Nutrición Hospitalaria

Nutr Hosp. 2013;28(4):1039-1048
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisión

Intestinal microbiota; relevance to obesity and modulation by prebiotics and probiotics

Sandra Tavares da Silva[1], Carolina Araújo dos Santos[1] and Josefina Bressan[2]

[1]MSc student in Nutritional Science. Federal University at Viçosa. Brazil. 2Professor at the Department of Nutrition and Health. Federal University of Viçosa. Brazil.

Abstract

Introduction: **The intestinal microbiota has several beneficial functions related to host health. Studies suggest that it may be related to the presence of metabolic diseases, including obesity.**

Objective: **A bibliographic survey was carried out upon the relationship between the intestinal microbiota and obesity and the possible impacts of the use of prebiotics and probiotics, aiming to understand this complex and promising interaction.**

Methods: **A search was conducted in the Lilacs, PubMed, SciElo and ScienceDirect databases, using the keywords "gut microbiota" and "obesity".**

Results and discussion: **We identified 613 original studies. After careful selection, 61 original articles were included in this review. The others indicated that there are differences in the microbial composition between obese and non-obese patients and the possible mechanisms involved. Alteration is caused in the energy homeostasis, in the use of dietary intake and storage of lipids due to the composition of the intestinal microbiota. Among the studies that evaluated the microbiota modulation, seven used probiotics; 24 used prebiotics, and five studies were performed using food. After dietary manipulation, the growth of bifidobacteria was obtained in 10 studies, in association with weight reduction, adipogenic effects of diet, intestinal permeability and inflammatory markers.**

Conclusion: **Knowledge on the impact of the microbiota on metabolic pathways allows to conceive new factors associated with obesity and modulation by prebiotics and probiotics. In this sense, the main effect observed was the increase in bifidobacteria, usually accompanied by weight loss and enhancement of parameters related to obesity.**

(*Nutr Hosp.* 2013;28:1039-1048)

DOI:10.3305/nh.2013.28.4.6525

Key words: *Intestinal microbiota. Obesity. Prebiotics. Probiotics.*

Correspondence: Josefina Bressan.
Department of Nutrition and Health.
Federal University of Viçosa.
Avenida PH Rolfs, s/n, Centro.
36 570-000 Viçosa, MG, Brazil.
E-mail: jbrm@ufv.br

Recibido: 22-II-2013.
Aceptado: 27-VI-2013.

MICROBIOTA INTESTINAL; RELEVANCIA PARA LA OBESIDAD Y LA MODULACIÓN DE LOS PREBIÓTICOS Y PROBIÓTICOS

Resumen

Introducción: **La microbiota intestinal tiene varias funciones beneficiosas relacionadas con la salud del hombre y estudios sugieren una posible relación con la presencia de enfermedades metabólicas como la obesidad.**

Objetivos: **Se realizó una revisión sobre la relación entre la microbiota intestinal y la obesidad, así como los posibles impactos del uso de pre y probióticos, a fin de conocer como ocurre esta compleja interacción.**

Métodos: **Se realizó una búsqueda electrónica de la literatura en las bases de datos Lilacs, PubMed, Science Direct y Scielo utilizandose las palabras clave "microbiota intestinal" y "obesidad".**

Resultados y discusión: **Se identificaron 613 estudios. Después de aplicar los criterios de inclusión y exclusión, 61 artículos originales fueron incluidos. La composición de la microbiota intestinal promueve alteración en la homeostasis energética, en la utilización de la dieta ingerida y en el almacenamiento de los lípidos. De los estudios que evaluaron la modulación de la microbiota, siete utilizaron probióticos y 24 prebióticos, de estos cinco estudios con alimentos. El aumento de bifidobacterias tras la manipulación dietética se observó en 10 estudios, asociándose a la reducción de peso, a los efectos adipogénicos de la dieta, a la permeabilidad intestinal y a los marcadores inflamatorios.**

Conclusiones: **La aclaración del impacto de la microbiota en las vías metabólicas permite encontrar nuevos factores asociados a la obesidad y la modulación por pre- y probióticos. En este sentido, el principal efecto observado fue un aumento de bifidobacterias, que usualmente está acompañado por la pérdida de peso y los parámetros relacionados con la obesidad.**

(*Nutr Hosp.* 2013;28:1039-1048)

DOI:10.3305/nh.2013.28.4.6525

Palabras clave: *Microbiota intestinal. Obesidad. Prebióticos. Probióticos.*

Abbreviations

AMP: Adenosine Monophosphate.
AMPK: AMP-Activated Protein Kinase.
ANGPTL 4: Angiopoietin-Like 4.
BMI: Body Mass Index.
CD 28: Cluster of Differentiation 28.
EG: EmuGold®.
FIAF: Fasting-Induced Adipose Factor.
FOS: Fructooligosaccharides.
GLP-1: Glucagon-Like Peptide-1.
GOS: Galactooligosaccharides.
IL-6: Interleukin-6.
Lilacs: Latin American and Caribbean Literature.
LPL: Lipoprotein Lipase.
LPS: Lipopolysaccharides.
MeSH: Medical Subject Headings.
n-3 PUFA: Omega-3 Polyunsaturated Fatty Acids.
PV: PreVitae®.
SCFA: Short Chain Fatty Acids.
Scielo: Scientific Eletronic Library Online.
SRCD: Mixture of aqueous extract of Salacia reticulate and Cyclodextrin.
TG: Triglycerides.
TLR4: Toll-Like Receptor-4.
TNF-α: Tumor Necrosis Factor α.
VLDL: Very Low Density Lipoprotein.

Introduction

Symbiosis between a host and the intestinal microbiota is essential for triggering local and systemic responses favorable to the health of the host. The intestinal microbiota is composed of about 100 trillion bacteria and encompasses more than 1,000 species.[1,2,3,4] It plays an important role in protection against pathogenic microorganisms, development and homeostasis of immune cells, digestion of polysaccharides that is indigestible by human enzymes and fat metabolism, among other functions.[1,2,5]

Food is the substrate for the growth of microbiota and directly affects its composition. Bazzocchi et al.[6] claim that increased consumption of refined sugars, saturated fat and sodium, to the detriment of fiber, minerals, vitamins and antioxidant compounds has led to significant changes in the intestinal ecosystem over the years, which may result in increased chronic diseases, such as obesity.[7]

Studies suggest that the intestinal microbiota plays an important role in energy homeostasis, and that the microbiota of individuals with predisposition to obesity is favorable to the occurrence of metabolic diseases.[8,9] It is considered the existence of an "obesogenic microbiota" that can extract energy from the diet more efficiently10 and relate to subclinical chronic inflammation due to dysbiosis and increased intestinal permeability.[11,12] Thus, knowledge on the intestinal microecology, as well as their signaling pathways and regulation, can help identify new therapeutic and intervention targets.[9] In this context, microbiota manipulation by prebiotics and probiotics becomes a possible modifier of the microbial profile and can favor the health of hosts, by triggering beneficial systemic responses.[13]

Therefore, this article aims to analyze scientific literature on the relevance of the intestinal microbiota to obesity and the possible mechanisms involved, highlighting possible ways of modulating it in order to prevent and/or treat obesity.

