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THERAPEUTIC STRATEGIES FOR MODULATION OF THE MICROBIOTA IN MIGRAINE CONTROL: AN INTEGRATIVE LITERATURE REVIEW

ESTRATÉGIAS TERAPÊUTICAS DE MODULAÇÃO DA MICROBIOTA NO CONTROLE DA ENXAQUECA: UMA REVISÃO INTEGRATIVA DA LITERATURA

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Abstract: Migraine is the third cause of disability in humans under 50 years of age. The gut microbiota has been identified as an influential factor in the brain-gut axis and in abnormalities related to neurological diseases such as migraine. The present study aimed to verify a possible relationship between microbiota composition and probiotic

supplementation in migraine patients, as well as its effects on the aforementioned pathology. This is an integrative review that gathers information to deepen the proposed theme. To this end, 20 articles were selected, including meta-analyses and reviews. The results found in the literature were inconclusive regarding the use of probiotics as a therapeutic or preventive approach for migraine. On the other hand, a human study demonstrated that short-chain fatty acids (SCFA) resulted in less hyperalgesia caused by nitroglycerin, in addition to reducing inflammatory cytokines. It has also been seen that the use of these SCFAs resulted in an alteration of the composition of the microbiota. Studies with Gastrodia-Uncaria, vitamin D3 and, tryptophan resulted in a greater diversity of the gut microbiome. In the case of H. pylori, the literature indicates positive results in the symptomatology of migraine when these microorganisms were eradicated. The findings of this study demonstrate that there are differences between the microbiota of patients with and without migraine. After the literature analysis, it was noted that the migraine group has a less diverse intestinal microbiota. Modulation of the gut microbiota could be considered as a potential therapeutic or preventive target for individuals affected with migraine, and further studies are needed to evaluate this possibility.

Keywords: Migrane, Probiotics; Short-Chain Fatty Acids; Helicobacter Pylori

Resumo: A enxaqueca é a terceira causa de incapacidade em humanos abaixo de 50 anos de idade. A microbiota intestinal tem sido apontada como fator influente no eixo cérebro-intestino e em anormalidades relacionadas às doenças neurológicas, como a enxaqueca. O objetivo do presente estudo foi verificar uma possível relação entre composição da microbiota e a suplementação de probióticos em portadores de enxaqueca, bem como seus efeitos na patologia citada. Esta é uma revisão integrativa que reúne informações para aprofundamento no tema proposto. Para tal, foram selecionados 20 artigos, incluindo metanálises e revisões. Os resultados encontrados na literatura apresentaram-se inconclusivos com relação ao uso de probióticos como abordagem terapêutica ou preventiva para a enxaqueca. Por outro lado, um estudo em humanos demonstrou que ácidos graxos de cadeia curta (AGCC), resultaram em menor hiperalgesia provocada pela nitroglicerina, além de reduzir citocinas inflamatórias. Também foi visto que o uso desses AGCC resultou em alteração da composição da microbiota. Estudos com Gastrodia-Uncaria, vitamina D3 e triptofano, resultaram em maior diversidade do microbioma intestinal. No caso do *H. pylori*,a literatura aponta resultados positivos na sintomatologia da enxaqueca quando esses microrganismos foram erradicados. Os achados deste estudo demonstram existir diferenças entre a microbiota de pacientes com e sem enxaqueca. Após a análise bibliográfica notou-se que o grupo enxaqueca possui uma microbiota intestinal menos diversa. A modulação da microbiota intestinal poderia ser considerada como um alvo terapêutico ou preventivo potencial para os indivíduos acometidos com enxaqueca, e estudos posteriores são necessários para avaliar essa possibilidade.

Palavras chaves: Enxaqueca**,** Probióticos; Ácidos Graxos de Cadeia Curta; Helicobacter Pylori

Introduction

In Brazil, about R$ 37.5 billion of expenses per year are due to migraine (PERES et al., 2019). These economic losses occur due to the lost days of work as a result of the disability caused by the pathology, which is the main cause of absenteeism due to headaches. Souza (2021) points out that in Brazil there is no public policy directed to the monitoring of this pathology, which can generate losses in the integral care of the single health system.

The symptoms of the disease include frequent headaches that can last from 4 to 72 hours and that have as characteristic, in most cases, unilateral pulsatile pain that may be accompanied by other symptoms such as nausea and vomiting, sensitivity to light and/or noise (DE ROOS et al., 2017). Currently, the treatment for migraine consists of medications for pain relief, which include anti-inflammatories, analgesics, triptans, and prophylactic medications that can be beta-adrenergic blockers, calcium channel blockers, antidepressants, and anticonvulsants (MIGRAINE, 2019). The pathophysiology of this disease has not yet been completely unraveled. However, studies suggest that it comes from a complex neurological disorder (DE ROOS et al., 2017).

