



## Revisión

# Mechanisms used by inulin-type fructans to improve the lipid profile

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## Abstract

**Aims:** The consumption of prebiotics has been associated with improvement in the lipid profile. Thus, this review aims to describe the main mechanisms by which inulin-type fructans improve the lipid profile and thereby reduce the cardiovascular risk.

**Data synthesis:** Inulin-type fructans have been demonstrated to improve the lipid profile through a number of mechanisms. These mechanisms include: decrease in gene expression of hepatic enzymes responsible for *de novo* synthesis of lipids; increase of muscle lipoprotein lipase enzyme activity, enhancing the production of short-chain fatty acids; altered production of polyamines which increases the production of satiogenic peptide; altered blood glucose and insulinemia; increase of fecal excretion of bile salts and cholesterol and increase of the *Bifidobacterium* population.

**Conclusions:** The consumption of inulin-type fructans enhances lipid profile. Generally, the mechanisms vary according to the physiologic state of the individual and the type of diet to which the inulin-type fructans are added. Thus, inulin may be used for the prevention and/or treatment of cardiovascular diseases.

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Key words: *Dyslipidemias. Inulin. Cardiovascular disease. Lipid metabolism.*

## Introduction

Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality worldwide, accounting for 17 million deaths, equivalent to 29% of all deaths an-

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## MECANISMOS UTILIZADOS POR LOS FRUCTANOS TIPO INULINA PARA MEJORAR EL PERFIL LIPÍDICO

## Resumen

**Objetivos:** El consumo de prebióticos ha sido asociado con el mejoramiento del perfil lipídico. Por tanto, esta revisión tiene como objetivo describir los principales mecanismos por los cuales fructanos tipo inulina, mejoran el perfil lipídico reduciendo el riesgo cardiovascular.

**Síntesis de los datos:** Los fructanos tipo inulina, han demostrado una mejora del perfil lipídico, a través de varios mecanismos, incluyendo: disminución de la expresión génica de las enzimas hepáticas responsables por la síntesis *de novo* de lípidos; aumento de la actividad enzimática del lipoproteína lipasa muscular; aumento de la producción de ácidos grasos de cadena corta; producción alterada de poliaminas que aumentan la producción del péptido Satiogen; alteración de la glicemia e insulinemia; aumento de la población de *Bifidobacterium* y el incremento de la excreción fecal de las sales biliares y el colesterol.

**Conclusiones:** El consumo de los fructanos tipo inulina mejora el perfil lipídico. Generalmente, los mecanismos varían de acuerdo con el estado fisiológico del individuo y el tipo de dieta, en la que son adicionados los fructanos tipo inulina. Por tanto, la inulina puede ser utilizada para la prevención y/o tratamiento de enfermedades cardiovasculares.

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nualmente<sup>1</sup>. It is estimated that in 2030, the number of victims of this disease will reach 23.3 million<sup>2</sup>. This disease has multiple risk factors, e.g. dyslipidemias, characterized by abnormal serum concentrations of cholesterol and/or triglycerides<sup>3</sup>. In the United States annual direct and overall costs resulting from CVD are estimated at \$273 billion and \$444 billion, respectively<sup>4</sup>; this is considered an important public health problem.

In the treatment of this pathology, non-pharmacological therapies, including nutritional therapy<sup>5</sup>, have been increasingly researched due to the absence of side effects and low cost compared with medication<sup>3</sup>.

Many foods with functional properties have been used for the treatment and/or prevention of CVD, such

as food sources of omega-3 fatty acids<sup>6</sup>, antioxidants<sup>7</sup>, fiber<sup>8</sup>, phytosterols<sup>5</sup>, and prebiotics<sup>9</sup>.

Prebiotics are non-digestible, fermentable food ingredients that selectively stimulate the growth and/or activity of some bacterial species that are part of the intestinal microbiota, conferring benefits to the host health<sup>10</sup>. Some oligosaccharides are considered prebiotics, such as inulin-type fructans<sup>11</sup>.

Wu et al.<sup>12</sup> conducted a systematic review on the efficacy of inulin-type fructans on lowering blood lipids. They found that blood lipids of subjects with hyperlipidemia could be decreased significantly by foods enriched with 17 g of inulin-type fructans per day, whereas the effects were absent in normal subjects. The consumption of inulin-type fructans has been associated with improved lipid profile and, consequently, reduction of cardiovascular risk<sup>9</sup> (Tables I and II). Thus, the focus of this review is to describe the main mechanisms by which inulin-type fructans improve the lipid profile and benefit human health.

