

Artigo de Revisão

Relationship of Gut Microbiota, Cell Integrity, and N-3 Polyunsaturated Fatty Acids in Inflammation**Relação da Integridade Celular, Microbiota Intestinal e Ácidos Graxos Poliinsaturados N-3 na Inflamação**<http://dx.doi.org/10.18316/sdh.v11i2.9528>

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ABSTRACT

Introduction: The gut microbiota is defined as microorganisms that inhabit the gastrointestinal tract. This population is involved in critical functions for host homeostasis, including nutrient digestion and synthesis, cell integrity, immune system development, a barrier against pathogens, and consequently local inflammatory processes. The composition of the microbiota can be altered by various factors such as maternal microbiota, age, genetic factors, antibiotic use, lifestyle, and especially diet. It is well known that dietary habits play a crucial role in altering the composition of the microbiota. **Objective:** The aim of this work was to investigate the relationship between cellular integrity, gut microbiota, and n-3 polyunsaturated fatty acids in inflammation. **Methods:** The study consists of a narrative literature review based on articles published in journals indexed in electronic databases. The descriptors in Health Sciences (DeCs): “Interactions between host and microorganisms”, “Gastrointestinal tract”, “Omega-3”, “Eicosapentaenoic acid” and “Inflammation”. The languages considered were: Portuguese, English and Spanish and there was no delimitation of the publication period. Results: Certain types of fats are known to improve symptoms of various diseases, including cardiometabolic and inflammatory diseases. In particular, the changes in the gut microbiota associated with n-3 fatty acids are poorly understood. In this review, we showed that experimental studies suggest that n-3 promotes improvement in gut microbiota and intestinal integrity, in addition to controlling local inflammation. **Conclusion:** This review shows that the systemic anti-inflammatory effects of n-3 polyunsaturated fatty acids have been widely studied in various medical conditions, and their consumption is beneficial for health.

Keywords: Gut Microbiota; Immune system; n-3 Polyunsaturated Fatty Acids; Inflammation.

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RESUMO

Introdução: A microbiota intestinal é definida como a população de microrganismos que habita o trato gastrointestinal e está envolvida em funções cruciais para a homeostasia do hospedeiro, como digestão e síntese de nutrientes, integridade celular, desenvolvimento do sistema imunitário, barreira contra patógenos e, conseqüentemente, processos inflamatórios locais. A composição da microbiota pode ser alterada por diversos fatores, como a microbiota materna, idade, fatores genéticos, uso de antibiótico, estilo de vida e especialmente a dieta. **Objetivo:** Analisar a relação da integridade celular, microbiota intestinal e ácidos graxos poliinsaturados n-3 na inflamação. **Métodos:** O estudo consiste em uma revisão de literatura do tipo narrativa baseada em artigos publicados em revistas indexadas em bases eletrônicas. Foram utilizados os descritores em Ciências da Saúde (DeCs): “Interações entre hospedeiro e microrganismos”, “Trato gastrointestinal”, “Ômega-3”, “Ácido eicosapentaenoico” e “Inflamação”. Os idiomas considerados foram: português, inglês e espanhol e não houve a delimitação do período de publicação. Resultados: Hábitos alimentares desempenham um papel crucial na criação de uma variação interindividual na composição da microbiota e tipos específicos de lipídeos melhoram os sintomas de várias doenças. Em particular, alterações da microbiota intestinal associadas aos ácidos graxos n-3 são pouco conhecidos. Nesta revisão são mostrados estudos experimentais que sugerem que o n-3 promove melhoras na microbiota intestinal, na integridade intestinal e adicionalmente controla a inflamação local. **Conclusão:** Esta revisão mostra que os efeitos anti-inflamatórios sistêmicos dos ácidos graxos poliinsaturados n-3 têm sido amplamente estudados em várias condições médicas e que seu consumo é benéfico para a saúde.

Palavras-chave: Microbiota Intestinal; Sistema Imune; Ácidos Graxos Poliinsaturados n-3; Inflamação.

INTRODUCTION

In recent years, knowledge and interest in the role of the gut microbiota in human health and disease have grown, mainly due to advances in molecular methods¹. New technologies, such as genomics, metabolomics, and metagenomics, have facilitated the large-scale analysis of the metabolic and genetic profiles of the microbial community, making it possible to consider it as a new organ in the human body and offer the possibility of new therapeutic approaches². The significant factor for this increase was the understanding that the commensal microorganisms that constitute the microbiota are not just simple passengers in the intestine but also develop relevant functions in the health of the host³.

Approximately 99% of the microorganisms in the human gut belong to about 1,200 bacterial species, with the remainder consisting of archaea, viruses, or other prokaryotes⁴. These bacterial species mainly belong to genera from one of the four known phyla: Firmicutes, Bacteroides, Proteobacteria, and Actinobacteria. The composition of the microbiota in the adult gut varies greatly from person to person and is directly related to factors such as genetic inheritance, diet, and environment⁵.

A balanced gut microbiota ensures the adequate performance of host physiological functions by aiding in the digestion and absorption of nutrients, producing vitamins, and reducing the proliferation of pathogens by excluding competition. In addition, it acts as a barrier against bacterial translocation, invasion of pathogens or harmful substances, and improves local immunity⁶. Therefore, intestinal homeostasis is regulated by a complex interaction between mucosal immunity, epithelial integrity, gut microbiota, and nutrient supply. The latter is increasingly recognized as a variable that plays an important role in this process, either by directly influencing the health of the epithelium or by altering the composition of the gut microbiota⁷.

Therefore, the imbalance may lead to increased permeability of the intestinal epithelium, allowing the translocation of intestinal bacteria and their products such as lipopolysaccharides (LPS) and toxins, and activating toll-like receptors (TLRs). This fact promotes a cascade of pro-inflammatory cell signaling leading to overproduction of inflammatory mediators and reactive oxygen

species (ROS) that damage and kill intestinal cells⁸.