One of the mechanisms that may relate to the development of migraine is the brain-gut axis (ARZANI et al., 2020). Both the brain is responsible for regulating peristalsis and secretion in the gastrointestinal system, and the gastrointestinal system can influence brain functions such as cognition and behavior.

Studies show the relationship between migraine and manifestations associated with changes in the gastrointestinal system such as constipation, diarrhea, dyspepsia, gastroesophageal reflux, irritable bowel syndrome, celiac disease, changes in the gut microbiota, gastroparesis, and gastric stasis (HINDIYEH; AURORA, 2015; CÁMARA-LEMARROY et al., 2016). On the other side, the imbalance of the brain-gut axis can influence other neurological conditions including multiple sclerosis, Alzheimer's, Parkinson's, anxiety, and migraine itself (ARZANI et al., 2020; HINDIYEH; AURORA, 2015). However, there is little information available on the relief of migraine symptoms or prevention through modulation of the intestinal flora.

The dietary pattern can alter the variety and proportion of the species that make up the intestinal flora (SLAVIN et al., 2019). In addition, the administration of probiotics, either in supplements or composing the food itself, in the correct amount, can bring benefits to the health of the host (SLAVIN et al., 2019).

One term that has been used is nutraceutical. This term has not yet been defined by law in the U.S. and is not yet recognized by Anvisa. However, the term can be understood as a product coming from a food or part of it, which has undergone a purification process and which possibly results in benefits beyond the nutritional (RONIS; PEDERSEN; WATT).

The current work sought to review scientific pieces of evidence regarding the potential effects of gut microbiota modulation by complementary therapies on migraine.

Methods

This study consists of an integrative review in which we sought to gather information that would provide a basis for deepening the proposed theme. The PubMed.gov database was chosen, and the research was conducted between July 4 and August 23, 2022. Initially, 14 articles from the years 2020, 2021, and 2022 were selected, using, concomitantly, keywords such as: "gut microbiota", "composition", and "migraine". These articles were selected through the analysis of the search tool that used the relevant words "migraine" and "microbiota" or "microbiome". The organization chart below presents the model for selecting the articles.

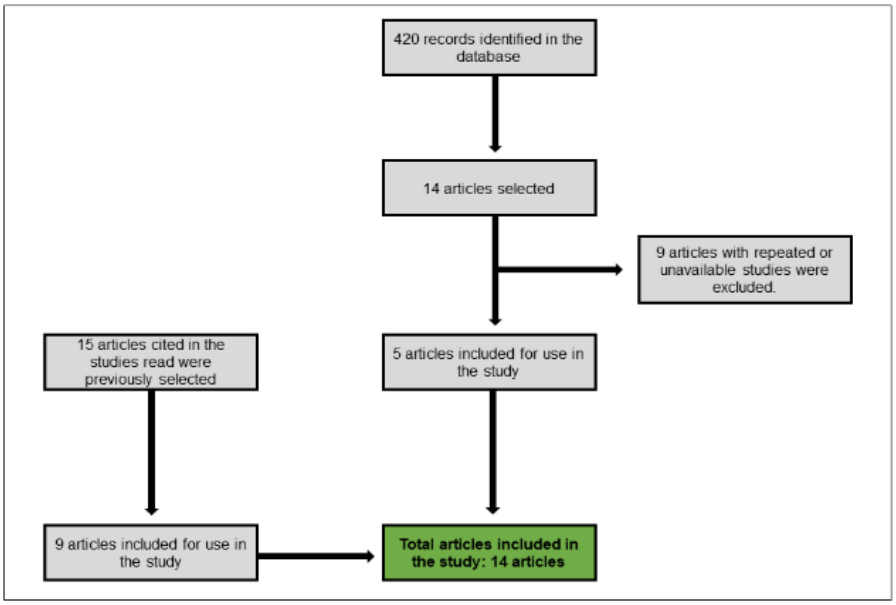

Figure 1: Organization chart of article selection.

Results and Discussion

Tables 1 and 2 summarize the main data related to the objective of this literature review. It is possible to observe that the studies were diversified into experimental studies with animals (Table 1) and clinical studies in humans (Table 2). However, all studies had as their central objective the search for an association between the gut microbiota and migraine.

