Journal of Functional Foods 41 (2018) 55–61

Contents lists available at ScienceDirect

Journal of Functional Foods

journal homepage: www.elsevier.com/locate/jff

Effect of the consumption of a synbiotic diet mousse containing *Lactobacillus acidophilus* La-5 by individuals with metabolic syndrome: A randomized controlled trial

Douglas Xavier-Santos[a,b], Egidio Dorea Lima[c], Andréa Name Colado Simão[d], Raquel Bedani[a,b], Susana Marta Isay Saad[a,b,*]

[a] Department of Biochemical and Pharmaceutical Technology, School of Pharmaceutical Sciences, University of São Paulo, Av. Prof. Lineu Prestes, 580, B16, 05508-000 São Paulo, SP, Brazil
[b] Food Research Center, University of São Paulo, São Paulo, Brazil
[c] University Hospital, University of São Paulo, Av. Prof. Lineu Prestes, 2565, 05508-000 São Paulo, SP, Brazil
[d] Department of Pathology, Clinical Analysis and Toxicology, University of Londrina, Av. Robert Koch, 60, 86039-440 Londrina, PR, Brazil

ARTICLE INFO

Keywords:
Probiotic
Prebiotic
Clinical trial
Metabolic syndrome
Mousse

ABSTRACT

This study aimed to evaluate the impact of a synbiotic diet mousse containing *Lactobacillus acidophilus* La-5 and the prebiotics inulin and fructooligosaccharides on anthropometric and blood pressure measurements, biochemical, inflammatory, haematological, and immunological parameters of volunteers with metabolic syndrome (MetS). In a randomized, double-blind, placebo-controlled trial, forty-five volunteers with MetS were assigned into two groups, each receiving 40 g/day of: synbiotic diet mousse (SDM) (n = 23) and placebo diet mousse (PDM) without pro- and prebiotics (n = 22). All the evaluated parameters were measured at the beginning and after 8 weeks of intervention. The daily intake of SDM and PDM led to significant reductions of total cholesterol and HDL-cholesterol, as well as of immunoglobulins (A and M), and interleukin-1β in both groups ($p < .05$). These results suggest that the presence of the probiotic and prebiotic ingredients in the diet mousse did not show any additional effects on the parameters evaluated in volunteers with MetS.

1. Introduction

The metabolic syndrome (MetS) has received a great deal of attention from the scientific community in recent years. This is largely influenced by the increase in the prevalence of MetS in the last two decades especially in countries with increased calorie consumption and decreased physical activities (Mazidi, Rezaie, Kengne, Mobarhan, & Ferns, 2016). In general, MetS is a group of risk factors comprising obesity (particularly abdominal obesity), insulin resistance, atherogenic dyslipidaemia, and hypertension, which are associated with increased risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (Grundy et al., 2005; Kakafika, Liberopoulos, Karagiannis, Athyros, & Mikhailidis, 2006). Moreover, subjects with these features usually present prothrombotic and proinflammatory states (Grundy et al., 2005). Clinical and epidemiological studies have indicated that low-grade inflammation may contribute to the development of metabolic disorders associated with obesity (Cani & Hul, 2015). In this sense, MetS is known to be a low grade systemic inflammatory condition (Synetos et al., 2016).

It has been shown that an intestinal dysbiosis could also be associated to MetS. In this context, a number of studies using animal models and clinical trials have reported a relationship between the composition of the intestinal microbiota and MetS risk factors, including obesity and diabetes (Larsen et al., 2010; Ley et al., 2005; Tremaroli & Bäckhed, 2012). In general, the composition of the microbiota of obese subjects has been characterized by an increased *Firmicutes/Bacteroidetes* ratio (Jonkers, 2016; Ley, Turnbaugh, Klein, & Gordon, 2006; Turnbaugh et al., 2009). Nevertheless, according to Scavuzzi et al. (2015), there is still no consensus as to the mechanisms relating intestinal microbiota modifications and the potential metabolic changes. On the other hand, these researchers reported that mechanisms possibly involve gut barrier alterations and low-grade inflammation.

The pathogenesis of MetS may have several origins; however, diet and lifestyle are considered important aspects that may influence the susceptibility of humans to MetS (Kovatcheva-Datchary & Arora, 2013). Thus, dietary approaches to manipulate the intestinal microbiota, in

* Corresponding author at: Department of Biochemical and Pharmaceutical Technology, School of Pharmaceutical Sciences, University of São Paulo, Av. Prof. Lineu Prestes, 580, B16, 05508-000 São Paulo, SP, Brazil.
E-mail address: susaad@usp.br (S.M.I. Saad).

https://doi.org/10.1016/j.jff.2017.12.041
Received 30 May 2017; Received in revised form 14 November 2017; Accepted 18 December 2017
Available online 22 December 2017
1756-4646/

particular the use of probiotic microorganisms and/or prebiotic compounds, have demonstrated health-improving effects on the host. Therefore, these approaches were proposed for MetS management (Bernini et al. 2016; Kovatcheva-Datchary & Arora, 2013; Scavuzzi et al., 2015). It is noteworthy that studies evaluating the impact of probiotics on obesity-related inflammation are limited and mainly based on animal studies (de Moreno de LeBlanc & Perdigon, 2010; Gøbel, Larsen, Jakobsen, Mølgaard, & Michaelsen, 2012).

Some researchers reported beneficial effects of the consumption of probiotic, prebiotic, and synbiotic products on parameters related to MetS (Barreto et al., 2014; Bernini et al., 2016; Gøbel et al., 2012). Akkasheh et al. (2016) showed significant decreases in serum insulin concentrations and the homoeostasis model of assessment of insulin resistance (HOMA-IR) after the daily consumption of one probiotic capsule containing *Lactobacillus acidophilus* YAB, *Lactobacillus casei* TD_2, and *Bifidobacterium bifidum* B12 during 8 weeks. Studies have also investigated the possible role of probiotic bacteria and prebiotic fibres on different risk factors of MetS, such as the reduction of CVD risk (Al-Sheraji et al., 2012; Gøbel et al., 2012). Along these lines, a meta-analysis of randomized controlled trials conducted by Guo et al. (2011) showed that the consumption of probiotics led to a decrease in the total cholesterol and the LDL-C in individuals with high, borderline high, and normal cholesterol levels.

Recently, inflammatory processes have also been considered as biomarkers in clinical trials with MetS patients (Brito-Luna et al., 2016; Karaman, Aydin, Geçkinli, Çetinkaya, & Karaman, 2015; Panahi et al., 2016). Barreto et al. (2014) observed that the consumption of fermented milk containing *Lactobacillus plantarum* Lp 115 led to a significant decrease in IL-6 levels in patients with MetS after 90 days of study.