Methods

Search strategy

This study is a literature review of scientific articles containing: (i) basic research on the relationship between intestinal microbiota and obesity, (ii) clinical studies about the intestinal microbiota and the modulation by prebiotics, (iii) clinical studies about the intestinal microbiota and the modulation by probiotics. This literature review was conducted in major health databases: Medline, Lilacs, PubMed and SciELO and ScienceDirect. The following keywords were used in the search: terms "gut microbiota" and "obesity" paired with "prebiotics" and "probiotics" and the same expressions in Portuguese and Spanish. MeSH (Medical Subject Headings) was consulted for guidance in the selection of the descriptors used in the review process. The titles and abstracts of all studies identified by the search on electronic platforms were screened. The full texts of potentially relevant studies were read to note the inclusion criteria. Full papers were obtained from journals available on the website of the CAPES Foundation (Ministry of Health, Brazil). We excluded those studies that did not make reference to the relationship between intestinal microbiota and obesity or modulation by prebiotics and probiotics. The period considered for inclusion of articles was from 2000 to 2012.

Identification of studies

Figure 1 shows the flowchart for the selection of the articles used in this study.

The initial search provided 1,041 articles. After exclusion of the review studies, and duplicated results, 613 articles were separated for the study. The first selection was carried through the reading of the titles, followed by analysis of the abstracts and, finally, the assessment of the full texts and selection. After this refinement, 61 articles that deal with intestinal microbiota and its relationship with obesity were selected. Twenty-nine experimental studies and five experimental trials were analyzed. The remaining articles addressed differences in microbial composition between obese and non-obese patients as well as the mechanisms involved.

The search for articles was conducted independently by two researchers, who selected together the works to be included in the study. The papers selected were organized into two themes: relevance of microbiota to obesity and modulation by prebiotics and probiotics.

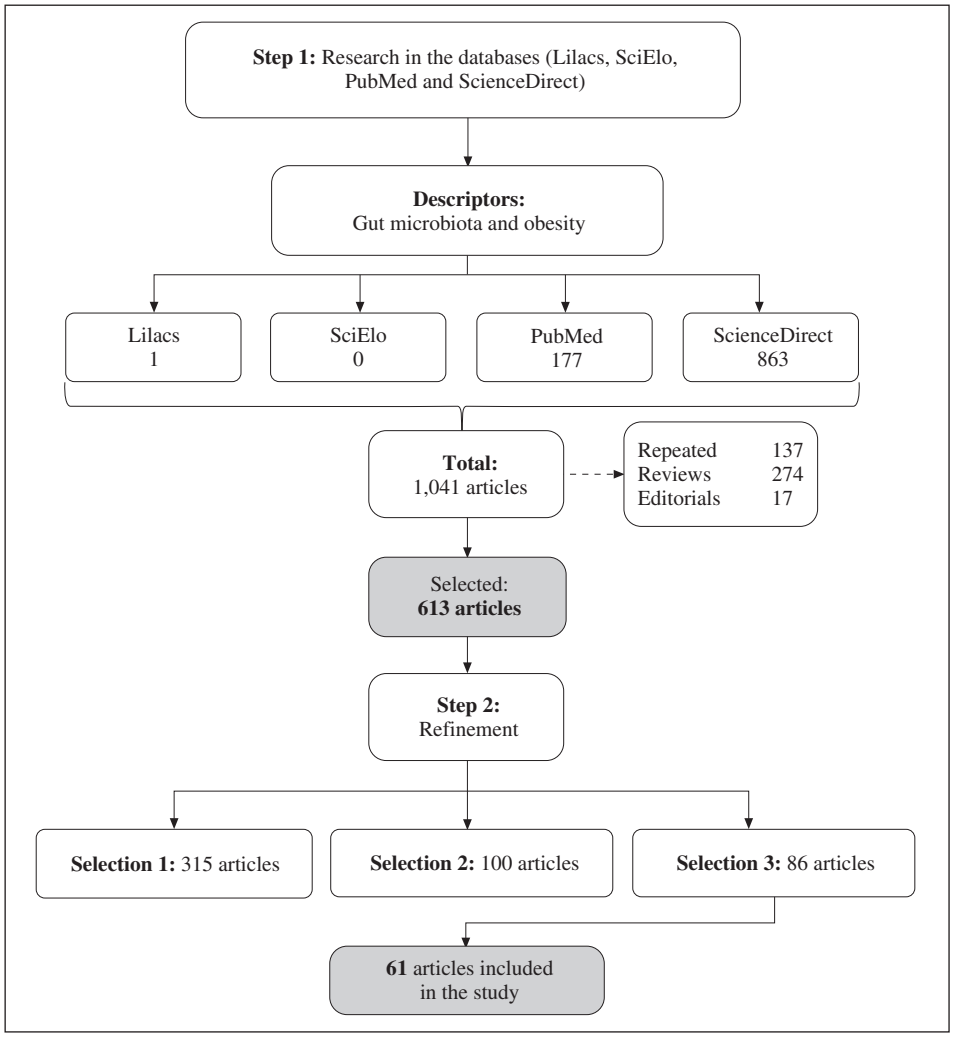

Fig. 1.—Flowchart for the selection of articles at the following databases: Lilacs, SciElo, PubMed and ScienceDirect virtual library.

Results and discussion

Intestinal microbiota and its relation with obesity

The identification of differences in the intestinal microbiota of obese and thin people[14] suggests the involvement of microbiota in energy homeostasis and storage of lipids.[11] Changes in microbial composition were observed in diabetic[15] animal models and in those with metabolic syndrome,[16] which reinforces its possible association with metabolic disorders.