Table 1: A literature review on microbiota and migraine experimental animal trials.

Article title	Model/ Audience Specifications	Intervention	Effect
Gut Microbiota Dysbiosis Enhances Migraine-Like Pain Via TNFα Upregulation (TANG et al., 2020)	Rats – migraine induced with NTG. Male C57BL/6 wild-type (WT) mice, germ-free (GF) mice, and TNFα knockout (KO) mice.	Treatment with a high-spectrum antibiotic for 10 days. Probiotic treatment for 10 days.	Prolongation of facial mechanical hypersensitivity; increased expression of tumor necrosis factor alpha (TNFα) in the caudalis spinal trigeminal nucleus. It reversed the effect caused by antibiotic treatment. However, probiotic treatment alone

			did not influence the pain threshold.
		Microbiota deprivation. Fecal microbiota transplantation (fecal paste obtained from wild mice free of specific pathogens).	Drastic prolongation of pain due to migraine. Significant pain backsliding.
Metabolomics and 16s rRNA gene sequencing analyses of changes in the intestinal flora and biomarkers induced by Gastrodia-Uncaria treatment in a rat model of chronic migraine. (WEN et al., 2019)	Rats – migraine induced with NTG. Sprague-Dawley females free of specific pathogens. Weight: 220 ± 20 g.	Chronic administration of nitroglycerin (10 mg/kg, i.p.).	Alteration of 30 species of bacteria: increase of Prevotella; decrease in Coprococcus Reduction of *Firmicutes* and increase of *Bacteroides.*
		Administration of Gastrodia elata Blume and Uncaria rhynchophylla (4 g/Kg/d), for 10 days, together with nitroglycerin.	Recovery of bacteria near control animal levels, as well as obtaining pain relief similar to sumatriptan treatment.
SCFA (short-chain fatty acids) treatment alleviates pathological signs of migraine and related intestinal alterations in a mouse model of ntg-induced migraine. (LANZA et al., 2021)	Rats – migraine induced with NTG. CD1 adult mice (females, 25 to 30 g).	Administration of SCFAs from *Bacteroidetes* and *Firmicutes.*	Reduction of hyperalgesia caused by nitroglycerin; decreased release of pro-inflammatory cytokines TNFα and IL1-β in the gut after injection of NTG. Results were seen with 30 mg/kg, and 100 mg/kg of SCFA. The 10 mg/kg test did not show the same result.
Supplementation with SCFAs Re-Establishes Microbiota Composition and Attenuates Hyperalgesia and	Rats – migraine induced with NTG. CD1 adult mice (females, weighing between 25 and 30 g).	Group treated with NTG.	Bacteroidetes filo mais abundante, seguido pelo Firmicutes; maior proporção de dois gêneros, Bacteroidetes e Muribaculum, e

Pain in a Mouse Model of NTG-Induced Migraine (LANZA et al., 2022)			Prevotella; maior proporção de Alistipes.
		Effect of SP (sodium propionate), SB (sodium butyrate), and sumatriptan (600 µg/kg). Dosages studied: 10, 30 and 100 mg/kg.	Highest ratio Firmicutes/Bacteroidetes; higher species richness Lactobacillus, being the most abundant genus (protective role against inflammatory diseases), except in the dosage of 100 mg/kg; Bifidobacterium showed a relationship with this group; Firmicutes major phylum.

Table 2: Review of the literature on microbiota and migraine clinical trials in humans.

Article title	Model/ Audience Specifications	Intervention	Effect
The effects of a multispecies probiotic on migraine and markers of intestinal permeability– results of a randomized placebo-controlled study (DE ROOS et al., 2017)	63 patients with migraine, 32 received a placebo and 31 received probiotics. Age: greater than or equal to 18 years.	The control group received a placebo and a group was treated with probiotics for 3 months.	There was no benefit from the probiotic group compared to the placebo group.