It is well known that in cases of dysbiosis and to restore cellular integrity, it is essential to stimulate the growth and multiplication of bifidobacteria and lactobacilli⁹. This stimulus can come from the diet with the consumption of soluble and insoluble fiber, resistant starch, and oligosaccharides, which after ingestion are fermented in the colon and stimulate the growth of these species beneficial to the host, resulting in significant changes in the composition of the gut microbiota by increasing the number of probiotics and reducing the number of potentially pathogenic bacteria¹⁰.

Our diet is directly related to the composition of the flora. Polyunsaturated fatty acids are important components of the phospholipids of all cell membranes, including cells of epithelial tissue, in which they provide the proper environment for membrane fluidity and cell signaling and serve as substrates for the synthesis of lipid mediators, thus contributing to integrity³. On the other hand, to eating these foods, sugars, saturated fats, and processed foods should be avoided as they increase intestinal permeability and contribute to the absorption of contaminants that increase systemic inflammation. Despite a large number of publications on the effects of carbohydrates, the effects of dietary fats on the gut microbiota are less well defined, especially when it comes to certain types of lipids, such as n-3 polyunsaturated fatty acids, which alter the gut microbiota¹¹.

Fish oil, an n-3 source, has been extensively studied in animal models, particularly in inflammatory bowel disease (IBD), for its protective effects against intestinal inflammation, and thus has been highlighted as an important component in controlling symptoms due to its influence on inflammation.

This review, therefore, aims to discuss the evidence on the relationship between cell integrity, gut microbiota, and omega-3 in local inflammation..

MATERIAL AND METHODS

The present study consists of a narrative literature review based on scientific articles published in journals indexed in electronic databases, manual search of citations in publications, in addition to the inclusion of dissertations and theses. The electronic databases consulted were: Pubmed, the Medical Literature analysis and Retrieval System Online (MEDLINE), the Scientific Electronic Library Online (SCIELO). The languages considered were: Portuguese, English and Spanish and there was no delimitation of the publication period.

To search for the articles, the descriptors in Health Sciences (DeCs) and their combinations were used: "Interactions between host and microorganisms", "Gastrointestinal tract", "Omega-3", "Eicosapentaenoic acid" and "Inflammation" in the languages cited. The localized terms were combined using the Boolean operators "and", "or" or "not".

The inclusion criteria were scientific articles with review methodology, clinical and experimental trials using humans and animals, available in full during the period of this search and with the content of at least one of the descriptors mentioned. Expanded abstracts were excluded.

RESULTS AND DISCUSSION

The intestine and its cellular integrity

It should be noted that the human intestine, due to its histological and functional nature, is capable of performing the function of processing, selecting, and absorbing nutrients. Therefore, it is in constant contact with agents and substances from the external environment and is thus also responsible for preventing foreign agents or substances from being absorbed into the body¹². In addition to the physical barriers that, when intact, limit the entry of pathogens into the gastrointestinal tract, there are a number of receptors widely distributed throughout the gastrointestinal mucosa that are specialized to recognize immunogens and are essential for immunity and inflammatory processes⁸.

The ability to preserve intestinal cells is important to prevent the occurrence of various pathologies and local and systemic changes. To this end, intestinal tissue provides an excellent physical barrier that prevents the invasion of antigenic molecules. It also lives in equilibrium with a large number of food components and microorganisms¹³.

However, when the integrity of the intestinal wall is compromised, permeability may change to the extent that pathogenic microorganisms, antigens, drugs, cytokines, and exogenous toxins can enter. The extent to which the competence of the intestinal barrier is compromised varies and the duration depends on the nature and presence of the aggressive stimulus¹⁴.

Barrier function is maintained by nonimmunological and immunological defenses. As for the nonimmunological defense system of the intestine, it has a large number of cells whose main characteristic is a high rate of epithelial regeneration¹⁵. Among these cells are a greater proportion of enterocytes, which constitute 80% of all epithelial cells in the intestine and form occlusion junctions that effectively assist in separating the luminal contents from the interior of the epithelium. These help the immune system as antigen-presenting cells (APCs) express molecules of the major histocompatibility complex (MHC) class II and toll-like receptors¹⁶.

The integrity of the intestine is also maintained by Paneth cells, goblet cells, and enteroendocrine cells. The main role of Paneth cells is to provide a physical barrier against contact with the surface of the epithelial tissue and the underlying immune cells, thus forming the first line of defense against microbial invasion¹⁷. Goblet cells are actively involved in the production of intraluminal mucin. Mucin, together with electrolytes and proteoglycans, forms the mucus that lines the surface of the intestinal villi and keeps the various pathogenic components separated from the epithelium¹⁸.

As for the mechanisms of immune defense, barrier function is maintained by secretory immunoglobulin A (IgA) production and by gut-associated lymphoid tissue (GALT) composed of intramucosal lymphocytes, Peyer's patches (PPs), and mesenteric lymph nodes. The PPs are a collection of peripheral lymph nodes rich in immune cells, particularly B and T lymphocytes, and covered by M cells that express MHC-II molecules and can produce interleukin-1 (IL-1)¹⁷. In addition, they capture antigens from the lumen and pass them to dendritic cells for antigen presentation. These cells in the gastrointestinal tract control the complex interactions of the gut microbiota with the innate and adaptive immune response by modulating tolerance to commensal microorganisms and the immune response to pathogens¹⁸.

When presented to T lymphocytes, they can differentiate into Th1 or Th2 cytokine-producing cells. Th1 type cytokines stimulate interferon-gamma (INF- γ) and tumor necrosis factor (TNF- α), which increase cell-mediated immunity. The predominant Th1 effect results in the activation of macrophages and Th, particularly cytotoxic ones¹⁴.

