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Leite fermentado e tecido adiposo visceral – possível efeito emagrecedor em obesos e portadores de síndrome metabólica

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Tese para obtenção do grau de

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Orientadora:

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RESUMO

Perina, N.P. **Leite fermentado e tecido adiposo visceral – possível efeito emagrecedor em obesos e portadores de síndrome metabólica.** 2015. 167 f. Tese (Doutorado) – Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo, 2015.

O trato gastrointestinal de humanos é rico em microrganismos que, podem tanto ser benéficos para a saúde do hospedeiro, prevenindo e/ ou tratando a intolerância à lactose, constipação intestinal, síndrome do intestino irritável, entre outras, quanto podem prejudicá-lo, afetando a aquisição de nutrientes e produção de mediadores inflamatórios. Estes distintos papéis da microbiota intestinal são tão marcantes que podem, inclusive, influenciar no desenvolvimento da obesidade em algumas pessoas, podendo levar até mesmo à Síndrome Metabólica. Probióticos e prebióticos podem conferir alterações nas propriedades da microbiota, afetando o crescimento bacteriano e seu metabolismo e, até mesmo, o uso de nutrientes. Assim, o objetivo geral deste trabalho foi avaliar o efeito do uso de leite fermentado simbiótico na obesidade e nos indicadores de Síndrome Metabólica, como circunferência de cintura, TGL, HDL-c, glicemia e pressão arterial, em pacientes com predisposição a esta doença, selecionados de acordo com os critérios de diagnóstico para síndrome metabólica. Para esta pesquisa foram desenhados quatro produtos, três deles inoculados com uma cultura comercial de probiótico - *Bifidobacterium lactis* (BL420), adicionados ou não de casca de maracujá em pó (prebiótico), sendo um deles preparado com uma emulsão de óleos vegetais, que apresenta efeito em prolongar a saciedade; e o quarto produto, fermentado apenas com a cultura clássica *Streptococcus thermophilus*. Avaliaram-se as propriedades tecnológicas dos produtos – físico-química, sensorial, microestrutura, microbiológica, e estudaram-se seus aspectos funcionais. Finalmente, os produtos foram testados em consumidores ao longo de um ensaio clínico durante 12 semanas, período no qual os voluntários tiveram que consumir 100 mL do produto, duas vezes ao dia, todos os dias. A avaliação dos voluntários foi feita antes do início do ensaio e também aos ao final dos 90 dias.

Palavras-chave: Probiótico, Fibra, Leite fermentado, Síndrome metabólica, Obesidade

ABSTRACT

Perina, N.P. **Fermented milk and adipose visceral tissue - possible slimming effects in obese and patients with metabolic syndrome.** 2015. 167 f. Tese (Doutorado) – Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo, 2015.

The gastrointestinal tract of humans is rich in microorganisms which can both be beneficial to host health, preventing and / or treating lactose intolerance, constipation, irritable bowel syndrome, among others, as they can harm, affecting nutrient acquisition and the production of inflammatory mediators. These distinctive roles of intestinal microbiota are so striking that can even influence the development of obesity in some people and may even lead to metabolic syndrome. Probiotics and prebiotics can confer alterations in the microbiota properties, affecting the bacteria growth and their metabolism, and the use of nutrients. Thus, the aim of this study was to evaluate the use of innovative symbiotic fermented milk in obesity and metabolic syndrome indicators such as waist circumference, TGL, HDL-C, blood glucose and blood pressure in patients with a predisposition to this disease, selected according to the diagnostic criteria for metabolic syndrome. For this, four fermented mik were designed, three of them inoculated with a commercial probiotic culture - *Bifidobacterium lactis* (BL420), added or not by passion fruit peel powder (prebiotic), one of them being prepared with an emulsion of vegetable oil, which has effect on prolonguing satiety; and the fourth product, fermented only with the classical culture *Streptococcus thermophilus*. Products´ technological properties were evaluated - physico chemical, sensory, microstructure, microbiology, and functional aspects were studied. Finally products were tested in consumers throughout a clinical trial during 12 weeks, period in which the volunteers had to consume 100 mL of the product twice a day, every day. The evaluation of the volunteers was done before the start of the test and also at the end of the 90 days.

