

The function of nutraceuticals in the intestinal modulation of animals with non-alcoholic steatohepatitis: a systematic review

Função dos nutracêuticos na modulação intestinal de animais com esteatose hepática não alcóolica: uma revisão sistemática

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ABSTRACT

Recent studies have observed the role of intestinal microbiota in the pathogenesis of non-alcoholic steatosis and described the relationship between alterations in the microbiota (dysbiosis) and inadequate dietary practices and obesity. Through a systematic synthesis, this review aims to establish which nutraceuticals can be used in the intestinal modulation of animal models with Non-Alcoholic Steatohepatitis. Based on Medical Subject Headings and *Descritores em Ciências da Saúde* descriptors, searches were performed on the PubMed, Web of Science, and Lilacs databases using the keywords: "Microbiota"; "Gastrointestinal Microbiome"; "Dysbiosis"; "Bacterial Translocation";

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“Non-alcoholic fatty liver disease”; “Nonalcoholic Steatohepatitis”, “Nutraceuticals”; and “Dietetic Supplements”. After the methodological screening, seven studies were included. A total of 246 male Sprague Dawley rats with a mean age of four to eight weeks were evaluated. More than half of the studies (57.1%) used probiotics as nutraceuticals, 28.7% used tomato products, and 14.3% used symbiotics. The results suggest the positive effects of probiotics, tomato products, and symbiotics in the composition and functions of microorganisms resident in the intestines of animals with NASH, according to different mechanisms. Modulation of intestinal microbiota may contribute to minimizing the development and progression of “Nonalcoholic Steatohepatitis”.

Keywords: Dysbiosis. Microbiota. Non-alcoholic fatty liver disease. Nutraceutical. Nutritional sciences.

RESUMO

Estudos recentes têm observado o papel da microbiota intestinal na patogênese da esteatose não alcoólica e descrito a relação entre as alterações na microbiota (chamada disbiose) com os e práticas alimentares inadequadas e obesidade. Por meio de síntese sistemática, esta revisão visa estabelecer quais nutracêuticos podem ser utilizados na modulação intestinal de modelos animais com esteato-hepatite não alcoólica. A partir da busca dos descritores MeSH e Decs, foram realizadas buscas nas bases de dados PubMed, Web of Science e Lilacs utilizando as palavras-chave “Microbiota”; “Microbioma Gastrointestinal”; “Disbiose”; “Translocação Bacteriana”; “Doença hepática gordurosa não alcoólica”; “Doença Esteatótica Não Alcoólica do Fígado”, “Nutracêuticos” e “Suplementos dietéticos”. Após a triagem metodológica, sete estudos foram selecionados incluídos. Um total de 246 Duzentos e quarenta e seis ratos Sprague Dawley machos com idade média de quatro a oito semanas foram avaliados. Mais da metade dos estudos (57,1%) utilizou probióticos como nutracêuticos, 28,7% das pesquisas utilizaram produtos à base de tomate e 14,3% utilizaram simbióticos. Os resultados sugerem efeitos positivos de probióticos, produtos do tomate e simbióticos na composição e funções de microrganismos residentes no intestino de animais com esteato-hepatite não alcoólica micro de acordo com diferentes mecanismos. A modulação da microbiota intestinal pode contribuir para minimizar o desenvolvimento e progressão da esteato-hepatite não alcoólica.

Palavras-chave: Disbiose. Microbiota. Doença hepática gordurosa não alcoólica. Nutracêuticos. Ciência da nutrição.

INTRODUCTION

The disease known as Non-Alcoholic Steatohepatitis (NASH) is the most severe form of Non-Alcoholic Fatty Liver Disease (NAFLD). Characterized by hepatic damage, inflammation, and the presence or absence of fibrosis, this pathology could pose a significant risk for hepatic cirrhosis and hepatocellular carcinoma. However, many patients are asymptomatic [1].

Recent studies have observed the role of intestinal microbiota in the pathogenesis of NASH and described the relationship between alterations in the microbiota (called dysbiosis) and inadequate dietary practices and obesity. The changes in the dietary pattern (nutritional transition) are characterized by an increase of inadequate dietary practices, with the consumption of ultra-processed foods, and a decreased consumption of natural and minimally processed foods, contributing directly to augment the prevalence of overweight and obesity and, consequently, to the development of chronic non-communicable diseases. Associated with inadequate dietary habits, this pathology contributes to an imbalance of the intestinal microbiota, incrementing intestinal permeability and favoring the bacterial translocation and the production of endotoxins, mainly

Lipopolysaccharide (LPS). To metabolize endotoxins, these are directed to the liver through the portal vein, lowering the Fasting-Induced Adipose Factor (FIAP) secretion and increasing Lipoprotein Lipase (LPL) activity, promoting fatty acid synthesis and triglyceride production, and activating inflammatory Toll-like receptors in hepatocytes. Thus, such changes in intestinal microbiota increase the liver's exposure to endotoxins contribute to the progression of NASH [2].