The colonization of germ-free mice with the intestinal microbiota of normal mice increased their body fat in about 60%, reduced lean body mass and caused insulin resistance, despite the decrease in 29%[9] of food intake. Germ-free animals, even when subjected to high fat diet, did not present hyperfagic behavior, nor increased adiposity or developed metabolic disorders, such as insulin resistance.[17] Hence it strengthens the hypothesis that intestinal microbiota affects the amount of energy extracted from diet and consequently helps increase the storage of lipids in the body. In the study conducted by Turnbaugh et al.,[10] the microbiota of obese mice was more effective in harnessing energy from food, and, when transferred to germ-free animals, it also promoted increased adiposity.

The increased expression of genes related to codification of enzymes which are responsible for the degradation of indigestible polysaccharides would lead obese animals to greater generation of fermentation products, with fewer calories remaining in the feces, compared to thin animals.[10] In this case, the intestinal microbiota would affect both sides of energy balance by acting in absorption and regulating host genes related to obesity.[18]

In another study on transfer of microbiota to germ-free animals, the acquisition of microbiota led to a rapid weight gain associated with the stimulation of hepatic glycogenesis and triglyceride synthesis. After installation of the microbiota, stimulation of detoxification pathways was observed with altered expression of cytochrome P450 enzymes, strengthening microbial activity in the process of xenobiotic metabolization.[19]

Human intestinal microbiota is composed predominantly of two phyla: *Firmicutes and Bacteroidetes.*[20] Both in humans and in animal models, obesity was correlated to changes in these groups[8,21-23] and obese

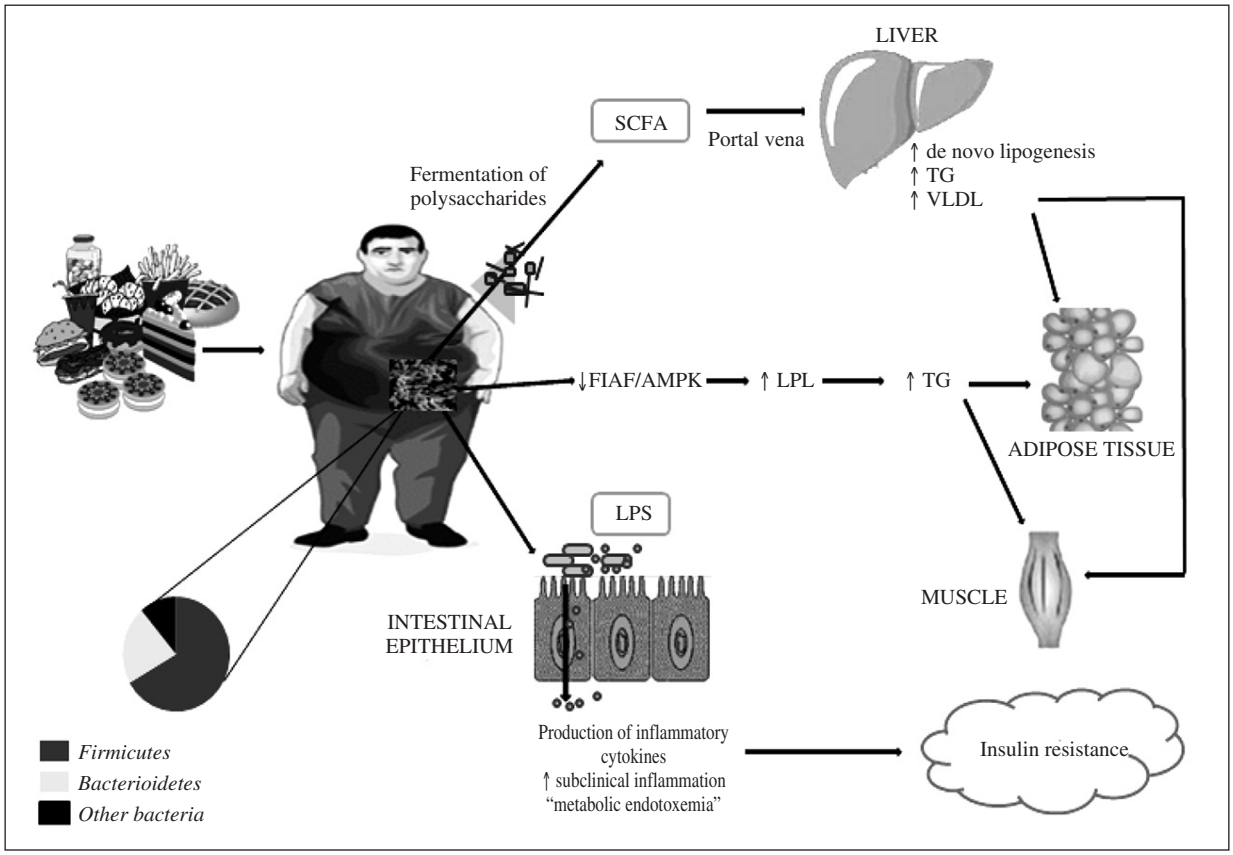

Fig. 2.—Possible mechanisms associated with the relationship between intestinal microbiota and obesity. SCFA: Short-chain fatty acids; LPS: Lipopolysaccharides; TG: Triglycerides; VLDL: Very low density lipoproteins; LPL: Lipoprotein lipase; FIAF: Fasting-induced adipose factor; AMPK: AMP-activated protein kinase (adenosine monophosphate).

individuals would present predominance of *Firmicutes* and a smaller proportion of *Bacteroidetes* when compared to non-obese.[15]

The comparison of sequences of 16S rRNA of intestinal bacteria of obese (ob/ob) and lean (ob/+ and +/+) mice showed a 50% reduction in the *Bacteroidetes* and proportional increase in the *Firmicutes.*[8] In obese pigs, the proportion of *Bacteroidetes* was negatively correlated with body weight when compared to lean pigs, even when both groups were fed with the same diet and underwent the same environmental conditions.[24]

In studies with humans, comparisons of the microbiota were made among 20 obese individuals to 20 healthy ones with normal weight (controls) and to 9 patients with anorexia nervosa. The comparison confirmed the reduction of *Bacterioidetes* in obese people, as observed in animal models; and there was no difference for *Firmicutes* among the groups. It was observed, however, a significant increase in *Lactobacillus* in obese. Since this species is widely used in food industry, people should be warned about its possible association with obesity. In the same study, the anorexic patients showed significantly higher concentration of *Methanobrevibacter smithii* suggesting a possible adaptive response to nutrient deprivation. Besides removing excess H_2 from the intestinal lumen, which compromises the fermentation process, *M. smithii* reduces H_2 with CO_2 for methane production leading to better use of a hypocaloric diet.[22]

