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Review Article

Non-steroidal anti-inflammatory drugs (NSAIDs) x microbiota: an intestinal symbiosis or dysbiosis?

Anti-inflamatórios não esteroidais (AINEs) x microbiota: uma simbiose ou disbiose intestinal?

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ABSTRACT: *Background*: Considering the widespread use of non-steroidal anti-inflammatory drugs (NSAIDs), the following study aimed to discuss their potential effects on the intestinal microbiota and the consequent repercussions in clinical practice. *Materials and methods*: The development of the bibliographic review was based on the "PubMed" research platform, through the use of the keywords: "NSAIDs"/"Non-steroidal anti-inflammatory drugs" and "Microbiota"/"Microbiome"/"Gut microbiota", with the full reading of those articles published in the last 5 years in Portuguese, English or Spanish. Meta-analyses, systematic reviews and other bibliographic reviews were excluded from the study, resulting in a final sample of 14 articles. *Results*: The evidence of quantitative and qualitative changes in the intestinal microbiome attributed to the use of these drugs was significant, with an increase in Gram-negative microorganisms and a reduction in Gram-positive microorganisms. However, the altered microorganisms, the observed pathologies, and other factors involved, as well as the intervention strategies addressed to treat the dysbiosis, do not yet have their mechanisms completely defined. *Conclusion*: Despite the inconclusive results, a therapeutic alternative for the presented dysbiosis would be the use of probiotics from Gram-positive strains. In addition, room is opened for the benefit of new studies in the area.

KEY WORDS: Anti-Inflammatory Agents, Non-Steroidal; Gastrointestinal Microbiota; Gastrointestinal Microbiome; Gastrointestinal Tract; Pharmacoepidemiology.

RESUMO: *Objetivos:* Levando em consideração o uso amplamente difundido dos anti-inflamatórios não esteroidais (AINEs), o seguinte estudo teve como objetivo discutir seus potenciais efeitos sobre a microbiota intestinal e as consequentes repercussões na prática clínica. *Materiais e métodos:* A revisão bibliográfica foi executada com base na plataforma de pesquisa "PubMed" através do uso dos descritores: "AINEs"/"Anti-inflamatórios não esteroidais" e "Microbiota"/"Microbioma"/"Microbiota intestinal", tendo sido realizada a leitura na íntegra daqueles artigos publicados nos últimos 5 anos nos idiomas português, inglês ou espanhol. Foram excluídos do trabalho as meta-análises, revisões sistemáticas e demais revisões de literatura, obtendo-se uma amostra final de 14 artigos. *Resultados:* No que diz respeito ao desenvolvimento de disbiose atribuída ao uso desses fármacos, a evidência de alterações de ordem quantitiva e qualitativa do microbioma intestinal foi representativa, sendo observado um aumento de microrganismos Gram-negativos em paralelo a uma redução de Gram-positivos. Entretanto, os microrganismos alterados, as patologias observadas e demais fatores envolvidos, assim como as estratégias de intervenção abordadas para correção da disbiose ainda não apresentam seus mecanismos completamente definidos. *Conclusão:* Apesar dos resultados inconclusivos, uma alternativa terapêutica para a disbiose apresentada seria o uso de probióticos de cepas Gram-positivas. Além disso, abre-se margem para o benefício de novos estudos na área.

PALAVRAS-CHAVE: Agentes Anti-Inflamatórios não Esteroidais; Microbiota Gastrointestinal; Microbioma Gastrointestinal; Trato Gastrointestinal; Farmacoepidemiologia.

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used classes of medicines worldwide, with over 30 million users per day. They are administered for analgesic, antipyretic and anti-inflammatory purposes, meaning for symptomatic relief of pain, fever and inflammation. Patients with chronic inflammatory diseases, osteoarthritis, back pain and non-rheumatic manifestations such as headache, flu-like symptoms and menstrual cramps benefit most from this group of drugs[1,2,3].

