ACTA
PORTUGUESA
DE NUTRIÇÃO

ASSOCIAÇÃO
PORTUGUESA
DE NUTRIÇÃO

ADJUVANT NUTRACEUTICALS IN THE MANAGEMENT OF GASTROINTESTINAL DISEASES

A.R.
ARTIGO DE REVISÃO

NUTRACÊUTICOS COM AÇÃO ADJUVANTE NA INTERVENÇÃO A NÍVEL DAS DOENÇAS GASTROINTESTINAIS

Beatriz Gandra Balio[1*] ; Rita Giro[1] ; Maria Roriz[1]

[1] Faculdade de Ciências da Nutrição e Alimentação da Universidade do Porto, Rua do Campo Alegre, n.º 823, 4150-180 Porto, Portugal

*Endereço para correspondência:

Beatriz Gandra Balio
Faculdade de Ciências da Nutrição e Alimentação da Universidade do Porto,
Rua do Campo Alegre, n.º 823,
4150-180 Porto, Portugal
beatrizcgandra@gmail.com

Histórico do artigo:

Recebido a 21 de outubro de 2022
Aceite a 30 de janeiro de 2023

ABSTRACT

The prevalence of gastrointestinal diseases has increased substantially in the last few years, bringing consequences not only to quality of life, but also to patients' emotional/psychological wellbeing. Preliminary data from experimental studies suggest that using nutraceuticals as an adjuvant therapy to improve gastrointestinal symptomology may be a relevant and innovative strategy, since first line pharmacological treatments may pose severe adverse effects, drug resistance and lack of patient compliance. This narrative review aimed to explore the potential of four bioactive compounds at improving gastrointestinal symptomatology and disease management. Additionally, the mechanisms of action and dosages underlying the positive effects of these substances in improving quality of life and risk of disease relapse are also explored.

According to the evidence found, peppermint oil and probiotics appear to ameliorate irritable bowel syndrome symptomatology, whereas polyphenols such as curcumin suggest a complementary effect in inducing and maintaining clinical remission among ulcerative colitis patients. Evidence regarding ginger's effect on gastrointestinal symptoms is lacking and demonstrates little to no expression in irritable bowel syndrome nor functional dyspepsia.In conclusion, the consumption of peppermint oil, polyphenols and probiotics may be a viable adjuvant in the management of gastrointestinal diseases, associated symptomology and quality of life. However, further randomized controlled trials are warranted to elucidate on the optimal dose, safety and long-term efficacy of supplementing with these components, and particularly on the potential relevance of ginger supplementation.

KEYWORDS

Clinical nutrition, Dietary supplement, Gastroenterology, Nutraceuticals, Therapeutic use

RESUMO

A prevalência de doenças do trato gastrointestinal tem aumentado substancialmente nos últimos anos, com consequências tanto sobre a qualidade de vida, como o bem-estar emocional/psicológico dos pacientes. Dados preliminares de estudos experimentais recentes sugerem que a utilização de nutracêuticos como tratamento adjuvante na melhoria da sintomatologia gastrointestinal parece ser uma estratégia pertinente e inovadora, uma vez que os tratamentos farmacológicos de primeira linha poderão despoletar efeitos adversos severos, resistência à medicação e reduzida adesão do paciente ao tratamento. Esta revisão narrativa teve como objetivo explorar os potenciais efeitos de quatro compostos bioativos na melhoria da sintomatologia e gestão das doenças gastrointestinais. Adicionalmente, os mecanismos de ação e dosagens subjacentes aos efeitos positivos destas substâncias na melhoria da qualidade de vida dos doentes e risco de recidiva das doenças também são explorados.

De acordo com a evidência encontrada, o óleo de hortelã pimenta e os probióticos parecem melhorar a sintomatologia de pacientes com a síndrome do intestino irritável, enquanto os polifenóis, como a curcumina, sugerem um efeito complementar na indução e manutenção da remissão clínica em pacientes com colite ulcerosa. Falta evidência que corrobore o efeito do gengibre na sintomatologia gastrointestinal, e a que existe tem pouca ou nenhuma expressão em doenças como a síndrome do intestino irritável e a dispepsia funcional.

Em suma, o consumo de óleo hortelã pimenta, polifenóis e probióticos poderá ser um adjuvante viável na gestão de doenças gastrointestinais, sintomatologia associada e qualidade de vida dos doentes. Contudo, mais ensaios clínicos randomizados são necessários para esclarecer a dosagem ideal, segurança e eficácia a longo prazo da suplementação com estes compostos e, particularmente, a potencial relevância da suplementação com gengibre.

