

REVIEW

# The Role of Probiotics, Prebiotics and Synbiotics in Adult Gastrointestinal Health

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**Abstract:** Gastrointestinal (GI) health is important because a healthy gut can maintain our general health and protect our body from infection or illness. Apart from vitamins and minerals, probiotics, prebiotics, and synbiotics have become increasingly famous as a supplement in our daily diet. Previously, a large number of studies had been performed to study the efficacy of probiotics in the prevention or treatment of illnesses. The purpose of our review is to discuss recent data on the benefits of probiotics in human's GI health. Promising results on the effect of probiotics in the treatment of inflammatory bowel disease, particularly ulcerative colitis and pouchitis have been obtained from studies. Other reports also showed that a few probiotics can improve symptoms in irritable bowel syndrome. *Saccharomyces boulardii* was shown to prevent traveler's diarrhea but further studies are needed for firm conclusions. *Lactobacillus rhamnosus* and *S. boulardii* are recommended in the treatment of acute infectious diarrhea. There are promising indications that probiotics could be useful in the prevention or treatment of antibiotic-associated diarrhea, and a *Lactobacillus*-containing combination has been shown to prevent diarrhea caused by *Clostridioides difficile*. Addition of probiotics to current *Helicobacter pylori* eradication regime can further increase the eradication rate.

**Keywords:** Probiotics, Prebiotics, Synbiotics, Gastrointestinal health

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## 1. Introduction

Gastrointestinal (GI) health is always a crucial issue in the community. The prebiotics, probiotics, and synbiotics collectively are a common topic of discussion. A healthy GI tract is equivalent to a healthy immune system, which protects us from any infections or illnesses. The GI tract starts from the mouth and ends at the anus. Every day, a significant number of living microorganisms, predominantly bacteria or amounting to about  $1 \times 10^{14}$  bacteria, may be ingested, and majority of them are found in the colon. The bacteria in the GI tract can be categorized as "good" and "bad" bacteria; the former help digest food and destroy disease-causing microorganisms while the latter cause harm to our health. On the basis of the beneficial effects, "good" bacteria are added to human's diet as probiotics nowadays, as the probiotic-containing products are believed to have beneficial effects for human health. Here, we aim to review the recent studies about the usage of probiotics in a variety of human's GI-related diseases.

## 2. Probiotic and its mechanisms

Probiotics proposed by Lilly and Stillwell in 1965 are defined as live organisms that can confer a health benefit on consumers when administered in a certain amount by the

Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) in 2001<sup>[1]</sup>. The *Lactobacillus*, *Bifidobacteria*, and *Saccharomyces boulardii* (yeast) are probiotics microorganisms that are more popularly used. Probiotic products that are available in the market now may contain either a single strain or a mixture of few strains. The effects of probiotic cannot be generalized as they are very strain-specific. Different types of probiotics may have different effects. Besides, the benefits of a single strain of probiotic could be different when used individually and in combination. In order to maximize therapeutic effects, probiotics should exhibit certain properties: gastric acid and bile tolerance, good adherence to the intestinal surface, good colonization on the intestinal tract, and antimicrobial activity against pathogenic bacteria.

There are mainly four mechanisms: antimicrobial mechanism by secreting the bacteriocins and antimicrobial substances such as organic acids and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), competition with pathogenic bacteria for limited nutrients, stimulation of the mucosal immune system, and inhibition of bacterial toxin production.

The benefits of a probiotic formulation also vary among the patient groups. Probiotics are naturally found in fermented dairy products such as milk, yogurts, ice cream, aged cheese, kimchi, and sauerkraut. Although there is a paucity of evidence about the minimum effective values that a probiotic should have, it is generally accepted that a daily intake of 10<sup>9</sup> – 10<sup>10</sup> colony forming units (CFU)/ml is associated with consumers' health benefit.

A few cases of *Lactobacillus* bacteremia were reported for their association with probiotic administration. Probiotics are believed to have potential to cause the side effects to consumers because probiotics, which are the live organisms, are inoculated directly into a consumer, and these colonies may turn from beneficial commensal to harmful pathogen.