The mechanism of action of these drugs consists of selective or non-selective inhibition of the isoforms of the cyclooxygenase (COX) enzyme, which participate in the arachidonic acid cascade and play an important role in prostaglandin formation. While COX-1 is constitutively expressed in most tissues, COX-2 activation is mainly induced by harmful stimuli, mediating the inflammatory state. The prostaglandins produced have a protective effect on the gastrointestinal mucosa, increasing the production of cytoprotective mucus and sodium bicarbonate and stimulating regional microcirculation[3].

In addition to the evident repercussions on the COX enzyme, NSAIDs promote interaction with membrane phospholipids, culminating in altering gastrointestinal permeability and barrier function, which induces an erosive-ulcerative inflammatory process[1].

Due to their widespread use, there has been an increase in the use of these medications inadvertently, without a prescription and above the recommended dose, prompting an alert about the impact of their possible adverse gastrointestinal events and on the intestinal microbiota[2,3].

This microbial community is formed by different species of bacteria, archaea, parasites, fungi and viruses which inhabit the gastrointestinal tract, and simultaneously and mutually acts with the host cells through a symbiotic process which plays several physiological roles, such as helping to metabolize food and form the epithelial barrier, in addition to participating in motor-sensitive activities and immune processes. The microbiota composition not only varies with its location in the digestive system, but also due to changes in pH, the physiology of epithelial cells, oxygen levels, medications used and the adopted dietary pattern[4].

In this sense, the mechanisms behind the potentially negative effects of NSAIDs on the intestinal microbiota have not yet been fully elucidated given the complexity of the relationship between these drugs and homeostasis regulation carried out by enteric flora[5].

OBJECTIVE

The objective of this study was to not only evaluate the mechanisms by which the use of nonsteroidal anti-inflammatory drugs is associated with changes in the intestinal microbiota, but also to measure the impacts attributed to this interrelationship. These implications include changes in the intestinal microbiota composition and predisposition to development of certain pathologies, as well as the factors generally involved in this imbalance process, demonstrating the risks to health professionals of indiscriminate and non-judicious administration of this pharmacological class to patients.

PROPOSED METHOD

This study is a theoretical descriptive study with a bibliographic review based on the analysis of articles selected through the "National Library of Medicine (PubMed)" research platform, whose descriptors were: "(NSAIDs OR Non-steroidal anti-inflammatory drugs) AND (Microbiota OR Microbiome OR Gut microbiota)".

The filters applied as inclusion criteria were: "Full text"; only those written in English, Portuguese or Spanish; and published within the last 5 years. Furthermore, exclusion criteria were applied to exclude articles related to meta-analyses, systematic reviews or other literature reviews.

After applying the aforementioned filters, a sample of 236 works was obtained. The articles were then selected based on the titles, abstract assessment and full reading. Articles that did not address the relationship between nonsteroidal anti-inflammatory drugs and intestinal microbiota or other factors which impact injuries related to their use, as well as possible commercial conflicts of interest, were discarded. Finally, a sample of 14 final articles was selected to compose the work, including research findings in both humans and animals.

RESULTS

After analyzing the selected articles, the role of NSAIDs in altering the intestinal microbiota and their implications became evident, despite the notable variability of the results evaluated. In this sense, it was possible to establish a comparative relationship between certain drugs belonging to this class of medicines and the microorganisms altered by their administration, as described in the following Table 1.

In view of the results obtained, it is worth noting that the following were not included in the table above: articles in which quantitative and qualitative relationships were not described regarding changes in species or genera of specific microorganisms; studies corresponding to the association of other factors inducing dysbiosis in addition to non-steroidal anti-inflammatory drugs (such as the use of polysorbate-80, proton pump inhibitors, a high-fat diet and psychological stress), authored by Furuhashi et al.[8](2020), Nadatani et al.[9](2019), Sugimura et al. [10](2019) and Yoshikawa et al.[11](2017), respectively.