Zhang et al.[14] observed an increase of the group *Archaea* in obese individuals, a group that in animal models was associated with higher extraction of polysaccharides from the diet, by the removal of H_2 formed by fermentation and increased production of short chain fatty acids (SCFA).[25]

Differences between the microbial profile of obese and non-obese were also observed in pregnant women[26,27] and children.[28,29] In a prospective study, it was observed that the composition and development of the microbiota in children is influenced by weight, Body Mass Index (BMI), and the weight gain during pregnancy. In the groups *Bacteroides, Clostridium* and *Staphylococcus,* a clear change was observed in the predisposition to greater energy storage and development of inflammatory processes.[26]

Organisms predisposed to obesity are believed to have an intestinal microbial community that promotes more efficient extraction and/or storage of energy from the diet consumed when compared to the microbiota of non-obese[8] and that the diet would be able to modulate the microbial ecology.[21] It is proposed that some mechanisms are interconnected (fig. 2): fermentation

of dietary polysaccharides that cannot be digested by human enzymes, subsequent intestinal absorption of monosaccharides and SCFA, transport to the liver and production of triglycerides by *de novo* synthesis, with lipid deposition in the adipocytes and transport to other tissues, such as muscles.[9,30]

Besides increased utilization of the nutrients ingested, recent studies suggest the occurrence of a relationship between the composition of the microbiota and subclinical chronic inflammation associated with obesity.[17] Bacterial lipopolysaccharides (LPS) are believed to trigger this process. LPS are products that degrade the cell wall of gram-negative bacteria that, in large quantities, are transported to the intestinal capillaries by a mechanism that depends on the TLR4 receptor (Toll-Like Receptor-4) of the intestinal mucosa. The binding of LPS to the TLR4 receptor initiates a cascade of inflammatory events with the secretion of proinflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α). Transported to other tissues by chylomicrons synthesized from a high fat diet, LPL stimulate the production of inflammatory cytokines and promote a condition called "metabolic endotoxemia.[11]

Thus, the sequence of the events that increase inflammatory condition relates to (1) increased LPS in the lumen due to changes in microbiota; (2) reduced activity of intestinal alkaline phosphatase, an enzyme which is present in the brush border related to LPL detoxification; (3) activation of TLR4 in the epithelium, leading to alterations in intestinal permeability; (4) passage of the luminal LPL to itself lamina; and (5) increased LPL plasma levels and subclinical inflammation.[17]

Chronic administration of high-fat diet for four weeks significantly increased LPS plasma concentration. When endotoxemia was induced by subcutaneous infusion of LPS, fasting glycemia, insulinemia and the body weight, liver and adipose tissue presented similar increase, as observed in the animals that ingested high-fat diet. Increased inflammatory markers and hepatic triglycerides were also observed. These findings demonstrate that endotoxemia alters inflammatory condition and is related to weight gain and diabetes. It suggests that LPS decrease could be an important strategy in the control of metabolic diseases.[11]

Another mechanism associated with obesity is the suppression of Fasting-Induced Adipose Factor (FIAF) by intestinal microbiota. FIAF is an inhibitor of lipoprotein lipase (LPL), an enzyme that hydrolyzes triglycerides and stimulates its storage in adipocytes. Colonization increases LPL activity and lipid storage through FIAF suppression, an essential procedure for the deposition of triglyceride in fat cells mediated by microbiota.[9,30]

Germ-free C57BL/6 mice were resistant to obesity when submitted to the consumption of a diet rich in fats and sugars. Protection against obesity is believed to be related to two independent but complementary mechanisms that result in reduced lipid storage: high levels of FIAF and increased activity of AMP-activated protein kinase (adenosine monophosphate) (AMPK), an enzyme that favors lipid oxidation in muscles and liver.[30]

Microbial profile can be changed by weight loss. Obese individuals, who initially presented predominance of *Firmicutes* in comparison to *Bacteroidetes,* altered their microbial profile to an inverse proportion after the intake of low-calorie diets (with restriction in carbohydrates or lipids) for one year, regardless of the diet[21] used. Reduced *Firmicute/Bacteroidete* ratio was observed in obese individuals after weight loss, which suggests that the manipulation of specific bacteria could benefit the treatment of obesity. In another study, the replacement of a standard diet by a high-fat diet in mice, led to a reduction of *Bacteroidetes* and increase of *Firmicutes* and *Proteobacteria,* regardless of the presence or absence of obesity, which suggests that a high fat diet, instead of obesity itself, as the main responsible for changes in intestinal microbiota and determines its composition.[31]

Also associated with weight loss, and possibly with changes in the amount and type of diet eaten, bariatric surgery is related to changes in microbial diversity.[32] Reduction in the phylum *Firmicutes* was evident in individuals after Roux en Y gastric bypass procedure, as well as a proportional increase in *Gammaproteobacteria.*[14]

Therefore, studies indicate the potential of intestinal microbiota as a biomarker, mediator and new therapeutic target for metabolic diseases,[10] including obesity.

Microbiota modulation through prebiotics and probiotics

Due to evidence of the relationship between intestinal microbiota and obesity, it is necessary to understand if it is possible to manipulate this microbiota to prevent obesity or contribute to weight reduction. In this sense, studies with animals and humans have been developed using food and compounds with prebiotic and probiotic allegation.

Studies with animal models are presented in table I,[33-57] focusing on the main objective, the test food/compound, and the main findings.

Only two studies with animal models were carried out with food, namely, wheat, artichoke[50] and rye.[51] Both presented results of less weight gain in the experimental groups.