It is noteworthy that probiotic beneficial effects, as well as mechanisms of action, are considered as strain specific. In addition, it has been suggested that different food matrices in which the probiotic bacteria are incorporated may influence their functionality, and, consequently, their potential health effects (Forssten, Sindelar, & Ouwehand, 2011; Sanders & Marco, 2010). Besides, there are indications that synbiotic products may be more effective than either probiotics or prebiotics alone (Sanders & Marco, 2010).

To the best of our knowledge, no study is available in the scientific literature on the impact of a synbiotic diet dessert on subjects with MetS. The aim of this study was therefore to assess the impact of a synbiotic diet dessert (mousse) containing *L. acidophilus* La-5 and the prebiotic ingredients inulin and fructooligosaccharides (FOS) on biochemical (plasmatic glucose, TC, HDL-C, LDL-C, TG, and insulin), inflammatory (TNF-α, CD40, IL-1β, IL-6, IL-8, IL-10, and IL-12), haematological (erythrocytes, leukocytes, lymphocytes, erythrocytes, neutrophils, eosinophils, monocytes, and haemoglobin), and immunological (IgA, IgE, IgG, and IgM) parameters of volunteers with MetS.

2. Materials and methods

2.1. Production of synbiotic and placebo diet mousses

The diet desserts were produced under suitable hygiene and sanitation criteria at the Laboratory of Food Technology of the Department of Biochemical and Pharmaceutical Technology of the School of Pharmaceutical Sciences of the University of São Paulo (SP, Brazil), according to the method described by Buriti, Castro, and Saad (2010). The ingredients employed in the production of the diet desserts and their compositions are shown in Tables 1 and 2, respectively.

Diet desserts were packaged in polypropylene plastic pots for food products (100 mL of capacity) (Tries Aditivos Plásticos, São Paulo, Brazil) in portions of 40 g. The pots were sealed with metallic covers with varnish in a sealer (Delgo Metalúrgica, Cotia, Brazil). The products were stored frozen (−18 °C) and delivered to each volunteer in plastic vials labelled with the date of manufacture and of expiration. Microbiological analyses of the synbiotic product showed that the average population of *L. acidophilus* La-5 ranged between 9.2 and 9.5 log CFU (colony-forming units) per daily serving portion (40 g) during the experimental period. Therefore, the probiotic population was above the minimum recommended level (6 log CFU/g) suggested for beneficial health effects (Champagne, Ross, Saarela, Hansen, & Charalampopoulos, 2011; Health Canada, 2009; Ministero della Salute, 2013). Coliforms, *Escherichia coli*, and yeasts and moulds were not detected during the products' storage period.

Table 1
Ingredients employed in the production of synbiotic diet mousse (SDM) and placebo diet mousse (PDM).

Ingredients (g/100 g)	SDM	PDM
Skimmed milk[1]	61.7	61.7
Skimmed milk powder[2]	4.0	14.0
Sucralose[3]	1.1	1.1
Pasteurized and frozen guava pulp[4]	20.0	20.0
Emulsifier/stabilizer[5]	2.8	2.8
FOS[6]	6.0	0.0
Inulin[7]	4.0	0.0
Lactic acid[8]	0.4	0.4
Lactobacillus acidophilus La-5[9]	0.05	0.0
Total	100.0	100.0

[1] Paulista (Danone, Guaratinguetá, SP, Brazil).
[2] Molico (Nestlé, Araçatuba, SP, Brazil).
[3] Sucralose (Línea Sucralose, São Paulo, SP, Brazil).
[4] Icefruit Comércio de Alimentos (Icefruit Comércio de Alimentos, Tatuí, SP, Brazil).
[5] Cremodan Mousse 30 (Danisco, Cotia, SP, Brazil).
[6] Beneo P95 (Orafti, Oreye, Belgium).
[7] Beneo HP (Orafti, Oreye, Belgium).
[8] Purac (Purac Sínteses, Rio de Janeiro, RJ, Brazil; 85 g/100 g food-grade solution).
[9] Strain La-5 (Christian Hansen, Hoersholm, Denmark).

Table 2
Chemical composition, energy contribution of macronutrients, and total energy values (TEV) of synbiotic diet mousse (SDM) and placebo diet mousse (PDM) in 100 g of whole mousses (dry weight).

	SDM	PDM
Composition (g/100 g)		
Ash	0.90 (0.06)^{B}	1.42 (0.17)^{A}
Proteins	6.77 (0.37)^{B}	8.55 (0.33)^{A}
Simple carbohydrates	10.24 (0.97)^{B}	17.53 (1.01)^{A}
Fructans	9.63^{B,*}	0.00^{A}
Lipids	0.22 (0.05)^{A}	0.12 (0.06)^{A}
Moisture	72.24 (1.59)^{A}	72.38 (1.84)^{A}
Total	100.0	100.0
Energetic value (kJ/100 g)		
Proteins	113.30 (6.67)	143.09 (5.52)
Lipids	8.28 (2.07)	4.52 (2.26)
Simple carbohydrates	171.38 (31.07)	293.24 (16.90)
Fructans	60.46	0.00
TEV	353.42 (27.91)	440.85 (11.42)

Values are expressed as mean (standard deviation).
* Estimate based on information given by the supplier (Orafti) for the prebiotic ingredients (Beneo P95 and Beneo HP).

2.2. Participants

Sixty subjects with MetS, aged between 19 and 65, were recruited (August 2014 up to June 2015) from the ambulatory of the University Hospital (São Paulo, SP, Brazil). The present study was conducted according to the guidelines laid down in the Declaration of Helsinki and approved by the Ethical Committees involving humans of the School of Pharmaceutical Sciences of the University of São Paulo (CAAE 30539214.6.0000.0067) and of the University Hospital (Protocol Number 663.138). All subjects provided written consent form before

participating in the study. The inclusion criteria were based on the MetS diagnosis criteria, according to the National Cholesterol Education Program, Adult Treatment Panel III (NCEP/ATP III) (Grundy et al., 2005). The subjects were eligible for the study if they had at least three of the five risk factors. The exclusion criteria were thyroid, renal, hepatic, gastrointestinal or oncological disease and use of drugs (including hormone replace therapy) that interfere with the lipids and/or glycaemic profile.

2.3. Study design

The present study was a randomized, double-blind, placebo-controlled trial in which subjects with MetS were randomly divided into two groups: group S (synbiotic group – individuals who consumed 40 g/d of SDM; n = 23) and group P (placebo group – individuals who consumed 40 g/d of PDM; n = 22). During the 8-week intervention period, 15 participants withdrew from the study due to various personal reasons; consequently, 45 individuals completed the study. The participants were paired by age, gender, ethnicity, and consumption of antihypertensive drugs (Simão et al., 2013). Throughout the study (8 weeks), the subjects were encouraged to maintain their lives as they normally would, with no change in their usual diets or physical activity. However, the volunteers were instructed to avoid the consumption of probiotic and prebiotic products during the 7 days that preceded the beginning of the intervention (run-in).