## Inulin-Type Fructans

Inulin-type fructans are reserve carbohydrates of plants that have in their structure 1–70 fructose units that may be linked to a terminal sucrose molecule. Due to the  $\beta$  configuration of the anomeric carbon 2 of fructose monomers, these molecules are resistant to hydrolysis by digestive enzymes in the gastrointestinal tract<sup>11</sup>.

Fructans are classified according to their degree of polymerization into inulin, high polymerization (HP) inulin, oligofructose (OFS), synergy, and fructooligosaccharides (FOS)<sup>11, 13</sup>. They are found in approximately 36 thousand species of plants<sup>14</sup>. Furthermore, inulin-type fructans have been widely used by the food industry because they present a number of technological and nutritional advantages<sup>13</sup>.

The consumption of inulin-type fructans brings several health benefits, including improved lipid profile<sup>11, 13, 14</sup>. Inulin can act directly on lipid meta-

**Table I**  
*Effects of consumption of inulin type fructans on lipid profile and glycemia in animal studies*

<i>Inulin type- fructans</i>	<i>Animals and diet</i>	<i>Experimental design</i>	<i>Dose</i>	<i>Duration</i>	<i>Effects</i>	<i>References</i>
HP inulin	LDLR <sup>-/-</sup> male mice; purified diets	Randomized, placebo-controlled, parallel.	10 % of diet	16 weeks	=TG, HDL-c →TC, LDL-c	Mortensen et al, <sup>40</sup>
Oligofructose	Male Wistar rats; high fructose diet or a starch-based diet	Randomized, placebo-controlled, parallel.	10 % of diet	4 weeks	→ TG = glycemia	Brusserolles et al, <sup>41</sup>
Oligofructose	Male Wistar rats; fat diet	Randomized, placebo-controlled, parallel.	10 % of diet	50 days	→ TG	Cani et al., <sup>27</sup>
Oligofructose	C57BL/6J male mice; fat diet	Randomized, placebo-controlled, parallel.	10 % of diet	28 days	→ glycemia	Cani et al., <sup>24</sup>
Oligofructose	C57BL/6 male mice; hypercholesterolemic diet.	Randomized, placebo-controlled, parallel.	10 % of diet	28 days	→ glycemia	Delmée et al., <sup>25</sup>
Oligofructose	ob / ob mice, diet A04.	Randomized, placebo-controlled, parallel.	10 % of diet	5 weeks	→ TG, glycemia	Everard et al., <sup>17</sup>
Oligofructose	Wistar Kyoto rats, normal diet or high-fat diet	Caso-control study	10 % of diet	7 weeks	→ TG	Correia-Sá et al., <sup>42</sup>
Oligofructose	Wistar rats supplemented with 10% OFS or dextrin	Caso-control study	10 % of diet	7 weeks	→ TG, TC, HDL, LDL	Kosmus et al., <sup>43</sup>
HP inulin, oligofructose and Synergy 1	Apo E <sup>-/-</sup> male mice; AIN-93G	Randomized, placebo-controlled, parallel.	10 % of diet	13 weeks	→ TC, TG	Rault-Nania et al., <sup>44</sup>
HP inulin, oligofructose and Synergy 1	Male Wistar rats; semi-purified starch or fructose-based diet	Randomized, placebo-controlled, parallel.	10 % of diet	4 weeks	→ TG =TC, glycemia	Rault-Nania et al., <sup>18</sup>
Inulins with different degree of polymerization	Rats fed a high-fat diet	Randomized, placebo-controlled, parallel.	5 % of diet	28 days	→ TC, TG = glycemia	Han et al., <sup>45</sup>

HP: high polymerization; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; LDLR<sup>-/-</sup>: low-density lipoprotein cholesterol receptor knockout; TC: total cholesterol; TG: triglycerides; OFS: oligofructose; →: decreased; ➡: increased; =: did not change.