Flow chart of the search methodology for reviewed articles (source: the authors)

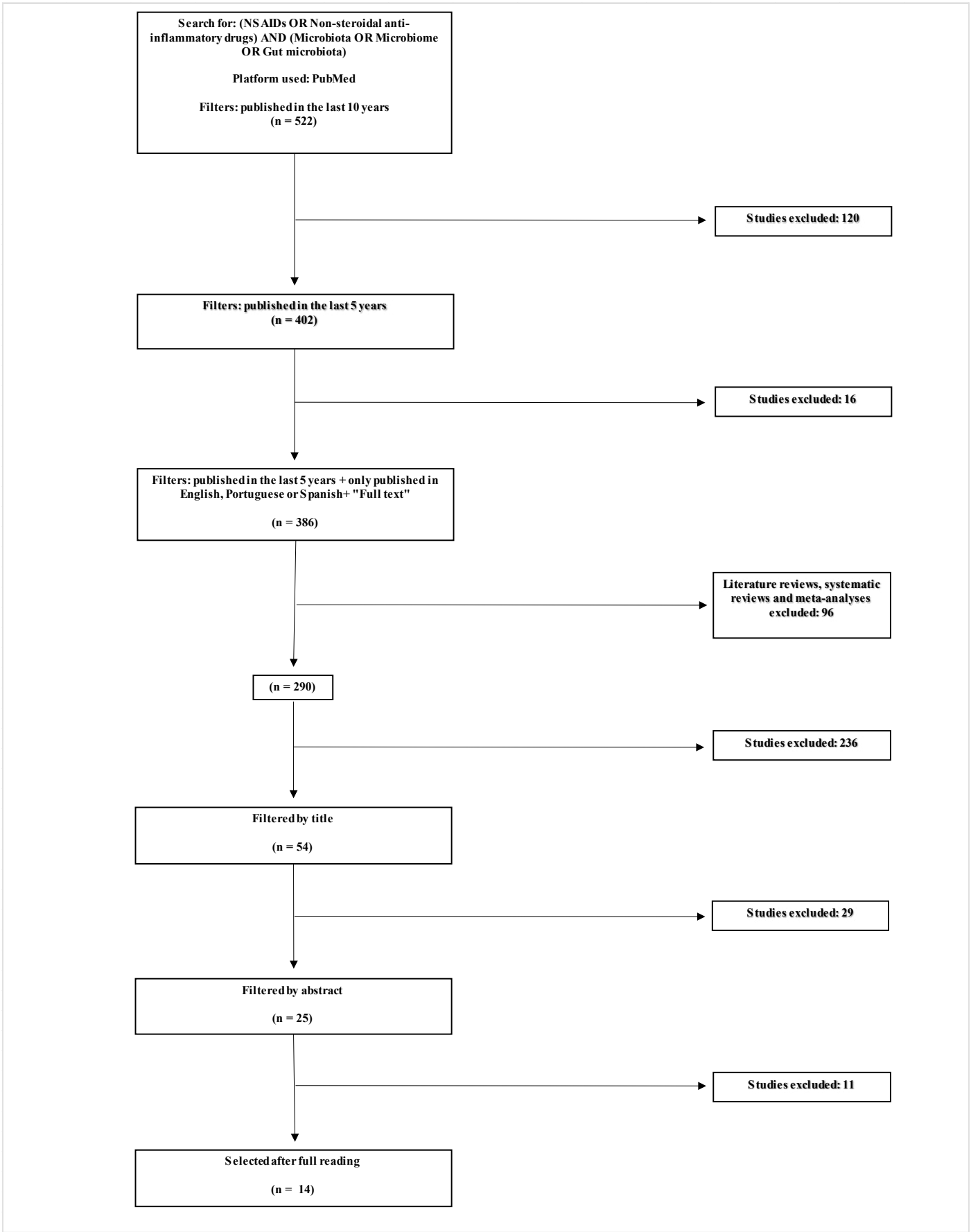

Table 1 - Relationship between drugs and changes observed in microbiota composition