PALAVRAS-CHAVE

Nutrição clínica, Suplemento nutricional, Gastrenterologia, Nutracêuticos, Uso terapêutico

INTRODUCTION

Gastrointestinal (GI) diseases can affect the gastrointestinal tract from the mouth to the anus and can be classified into two types: (1) functional GI disorders and (2) structural GI disorders, with the first ones being the most common type among the two (1). Irritable bowel syndrome (IBS) and functional dyspepsia (FD) are the two most common examples of functional GI disorders with a very broad spectrum of reported prevalence (1.1%-45.0% for IBS and 1.8%-57.0% for FD) (2). In order to help diagnose these patients, the Rome Criteria*, a set of criteria used by clinical personnel and scientists, is applied (3). Although the exact aetiology and pathophysiology underlying these diseases are complex, it is known that altered regulation of the gut-brain axis and immune function, visceral hypersensitivity and abnormal GI motility are intimately associated with IBS and FD (1, 4). Inflammatory bowel disease (IBD) is a chronic and refractory inflammation of the GI tract which mainly comprises Chron's disease (CD) and ulcerative colitis (UC), with a prevalence rising and surpassing 0.3% (5). Similarly to IBS and FD, IBD's aetiology remains largely unknown. However, it is suggested to be associated with genetic susceptibility and an interaction between intestinal mucosa cells and an abnormal immune response that can been triggered by environmental factors (6-8).

The present management strategies for these diseases involve the use of antidepressants, spasmolytics, 5-HT3 antagonists, histamine H2-receptor antagonists and anti-inflammatory agents such as amino salicylates and immunosuppressive drugs, with patients reporting poor efficacy of the therapy and occurrence of various, serious adverse effects (AE) with long-term use (9-11).

In the last years, growing evidence suggests a possible benefit when combining pharmacological treatment along with nutritional substances that have shown not only to be effective in the management of the abovementioned GI disorders, but also to improve quality of life (QOL) and psychological wellbeing (1, 7, 10). To the best of our knowledge, no review to date has focused exclusively on the effects of bioactive compounds in the attenuation of GI symptomology, nor specifically in emerging substances such as menthol, ginger, polyphenols and probiotics, which have recently been proposed as potential adjuvants to the treatment of diagnosed GI diseases, due to their promising actions in the relief of symptoms and clinical remission. The mechanisms underlying these benefits are not yet clear, although they may come down to blocking calcium channels (12), inhibiting serotonergic 5-HT3/5-HT4 receptors (11), antioxidant action on free radicals (13) and modulating inflammatory gene expression (14).

Therefore, this study aims to review randomized controlled trials in humans assessing the effects of nutritional supplementation with bioactive compounds in GI disorders and explore whether it could be an effective complementation to consider to first-line pharmacological treatment.

METHODOLOGY

The construction of the search strategy was performed using database-specific subject headings and keywords in PubMed. The heading terms included combinations of "gastrointestinal diseases" with "menthol" or "peppermint" or "L-menthol" or "mint"; "gastrointestinal diseases" with "ginger" or "ginger oil" or "ginger extract" or "ginger root"; "gastrointestinal diseases" with "antioxidants" or "flavonoids" or "polyphenols" or "catechins"; and "gastrointestinal diseases" with "probiotics" or "*bifidobacterium*" or "*lactobacillus*" or "*escherichia coli*". Articles published up to November 2021, whose titles or abstracts included related topics or matters were included. This search strategy was complemented by manually searching for other references cited in these specific articles. Searches were limited to randomized controlled trials (RCT's) and clinical trials. Studies with the following criteria were eligible for inclusion: (1) studies of different bioactive compounds (menthol, ginger, polyphenols or probiotics) with impact on gastrointestinal symptomatology or induction of remission in gastrointestinal diseases; (2) subjects suffering from a diagnosed disease associated with the gastrointestinal tract; (3) participants >18 years old; (4) having a control group. All the references were exported to a citation management program, EndNote X20 and all the full texts were obtained.

Menthol

Peppermint oil (PO) (*Mentha piperitae aetheroleum*) is originated from the fresh leaves of peppermint (*Mentha piperita L.*) and followed by a steam distillation (15). It contains L-menthol which is known to have antagonistic properties responsible for interfering with the movement of calcium across the cell membrane, by blocking calcium channels in the smooth muscle, and therefore acting like an antispasmodic on the GI tract (12, 15-17). Other mechanisms of action include anti-inflammatory (12, 18), antimicrobial (12, 19) and carminative effects (12, 18, 20) as well as kappa opioid receptor agonism that can lead to an anaesthetic action (12, 18, 19). Thus, PO has been studied and evaluated as promising GI therapy treatment for several years now, especially in disorders such as IBS where intestinal spasms are frequent as well as persistent and antispasmodic properties can be useful at improving the patients' symptoms.

