

Short-chain fatty acids: nutritional strategies to modulate intestinal microbiota

Abstract

Introduction: The intestinal microbiota has been the subject of research due to its association in physiological and pathological conditions. The production of short chain fatty acids obtained by fermentation of the intestinal microbiota has shown important effects on the gastrointestinal tract, adipose tissue, immune system and nervous system.

Objective: This literature review aims to present different nutritional strategies with the potential to modulate the intestinal microbiota by increasing the production of short chain fatty acids.

Methods: The research was considered a review work, through a bibliographic survey carried out from the collection of articles in English, published in the PubMed database, in the period from 2013 to 2020. The articles were selected from the descriptors: gut microbiota, soluble fiber, resistant starch, pectin, dietary fiber, short chain fatty acids (SCFA) with the combinations of the Boolean operators “and” and “or”. Studies considered as gray literature were excluded, as well as studies in which the titles were not related to the theme of the proposed research.

Results: There are many benefits to consuming foods that may favor the increase of short chain fatty acids. This increase in the gastrointestinal tract is of fundamental importance for the maintenance of intestinal microbiota and prevention of diseases. Some nutritional strategies can be used in clinical therapy, such as increased consumption of fruits, vegetables and whole grains that are plant foods and important sources of fiber. The type of food must be observed, since each one can contain fibers of diverse types. Soluble fiber is the basis for the metabolism of short chain fatty acids and is found in various foods that can be inserted into the food plan, such as: bananas, apples, oats, barley, cooked and cooled potatoes, partially ground seeds, corn, morning cereal, agave, artichoke, asparagus, chicory root, garlic, onion, leeks and wheat.

Conclusion: Scientific evidence of the relationship between nutrition, intestinal microbiota and short-chain fatty acid production demonstrates the importance of implementing simple nutritional strategies by health professionals, which can contribute to the modulation of the intestinal microbiota and the development of new perspectives in the development of therapies for prevention and treatment of diseases.

Keywords: microbiota intestinal, soluble fibers, butyrate, starch resistant

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Introduction

Intestinal microbiota and their products are increasingly recognized as being physiologically important to human health. Changes in the intestinal microbiota can influence nutritional and health status through multiple mechanisms. Changes in the composition and activity of the intestinal microbiota are strongly influenced by the disease state and diet.^{1,2} Food, in turn, is considered one of the main external modulators in the human intestinal microbiota.³

The lack of SCFAs in the human intestine can lead to intestinal dysbiosis and, consequently, changes in this system can be associated with pathological conditions such as: inflammatory bowel diseases and chronic non-communicable diseases, for example: obesity, diabetes and colon cancer.⁴

AGCCs have a straight or branched chain and are composed of less than 6 carbons, most of which have two, three or four carbons in their structure, namely: acetate, propionate and butyrate, respectively. They result from fermentation carried out by anaerobic bacteria that use as substrate only the soluble fibers present in the gastrointestinal tract, which escape from the small intestine and are fermented specifically

in the cecum and colon. Furthermore, a small portion of SCFAs can be produced through the fermentation of amino acids that are derived from the protein.^{1,4}

The multifunctional potential of SCFAs in the human body plays an extremely important role in health, especially in the regulation of inflammation, through the inhibition of inflammatory cytokines, reduction of luminal pH that contributes to the inhibition of pathogenic microorganisms and increases the absorption of some nutrients.^{2,5}

Thus, intestinal microbiota can influence health and nutritional status, and it is extremely important to use effective nutritional strategies in clinical practice to modulate the intestinal microbiota through the production of SCFAs.⁶ Thus, this literature review aims to present different nutritional strategies with the potential to modulate the intestinal microbiota by increasing the production of short-chain fatty acids.

Methods

The research was considered a review work, through a bibliographic survey carried out from the collection of articles in English, published

in the PubMed database, in the period from 2013 to 2020. The articles were selected from the descriptors: gut microbiota, soluble fiber, resistant starch, pectin, dietary fiber, short chain fatty acids (SCFA) with the combinations of the Boolean operators “and” and “or”. Studies considered as gray literature were excluded, as well as studies in which the titles were not related to the theme of the proposed research.