**Table II**  
Effects of consumption of inulin type fructans on lipid profile and glycemia in human studies

Inulin type- fructans	Volunteers	Experimental design	Dose	Duration	Effects	References
Inulin	Men with hypercholesterolemia.	Randomized, double-blind, crossover.	20 g/day	3 weeks	= TC, LDL-c, HDL-c, glycemia → TG	Causes et al., <sup>46</sup>
Inulin	Type 2 diabetic volunteers (n=36)	Randomized, double-blind design	10 g/day	12 weeks	= TC, LDL, HDL, TG hemoglobin A1c	Bonsu et al., <sup>47</sup>
FOS	Type 2 diabetic volunteers	Randomized, double-blind, crossover controlado com placebo.	20 g/day	4 weeks	= TC, LDL, HDL, TG, glycemia	Luo et al., <sup>48</sup>
HP Inulin	23-32 years old, normal lipid profile and glucose.	Randomized, double-blind, placebo-controlled, crossover.	10 g/day	6 weeks	=TC,LDL, HDL, glycemia → TG	Letexier et al., <sup>15</sup>
Oligofructose and inulin mixture	Healthy adults	Randomized, double blind, placebo-controlled.	9g/day	6 months	=TC, LDL, HDL, TG, glycemia	Forcheron & Beylot, <sup>49</sup>

FOS: fructooligosaccharides; HP: high polymerization; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides; →: decreased; ➔: increased; =: did not change.

bolism and can be used as substitutes for lipids in food, contributing to reducing the caloric density of the diet<sup>11</sup>.

According to Letexier et al.<sup>15</sup>, the improvement of the lipid profile, resulting from the consumption of inulin-type fructans, depends on the kind of diet to which the fructan is added and the pathophysiological condition of the animal/person studied. The main mechanisms used by inulin-type fructans to improve the lipid profile are presented in Figure 1.

## Physiological mechanisms

### Decreased hepatic lipogenesis

Animals and humans fed diets containing inulin-type fructans had lower serum levels and/or hepatic triglycerides (TG)<sup>15-18</sup>. Considering that the newly synthesized fatty acids are preferentially secreted with very low density lipoprotein (VLDL), it has been

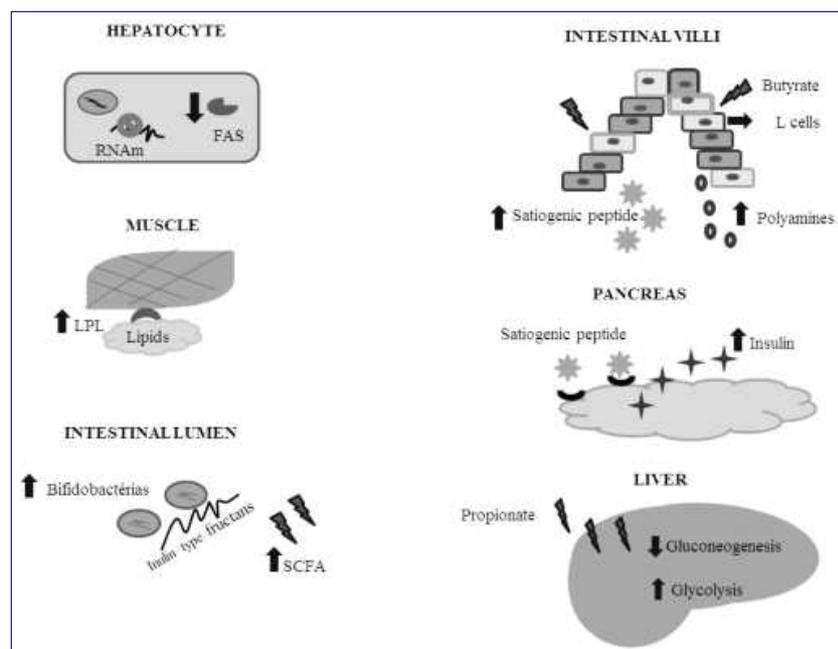


Fig. 1.—Mechanisms used by inulin-type fructans to improve the lipid profile: decrease in gene expression of hepatic enzymes responsible for de novo synthesis of lipids, as FAS; increased muscle LPL enzyme activity; increased population of Bifidobacteria and the production of SCFA; butyrate stimulates the differentiation of crypt cells in enteroendocrine L cells, increasing the production of satiogenic peptide, and increases the activity of ornithine decarboxylase, enhancing the production of polyamines; the satiogenic peptides stimulate the secretion of insulin by the pancreas; propionate stimulates glycolysis and inhibits hepatic gluconeogenesis. FAS: fatty acid synthase; LPL: lipoprotein lipase; SCFA: short-chain fatty acid.

hypothesized that the consumption of inulin-type fructans reduces the *de novo* synthesis of fatty acids in the liver<sup>19</sup>.