Keywords: Probiotic, Fiber, Fermented Milk, Metabolic Syndrome, Obesity.

CHAPTER 1

1. INTRODUCTION AND LITERATURE REVIEW

1.1. INTRODUCTORY REMARKS

The gastrointestinal tract (GUT) of mammals contains a society of non-pathogenic bacteria, which is complex, dynamic and diverse (TEITELBAUM and Walker, 2002).

Evidence suggests that these trillions of bacteria that typically reside in the humans GUT, collectively called intestinal microbiota, affect the acquisition of nutrients and energy regulation. It is also suggested that lean and obese people have a distinct intestinal microbiota. Together these findings raise the possibility that intestinal microbiota plays an important role in the control of body weight and may be partially responsible for the development of obesity in some people (DIBAISE et al., 2008), which is currently one of the major public health problems that affects both developed and developing countries (SBEM, 2007).

The introduction presented in the following section comprises the main topics approached in this thesis. A brief overview of fermented milk as well as of probiotic bacteria and their importance in human health, especially in obesity, is presented.

1.2. GENERAL INTRODUCTION

1.2.1. Fermented Milk

Fermentating dairy foods are one of the oldest methods of long-term preservation of milk sources. Fermentating milk is quite old and can be placed in the Middle East and traced back long before the Phoenician era (VASILJEVIC; SHAH, 2008). According to the Codex standard for fermented milks (CODEX STAN 243-2003) (WHO / FAO, 2011), “Fermented Milk is a milk product obtained by fermentation of milk, which milk may have been manufactured from products obtained

from milk with or without compositional modification (…), by the action of suitable microorganisms and resulting in reduction of pH with or without coagulation (iso-electric precipitation). These starter microorganisms shall be viable, active and abundant in the product to the date of minimum durability. If the product is heattreated after fermentation the requirement for viable microorganisms does not apply."

Although the preservation role of fermented dairy products was widely recognized and appreciated early, scientists realized in the late 19th century that a wide range of traditional milk products had further advantages in prolonging shelf-life and pleasant sensory properties. Actually, health benefits associated to these fermented dairy products consumption are of growing interests in reseach worldwide.

1.2.2. Probiotics and its beneficial health effects

The term probiotics is derived from Greek and means "for life" (SCHREZENMEIR; VRESE, 2001; NICHOLS, 2007). This name was first used in 1965, in contrast to the word antibiotic to describe substances secreted by a microorganism which stimulates the growth of another (SCHREZENMEIR; VRESE, 2001). Fuller definitions used to describe the word probiotic live bacteria normally associated with substances that promote bacterial growth, constituting components of food or added to foods to provide a pharmacological effect (UTERMOHLEN, 2003).

The original concept of using bacteria to prevent and treat disease appeared about 100 years ago, with the Nobel earner Eli Metchnikoff, who noted that the lactic fermentation prevented putrefaction of milk, and had the idea of using the same principle in the digestive tract, looking for the same purpose, which was proven to be true by the Bulgarian peasants, who had a regular consumption of fermented dairy products and had longer and healthier life expectancy (TANNOCK, 2004).

Currently, the most internationally accepted definition is that probiotics are live microorganisms that when administered in adequate amounts confers a health benefit on the host (FAO / WHO, 2002). According to Teitelbaum and Walker (2002) some of the current criteria used to define probiotics says that they must be of human origin; be non-pathogenic in nature; be resistant to destruction by technical processing; be resistant to destruction by gastric acid and the bile; adhere to the intestinal epithelial tissue; be able

to colonize the GUT, even for a short period of time; produce antimicrobial substances; modulating the immune response and influence human metabolic activities (e.g., cholesterol assimilation, the production of vitamins, etc.).