Results

Short chain fatty acids

AGCCs are organic fatty acids that have less than six carbons in their composition in the straight or branched chain, of which about 90 to 95% are represented by acetate (two carbons), propionate (three carbons) and butyrate (four carbons) being the main ones found in the human intestinal tract.^{5,7,8}

The other acids, such as isobutyrate, valerate, isovalerate and caproate, represent around 5-10%.⁷ It is known that SCFAs are metabolized by the microbiota in the cecum and colon by fermentation of both dietary and endogenous carbohydrates, proteins and non-hydrolyzed peptides by host enzymes.^{7,8} Protein fermentation most often results in branched-chain fatty acids, such as 2-methylbutyrate and isovalerate, exclusively originating from branched-chain amino acids (valine, isoleucine and leucine).⁹

The concentration of SCFAs along the intestine may vary, as carbohydrate fermentation is predominant in the proximal colon, which explains the decrease in SCFA concentrations towards the distal colon.¹⁰

SCFAs are produced from a series of events, such as acetate can be produced from pyruvate by intestinal bacteria via acetyl-CoA or via Wood-Ljungdahl. The latter can synthesize SCFAs through two pathways: first via reduction of CO₂ and second via reduction of CO₂ to CO combined with a methyl group and thus producing acetyl-CoA.⁹ The propionate can be synthesized via the succinate pathway, through the conversion of succinate into methyl malonyl-CoA, it can also be synthesized through the acrylate pathway, having lactate as a precursor, and through propanediol having as substrate deoxyhexose sugars (fucose and rhamnose).⁹

G proteins have receptors (GPR43 and GPR41) for acetate, thus demonstrating their power to act at the level of mRNA, proteins in the human colon and small intestine, more specifically in the ileum. Intracellularly, acetate can be converted to acetyl-CoA and incorporated into the tricarboxylic acid cycle in many peripheral tissues.¹¹⁻¹⁴ A study¹⁵ showed that acetate can improve insulin sensitivity and maintenance of body weight in obese people through the control of body weight, central effects of appetite regulation and satiety hormones and energy expenditure.

Propionate has poor organoleptic properties, short circulation half-life, is absorbed in the small intestine, these characteristics limit its use as a food supplement. But this AGCC plays a role in appetite regulation, improves metabolic and weight control. In turn, water solubility has been shown to be an important factor in determining the kinetics of SCFA release from the ester and selective modulation of this compound can be achieved by SCFA inulin esters.¹⁶

The formation of butyrate occurs through the classical pathway, where two acetyl-CoA molecules are used and subsequent reduction to butyryl-CoA, converting it into butyrate by phosphotransbutyrylase and butyrate kinase. Furthermore, butyryl-CoA can be transformed into butyrate via the butyryl-CoA pathway. Some microorganisms can favor the reduction of lactate accumulation by stabilizing the

intestinal environment, as they use succinate and 1,2-propanediol to synthesize butyrate.¹¹

Butyrate is the main primary energy source for colonocyte intestinal epithelial cells, and this SCFA is absorbed locally, unlike others that need to be drained into the portal vein.⁹ The other metabolites are absorbed by colonic epithelial cells, pass through the portal vein and are metabolized in liver hepatocytes, as is the case of propionate, which is present in low concentration in the periphery.^{5,9}

Butyrate is responsible for promoting the intestinal epithelial barrier function and balancing the host mucosal immune system. It is characterized by being the first defense factor against invading pathogens. It is also capable of regulating stem cell turnover in intestinal epithelial crypts as well as promoting regulatory T cells (Treg) in the colon by inactivating histone deacetylase (HDAC) activity at the Foxp3 locus. It is noteworthy that butyrate coming into contact with neutrophils, macrophages, dendritic cells or other histone deacetylase (HDAC) inhibitors, such as trichostatin, is capable of inhibiting the production of inflammatory cytokines.¹² Another benefit highlighted by the ingestion of SCFAs is the protection against the development of colorectal cancer, which may highlight, through studies, butyrate as a focus, as it promotes colonic motility, reduces inflammation, increases visceral irrigation, stimulates apoptosis and inhibits cell proliferation tumors, which in general have beneficial properties in preventing colorectal cancer.²