Luminal immunoglobulins also function of capturing antigens or microorganisms and may prevent the binding of these antigens to host cell receptors, thereby reducing the inflammatory response. IgA is the main representative of gut humoral immunity, and its products can be influenced by the commensal microbiota¹⁹.

The gut microbiota

Each person has a different microbiota composition, which is partly genetic and partly determined by individual and environmental characteristics, such as type of birth (normal delivery or caesarean section), breastfeeding, age, dietary habits, hormonal status, and even personal hygiene, resulting in a large intra- and interindividual variability²⁰.

During the establishment of the gut microbiota, the high oxygen content in the neonate's gut primarily favors the growth of aerobic or facultative anaerobic bacteria, such as enterobacteria, enterococci, and staphylococci¹³. As these groups consume oxygen, the environment is favorable for

the growth of obligate anaerobic bacteria causing the proliferation of *Bacteroides*, *Bifidobacteria*, and *Clostridia*. Thus, *Lactobacillus* is the major component of the gut microbiota until the onset of solid food intake by the child, when *Escherichia coli* becomes predominant in the distal ileum. Stability of the gut microbiota is achieved by two years of age, and considerable stability exists in adults²¹.

After emergence, the Firmicutes and *Bacteroides* phyla have a significant prevalence in the composition of the gut microbiota. The Firmicutes phylum is characterized by being constituted of aerobic and anaerobic Gram-positive bacteria¹³. These microorganisms are considered strategists because they multiply rapidly in the environment in which they live in response to a large supply of nutrients. They are also cellulosic organisms and play an important role in the degradation of cellulose¹¹. The second most common phylum is *Bacteroides*, which is composed of Gram-negative bacteria that have chemoorganotrophic properties and are capable of degrading polymers such as cellulose, pectin, and glycans, especially in anaerobic environments.²¹.

The populations that make up the microbiota vary throughout the intestinal region because there are specific sites where bacteria adhere to the intestinal mucosa and adhesion is critical for their colonization. Although the stomach has specific sites, there is usually little bacterial activity there because hydrochloric acid acts as a microbicidal agent⁵.

The composition of the microbiota of the small intestine, especially the duodenum, is similar to that of the stomach. This similarity is due to the fact that the duodenum is the first part of the intestine into which the food pulp enters from the still acid stomach²². However, from the duodenum to the ileum, the acidity gradually decreases. The ileocecal junction contains many microorganisms because the digestive enzymes released in this region produce more bicarbonate to function properly²³.

Three distinct levels can be observed in the colon: the dominant, the subdominant, and the residual microbiota. The dominant microbiota consists only of strictly anaerobic bacteria: *Bacteroides*, *Eubacterium*, *Fusobacterium*, *Peptostreptococcus*, *Bifidobacterium*, while the subdominant microbiota is predominantly anaerobic-facultative: *Escherichia coli*, *Enterococcus faecalis* and sometimes *Lactobacillus*. The remaining microbiota contains a variety of prokaryotic microorganisms: Enterobacteriaceae, *Pseudomonas* spp., *Veillonella* spp., and eukaryotes: yeasts and protozoa⁵.

Relationship between the gut microbiota and the inflammatory response

The intestinal tissue is responsible for the secretion of various substances, absorption of nutrients, and lining, but it also separates the internal organs from an environment full of potential aggressors and pathogens that can promote lesions and consequently local inflammatory processes²⁴.

For protection, the mucous membranes have a complex defense system known as the mucosal immune system (MIS) that promotes defense against infectious agents, provides tolerance to self-antigens and those from digestion and absorption of nutrients. This system has not only cells but also an active local microbiota that tends to develop and positively stimulate components of the immune system as it helps to control microorganisms, prevent their translocation into the bloodstream, and reduce susceptibility to infection while stimulating itself to act as an immune barrier²⁵.

The process promoted by resident bacteria results in local immunological tolerance that favors the persistence of these and their commensal functions and, in parallel, controls the release of inflammatory mediators as such cell membrane receptors recognize and discriminate normal internal molecular signals, dysfunction, or dangerous situations¹¹. Thus, the gut is in a baseline state of low-grade inflammation due to the environmental and bacterial stimuli it receives¹⁷. However, alterations in immune and cellular functions, as well as in the composition of the gut microbiota, lead to structural damage in the gut and alter its functioning, reducing barrier function and increasing the number of microorganisms and/or their potentially pathogenic metabolites¹¹. As a result, dysbiosis and imbalance in the gut microbiota occur with deleterious effects and increased release of pro-inflammatory cytokines²⁶.

When the inflammatory reaction has subsided and the infectious agents have been eliminated, the phase of tissue repair and elimination of inflammation begins⁶. However, if the inflammatory response fails to clear infectious agents, the condition of chronic inflammation is promoted. In this case, neutrophils are replaced by macrophages and T cells¹⁴. This change promotes tissue damage due to the degree of inflammation, which is increased by the aggravation of the innate and adaptive immune response through the action of macrophages, dendritic cells, pro-inflammatory T helper (Th), Th1, Th2, and Th17 lymphocytes, which begin to produce amounts of pro-inflammatory cytokines (TNF- α , IL -1, IL -6, IL -8, and IL -17)⁹. There is also an increase in the expression of nuclear factor-kappa (NF- κ B), which further promotes the production of pro-inflammatory cytokines²⁶.

Gut microbiota and food consumption

In adults, 60 to 70% of the microbiota composition remains stable throughout life. However, 30% to 40% of the population of resident microbiota can be altered by factors such as lifestyle, bacterial infections, antibiotic use, surgical treatments, and dietary changes²⁷. Among these factors, the one most strongly related to the gut microbiota is diet, as dietary habits are associated with gut microbial composition, which in turn may interact with host metabolism²⁸.