The term 'nutraceutical' was coined in 1989 by Stephen L. Defelice and is defined as "a food or part of a food, such as a dietary supplement, that has a medical or health benefit, including the prevention and treatment of diseases" [3]. Based on this definition, studies that evaluate the use of nutraceuticals in NASH/NAFLD show their benefits mainly in the modulation of the intestinal microbiota and consequently to control the progression of the disease.

Scientific studies on intestinal microbiota are recent, especially after specific research of pathologies like NASH/NAFLD has clarified the links between the pathology and the disorder in the intestinal microbiota. Hence, to reduce the risks of health damages, animal experiments are of utmost importance before further testing in humans [4]. Therefore, this systematic review will promote the synthesis of recent studies (until 2019) on the subject to investigate the function of nutraceuticals in the intestinal modulation of animals with NASH.

DEVELOPMENT

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist to conduct the systematic review. The protocol for this systematic review was recorded on PROSPERO CRD 42019134697 [5].

Searches were conducted in PubMed (by Medline-OVID), Web of Science, and Lilacs databases to recover studies aiming to investigate the functions of nutraceuticals in the intestinal modulation of animals with NASH. No date or language restrictions were applied and the descriptors used were: "Microbiota"; "Gastrointestinal Microbiome"; "Dysbiosis"; "Bacterial Translocation"; "Non-alcoholic fatty liver disease"; "NAFLD"; "Nutraceutical"; and "Dietary Supplements". In addition, we employed search references from previous systematic reviews in the field to find possible uncovered references with our search strategy.

We included all the studies published with the objective of investigating the function of nutraceuticals in the intestinal modulation of animals with NASH. The inclusion criteria were: studies with animals of both sexes, studies assessing the role of nutraceuticals (such as probiotics and prebiotics), studies that evaluated the intestinal microbiota of animals, and with a control group. The exclusion criteria were: in vitro studies, studies with humans, studies that did not evaluate nutraceuticals, and studies without control groups.

References retrieved with our search strategies were exported to an Endnote® file, and the duplicates were removed. Two independent researchers (Pâmela Gracielle da Fonseca and Fabiana de Faria Ghetti) selected the titles and abstracts, and the potential full texts were evaluated for the previously described eligibility criteria. The discrepancies were resolved by a third-party investigator (Sônia Maria Figueiredo).

Two independent researchers (Pâmela Gracielle da Fonseca and Fabiana de Faria Ghetti) extracted the data on the studies' characteristics (i.e., study design, source of participants, sample size, investigated factors) and outcomes (i.e., measures of association for each investigated factor). The discrepancies were resolved by a third-party investigator (Nathalia Sernizon Guimarães). When outcome data were not reported in included studies, authors were contacted at the baseline, and data input was carried out following Cochrane's recommendations.

The assessment of the risk of bias of all the included studies was performed by two independent researchers and was ranked as high, low, or uncertain. A third-party investigator solved the discrepancies when

necessary. The quality evaluation of the studies was performed with the SYRCLE tool provided by SYRCLE at Central Animal Laboratory, which makes it possible to assess the risk of bias based on the criteria: random allocation (selection bias), similarity in the groups (selection bias), blinding of participants and professionals (selection bias), blinding of outcome evaluators (detection bias), incomplete endpoints (friction bias), report of selective endpoint (bias), and other sources of bias (other biases) [6]. The tool suggests 10 questions that should be applied to the articles included in the systematic review. These questions may be answered with “YES” (for low risk of bias), “NO” (for high risk of bias), and “?” (unclear, for uncertain risk of bias) [6].

RESULTS

The searches recovered 51 titles without duplicates. After screening titles and abstracts, nine potential full texts were evaluated. Two studies were excluded, and seven published studies were included in the review (Figure 1). Among the seven selected studies, only six specified the number of animals used for the research. Out of a total of 246 animals evaluated, all were male Sprague Dawley rats (100%) with a mean age of four to eight weeks; all were evaluated (Table 1).