### 3. Prebiotic with its mechanisms

In 2007, prebiotics was defined as a nonviable food component that brings health benefits to consumers associated with modulation of the microbiota<sup>[2]</sup>. Prebiotics are mostly fibers that are not digestible and do not actually contain bacteria. They are not systemically absorbed and therefore seldom cause side effects. The classification of a prebiotic includes the following features: resistance to stomach's acidity, resistance to hydrolysis by the digestive enzymes and inability to be absorbed in the GI tract. Prebiotics are fermentable by our GI microbiota and stimulate our intestinal bacteria's growth and activity that further improves health condition.

Prebiotics exert a more direct effect while the probiotics cause an indirect effect on the microbiome through metabolic pathways and the growth of commensal organisms. They are essential for the growth of these

bacteria. They improve the balance of microorganisms by selectively stimulating the microorganisms' growth and activity in the GI tract, particularly the *Lactobacilli* and *Bifidobacteria*. The diet which is rich in prebiotics are fruits, vegetables, and whole grains, such as barley's.

## 4. Synbiotics

In general, prebiotics and probiotics are "good" bacteria promoters. In other words, prebiotics is "nutrient" which known to be functional food component for probiotics, that restores and improves GI health. A synbiotic is a mixture of probiotics and prebiotics, allowing them to work together to benefit the host by improving the survival and activity of "good" microorganisms in the colon. The synbiotic concept was first described about 25 years ago which they are categorized into different strains: *Lactobacillus*, *Bifidobacteria*, and *S. boulardii* (yeast). The commonly used prebiotics in synbiotic supplements include inulin-type fructans and fructo-oligosaccharides, and galactans, for example, galacto-oligosaccharides<sup>[3]</sup>.

## 5. Current research on the benefits of probiotics in adult GI health

A growing line of evidence supports positive health effects attributed to probiotics. These studies have shown that probiotics consumption can benefit digestive-related diseases, cancer, obesity and type 2 diabetes, and skin diseases<sup>[4-8]</sup>.

The interpretation of probiotics in GI diseases remains challenging as studies have employed different species, strains, doses, and preparations in different patient populations. Moreover, the studies were run at different standards and phases of disease. The probiotic agents had been studied either as a single agent or as combination. Unfortunately, the majority of the studies have not been reproduced or reconfirmed. Until today, the use of certain probiotic strains in treating or improving certain GI conditions is supported by evidence. Here, we discuss the evidence of probiotics in each GI disease.

### 5.1. Inflammatory bowel disease (IBD)

IBD is a common chronic illness that is characterized by inflammation of the GI tract, mainly intestines. It is believed to be resulted from the host-microbial interactions occurring in a genetically susceptible individual. There are three common types of IBD: Ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis (IC). The medical cure for IBD is not known until today. There is strong evidence suggesting the key role of bacteria in IBD. It is known that the modification and diversion of gut flora led to improvement in IBD. Therefore, probiotics can be considered as a good choice in IBD management.

Consistent results have been obtained only with certain probiotics, including *Lactobacillus*, *Escherichia coli* Nissle 1917, VSL#3, *Bifidobacterium*, and *S. boulardii*<sup>[9]</sup>.

A number of animal experiments had shown the evidence implicating the intestinal bacterial flora in IBD. *Lactobacillus* had shown to attenuate the development of colitis, and to reduce the established colitis in interleukin-10 (IL-10) deficient mice<sup>[10]</sup>. Besides, Dalmasso *et al.* has reported that the fungus *S. boulardii* may have a beneficial effect in IBD treatment by trapping the T cells to mesenteric lymph nodes<sup>[11]</sup>.

The studies on probiotics on animal models of colitis are promising; therefore, the basic research was taken further into clinical studies. According to Kruis *et al.*, the study<sup>[12]</sup> which involved 120 patients with inactive UC showed no significance difference between mesalazine group and probiotic group using *E. coli Nissle* (Serotype 06: K5: H1) for maintenance therapy. However, due to some drawbacks in this study, another study was done as a continuation on UC remission patients<sup>[13]</sup>. They have been assigned to a one-year, double-blind, and double-dummy trial to receive either the probiotic 200 mg once daily (n = 162) or mesalazine 500 mg three times a day (n = 165). This study had demonstrated that *E. coli* strain *Nissle* provides equivalent efficacy as mesalazine in preventing UC relapses with no significance difference.