This effect is due to the quality and quantity of nutrients that the diet provides and its ability to create a favorable or unfavorable environment for gut bacteria²⁷. Especially in the colon, it provides a great metabolic activity that affects the fermentation process of substances that are not absorbed by the mucosa, such as some polysaccharides, oligosaccharides, proteins, and mucins. However, the nature of this fermentation can have different effects on health. For example, products derived from carbohydrate metabolism are beneficial, whereas products derived from proteins can have toxic effects¹⁷. Therefore, it is important to consider that the use of certain substances in the diet may promote the development of microbiota with positive or negative effects on human health⁵.

As for the beneficial effects, prebiotics are highlighted because they are complex carbohydrates that are considered fiber and are resistant to the action of salivary and intestinal enzymes. They are not digested or absorbed in the gastrointestinal tract and do not provide direct energy to intestinal cells, but they perform important functions in the body as they are fermented by intestinal bacteria and converted into other metabolites. These fibers are used in particular by the genera *Bacteroides*, *Bifidobacterium*, *Ruminococcus*, *Eubacterium*, and *Lactobacillus*²⁹.

Microbial activity leads to the production of Short-Chain Fatty Acids (SCFAs), mainly acetate, propionate, and butyrate, which are absorbed in the colon and each of which has a specific function³⁰. Butyrate, for example, serves as an energy substrate for colonic epithelial cell metabolism and, according to some studies, may also decrease the expression of pro-inflammatory cytokines responsible for Inflammatory Bowel Diseases (IBD)¹⁰. The rest goes to the liver and serves as a substrate for gluconeogenesis and lipogenesis, which are fundamental for the formation of glucose and fatty acids, respectively. In addition, they promote the formation of intestinal cell structures by inducing the expression of genes encoding cell junction proteins³¹.

Some food components have already been sufficiently studied to be classified as pro-inflammatory or anti-inflammatory. Foods that are considered anti-inflammatory include whole grains, fiber, fruits, vegetables, soy, nuts, and fish. Food components that are considered pro-inflammatory include advanced glycation products (AGEs), saturated fat, trans fat, omega-6, and carbohydrates⁷.

Omega 3

Fat is one of the components of the human diet and is characterized by providing a greater amount of energy compared to carbohydrates and proteins because it is a structural component of cell membranes, messengers for metabolic processes, enzymatic cofactors, and provides essential

fatty acids³².

Fatty acids (FA) with single bonds are termed saturated, and FA with double bonds are termed unsaturated, which are classified as monounsaturated and polyunsaturated³³.

There are two main families of polyunsaturated fatty acids: omega-6 (W-6), linoleic acid (LA), and omega-3 (W-3), α -linolenic acid (ALA). W-3 polyunsaturated fatty acids are found in plant and animal foods³⁴. Foods of plant origin on land are sources of ALA, which can be converted in the human body to docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Most foods of marine origin (plant or animal) are sources of both DHA and EPA, but in their composition, DHA predominates³⁵. Chia seeds, seeds, and flaxseed oil are examples of plant sources of ALA; microalgal oil, fish oil, salmon oil, herring, and horsetail are examples of marine sources of EPA and DHA plant or animal origin. As for sources of W-6 polyunsaturated fatty acids, we can mention canola oil, corn oil, and soybean oil as sources of plant origin, and chicken meat, chicken eggs, and cow's milk as sources of animal origin³⁶.

DHA plays an important role in retinal and brain function and development, being predominant in most cell membranes. EPA and arachidonic acid (AA) produce eicosanoids, inflammatory mediators of lipidic origin, with AA being the main substrate for the synthesis of eicosanoids³⁷. Research suggests that EPA impairs the production of prostaglandin series 3 (PG), a hormone-like substance that regulates and protects the body from effects such as platelet aggregation (due to its antithrombotic effect), inflammation, and decreased immune responses. The n-3 and n-6 polyunsaturated fatty acids have different effects on the immune and inflammatory response³⁸.

The balance in the uptake of these fatty acids and consequently the incorporation of polyunsaturated fatty acids into the immune cell membrane is important in determining the severity of the inflammatory process³⁴. The n-3 polyunsaturated fatty acids have suppressive effects, such as inhibition of lymphocyte proliferation, production of antibodies and cytokines, expression of adhesion molecules, and activation of Natural Killers (NK) cells³⁸.

The nutritional, structural, and regulatory functions of w-3 have a significant impact on important physiological processes such as the immune response and inflammation³⁹. Currently, supplementation of this nutrient is being studied in various clinical settings to evaluate its effects on complications related to immune and inflammatory function promoted by some diseases⁴⁰.

Relationship between cell integrity, gut microbiota, and n-3 polyunsaturated fatty acids in inflammation.

Inflammation is part of the body's natural defense mechanism to ward off pathogenic organisms and other damage to body homeostasis⁴¹. Inflammation creates an antagonistic environment for pathogen survival by initiating combative actions and inducing changes in host metabolism, as well as stimulating tissue repair processes that support the restoration of homeostasis at infected or damaged sites⁴².

Processes include an increase in local blood flow and vascular permeability, which allows the passage of plasma and molecules through the endothelium⁴³. Thus, cells such as leukocytes migrate from the blood to surrounding tissues due to the local production of chemoattractants and upregulation of adhesion molecules in the endothelium⁴⁴. These in turn release mediators derived from lipid precursors such as prostaglandins and leukotrienes, and others such as ROS, platelet-activating factor, cytokines, and chemokines (peptide mediators) derived from amino acids and enzymes⁴⁵. However, this response depends on factors such as the type of inflammation, the stage of the inflammatory reaction, the anatomical location, and the defense of the affected tissue cells⁴⁶.