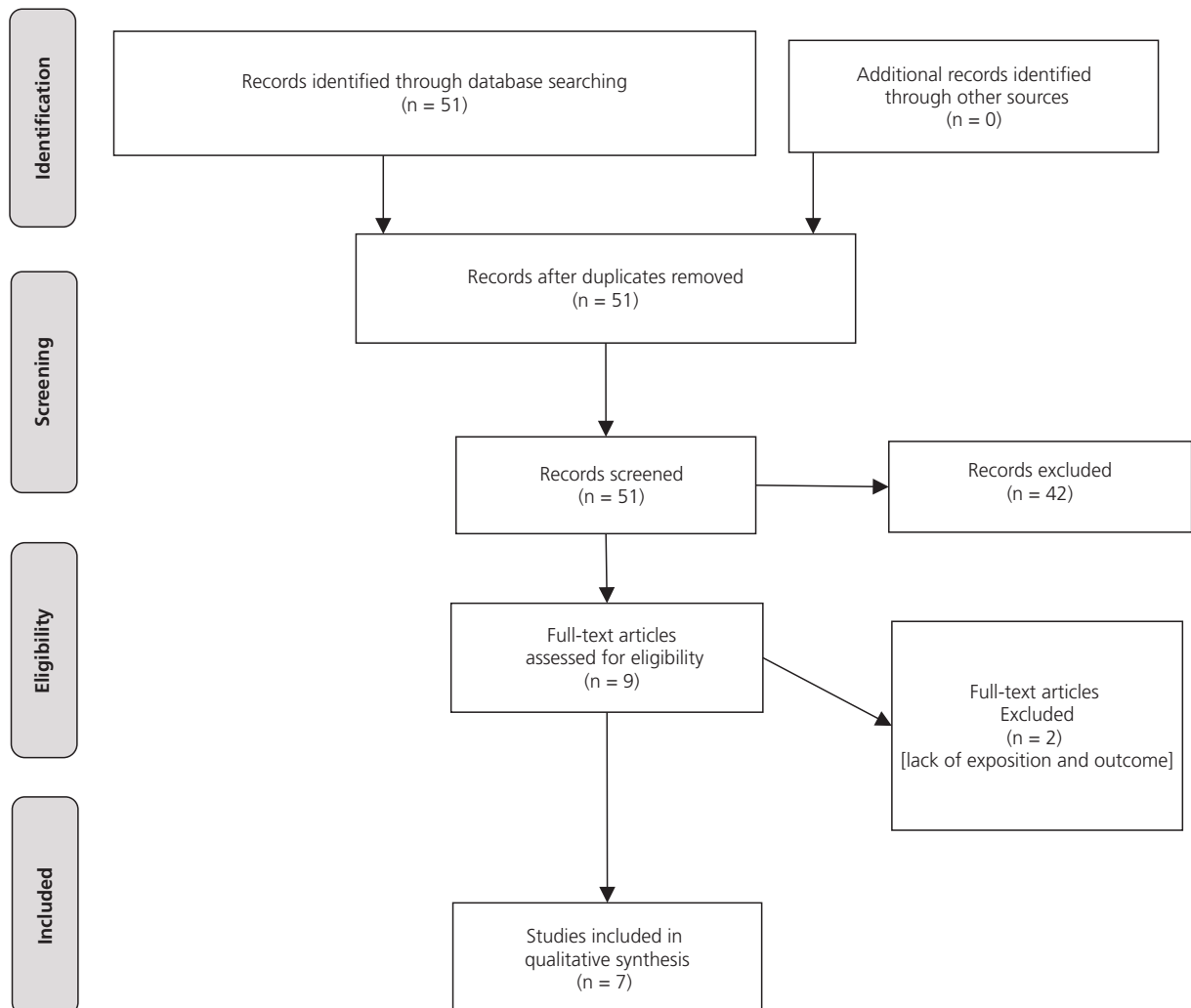


Figure 1 – PRISMA 2009 flow diagram of the studies included in the review.

Table 1 – Distribution of studies selected according to author/year of publication, population (gender and quantity), NASH diagnostic method, microbiota analysis method, nutraceuticals used and posology, main results.