The VSL#3<sup>[14]</sup> is a widely studied multispecies probiotics preparation that contains three strains of *Bifidobacteria*, four strains of *Lactobacilli*, and one strain of *Streptococcus salivarius* sp., *Thermophilus*. or Gionchetti<sup>[15]</sup>. The effect of VSL#3 was examined for nine months in 40 patients with pouchitis who were in both clinical and endoscopic remission. The VSL#3 has significantly prevented the flare-ups of pouchitis among the patients by 15% relapse compared to 100% relapse in placebo group ( $P < 0.001$ ).

In Sivanathan's review of *S. boulardii*, all three of the clinical trials showed the effectiveness of *S. boulardii* in treating IBD (two CDs, one UC), while one trial did not show any effects on CD. Unfortunately, the number of studies conducted on *S. boulardii* in treating IBD is limited, and not conclusive<sup>[16]</sup>.

There is also paucity of data to support the role for probiotics in CD. Most of these studies involved only small populations, short observation duration of non-blinded study, and a lack of standardization of the therapeutic protocols. According to a recent review by Berkeley, there was inadequate evidence to make any conclusions if probiotics were effective in treatment of CD<sup>[17]</sup>.

## 5.2. Antibiotic-associated diarrhea (AAD)

AAD can be diagnosed if a patient's stool sample is loose and watery at least 3 times in 24 h after antibiotics treatment. It occurs when the natural balance of "good" and "bad" bacteria in the GI tract is disrupted by antibiotics, causing multiplication of harmful germs until serious illness is resulted. Numerous probiotics had been studied for their efficacy in both treatment and prevention of AAD.

A study done by Goldenberg indicated that probiotics could reduce the AAD incidence from 18% to 12% among 8870 patients<sup>[18]</sup>.

McFarland had clarified that the efficacy of probiotics is both strain-specific and disease-specific in his review of 228 trials<sup>[19]</sup>. *Lactobacillus rhamnosus* GG and *S. boulardii* CNCM I-745 were proven to be efficient as treatment in patients with AAD, while mixture of *Lactobacillus acidophilus* CL1285, *Lactobacillus casei* LBC80R, and *L. rhamnosus* CLR were effective for the prevention of AAD<sup>[20]</sup>. A recent meta-analysis from Netherlands showed similarity in the effectiveness of probiotics *L. rhamnosus* GG in prevention of AAD<sup>[21]</sup>. American Gastroenterological Association had published the Clinical Practice Guidelines on the role of probiotics in the management of GI disorders in 2020, suggesting the use of *S. boulardii* or the two-strain combination of *L. acidophilus* CL1285 and *L. casei* LBC80R for AAD prevention<sup>[22]</sup>.

Probiotics play a vital role in the prevention and treatment of AAD. However, this may not be practical as clinicians are unable to identify the patients who are at the risk of AAD. Moreover, we are unable to confirm the strain type of probiotics for antibiotics that is causing the AAD.

## 5.3. Traveler's diarrhea (TD)

TD affects at least a quarter of people traveling from industrialized countries to developing countries annually. Faecal-oral route was the most common route of transmission, with enterotoxigenic *E. coli* as the most common pathogen. Although the majority of patients with TD will recover with sufficient rest and rehydration, 1% of them still require hospitalization.

In 2017, the International Society of Travel Medicine had published a guideline stating that probiotics were not recommended in either prevention or treatment of TD due to insufficient evidence<sup>[23]</sup>. However, some other studies concluded that probiotics were efficient in TD prevention. In McFarland's systematic review and meta-analysis, *S. boulardii* CNCM I-745 is the only one probiotic that presented with significant efficacy in the prevention of TD when compared to *L. rhamnosus* GG and *L. acidophilus*<sup>[16,24]</sup>. Furthermore, Bae's meta-analysis on eleven articles which was published in 2018 supports probiotics' efficacy in the prevention of TD<sup>[25]</sup>.

## 5.4. Acute infectious diarrhea

Acute infectious diarrhea is defined as the infection-induced passage of at least three loose stools in a 24-h period. It is a major global disease burden that primarily affects people in developing countries<sup>[26]</sup>. However, it is difficult to conduct analysis for the application of probiotics in the prevention and/or treatment of acute infectious diarrhea. The infectious agents that can cause diarrhea include *E. coli*, *Clostridioides difficile*, *Salmonella*, *Shigella*, and

rotavirus. Besides, the cause of infectious diarrhea was not identified in majority of the studies.