Under homeostatic conditions, the intestinal epithelial cell layer allows efficient uptake of nutrients by the body while providing a physical barrier that prevents the transport of harmful substances from the luminal area into the bloodstream and adjacent tissues, mainly through tight junctions (TJ) responsible for

selective permeability¹⁷. TJ are protein complexes formed by transmembrane proteins such as claudin, occludin, and junctional adhesion molecules (JAM) as well as a wide range of cytosolic molecules such as zona occludens (ZO) proteins that are essential for cell integrity⁴⁷. They are dynamically coordinated by numerous external factors, such as various types of food⁴⁸.

Recent studies have shown that mice fed a diet rich in saturated fat exhibited changes in intestinal permeability, as a decrease in the expression of ZO-2, claudin 1 and 3, and JAM -1 proteins were observed in the colon of these animals compared with mice fed a control diet⁴⁹. In addition, it was demonstrated that the high-fat diet also resulted in changes in the composition of the gut microbial population, increasing the number of Gram-negative bacteria to the detriment of Gram-positive bacteria⁵⁰. These changes led to the breakdown of the intestinal barrier and a marked increase in LPS levels and its extravasation into the bloodstream⁵¹.

The presence of LPS in the bloodstream and tissues enables its interaction with Toll-like receptors, such as TLR4, which are present on the membrane surface of numerous cells of the immune system and other nonimmune cells such as adipocytes, hepatocytes, and cells such as enterocytes and colonocytes⁴². When LPS binds to TLR4, a cascade of pro-inflammatory signaling pathways is activated, culminating in the production of cytokines such as IL-6, TNF- α and the expression of inducible nitric oxide synthase (iNOS), which induce an inflammatory state⁵². On the other hand, some studies show that polyunsaturated fatty acids, especially n-3, reduce inflammation and improve symptoms of inflammatory and cardiovascular diseases, asthma, allergies, and diabetes⁵³. And in the gut, they have also been shown to be strongly protective against local inflammation in animal models³⁶.

In relation to inflammation, the role of n-3 is of great importance as it reduces the production of pro-inflammatory eicosanoids due to competition for the converting enzyme and stimulates the production of anti-inflammatory agents such as prostaglandins and leukotrienes, which are used to prevent and treat various inflammatory diseases in animals and humans⁴.

Pusceddu et al. showed that long-term administration of EPA / DHA resulted in a positive anti-inflammatory effect associated with the restoration of the composition of the gut microbiota, as it stimulated the increase of butyrate-producing bacteria, Firmicutes and Bacteroidetes, in rats separated early from the mother and decreased the amount of pro-inflammatory bacterial genera, such as *Akkermansia* and *Flexibacter*⁶⁴.

In a study aimed at investigating the associations between n-3 fatty acids, gut microbiota composition, and fecal metabolomic profiles in middle-aged and elderly women, it was found that there was an association between n-3 fatty acid intake and microbiota composition, independent of dietary fiber intake^{38,54}.

Butyrate is one of the three major short-chain fatty acids formed in the colon. The first is acetate (50-60%), the second is propionate (20-25%), and the third is butyrate (15-20%)³⁰. Although all SCFAs are important for colonocyte trophism, butyrate is the most important because it is the main energy producer for these colon cells. In addition, butyrate exerts other important actions related to the cellular homeostasis of colonocytes, such as anti-inflammatory, antioxidant, and anticarcinogenic¹³, since a deficiency of butyrate increases the production of free radicals, which favors the destruction of the defense mechanisms that form the intestinal mucosa and allows the infiltration of bacteria and antigens into the layers of the intestinal wall³⁰.

Watson et al. conducted a randomized study aimed at investigating the effect of 2 formulations, capsule, and drink containing n-3 polyunsaturated fatty acids (EPA /DHA) for 8 weeks at a level of 4 g on the human gut microbiota, using healthy volunteers with an average age of 50 years of both sexes. As a result, it was found that the diversity of phyla did not change, but that regardless of the formulation, there was an increase in Bifidobacterium, Roseburia, and Lactobacillus, which are already known to produce short-chain fatty acids⁵⁵.

Another role of the gut microbiota is to continuously stimulate macrophages to release amounts of IL -10, which promote the induction of regulatory T cells (Treg) and inhibit the overdevelopment of

helper T cells 17 (Th17). Symbiotic gut bacteria are important for the development and function of specific lymphocyte subsets⁵⁶.

Minimal amounts of LPS in the systemic circulation, have the potential to trigger an inflammatory response in humans⁴⁷. LPS is known to enter the bloodstream through the intestinal epithelium or the openings of intestinal tight junctions between two epithelial cells. This demonstrates the importance of not only interventions that improve the profile and quantity of bacteria, but also cell integrity and control of local inflammation⁵⁷.

In a study of two different groups of rodents, one fed fish oil, and the other lard, the results showed that mice fed oil had higher levels of *Lactobacillus* and *Akkermansia muciniphila* than mice fed lard, with *Bifidobacteria* being more abundant. The increase in *Lactobacillus* is associated with the reduction of inflammation in various inflammatory bowel diseases and the greater presence of *Akkermansia muciniphila* improves barrier function and glucose metabolism⁵⁸. Based on the studies analyzed, n-3 may be a useful tool for the prevention of diseases associated with dysbiosis⁵⁹.

CONCLUSION

Taken together, this review shows that the systemic anti-inflammatory effects of n-3 polyunsaturated fatty acids have been widely studied in various medical conditions, and their consumption is beneficial for health. However, their mechanisms of action in local inflammatory processes, e.g. in intestinal cells, are still poorly understood, as is their influence on the composition of the gut microbiota. However, the presence of this specific nutrient in the diet is able to promote positive changes in the normal architecture of the intestinal barrier and gut microbiota, and consequently control the development of a low-grade systemic inflammatory process in the presence of dysbiosis.

