UNIVERSITI PUTRA MALAYSIA

EFFECTS OF PROBIOTIC SUPPLEMENTATION ON OBESITY MARKERS IN HIGH FAT DIET-INDUCED OBESE RATS

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By

GOLGIS KARIMI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

August 2015

DEDICATION

This thesis work is dedicated to my Father (Hekmatollah Karimi) and my mother (Maliheh abolghasemi), who have been a constant source of support and encouragement during the challenges of graduation and life. I am truly thankful for having you in my life.

This work is also dedicated to my sisters and my brother who love me unconditionally and whose good examples have taught me to work hard for the things that I aspire to achieve.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

EFFECTS OF PROBIOTIC SUPPLEMENTATION ON OBESITY MARKERS IN HIGH FAT DIET-INDUCED OBESE RATS

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August 2015

Chairman : Rosita Binti Jamaluddin, PhD

Faculty: Medicine and Health Sciences

Obesity and overweight are the major public health problems in the recent years. Some recent studies revealed that gut microbiota plays an important role in energy homeostasis and food intake in both human and animals. Therefore, this study aimed to investigate the effect of *LcS* and *B. longum* as a single strain and a combination on obesity and related metabolites in high fat diet-induced obese rats.

A total of 50 male Sprague-Dawley (SD) rats at the age of 6 weeks were fed a standard diet for two weeks to stabilize all metabolic conditions and achieved ±200g weight. After two weeks, the rats were randomly selected and assigned to six groups (8 rats per group). Group 1 was fed with standard diet (SD) and group 2-6 were fed with high fat diet (HFD) (40% beef tallow) for 12 weeks. After 12 weeks of obesity induction 5ml blood were collected to measure lipid profile, inflammatory, anti-inflammatory and pro-inflammatory biomarkers. Besides rats were assigned into new six groups randomly. SD group fed by standard diet; HFD group fed high fat diet ; HFD-*B.longum* fed HFD HFD-orlistat fed by HFD and 10mg /kg body weight Orlistat, HFD-mix fed by HFD and the combination of *LcS* and *B.longum*. The rats were gavaged by probiotic (10^8 ~ 10^9 CFU) once a day for 15 weeks. Their body weight was measured weekly and body mass index (BMI) was calculated at week 12 and week 27 of the study. Besides, food intake of rats was measured daily. After 15 weeks of probiotic supplementation rats were sacrificed. Their blood was collected to measure the second round of serological biomarkers. Besides rats organs (liver, kidney, spleen and heart) were weighted. A small part of liver were cut and stored in RCL2 to measure the expression of some obesity related genes. Histological analysis was carried on the liver and adipose tissue.

Probiotic supplementation either single strain or a combination made a reduction trend in body weight, fat mass, BMI and food intake. Between group analysis of lipid profile indicated that TG level in HFD group (1.25±0.44 mg/dl) was significantly higher than HFD-*B.longum* (0.57±0.11 mg/dl, P=0.02) and HFD-mix (0.68±0.27 mg/dl, P=0.049). Besides HFD-mix group had higher levels of HDL (1.5 ± 0.17 mg/dl) in comparison with HFD group (0.67 ± 0.07 mg/dl, p=0.001), HFD-*B.longum* (0.85 ± 0.1 mg/dl, p=0.001) and HFD-LcS (0.94 ± 0.11 mg/dl, p=0.004). No significant changes in LDL and cholesterol level were observed between HFD group with probiotic supplemented groups. Besides, present study depicted that inflammatory factors including IL-6, TNF-Ŭ and hs-CRP were remained constant in all treated groups.

Leptin and adiponectin play an important role in energy intake and body weight management. In the present study over 15 weeks of probiotic supplementation leptin was significantly decreased and adiponectin was significantly increased in all treatment groups with no significant differences between single strain group with mixture group. These changes result in a reduction in body weight and food intake in all supplemented groups. Moreover, between groups analysis of leptin at week 27 showed that, rats supplemented by probiotic either single or a combination had lower concentration of leptin compared with HFD group ($F= 3.24$, $p= 0.017$). In addition, adiponectin concentration was significantly higher supplemented groups as compared to HFD group (P Ò 0.05).