One of the first studies that examined the effect of this substance in a significant large group of people was a prospective, randomized double blinded clinical trial, conducted more than two decades ago by Liu *et al.*, in 110 Chinese IBS patients, for a period of 4 weeks (21). They compared the effects of an enteric- coated peppermint-oil formulation named *Colpermin* (a pH-dependent, enteric- coated, hard gelatine capsule that contains the active substance which is released in an intestinal pH of 6.8 or higher) (22) in an intervention group (IG) (one capsule with 187 mg of peppermint oil, three to four times a day, 15 to 30 min before the main meals) with a placebo group (PG) (one similar capsule containing an inert oil, with the same dose and timing). The authors observed a significant improvement of most symptoms of the disease in the IG, after 1 month, with better results 2 weeks into the treatment. The IG had a level of improvement of 79.0% and 83.0% on abdominal pain and distension, respectively, 83.0% on stool frequency derived from change of faecal consistency from liquid to soft or normal, 73.0% on bowel sounds and 79.0% on flatulence, meaning that the control of symptomatology was significantly more effective in the IG comparing to PG ($P<0.050$). However, no significant differences were found when it comes to the upper GI tract symptoms such as nausea, heartburn, acid reflux and belching.

In another 8-week *Colpermin* intervention, 90 participants that met the Rome II Criteria were randomized to two groups differing from the content of the capsules given 3 times daily before each meal. The IG had 187 mg of PO inside the pill and the placebo group had a similar placebo pill (23). Merat and colleagues found in the PO group, versus de PG, an increase in the number of patients free from any abdominal discomfort or pain (42.5% *vs*. 22.2%, respectively, $P<0.001$), as well

* In 1988, a group of experts met in Rome to debate about functional GI disorders and ended up defining criteria to more accurately diagnose diseases such FD and IBS. This culminated in the publication of the first Rome Criteria, in 1992 – Rome I Criteria. This set of guidelines helps to outline symptomatology and applies parameters such as frequency and duration, making it possible to establish a more accurate diagnose. The Rome Criteria are updated every 6 to 10 years, being the Rome IV Criteria the latest one.

as a greater reduction in the frequency and severity of persistent abdominal pain or discomfort (52.0% *vs*. 15.0%, P<0.001) and greater improvement in a general assessment of QOL (4.1 to 4.7 *vs*. 5.8 to 4.0, P< 0.016) from baseline until week 8 (23). Furthermore, the abdominal pain/discomfort outcome was also taken in consideration by Cappelo *et al.* (17), demonstrating that 225 mg of PO twice a day significantly lowered this symptoms' score at the end of the 4th week of intervention and persisted through the follow up period at week 8 (P<0.050). In subjects with moderate to severe non-constipated IBS (N=72), Cash *et al.* (18) observed a significant reduction in the IG, after 28 days of intervention, compared to the PG, in symptom scores for abdominal pain/discomfort (41.8% *vs*. 22.1%, respectively, P=0.049) and in the number of severe and unbearable symptoms (66.8% *vs*. 34.9%, respectively, P=0.028).

More recently, a randomized double-blind trial (N=189 patients diagnosed with IBS through Rome IV Criteria) aimed to evaluate, besides the effect of the active substance, if there was any difference between small intestine and ileocolonic- release PO. The results showed no significant difference between groups when it came to primary outcome measures (24). However, when talking about secondary outcomes small-intestinal PO release appeared to have a significantly better result for the abdominal pain parameter, after 8 weeks, compared to PG [-0.63 (- 1.14;0.12); P=0.016]. These changes didn't occur in the ileocolonic-release group (24).

Considering the literature reviewed, in a period range of 4 to 8 weeks, PO does have an interesting efficacy when it comes to abdominal pain and discomfort relief and therefore improvement of IBS patients' wellbeing. Nevertheless, more studies are warranted to assess its long-term efficacy and safety as a treatment for active IBS.

Ginger

Ginger (*Zingiber officinale*) is a herbal component that has been used to manage gastrointestinal symptomatology, such as nausea, vomiting and gastric hypomotility, in many health conditions (25-27). The exact mechanisms of action of ginger are not fully understood yet, but the inhibitory effect of gingerols and shogaols (ginger's chemical constituents) likely play a role in serotonergic 5- HT3/5-HT4 receptors (11, 28).

In a randomized double-blind study, ginger actions were evaluated in a sample of 11 patients diagnosed with FD based on Rome III Criteria. After an 8-hour fasting period, the IG who took 3 capsules containing 1.2 g of ginger root powder in total, followed by a 500 mL low nutrient soup (1 hour post capsule treatment) showed a higher frequency of antral contractions (P=0.060) and a quicker gastric emptying (Gastric half-emptying time:12.3 min *vs*. 16.1 min, respectively, P≤0.050), compared to placebo. Due to the small sample size and short duration of the intervention (two afternoons), no strong conclusions could be drawn (25).

Since ginger has been found to positively impact pain and gut motility, van Tilburg *et al.* conducted a 28-day pilot study to understand whether this could be an adjuvant strategy for the treatment of IBS. Forty-five subjects were randomized into 3 groups differing in capsule content and ginger dose (two IG with 1 gr and 2 gr of ginger, respectively, and one PG with brown sugar). The authors found no differences between groups and surprisingly observed a trend for improvement in IBS symptoms with placebo rather than ginger (reduction in symptoms: 34.8% *vs*. 26.4%, respectively; number of treatment responders: 57.1% *vs*. 46.7% with 1 gr ginger and 33.3% with 2 gr ginger, respectively; adequate relief: 53.3% in all groups) (29).