Reference	Population	Nutraceuticals	Results
Zhou <i>et al.</i> [11]	50 male rats	Probiotic's supplementation with <i>Bifidobacterium longum</i> , <i>Lactobacillus acidophilus</i> and <i>Enterococcus faecalis</i> (0.5x10 ⁶ CFU)	Improvement of dysbiosis; restoration of the microecosystem of microbiota via positive regulation of adiponectin; reduction of pro-inflammatory hepatic and systemic responses caused by the signaling of adiponectin DNA methylation.
Chen <i>et al.</i> [13]	60 mice	<i>Lactobacillus mali</i> APS1 extracted from Kefir (108 CFU)	Improvement of hepatic steatosis picture; modulation of lipid metabolism; antioxidant activity through the manipulation of the intestinal microbiota associated with NAFLD in vivo.
Li <i>et al.</i> [7]	18 male rats	Tomato powder (41.9 g/kg)	Inhibits NAFLD by suppressing inflammatory responses and increasing SIRT1 activity and adiponectin production in fat tissues; increases the microbial richness and decreases the abundance of <i>Clostridium</i> , associated with a lower incidence of NAFLD.
García <i>et al.</i> [8]	24 male rats	Tomato juice (NS)	Possible role of tomato antioxidants (D9 prevention of lipid oxidation of the diet during D8 and vitamin C) in the D5 which could also have a relevant impact on the intestinal microbiota.
Rivero <i>et al.</i> [17]	30 male rats	Symbiotic composed of Fructooligosaccharide + <i>Lactobacillus fermentum</i> (CECT5716 1.25 x 10 ¹⁰ CFU/L) diluted in water	Prevents intestinal permeability, systemic inflammation, hepatic steatosis, and insulin resistance, acting through mechanisms that seem to involve the modulation of microbiota.
Xue <i>et al.</i> [12]	48 male rats	Probiotic composed of 0.5 x 10 ⁶ CFU of <i>Bifidobacterium infantis</i> and <i>Lactobacillus acidophilus</i> and 0.5 x 10 ⁵ CFU of <i>Bacillus cereus</i>	Improves the structure of the intestinal microbiota and the liver pathology; negatively regulates serum LPS and TLR4 in the liver; may delay the progression of NAFLD through LPS / TLR4 signaling.
Kim <i>et al.</i> [14]	16 male rats	<i>Lactobacillus rhamnosus</i> GG 1x10 ⁸ CFU (one dose per day)	Protection against dyslipidemia induced by a high-fat diet; modulation of liver triglycerides and synthesis of cholesterol, and increased synthesis of bile acids and cholesterol carrier; suppression of immune cell infiltration and by the secretion of pro-inflammatory cytokines.

Note: CFU: Colony Forming Units; DNA: Deoxyribonucleic acid; NAFLD: Non-Alcoholic Fatty Liver Disease; NS: Not Specified Quantity; W: Weeks.

More than half of the studies (57.1%) used probiotics as nutraceuticals, 28.7% of the studies used tomatoes (n=2), and 14.3% used symbiotics (n=1).

To assess the risk of bias in animal studies, we applied the SYRCLE tool made available by SYRCLE at the Central Animal Laboratory [6]. The risk of bias was assessed individually in each study. The seven studies included in this review met the criteria for classification as low risk of bias (Chart 1).

Chart 1 – Authors' evaluation of each item of the included studies for risk of bias.

Questions	Study						
	1	2	3	4	5	6	7
Was the allocation sequence adequately generated and applied?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the groups similar at baseline or were they adjusted for confounders in the analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the allocation in the different groups adequately concealed during the study?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the animals randomly housed during the experiment?	No	No	No	No	No	No	No
Were the caregivers and/or investigators blinded from knowledge on which intervention each animal received during the experiment?	No	No	Yes	No	No	Yes	No
Were animals randomly selected for outcome assessment?	No	No	No	No	No	No	No
Was the outcome assessor blinded?	No	No	No	No	No	No	No
Were incomplete outcome data adequately addressed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are reports of the study free of selective outcome reporting?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the study apparently free of other problems that could result in high risk of bias?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Note: No: high risk of bias; Yes: low risk of bias.

DISCUSSION

The scientific evidence from the randomized clinical trials included in this article suggests the efficacy of nutraceuticals in slowing the progression of NASH, as well as the improvement of some of its symptoms. Out of the seven articles analyzed, four approach the use of some type of probiotic like the variety of *Lactobacillus*, two assess the use of tomato sub-products, and the last evaluates a compound of one type of *Lactobacillus* and the *Fructooligosaccharides* (FOS) also called *Symbiotic*.

Lycopene belongs to the class of carotenoids and is responsible for the red pigmentation in some foods. Although it is devoid of pro-vitamin A activity, it may act as a potent antioxidant [7]. Tomato products are rich in this component. The study that evaluated the use of tomato powder showed a significant improvement in the NAFLD framework. NAFLD was inhibited independently of carotenoid cleavage enzymes, potentially by the suppression of inflammatory responses, increases in the Sirtuin 1 (SIRT1) activity, and adiponectin production in fat tissues. In addition, dietary tomato powder may increase the microbial richness of the intestine and decrease the abundance of *Clostridium*, which may be associated with a lower incidence of NAFLD induced by a high-fat diet [8].