Studies show the contribution of SCFAs in improving diabetes, as observed in a study where the use of *Plantago asiatica* L. favored the increase in SCFA production in diabetic rats after 4 weeks of consumption. There was a reduction in the concentrations of blood glucose, insulin, total cholesterol, triglycerides, non-esterified fatty acid and maleic dialdehyde, increased levels of high-density lipoprotein cholesterol, in addition to improving the activity of antioxidant enzymes.¹⁷ Fatty acids, propionate and butyrate, when administered intravascularly, can stimulate insulin secretion in ruminant animals, thus having an even stronger potential than glucose.¹⁸ Thus, it is evident the numerous benefits that SCFAs are associated, for example, in reducing the risk of developing some diseases, such as irritable bowel syndrome, inflammatory bowel disease, intestinal dysbiosis, cardiovascular disease and cancer. Therefore, it is extremely important to use nutritional strategies for the production of SCFA and for the health of the individual.

Nutritional strategies for SCFA production

Functional foods are a strategy to modulate the intestinal microbiota, such as probiotics, which contain microorganisms that help prevent disorders of the intestinal microbiota in their composition. Kefir is a probiotic with dairy content that contains beneficial bacteria such as *Lactobacillus kefirifaciens*, *Bifidobacterium* and yeasts such as *Candida kefir*, these kefir grains can preserve intestinal eubiosis and alter dysbiosis by adhering to gastrointestinal mucus.¹⁹ In a study using the *Lactobacillus kefir* strain in healthy Swiss mice for 21 days and then their feces were analyzed in which the levels of Immunoglobulin A (IgA) increased and there was a reduction of pro-inflammatory mediators in Peyer's patches and in the mesentery, as well as an increase in Interleukin-10 (IL-10) in the ileum.²⁰

Fermented foods have important characteristics, being used as nutritional strategies and have associations in studies with the prevention of obesity and with the reduction of risk of different diseases, including immunological and cardiometabolic ones.²¹ Lactic acid bacteria are the main microorganisms used in the production of fermented dairy products such as yogurt, cheese and milk kefir. They

produce lactic acid from lactose, the sugar in milk. This increases acidity and hinders the growth of bad (pathogenic) microorganisms. During dairy fermentation, many beneficial compounds are produced or increased by the metabolic activity of lactobacilli,²² being able to produce vitamins and bioactive molecules such as probiotics, which are live microorganisms capable of modulating the effects on health and disease, modulating the microbiota-gut-brain axis and grants a health benefit to the host.²³

In a study carried out with 130 individuals, it is proposed that fermented dairy products in general can be a solution that influences the relationship between diet and health through modulation of the composition of the intestinal microbiota. Individuals who consumed cheese had significantly higher levels of the main fecal SCFA, acetate, propionate and butyrate, while consumers of fresh cheese had specifically higher levels of propionate and butyrate than non-consumers.²⁴ fermented foods can influence the resident microbiome and exert host-specific health benefits.²⁵ Diet is an important factor in the modulation of the intestinal microbiota and, consequently, the production of SCFAs, which are extremely relevant for the health of human beings. AGCCs can be used as biomarkers of a healthy state. It is observed that diets rich in fiber and low-fat consumption result in a greater production of SCFAs.²

One of the strategies for SCFA production via colonic fermentation is through fiber consumption. The term “dietary fiber” is quite broad and represents a diverse group of non-digestible carbohydrates that are not even absorbed in the human small intestine, which has ten or more monomeric units (in Brazil, non-digestible carbohydrates are those with more than three monomeric units). Soluble fibers have variable structural and functional properties, including the ability to retain water (solubility), and are metabolized to SCFAs by the intestinal microbiota.^{7,13}

These fibers are quite heterogeneous, where their chemical composition, physicochemical properties, degree of polymerization are important factors to define their properties and, consequently, affect microbial fermentation in a distinct way.¹³