Among the studies that used probiotics, the *Lactobacillus* species were the most explored and presented different results. While the administration of *Lactobacillus ingluvieie* and *Lactobacillus* increased body weight[44,49,56] and inflammatory markers in mice,[44] doses of *Lactobacillus paracasei* reduced fat accumulation. This result was explained by the authors as an effect of *L. paracasei,* which increased gene expression for

Table I
Experimental studies relevant to the topic of obesity, available at the following databases: Lilacs, SciElo, PubMed and ScienceDirect, virtual library, from 2000 to 2012

Main objective	*Prebiotics, probiotics or others*	*Results*	*Ref.*
Modulation of the microbiota	Resistant starch	↑ de *Bifidobacterium;* ↓ weight, ↑ in butyrate production, ↓ of inflammation and apoptosis of ridges	33, 34
	Wheat arabinoxylans	↓ adipogenic effects of the high fat diet, ↑ of *Bifidobacterium, Bacterioidetes* and *Roseburia sp.*	35
	Cellulose	↑ of *Bifidobacterium* and total bacteria	36
	High fat diet	↑ of permeability and ↓ in the protein expression of the intercellular junctions	37
	Lipid extract of Sorghum	↑ of *Bifidobacterium*	38
	Dietary Fiber	↑ in the total amount of bacteria	33
	Chitin-glucan in fungi	↓ weight gain, ↑ of *Roseburia sp.*	39
	Inulin	↑ of *Bifidobacterium, Roseburia sp., Clostridium cluster* XIVa; ↓ of *Bacterioidetes* and ↑ of *Firmicutes*	40, 41
	Various *Lactobacillus*	↑ in Lactobacilos diversity; ↑ weight gain, ↑ in the number of DNA copies for *Lactobacillus* and *Firmicutes;* ↑ of inflammation	42, 43, 44
	Brewer's yeast	↓ of *Bacterioidetes* and ↑ in the production of SCFA*	45
	n-3 PUFA	Absence of results	46
	Oligofructose	↑ of *Bifidobacterium, Lactobacillus* and *Clostridium coccoides,* with ↓ of intestinal permeability and inflammation	36, 41
	Various prebiotics	↓ of Firmicutes and ↑ of *Bacterioidetes*	47
Lipid reserve	Various *Lactobacillus*	↓ in the fat store; ↓ in the size of adipocytes	48, 49
Metabolic effects	Artichokes (FOS)	↓ food consumption, weight gain and gastric emptying	50
	Rye	↓ weight gain, adiposity, total cholesterol, TG**	51
	High fat diet	↑ *Bifidobacterium* and *Lactobacillus,* ↓ IL-6 and CD68	52
	Mixture of Salacia reticulata and ciclodextrina (SRCD)	↓ food intake, weight gain, visceral fat, TG** in the liver, butyrate and SCFA*	53
	Isoflavones and Lignans	*Germ-free* animals absorb phytoestrogen of isoflavones and lignans, but the production of equol is limited by the presence of microbiota with ↑ capacity to produce equol	54
	Lactitol	↓ weight gain and ↑ of postprandial Peptide YY	55
	Lactobacillus plantarum	↑ in weight gain and ↓ glycemic response	56
	Wheat	Absence of significant effects	51
Risk of Diabetes	High fat diet + Guar gum	↓ weight gain and ↑ in IR ↑ markers and production of SCFA*	57

*SCFA: Short Chain Fatty Acids; **TG: Triglycerides; # IR: Insulin Resistance; ↑ :increase; ↓ : decrease.

ANGPTL 4 *(Angiopoietin-Like* 4), a circulating lipoprotein lipase inhibitor.[48] In another study, the addition of Lactobacillus plantarum to the high fat diet reduced the average size of adipocytes compared to the control diet.[49]

Supplementation with *Lactobacillus ingluviei* in the diet of BALB/C mice led to increased DNA expression for *Firmicutes* and *Lactobacillus.*[44] As previously demonstrated, increased proportion of *Firmicutes* is a common finding in obese mice[12,41,47] and some studies with probiotics have shown effects that favored reduction in this proportion.[41,47]

Everard et al.[47] administered prebiotics to genetically obese animals and observed reduction in the amount of *Firmicutes* and increase in the amount of *Bacterioidetes,* as well as reduced lipid reserves. In the study of Panell and Reiner,[41] the amount of *Bacterioidetes* was negatively correlated with the consumption of energy, fat percentage, and body weight.

Other microorganisms seem to have a significant effect on the "obesogenic microbiota", such as bifidobacteria. Among the legumes studied by Queiróz-Monici et al.,[33] dietary fiber and resistant starch from pea led to a significant increase in the content of bifidobacteria. When analyzing the effects of fermentable (oligofructose) and non-fermentable (cellulose) fibers on the intestinal microbiota of obese mice, Cani et al.[36] found more significant results in the groups that received oligofructose. This group, compared to control, showed increased total content of bacteria, *Bifidobacterium* spp., *Lactobacillus* spp. and *Clostridium coccoides.* In the group treated with cellulose,

increased total content of bacteria and the *Bifidobacterium* spp. was observed. In this study, it was also concluded that the use of prebiotics reduced intestinal permeability, and the latter was related to the growth of *Bifidobacterium* spp.

High fat diets increase intestinal permeability[12,37] and one of the reasons for that may be the reduction of gene expression that encode the proteins of the junctions among colonocytes.[37] The results presented by Cani et al.[36] point out that the modulation of the microbiota by using prebiotics in mice may favor the intestinal wall by reducing endotoxemia and systemic and liver inflammation, which brings beneficial consequences for metabolic disorders.

The use of prebiotics and probiotics aiming to modulate the hormonal response of the gastrointestinal tract has also been investigated in animals.[41,44,53,55] The administration of a mixture of aqueous extracts during six months reduced food intake and, consequently, weight gain, followed by an increase in serum adiponectin, a hormone with significant anti-inflammatory[53] activity. The lactitol supplementation increased the acute postprandial of peptide YY.[55] The addition of inulin and oligofructose also increased the serum concentrations of this peptide, which is a hormone with anorexigenic action.[41] The hormone leptin is another appetite suppressant that has been positively correlated with weight.[49,51] Cani et al.[36] reported that oligofructose caused an increase in the concentrations of GLP-1 *(Glucagon-Like Peptide-1),* a hormone that acts on gastric emptying.

The addition of prebiotics and probiotics to the diet of animals is also associated with increased tolerance to glucose,[39,47,51] reduction of low-grade inflammation[47] as well as in rate of total cholesterol,[49,56] which are conditions often related to obesity.