The consumption of inulin-type fructans was able to reduce the activity of some liver enzymes involved in the synthesis of fatty acids (acetyl-CoA carboxylase, fatty acid synthase, malic enzyme, ATP-citrate lyase, and glucose 6-phosphate dehydrogenase) in animal model<sup>20, 21</sup>.

The modification of the enzymes gene expression is necessary to reduce their activity<sup>19</sup> and consistent with this, Delzenne and Kok<sup>21</sup> observed a 40% decrease in the amount of mRNA of fatty acid synthase (FAS). These results demonstrated that inulin-type fructans are able to alter the gene expression of enzymes involved in hepatic TG synthesis, contributing to the improvement of the lipid profile.

#### *Increased extra-hepatic lipid catabolism*

According to investigations of Delzenne et al.<sup>21</sup>, the consumption of inulin-type fructans is not capable of increasing hepatic lipid catabolism, since it does not alter the activity of the enzyme carnitine palmitoyl-transferase I. This finds support that consumption of inulin-type fructans is associated with reduced serum TG by increased extrahepatic lipid catabolism<sup>22, 23</sup>.

In a study by Everard et al.<sup>17</sup> on *ob/ob* mice fed the OFS, it was observed that they had lower levels of serum TG and muscle lipids, and this was associated with an increase of 70% in the amount of mRNA of lipase lipoprotein (LPL) present in muscle tissue. The LPL enzyme is responsible for cleavage and release of TG molecules present in lipoprotein particles<sup>17</sup> and, consequently, lowering the TG serum levels. Therefore, the chance of the TG molecules suffering some deterioration and becoming atherogenic is reduced.

#### *Increased production of satiogenic intestinal peptide*

The reduction of body fat contributes to the improvement of the lipid profile, since there is a reduction in the amount of free fatty acids for the hepatic synthesis. It has been suggested that the consumption of inulin-type fructans may increase the production of satiogenic intestinal peptides and, consequently, reduce body fat<sup>16, 24, 25</sup>.

In the intestinal mucosa, proglucagon peptide is produced by enteroendocrine L cells and is converted to glucagon-like peptide 1 (GLP-1) or glucagon-like peptide 2 (GLP-2) by the action of the enzyme prohormone convertase I (PCI)<sup>26</sup>. The K cells are responsible for producing gastric inhibitory polypeptide (GIP)<sup>19, 26</sup>. These peptides are inactivated by the action of the enzyme dipeptidyl peptidase-IV (DPP-IV), which is produced by intestinal epithelial cells<sup>26</sup>.

The main function of the peptides GLP-1 and GIP is the stimulation of post-prandial secretion of insulin by pancreatic  $\beta$ -cells, influencing the metabolism of glucose and lipids<sup>26</sup>. In addition, the hormone GIP directly stimulates the activity of the enzymes LPL and FAS in adipose tissue<sup>21, 23</sup>, and the production and secretion of GLP-1<sup>27</sup>. This peptide acts as a regulator of food intake<sup>16</sup>. GLP-2 performs its functions at the local level, mainly related to cell proliferation, inhibition of acid secretion, and gastric emptying; therefore, it can act as a regulator of food intake<sup>27</sup>.

Cani et al.<sup>16</sup> observed that animals fed diets containing inulin-type fructans presented an increase in proglucagon mRNA in the region of the proximal colon, a two-fold increase in GLP-1 and GLP-2 in the region of the proximal colon, a two-fold increase in serum GLP-1 and 30% lower DPP-IV and serum ghrelin, compared with the animal that did not receive fructan. Also, animals with induced diabetes by the use of streptomycin and fed OFS, presented four times more serum GLP-1 and gained 60% less weight than the animals treated only with streptomycin<sup>27</sup>.