Ginger's treatment effects were not as pronounced as anticipated and no strong or cohesive evidence was found for its use neither in IBS nor FD, meaning that larger samples and higher doses of ginger may be needed to find any outcomes.

Polyphenols

Polyphenols, such as green tea polyphenol, resveratrol, quercetin and curcumin, are phytochemicals derived from plants (13). They have been suggested as a complement to the treatment of GI diseases that may be triggered and worsened by oxidative stress (OS) and excessive free radicals (13, 30, 31). The antioxidant, anti-inflammatory and immunomodulatory properties of polyphenols seem promising as an add-on treatment to first line therapy options (10, 13, 31).

More recently, curcumin, a natural active ingredient present in one of the most popular spices, turmeric (*Curcuma longa L.*), has called to attention due to its capacity to inhibit inflammatory pathways, especially nuclear factor kappa B (NF-kB) (7, 10, 32-34). In 2021, Banerjee *et al.* investigated a new proposed form of bioenhanced curcumin (BEC), through an innovative delivery system, with seemingly higher solubility and consequently bioavailability (35). Sixty-nine mild to moderately UC patients were recruited to this randomized double-blind placebo-controlled trial, where 34 of them received 50 mg of BEC twice a day along with mesalamine, a 5-aminosalicylate (5 ASA), and the other 35 were given a placebo with 5 ASA, as well. The patients in the BEC arm showed a much higher induction of clinical and endoscopic remission compared to placebo (55.9% *vs*. 5.7%, respectively and 44.0% *vs*. 5.7%, respectively) (35). Lang *et al.* studied 50 patients again suffering from mild to moderate UC who got 3 g/day of curcumin in capsules administered with 5 ASA or an identical placebo with 5 ASA. Of all patients in the IG, 54.0% achieved clinical remission and 36.0% endoscopic remission, unlike those in the placebo group where no changes happened (0.0%) (36). Singla *et al.* also found a higher clinical remission rate in patients taking a curcumin enema (74.0%), comparing to PG (0.0%) (32). Lastly, in an 8-week randomized double-blind controlled trial, 41 patients with mild to moderate UC were allocated to two groups, where the authors studied a low oral dose of curcumin (450 mg/daily) as a complementary treatment to the already established first line 5-ASA therapy (33). No significant differences were found between the IG and PG, therefore demonstrating that higher doses of curcumin may be required for optimal results and efficacy, when no advanced drug delivery system is used (33).

Resveratrol is also a naturally occurring polyphenol that can be found in foods like grapes, blueberries, pomegranates and peanuts and has been popular for its pharmacological anti-inflammatory and antioxidant properties (7, 13, 31, 37, 38). A few of its' targets are referred to occur on cyclooxygenase (COX), 5- lipoxygenase (5-LOX) an also protein kinase B, and therefore inhibiting COX-1 and COX-2 activity, as well as transcription factors (38).

A 2016 randomized double-blind controlled trial, performed in 56 patients with active UC, aimed to evaluate whether this nutrient could help in the treatment of the disease (37). Half of the group got 500 mg of resveratrol per day, while the other received a placebo with Medium-chain triglycerides. Patients in the IG showed a significant reduction in serum levels of malondialdehyde, a biomarker that portraits the levels of OS, and a in the activity of the disease, assessed by the Simple Clinical Colitis Activity Index Questionnaire, which revealed a better QOL score (P<0.001) (37).

Epigallocatechin gallate (EGCG) is the component with most clinical relevance in green tea (10, 13, 39-41). These polyphenols from the catechin family may contribute positively to lower the incidence of inflammation and OS, thus lowering the symptoms of IBD (13, 39, 41) through regulation of inflammatory signalling pathways, including NF-kB and mitogen-activated protein kinases (MAPKs) (41). A pilot

ACTA PORTUGUESA DE NUTRIÇÃO 32 (2023) 60-65 | LICENÇA: cc-by-nc | http://dx.doi.org/10.21011/apn.2023.3210
ASSOCIAÇÃO PORTUGUESA DE NUTRIÇÃO® | WWW.ACTAPORTUGUESADENUTRICAO.PT | ACTAPORTUGUESADENUTRICAO@APN.ORG.PT

trial conducted by Dryden and colleagues concluded that patients with UC who ingested 200 mg and 400 mg of commercial EGCG (*Polyphenon E*), respectively, for 56 days, experienced positive outcome, more than the placebo did, when it came to response rates (66.7% *vs*. 0.0%, respectively; P=0.030), remission rates (53.3% and 0.0%, respectively; P=0.100), QOL and endoscopic response (39). That being said, these positive results must be interpretated with caution, since the sample size can be perceived as a limitation (N=20).
All things considered, the literature suggests that polyphenols such as curcumin, as a complementary therapy with optimized 5-ASA, and resveratrol may present a safe and effective therapy by not only inducing clinical remission but also maintaining it, as well as reducing disease activity and improving QOL among UC patients.