Furthermore, after 15 weeks of probiotic supplementation, expressions of PPAR-ɔ, ANGPTL-4 were up regulated while IL-6 expression was down. These changes decreased the lipid metabolism which consequently increases the fat excretion in feces. Increased expression of PPAR-ɔ lead to an increase in adiponectin secretion which lead to a decreased in food intake. Although the plasma level of IL-6 was not decreased, a significant reduction of IL-6 expression was observed at the molecular level. Therefore, prolong the probiotic period supplementation might result in inflammatory markers reduction. Results of the present study also demonstrated that probiotic supplementation in a dose of 10^8-10^9 CFU/day is a safe dose with no harmful singe or damage to liver and kidney.

To sum up, this study observed that single strain of bacteria either *LcS* or *B. longum* has more beneficial health effect on obesity rather than the mixture.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah.

KESAN-KESAN SUPLEMEN PROBIOTIK TERHADAP PENANDA-PENANDA OBESITI DI DALAM TIKUS TERARUH DIET LEMAK TINGG

Oleh

GOLGIS KARIMI

Ogos 2015

Pengerusi : Rosita Binti Jamaluddin, PhD

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Obesiti dan berlebihan berat badan adalah masalah kesihatan awam yang utama kebelakangan ini. Beberapa kajian baru-baru ini mendedahkan bahawa mikrobiota usus memainkan peranan penting dalam homeostasis tenaga dan pengambilan makanan di dalam kedua-dua manusia dan haiwan.

Oleh itu, kajian ini bertujuan untuk mengkaji kesan *LcS* dan *B. longum* secara tunggal dan gabungan keatas obesiti serta metabolit berkaitan dalam diet tinggi lemak yang mendorong tikus obes.

Sejumlah 50 tikus jantan Sprague-Dawley (SD) pada usia 6 minggu telah diberi makan diet yang standard selama dua minggu untuk menstabilkan semua keadaan metabolik dan mencapai berat ±200g. Selepas 2 minggu, tikus-tikus itu dipilih secara rawak dan dibahagikan kepada enam kumpulan (8 tikus setiap kumpulan). Kumpulan 1 diberi makan dengan diet standard (SD) dan kumpulan 2-6 diberi makan dengan diet yang tinggi lemak (HFD) (40% lemak lembu) selama 12 minggu. Selepas 12 minggu induksi obesiti, 5ml darah telah dikumpulkan untuk mengukur profil lipid, keradangan, anti-keradangan dan penanda biologi pro-radang. Selain itu, tikus-tikus ini dibahagikan kepada enam kumpulan secara rawak. Kumpulan SD diberi makan dengan diet standard; kumpulan HFD diberi makan dengan diet tinggi lemak ; HFD-*B.longum* diberi makan HFD HFD-orlistat diberi makan dengan HFD dan 10mg /kg berat badan Orlistat, HFD-campuran diberi makan dengan HFD dan gabungan *LcS* dan *B.longum*. Tikus-tikus telah diberikan probiotik (10^8 ~ 10^9 CFU) sekali sehari selama 15 minggu. Berat badan mereka diukur seminggu sekali dan Indeks Jisim Badan (BMI) dikira pada minggu ke 12 dan minggu ke 27 kajian. Selain itu, pengambilan makanan tikus diukur setiap hari. Selepas 15 minggu suplemen probiotik, tikus-tikus dikorbankan. Darah mereka dikumpulkan untuk mengukur pusingan kedua penanda biologi serologi. Selain itu, organ tikus (hati, buah pinggang, limpa dan jantung) ditimbang. Sebahagian kecil hati dipotong dan disimpan dalam RCL2 untuk mengukur penyataan beberapa gen obesiti yang berkaitan. Analisis histologi dijalankan pada hati dan tisu adipos.