According to Cani et al.<sup>27</sup>, the short chain fatty acid (SCFA) butyrate is capable of increasing the production of GLP-1, since this enhances the expression of the protein *cdx-2*, a transcription factor that acts by activating the proglucagon gene promoter, thereby increasing GLP-1 expression. Moreover, it stimulates the differentiation of crypt cells in enteroendocrine L cells. Cani et al.<sup>28</sup> noted that animals fed OFS had twice as many L-cells in the region of the proximal colon, which was associated with increased amounts of *Ngn3* and *NeuroD* mRNA, proteins that are directly associated with the differentiation of crypt cells in L cells.

In summary, the inulin-type fructan increases the production of the satiogenic intestinal peptides. These peptides influence food intake, and the metabolism of carbohydrates and lipids, thus improving the lipid profile, contributing to cardiovascular health.

#### *Alteration of blood glucose and insulinemia*

Serum glucose and insulin also exert great influence on lipid profile, with high levels of these usually associated with a worse lipid profile. It is known that glucose is able to stimulate gene transcription of the enzymes involved in lipogenesis, and the presence of insulin potentiates this effect<sup>21</sup>, thereby exerting great influence on the lipid profile.

The results of studies evaluating the effects of inulin-type fructans on glycemia and insulinemia are still controversial. The results depend on the physiologic state (fasting or postprandial) and the presence/absence of any pathology<sup>23</sup>.

Cani et al.<sup>16</sup> observed that animals treated with streptomycin and fed 10% OFS presented better results on tests of oral glucose tolerance, lower postprandial glycemia, and higher serum insulin and C-peptide than

the animals that were treated with streptomycin but received no fructans. In addition, *ob/ob* mice fed for five weeks with OFS had the lowest fasting blood glucose and improved glucose tolerance compared with animals that did not receive OFS<sup>17</sup>.

Inulin-type fructans are not viscous and do not form a gel in the gastrointestinal tract. Therefore, gastric emptying time and/or intestinal transit time are not changed, as this is not one of the mechanisms by which they influence blood glucose levels and the insulin response<sup>13</sup>. According to Cani et al.<sup>24</sup>, the antidiabetic effects of OFS are dependent on the action of the hormone GLP-1, since the effect is abolished in glucagon-like peptide 1 receptor knockout (GLP-1R<sup>-/-</sup>) animals or when using exendin 9-39 (Ex-9), a receptor antagonist of GLP-1. Furthermore, these authors noted that OFS was capable of reversing hepatic insulin resistance by increasing phosphorylation of the intracellular proteins Akt and IRS2<sup>24</sup>. Inulin-type fructans are also capable of increasing the mass of pancreatic  $\beta$ -cells<sup>16</sup>.

Another proposed mechanism is related to increased production of SCFA propionate, which is able to inhibit the process of gluconeogenesis. Thereafter, it is converted into methylmalonyl-CoA and succinyl-CoA, and is capable of inhibiting the activity of the enzyme pyruvate carboxylase. This SCFA is also able to enhance glycolysis, since it depletes hepatic citrate, which is the main inhibitor of the enzyme phosphofructokinase<sup>29</sup>. This enzyme is one of the most important regulatory enzymes of glycolysis.

#### *Increased fecal excretion of bile salts and cholesterol*

The main form of cholesterol excretion by the body is through the bile, since cholesterol is used for the synthesis of bile acids. With the increased excretion of bile acids, fewer of them are carried back to the liver via the enterohepatic circulation, which increases the hepatic uptake of serum cholesterol for *de novo* synthesis of bile salts in this organ.

Inulin-type fructans do not seem to be able to bind the bile acids present in the intestinal lumen<sup>30</sup>. However, the fermentation of inulin-type fructans in the intestinal mucosa leads to the production of organic acids, reducing the pH in the intestinal lumen. Thus, the bile acids become less soluble and may be eliminated with the feces, which reduces their intestinal absorption<sup>31</sup>.

Trautwein et al.<sup>33</sup> analyzed the composition of the bile acids present in the gallbladder of animals fed inulin and observed that the proportion of glycine-conjugated bile acids was greater than the proportion of taurine-conjugated bile acids, and the amount of taurochenodeoxycholic bile acid was lower in these animals than those which did not receive the fructan. According to the authors, hepatic synthesis of bile acids was inhibited more strongly by dihydroxy bile acids such as taurochenodeoxycholic bile acid. Therefore, the in-

creased synthesis of bile acids in these animals may have contributed to the decrease in serum and liver cholesterol. Also, as a consequence of the fermentation process, the production of butyrate increases the thickness of the intestinal wall, which hinders the absorption of cholesterol molecules<sup>9</sup>.