World Gastroenterology Organization Global Guidelines had recommended the use of probiotics *L. rhamnosus* GG, and *S. boulardii* CNCM I-745 in the treatment of acute infectious diarrhea<sup>[20]</sup>. Besides that, the Infectious Diseases Society of America (IDSA) had also published its guidelines in 2017<sup>[27]</sup>, stating that probiotic preparations may be offered to immunocompetent adults and children with infectious or antimicrobial-associated diarrhea to reduce the severity and duration of symptom.

Many studies had been carried out to study the effects of probiotics in acute infectious diarrhea. Allen conducted a meta-analysis involving 63 studies that compared a specified probiotic with a placebo or no probiotic in 8014 patients with acute infectious diarrhea (56 trials involved infants and young children). The probiotics effect was proven significant in three ways: to reduce the mean duration of diarrhea, to reduce the stool frequency of diarrhea lasting at least 4 days, and to reduce the stool frequency on day two of diarrhea<sup>[28]</sup>. However, this was not supported by Collinson's review which included 82 studies with a total of 12,127 patients. In his analysis which was based on large trials with low risk of bias, there was no difference between probiotic and control groups in the risk of diarrhea lasting at least 48 hours, or for the duration of diarrhea<sup>[29]</sup>.

### 5.5. *C. difficile* infection (CDI)

*C. difficile* is formerly known as *Clostridium difficile*. *C. difficile* is a Gram-positive, spore-forming anaerobe that causes diarrhea and colitis. It is associated strongly with the use of antibiotics. Antibiotics can affect the microbial diversity and the richness of the GI's microbial communities, leading to reduced resistance to colonization of gut pathogens such as *C. difficile*. Many patients with CDI will recover after discontinuation of antibiotics and treatment with metronidazole or vancomycin. However, up to 25% of them experienced recurrent CDI within 30 days of completion of treatment.

In contrast to guidelines on managing CDI which was last published in 2013, the American College of Gastroenterology (ACG) had included new recommendations for treating patients in recurrent CDI with fecal microbiota transplantation, preferably to be administered through colonoscopy or capsule. ACG also discouraged the use of probiotics for both primary and secondary prevention<sup>[30]</sup>. The decision by ACG was supported by IDSA and Society for Healthcare Epidemiology of America<sup>[31]</sup>.

In another study conducted on Bio-K+ which is a formulation containing *L. acidophilus* CL1285, *L. casei* LBC80R, and *L. rhamnosus* CLR2 is known to be available in North America for more than twenty years. A study done by McFarland<sup>[32]</sup> and Gao has revealed that Bio-K+ was

also found to prevent CDI. In Gao's study<sup>[33]</sup>, 255 adult inpatients receiving antibiotics at a hospital took part in a randomized clinical trial. The probiotic capsules given contained 50 billion CFU of *L. acidophilus* CL1285<sup>®</sup> + *L. casei* LBC80R<sup>®</sup> Bio-K+ CL1285). Capsules were given within 36 hours of initial administration of antibiotic, continued for five days after the last antibiotic dose, and then patients were monitored for another three weeks. In this study, the placebo-treated subjects had a higher CDI incidence (23.8%). The double dose of Bio-K+ yielded (1.2%) compared to the placebo group (23.8%), and single-dose group of Bio-K+ (9.4%).

In a recent studies<sup>[34]</sup> of probiotics and CDI in adult patients taking antibiotics, it was concluded that probiotics were significantly more effective in reduction of CDI risk if given earlier or within two days of antibiotic initiation, and close to the first dose of antibiotic.

### 5.6. Irritable bowel syndrome (IBS)

IBS is a chronic gut-brain disorder that can cause a variety of GI discomfort including abdominal pain or bloating and diarrhea, constipation, or a combination of the two. IBS is defined by the Rome IV Criteria: recurrent abdominal pain at least one day weekly in the last three months associated with at least two of the following criteria: (1) Defecation-related, (2) a change in appearance of the stool, and/or (3) a change in frequency of bowel movement. Although the actual etiology of IBS remains unclear, current research suggests that an imbalance in GI microbiota and a dysfunctional intestinal barrier may lead to IBS in some patients and no specific treatment is available for IBS.

