactobacillus acidophilus* and *Lactobacillus casei* significantly delayed the progression of high fructose-induced glucose intolerance and especially *L. casei* decreases the plasma glucose levels [14]. At the same time the

increased number of *Bifidobacterium* species correlates with improved glucose tolerance and insulin secretion [15].

It is interesting to note that gaining body weight is associated with increase number of bacteria from phyla *Firmicutes* and *Bacteroidetes* [13] and antibiotics treatment of obese mice modify the gut microflora which leads to decrease of body weight and improves glucose tolerance [16]. These observations draw attention to gut microflora as a potential target for treatment of metabolic diseases [6, 8].

Obesity and diabetes are metabolic disorders with epidemiological distribution in USA and Europe [17]. Diabetes and impaired glucose tolerance are connected with obesity, which is widely discussed elsewhere [18, 19]. Nowadays about 190 millions people worldwide are with diabetes and until 2025 this number is expected to reach 300 millions. It is thought that in Bulgaria about 2.5-3% of the population suffers from diabetes [20]. Type 2 diabetes mellitus (T2D) formerly non insulin-dependent diabetes mellitus (NIDDM) or adult onset diabetes is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. T2D is due to insufficient insulin production from β -cells or in the setting of insulin resistance. Insulin resistance, which is the inability of cells to respond adequately to normal levels of insulin, occurs primarily within the muscles, liver and fat tissue. In the liver, insulin normally suppresses glucose release. However in the setting of insulin resistance, the liver inappropriately releases glucose into the blood. The proportion of insulin resistance versus β -cell dysfunction differs among individuals with some having primarily insulin resistance and only a minor defect in insulin secretion and others with slight insulin resistance and primarily a lack of insulin secretion.

Other potentially important mechanisms associated with T2D and insulin resistance include: increased breakdown of lipids within adipose cells, resistance to and lack of insulin, high glucagon levels in the blood, increased retention of salt and water by the kidneys, and inappropriate regulation of metabolism by the central nervous system. However not all people with insulin resistance develop

diabetes, since an impairment of insulin secretion by pancreatic β -cells is also required.

The pathogenesis of diabetes mellitus is complex and one of the factors implemented is the oxidative stress. Probiotic-containing foods have been reported to suppress oxidative stress. *L. acidophilus* and *L. casei* also attenuate oxidative stress and have antidiabetic effects. It was shown that *L. casei* decreased the oxidative stress [21] and suppressed the effector functions of CD4⁺ T cells, accompanied by reducing the proinflammatory molecules [1], thus having antioxidant, immune-modulatory effects and antidiabetic effects.

Basic risk factors for development of T2D are age above 40 years, overweight, family predisposition, etc. Chronic stress, lack of muscle activity and inappropriate diet are considered to be the main triggering causes of T2D [22]. Recent studies have shown that genetic factors are implemented in development of only 10-20% of cases of diabetes, whereas the way of alimentation and social behavior predominate [8].

PROBIOTICS AND DIABETES MELLITUS

Three major groups of probiotics' positive effects can be distinguished: 1. Modulation of the innate as well as the acquired immune system of the host, implemented in the prevention and therapy of infectious diseases but also for the treatment of chronic inflammation of the digestive tract. It is thought that this probiotic activity could support the host immune system in dealing with neoplastic host cells. 2. Regulation and restoration of the microbial equilibrium in the gut, interacting with other microorganisms, commensal and/or pathogenic ones. This has its importance for the prevention and therapy of infections. 3. Inactivation of toxins and detoxification of toxins, xenobiotics, microbial products, endogenous products (e.g. bile salts) and food ingredients in the gut. As a matter of fact probiotics are involved in infection defense, prevention of cancer and in maintaining the physiological balance within the intestinal microbiota. It is important to note that there is no such probiotic microorganism capable to provide all three effects at once, so it depends on the metabolic properties, the kind of surface molecules expressed and

components to be secreted from a certain probiotic strain. [23].