Given the increasing incidence of inflammatory bowel disease and the association of dysbiosis with various pathologies and alterations in intestinal homeostasis, it is important to further investigate the relationship between the gut microbiota and diet, with a focus on specific nutrients such as n-3 polyunsaturated fatty acids, to better understand their influence on the composition of the microbiota, but also the local inflammatory state that develops following such imbalances.

Authors' contributions

TACC: Designed the manuscript and supervised the data collection, conducted the study and prepared the manuscript for publication.

AGA: Designed the manuscript and supervised the data collection, conducted the study and prepared the manuscript for publication.

MCC: Conducted the study and prepared the manuscript for publication, final revision of the manuscript.

ISCS: Conducted the study and prepared the manuscript for publication, final revision of the manuscript.

The final version was read and approved by all contributors.

Conflict of interest

Authors declare no conflict of interest.

REFERENCES

1. Sebastián-Domingo JJ, Sánchez-Sánchez C. From the intestinal flora to the microbiome. Vol. 110, *Revista Española de Enfermedades Digestivas*. ARAN Ediciones S.A.; 2018. p. 51–6.

2. Arumugam M, Raes J, Pelletier E, le Paslier D, Yamada T, Mende DR, et al. Enterotypes of the human gut microbiome. *Nature*. 2011 May 12;473(7346):174–80.
3. Lee JM, Lee H, Kang SB, Park WJ. Fatty acid desaturases, polyunsaturated fatty acid regulation, and biotechnological advances [Internet]. Vol. 8, *Nutrients*. MDPI AG; 2016 [cited 2020 Dec 4]. Available from: <https://pubmed.ncbi.nlm.nih.gov/26742061/>
4. Pusceddu MM, el Aidy S, Crispie F, O’Sullivan O, Cotter P, Stanton C, et al. N-3 polyunsaturated fatty acids (PUFAs) reverse the impact of early-life stress on the gut microbiota. *PLoS ONE*. 2015 Oct 1;10(10).
5. Tojo R, Suárez A, Clemente MG, de Los Reyes-Gavilán CG, Margolles A, Gueimonde M, et al. Intestinal microbiota in health and disease: Role of bifidobacteria in gut homeostasis. Vol. 20, *World Journal of Gastroenterology*. WJG Press; 2014. p. 15163–76.
6. Saffouri GB, Shields-Cutler RR, Chen J, Yang Y, Lekatz HR, Hale VL, et al. Small intestinal microbial dysbiosis underlies symptoms associated with functional gastrointestinal disorders. *Nature Communications*. 2019 Dec 1;10(1).
7. de Angelis M, Garruti G, Minervini F, Bonfrate L, Portincasa P, Gobbetti M. The food-gut human axis: the effects of diet on gut microbiota and metabolome. *Current Medicinal Chemistry*. 2017 May 2;26(19):3567–83.
8. Kayama H, Takeda K. Functions of innate immune cells and commensal bacteria in gut homeostasis. Vol. 159, *Journal of Biochemistry*. Oxford University Press; 2015. p. 141–9.
9. Tomasello G, Mazzola M, Leone A, Sinagra E, Zummo G, Farina F, et al. Nutrition, oxidative stress and intestinal dysbiosis: Influence of diet on gut microbiota in inflammatory bowel diseases. *Biomedical Papers*. 2016;160(4):461–6.
10. Rizzetto L, Fava F, Tuohy KM, Selmi C. Connecting the immune system, systemic chronic inflammation and the gut microbiome: The role of sex. *Journal of Autoimmunity*. 2018 Aug 1;92:12–34.
11. Stecher B. The roles of inflammation, nutrient availability and the commensal microbiota in enteric pathogen infection. *Microbiology Spectrum*. 2015 Jun 18;3(3).
12. Nébot-Vivinus M, Harkat C, Bziouche H, Cartier C, Plichon-Dainese R, Moussa L, et al. Multispecies probiotic protects gut barrier function in experimental models. *World Journal of Gastroenterology*. 2014;20(22):6832–43.
13. Buffie CG, Pamer EG. Microbiota-mediated colonization resistance against intestinal pathogens. *Nature Reviews Immunology* 2013 13:11 [Internet]. 2013 Oct 7 [cited 2021 Aug 3];13(11):790–801. Available from: <https://www.nature.com/articles/nri3535>
14. Thevaranjan N, Puchta A, Schulz C, Naidoo A, Szamosi JC, Verschoor CP, et al. Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. *Cell Host and Microbe* [Internet]. 2017 Apr 12 [cited 2020 Dec 3];21(4):455-466.e4. Available from: <https://pubmed.ncbi.nlm.nih.gov/28407483/>
15. Bischoff SC, Barbara G, Buurman W, Ockhuizen T, Schulzke J-D, Serino M, et al. Intestinal permeability – a new target for disease prevention and therapy. *BMC Gastroenterology* [Internet]. 2014 Nov 18 [cited 2021 Aug 2];14(1). Available from: [/pmc/articles/PMC4253991/](https://pubmed.ncbi.nlm.nih.gov/2539911/)
16. De Oliveira GLV, Leite AZ, Higuchi BS, Gonzaga MI, Mariano VS. Intestinal dysbiosis and probiotic applications in autoimmune diseases. Vol. 152, *Immunology*. Blackwell Publishing Ltd; 2017. p. 1–12.
17. Kim YS, Ho SB. Intestinal goblet cells and mucins in health and disease: recent insights and progress. *Current gastroenterology reports* [Internet]. 2010 Oct [cited 2022 Jan 23];12(5):319–30. Available from: <https://pubmed.ncbi.nlm.nih.gov/20703838/>
18. Pelaseyed T, Bergström JH, Gustafsson JK, Ermund A, Birchenough GMH, Schütte A, et al. The mucus and mucins of the goblet cells and enterocytes provide the first defense line of the gastrointestinal tract and interact with the immune system. *Immunological Reviews*. 2014;260(1):8–20.
19. Palm NW, de Zoete MR, Flavell RA. Immune-microbiota interactions in health and disease. Vol. 159, *Clinical Immunology*. Academic Press Inc.; 2015. p. 122–7.