Drug(s)	Change	Related microorganisms	References
Diclofenac	Increase	Proteobacteria, Actinobacteria, Bacteroidetes, *Lucibacterium, Arcobacter and Albirhodobacter*	6
Diclofenac	Reduction	Firmicutes, *Shewanella, Aeromonas, Acinetobacter, Shinella and Lactobacillus*	6, 7
Celecoxib + Ibuprofen	Increase	Acidaminococcaceae and Enterobacteriaceae	13
Phenylbutazone + Firocoxib	Reduction	Firmicutes (Lachnospiraceae, Clostridiaceae and Ruminococcaceae)	14
Indomethacin	Increase	Firmicutes and Ruminococcus (in males), Prevotella (in females)^17 Firmicutes (including Ruminoccaceae and Lachnospiraceae), Alphaproteobacteria, Gastranaerophilales and Alistipes^18	17, 18
Indomethacin	Reduction	Firmicutes and Ruminococcus (in females), Turicibacter^15,17 Bacteroidetes (including Porphyrominadaceae, Bacteroidaceae, Prevotellaceae, Rikenellaceae), Erysipelotrichaceae and Defluviitaleaceae^18	15, 17, 18
Acetylsalicylic acid*	Increase	Bacteroidetes	20
Acetylsalicylic acid*	Reduction	Firmicutes	20

DISCUSSION

Based on the results obtained and the findings described in Table 1, we can state that the variations in the abundance of different species, genera and phyla regarding the composition of the microbiota were diverse and dependent on the non-steroidal anti-inflammatory drug used in each study. For example, diclofenac administration was related to an increase in the rates of Proteobacteria, Actinobacteria, Bacteroidetes, *Lucibacterium, Arcobacter* and *Albirhodobacter*, while at the same time a decrease was observed between Firmicutes, *Shewanella, Aeromonas, Acinetobacter* and *Shinella.* In this context, the greater expression of Acinetobacter and Aeromonas was related to a greater risk of diarrheal conditions and gastrointestinal infections[6]. A deficiency of *Lactobacillus* was also associated with this drug, which may contribute to develop intestinal lesions, since this genus has a protective effect on the intestinal barrier and acts by reducing intestinal permeability[6,7].

Such changes in the composition of this microbiome have often been shown to be linked to the NSAID doses used during clinical studies. In the case of diclofenac, it was found that exposure to 1 mg/L of the active ingredient significantly reduced the proportion of *Anaerobdus*, while exposure to a higher dose of 10 mg/L promoted a clear increase in the corresponding genus[6].

The deleterious effects of NSAIDs on the microbiota and the consequent intestinal lesions caused by their use are increasingly significant. Additionally, there are circumstances capable of potentiating or aggravating these lesions, such as the use of polysorbate-80 and Proton Pump Inhibitors (PPIs). Pretreatment with polysorbate-80, a dietary emulsifier, demonstrated an exacerbation of ileitis developed from the use of indomethacin. PPIs, more specifically rabeprazole and vonoprazan, increased the lesion rates and area induced by indomethacin due to an increase in the IL-1β and TNF-α mRNA expression in the small intestine. However, in the case of PPIs, supplementation with *Lactobacillus johnsonii* showed an improvement in the lesions, neutralizing the harmful impacts of using this pharmacological class[8,9].

The existence of some non-pharmacological factors which contribute to potentially activating the harmful effects mediated by NSAIDs when associated with their use was also investigated, including stress and the diet adopted by the individual. Regarding diet, it was found that rats exposed to a high-fat diet (HFD) presented a decrease in the population of *Bifidobacterium* spp., Gram-positive anaerobic bacilli, with repercussions such as an increase in the injured area, intestinal ulceration and an increase in the pro-inflammatory cytokine level. The decrease in the protein levels which compose the intercellular junctions in fact caused an exacerbation of dysbiosis and an increase in intestinal permeability, facilitating invasion of the mucosa by enterobacteria and the risk of metabolic endotoxemia[10]. Regarding the psychological aspect, according to Yoshikawa et al. [11] (2017), stress potentiated the enteropathy triggered by the use of indomethacin. Among the findings observed, we can mention an increase in the total number of bacteria, an increase in the proportion of the Bacteroidetes and Actinobacteria phyla, and an also increased intestinal permeability[11].