Probiotics

According to the World Health Organization and The Food and Agriculture Organization's most recent definition, probiotics are "live microorganisms which when administered in adequate amounts, confer a health benefit in the host" (42). The most commonly used probiotic species are the Gram- positive *Lactobacillus* and *Bifidobacterium*, as well as some Gram-negative bacteria, such as *E.coli* Nissle 1917 (7, 14, 43). Probiotic supplements have been widely investigated for their numerous benefits, and although several mechanisms have been proposed to explain how they may exert significant improvements in some GI diseases, the exact reasons are not fully understood yet (14, 42). Nonetheless, they may present an advantage to diseases characterized by gut barrier alterations, immune dysfunction and dysbiosis leading to low-grade inflammation of the gut, thus standing as a promising adjuvant to their treatment by limiting growth and colonization of pathogenic bacteria, improving epithelial barrier function and modulating the host inflammatory gene expression and immune responses (7, 14, 43-45).
Recently, Preston *et al*. published a double-blind, randomized, placebo-controlled study where a combination of three strains of Lactobacillus was compared to placebo for relief of IBS symptomatology and improvement in QOL for 12 weeks, in a population of 113 patients with various IBS subtypes (IBS-C, IBS- D and IBS-M) (46). The patients in the IG were given 2 capsules containing a minimum of 50×109 colony forming units (CFU) (*L. acidophilus* CL1285, *L. casei* LBC80R and *L. rhamnosus* CLR2), every day at breakfast. They found probiotics to be better than placebo in relieving symptoms and improving QOL (mean differences of 30.0% or more in favour of the active treatment), particularly in female patients with the IBS-D subtype (46). In the same year, another probiotic study conducted by Sun *et al.* among 200 participants diagnosed with IBS-D subtype, as per the Rome III Criteria, used *Clostridium butyricum* capsules (420 mg *per* capsule, 1.5x107 CFU/g) to assess its efficacy and safety. Patients and researchers were both blinded to the probiotic or placebo condition and all patients took 3 capsules 3 times/day for 4 weeks. A significant reduction, from baseline to week 4, of the IBS symptom severity scale (-62.12 ± 74.00; P= 0.038) was observed in the IG, indicating an improvement of IBS-D symptoms, as well as a positive change of the QOL score (7.23 ± 14.06; P=0.032) (47). In contrast, Hod *et al.* did not find a superior outcome vs the placebo when using a multispecies probiotic combination (BIO-25) in a population of 107 women suffering from IBS-D (48). No significant differences with respect to pain intensity (P=0.068) and stool consistency (P=0.423) were observed between groups. In fact, when the variables abdominal pain and bloating were adjusted to time, they surprisingly improved in the placebo group compared to the probiotic one (48). Two RCTs by Mezzasalam *et al.* (49) and Yoon *et al.* (50) found multispecies probiotics to have more beneficial effects in IBS patients than the placebo, regarding an adequate symptom relief and enhancing the gut tract with the probiotic strains ingested, with the exception of *Bifidobacterium species*.
Among patients with UC, which often suffer from symptoms of rectal bleeding, Matthes *et al.* (51) and Tursi *et al.* (52) found an improvement of this parameter in all treatment groups vs placebo, with only Tursi et al study reaching statistical significance (P=0.014) (52).
Based on the rundown of studies mentioned above, probiotics have shown promising positive results regarding symptomatology, QOL and stool frequency/consistency in IBS patients, and rectal bleeding in UC patients.

CRITICAL ANALYSIS

Understanding the potential medical and health benefits of implementing nutraceuticals represents a new challenge in nutrition that requires a careful and well-studied approach. This narrative review is in agreement with prior findings disclosing that menthol, polyphenols and probiotics may be considered a worthwhile treatment option for the management of GI diseases' symptomatology, whereas further studies are relevant to dictate if ginger can be a convenient therapeutic approach. Nevertheless, a clear need exists for larger sample sizes studies to investigate the safety profile and efficacy concerning the previously mentioned bioactive compounds, given that a few AE were observed (specially with PO), although they were mild and transient and therefore indicating a rather good tolerability. Longer treatment periods should also be carried out since there is little evidence for long term benefits after discontinuing these substances, particularly conditions such as IBS that is per definition a chronic and intermittent disease. Besides that, all patients involved in IBS clinical trials, apart from Liu *et al.*, had to meet the Rome Diagnostic Criteria to be eligible, however different criteria were applied through the trials (Rome II, III and IV Criteria), making it hard to determine menthol's true outcomes since IBS diagnose became more specific through all Rome updates. Furthermore, a large placebo effect is characteristic from IBS clinical trials regarding subjective outcomes measures and its range can go up to 40.0% (53), turning it difficult to show, in some cases, a superior clinical efficacy for any agent over placebo. Thus, strategies to minimize the placebo response must be taken into consideration when designing a clinical trial with IBS participants. Regarding UC, all interventions with either polyphenols or probiotics, were conducted in patients with mild to moderate disease activity, excluding the possibility to see results in patients suffering from severe disease, which would be interesting and pertinent in future investigations, along with specifying interventions even more by focusing on probiotic strain, type and dose in order to tailor particular microorganisms to the patient as an individual and potentially isolate each polyphenol's metabolite, stabilize them and test if any favourable effect is reflected. Taking everything into consideration, nutraceuticals should not be ignored as an adjuvant option in the management of GI diseases in everyday practice, however, regardless of the substance, there is for sure still a long way to go before establishing clear and safe considerations about their use and implementation, and if so, it must be done with the guidance of a healthcare professional.