2.4. Anthropometric, heart rate, and laboratory blood analysis

Fasting blood samples, anthropometric, heart rate, and blood pressure measurements were collected at baseline (T0) and at the end of week 8 (T8). Body mass index (kg/m^2) was calculated as body weight (kg) divided by height (m) squared. Waist circumference was determined using a tape measure. After the subjects had been seated for five minutes, three blood pressure measurements, obtained at one-minute intervals, were recorded. The average of the last two measurements was used. These clinical and anthropometric parameters were measured according to Mill et al. (2013).

After fasting for 12 h, blood samples were drawn from the forearm vein into Vacutainer tubes (Becton Dickinson, Rutherford, USA). Samples were immediately centrifuged at 3000 rpm for 15 min at 4 °C (Eppendoff, Hamburg, Germany), and the serum were collected and stored at −80 °C until the analysis. The plasmatic glucose levels and the serum levels of TC, HDL-C, LDL-C, TG, IgA, IgE, IgG, and IgM were assayed by an automated biochemical analyser (Labmax 240, Tokyo, Japan), using specific enzyme kits (Labtest Diagnostics, Lagoa Santa, Brazil). Plasma insulin level was determined by chemiluminescence microparticle immunoassay (Architect, Abbott Laboratory, Abbott Park, IL, USA). TNF-α, CD40, IL-1β, IL-6, IL-8, IL-10, and IL-12 were evaluated using commercially available immunoassay kit #HCYTOMAG-60K (Millipore, Billerica, USA) with a series of magnetic beads and the MAGPIX system (Luminex, Austin, USA). Haematological parameters were evaluated at the University Hospital Clinical Laboratory of the University of São Paulo through an automated haematology analyser (Sysmex-XT 2000i, Kobe, Japan), using routine analysis based on electrical impedance (erythrocytes), flow cytometry (leukocytes, lymphocytes, erythrocytes, neutrophils, eosinophils, and monocytes) and colorimetric (haemoglobin) methods.

2.5. Statistical analysis

The size of the sample was determined in order to achieve a statistically significant result for changes of the parameters evaluated at a ≥10% level. The study was planned for obtaining an 80% statistic power. The chi-squared test was used to evaluate the differences between synbiotic and placebo groups with respect to the gender, ethnicity, consumption of antihypertensive drugs, and student-*t* test to age.

Table 3
General characteristics of the participants of the placebo and synbiotic groups at the beginning of the study.

Parameters	Group P (n = 22)	Group S (n = 23)	*P*
Gender (M/F)	(10/12)	(13/10)	.4578
Antihypertensive drugs (yes/no)	(6/16)	(5/18)	.6659
Non-Caucasian/Caucasian	(11/11)	(10/13)	.6611
Age (years)	49.5 (39.5–59.5)	47.0 (41.0–53.0)	.4674

Values are expressed as median (25–75%). Group P: Placebo group; Group S: Synbiotic group. M/F: male/female.

The Mann-Whitney test was performed to compare differences among parameters of groups at baseline and differences across treatment groups (intergroup changes). The Wilcoxon matched pairs test was performed to verify changes from baseline (intragroup changes). Data were presented as median (25–75%), and the significance was declared when the *p*-value was < .05. Statistical analyses were carried out using the Statistica version 12.0 (Statsoft Inc, Tulsa, USA) and GraphPad Prism version 3.0 (GraphPad Software Inc, La Jolla, USA) programs.

3. Results

In general, the two experimental groups were similar (Table 3) since there were no significant differences between the synbiotic and the placebo groups related to age, gender, ethnicity, and the consumption of antihypertensive drugs at baseline ($p > .05$). Despite the known influence on the lipid and the glucose metabolism, we could not request the volunteers to interrupt taking the antihypertensive medication to participate in our study, since this could compromise their health, as also described in previous studies (Barreto et al., 2014; Bernini et al., 2016). However, as there were no significant differences between the synbiotic and the placebo groups also related to the consumption of antihypertensive drugs ($p > .05$), we were able to keep these volunteers in the study.

During the period of daily diet mousse consumption (from T0 to T8), there were no significant differences for anthropometric and haematological parameters, systolic and diastolic blood pressure levels, heart rate, glucose, TG, LDL-C, TC/HDL-C and LDL-C/HDL-C ratios, insulin, TNF-α, CD40, IL-8, IL-10, IL-12, and IgG (Tables 4–6) for both groups. The exceptions were verified for haemoglobin (Hb) levels ($p = .0356$), IgE ($p = .0451$), and IL-6 ($p = .0396$), since the placebo group showed a decrease in these parameters after 8 weeks of the study (Tables 5 and 6). In relation to the other parameters, there were significant reductions in TC, HDL-C, IgA, IgM, and IL-1β for both groups throughout the experimental period (Tables 4 and 6). Comparing the median differences (T8 to T0) between the two groups, there was a slight trend for a LDL-C decrease in group S (15.0 mg/dL; $p = .0606$), compared to group P (2.5 mg/dL; $p = .1292$). Nevertheless, regarding inter-group changes, no significant differences were verified for all parameters at baseline and after 8 weeks of diet dessert consumption ($p > .05$).

4. Discussion

The present study evaluated the impact of a synbiotic diet mousse containing *L. acidophilus* La-5 and the prebiotic ingredients inulin and FOS on some biochemical, haematological, inflammatory, and immunological parameters of subjects with MetS through a randomized, double-blind, and placebo-controlled trial. We did not find any effects of the intervention with SDM on blood pressure, heart rate, anthropometric, and various laboratory blood parameters (TG, LDL-C, TC/HDL, insulin, glucose, TNF-α, CD40, IL-8, IL-10, IL-12, and IgG) assessed in the present study. Similarly, Bernini et al. (2016) verified that the daily ingestion of fermented milk containing *Bifidobacterium animalis* ssp. *lactis* HN019 by patients with MetS did not cause any significant

Table 4
Anthropometric, blood pressure, and biochemical parameters at baseline (T0) and after 8 weeks (T8) of mousse consumption.