20. Li D, Wang P, Wang P, Hu X, Chen F. Targeting the gut microbiota by dietary nutrients: A new avenue for human health. *Critical Reviews in Food Science and Nutrition*. 2019 Jan 19;59(2):181–95.
21. Spencer SP, Fragiadakis GK, Sonnenburg JL. Pursuing Human-Relevant Gut Microbiota-Immune Interactions [Internet]. Vol. 51, *Immunity*. Cell Press; 2019 [cited 2020 Nov 30]. p. 225–39. Available from: <https://pubmed.ncbi.nlm.nih.gov/31433970/>
22. Ahern PP, Maloy KJ. Understanding immune–microbiota interactions in the intestine. Vol. 159, *Immunology*. Blackwell Publishing Ltd; 2020. p. 4–14.
23. Wells JM, Spence JR. How to make an intestine. *Development (Cambridge)*. 2014 Feb 15;141(4):752–60.
24. Yu Y, Yang W, Li Y, Cong Y. Enteroendocrine cells: sensing gut microbiota and regulating inflammatory bowel diseases. *Inflammatory Bowel Diseases*. 2020 Jan 1;26(1):11–20.
25. Bayer F, Dremova O, Khuu MP, Mammadova K, Pontarollo G, Kiouptsi K, et al. The interplay between nutrition, innate immunity, and the commensal microbiota in adaptive intestinal morphogenesis. *Nutrients* [Internet]. 2021 Jun 26 [cited 2021 Aug 2];13(7). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/34206809>
26. Weiss GA, Hennet T. Mechanisms and consequences of intestinal dysbiosis [Internet]. Vol. 74, *Cellular and Molecular Life Sciences*. Birkhauser Verlag AG; 2017 [cited 2020 Dec 3]. p. 2959–77. Available from: <https://pubmed.ncbi.nlm.nih.gov/28352996/>
27. Fallucca F, Fontana L, Fallucca S, Pianesi M, Francesco. Gut microbiota and Ma-Pi 2 macrobiotic diet in the treatment of type 2 diabetes. *World Journal of Diabetes*. 2015;6(3):403.
28. Lin L, Zhang J. Role of intestinal microbiota and metabolites on gut homeostasis and human diseases. Vol. 18, *BMC Immunology*. BioMed Central Ltd.; 2017.
29. Madore C, Leyrolle Q, Lacabanne C, Benmamar-Badel A, Joffre C, Nadjar A, et al. Neuroinflammation in Autism: Plausible Role of Maternal Inflammation, Dietary Omega 3, and Microbiota. *Neural Plasticity*. 2016;2016:1–15.
30. Tmdm L, Cmgd S, Lhs M, Fld C, Mgd A. Efeitos do butirato nos níveis de peroxidação lipídica em células da mucosa cólica sem trânsito fecal: estudo experimental em ratos. *Rev bras Coloproct*. 2011;31(2).
31. Nava GM, Carbonero F, Croix JA, Greenberg E, Gaskins HR. Abundance and diversity of mucosa-associated hydrogenotrophic microbes in the healthy human colon. *ISME Journal*. 2012 Jan;6(1):57–70.
32. Calder PC. Omega-3 fatty acids and inflammatory processes: From molecules to man. Vol. 45, *Biochemical Society Transactions*. Portland Press Ltd; 2017. p. 1105–15.
33. Calder PC, Willemsen LEM. Immunopharmacology of fatty acids [Internet]. Vol. 785, *European Journal of Pharmacology*. Elsevier B.V.; 2016 [cited 2020 Dec 1]. p. 1. Available from: <https://pubmed.ncbi.nlm.nih.gov/27492754/>
34. Calder PC. Omega-3 fatty acids and inflammatory processes: From molecules to man [Internet]. Vol. 45, *Biochemical Society Transactions*. Portland Press Ltd; 2017 [cited 2020 Dec 4]. p. 1105–15. Available from: <https://pubmed.ncbi.nlm.nih.gov/28900017/>
35. Calder PC. Omega-3 fatty acids and inflammatory processes. Vol. 2, *Nutrients*. MDPI AG; 2010. p. 355–74.
36. Kaliannan K, Wang B, Li XY, Kim KJ, Kang JX. A host-microbiome interaction mediates the opposing effects of omega-6 and omega-3 fatty acids on metabolic endotoxemia. *Scientific Reports*. 2015 Jun 11;5.
37. Xiao G, Tang L, Yuan F, Zhu W, Zhang S, Liu Z, et al. Eicosapentaenoic acid enhances heat stress-impaired intestinal epithelial barrier function in caco-2 cells. *PLoS ONE*. 2013 Sep 16;8(9).
38. Calder PC. Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. Vol. 1851, *Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids*. Elsevier; 2015. p. 469–84.