CONCLUSIONS

In conclusion, literature describing the possible effects of nutritional supplementation as an adjuvant in the management of GI diseases is in its early stages. Nonetheless, there is an increasing number of clinical trials and publications demonstrating the benefit of using these

substances, in clinical practice, as an add-on therapy to decrease symptomatology inherent to IBS, FD and UC, and improve patient QOL. Reviewed evidence suggests, while PO, polyphenols and probiotics can have a leading role in the management of GI, ginger did not meet the expected outcomes for its' role in the upper GI tract, and thus more robust investigation should be taken, specifically in this population. Further studies should be conducted focusing on the safety profile and effects of longer treatment periods, and research should also be undertaken to determine the most adequate dose of each compound before any definitive nutritional recommendations can be drawn for patients suffering from GI diseases.

CONFLICTS OF INTEREST

None of the authors reported a conflict of interest.

AUTHORS' CONTRIBUTIONS

BGB, RG and MR: Conceptualization; BGB: Search methodology, article reading and selection; BGB: Writing; BGB, RG and MR: Review and editing; All authors have read and agreed to the published version of the article.

REFERENCES

1. Gao X, Liu J, Li L, Liu W, Sun M. A Brief Review of Nutraceutical Ingredients in Gastrointestinal Disorders: Evidence and Suggestions. Int J Mol Sci. 2020; 21(5).

2. Sperber AD, Bangdiwala SI, Drossman DA, Ghoshal UC, Simren M, Tack J, et al. Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. Gastroenterology. 2021; 160(1):99- 114.e3.

3. Lacy BE, Patel NK. Rome Criteria and a Diagnostic Approach to Irritable Bowel Syndrome. J Clin Med. 2017; 6(11).

4. Black CJ, Drossman DA, Talley NJ, Ruddy J, Ford AC. Functional gastrointestinal disorders: advances in understanding and management. Lancet. 2020; 396(10263):1664-74.

5. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017; 390(10114):2769-78.

6. Dore MP, Rocchi C, Longo NP, Scanu AM, Vidili G, Padedda F, et al. Effect of Probiotic Use on Adverse Events in Adult Patients with Inflammatory Bowel Disease: a Retrospective Cohort Study. Probiotics Antimicrob Proteins. 2020; 12(1):152-59.

7. Malinowski B, Wiciński M, Sokołowska MM, Hill NA, Szambelan M. The Rundown of Dietary Supplements and Their Effects on Inflammatory Bowel Disease-A Review. Nutrients. 2020; 12(5).

8. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2020; 5(1):17-30.

9. Zhang Y, Li L, Guo C, Mu D, Feng B, Zuo X, et al. Effects of probiotic type, dose and treatment duration on irritable bowel syndrome diagnosed by Rome III criteria: a meta-analysis. BMC Gastroenterol. 2016; 16(1):62.

10. Yang N, Sampathkumar K, Loo SCJ. Recent advances in complementary and replacement therapy with nutraceuticals in combating gastrointestinal illnesses. Clin Nutr. 2017; 36(4):968-79.

11. Nikkhah Bodagh M, Maleki I, Hekmatdoost A. Ginger in gastrointestinal disorders: A systematic review of clinical trials. Food Sci Nutr. 2019; 7(1):96-108.

12. Alammar N, Wang L, Saberi B, Nanavati J, Holtmann G, Shinohara RT, et al. The impact of peppermint oil on the irritable bowel syndrome: a meta-analysis of the pooled clinical data. BMC Complement Altern Med. 2019; 19(1):21.

13. Chiu HF, Venkatakrishnan K, Golovinskaia O, Wang CK. Gastroprotective Effects of Polyphenols against Various Gastro-Intestinal Disorders: A Mini-Review with Special Focus on Clinical Evidence. Molecules. 2021; 26(7).