The effects of a multispecies probiotic supplement on inflammatory markers and episodic and chronic migraine characteristics: A randomized double-blind controlled trial (MARTAMI et al., 2019)	Double-blind study with 40 episodic patients and 39 with chronic migraine. Age: 18 to 60 years.	Use of probiotics for 8 and 10 weeks (chronic and sporadic migraines, respectively).	Improvement in frequency and severity, as well as lower use of abortive medications, were observed in the probiotic group when compared to the placebo group.
Beneficial effects of Helicobacter pylori eradication on migraine: a 12-month follow-up study (GABRIELLI et al., 2001)	148 patients with migraine, of which 62 were infected with H. Pylori. Age: 45±8 years	H.Pylori eradication	After 6 months of eradication, the patients showed significant improvement in intensity, duration, and frequency, and 25% of the cases did not present more migraine.
Evaluation of Helicobacter pylori infection in patients with common migraine headache (HOSSEINZADEH et al., 2011)	70 patients diagnosed with migraine and 70 considered control (healthy). Age: 17 to 52 years.	Evaluation of IgG and IgM for H. pylori.	H. pylori infection is strongly related to migraine.
Effects of high doses of vitamin D3 on mucosa-associated gut microbiome vary between regions of the human gastrointestinal tract (BASHIR et al., 2016)	16 volunteers (7 women and 9 men). Age: 18 to 40 years. BMI between 20 and 30 kg/m2.	Vitamin D3 supplementation in healthy adults for 8 weeks.	Decrease of Helicobacter sp. nov. In the microbiota, in addition to lower frequency and lower severity of migraine.

BMI, Alcohol Consumption, and Gut Microbiome Species Richness Are Related to Structural and Functional Neurological Abnormalities (GEISLER et al., 2021)	238 patients suffering from (1) structural neurological abnormalities and 612 healthy controls.	They were analyzed by a validated food frequency questionnaire (FFQ) for 12 months and 16S rRNA microbiome sequencing (from stool samples).	The lower richness and lower Shannon index in the chronic pain group (which includes migraine) when compared to the reference group. In addition, the chronic pain group showed a higher distribution of species (evenness).
The effects of the multispecies probiotic mixture Ecologic®Barrier on migraine: results of an open-label pilot study (DE ROOS et al., 2015)	27 adults who met the International criteria Headache Classification (ICHD-II) and had 4 or more migraine attacks per month. There was no control group. Greater than or equal to 18 years.	2 g probiotic (Ecologic®Barrier, for 12 weeks, containing: Bifidobacterium bifidum W23, B. lactis W52, Lactobacillus acidophilus W37, L. brevis W63, L. casei W56, L. salivarius W24, Lactococcus lactis W19 and Lactococcus lactis W58.	It decreased the frequency (by 25%), the disability related to migraine, and the impact and severity of migraine.
The Effect of Helicobacter Pylori Eradication on Migraine: A Randomized, Double-Blind, Controlled Trial FARAJI, et al., 2012	Treatment group: 32 (25 M and 7 H), aged = 44.6 ± 8.8 years; Control group (placebo): 32 (22M and 10 H), aged = 43.8 ± 13.8 years. A Randomized double-blind study.	-	Patients in the treatment group (PH eradication) had a lower level of migraine-related disability compared to those in the control group.
Structural and Functional Characterization of the Gut Microbiota in Elderly Women With Migraine (CHEN et al., 2020)	108 elderly women: 54 healthy and 54 with migraine, with matched age and BMI.	Characterization of the microbiota through fecal samples.	The phylum Firmicutes, especially Clostridium ssp, was significantly higher in the migraine group. The healthy control, on the other hand, presented more beneficial strains. There was also a decrease in short-chain fatty acid producers: Butyrivibrio, and

			Bifidobacterium adolescents.
Migräneprophylaxe mit einem Probiotikum (Migraine prophylaxis with a probiotic) STRAUBE et al., 2018	Uncontrolled observational study with 1020 patients. Age: 44 ± 13.6.	3 g multispecies probiotic (2x/day for 8 weeks).	After 8 weeks there was a decrease in the frequency and intensity (from 5.1 to 2.1) of migraines. Reduction of 46% of individuals who took analgesics after 8 weeks. Average reduction of more than 70% in all reported migraine-related symptoms.

From the literature, it is possible to observe a relationship between intestinal microbiota and migraine. De Roos et al. (2017) demonstrated that there is no statistical difference in probiotic use compared to the control group (placebo). However, some authors have reported improvement in migraine (DE ROOS et al., 2015; Straube et al., 2018). It is worth mentioning that the individuals evaluated by this last author showed an improvement of 70% in all migraine symptoms and that the probiotic dose was higher and taken twice a day, which may have contributed to the more expressive result, even in a shorter time.

Roth et al. (2021) point out that migraine medications that use serotonin agonists are can decrease the effects caused by migraine due to their vasoconstrictor effect. This study also cites an experiment conducted with rats, where tryptophan, the precursor of serotonin, was increased in association with a lower inflammatory state after administration of probiotics containing Bifidobacterium infantis.