Host defenses in the gut is stimulated by the interaction between colonizing the gastrointestinal mucosa bacteria and the underlying epithelial and mucosal lymphoid elements [24, 25], which is so-called bacterial-epithelial cross talk at the cellular level which notion is supported from a variety of microbial molecular patterns identified as ligands of Toll-Like Receptors (TLRs) [26]. This interaction with mesenteric lymph nodes can result in an up-regulation of IgA against intestinal pathogens and food antigens [27]. It was shown that the probiotic fungus *Saccharomyces boulardii*, enhances the specific IgG and IgA antibody response to *Clostridium difficile* toxin A [28]. *Lactobacillus rhamnosus* strain GG given to infants with rotaviral gastroenteritis appeared to increase IgA response to the virus [29]. The same strain invigorates also the immune response to typhoid vaccination, leading to significantly higher levels of antityphoid antibodies [30]. *Lactobacillus* strains are known as a probiotics which could stimulate up-regulation of mucous genes in intestinal goblet cells [31, 32].

The use of probiotics has also been effective in enhancing the mucosal barrier to pathogens and antigen presentation. Furthermore, the effect of these probiotics on the activation and secretion of mucus in the intestine was directly correlated with the inhibition of pathogenic *Escherichia coli* attachment and of damage to the intestinal tract. Different probiotics can function differently in the development of intestinal host defenses, as an adjuvant of immune responses or to strengthen the mucosal barrier [25].

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 [13]. It was shown a significant positive correlation between the ratios of *Bacteroidetes* to *Firmicutes* and reduced glucose tolerance as well as the reverse tendency was observed between the ratios of bacteria and body mass index (BMI) [13]. These results suggest that overweight and diabetes are associated with

different groups of the intestinal microbiota. Non-diabetic microbiom includes bacterial groups from *Bacteroides* and *Prevotella* group whereas in diabetic persons the ratios of class *Clostridia* (*C. coccoides*) and class *Escherichia* (*E. rectale*) are significantly higher. Other studies have previously confirmed that reduction in *Bacteroides* and *Prevotella* is associated with noticable decrease of metabolic endotoxemia and inflammation in type 2 diabetes mice [33]. It is interesting to note that in human studies the weight loss leads to a significant reduction in *Clostridium* ssp, *C. coccoides* and an increase in the *Bacteroides-Prevotella* group [34, 35]. Recent studies have shown that in diabetic and obese patients, confirmed with mice models, the levels of *Bacilli* and the *Lactobacillus* are significantly higher [33, 35, 36]. Reduced bacterial diversity is observed in obese individuals and diabetic patients, which can be explained with differences in diet, lifestyle or other factors [19, 37]. Cani and co-workers hypothesized [38] 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. Gram-negative bacteria, belonging to the phyla *Bacteroidetes* and *Proteobacteria* prevalence is observed in the intestinal microbiota of patients with type 2 diabetes. The lipopolysaccharides (LPS), main compounds of outer membranes in gram-negative bacteria are known as potent stimulators of inflammation and inflammatory response, which can exhibit endotoxaemia [39] and play a role in the development of diabetes.

Several recent studies have proved that lactic acid bacteria and probiotics have prominent positive effect in humans or animals with type 1 and 2 diabetes. In animal models of T2D it was investigated and confirmed the ability of *Lactobacilli* to reduce the risk of its development [14]. As a probiotic supplements *Lactobacillus plantarum* DSM 15313 and *L. gasseri* BNR17 are studied in mice model of induced by high lipid diet obesity and diabetes, representing anti-diabetes effect by decreasing blood glucose level and improves glucose tolerance without influence of lipid and insulin levels [14, 40]. Analogical results are observed in rats on high fructose diet supplemented with degreased milk and dahi: the fermented dairy product containing *Lactobacillus acidophilus* and *L. casei*, significantly delayed the