As the fermented milk used by Metchnikoff, other products containing probiotics can promote positive effects on health, such as yogurt, Yakult®, kefir, among others, that have the ability to positively change the intestinal flora (JONES, 2002).

Various bacteria have been identified according to the definition of criteria for probiotics (TEITELBAUM; WALKER, 2002). Bacteria belonging to the genera Lactobacillus and Bifidobacterium, and, to a lesser extent, Enterococcus faecium, are the most often used probiotics in food supplements (SAAD, 2006). Other types of bacteria studied, used or considered suitable for commercial use, which have probiotic properties such as: *L. casei* spp, *L.* delbrueckii bulgaricus, *Bifidobacterium bifidum*, *B. longum*, *Enterococcus faecium*, *Saccharomyces boulardii*, among others (NICHOLS, 2007).

Probiotic bacteria are associated with many beneficial health effects, which can contribute to the prevention and treatment of various medical conditions including, lactose intolerance, colon cancer, hypercholesterolemia, hypertension, immune system, mineral absorption in the GUT, diarrhea, constipation, irritable bowel syndrome, inflammatory bowel disease, allergies, among others (HASLER, 2002; NICHOLS, 2007). Other possible effects of probiotics are their role in prevention and treatment of hypertension, osteoporosis, atherosclerotic vascular disease associated with dyslipidemia, obesity, allergies and inflammation (TEITELBAUM; WALKER, 2002; Nichols, 2007).

Is important to emphasize that many probiotic bacteria express their most significant effect in improving the overall health of the individual through the gastrointestinal tract, which depends on their ability to adhere to and colonize the intestinal mucosa (NICHOLS, 2007).

1.2.3. Obesity and Metabolic Syndrome

Obesity is a chronic disease characterized by excessive fat accumulation (CARVALHO et al., 2009). Its etiology is complex and multifactorial, resulting of interactions of the genes, environment, lifestyle and emotional factors (ABESO, 2009).

Besides representing a risk factor for many other chronic diseases, obesity is associated with dyslipidemia, diabetes, hypertension and left vascular hypertrophy, which are coronary risk factors. Obesity also favors increased frequency of colon cancer, rectum and prostate in men and bladder cancer, endometrial and breast cancer in women (CARVALHO et al., 2009).

Following the global trend, the prevalence of overweight and obesity is increasing in Brazil. The number of overweight women increased by 67 % since the first evaluation in the period from 1974 to 1985, and among men the increase was even greater, 170 %, giving a jump of 18.5 % of overweight men in 1974- 1985 to 50.1 % in 2009. Obesity also gave big jumps, increasing 25 % among women and 37 % among men in the period 2002-2003 to 2008-2009 (IBGE, 2010).

The Ministry of Health also noted the high prevalence of obesity in Brazil, by the Risk and Protective Factors for Chronic Diseases Surveillance Study through telephone inquiry (VIGITEL). In this research, it was observed that 13.9% of adults are obese, with the highest rate in the population between 55 and 64 years, reaching 19.9 % for men and 21.3 % for women (BRASIL, 2010).

Metabolic Syndrome (MS), in turn, refers to the group of cardiovascular risk factors including diabetes, obesity, dyslipidemia and hypertension (DUVNJAK; DUVNJAK, 2009), increasing the overall mortality by about one and a half times, Cardiovascular in about two and a half times (DBSM, 2005).

According to the First Brazilian Guidelines for Diagnosis and Treatment of Metabolic Syndrome, MS represents the combination of at least three of the following risk factors: abdominal obesity, measured by waist circumference (> 102.0 cm in men and > 88.0 cm in women); high triglycerides (≥ 150 mg /dl); HDL cholesterol (< 40 mg /dl for men and <50 mg / dl for women); high blood pressure (≥ 130 mmHg or ≥ 85 mmHg); impaired fasting glucose (≥ 110 mg /dl, whereas the use of

antihypertensive medication or lipid-lowering, as well as the previous diagnosis of diabetes, in itself, meet the specific criteria (DBSM, 2005).