Suplemen probiotik sama ada secara tunggal atau gabungan menunjukkan pengurangan dalam berat badan, jisim lemak, BMI dan pengambilan makanan. Di antara analisis kumpulan profil lipid menunjukkan bahawa tahap TG dalam kumpulan HFD (1.25±0.44 mg/dl) adalah jauh lebih tinggi berbanding HFD-*B.longum* (0.57±0.11 mg/dl, P=0.02) dan HFD-campuran

(0.68±0.27 mg/dl, P=0.049). Selain itu, kumpulan campuran HFD mempunyai tahap HDL yang lebih tinggi (1.5 ± 0.17 mg/dl) berbanding dengan kumpulan HFD (0.67 ± 0.07 mg/dl, p=0.001), HFD-*B.longum* (0.85 ± 0.1 mg/dl, p=0.001) dan HFD-LcS (0.94 ± 0.11 mg/dl, p=0.004). Tiada perubahan yang ketara dalam LDL dan tahap kolestrol diperhatikan di antara kumpulan HFD dengan kumpulan ditambah probiotik. Selain itu, kajian ini digambarkan bahawa faktor radang termasuk IL-6, TNF-Ŭ dan hs-CRP tetap kekal sama dalam semua kumpulan rawatan.

Leptin dan adiponektin memainkan peranan yang penting dalam pengambilan tenaga dan pengurusan berat badan. Dalam kajian ini, setelah lebih 15 minggu pengambilan suplemen probiotik, leptin telah menurun dengan ketara dan adiponektin telah meningkat dengan ketara dalam semua kumpulan rawatan dengan tiada perbezaan yang signifikan diantara kumpulan secara individu dengan kumpulan campuran. Ini menyebabkan perubahan dalam pengurangan berat badan dan pengambilan makanan dalam semua kumpulan yang diberi suplemen. Selain itu, diantara analisis kumpulan leptin pada minggu ke 27 menunjukkan bahawa, tikus yang ditambah dengan probiotik samaada tunggal atau gabungan mempunyai kepekatan leptin yang lebih rendah berbanding kumpulan HFD (F= 3.24, p= 0.017). Di samping itu, kepekatan adiponektin adalah signifikan lebih tinggi dalam kumpulan tambahan berbanding kumpulan HFD (P Ò 0.05).

Tambahan pula, selepas 15 minggu suplemen probiotik, ekspresi PPAR-ɔ, ANGPTL-4 dikawal selia manakala ekspresi IL-6 menurun. Perubahan ini menurunkan metabolisma lemak lantas meningkatkan perkumuhan lemak dalam najis. Peningkatan ekspresi PPAR-ɔ membawa kepada peningkatan dalam rembesan adinopektin yang membawa kepada penurunan dalam pengambilan makanan. Walaupun tahap plasma IL-6 tidak menurun, pengurangan ketara ekspresi IL-6 diperhatikan pada peringkat molekul. Oleh itu, memanjangkan tempoh suplemen probiotik mungkin menyebabkan pengurangan penanda radang. Hasil kajian ini juga menunjukkan bahawa suplemen probiotik dalam dos 10^8-10^9 CFU/hari adalah dos yang selamat dengan tidak membahayakan atau merosakkan hati dan buah pinggang.

Sebagai kesimpulan, kajian ini mendapati bahawa bakteria secara individu sama ada *LcS* atau *B. longum* mempunyai kesan kesihatan yang lebih baik terhadap obesiti berbanding campuran.

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I certify that a Thesis Examination Committee has met on 19 August 2015 to conduct the final examination of Golgis Karimi on her thesis entitled "Effects of Probiotic Supplementation on Obesity Markers in High Fat Diet-Induced Obese Rats" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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Declaration by graduate student

I hereby confirm that:

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This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
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+ve	Positive
ACUC	Animal Care and Use Committee
AgRP	Agouti-related peptide
Alb	Albumin
ALP	Alkaline phosphatase
Alpha-MSH	Ŭ-Melanocyte-stimulating hormone
ALT	Alanine amino transferase
ANGPTL4	Angiopoetin like protein 4
ANOVA	Multi-variate analysis of variance
AST	Aspartate amino transferase
ATCC	American Type Culture Collection
B. longum	*Bifidobacterium longum*
BMI	Body mass index
bp	Base pair
CFU	Colony forming unit
CKD	Chronic kidney disease
CLA	Conjugated linoleic acid
CNS	Central nervous system
Cr	Creatinin
CT	Cycle threshold
CVD	Cardiovascular disease
DNA	Deoxyribonucleic acid
ER	Endoplasmic reticulum
FIAF	Fasting-induced adipose factor
FIAF	Fasting-induced adipose factor
H & E	Hematoxylin and eosin
HbA_1c	Hemoglobin A1c
HDL	High density lipoprotein
HFD	High fat diet
hs-CRP	High sensitive c-reactive protein
IL-6	Interleukin-6
LAB	Lactic acid bacteria
LBP	Lipo-polysaccharide binding protein
LcS	*Lactobacillus casei strain Shirota*
LDL	Low density lipoprotein