14. Cremon C, Barbaro MR, Ventura M, Barbara G. Pre- and probiotic overview. Curr Opin Pharmacol. 2018; 43:87-92.

15. Grigoleit HG, Grigoleit P. Gastrointestinal clinical pharmacology of peppermint oil. Phytomedicine. 2005; 12(8):607-11.

16. Cappello G, Spezzaferro M, Grossi L, Manzoli L, Marzio L. Peppermint oil (Mintoil) in the treatment of irritable bowel syndrome: a prospective double blind placebo-controlled randomized trial. Dig Liver Dis. 2007; 39(6):530-6.

17. Cash BD, Epstein MS, Shah SM. A Novel Delivery System of Peppermint Oil Is an Effective Therapy for Irritable Bowel Syndrome Symptoms. Dig Dis Sci. 2016; 61(2):560-71.

18. Mosaffa-Jahromi M, Lankarani KB, Pasalar M, Afsharypuor S, Tamaddon AM. Efficacy and safety of enteric coated capsules of anise oil to treat irritable bowel syndrome. J Ethnopharmacol. 2016; 194:937-46.

19. Khanna R, MacDonald JK, Levesque BG. Peppermint oil for the treatment of irritable bowel syndrome: a systematic review and meta-analysis. J Clin Gastroenterol. 2014; 48(6):505-12.

20. Liu JH, Chen GH, Yeh HZ, Huang CK, Poon SK. Enteric-coated peppermint- oil capsules in the treatment of irritable bowel syndrome: a prospective, randomized trial. J Gastroenterol. 1997; 32(6):765-8.

21. Somerville KW, Richmond CR, Bell GD. Delayed release peppermint oil capsules (Colpermin) for the spastic colon syndrome: a pharmacokinetic study. Br J Clin Pharmacol. 1984; 18(4):638-40.

22. Merat S, Khalili S, Mostajabi P, Ghorbani A, Ansari R, Malekzadeh R. The effect of enteric-coated, delayed-release peppermint oil on irritable bowel syndrome. Dig Dis Sci. 2010; 55(5):1385-90.

23. Weerts Z, Masclee AAM, Witteman BJM, Clemens CHM, Winkens B, Brouwers J, et al. Efficacy and Safety of Peppermint Oil in a Randomized, Double-Blind Trial of Patients With Irritable Bowel Syndrome. Gastroenterology. 2020; 158(1):123- 36.

24. Hu ML, Rayner CK, Wu KL, Chuah SK, Tai WC, Chou YP, et al. Effect of ginger on gastric motility and symptoms of functional dyspepsia. World J Gastroenterol. 2011; 17(1):105-10.

25. Sahib AS. Treatment of irritable bowel syndrome using a selected herbal combination of Iraqi folk medicines. J Ethnopharmacol. 2013; 148(3):1008-12.

26. Giacosa A, Morazzoni P, Bombardelli E, Riva A, Bianchi Porro G, Rondanelli M. Can nausea and vomiting be treated with ginger extract? Eur Rev Med Pharmacol Sci. 2015; 19(7):1291-6.

27. Marx W, Kiss N, Isenring L. Is ginger beneficial for nausea and vomiting? An update of the literature. Curr Opin Support Palliat Care. 2015; 9(2):189-95.

28. van Tilburg MA, Palsson OS, Ringel Y, Whitehead WE. Is ginger effective for the treatment of irritable bowel syndrome? A double blind randomized controlled pilot trial. Complement Ther Med. 2014; 22(1):17-20.

29. Sies H. Oxidative stress: oxidants and antioxidants. Exp Physiol. 1997; 82(2):291-5.

30. Khan I, Samson SE, Grover AK. Antioxidant Supplements and Gastrointestinal Diseases: A Critical Appraisal. Med Princ Pract. 2017; 26(3):201- 17.

31. Singla V, Pratap Mouli V, Garg SK, Rai T, Choudhury BN, Verma P, et al. Induction with NCB-02 (curcumin) enema for mild-to-moderate distal ulcerative colitis - a randomized, placebo-controlled, pilot study. J Crohns Colitis. 2014; 8(3):208-14.

32. Kedia S, Bhatia V, Thareja S, Garg S, Mouli VP, Bopanna S, et al. Low dose oral curcumin is not effective in induction of remission in mild to moderate ulcerative colitis: Results from a randomized double blind placebo controlled trial. World J Gastrointest Pharmacol Ther. 2017; 8(2):147-54.

33. Mantzorou M, Pavlidou E, Vasios G, Tsagalioti E, Giaginis C. Effects of curcumin consumption on human chronic diseases: A narrative review of the most recent clinical data. Phytother Res. 2018; 32(6):957-75.

34. Banerjee R, Pal P, Penmetsa A, Kathi P, Girish G, Goren I, et al. Novel Bioenhanced Curcumin With Mesalamine for Induction of Clinical and Endoscopic Remission in Mild-to-Moderate Ulcerative Colitis: A Randomized Double-Blind Placebo-controlled Pilot Study. J Clin Gastroenterol. 2021; 55(8):702-08.