According to Martami et al. (2019) the consumption of probiotics for 8 and 10 weeks in patients with chronic migraines (more than 15 crises per month) and sporadic migraines (less than 15 crises per month), respectively, showed a decrease in the frequency, severity, and use of abortifacient drugs. Abortifacient drugs are triptans, non-steroidal anti-inflammatory drugs (NSAIDs), and other analgesics, used to stop the headache. The decrease in the use of abortifacient medications may be related precisely to the decrease in the frequency and severity of crises experienced by

individuals with chronic and sporadic migraine, resulting in less need for therapies that relieve pain.

Studies evaluating the use of SCFAs demonstrate that such substances inhibit the inflammatory cascade and oxidative stress (OLESKIN; SHENDEROV, 2016). The genus Lactobacillus helps in the absorption of SCFA, which can help in migraine due to the reduction of the general inflammatory state (HEMARAJATA; Versalovic, 2013; VENEGAS et al., 2019). In addition, Lactobacillus spp. exert some functions that characterize them as protective against inflammatory diseases, such as elimination of pathogens, immune modulation, promotion of proliferation and differentiation of epithelial cells, the integrity of the intestinal barrier, and repair of balance in intestinal disorders (DE ROOS et al., 2015).

Gastrodia-Uncaria demonstrated recovery of the microbiota impaired by the use of nitroglycerin, while the administration of vitamin D also impacted the composition of the microbiota (ROTH et al., 2021). The role of probiotics in the production of tryptophan has also been demonstrated in humans, as well as their connection with the decrease in migraine symptoms through their vasoconstrictor effects, caused by serotonin (ROTH et al., 2021). This work explains that migraine medications using serotonin agonists lead to a decrease in migraine symptoms due to its vasoconstrictor effect. Moreover, tryptophan, the precursor of serotonin, was increased in association with a lower inflammatory state after administration of probiotics containing Bifidobacterium infantis (ROTH et al., 2021).

By linking H Pylori and migraine studies show that 45% of migraine patients are infected with H Pylori. In healthy control cases, the prevalence is 33% (SU, ZHOU, ZHANG 2014). Therefore, there is a higher prevalence of H Pylori in the migraine group. In addition, the authors attribute the higher prevalence of migraine in people infected with H. Pylori to the constant release of vasoactive substances such as cytokines and prostaglandins (ASGHAR et al., 2011).

Studies on the composition of the gut microbiota of individuals with and without migraine show that there is a decrease in SCFA producers in migraine patients (ENGELS et al., 2016). As previously seen, SCFAs as well as the microorganisms that produce them have been studied as possible adjuvants for the management of the inflammatory state present in migraine. The reduction of SCFA producers may be an

interesting indicator about an imbalance of the microbiota of individuals with migraine (HOLDEMAN; MOORE, 1974).

On the other hand, the control group without migraine showed more beneficial strains (Faecalibacterium prausnitzii, Bifidobacterium adolescentis, and Methanobrevibacter Smithii) in the microbiota analysis, indicating an environment less conducive to the emergence of factors that contribute to migraine. Overall, a greater number of bacteria considered beneficial were found in the control group, such as C. catus which participates in the production of SCFA (HOLDEMAN; MOORE, 1974), and E. hallii which acts on the formation of propionate and improves insulin sensitivity (ENGELS et al., 2016; UDAYAPPAN et al., 2016).

Final Considerations

The use of probiotics to reduce migraine-related symptoms still has inconclusive studies. The authors present controversial results.

Research with SCFA has shown less hyperalgesia and reduced inflammatory cytokines. It has also been seen that the use of these SCFAs resulted in an alteration of the composition of the microbiota. It was noted that the decrease of SCFA-producing microorganisms in the migraine group pointed to these compounds as possible protectors in the inflammatory aspect of migraine.

In the case of Gastrodia-Uncaria, vitamin D3, and tryptophan, the results show alteration of the gut microbiome, providing a positive impact related to migraine symptoms. The correlation of migraine with H. pylori showed positive results in symptomatology when these microorganisms were eradicated, in addition to studies demonstrating that individuals infected with H. pylori are more prone to migraine. Concerning the difference between the gut microbiota of patients with and without migraine, a lower species diversity was demonstrated in the migraine group.

Therefore, the findings of the current study suggest a relationship between intestinal microbiota and migraine manifestations and onset. However, the usefulness of probiotics to reduce migraine symptoms is still unclear. It is necessary further studies are necessary to evaluate this subject in depth and seek more enlightening results.

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