Parameters	Groups	T0	T8	*P*
Weight (kg)	P	87.8 (61.9–96.5)	88.1 (78.1–97.3)	.6158
	S	84.6 (59.9–99.3)	84.0 (72.2–100.5)	.5392
BMI (kg/m^2)	P	33.9 (29.1–37.1)	33.9 (29.0–37.4)	.5536
	S	30.7 (28.0–33.4)	30.9 (28.6–33.1)	.3764
WC (cm)	P	101.9 (94.5–112.8)	103.0 (96.0–113.8)	.8552
	S	99.0 (91.5–112.2)	97.5 (91.0–109.5)	.6671
SBP (mm Hg)	P	130.0 (115.5–139.5)	127.0 (115.0–137.5)	.9759
	S	133.0 (127.0–142.0)	131.0 (127.0–142.0)	.6089
DBP (mm Hg)	P	81.5 (74.0–89.0)	80.0 (74.0–87.0)	.3543
	S	82.0 (73.0–91.0)	82.0 (77.0–89.0)	.7779
Heart rate (bmp)	P	77.0 (65.8–86.2)	76.0 (65.5–85.3)	.6017
	S	71.0 (66.0–78.0)	70.0 (66.0–76.0)	.4885
Glucose (mg/dL)	P	94.5 (89.0–99.0)	91.5 (79.0–96.0)	.1469
	S	95.0 (88.0–99.0)	95.0 (83.0–101.0)	.2592
TG (mg/dL)	P	127.0 (93.5–163.0)	120.0 (75.5–168.0)	.5645
	S	123.0 (89.0–159.0)	131.0 (102.0–194.0)	.2511
TC (mg/dL)	P	183.5 (149.5–211.5)	160.0 (133.0–209.5)	.0023
	S	203.0 (194.0–229.0)	189.0 (168.0–206.0)	.0064
LDL-C (mg/dL)	P	109.0 (87.5–133.0)	106.5 (74.0–137.5)	.1292
	S	123.0 (103.0–137.0)	108.0 (103.0–118.0)	.0606
HDL-C (mg/dL)	P	46.0 (37.0–51.0)	43.0 (35.5–48.5)	.0054
	S	48.0 (38.0–60.0)	44.0 (38.0–51.0)	.0050
TC/HDL-C	P	4.0 (3.5–5.2)	4.1 (13.4–4.6)	.0785
	S	4.2 (4.0–5.1)	4.3 (3.7–4.9)	.4702
LDL-C/HDL-C	P	2.4 (2.2–3.0)	2.5 (2.1–2.7)	.6321
	S	2.5 (2.3–3.1)	2.6 (2.1–2.9)	.8137
Insulin (μU/mL)	P	12.3 (8.5–17.5)	11.9 (8.4–16.7)	.7086
	S	13.3 (8.7–18.4)	12.3 (9.1–16.2)	.0830

Values are expressed as median (25–75%). Wilcoxon matched pairs test was performed to verify changes from the baseline (intragroup changes). Mann-Whitney was performed to compare differences at baselines and across treatments groups (intergroup changes). The differences were significant for $p < .05$ and $p < .01$. No differences between groups were found. BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TC/HDL-C: total cholesterol to HDL-cholesterol ratio; LDL-C/HDL-C: LDL-cholesterol to HDL-cholesterol ratio; IgA: immunoglobulin A; IgM: immunoglobulin M. Group P: individuals who consumed the placebo product (n = 22); Group S: individuals who consumed the synbiotic diet mousse (n = 23). T0: baseline; T8: 8 weeks of daily consumption of diet desserts.

changes in blood pressure, glucose, WC, TG, HDL-C, insulin, and HOMA-IR. Nevertheless, the authors showed a significant reduction in BMI, TC, and LDL-C in the probiotic group compared to the baseline and the control group values.

On the other hand, in our study a significant reduction of TC and HDL-C levels was observed for both groups after 8 weeks of intervention. It is noteworthy that the TC decrease was higher in the placebo group compared to the synbiotic group (a reduction of 23.5 and of 14.0 mg/dL, respectively). A possible explanation for this result may be related to the differences found in the food matrix of the PDM and the SDM. The first product presented 14.0% of skimmed milk powder (non-fat solids source), while the SDM had only 4.0% (Table 1).

In this sense, during the intervention period of 8 weeks, the placebo and the synbiotic groups ingested, respectively, 0.14 and 0.04 g/day of skimmed milk powder. Some evidence suggests a possible interaction of the dietary calcium with fatty acids through the formation of chelates during the process of lipids digestion, resulting in a reduction of the absorption of some fatty acids by the precipitation and excretion of the salts formed in faeces (Cominetti, Marreiro, & Cozzolino, 2012; Jolma et al., 2003; Vaskonen, Mervaala, Sumuvuori, Seppänen-Laakso, & Karppanen, 2002). Thus, the highest content of calcium in PDM compared to SDM might have had a greater influence on the lipid profile of volunteers. Indeed, Barreto et al. (2014) attributed the reduction of cholesterol levels in the placebo group after 90 days of intervention with unfermented milk (not containing probiotic and prebiotic) to calcium and magnesium.

Although the LDL-C reduction was not statistically significant, there was a higher tendency ($p = .0606$) of reduction of this parameter in the group S (around 12%) when compared to group P (around 2%). Several hypotheses have been proposed to explain the potential cholesterol-lowering effects of probiotics and/or prebiotics including the production of short chain fatty acids resulting from fermentation of prebiotics, incorporation of the cholesterol molecule by the cell membrane, dissociation of bile salts by the action of bile salt hydrolases, and conversion of cholesterol into coprostanol by desconjugated bile (Ishimwe, Daliri, Lee, Fang, & Du, 2015).

It is important to point out that the findings of different studies on probiotic and prebiotic hypocholesterolemic effect are still controversial. For instance, studies developed by Ahn et al. (2015) and Jung et al. (2015) did not show any effect of probiotic strains *L. curvatus* HY7601 and *L. plantarum* KY1032 on TC, HDL-C, and LDL-C levels of subjects with triglyceridemia (without diabetes) and overweight, respectively. However, a meta-analysis of randomized controlled trials revealed that the consumption of probiotics has positive health effects on TC and LDL-C in volunteers with high, borderline high, and normal cholesterol levels (Guo et al., 2011).

Regarding the haematological parameters, we observed a significant reduction ($p < .05$) in the Hb level only in the placebo group after 8 weeks of study. However, no significant difference was observed between the groups at the end of the intervention period. Studies suggest a relationship between Hb levels and the risk of developing MetS (Chuang et al., 2016; Hu, Kuo, & Wu, 2016). It is important to emphasize that hypertrophy and hyperplasia are characteristic features of obesity and lead to a reduction in the blood supply to adipocytes, due to the adipocytes enlargement. This reduction causes a tissue hypoxia, leading to metabolic changes, besides stimulating erythropoietin production and Hb synthesis (Chuang et al., 2016). In this sense, the Hb levels may be correlated to MetS and used to predict this syndrome in subjects (Chuang et al., 2016). Past studies showed that among various CVD risk factors associated with Hb levels are white blood cell counts, cigarette smoking, diastolic blood pressure, and serum albumin (Shimakawa & Bild, 1993).

Regarding proinflammatory cytokines, the present study showed that PDM as well as SDM consumption led to a reduction in IL-1β after 8 weeks. On the other hand, a significant decrease in the IL-6 levels was found only in the placebo group. Nevertheless, there were no significant differences between the experimental groups after 8 weeks of intervention. Further studies are necessary to investigate the role of each mousse ingredient on the inflammatory parameters of MetS subjects. However, it is noteworthy that lactic acid bacteria, including probiotic strains, differ in their immunomodulatory properties regarding their differences in their cytokine profile and regulatory T cell responses (Ashraf, Vasiljevic, Day, Smith, & Donkor, 2014).