However, these values were reviewed by the IDF - International Diabetes Federation, which defines some lower parameters for the diagnosis of MS, such as waist circumference (WC), which must have less tolerance for individuals from South and Central America, being > 90.0 cm for men and > 80.0 cm for women, and also fasting glucose ≥ 100 mg /dl (IDF, 2006).

In line with the increasing prevalence of obesity, MS is also growing in developing countries. High prevalence of MS was observed in sub-Saharan Africa and the Middle East. South Africa, Morocco, Oman, Turkey, and Iran showed prevalence of 33.5, 16.3, 21.0, 33.4 and 33.7 %, respectively. Prevalence rates are also high in Venezuela (31.2 %) and in the urban area of Brazil (25.4 %). The situation appears to be similar in South Asian countries (MISRA; KHURANA, 2008).

1.3. THESIS OVERVIEW

Given the high prevalence of obesity and metabolic syndrome, which is strongly associated with increased cardiovascular risk, is evident the importance of seeking healthy food alternatives that can benefit both the control and treatment of individuals already affected by the disease, as well as to prevent this pathology. As seen, probiotics play an important role in modulating the intestinal microbiota, with possible beneficial effects in cases of obesity and metabolic syndrome, controlling hypertension, dyslipidemia, obesity and other risk factors. However, as these effects are not well established in the literature, more research seems necessary to increase knowledge of the role of probiotics in the prevention and treatment of chronic diseases, in particular, of the Metabolic Syndrome.

So, the ultimate goal of this thesis is to evaluate the metabolic effect of new fermented milk consumption in overweight patients and people in risk of Metabolic Syndrome. For this, innovative fermented milks were designed; their technological properties were evaluated - physico chemical, sensory, microstructure, microbiology, and functional aspects were studied. Finally products were tested in consumers throughout a clinical trial. In chapter 2 the effect of the addition of fiber and substituting

milk-fat by a vegetal-oil emulsion and homogenization on viable cell-counts and physicochemical properties of yoghurt were studied. Sensorial analyses and acceptation test of the first tested formulations were investigated in chapter 3, with the application of hedonic scale and projective mapping. In chapter 4 the survival of the probiotic specie and the starter culture was verified. Chapter 5 and 6 presents and discusses the results of the clinical trial realized at University of São Paulo Clinical Hospital HCFM/USP.

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CHAPTER 7

7. SUMMARY AND FUTURE WORK

7.1. THESIS SUMMARY

Chapter 2 discussed about designing a innovatively functional probiotic fermented milk with the enrichment of the milk matrix with passion fruit peel-powder and vegetal oil emulsion (Fabuless™) in six different formulations, fermented with the starter cultures *Streptococcus thermophilus* (TA040) and *Lactobacillus delbrueckii* subsp. *bulgaricus* (LB340) and the probiotic bacteria *Bifidobacterium lactis* (BL420). It was observed that the passion fruit peel-powder's addition had a beneficial effect on the counts of *B. lactis* strains. Besides, an improved fatty acids' profile, due to the substitution of milk cream by the vegetal oil emulsion, with reduced saturated and increased mono-unsaturated and poly-unsaturated fatty acids as an additional beneficial and nutritional factor was noted. The results showed that the microstructure network may indeed affect probiotic viability and its survival in the intestinal tract. Moreover, probiotic yoghurt enriched with passion fruit peel powder and vegetal oil emulsion could, possibly, suppress appetite due to its technological behaviour on fermentation counts of viable bacteria and texture.