progression of hyperglycemia, hyperinsulinemia, dyslipidemia and oxidative stress in rats, which was associated with low levels of glycated hemoglobin, total cholesterol, LDL, VLDL, triglycerides and free fatty acids comparing to animals without supplementation [41, 42]. Matsuzaki (1997) have shown that oral administration of *L. casei* in KK-Ay mice significantly decreased plasma glucose levels and inhibited the production of β -cells specific CD4 T-cells and cytokines that are the bidding factors for induction of autoimmune diabetes [43]. Another positive effect of probiotic administration in diabetes is the suppression of the inflammation process, which is accompanying process of the development and progression of the disease [32]. It is reported that in experimentally induced diabetes with streptozotocin in rats, the strain *L. casei* Shirota significantly decreased the blood levels of pro-inflammatory cytokine IL-6 and acute-phase protein CRP, lowered the concentration of neutrophils and the risk of diabetic complications [44]. Tabuchi (2003) reported that feeding with *L. rhamnosus* GG improved glucose tolerance in rats with streptozotocin-induced diabetes [45].

Probiotics may be able to improve the lipid profile, which is the main risk factor for cardio-vascular diseases (CVD). Probiotic bacteria improve insulin sensitivity by attenuating systemic inflammation. The chronic low-grade inflammation with persistently elevated levels of circulation pro-inflammatory cytokines is considered a principal pathogenetic component of insulin resistance and T2D. Probiotics has immune-modulatory effects. Probiotic supplementation improves high-fat diet-induced insulin resistance and hepatic steatosis.

A number of reports confirmed experimentally and clinically that oxidative stress is involved in the pathogenesis and progression of diabetes mellitus as well as the subsequent complications [46]. Generation of oxygen free radicals due to non-enzymatic protein glycosylation, auto-oxidation of glucose and impaired antioxidant defense enzymes are the most common consequences in diabetes [47]. This impaired balance of oxidants/antioxidants may lead to cellular damages, development of insulin resistance and dysfunction in a variety of enzymes, occurrence of inflammation process and lipid peroxidation [46, 48]. Probiotic foods have been reported to repress

the oxidative stress. *L. acidophilus* and *L. casei* attenuate oxidative stress and have antidiabetic effects. The antioxidative mechanisms of probiotics could be assigned to reactive oxygen species scavenging, metal ion chelation, pro-oxidant enzyme inhibition and the reduction activity and inhibition of ascorbate oxidation [49].

Probiotic strain *Bifidobacterium animalis subsp. lactis* could significantly improve the metabolic changes by counter acting the adverse effects of a high-fat diet [50]. The increase in number of *Bifidobacterium* spp. was significantly and positively correlated with improved glucose-tolerance, glucose-induced insulin secretion and normalized low-grade inflammation. In another study it was proved that strains *L. acidophilus* La5 и *B. lactis* Bb12 noticeably reduce blood glucose levels, glycated hemoglobin and remarkably improve antioxidant status and total serum antioxidant capacity with elevation of erythrocyte SOD (superoxide dismutase) and GPX (glutathione peroxidase) levels in patients with T2D [51].

CONCLUSIONS

Speaking by and large for microbiota and its implication in development and progression of diabetes, obesity and other metabolic diseases in humans it has to be considered the levels of glucose tolerance or severity of the metabolic disorder. As these conditions might be associated with different bacterial populations it is especially important to develop the strategies to modify the gut microbiota [13].

Literature data assumed that intestinal microflora is a factor influencing metabolic diseases such as obesity [12] and diabetes [13]. These diseases are associated with significant changes in the composition and metabolic functions of gut microbiota [6]. It has been shown that the increase of body weight is associated with more *Firmicutes* bacteria type and less *Bacteroidetes* [13], and the use of antibiotics influencing the intestinal microflora in obese mice reduces weight and improves glucose tolerance [16]. This proves that the intestinal microflora may be an important new target for treatment of metabolic diseases [6, 8].