In another study that used tomato juice as a nutraceutical, a partial attenuation of the disorders induced by the hyper-lipidic diet was evidenced, particularly by increasing the *Lactobacillus* count. Tomato antioxidants (carotenoids and vitamin C) possibly played a role in the prevention of lipid oxidation during digestion, which could also have a relevant impact on the intestinal microbiota [9]. Moreover, the authors reported an increase in the density of the *Lactobacillus* count, which is a gut barrier-protecting bacteria [9]. The disruption of the integrity of the intestinal mucosa barrier may lead to increased intestinal permeability and excessive absorption of LPS, resulting in low-grade inflammation and hepatic fibrosis [10].

Probiotics are living microorganisms that, consumed in adequate quantities, promote benefits for the host's health. Currently, they have been used in diseases such as NAFLD and cirrhosis due to their action in the regulation of microbiota, modifying intestinal barriers, and having immunomodulatory and anti-inflammatory effects at the liver level [11].

Different bacteria strains, concentrations, and combinations were used in the studies with probiotics, and only *Lactobacillus Acidophilus* was repeated on the methodology [12]. Probiotics may delay the progression of non-alcoholic fatty liver disease by restoring the gut microbiota structure and improving intestinal endotoxemia. The studies induced NASH/NAFLD through a High-Fat Diet (HFD) and used probiotics as a therapeutic form concomitantly with or after disease induction. Live strains of *Bifidobacterium longum*, *Lactobacillus acidophilus*, *Enterococcus faecalis* live, *Lactobacillus mali* APS1 (extract from Kefir), *Bifidobacterium infantis*, *Bacillus cereus*, and *Lactobacillus Rhamnosus* GG were used [12-15].

As a result, it was possible to observe that the supplementation provided improvement of the dysbiosis in NAFLD, restoration of the micro-ecosystem of the intestinal microbiota via positive regulation of adiponectin, reduction of pro-inflammatory hepatic and systemic responses caused by signaling of adiponectin DNA methylation, and improvement in the regulation of lipid metabolism [14-15].

Experimental studies suggest that probiotics differ greatly in their effects and mechanisms of action. Significant differences exist not only among the species of probiotics but also within the same strain. Although the molecular mechanisms of probiotics are not fully elucidated, many of their effects may prove beneficial in the gastrointestinal tract, including the modulation of the intestinal microbiota, the antibacterial substance production, the epithelial barrier function, intestinal inflammation, or effects on the immune system [16].

The term symbiotic has been used when a product contains both probiotics and prebiotics. The first term was defined above; the second includes non-digestible carbohydrates that beneficially affect the host by selectively stimulating the proliferation and/or activity of populations of desirable bacteria in the colon. There is evidence that symbiotics are more effective than probiotics in modulating the gut microbiota [17].

Only one study evaluated the use of symbiotics in animals with NASH [18]. It was observed that the association of the probiotic *Lactobacillus fermentum* CECT5716 with the prebiotic Fructooligosaccharides (FOS) resulted in the prevention of intestinal hyperpermeability, inflammation, and systemic hepatic steatosis and insulin resistance, resulting in protective changes in metabolic and immunological levels.

It had been previously demonstrated that FOS modifying the gene expression of lipogenic enzymes reduced the de novo liver fatty acid synthesis, contributing to the decrease in triglyceride accumulation in the liver [19]. Moreover, the fermentation of FOS by strains of lactobacilli produces Short-Chain Fatty Acids (SCFA), which have an important role in decreasing the pH and inhibiting the growth of a wide range of Gram-negative pathogenic bacteria with LPS-containing membranes [20].

Therefore, the capability of symbiotics to decrease liver fat and improve gut ecology and microbial composition, inhibiting pathogenic bacteria growth and/ or competing with and displacing pathogenic bacteria, is likely to prevent NASH, Small Intestinal Bacterial Overgrowth (SIBO), and endotoxemia.

CONCLUSION

To this date, studies that evaluated the functions of nutraceuticals in the modulation of intestinal microbiota in animals with NASH are scarce. The results suggest positive effects of tomato products, probiotics, and symbiotics on the composition and functions of microorganisms residing in the intestines. Modulation of the intestinal microbiota may contribute to minimizing the development and progression of NASH. Therefore, the role of nutraceuticals on the gut-liver axis offers new challenges for future studies.

CONTRIBUTORS

PG FONSECA was responsible for study conception and design, data analysis and interpretation, revision and approval of the final version. FF GHETTI, was responsible for data analysis and interpretation, revision and approval of the final version. SM FIGUEIREDO: data analysis and interpretation, revision and approval of the final version; NS GUIMARÃES was responsible for study conception and design, data analysis and interpretation, revision and approval of the final version.

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