ACG had conducted a series of systematic reviews which<sup>[35]</sup> summarized that probiotics can improve overall symptoms, bloating, and flatulence in patients with IBS. However, there was insufficient evidence to recommend the use of prebiotics or synbiotics among patients with IBS.

Although many studies have used combination of probiotics instead of single probiotics in their intervention of IBS, a study conducted by Zhang showed that IBS treatment with single and low dose of probiotics for a short duration could be more effective in improving IBS patients' overall symptoms response and quality of life<sup>[36]</sup>.

In the contrary, Yuan *et al.*<sup>[37]</sup> found that abdominal pain and bloating or distention were significantly reduced among the IBS patients who received composite probiotics containing *B. infantis*, but not with single probiotic *B. infantis* treatment. In addition, a study by Enck had reported that the mixture of *E. coli* (DSM 17252) and *Enterococcus faecalis* (DSM 16440) is a highly effective IBS treatment<sup>[38]</sup>. However, that study had raised a conflict about potential mechanism of action because the cytokine expression of both strains differs from the cytokine expression of the mixed compound. Then, Enck recruited another 298 IBS patients, who were assigned to an eight-week trial to receive either single probiotic preparation containing *E. coli* (DSM 17252)

**Table 1.** Summary of clinical trials for IBD treatment

Trial	Patients (n)	IBD	Probiotics	Duration of study	Outcomes
Kruis <i>et al.</i> <sup>[12]</sup>	120	Inactive UC	<i>Escherichia coli</i> Nissle (Serotype 06: K5: H1)	12 weeks	No differences between mesalazine group and probiotic group for maintenance therapy.
Kruis <i>et al.</i> <sup>[13]</sup>	327	UC in remission	<i>Escherichia coli</i> Nissle (Serotype 06: K5: H1)	1 year	<i>Escherichia coli</i> strain Nissle provides equivalent efficacy as mesalazine in preventing UC relapses.
Gionchetti <i>et al.</i> <sup>[15]</sup>	40	Pouchitis in remission	VSL#3 (three strains of <i>Bifidobacteria</i> , four strains of <i>Lactobacilli</i> , and one strain of <i>Streptococcus salivarius</i> sp. and <i>Thermophilus</i> ).	9 months	VSL#3 significantly prevents flare-ups of pouchitis.

(n = 148) or placebo (n = 150)<sup>[39]</sup>. This study concluded that treatment with single probiotic *E. coli* (DSM 17252) was effective in reducing IBS symptoms. *Lactobacillus plantarum* 299v had been shown to reduce IBS symptoms (resolution of abdominal pain [ $P < 0.001$ ], normalization of stools frequency in constipated patients and improvement in all IBS symptoms [ $P < 0.001$ ])<sup>[40]</sup>.

A study conducted using an animal mouse model of IBS with *S. boulardii* CNCM I-745 treatment had shown a positive outcome but evidence is scarce to corroborate the efficacy of long-term use of *S. boulardii* in IBS patients<sup>[41,42]</sup>.

### 5.7. *Helicobacter pylori* infection

*H. pylori* is a Gram-negative bacterium, causing common infection that is closely related to gastritis, peptic ulcer disease, stomach cancer, and MALT lymphoma, particularly in developing countries. Since the 90's, the standard triple therapy containing both antibiotics and proton pump inhibitor (PPI) had achieved a high eradication rate which is up to 90% in eradication of *H. pylori*. Recently, however, the increasing failure of the treatment among the patients with *H. pylori* infection may be attributed to the development of clarithromycin resistance and its side effects. Many patients have side effects with standard *H. pylori* treatment, including diarrhea, altered taste, nausea, and vomiting.

The potential of probiotics in antagonizing *H. pylori* had been demonstrated in a few in vitro experiments. Probiotics inhibit *H. pylori* via a few immunological and non-immunological mechanisms. The probiotics modulate the secretion of anti-inflammatory cytokines, which then reduce the gastric acidity and inhibit the inflammatory response mediated by IL after a *H. pylori* infection<sup>[43]</sup>. In another non-immunological mechanism, probiotics inhibit the adhesion of *H. pylori* by secreting antibacterial substances such as lactic acid, short-chain fatty acids (SCFAs), H<sub>2</sub>O<sub>2</sub> and bacteriocins<sup>[44]</sup>. *Lactobacillus* species have been shown to decrease the proinflammatory cytokines levels, stimulate mucin secretion, inhibit

*H. pylori* adhesion to the gastric epithelium, and suppress the bacterial growth<sup>[45]</sup>.