These findings suggest that yogurt containing different probiotics is a functional food that may exert antidiabetic and antioxidant properties. The interest in human microflora

has only recently been developed, and it has been suggested that it probably has a major role in maintaining the homeostasis of human metabolism. However the underlying mechanisms are still not fully clarified..

In conclusion, probiotics have a large variety of beneficial actions in health and disease, reducing extrinsic nuisances, inhibiting of inflammation and having antioxidant capacity via reducing and preventing the formation of reactive free radicals with improvement of antioxidant defense in diabetic patients.

REFERENCES

1. So JS, Kwon HK, Lee CG, Yi HJ, Park JA, Lim SY, Hwang KC, Jeon YH, Im SH: Lactobacillus casei suppresses experimental arthritis by down-regulating T helper 1 effector functions. *Mol Immunol* 2008, 45:2690-2699.
2. Hamilton-Miller JM, Gibson GR, Bruck W: Some insights into the derivation and early uses of the word 'probiotic'. *Br J Nutr* 2003, 90:845.
3. Isolauri E: Probiotics: from anecdotes to clinical demonstration. *J Allergy Clin Immunol* 2001, 108.
4. FAO/WHO: Guidelines for the Evaluation of Probiotics in Food: . In *Joint FAO/WHO Working Group meeting; 30 April-1 May; London Ontario, Canada*. 2002
5. Sanders ME: Probiotics: considerations for human health. *Nutr Rev* 2003, 61:91-99.
6. Kootte RS, Vrieze A, Holleman F, Dallinga-Thie GM, Zoetendal EG, de Vos WM, Groen AK, Hoekstra JB, Stroes ES, Nieuwdorp M: The therapeutic potential of manipulating gut microbiota in obesity and type 2 diabetes mellitus. *Diabetes Obes Metab* 2012, 14:112-120.
7. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI: The human microbiome project. *Nature* 2007, 449:804-810.
8. Burcelin R, Serino M, Chabo C, Blasco-Baque V, Amar J: Gut microbiota and diabetes: from pathogenesis to therapeutic perspective. *Acta Diabetol* 2011, 48:257-273.
9. Quigley EM: Probiotics in gastrointestinal disorders. *Hosp Pract* 2010, 38:122-129.
10. Dethlefsen L, McFall-Ngai M, Relman DA: An ecological and evolutionary perspective on human-microbe mutualism and disease. *Nature* 2007, 449:811-818.

