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PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 78309

Title: The role of short chain fatty acids in gut health and possible therapeutic approaches in inflammatory bowel diseases

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04010086
Position: Peer Reviewer
Academic degree:
Professional title:
Reviewer's Country/Territory: China
Author's Country/Territory: Brazil

Manuscript submission date: 2022-06-19
Reviewer chosen by: AI Technique
Reviewer accepted review: 2022-06-21 02:23
Reviewer performed review: 2022-06-27 12:57
Review time: 6 Days and 10 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

作者在阅读大量文献基础上，该综述主要为了讨论短链脂肪酸在炎症性肠病治疗中可能的作用，选题较好。但文中使用了大量的篇幅讨论炎症性肠病、肠道菌群和肠粘膜屏障的基础知识，有目的不明确之嫌。建议删除很多关于炎症性肠病、肠道菌群和肠粘膜屏障基础知识的段落。

R: We would like to thank the reviewer for their helpful comments and insights regarding our previous submission. We have made the changes discussed below to address the reviewer' concerns.

As suggested by the advisory, paragraphs on the foundations of inflammatory bowel disease, the gut microbiota and the intestinal mucosal barrier were excluded. In addition, the English of the manuscript has been revised.

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Reviewer's code: 03795731
Position: Peer Reviewer
Academic degree: PhD
Professional title: Associate Professor
Reviewer's Country/Territory: Croatia
Author's Country/Territory: Brazil

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Reviewer performed review: 2022-06-30 06:33
Review time: 5 Days

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors systematically and in good English presented the latest knowledge on short-chain fatty acids and inflammatory bowel diseases, and on the possibilities of their implementation in the treatment of inflammatory bowel diseases. The article can be accepted for publication.

R: We would like to thank the reviewer for their helpful comments and insights regarding our previous submission. We have made the changes discussed below to address the reviewer's concerns.

The English of the manuscript has been revised.

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Reviewer's Country/Territory: Russia

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Review time: 12 Days and 4 Hours

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Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [Y] Rejection
Re-review	[ ] Yes [Y] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Despite the high relevance of the topic, the review is written at a low scientific level. Sketchy and fragmentary information about IBD, microbiota, SCFA, and their effects are presented. The microbiota origin of SCFA and its production in health and dysbiosis are practically not discussed. Of the SCFAs, practically only butyrate is discussed, while the barrier-supporting and anti-inflammatory role of propionate in IBD, which has been actively studied recently, is not discussed at all by the authors. The important section MODULATION OF SCFAs PRODUCTION AND FUTURE PROSPECTS is superficially written and is not state-of-the-art. Scientific literary sources for the last 5 years make up no more than 25% of all references, which is not enough. There are only 5 references to 2021 articles and no references to 2022 papers. The articles reviewed by the authors do not fully reflect the topic of the manuscript. Unfortunately, the manuscript cannot be recommended for publication.

R: We would like to thank the reviewer for their helpful comments and insights regarding our previous submission. We have made the changes discussed below to address the reviewer's concerns.

We have revised the entire manuscript and added more references on SCFAs and updated the references. Changes are highlighted in red in the text. In addition, the English of the manuscript has been revised.

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INFLAMMATORY BOWEL DISEASES

The pathogenesis of IBDs is still not fully understood[19–21], but several studies indicate that it tends to be caused by an association between genetic susceptibility and environmental alterations in the gut microbiota, along with an intestinal barrier dysfunction, causing a dysregulation of the immune system[22,23]. Genome-wide association studies identified 201 IBD-related loci, 41 of which were specific for CD and 30 for UC[23,24]. Mutations in the NOD2 gene, as well as mutations in the interleukin (IL) 10 receptor gene region and polymorphisms in the 16-like 1 gene are examples of genetic alterations related to the development of IBDs[25–28]. In addition, many of the IBD-related loci are also associated with autoimmune and immunodeficiency diseases, indicating the important relationship of IBDs to immune system disorders[23,29].