#### *Increased production of SCFA*

The SCFA (propionate, butyrate, and acetate) are the major end products of bacterial fermentation of carbohydrates that are not digested in the upper gastrointestinal tract<sup>34</sup>, such as inulin-type fructan. The amount and molar ratio of SCFA varies depending on the type of fermented fructan and microorganisms available to complete this process<sup>35</sup>.

Daubioul et al.<sup>20</sup> evaluating the concentration of SCFA in blood collected in the portal vein of Zucker (fa/fa) rats fed OFS found that propionic acid was found at concentrations of up to 0.6 mmol/L. Through the use of hepatocytes in culture, they observed that this concentration is capable of inhibiting the incorporation of acetate to lipids, thereby inhibiting the lipogenesis process<sup>20</sup>. According to Arora et al.<sup>36</sup>, propionate is able to inhibit the synthesis of cholesterol and triglycerides at a concentration of 0.1 mmol/L in rat hepatocytes, while for humans, concentrations of 10-20 mmol/L are necessary.

The SCFA propionate is capable of lowering serum cholesterol levels because it inhibits the activity of 3-hydroxy-methyl-3-glutaryl-CoA (HMG-CoA) reductase enzyme; redistributes plasma cholesterol to the liver; increases the synthesis and secretion of bile acids, since it stimulates the activity of 7 $\alpha$ -hydroxylase enzyme by increasing the concentration of mitochondrial succinyl-CoA; and inhibits expression of the genes involved in intestinal cholesterol biosynthesis<sup>36</sup>. Furthermore, SCFA are also associated with increased production of satiogenic intestinal hormones<sup>16,28</sup> and improvement in glycemic levels and insulin<sup>29</sup>.

#### *Alteration of production of polyamine*

Fermentation of inulin-type fructans not only increases the production of SCFA, but also some intestinal polyamines<sup>23</sup>. These molecules are involved in several processes important for maintaining homeostasis of the intestinal cells, and their production is monitored by the enzyme ornithine decarboxylase<sup>37</sup>.

Delzenne et al.<sup>37</sup> observed that mice fed 10% inulin for four weeks showed a lower concentration of spermine in the portal vein. This result was associated with decreased hepatic TG production because spermine stimulates the esterification of fatty acids, by increasing the action of glycerol-3-phosphate acyltransferase and phosphatidyl fosfohidrolase, which are key enzymes in this process.

One possible mechanism through which inulin-type fructans alters the production of intestinal polyamines is by the increased SCFA production, because they may increase the activity of some enzymes in the gut wall such as ornithine decarboxylase<sup>29</sup>.

#### *Increasing the population of bifidobacterium*

*Bifidobacterium* are anaerobic bacteria that are part of the intestinal microbiota. These bacteria are known for bringing much benefit to the host, such as immunostimulation, anticarcinogenic activity, inhibiting the growth of intestinal pathogens, producing SCFA, vitamins, and amino acids, and reducing the conversion of primary to secondary bile acids, among others<sup>38</sup>. Because they produce SCFA, molecules essential for improvement of the lipid profile, increasing the population of this group of bacteria in the intestinal microbiota is extremely important for cardiovascular health.

The use of fructan can increase the population of these bacteria in the intestinal tract, thereby increasing the production of SCFA. Studies in humans and animals confirm that consumption of inulin-type fructan increases the amount of *Bifidobacterium* in the intestinal microbiota<sup>17, 39</sup>.

According to Roberfroid<sup>13</sup>, the dose, duration, and location of the fermentation process (proximal or distal colon), as well as the initial microbiota, are important factors that directly influence the effect of inulin-type fructans on the modulation of the initial microbiota. These are the main factors that lead to different results between studies.

#### **Conclusions**

The consumption of inulin type fructans can help to improve the lipid profile. However, many of the proposed mechanisms and experimental evidence remain controversial. It has been observed that the results of studies vary according to the degree of polymerization of the inulin-type fructans used, the type of diet in which they are added, and the pathophysiological condition of the individual.

More studies are needed in order to establish a daily recommendation intake of fructan inulin type for prevention and/or treatment of cardiovascular diseases. Furthermore, the results differ according to the fructan type used. Thus, studies should be designed to try to establish which fructan or mixtures of these provide the best results.

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