11. Tsukumo DM, Carvalho BM, Carvalho-Filho MA, Saad MJ: Translational research into gut microbiota: new horizons in obesity treatment. *Arq Bras Endocrinol Metabol* 2009, 53:139-144.
12. Ley RE, Turnbaugh PJ, Klein S, Gordon JI: Microbial ecology: human gut microbes associated with obesity. *Nature* 2006, 444:1022-1023.
13. Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, Al-Soud WA, Sorensen SJ, Hansen LH, Jakobsen M: Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One* 2010, 5.
14. Andersson U, Branning C, Ahrne S, Molin G, Alenfall J, Onning G, Nyman M, Holm C: Probiotics lower plasma glucose in the high-fat fed C57BL/6J mouse. *Benef Microbes* 2010, 1:189-196.
15. Yin YN, Yu QF, Fu N, Liu XW, Lu FG: Effects of four Bifidobacteria on obesity in high-fat diet induced rats. *World J Gastroenterol* 2010, 16:3394-3401.
16. Vrieze A, Holleman F, Zoetendal EG, de Vos WM, Hoekstra JB, Nieuwdorp M: The environment within: how gut microbiota may influence metabolism and body composition. *Diabetologia* 2010, 53:606-613.
17. Shamseddeen H, Getty JZ, Hamdallah IN, Ali MR: Epidemiology and economic impact of obesity and type 2 diabetes. *Surg Clin North Am* 2011, 91:1163-1172.
18. Schwartz A, Taras D, Schafer K, Beijer S, Bos NA, Donus C, Hardt PD: Microbiota and SCFA in lean and overweight healthy subjects. *Obesity* 2009, 18:190-195.
19. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, et al: A core gut microbiome in obese and lean twins. *Nature* 2009, 457:480-484.
20. БДЕ: Препоръки за добра практика по захарен диабет. In: *София. Българско Дружество по Ендокринология*; 2005
21. Villarini M, Caldini G, Moretti M, Trotta F, Pasquini R, Cenci G: Modulatory activity of a Lactobacillus casei strain on 1,2-dimethylhydrazine-induced genotoxicity in rats. *Environ Mol Mutagen* 2008, 49:192-199.
22. Stefanov TS, Vekova AM, Kurkschiev DP, Temelkova-Kurkschiev TS: Relationship of physical activity and eating behaviour with obesity and type 2 diabetes mellitus: Sofia Lifestyle (SLS) study. *Folia Med* 2011, 53:11-18.
23. Oelschlaeger TA: Mechanisms of probiotic actions - A review. *Int J Med Microbiol* 2009, 300:57-62.
24. Shi HN, Walker A: Bacterial colonization and the development of intestinal defences. *Can J Gastroenterol* 2004, 18:493-500.
25. Walker WA: Mechanisms of action of probiotics. *Clin Infect Dis* 2008, 1:S144-151.
26. Kawai T, Akira S: TLR signaling. *Cell Death Differ* 2006, 13:816-825.
27. Macpherson AJ, Uhr T: Induction of protective IgA by intestinal dendritic cells carrying commensal bacteria. *Science* 2004, 303:1662-1665.
28. Qamar A, Aboudola S, Warny M, Michetti P, Pothoulakis C, LaMont JT, Kelly CP: Saccharomyces boulardii stimulates intestinal immunoglobulin A immune response to Clostridium difficile toxin A in mice. *Infect Immun* 2001, 69:2762-2765.
29. Isolauri E, Juntunen M, Rautanen T, Sillanauke P, Koivula T: A human Lactobacillus strain (Lactobacillus casei sp strain GG) promotes recovery from acute diarrhea in children. *Pediatrics* 1991, 88:90-97.
30. Teitelbaum JE, Walker WA: Nutritional impact of pre- and probiotics as protective gastrointestinal organisms. *Annu Rev Nutr* 2002, 22:107-138.
31. Mack DR, Michail S, Wei S, McDougall L, Hollingsworth MA: Probiotics inhibit enteropathogenic E. coli adherence in vitro by inducing intestinal mucin gene expression. *Am J Physiol* 1999, 276:G941-950.
32. Andreasen AS, Larsen N, Pedersen-Skovsgaard T, Berg RM, Moller K, Svendsen KD, Jakobsen M, Pedersen BK: Effects of Lactobacillus acidophilus NCFM on insulin sensitivity and the systemic inflammatory response in human subjects. *Br J Nutr* 2010, 104:1831-1838.
33. Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O, Geurts L, Naslain D, Neyrinck A, Lambert DM, et al: Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* 2009, 58:1091-1103.
34. Nadal I, Santacruz A, Marcos A, Warnberg J, Garagorri M, Moreno LA, Martin-Matillas M, Campoy C, Marti A, Moleres