LPL	Lipoprotein lipase
LPS	Lipopolysaccharide
MSG	Mono sodium glutamate
NEFA	Non-esterified fatty acids
NEFA	Non-esterified fatty acids
NK	Natural killer
NPY	Neuropeptide Y
PCR	Polymerase chain reaction
PMN	Polymorphonuclear neutrophil
POMC	Pro-opiomelanocortin
PPARɔ	Peroxisome proliferator-activated receptor gamma
PTPs	Protein tyrosine phosphatase
RNA	Ribonucleic acid
RT-PCR	Real time polymerase chain reaction
SAT	Subcutaneous adipose tissue
SCFA	Short chain fatty acids
SD	Standard diet
SE	Standard error
T2DM	Type two diabetes
TG	Triglyceride
TLR	Toll-like receptor
TLR4	Toll like receptor 4
TNF-Ű	Tumour necrosis alpha
VAT	Vesicular adipose tissue
-ve	Negative
VMH	Ventromedial nucleus of the hypothalamus
WAT	White adipose tissue
WC	Waist circumference

CHAPTER 1

INTRODUCTION

Background

Obesity and overweight are the major public health problems (An et al., 2011). In 2005, more than 300 million people were obese (BMI Ó 30 kg/m^2) and more than one billion people were overweight (BMI Ó 25 kg/m^2), worldwide. Overweight and obesity have an upward trend in almost all countries and all parts of the world such as South-East Asia and Middle East. Obesity and overweight increase the risk of cardiovascular and different chronic disorders including cancer, arthritis, obstructive sleep apnea, hypertension, hyperlipidemia, and type 2 diabetes associated with insulin resistance (Wickelgren, 1998). A recent growing number of evidences show that the increased prevalence of obesity and type 2 diabetes cannot be solely attributed to changes in the human genome, nutritional habits, or reduction of physical activity in our daily lives (An et all., 2011, Million et al., 2012, Kang et al., 2013).

Gut microþora may play an important role in maintaining human health. Recent data suggests that gut microbiota affects host nutritional metabolism with consequences on energy storage. Several mechanisms are proposed, linking events occurring in the colon and the regulation of energy metabolism. However, the effect of different species of bacteria on long-term weight loss is still uncertain (Million et al., 2012; An et al., 2011). In spite of these findings, and the relationship between diabetes and abdominal fat, few studies have been aimed to assess the correlations between the composition of the microbiota and the occurrence of inflammation and metabolic alterations in individuals with obesity (Larsen et al., 2010; Fuert et al., 2010). Therefore, further research is needed to discover new drug therapies that can be used to reduce the prevalence of obesity.

Probiotic is a kind of functional food which is defined by the Food and Agriculture Organization and World Health Organization as ñlive microorganisms (FAO/WHO, 2002). Probiotic consumption in adequate amounts confer a health benefit including improving gastrointestinal tract health, synthesizing and enhancing the bioavailability of nutrients, enhancing the immune system, decreasing the prevalence of allergy in susceptible individuals, reducing the symptoms of lactose intolerance, and reducing risks of certain cancers (Lee et al., 1995 ; Murthy, 2000). Preventive effects of some bacterial strains on obesity have been demonstrated in recent experimental studies. Bifidobacteria, a type of lactic acid bacteria, are one of the most numerous probiotics in the mammalian gut. Bifidobacteria are widely used and well tolerated. Xia et al. (2003) reported that, the effects of the *Bifidobacterium longum* srtrain in lowering serum total cholesterol is more than a mixed culture of *Lactobacillus delbrueckii* subspecies *bulgaricus* (SL) and *Streptococcus thermophilus* in both rats and humans. Canai et al. (2007) showed that *Bifidobacterium spp.* significantly and positively correlated with improved glucose-tolerance, glucose-induced insulin- secretion, and normalized inflammatory markers (decreased endotoxemia, plasma and adipose tissue pro-inflammatory cytokine) in probiotic treated-mice. Ma et al. (2008) reported that diet-induced obesity and its related hepatic steatosis and insulin resistance will be

improved by a mixture of viable lyophilized bifidobacteria, lactobacilli and *Streptococcus thermophilus* via increasing hepatic natural killer T-cells and reducing inflammatory signalling in mice. These data suggest that some specific strains of bifidobacteria related to lipid metabolism and body weight may be potential therapeutic candidates for the management of obesity.