The host-microbiota interaction also plays an important role in the pathogenesis of CD and UC and involves gene regions that regulate microbial defense and intestinal inflammation[4,30–32]. Changes in the gut microbiota are frequent among individuals with IBDs[33,34]. However, it is not known whether the alteration of the microbiota is a cause or a consequence of these diseases[35,36]. Furthermore, eating habits are also related to IBDs[37]. A diet rich in processed foods, with high amounts of saturated fat and filled with protein is often associated with a higher chance of developing IBDs[38,39], while a high fiber diet reduces the chances of developing these disorders[40,41].

INTESTINAL MICROBIOTA

In the colon, of all microorganisms that constitute the IM, anaerobic bacteria are seen in greater quantity, with a predominance of the phyla *Firmicutes* and *Bacteroidetes*, followed by *Actinobacteria* and *Proteobacteria*, although this composition may vary between individuals and among the different structures of the GIT[54,55]. The profile of

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these bacteria is influenced by diet and by the use of medications, particularly antibiotics[56–58].

When a variation in the composition and diversity of the microorganisms that make up the IM happens, it generates an imbalance between symbiotic and pathogenic microorganisms, promoting an instability in the IM-host relationship[33,72]. This harmful alteration of the IM is called dysbiosis[73]. Intestinal dysbiosis leads to a pro-inflammatory response with the activation of immune system cells and, in addition, causes a reduction in the synthesis of vitamins as well as in the carbohydrate metabolism, consequently, the beneficial effects of a healthy IM are suppressed, and individuals become more susceptible to the development of diseases[74,75]. Dysbiosis is associated with the pathogenesis of several diseases, including IBDs[76–79].

SHORT-CHAIN FATTY ACIDS

The fermentation of dietary fibers and the production of SCFAs is promoted by specific enzymes of IM microorganisms[85]. Under certain physiological conditions, the main SCFAs, namely the acetate, propionate and butyrate are produced by intestinal bacteria such as, for example, the *Bacteroides* spp., the *Bifidobacterium* spp. and the *Faecalibacterium prausnitzii*[86–88]. Acetate is produced from pyruvate via acetyl-CoA[86]. Propionate is produced via the succinate, acrylate, and propanediol pathways[87,89]. In turn, butyrate is produced from two molecules of acetyl-CoA, which are transformed into butyrate via phosphotransbutyrylase and butyrate kinase[88]. The butyryl-CoA:acetate CoA-transferase also leads to the production of butyrate, and some bacteria use acetate as a substrate for butyrate production[85].

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In a dysbiosis condition, the composition and diversity of SCFA-producing microorganisms are altered[33,34]. A particular reduction in butyrate-producing bacteria such as *Faecalibacterium prausnitzii* is seen in patients with IBDs[90], as well as reduced levels of propionate acetate and butyrate in the feces of these patients [91,92].

Effects of SCFAs on the Intestinal Barrier

The occludins form a barrier mainly to macromolecules[119,120], while the claudins, particularly claudin-1, can maintain the intestinal barrier functionality even in the absence of other tight junctions[116,121–123]. The JAM, a protein belonging to the Immunoglobulins (Ig) superfamily[124–126], is capable of forming homophilic interactions adjacent to tight junctions as well as interacting with integrins or other members of the JAM family[125,126], playing an important role in the constitution of the intestinal barrier[118,127,128]. The ZOs proteins, such as ZO-1, ZO-2, and ZO-3 are located in the cytoplasm[129,130] acting as an anchor for proteins by joining them to the cytoskeleton and, therefore, are key to maintaining the integrity of the intestinal barrier, mainly due to its relationship with the claudins and the occludins[117,131].

Although most of the beneficial effects of SCFAs at the intestinal barrierare attributed to the butyrate, some studies have shown recently that the propionate is also able to improve the functionality of such barrier[141]. In an experimental model of UC, propionate was able to attenuate the decrease in the expression of tight junctions such as ZO-1 and occludin in the large intestine[142]. These SCFAs were also able to attenuate the intestinal barrier dysfunction induced in Caco-2 Cell monolayers, however, the amount

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of propionate needed in order to observe its effects on the intestinal barrier is greater than that of butyrate[143]. In addition, propionate also appears to influence the differentiation and proliferation of the intestinal epithelium[144].