Studies have suggested a great potential for immune and inflammatory response associated with daily supplementation with lactobacilli strains (Akoğlu, Loytved, Nuiding, Zeuzem, & Faust, 2015; Matsusaki et al., 2016; Štofilová et al., 2015). Nevertheless, a double-blind, randomized, placebo-controlled trial conducted by Tonucci, Santos, Oliveira, Ribeiro, and Martino (2017) showed that the intake of fermented goat milk containing *L. acidophilus* La-5 and *Bifidobacterium animalis* Bb-12 did not influence the IL-6 levels in subjects with type 2 diabetes mellitus after 6 weeks of intervention.

Additionally, an immunostimulatory effect of the bioactive peptides resulting from the digestive process of milk proteins was suggested by Solieri, Rutella, and Tagliazucchi (2015), since milk proteins, particularly casein, are precursors of biologically active peptides. Besides,

Table 5
Haematological parameters at baseline (T0) and after 8 weeks (T8) of mousse consumption.

Parameters	Groups	T0	T8	*P*
Haemoglobin (g/dL)	P	14.5 (13.1–15.3)	13.9 (13.0–15.1)	.0356
	S	14.6 (13.3–15.6)	14.7 (13.2–15.7)	.8771
Leukocytes (mm^3)	P	7160.0 (6025.0–9275.0)	7060.0 (5910.0–9875.0)	.6083
	S	6960.0 (5730.0–7570.0)	6830.0 (6270.0–7970.0)	.3989
Lymphocytes (mm^3)	P	2124.0 (1960.0–2511.0)	2148.0 (1775.0–2598.0)	.9935
	S	2241.0 (1869.0–2760.0)	2351.0 (1871.0–2871.0)	.0528
Erytrocytes (mm^3)	P	5.02×10^6 (4.59×10^6–5.38×10^6)	4.98×10^6 (4.41×10^6–5.31×10^6)	.2392
	S	4.93×10^6 (4.70×10^6–5.29×10^6)	5.08×10^6 (4.75×10^6–5.34×10^6)	.4479
Neutrophils (mm^3)	P	4429 (3087–5652)	4176 (3209–5990)	.7640
	S	3783 (2854–4413)	3953 (2700–4655)	.5894
Eosinophils (mm^3)	P	190.0 (120.5–255.5)	194.0 (137.5–294.5)	.1605
	S	160.0 (100.0–314.0)	162.0 (120.0–277.0)	.9454
Monocytes (mm^3)	P	549.5 (446.0–679.9)	531.5 (469.0–642.0)	.7029
	S	592.0 (500.0–709.0)	577.0 (542.0–700.0)	.7553

Values are expressed as median (25–75%). Wilcox matched pairs test was performed to verify changes from baseline (intragroup changes). Mann-Whitney was performed to compare differences at baselines and across treatments groups (intergroup changes). The differences were significant for $p < .05$ and $p < .01$. No differences between groups were found. Group P: individuals who consumed the placebo product (n = 22); Group S: individuals who consumed the synbiotic diet mousse (n = 23). T0: baseline; T8: 8 weeks of daily consumption of diet desserts.

Table 6
Inflammatory parameters and antibodies at baseline (T0) and after 8 weeks (T8) of mousse consumption.

Parameters	Groups	T0	T8	*P*
IL-10 (pg/mL)	P	1.9 (1.9–1.9)	0.1 (0.0–6.5)	.1680
	S	1.9 (1.9–4.9)	0.7 (0.1–2.1)	.2783
IL-12 (pg/mL)	P	0.3 (0.30–108.9)	0.0 (0.0–27.2)	.2035
	S	0.3 (0.30–108.9)	0.0 (0.0–27.2)	.2035
CD40 (pg/mL)	P	6210 (1890–12,100)	2690 (2220–26,200)	.9645
	S	4540 (3525–11,450)	2690 (2280–6060)	.1677
IL-1β (pg/mL)	P	2.8 (2.9–7.6)	1.1 (0.5–2.1)	.0137
	S	2.8 (2.9–2.9)	1.5 (0.8–2.3)	.0360
IL-6 (pg/mL)	P	1.9 (1.9–1.9)	0.00 (0.0–0.0)	.0396
	S	1.9 (1.9–1.9)	0.00 (0.0–1.2)	.1274
IL-8 (pg/mL)	P	15.3 (7.0–20.9)	15.6 (6.5–18.6)	.5195
	S	22.1 (16.3–47.2)	18.6 (16.2–24.0)	.2163
TNF-α (pg/mL)	P	29.2 (22.8–44.8)	29.3 (27.1–37.6)	.5195
	S	30.6 (23.1–37.4)	34.0 (29.3–45.2)	.3757
IgA (mg/dL)	P	201.5 (145.0–249.0)	149.5 (126.5–214.0)	.0001
	S	186.0 (136.0–292.0)	183.0 (116.0–267.0)	.0410
IgE (UI/mL)	P	71.5 (25.6–169.9)	67.2 (32.6–232.5)	.0451
	S	65.9 (27.15–354.5)	75.5 (25.0–319.4)	.4505
IgG (mg/dL)	P	1142.0 (949.5–1329.0)	1012.0 (787.5–1286.0)	.0841
	S	1128.0 (957.0–1222.0)	1073.0 (985.0–1208.0)	.2512
IgM (mg/dL)	P	53.0 (42.5–97.5)	36.0 (14.0–80.0)	.0028
	S	61.9 (38.0–101.5)	41.0 (19.5–79.5)	.0003

Values are expressed as median (25–75%). Wilcox matched pairs test was performed to verify changes from baseline (intragroup changes). Mann-Whitney was performed to compare differences at baselines and across treatments groups (intergroup changes). The differences were significant for $p < .05$ and $p < .01$. No differences between groups were found. IL-10: interleukin 10; IL-12: interleukin 12; CD40: cluster of differentiation 40; IL-1β: interleukin 1β; IL-6: interleukin 6; IL-8: interleukin 8; TNF-α: tumor necrosis factor alpha; IgA: immunoglobulin A; IgE: immunoglobulin E; IgG: immunoglobulin G; IgM: immunoglobulin M. Group P: individuals who consumed the placebo product (n = 22); Group S: individuals who consumed the synbiotic diet mousse (n = 23). T0: baseline; T8: 8 weeks of daily consumption of diet desserts.

these researchers reported that bioactive peptides can be released from milk proteins by gastrointestinal digestion or by enzymatic hydrolysis during food processing and fermentation. Moreover, they may exert several beneficial properties, including the fact that immunomodulation, and immunomodulatory peptides can increase immune cell functions, such as lymphocyte proliferation, natural killer cell activity, antibody synthesis, and cytokine regulation (Singh, Vij, & Hati, 2014). In this context, the effect of the diet mousses studied, in particular the placebo product, on the reduction of the IL-1β and IL-6 levels might be related to an increased formation of bioactive peptides in the products. As mentioned before, the amount of milk proteins in the placebo product was higher compared to the synbiotic product. Bioactive peptides may inhibit inflammatory biomarkers such as IL-1β, cyclooxygenase-2, and TNF-α mRNA expression (Ma, Liu, Shi, & Yu, 2016).