A few meta-analyses demonstrated that probiotics supplementation to the standard eradication regime is associated with a higher successful rate of eradicating *H. pylori* infection compared to standard eradication regime alone<sup>[46-48]</sup>. Lau *et al.* had concluded that probiotics supplementation significantly increased eradication rates of *H. pylori* infection by 12%, and reduced the risk of GI adverse events<sup>[46]</sup>. A different study performed in Thailand reported a 96% eradication rate of *H. pylori* infection after two weeks of high-dose PPI- and Bismuth-containing quadruple therapy combined with *Lactobacillus reuteri*<sup>[48]</sup>. Meanwhile, McFarland has found that only one probiotic strain, *S. boulardii* CNCM I-745, was found to significantly increase eradication rates of *H. pylori* infection, and only *S. boulardii* CNCM I-745 significantly prevented any side effects<sup>[47]</sup>.

However, probiotics alone cannot be considered an alternative to standard *H. pylori* eradication treatment. Dore *et al.* had performed a study involving more than 4,000 patients, showing that the addition of probiotic to PPI alone could only achieve about 12.5% eradication rate<sup>[49]</sup>.

## 6. Conclusions

The development of probiotics for disease treatment is still at its early stage. However, the use of probiotics in the treatment of GI disorders is increasing with the discovery of significant therapeutic advance of these agents. As listed in **Table 1**, certain probiotics had shown promising effect in improving GI conditions but some probiotics may not show any differences if compared with placebo. A summary of the use of probiotics in adults with GI diseases had been listed in **Table 2**. Studies of probiotics in GI health need further confirmation. In general, probiotics have an extensive history of apparently safe use as a dietary supplement. Clinicians should carefully consider probiotics as part of an overall treatment plan which includes medication, dietary or nutrition intervention, and

**Table 2.** Summary of the use of probiotics in adult with GI diseases

GI diseases	Proven efficacy
Inflammatory bowel disease	As a treatment: <i>Lactobacillus</i> , <i>Escherichia coli</i> Nissle 1917, VSL#3, <i>Bifidobacterium</i> , and <i>Saccharomyces boulardii</i> <sup>[9]</sup>
Antibiotic-associated diarrhea	As a treatment: <i>L. rhamnosus</i> GG and <i>S. boulardii</i> CNCM I-745 <sup>[20]</sup> For prevention: Mixture of <i>L. acidophilus</i> CL1285, <i>L. casei</i> LBC80R and <i>L. rhamnosus</i> CLR <sup>[20]</sup>
Traveler’s diarrhea	For prevention: <i>S. boulardii</i> CNCM I-745 <sup>[16,24]</sup>
Acute infectious diarrhea	As a treatment: <i>L. rhamnosus</i> GG, <i>S. boulardii</i> CNCM I-745 <sup>[20]</sup>
<i>Clostridioides difficile</i> infection	For prevention: Mixture containing <i>L. acidophilus</i> CL1285, <i>L. casei</i> LBC80R and <i>L. rhamnosus</i> CLR2 <sup>[32,33]</sup>
Irritable bowel syndrome	As a treatment: <i>Bifidobacterium infantis</i> 35624 <sup>[37]</sup> , <i>E. coli</i> (DSM 17252) <sup>[39,39]</sup> , <i>L. plantarum</i> 299v <sup>[40]</sup>
<i>Helicobacter pylori</i> infection	As a treatment: (higher successful rate of eradication with probiotics supplementation to the standard eradication regime): <i>L. reuteri</i> <sup>[40]</sup> , <i>S. boulardii</i> CNCM I-745 <sup>[47]</sup>

lifestyle modification. Further research, especially in the form of controlled human studies, should be carried out to determine the strain of probiotics, its dosages, and duration of consumption. Its greatest efficacy on different patients’ conditions as well as their safety and limitations are also essential to be studied in future research.

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**Conflict of interest**

The authors do not have any conflict of interests to declare.

**Author contributions**

J.Y.C. conceived the idea of this manuscript, and wrote, edited and reviewed the manuscript. Y.P. edited and reviewed the manuscript. Both authors read and approved the final manuscript.

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