Effects of SCFAs on Intestinal Inflammation

Still in a DSS-induced colitis model, the propionate was able to inhibit the expression of pro-inflammatory markers such as IL-6, IL-1β and TNF-α in the colon[142]. Moreover, the propionate is also capable of modulating the activation of immune system cells and reducing the levels of reactive oxygen species in the tissues. [171,172].

MODULATION OF SCFAs PRODUCTION AND FUTURE PROSPECTS

In other words, a person's diet exerts a strong influence on the composition of their IM and, consequently, on the modulation of the SCFAs production[190,192]. A plant-based diet, such as the Mediterranean diet, tends to increase the source of dietary fiber and, consequently, the production of SCFAs[193–195]. On the other hand, a diet low in vegetables and rich in meats, sugars or saturated fats, such as the Western diet, not only alters the IM profile, but reduces the availability of fiber and, consequently, the production of SCFAs[196,197]. In this sense, the association between the use of probiotics, prebiotics and a Mediterranean-like diet optimizes the production of SCFAs in the intestine[187,193,198,199].

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Many animal models of IBDs seek to identify a possible effectiveness of the use of probiotics as a treatment for this disease[200]. In the TNBS-induced UC models, the microorganisms *Bifidobacterium infantis* and *Bifidobacterium bifidum* demonstrated beneficial effects in animals by attenuating the clinical manifestations of UC, promoting a greater preservation of the mucus layer and a reduction of pro-inflammatory cytokines such as the IL-10 and the IL-1β in the intestine[201,202]. In the DSS-induced UC model, the microorganisms *Bifidobacterium longum* subsp. *infantis* BB-02 and the *Bifidobacterium animalis* subsp. *lactis* BB12 also demonstrated to have a positive influence on the clinical, histological and inflammatory manifestations of this disorder[203,204]. Ultimately, a reduction of potentially pathogenic microorganisms was observed after the administration of *Bifidobacterium lactis*[205]. The improvement of the results observed with the administration of these probiotics may be related to an increase in the production of the SCFAs[206].

As for the clinical studies, the effectiveness of using probiotics in patients with IBDs is controversial[207]. The *Bifidobacterium bifidum*, *Lactobacillus acidophilus*, *Escherichia coli* Nissle1917 and *Bifidobacterium breve* appear to exert favorable effects on UC remission [208–210]. In addition, the use of the referred probiotics caused an increase of butyrate and propionate levels in the subject's fecal matter[210]. The combination of some microorganisms has also been used in clinical studies. This is the case of VSL#3, consisting essentially of 8 strains of microorganisms: *Lactobacillus paracasei*, *Lactobacillus plantarum*, *Lactobacillus acidophilus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Bifidobacterium longum*, *Bifidobacterium breve*, *Bifidobacterium infantis* and *Streptococcus thermophilus*[211]. Patients with UC who used VSL#3 showed a clinical improvement, with a reduction in fecal bleeding as well as a decrease in the frequency of stool

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evacuation[212,213]. These findings do not appear to be applicable to CD[214]. It is important to mention that VSL#3 microorganisms are producers of SCFAs and this may be related to the improvements observed with the use of this probiotic for UC[206].

Another approach studied for the modulation of SCFAs production and for the treatment of IBDs is the Fecal Microbiota Transplantation (FMT)[215]. FMT is able to change the composition of the recipient's IM, in order to reduce the proliferation of potentially pathogenic microorganisms and increase the production of SCFAs, especially butyrate[216-218]. Furthermore, fecal levels of *Eubacterium* and *Lactobacillus* spp. increased after the FMT, which are producers of Butyrate[216,219,220]. Although FMT is classically studied for the treatment of *Clostridium difficile* infection, several studies have observed that FMT has proven to be an effective, safe, and promising alternative to the treatment of IBDs, including UC and CD[215,221-223].

Sincerely,

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