Regarding the immunoglobulins, we observed a significant reduction in IgM and IgA levels for both experimental groups studied. According to Gonzalez-Quintela et al. (2008), high levels of IgA may represent an important immunological marker for the prevalence of obesity and MetS. In addition, these researchers reported an association between serum levels of IL-6 and IgA between people with this profile of metabolic abnormalities. In the present study, IL-6 and IgA levels showed a significant reduction ($p < .05$) in the placebo group.

According to Song et al. (2014), IgM is reactive to several autoantigens and is implied to be important for autoimmunity, suggesting that this immunoglobulin may be a potential risk factor for MetS. In this context, these researchers designed a cross-sectional study with around one thousand subjects to evaluate the relationship between IgM and MetS. The results showed that IgM may be a useful predictive factor for MetS in an adult population. Although further studies are required to explain the exact mechanisms of IgM in MetS, we could observe a significant reduction in IgM levels in both experimental groups after 8 weeks of study.

In the present study, a significant decrease in IgE levels was only verified in the group that received the placebo product. Evidence suggests that high levels of IgE in plasma or tissues contribute to the activation of mast cells in the extracellular environment involved in the inflammation process and immunity (Madjene et al., 2015; Wang et al., 2013). Studies suggest the association between high levels of IgE and mast cells, which are important biomarkers for the development of type 2 diabetes mellitus in humans (Wang, Shen, Feng, & Qiu, 2017; Wang et al., 2011). Besides, Zhang and Shi (2012) related the mast cell presence to other diseases associated with MetS, including obesity, insulin resistance, hypertension, and dyslipidemia.

Some limitations of the present study, including the duration of the intervention and sample size, need to be considered to analyse the

results obtained. Long-term interventions using a larger number of volunteers would be required to confirm the effects of the synbiotic product on biochemical, haematological, inflammatory, and immunological parameters. Moreover, we speculate that the aggressive conditions of the gastrointestinal tract (TGI) (digestive agents present in the gastric and pancreatic secretions, as well as other physiological factors) may have affected the *L. acidophilus* La-5 survival and functionality, which could explain why the results of the synbiotic group were not so expressive in the present study. Buriti et al. (2010) demonstrated the low tolerance of *L. acidophilus* La-5, incorporated in a mousse similar to the one applied in the present study, to artificial gastrointestinal juice in an *in vitro* assay that simulated the TGI conditions. The survival of this probiotic strain was drastically reduced after 6 h of the *in vitro* assay. On the other hand, in a study conducted by our research group, we tested a synbiotic mousse containing *L. acidophilus* La-5 microencapsulated with inulin, where the probiotic strain showed a high survival rate (around 82%) when submitted to simulated gastrointestinal conditions, suggesting that the microencapsulation may be an alternative to increase the strain survival and potential health effects (unpublished data). This technology enables the development of more stable probiotic products, preserving the viability of microorganisms throughout processing, distribution, storage, and especially during the passage through the gastrointestinal tract (Amine et al., 2014). Nevertheless, further studies will be required to verify whether the mousse incorporated with microencapsulated *L. acidophilus* La-5 could have a greater influence on risk factors related to MetS.

In brief, our results suggest that the presence of probiotic and prebiotic ingredients in the diet mousse did not significantly affect the parameters evaluated after 8 weeks of intervention in the volunteers with MetS.

5. Conclusion

The observations here reported suggest that daily consumption of either the synbiotic mousse or the placebo product contributed to the reduction of TC, HDL-C, IL-1β, IgA, and IgM in the volunteers with MetS. Therefore, these results suggest that the presence of probiotic and prebiotic ingredients in the diet mousse did not significantly affect the risk factors related to MetS. Further clinical studies are necessary to support the results here reported, such as a long-term experimental protocol and the inclusion of an evaluation of the intestinal microbiota to determine whether the synbiotic dessert might cause specific changes in the composition and/or activity of the intestinal microbiota of subjects with MetS.

Conflict of interest

There are no conflicts of interest to declare.

Acknowledgements

The authors thank Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (Projects #2013/04422-7 and 2013/07914-8), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) (Projects #1575592 and BEX 6602/15-0), and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (Project # 306330/2016-4) for financial support and fellowships, and DuPont, Clariant, and Purac Síntese companies for providing part of the material resources employed in this study. The authors gratefully acknowledge Juanita Hernández Solano, Nilton de Moraes Bloisi, Ivanir Santana de Oliveira Pires, and José Alexandre Pimentel for their technical assistance during part of the project. The authors would also like to thank all the volunteers for their participation in this study.

References

Ahn, H.-Y., Kim, M., Chae, J. S., Ahn, Y.-T., Sim, J.-H., Choi, Il.-D., ... Lee, J. H. (2015). Supplementation with two probiotic strains, *Lactobacillus curvatus* HY7601 and *L. plantarum* KY1032, reduces fasting TG and enhances apolipoprotein A-V levels in non-diabetic subjects with hypertriglyceridemia. *Atherosclerosis, 241*, 649–656.

Akkasheh, G., Kashani-Poor, Z., Tajabadi-Ebrahimi, M., Jafari, P., Akbari, H., Taghizadeh, M., ... Esmaillzadeh, A. (2016). Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. *Nutrition, 32*, 315–320.

Akoğlu, B., Loytved, A., Nuiding, H., Zeuzem, S., & Faust, D. (2015). Probiotic *Lactobacillus casei* Shirota improves kidney function, inflammation and bowel movements in hospitalized patients with acute gastroenteritis – A prospective study. *Journal of Functional Foods, 17*, 305–313.

Al-Sheraji, S. H., Ismail, A., Manap, M. Y., Mustafa, S., Yusof, R. M., & Hassan, F. A. (2012). Hypocholesterolemic effect of yoghurt containing *Bifidobacteriumpseudocatenulatum* G4 or *Bifidobacteriumlongum* BB536. *Food Chemistry, 135*, 356–361.

Amine, K. M., Champagne, C. P., Raymond, Y., St-Gelais, D., Britten, M., Fustier, P., ... Lacroix, M. (2014). Survival of microencapsulated *Bifidobacterium longum* in Cheddar cheese during production and storage. *Food Control, 37*, 193–199.