39. Costanza M, Cesi V, Prete E, Negroni A, Palone F, Cuchiaro S, et al. Óleo de krill reduz a inflamação intestinal, melhorando a integridade do epitélio e reduzindo a patogenicidade da escherichia coli aderente-invasiva. 2016;48:34–42.
40. Innes JK, Calder PC. Omega-6 fatty acids and inflammation [Internet]. Vol. 132, Prostaglandins Leukotrienes and Essential Fatty Acids. Churchill Livingstone; 2018 [cited 2020 Dec 4]. p. 41–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/29610056/>
41. Guarner F. Microbiota intestinal y enfermedades inflamatorias del intestino. Gastroenterología y Hepatología [Internet]. 2011 Mar 1 [cited 2022 Jan 23];34(3):147–54. Available from: <https://www.elsevier.es/es-revista-gastroenterologia-hepatologia-14-articulo-microbiota-intestinal-enfermedades-inflamatorias-del-S0210570511000379>
42. Onali S, Favale A, Fantini MC. The resolution of intestinal inflammation: the peace-keeper's perspective. Cells [Internet]. 2019 Apr 11 [cited 2022 Jan 23];8(4):344. Available from: [/pmc/articles/PMC6523641/](https://pubmed.ncbi.nlm.nih.gov/6523641/)
43. Avinash K, Christoph R. Gut microbiota – architects of small intestinal capillaries. Frontiers In Bioscience. 2018 Jan;752–66.
44. Cehreli R, Akpınar H, Artmann AT, Sagol O. Effects of Glutamine and Omega-3 Fatty Acids on Erythrocyte Deformability and Oxidative Damage in Rat Model of Enterocolitis. Original Article Gastroenterol Res [Internet]. 2015;8(5):265–73. Available from: <http://dx.doi.org/10.14740/gr683w>
45. M Chan SS, Luben R, Olsen A, Tjønneland A, Kaaks R, Lindgren S, et al. Association between high dietary intake of the n-3 polyunsaturated fatty acid docosahexaenoic acid and reduced risk of Crohn's disease. Aliment Pharmacol Ther. 2014;39(8):834–42.
46. Serino M, Luche E, Gres S, Baylac A, Bergé M, Cenac C, et al. Metabolic adaptation to a high-fat diet is associated with a change in the gut microbiota. Gut microbiota [Internet]. 2012;61(4):543–53. Available from: <https://mulcyber.toulouse.inra.fr/>.
47. Costantini L, Molinari R, Farinon B, Merendino N. Molecular Sciences Impact of Omega-3 Fatty Acids on the Gut Microbiota. Int J Mol Sci [Internet]. 2017;18(12):1–18. Available from: www.mdpi.com/journal/ijms
48. Paula Boroni Moreira A, Fliche Salles Texeira T, Barbosa Ferreira A, do Carmo Gouveia Peluzio M, de Cássia Gonçalves Alfenas R. Review Article Influence of a high-fat diet on gut microbiota, intestinal permeability and metabolic endotoxaemia. British Journal of Nutrition [Internet]. 2001;108:801–9. Available from: <https://doi.org/10.1017/S0007114512001213>.
49. Patterson E, O' Doherty RM, Murphy EF, Wall R, O' Sullivan O, Nilaweera K, et al. Impact of dietary fatty acids on metabolic activity and host intestinal microbiota composition in C57BL/6J mice. British Journal of Nutrition(2014),111, 1905–1917 [Internet]. 2014;111:1905–17. Available from: <https://doi.org/10.1017/S0007114514000117>
50. Caricilli AM, Saad MJA. The Role of Gut Microbiota on Insulin Resistance. Nutrients [Internet]. 2013;5:829–51. Available from: www.mdpi.com/journal/nutrients
51. Barbier de La Serre C, Ellis CL, Lee J, Hartman AL, Rutledge JC, Raybould HE, et al. Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation. Am J Physiol Gastrointest Liver Physiol [Internet]. 2010;299:440–8. Available from: <http://www.ajpgi.org>
52. Schirmer M, Smeekens SP, Vlamakis H, Jaeger M, Oosting M, Franzosa EA, et al. Linking the human gut microbiome to inflammatory cytokine production capacity. Cell [Internet]. 2016 Nov 3 [cited 2021 Aug 2];167(4):1125. Available from: [/pmc/articles/PMC5131922/](https://pubmed.ncbi.nlm.nih.gov/27131922/)
53. Jayapala H, Lim SY. N-3 Polyunsaturated Fatty Acids and Gut Microbiota. Combinatorial Chemistry & High Throughput Screening. 2022 Jul. DOI: 10.2174/1386207325666220701121025. PMID: 35786331
54. Biddle A, Stewart L, Blanchard J, Leschine S. Untangling the genetic basis of fibrolytic specialization by lachnospiraceae and ruminococcaceae in diverse gut communities. Diversity 2013, Vol 5, Pages 627-640 [Internet]. 2013 Aug 9 [cited 2022 Jan 23];5(3):627–40. Available from: <https://www.mdpi.com/1424-2818/5/3/627/htm>

55. Watson H, Mitra S, Croden FC, Taylor M, Wood HM, Perry SL, et al. A randomised trial of the effect of omega-3 polyunsaturated fatty acid supplements on the human intestinal microbiota. *Gut*. 2018 Nov 1;67(11):1974–83.
56. Rivollier A, He J, Kole A, Valatas V, Kelsall BL. Inflammation switches the differentiation program of Ly6Chi monocytes from antiinflammatory macrophages to inflammatory dendritic cells in the colon. *The Journal of experimental medicine* [Internet]. 2012 Jan [cited 2022 Jan 23];209(1):139–55. Available from: <https://pubmed.ncbi.nlm.nih.gov/22231304/>.
57. Campbell EL, MacManus CF, Kominsky DJ, Keely S, Glover LE, Bowers BE, et al. Resolvin E1-induced intestinal alkaline phosphatase promotes resolution of inflammation through LPS detoxification. *Proceedings of the National Academy of Sciences of the United States of America*. 2010 Aug 10;107(32):14298–303.
58. Caesar R, Tremaroli V, Kovatcheva-Datchary P, Cani PD, Bäckhed F. Crosstalk between gut microbiota and dietary lipids aggravates WAT inflammation through TLR signaling. *Cell Metabolism*. 2015 Oct 6;22(4):658–68.
59. Fu Y, Wang Y, Gao H, Li D, Jiang R, Ge L, et al. Associations among Dietary Omega-3 Polyunsaturated Fatty Acids, the Gut Microbiota, and Intestinal Immunity. Vol. 2021, *Mediators of Inflammation*. Hindawi Limited; 2021.