The works on humans are summarized in table II.[4,58-61]

Among the studies analyzed, four deal with the modulation of intestinal microecology, three of those describe the expansion in the number of bifidobacteria.[4,58,59] Although these studies do not report significant effects on food intake, except for the study with gums,[61] works using animals associate increased bifidobacteria to reduced food intake[12] and increased concentrations of anorexigenic hormones.[36,41]

The increase in bifidobacteria observed among coffee drinkers was explained by the inhibition of oxidant species, propitiating the proliferation of *Bifidobacterium spp.*[52] On the other hand, the bifidogenic effect found by Davis et al.[59] was not supported by all volunteers, even with high doses of chocolate with galactooligosaccharides. Such fact may indicate the

Table II

Clinical trials relevant to the topic of obesity, available at the following databases: Lilacs, SciElo, PubMed and ScienceDirect virtual library, from 2000 to 2012

Intervention	*Allegation*	*Study*	*Results*	*Ref.*
Coffee	Prebiotics. Antioxidant effects	16 healthy individuals, between 21 and 57 years of age; 3,4g of instant coffee, in 150 to 200 ml of water, for 3 weeks	↑ bifidobacteria	58
Chocolate with Galactooligosaccharides (GOS)	Prebiotics. Bifidogenic effect.	18 individuals, between19 and 60 years of age, received chocolate containing: 0 g, 2,5 g, 5 g or 10 g of GOS, with duration of 3 weeks for each dose and washout of 2 weeks	Chocolate with 5 and 10 g of GOS resulted in ↑ increased bifidobacteria, but this effect cannot be sustainable for all individuals.	59
Lactobacillus rhamnosus	Probiotics and transferable from mother to child, and can be maintained over time	159 pregnant women received probiotics for 4 weeks before delivery and six months after delivery	Excessive weight gain was observed from fetal period to 24-48 months or after 24-48 months, and the intervention prevented weight gain in the fetal period up to 24-48 months.	60
Apple	Prebiotics. Hypolipidemic, antioxidative; bacteriostatic effect on *Staphylococcus aureus, Streptococcus faecalis, Pseudomonas aeruginosa* and *Escherichia coli*	Eight healthy men between 21 and 60 years of age, with free diet; addition of two apples/day for two weeks	↑ in the amount of *Bifidobacterium* and *Enterobacteriaceae* and ↓ of *Clostridium;* tendency to ↑ in the content of SCFA*; ↓ in the content of fecal ammonia	4
EmuGold (EG) and PreVitae (PV) - Arabic gum	Increased saciety	58 healthy individuals, mean age of 36 years, received different doses of EG and PV	Intake of 40 g of PV ↓ food consumption and ↑ saciety	61

SCFA*: Short Chain Fatty Acids; ↑: increase; ↓: reduction.

development of resistance to probiotics, which may also occur with other species, and should be considered during investigation.

Shinohara et al.[4] assessed the effects of apple consumption in healthy volunteers and found increased content of *Bifidobacterium* and *Lactobacillus* in feces while *Bacterioidetes* presented reduction. The authors contend that the increased amount of SCFA, resulting from the increase of certain groups of bacteria by pectin fermentation, inhibited the growth of Bacterioidetes. Moreover, they claim that regular use of apple, one of the most common fruits worldwide, may have beneficial effects on health. According to Calame et al.,[61] Arabic gum may be important for the treatment of obesity or weight maintenance once they increase satiety, thus reducing food intake.

In order to evaluate the impact of a prenatal intervention with probiotics on the development of obesity in children in a period of 10 years, units containing *Lactobacillus rhamnosus* or placebo were administered to pregnant women. Through the anthropometric measurements the concluded that early modulation of the microbiota could modify the standard of weight gain in children during the first six months of life.[60] However, the breast-feeding condition of the children involved in the study was not clear and may cause some confusion since breast-feeding itself provides numerous benefits, including prevention of obesity in childhood and adult life.[62]

Ten of the animal studies that analyzed microbiota modulation reported increased amount of bifidobacteria,[4,33,34,35,36,38,40,41,52,58] which was followed by reduced weight gain,[33,34] reduced adipogenic effects of a high fatdiet,[35] reduced intestinal permeability[36,41] and decreased inflammatory markers.[34,52] The modulation of these microorganisms is supposed to contribute to the prevention and even reduction of the impacts of excessive weight. In the clinical trials analyzed, increased *Bifidobacterium* was observed after three weeks of coffee intake (three cups a day); two weeks of apple intake (two units a day);[34,52] and three weeks of consumption of 5 g or 10 g of chocolate containing galactooligosaccharides.[58] Other effects were reported in the work of Shinohara et al.,[4] including increased production of SCFA. The relatively short period of the clinical trials may have been insufficient to make the benefits that accompany the increased bifidobacteria, which were found in the experimental studies, could be clinically visible in humans.

Advances achieved in knowledge about the role of each species may contribute to the "obesogenic microbiota". Neyrink et al.[35] analyzed the effects of chitinglucan on dysbiosis in mice with obesity induced by high fat diet and found a negative correlation between the bacterium *Clostridium* XIV (e.g. *Roseburia* spp) and weight gain and lipid accumulation. Million et al.[13] examined feces of lean and obese individuals and identified the depletion of *Methanobrevibacter smithii* and *Bacterioidetes* and the presence of *Lactobacillus reuteri,* under obesity condition.

Progress in genomics techniques will soon allow the determination of which microorganisms among the species are the main responsible for increased conversion of food into energy in the large intestine. It will also reveal the most effective probiotics in the modulation of "obesogenic microbiota".

Conclusion

The participation of the intestinal microbiota in weight gain and the elucidation of its impact on metabolic pathways lead to factors associated with obesity and indicate new possible intervention targets. Regarding modulation by prebiotics and probiotics, differences in methods and results were observed. However, increased bifidobacteria were the main modulator effect observed, usually accompanied by weight loss and obesity-related parameters, supposing the minimization of the impact of excess weight on health. The short period of intervention of some studies may have been the cause of little apparent effects, which are promising, though.

References

1. Kassinen A, Krogius-Kurikka L, Mäkivuokko H, Rinttilä T, Paulin L, Corander J et al. The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects. *Gastroenterology* 2007; 133 (1): 24-33.
2. Fletcher CM, Coyne MJ, Villa OF, Chatzidaki-Livanis M, Comstock LE. A general o-glycosylation system important to the physiology of a major human intestinal symbiont. *Cell* 2009; 137 (2): 321-31.
3. Garrett WS, Gallini CA, Yatsunenko T, Michaud M, DuBois A, Delaney ML, et al. Enterobacteriaceae act in concert with the gut microbiota to induce spontaneous and maternally transmitted colitis. *Cell* 2010; 8 (3); 292-300.
4. Shinohara K, Ohashi Y, Kawasumi K, Terada A, Fujisawa T. Effect of apple intake on fecal microbiota and metabolites in humans. *Anaerobe* 2010; 16 (5): 510-5.
5. Holmes E, Li JV, Athanasiou T, Ashrafian H, Nicholson JK. Understanding the role of gut microbiome-host metabolic signal disruption in health and disease. *Trends Microbiol* 2011; 19 (7): 349-59.
6. Bazzocchi G, Gionchetti F, Almerigi PF, Amadini C, Campieri M. Intestinal microflora and oral bacteriotherapy in irritable bowel syndrome. *Dig Liver Dis* 2002; 34 (2): S48-53.
7. Lobstein T. Prevalence and costs of obesity. *Medicine* 2011; 39 (1): 11-3.
8. Ley RE, Backhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Nat Acad Sci USA* 2005; 102 (31): 11070-5.
9. Backhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A et al. The gut microbiota as an environmental factor that regulates fat storage. *Proc Nat Acad Sci USA* 2004; 101 (44): 15718-23.
10. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 2006; 444 (7122): 1027-31.
11. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* 2007; 56 (7): 1761-72.
12. Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O 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 (8): 1091-103.