Ashraf, R., Vasiljevic, T., Day, S. L., Smith, S. C., & Donkor, O. N. (2014). Lactic acid bacteria and probiotic organisms induce different cytokine profile and regulatory T cells mechanisms. *Journal of Functional Foods, 6*, 395–409.

Barreto, F. M., Simão, A. N. C., Morimoto, H. K., Lozovoy, M. A. B., Dichi, I., & Miglioranza, L. H. S. (2014). Beneficial effects of *Lactobacillus plantarum* on glycemia and homocysteine levels in postmenopausal women with metabolic syndrome. *Nutrition, 30*, 939–942.

Bernini, L. J., Simão, A. N. C., Alfieri, D. F., Lozovoy, M. A. B., Mari, N. L., Souza, C. H. B., ... Costa, G. N. (2016). Beneficial effects of *Bifidobacterium lactis* on lipid profile and cytokines in patients with metabolic syndrome: A randomized trial. Effects of probiotics on metabolic syndrome. *Nutrition, 32*, 716–719.

Brito-Luna, M. J., Villanueva-Quintero, D. G., Sandoval-Talamantes, A. K., Fatutis-Morris, M., Graciano-Machuca, O., Sanchez-Hernandez, P. E., & Alvarado-Navarro, A. (2016). Correlation of IL-12, IL-22, and IL-23 in patients with psoriasis and metabolic syndrome. Preliminary report. *Cytokine, 85*, 130–136.

Buriti, F. C. A., Castro, I. A., & Saad, S. M. I. (2010). Viability of *Lactobacillus acidophilus* in synbiotic guava mousses and its survival under *in vitro* simulated gastrointestinal conditions. *International Journal of Food Microbiology, 137*, 121–129.

Cani, P. D., & Hul, M. V. (2015). Novel opportunities for next-generation probiotics targeting metabolic syndrome. *Current Opinion in Biotechnology, 32*, 21–27.

Champagne, C. P., Ross, R. P., Saarela, M., Hansen, K. F., & Charalampopoulos, D. (2011). Recommendations for viability assessment of probiotics as concentrated cultures and in food matrices. *International Journal of Food Microbiology, 149*, 185–193.

Chuang, T.-J., Liu, J.-S., Li, P.-F., Wen Chang, H., Hsieh, C.-H., Chang, J.-B., ... Chen, Y.-L. (2016). The relationships between hematogram and metabolic syndrome in elderly subgroups: A Taiwan cohort study. *Archives of Gerontology and Geriatrics, 63*, 59–66.

Cominetti, C., Marreiro, D. N., & Cozzolino, S. M. F. (2012). Minerais e obesidade. In S. M. F. Cozzolino (Ed.), *Biodisponibilidade de nutrientes* (4th ed., pp. 971–1005). Barueri: Manole. cap.40.

de Moreno de LeBlanc, A., & Perdigon, G. (2010). The application of probiotic fermented milks in cancer and intestinal inflammation. *The Proceedings of the Nutrition Society, 69*, 421–428.

Forssten, S. D., Sindelar, C. W., & Ouwehand, A. C. (2011). Probiotics from an industrial perspective. *Anaerobe, 17*, 410–413.

Gøbel, R. J., Larsen, N., Jakobsen, M., Mølgaard, C., & Michaelsen, K. F. (2012). Probiotics to adolescents with obesity: Effects on inflammation and metabolic syndrome. *Journal of Pediatric Gastroenterology and Nutrition, 55*, 673–678.

Gonzalez-Quintela, A., Alende, R., Gude, F., Campos, J., Rey, J., Meijide, L. M., ... Vidal, C. (2008). Serum levels of immunoglobulins (IgG, IgA, IgM) in a general adult population and their relationship with alcohol consumption, smoking and common metabolic abnormalities. *Clinical and Experimental Immunology, 151*, 42–50.

Grundy, S. M., Cleeman, J. I., Daniels, S. R., Donato, K. A., Eckel, R. H., Franklin, B. A., ... Costa, F. (2005). Diagnosis and management of the metabolic syndrome an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation, 112*, 2735–2752.

Guo, Z., Liu, X. M., Zhang, Q. X., Shen, Z., Tian, F. W., Zhang, H., ... Zhang, H. P. (2011). Influence of consumption of probiotics on the plasma lipid profile: A meta-analysis of randomised controlled trials. *Nutrition, Metabolism & Cardiovascular Disease, 21*, 844–850.

Health Canada (2009). Guidance document – The use of probiotic microorganisms in food. Available at: < http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/legislation/probiotics_guidance-orientation_probiotiques-eng.pdf > Accessed May 25th, 2016.

Hu, Y.-H., Kuo, S.-W., & Wu, D.-A. (2016). Relationships between hemoglobin and each component of metabolic syndrome: A special focus on elderly without medication. *International Journal of Gerontology, 10*, 22–27.

Ishimwe, N., Daliri, E. B., Lee, B. H., Fang, F., & Du, G. (2015). The perspective on cholesterol-lowering mechanisms of probiotics. *Molecular Nutrition & Food Research, 59*, 94–105.

Jolma, P., Kööbi, P., Kalliovalkama, J., Kähönen, M., Fan, M., Saha, H., ... Pörsti, I. (2003). Increased calcium intake reduces plasma cholesterol and improves vaso relaxation in experimental renal failure. *American Journal of Physiology Heart and Circulatory Physiology, 285*, H1882–H1889.

Jonkers, D. M. A. E. (2016). Role of microbes (probiotics and prebiotics). *Best Practice &*