- A, et al: Shifts in clostridia, bacteroides and immunoglobulin-coating fecal bacteria associated with weight loss in obese adolescents. *Int J Obes* 2009, 33:758-767.
35. Santacruz A, Marcos A, Warnberg J, Marti A, Martin-Matillas M, Campoy C, Moreno LA, Veiga O, Redondo-Figuero C, Garagorri JM, et al: Interplay between weight loss and gut microbiota composition in overweight adolescents. *Obesity* 2009, 17:1906-1915.
36. Armougom F, Henry M, Vialettes B, Raccach D, Raoult D: Monitoring bacterial community of human gut microbiota reveals an increase in *Lactobacillus* in obese patients and *Methanogens* in anorexic patients. *PLoS One* 2009, 4.
37. Dicksved J, Floistrup H, Bergstrom A, Rosenquist M, Pershagen G, Scheynius A, Roos S, Alm JS, Engstrand L, Braun-Fahrlander C, et al: Molecular fingerprinting of the fecal microbiota of children raised according to different lifestyles. *Appl Environ Microbiol* 2007, 73:2284-2289.
38. Cani PD, Neyrinck AM, Fava F, Knauf C, Burcelin RG, Tuohy KM, Gibson GR, Delzenne NM: Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. *Diabetologia* 2007, 50:2374-2383.
39. Allcock GH, Allegra M, Flower RJ, Perretti M: Neutrophil accumulation induced by bacterial lipopolysaccharide: effects of dexamethasone and annexin 1. *Clin Exp Immunol* 2001, 123:62-67.
40. Yun SI, Park HO, Kang JH: Effect of *Lactobacillus gasseri* BNR17 on blood glucose levels and body weight in a mouse model of type 2 diabetes. *J Appl Microbiol* 2009, 107:1681-1686.
41. Yadav H, Jain S, Sinha PR: Effect of skim milk and dahi (yogurt) on blood glucose, insulin, and lipid profile in rats fed with high fructose diet. *J Med Food* 2006, 9:328-335.
42. Yadav H, Jain S, Sinha PR: Antidiabetic effect of probiotic dahi containing *Lactobacillus acidophilus* and *Lactobacillus casei* in high fructose fed rats. *Nutrition* 2007, 23:62-68.
43. Matsuzaki T, Yamazaki R, Hashimoto S, Yokokura T: Antidiabetic effects of an oral administration of *Lactobacillus casei* in a non-insulin-dependent diabetes mellitus (NIDDM) model using KK-Ay mice. *Endocr J* 1997, 44:357-365.
44. Zarfeshani A, Khaza'ei H, Mohd Ali R, Hambali Z, Wahle KWJ, Mutalib MSA: Effect of *Lactobacillus casei* on the Production of Pro-Inflammatory Markers in Streptozotocin-Induced Diabetic Rats. *Probiotics & Antimicro Prot* 2011:168-174.
45. Tabuchi M, Ozaki M, Tamura A, Yamada N, Ishida T, Hosoda M, Hosono A: Antidiabetic effect of *Lactobacillus GG* in streptozotocin-induced diabetic rats. *Biosci Biotechnol Biochem* 2003, 67:1421-1424.
46. Ceriello A, Motz E: Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. *Arterioscler Thromb Vasc Biol* 2004, 24:816-823.
47. Sarkhail P, Abdollahi M, Fadayevatan S, Shafiee A, Mohammadirad A, Dehghan G, Esmaily H, Amin G: Effect of *Phlomis persica* on glucose levels and hepatic enzymatic antioxidants in streptozotocin-induced diabetic rats. *Pharmacogn Mag* 2010, 6:219-224.
48. Maritim AC, Sanders RA, Watkins JB, 3rd: Diabetes, oxidative stress, and antioxidants: a review. *J Biochem Mol Toxicol* 2003, 17:24-38.
49. Ejtahed HS, Mohtadi-Nia J, Homayouni-Rad A, Niafar M, Asghari-Jafarabadi M, Mofid V: Probiotic yogurt improves antioxidant status in type 2 diabetic patients. *Nutrition* 2012, 28:539-543.
50. Mallappa RH, Rokana N, Duary RK, Panwar H, Batish VK, Grover S: Management of metabolic syndrome through probiotic and prebiotic interventions. *Indian J Endocrinol Metab* 2012, 16:20-27.
51. Ejtahed HS, Mohtadi-Nia J, Homayouni-Rad A, Niafar M, Asghari-Jafarabadi M, Mofid V, Akbarian-Moghari A: Effect of probiotic yogurt containing *Lactobacillus acidophilus* and *Bifidobacterium lactis* on lipid profile in individuals with type 2 diabetes mellitus. *J Dairy Sci* 2011, 94:3288-3294.