35. Lang A, Salomon N, Wu JC, Kopylov U, Lahat A, Har-Noy O, et al. Curcumin in Combination With Mesalamine Induces Remission in Patients With Mild-to- Moderate Ulcerative Colitis in a Randomized Controlled Trial. Clin Gastroenterol Hepatol. 2015; 13(8):1444-9.e1.

36. Samsamikor M, Daryani NE, Asl PR, Hekmatdoost A. Resveratrol Supplementation and Oxidative/Anti-Oxidative Status in Patients with Ulcerative Colitis: A Randomized,

ACTA PORTUGUESA DE NUTRIÇÃO 32 (2023) 60-65 | LICENÇA: cc-by-nc | http://dx.doi.org/10.21011/apn.2023.3210
ASSOCIAÇÃO PORTUGUESA DE NUTRIÇÃO® | WWW.ACTAPORTUGUESADENUTRICAO.PT | ACTAPORTUGUESADENUTRICAO@APN.ORG.PT

Double-Blind, Placebo-controlled Pilot Study. Arch Med Res. 2016; 47(4):304-9.
37. Salehi B, Mishra AP, Nigam M, Sener B, Kilic M, Sharifi-Rad M, et al. Resveratrol: A Double-Edged Sword in Health Benefits. Biomedicines. 2018; 6(3).
38. Dryden GW, Lam A, Beatty K, Qazzaz HH, McClain CJ. A pilot study to evaluate the safety and efficacy of an oral dose of (-)-epigallocatechin-3-gallate- rich polyphenon E in patients with mild to moderate ulcerative colitis. Inflamm Bowel Dis. 2013; 19(9):1904-12.
39. Afzal M, Safer AM, Menon M. Green tea polyphenols and their potential role in health and disease. Inflammopharmacology. 2015; 23(4):151-61.
40. Fan FY, Sang LX, Jiang M. Catechins and Their Therapeutic Benefits to Inflammatory Bowel Disease. Molecules. 2017; 22(3).
41. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014; 11(8):506-14.
42. Ooi SL, Correa D, Pak SC. Probiotics, prebiotics, and low FODMAP diet for irritable bowel syndrome - What is the current evidence? Complement Ther Med. 2019; 43:73-80.
43. Fujiya M, Ueno N, Kohgo Y. Probiotic treatments for induction and maintenance of remission in inflammatory bowel diseases: a meta-analysis of randomized controlled trials. Clin J Gastroenterol. 2014; 7(1):1-13.
44. Li B, Liang L, Deng H, Guo J, Shu H, Zhang L. Efficacy and Safety of Probiotics in Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis. Front Pharmacol. 2020; 11:332.
45. Preston K, Krumian R, Hattner J, de Montigny D, Stewart M, Gaddam S. Lactobacillus acidophilus CL1285, Lactobacillus casei LBC80R and Lactobacillus rhamnosus CLR2 improve quality-of-life and IBS symptoms: a double-blind, randomized, placebo-controlled study. Benef Microbes. 2018;9(5):697-706.
46. Sun YY, Li M, Li YY, Li LX, Zhai WZ, Wang P, et al. The effect of Clostridium butyricum on symptoms and fecal microbiota in diarrhea-dominant irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. Sci Rep. 2018; 8(1):2964.
47. Hod K, Sperber AD, Ron Y, Boaz M, Dickman R, Berliner S, et al. A double- blind, placebo-controlled study to assess the effect of a probiotic mixture on symptoms and inflammatory markers in women with diarrhea-predominant IBS. Neurogastroenterol Motil. 2017; 29(7).
48. Mezzasalma V, Manfrini E, Ferri E, Sandionigi A, La Ferla B, Schiano I, et al. A Randomized, Double-Blind, Placebo-Controlled Trial: The Efficacy of Multispecies Probiotic Supplementation in Alleviating Symptoms of Irritable Bowel Syndrome Associated with Constipation. Biomed Res Int. 2016; 2016:4740907.
49. Yoon H, Park YS, Lee DH, Seo JG, Shin CM, Kim N. Effect of administering a multi-species probiotic mixture on the changes in fecal microbiota and symptoms of irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. J Clin Biochem Nutr. 2015; 57(2):129-34.
50. Matthes H, Krummenerl T, Giensch M, Wolff C, Schulze J. Clinical trial: probiotic treatment of acute distal ulcerative colitis with rectally administered Escherichia coli Nissle 1917 (EcN). BMC Complement Altern Med. 2010; 10:13.
51. Tursi A, Brandimarte G, Papa A, Giglio A, Elisei W, Giorgetti GM, et al. Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. Am J Gastroenterol. 2010; 105(10):2218- 27.
52. Shah ED. Optimising clinical trial design to manage placebo response in randomised controlled trials of irritable bowel syndrome. Lancet Gastroenterol Hepatol.2021;6(6):416-17.