Research Clinical Gastroenterology, 6, 181–183.
Jung, S., Lee, Y. J., Kim, M., Kim, M., Kwak, J. H., Lee, J.-W., ... Lee, J.-H. (2015). Supplementation with two probiotic strains, *Lactobacillus curvatus* HY7601 and *Lactobacillus plantarum* KY1032, reduced body adiposity and Lp-PLA 2 activity in overweight subjects. *Journal of Functional Foods, 19*, 744–752.
Kakafika, A. I., Liberopoulos, E. N., Karagiannis, A., Athyros, V. G., & Mikhailidis, D. P. (2006). Dyslipidaemia, hypercoagulability and the metabolic syndrome. *Current Vascular Pharmacology, 4*, 175–283.
Karaman, A., Aydin, H., Geçkinli, B., Çetinkaya, A., & Karaman, S. (2015). DNA damage is increased in lymphocytes of patients with metabolic syndrome. *Mutation Research, 782*, 30–35.
Kovatcheva-Datchary, P., & Arora, T. (2013). Nutrition, the gut microbiome and the metabolic syndrome. *Best Practice & Research Clinical Gastroenterology, 27*, 59–72.
Larsen, N., Vogensen, F. K., van den Berg, F. W. J., Nielsen, D. S., Andreasen, A. S., Pedersen, B. K., ... Jakobsen, M. (2010). Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS ONE, 5*, e9085.
Ley, R. E., Bäckhed, F., Turnbaugh, P., Lozupone, C. A., Knight, R. D., & Gordon, J. I. (2005). Obesity alters gut microbial ecology. *PNAS, 102*, 11070–11075.
Ley, R. E., Turnbaugh, P. J., Klein, S., & Gordon, J. I. (2006). Microbial ecology: Human gut microbes associated with obesity. *Nature, 44*, 1022–1023.
Ma, Y., Liu, J., Shi, H., & Yu, L. (2016). Isolation and characterization of anti-inflammatory peptides derived from whey protein. *Journal of Dairy Science, 99*, 6902–6912.
Madjene, L. C., Pons, M., Danelli, L., Claver, J., Ali, L., Madera-Salcedo, I. K., ... Blank, U. (2015). Mast cells in renal inflammation and fibrosis: Lessons learnt from animal studies. *Molecular Immunology, 63*, 86–93.
Matsusaki, T., Takeda, S., Takeshita, M., Arima, Y., Tsend-Ayush, C., Oyunsuren, T., ... Kurokawa, M. (2016). Augmentation of T helper type 1 immune response through intestinal immunity in murine cutaneous herpes simplex virus type 1 infection by probiotic *Lactobacillus plantarum* strain 06CC2. *International Immunopharmacology, 39*, 320–327.
Mazidi, M., Rezaie, P., Kengne, A. P., Mobarhan, M. G., & Ferns, G. A. (2016). Gut microbiome and metabolic syndrome. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 10S*, S150–S157.
Mill, J. G., Pinto, K., Griep, R. H., Goulart, A., Foppa, M., Lotufo, P. A., ... Bensenor, I. M. (2013). Aferições e exames clínicos realizados nos participantes do ELSA-Brasil. *Revista de Saúde Pública, 47*, 54–62.
Ministero della Salute (2013). Commissione unica per la nutrizione e la dietetica – Guidelines on probiotics and prebiotics. Available at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_1016_allegato.pdf Accessed May 24th, 2016.
Panahi, Y., Hosseini, M. S., Khalili, N., Naimi, E., Simental-Mendía, L. E., Majeed, M., & Sahebkar, A. (2016). Effects of curcumin on serum cytokine concentrations in subjects with metabolic syndrome: A post-hoc analysis of a randomized controlled trial. *Biomedicine & Pharmacotherapy, 82*, 578–582.
Sanders, M. E., & Marco, M. L. (2010). Food formats for effective delivery of probiotics. *Annual Review of Food Science and Technology, 1*, 65–85.
Scavuzzi, B. M., Miglioranza, L. H. S., Henrique, F. C., Paroschi, T. P., Lozovoy, M. A. B., Simaão, A. N. C., & Dichi, I. (2015). The role of probiotics on each component of the metabolic syndrome and other cardiovascular risks. *Expert Opinion on Therapeutic Targets, 19*, 1127–1138.
Shimakawa, T., & Bild, D. E. (1993). Relationship between hemoglobin and cardiovascular risk factors in young adults. *Journal of Clinical Epidemiology, 46*, 1257–1266.
Simão, T. N. C., Lozovoy, M. A. B., Simão, A. N. C., Oliveira, S. R., Venturini, D., Morimoto, H. K., ... Dichi, I. (2013). Reduced-energy cranberry juice increases folic acid and adiponectin and reduces homocysteine and oxidative stress in patients with the metabolic syndrome. *British Journal of Nutrition, 110*, 1885–1894.
Singh, B. P., Vij, S., & Hati, S. (2014). Functional significance of bioactive peptides derived from soybean. *Peptides, 54*, 171–179.
Solieri, L., Rutella, G. S., & Tagliazucchi, D. (2015). Impact of non-starter lactobacilli on release of peptides with angiotensin-converting enzyme inhibitory and antioxidant activities during bovine milk fermentation. *Food Microbiology, 51*, 108–116.
Song, K., Du, H., Zhang, Q., Wang, C., Guo, Y., Wu, H., ... Niu, K. (2014). Serum immunoglobulin M concentration is positively related to metabolic syndrome in an adult population: Tianjin chronic low-grade systemic inflammation and health (TCLSIH) cohort study. *PLoS ONE, 9*, e88701.
Štofilová, J., Szabadosová, V., Hrčková, G., Salaj, R., Bertková, I., Hijová, E., ... Bomba, A. (2015). Co-administration of a probiotic strain *Lactobacillus plantarum* LS/07 CCM7766 with prebiotic inulin alleviates the intestinal inflammation in rats exposed to N, N-dimethylhydrazine. *International Immunopharmacology, 24*, 361–368.
Synetos, A., Papanikolaou, A., Toutouzas, K., Georgiopoulos, G., Karanasos, A., Drakopoulou, M., ... Tousoulis, D. (2016). Metabolic syndrome predicts plaque rupture in patients with acute myocardial infarction. An optical coherence study. *International Journal of Cardiology, 209*, 139–141.
Tonucci, L. B., Santos, K. M. O., Oliveira, L. L. O., Ribeiro, S. M. R., & Martino, H. S. D. (2017). Clinical application of probiotics in type 2 diabetes mellitus: A randomized, double-blind, placebo-controlled study. *Clinical Nutrition, 36*, 85–92.
Tremaroli, V., & Bäckhed, F. (2012). Functional interactions between the gut microbiota and host metabolism. *Nature, 489*, 242–249.
Turnbaugh, P. J., Hamady, M., Yatsunenko, T., Cantarel, B. L., Duncan, A., Ley, R. E., ... Gordon, J. I. (2009). A core gut microbiome in obese and lean twins. *Nature, 457*, 480–484.
Vaskonen, T., Mervaala, E., Sumuvuori, V., Seppänen-Laakso, T., & Karppanen, H. (2002). Effects of calcium and plant sterols on serum lipids in obese Zucker rats on a low-fat diet. *British Journal of Nutrition, 87*, 239–245.
Wang, Z., Shen, X.-H., Feng, W.-M., & Qiu, W. (2017). Mast cell specific immunological biomarkers and metabolic syndrome among middle-aged and older Chinese adults. *Endocrine Journal, 64*, 245–253.
Wang, Z., Zhang, H., Shen, X.-H., Jin, K.-L., Ye, G.-F., Qian, L., ... Shi, G.-P. (2011). Immunoglobulin E and mast cell proteases are potential risk factors of human prediabetes and diabetes mellitus. *Ploes One, 6*, e28962.
Wang, Z., Zhang, H., Shen, X.-H., Jin, K.-L., Ye, G.-F., Qiu, W., ... Shi, G.-P. (2013). Increased levels of IgE in plasma or tissues may activate mast cells and increase mast cell mediators in the extracellular milieu. *Annals of Medicine, 45*, 220–229.
Zhang, J., & Shi, G. P. (2012). Mast cells and metabolic syndrome. *Biochimicaet Biophysica Acta, 1822*, 14–20.