In chapter 3 the influence of milk supplementation with passion fruit peel powder and /or vegetal oil emulsion (Fabuless™) was investigated in instrumental firmness, and also about its sensory characteristics, such as flavour, texture (on spoon), creaminess (in the mouth) and overall liking. Milk without supplementation was used as control. The sensory evaluations were conducted by the application of two methods: hedonic scale, that is an affective test, and projective mapping, that is a descriptive test. Despite the observed differences in flavor and global impression there were no

significant changes in consumers' overall liking between supplemented and conventional yoghurts. Overall, the insertion of the vegetal oil and the peel-powder did not provide positive results for the samples mainly for affecting the firmness, which is an attribute of considerable importance for yogurts. In this sense, the supplementation of vegetal oil emulsion and passion fruit peel-powder in yoghurt, although can be an attractive for consumers, with potential benefits to the health, besides the intrinsic role of nutrition, should be carefully evaluated.

In chapter 4 the survival of the classical starter cultre *Streptococcus thermophilus* trought gastrointestinal system by the dynamic simulation of the human digestion was investigated. At the end of simulated dynamic digestion there had been observed a significant reduction of *S. thermophilus* viability mainly due to the low pH and gastric enzyme's action in the stomach. It was also investigated the survival of *L. Bulgaricus* and *Bifidobacterium lactis* strain 420. The first did not survivaled the intestine digestion, but the second reached the end of the GUT in great number, confirming its stronger digestion resistance.

Chapters 5 and 6 described the results of the clinical trial decelloped in collaboration with the team of doctors of the gastroenterology department of the Clinical Hospital of University of São Paulo School of Medicine. In these chapters the effect of the increase in fermented milk consumption was studied and a lot of benefits were observed. In chapter 5 specifically it was observed that, although there is still no consensus on the effect of fermented milk intake on weight control, its consumption, added or not by probiotic cultures and other functional ingredients, combined with diet and exercise may be a good strategy for the long-term prevention of weight gain. In chapter 6, in turn, the increase in fermented milk consumption, especially formulations FM1 and FM3, demonstrated to successfully attenuate metabolic syndrome symptoms

such as waist circumference and blood pressure, with an increase in high-density lipoprotein cholesterol for FM3 group. Some important ACE inhibitors peptides were identified, with possible antihypertensive effect; however, it was not confirmed.

The results indicate a positive effect of B420 on Syndrome Metabolic, when using the fermented milk with B420; the time of consuming the product (3 months) was small to verify a very significant effect. Nevertheless, the results showed a very clear tendency. The product containing only S. thermophilus TA040 has shown positive effects. It was observed also, when consuming this product, an effect on blood pressure, and a bioactive peptide production - antihypertensive peptide, in this product was detected. In this product we observed also a great production of exopolysaccharide – EPS that could justify the observed effects, and more investigation is required to attest this hypothesis. Finally, although very promising, more studies using the same methodology must be conducted to better understand the relation between fermented milk consumption and metabolic syndrome parameters.

7.2. FUTURE WORK

As it has been exposed the consumption of dairy food, specially, as showed in this study, the consumption of fermented milks, is a promissor nutritional strategy to prevent and even ease the metabolic syndrome parameters (ABETE et al., 2011; CRICHTON et al., 2011; PFEUFFER; SCHREZENMEIR, 2006), and also contribute to long-term weight control (ORZANO; SCOTT, 2004). One of the possible promoters of these benefits is the milk fermentation resulting compounds and bioactive peptides (KHALESI et al., 2014; PFEUFFER; SCHREZENMEIR, 2006).

Unfortunatelly, it is still not possible to confirm this hypotese and more research regarding the effect os fermented milk bioactive coumpounds is still needed to better

understand its effect in humam health. Additionaly, the complete knowledge of the benefits of fermented milk consumption could be an important nutritional strategy for public health.

Intestinal microbiota must also be deeply investigates as it can be profoundly influenced by food intake, specially by probiotics, prebiotics and antibiotics intake, by lifestily, subjects country of origin and age, and the manipulation of it's composition is intimately linked with obesity and associated deseases (ANGELAKIS et al., 2012).

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