13. Million M, Maraninchi M, Henry M, Armougom F, Richet H, Carrieri P et al. Obesity-associated gut microbiota is enriched in *Lactobacillus reuteri* and depleted in *Bifidobacterium animalis* and *Methanobrevibacter smithii. Int J Obes* 2012; 36 (6): 817-25.
14. Zhang H, Dibaise JK, Zuccolo A, Kudrna D, Braidotti M, Yu Y et al. Human gut microbiota in obesity and after gastric bypass. *Proc Nat Acad Sci USA* 2009; 106 (7): 2365-70.
15. Geurts L, Lazarevic V, Derrien M, Everard A, Van Roye M, Knauf C et al. Altered gut microbiota and endocannabinoid system tone in obese and diabetic leptin-resistant mice: impact on apelin regulation in adipose tissue. *Front Microbial* 2011; 2: 149.
16. Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science* 2010; 328 (5975): 228-31.
17. De La Serre CB, Ellis CL, Lee J, Hartman AL, Rutledge JC, Raybould HE. Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation. *Am J Physiol Gastrointest Liver Physiol* 2010; 299 (2): G440–8.
18. Jumpertz R, Le DS, Turnbaugh PJ, Trinidad C, Bogardus C, Gordon JI et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. *Am J Clin Nutr* 2011; 94 (1): 58-65.
19. Claus SP, Ellero SL, Berger B, Krause L, Bruttin A, Molina J et al. Colonization-induced host-gut microbial metabolic interaction. *MBio* 2011; 2 (2): e00271-10.
20. Mahowald MA, Rey FE, Seedorf H, Turnbaugh PJ, Fulton RS, Wollam A et al. Characterizing a model human gut microbiota composed of members of its two dominant bacterial phyla. *Proc Natl Acad Sci USA* 2009; 106 (14): 5859-64.
21. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature* 2006; 444 (7122): 1022-3.
22. Armougom F, Henry M, Vialettes B, Raccah 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 (9): e7125.
23. Sefcíková Z, Kmet V, Bujnáková D, Racek L, Mozes S. Development of gut microflora in obese and lean rats. *Folia Microbiol (Praha)* 2010; 55 (4): 373-5.
24. Guo X, Xia X, Tang R, Zhou J, Zhao H, Wang K. Development of a real-time PCR method for Firmicutes and Bacteroidetes in faeces and its application to quantify intestinal population of obese and lean pigs. *Lett Appl Microbiol* 2008; 47 (5): 367-73.
25. Samuel BS, Gordon JI. A humanized gnotobiotic mouse model of host-archaeal bacterial mutualism. *Proc Natl Acad Sci USA* 2006; 103 (26): 10011-6.
26. Collado MC, Isolauri E, Laitinen K, Salminen S. Effect of mother's weight on infant's microbiota acquisition, composition, and activity during early infancy: a prospective follow-up study initiated in early pregnancy. *Am J Clin Nutr* 2010; 92 (5): 1023-30.
27. Santacruz A, Collado MC, García-Valdés L, Segura MT, Martín-Lagos JA, Anjos T et al. Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. *Br J Nutr* 2010; 104 (1): 83-92.
28. Kalliomäki M, Collado MC, Salminen S, Isolauri E. Early differences in fecal microbiota composition in children may predict overweight. *Am J Clin Nutr* 2008; 87 (3): 534-8.
29. Balamurugan R, George G, Kabeerdoss J, Hepsiba J, Chandragunasekaran AM, Ramakrishna BS. Quantitative differences in intestinal Faecalibacterium prausnitzii in obese indian children. *Br J Nutr* 2010; 103 (3): 335-8.
30. Bäckhed F, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc Nat Acad Sci USA* 2007; 104 (3): 979-84.
31. Hildebrandt MA, Hoffmann C, Sherrill-Mix SA, Keilbaugh SA, Hamady M, Chen YY et al. High fat diet determines the composition of the murine gut microbiome independently of obesity. *Gastroenterology* 2009; 137 (5): 1716-24.
32. Furet JP, Kong LC, Tap J, Poitou C, Basdevant A, Bouillot JL et al. Differential adaptation of human gut microbiota to bariatric surgery–induced weight loss links with metabolic and low-grade inflammation markers. *Diabetes* 2010; 59 (12): 3049-57.
33. Da S Queiroz-Monici K, Costa GE, da Silva N, Reis SM, de Oliveira AC. Bifidogenic effect of dietary fiber and resistant starch from leguminous on the intestinal microbiota of rats. *Nutrition* 2005; 21 (5): 602-8.
34. Nofrarías M, Martínez-Puig D, Pujols J, Majó N, Pérez JF. Long-term intake of resistant starch improves colonic mucosal integrity and reduces gut apoptosis and blood immune cells. *Nutrition* 2007; 23 (11-12): 861-70.
35. Neyrinck AM, Possemiers S, Druart C, Van de Wiele T, De Backer F, Cani PD et al. Prebiotic effects of wheat arabinoxylan related to the increase in bifidobacteria, Roseburia and Bacteroides/Prevotella in diet-induced obese mice. *PLoS One* 2011; 6 (6): e20944.
36. Cani PD, Lecourt E, Dewulf EM, Sohet FM, Pachikian BD, Naslain D, et al. Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. *Am J of Clin Nutr* 2009; 90 (5): 1236-43.
37. Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* 2008; 57 (6): 1470-81.
38. Martínez I, Wallace G, Zhang C, Legge R, Benson AK, Carr TP et al. Diet-induced metabolic improvements in a hamster model of hypercholesterolemia are strongly linked to alterations of the gut microbiota. *Appl Environ Microbiol* 2009; 75 (12): 4175-84.
39. Neyrinck AM, Possemiers S, Verstraete W, De Backer F, Cani PD, Delzenne NM. Dietary modulation of clostridial cluster XIVa gut bacteria (Roseburia spp.) by chitin-glucan fiber improves host metabolic alterations induced by high-fat diet in mice. *J Nutr Biochem* 2012; 23 (1): 51-9.
40. Dewulf EM, Cani PD, Neyrinck AM, Possemiers S, Van Holle A, Muccioli GG et al. Inulin-type fructans with prebiotic properties counteract GPR43 over expression and PPAR - related adipogenesis in the white adipose tissue of high-fat diet-fed mice. *J Nutr Biochem* 2011; 22 (8): 712-22.
41. Parnell JA, Reimer RA. Prebiotic fibres dose-dependently increase satiety hormones and alter Bacteroidetes and Firmicutes in lean and obese JCR: LA-cp rats. *Br J Nutr* 2012; 107 (4): 601-13.
42. Fuentes S, Egert M, Jiménez-Valera M, Ramos-Cormenzana A, Ruiz-Bravo A, Smidt H et al. Administration of Lactobacillus casei and Lactobacillus plantarum affects the diversity of murine intestinal lactobacilli, but not the overall bacterial community structure. *Res Microbiol* 2008; 159 (4): 237-43.
43. Angelakis E, Raoult D. The Increase of Lactobacillus Species in the Gut Flora of Newborn Broiler Chicks and Ducks Is Associated with Weight Gain. *PLoS One* 2010; 5 (5): e10463.
44. Angelakis E, Bastelica D, Amara AB, El Filali A, Dutour A, Mege JL et al. An evaluation of the effects of Lactobacillus ingluviei on body weight, the intestinal microbiome and metabolism in mice. *Microb Pathog* 2012; 52 (1): 61-8.
45. Nakashimada Y, Michinaka A, Watanabe K, Nishio N, Fujii T. Brewer's yeast cell wall affects microbiota composition and decreases Bacteroides fragilis populations in an anaerobic gut intestinal model. *J Biosci Bioeng* 2011; 111 (2): 178-84.
46. Andersen AD, Mølbak L, Thymann T, Michaelsen KF, LauritzenL. Dietary long-chain n-3 PUFA, gut microbiota and fat mass in early postnatal piglet development-exploring a potential interplay. *Prostaglandins Leukot Essent Fatty Acids* 2011; 85 (6): 345-51.
47. Everard A, Lazarevic V, Derrien M, Girard M, Muccioli GG, Neyrinck AM et al. Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. *Diabetes* 2011; 60 (11): 2775-86.
48. Aronsson L, Huang Y, Parini P, Korach-André M, Håkansson J, Gustafsson JÅ et al. Decreased fat storage by Lactobacillus