The speciýc mechanism(s) by which the probiotic exerts anti-obesity effects remains unknown. In fact, the serum level of leptin is correlated with adipose tissue weight or adipocyte size as an important factor in obesity management in both rodents (Gue et al., 2004) and humans (Lo¨nnqvist et al., 1997; Hamad et al., 2009). Leptin has been identified as an anti-obesity hormone that regulates body weight by controlling food intake and energy expenditure via the hypothalamic-pituitary gonadal axis (Jéquier, 2002; Friedman, 2002). Leptin is a 16 KDa secreted protein produced by the ob gene. Adipose tissue produces leptin and releases it into the blood stream. As fat deposits grow, blood leptin levels tend to increase. Thus, leptin levels are closely related to the percentage of body fat; markedly higher serum leptin levels have been found in obese individuals compared with non-obese individuals (Hamilton et al., 1995; Considine et al., 1996). In contrast, leptin levels are severely reduced in underweight individuals compared with normal weight individuals (Ginspoon et al., 1996; Ferron et al., 1997). The results of the previous studies suggest that reductions in fat mass and body weight are associated with a reduction in leptin.

Furthermore, the adipose tissue expansion that occurs during the development of obesity is initially characterised either by an increase in fat cell size or by an increase in fat cell number. A recent study by Sato et al. (2008) showed that a fermented milk product containing *Lactobacillus gasseri SBT2055* (LGSP) exerts a beneýcial effect on the onset of obesity by lowering adipocyte size and the level of leptin in Sprague-Dawley rats. Although the mechanism of this effect of *Lactobacillus gasseri* on adipocyte size has not been elucidated, it is likely that LGSP may affect adipocyte size through inhibition of energy input. In fact, it was found that inhibitors of lipid absorption affect the body fat mass through increased excretion of faecal lipids (Thornton et al., 2007). Furthermore, *L. gasseri* strains have been reported to bind micellar lipids, thereby raising a possibility of inhibiting the absorption of fatty acids and cholesterol (Usman & Hosono, 1999).

Problem statement

Obesity and overweight are escalating and raising considerable public concern because they increase the prevalence of severe cardiovascular events and other systemic diseases, causing great costs and burden to both society and families (Zhou et al., 2012). Obesity prevalence is approximately 23% in southern European countries and increasing in developing countries. Obesity is particularly striking, both for the novelty and for the associated risk of developing type 2 diabetes mellitus, hypertension, hyperlipidemia and atherosclerosis, which ultimately translates into increased rates of cardiovascular morbidity and mortality in adulthood (Díaz & Folgueras, 2011).

In Malaysia, at the population level, a high prevalence of obesity results from a complex interaction between changes in the populationôs lifestyle, involving a higher energy and fat consumption and an increasingly sedentary lifestyle (WHO, 2000).The effects of these changes being particularly severe if the population has an inherited metabolic predisposition to fatness (a óthrifty genotypeô). Several previous studies, albeit not representative of the population, have reported that obesity is prevalent in all age-groups, in children, male 12.5% and females 5.0% (Ismail et al., 2002); in male adolescents, 1.0% in 1990 to 6% in 1997; and in adults, 21.0% overweight and 6.2% obese using World Health Organization (2000) criteria (Ismail et al., 2002). The best strategy is prevention, but once patients suffer overweight or obesity, conventional treatment, consisting of a low calorie diet, physical exercise and a change in lifestyle, offers modest results.