A diet rich in cereals and grains, fruits, vegetables and nuts, that is, based on plant-based foods, is essential for obtaining dietary fiber, but it is emphasized that it is important to note that the impact of fiber consumption in the intestinal microbiota it varies according to the type of fiber consumed.¹³ Researchers⁶ point out that even dietary fibers do not contain butyrate when they reach the cecum and colon, they undergo fermentation by microorganisms, which results in SCFAs. Soluble fibers such as β -glucan, a soluble fiber found in oats and barley, and pectin, found in fruits such as apples, are highly fermentable.¹³ There are also sources of non-viscous soluble fiber such as resistant maltodextrins, resistant starch, polydextrose, soluble corn fiber, and inulin-type fructans, present in agave, artichoke, asparagus, banana, chicory root, garlic, onion, leeks and wheat.¹³

Oats have several important functions, such as greatly reducing plasma total cholesterol and low-density lipoprotein (LDL) cholesterol, thus reducing the chances of cardiovascular disease. The benefits of oats for human health are attributed to its components, in particular the B-glucan. Effects of different cooking methods of oatmeal on preventing the diet-induced increase in cholesterol level in hypercholesterolemic rats. Oat B-glucan increases intestinal viscosity, thus decreasing the absorption of bile acids, which leads to a lower amount of plasma lipid levels.²⁶

The consumption of soluble corn fiber, in healthy adults, who underwent test meals in the amount of 20-25g/day for one week,

favoring the increase in SCFA production, and treatment with resistant starch (high-content corn starch of amylose) resulted in higher values of colon-derived butyrate. This demonstrates that the properties of fibers are related to the metabolism of the gastrointestinal microbiota, thus altering the microbial diversity and the production of SCFAs in the colon.²⁶ Inulin can be considered a dietary strategy to improve human metabolism, promoting the production of SCFA in obese or overweight men, through the oxidation of fats. In general, the replacement of digestible carbohydrates by fermentable inulin can favor the metabolism of the human substrate.²⁷

Starch is a polysaccharide carbohydrate, composed of amylose and amylopectin, found in plant foods, as it is stored in plants as a form of energy reserve, mainly in the germination period, that is, present mainly in the endosperm of the seed. Starch can be classified into: rapidly digestible starch, slow digesting starch and resistant starch. Some of the starch is digestible, but some is not, and this portion, which is fermented in the large intestine, is called resistant starch.⁶

It is considered a form of dietary fiber and has the ability to bind water to form a gel. The composition of resistant starch that dictates the production of SCFAs through bacterial fermentation. And many benefits are reported due to the consumption of this compound, such as: slow release of glucose and favors colon health due to increased crypt cell production rate or decreasing colon epithelial atrophy when compared to diets without fiber.²⁸ Not only are bananas rich in resistant starch, but also vegetables such as boiled and chilled potatoes, partially ground seeds, corn and breakfast cereals.⁶

A food well known for its high content of dietary fiber and resistant starch, with approximately 74% in its composition, is the green banana biomass. Due to this large amount, researchers carried out a study where they used the combination of green banana biomass with some laxatives used in the conventional treatment of constipation in children and adolescents.²⁹ They reported that until the present moment of their study there was no ideal dosage for starch resistant, so they chose to use 30g of green banana biomass together with some laxatives and obtained positive results, as there was improvement in constipation symptoms, including a reduction in laxatives, when this combination was used for 8 weeks.²⁹ Thus, not only dietary fiber promotes benefits such as laxation, blood cholesterol attenuation and blood glucose reduction, but also resistant starch, as foods rich in resistant starch are also important sources for the production of SCFAs.²⁸

Conclusion

This research evidenced the importance of consuming plant-based foods to obtain SCFAs, emphasizing nutritional strategies with therapeutic potential in modulating the intestinal microbiota, preventing the development of diseases and helping to treat them. This study, in addition to contributing to the scientific community, aims to support new research on the role of food in the modulation of the intestinal microbiota, as well as new discoveries, strategies and preparations always aiming to improve the population's quality of life.

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Conflicts of interest

Author declare that there is no conflict of interest.

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