paracasei is associated with increased Levels of Angiopoietin-Like 4 Protein (ANGPTL4). *PLoS One* 2010; 5 (9): e13087.
49. Takemura N, Okubo T, Sonoyama K. Lactobacillus plantarum strain No. 14 reduces adipocyte size in mice fed high-fat diet. *Exp Biol Med (Maywood)* 2010; 235 (7): 849-56.
50. Goñi I, Jiménez-Escrig A, Gudiel M, Saura-Calixto, FD. Artichoke (Cynara scolymus L) modifies bacterial enzymatic activities and antioxidant status in rat cecum. *Nutr Res* 2005; 25 (6): 607-15.
51. Andersson U, Rosén L, Östman E, Ström K, Wierup N, Björck I et al. Metabolic effects of whole grain wheat and whole grain rye in the C57BL/6J mouse. *Nutrition* 2010; 26 (2): 230-9.
52. Neyrinck AM, Backer F, Cani PD, Bindels LB, Stroobants A, Portetelle D et al. Immunomodulatory properties of two wheat bran fractions – aleurone-enriched and crude fractions – in obese mice fed a high fat diet. *Int Immunopharmacol* 2008; 8 (10): 1423-32.
53. Kishino E, Ito T, Fujita K, Kiuchi Y. A mixture of Salaciareticulata (Kotalahimbutu) aqueous extract and cyclodextrin reduces body weight gain, visceral fat accumulation, and total cholesterol and insulin increases in male Wistar fatty rats. *Nutr Res* 2009; 29 (1): 55-63.
54. Bowey E, Adlercreutz H, Rowland I. Metabolism of isoflavones and lignans by the gut microflora: a study in germ-free and human flora associated rats. *Food Chem Toxicol* 2003; 41 (5); 631-6.
55. Gee JM, Johnson IT. Dietary lactitol fermentation increases circulating peptide YY and glucagon-like peptide-1 in rats and humans. *Nutrition* 2005; 21 (10): 1036-43.
56. Andersson U, Bränning C, Ahrné S, Molin G, Alenfall J, Onning G et al. Probiotics lower plasma glucose in the high-fat fed C57BL/6J mouse. *Benef Microbes* 2010; 1 (2): 189-96.
57. Isken F, Klaus S, Osterhoff M, Pfeiffer AF, Weickert MO. Effects of long-term soluble vs. insoluble dietary fiber intake on high-fat diet-induced obesity in C57BL/6J mice. *J Nutr Biochem* 2010; 21 (4): 278-84.
58. Jaquet M, Rochat I, Moulin J, Cavin C, Bibiloni R. Impact of coffee consumption on the gut microbiota: A human volunteer study. *Int J Food Microbiol* 2009; 130 (2): 117-21.
59. Davis LM, Martinéz I, Walter J, Hutkins R. A dose dependent impact of prebiotic galactooligosaccharides on the intestinal microbiota of healthy adults. *Int J Food Microbiol* 2010; 144 (2): 285-92.
60. Luoto R, Kalliomäki M, Laitinen K, Isolauri E. The impact of perinatal probiotic intervention on the development of overweight and obesity: follow-up study from birth to 10 years. *Int J Obes (Lond)* 2010; 34 (10): 1531-7.
61. Calame W, Thomassen F, Hull S, Viebke C, Siemensma AD. Evaluation of satiety enhancement, including compensation, by blends of gum arabic. A methodological approach. *Appetite* 2011; 57 (2): 358-64.
62. World Organization Health. Indicators for assessing infant and young child feeding practices part 3: country profiles. WHO: Geneva; 2010.