Additionally, it is generally known that high-fat diet (HFD) is one of the factors causing obesity, and that long-term intake of HFD evokes significant increase in abdominal fat weight in mammals (Iwashita et al., 2002). Thus, in the field of food science, finding food or beverage having the function which prevents HFD-induced obesity such as probiotics, is now in growing importance (Tanida et al., 2008). Some previous studies have been carried out using probiotics to promote specific changes in the gut microbiota. Angiopoetin-related protein 4 (ANGPTL4), a lipoprotein lipase inhibitor which inhibits the uptake of fatty acids from circulating triglyceride-rich lipoproteins in white adipose and muscle tissues was found to be increased in mice fed a high fat diet supplemented with *L. paracasei* (Aronsson et al., 2010). Obese individuals when administered *Lactobacillus acidophilus NCFM* and *Lactobacillus gasseri SBT2055* showed a decrease in fat mass and the risk of type 2 diabetes mellitus and insulin resistance (Andreasen et al., 2010; Kadooka et al., 2010). It has been also reported *L. gasseri* supplementation significantly decreased the body weight as well as abdominal, visceral and subcutaneous fat (Vyas & Ranganathan, 2012).

Furthermore, it has been demonstrated that drugs such as sibutramine, or orlistat, may play a role in the management of overweight and obesity (Díaz & Folgueras, 2011). Orlistat is a member of a class of drugs that has been proposed to be used for the long-term treatment of obesity (Harp, 1999). However the side effect of orlistat treatment on other diseases (Ballinger & Peikin, 2002), its long-term safety has not been determined (Heck et al., 2000). Orlistat acts locally in the gastrointestinal tract to inhibit lipase, an enzyme that is crucial for the digestion of the long-chain triglycerides. Thus, the faecal fat excretion is significantly greater with orlistat (Guerciolini et al., 2001).

In addition, however drugs such as orlistat, have been demonstrated to be effective in weight management (Díaz & Folgueras, 2011), but finding an effective treatment strategy for obesity is still an on-going struggle by considering its prevalence. This shows that we need to demonstrate new treatments or some complementary supplements to cope with this problem. Therefore, the present study aimed to determine and compare the effects of single strain of bacteria including LcS, *B. longum* and a combination of these two strains in high fat diet induced rats.

Significance of the study

Overweight and obesity were reported in all around the world in both sexes which increase the risk of chronic diseases such as CVD, stroke and T2DM (Greene et al., 2006). Even though there are some studies which determine the obesity prevalence in Malaysia, no study has been conducted to investigate the effect of probiotic supplementation as an adjunct treatment for obesity and body weight management.
Earlier studies reported that microbiota and gut microbiota plays an important role in energy intake from food and energy stores in the body (Zarrati et al., 2014). It has been reported that different strain of bacteria has diverse effect on obesity such as reducing body weight, lipid profile and inflammatory markers. There is little known about the effectiveness of probiotic as a single strain compared to multi strain. Hence this research investigates the effectiveness of single strain and multi strain of bacteria on body weight management and related metabolites.

Research question

- Are there any significant differences between effects of single strain and combination strains of bacteria on body weight and obesity related markers in high fat diet-induced obese rats?

Objectives

General objective

To study the effects of probiotic supplementation on markers of obesity in high fat-diet induced obese rats.

Specific objectives

i. To determine and compare the efficacy of single strain and combination of bacteria strains on body composition and visceral fat.
ii. To determine and compare the effects of single strain and combination of bacteria strains on the lipid profile (HDL, LDL, TG, total cholesterol) of obese rats.
iii. To determine and compare the effects of single strain and combination of bacteria strains on pro-inflammatory (leptin), anti-inflammatory (adiponectin) and inflammatory (IL-6, TNF-Ů, CRP) markers in obese rats.
iv. To determine and compare the quantity expression of ANGPTL-4, PPARɔ, LPL and IL-6 genes affected by *B.longum* and LcS as a single strain or a combination in high fat diet-induced obese rats.
v. To determine and compare the bacterial colonization of LcS and *B.longum* in fecal of all supplemented rats.

Hypothesis

- There is a significant difference in the efficacy of single strain and combination strains of bacteria on body weight, fat visceral, lipid profile, inflammatory, anti inflammaltory and pro-inflmmatory biomarkers of obese rats.
- There is a significant difference in quantity expression of some genes related to obesity in rats supplemented with single strain and combination strains of bacteria.

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