An important observation of the evaluated studies was the divergences in repercussions from the use of NSAIDs, depending on the selectivity for COX enzymes. Long-term administration of rofecoxib, a selective COX-2 inhibitor, did not cause significant dysbiosis in the small intestine of the rats tested, serving as a basis for the fact that the changes in the microbiota cannot exclusively be explained by inhibition of the

enzyme. Consequently, other specific properties of the drugs must contribute to a greater extent to the dysbiosis attributed to these anti-inflammatory drugs[12].

However, Rogers, Aronoff[13](2016) apud Lázár (2019) found contradictory results to the hypothesis of the absence of dysbiotic potential among the "coxib" group. The use of celecoxib and ibuprofen in human fecal samples for 30 days led to an enrichment of Acidaminococcaceae and Enterobacteriaceae in the microbiota composition. Whitfield-Cargile[14] (2018) apud Lázár (2019) also demonstrated that horses treated with phenylbutazone and firocoxib presented a decrease in members of the Firmicutes phylum, specifically the Lachnospiraceae family, and to a lesser extent, the Clostridiaceae and Ruminococcaceae families.

Similarly, Whitfield-Cargile et al.[14](2018) suggests that regardless of COX selectivity, NSAIDs transiently alter the fecal microbiota and inferred metagenome of adult horses when administered for 10 days, reinforcing the hypothesis that these drugs induce dysbiosis in both humans and animals. Taken together, all these data contradict the idea of greater safety in the use of selective COX-2 inhibitors in general, since again, changes in the microbiota composition were revealed which varied according to the drug used[14].

Another issue raised in the impact analysis on the use of these medications was their contribution to developing certain pathologies when associated with a causative factor. In a study conducted with rats, indomethacin proved capable of potentiating the severity of colitis induced by *Clostridium difficile* infection, in addition to reducing body weight and promoting an increase in mortality in infected animals, despite not affecting the colonization and cytotoxicity of the pathogen. It was also found that indomethacin administration caused a significant reduction in PGE2 levels, suggesting that prostaglandins may be related to a reduction in mortality and histopathological damage caused by infection of *C. difficile*[15,16].

In addition to the effects related to the genetic expression of prostaglandins, cell recruitment and epithelial junctions, the disturbances identified in the intestinal microbiota appeared to be relevant to the outcome obtained. One of the changes present was a decrease in the expression of the *Turicibacter* genus, which has been attributed as an important factor of resistance to colonization by *C. difficile* in the literature[15].

Then, an important question was raised regarding the diversity of results: were the changes observed resulting from the use of NSAIDs the same in both sexes? It was found that healthy women have lower intestinal permeability and higher microbial alpha-diversity than healthy men, demonstrating a divergence in the basal composition of the microbiota between the sexes. However, after indomethacin administration it was found that although both sexes showed an increase in permeability and a reduction in the diversity of the duodenal microbiota, only the female sex had a decrease in the diversity of the fecal microbiota upon exposure to the drug. An increase in Firmicutes and Ruminococcus was detected in male fecal samples, which had a reduced abundance in women. In addition, the *Prevotella* genus increased in the female fecal microbiota, but did not show significant changes in men. All of these results prove that although the disparity between the microbiota of men and women is present even at baseline, the pharmacological effect also induced distinct changes in each sex. Furthermore, although the mechanisms that lead to such sex-dependent differences in the impacts of this therapeutic class are not fully elucidated, it is believed that estrogen plays an important role in maintaining the female intestinal barrier and may be one of the factors for the variations analyzed[17].

When exposed to these drugs, the human body has shown itself capable of actively adapting to protect itself against the potential harmful effects associated with their use. According to Xiao et al.[18](2017), rats exposed to indomethacin developed an adaptation in their intestinal microbiome, which became more resistant to the harmful effects of the drug. Proof of this finding was that when healthy mice were submitted to a transplant receiving the microbiota of a donor previously exposed to indomethacin, they showed a lower rate of intestinal lesions when also subjected to the action of the drug. Furthermore, despite the improvement in lesions observed in cases of pre-treatment with antibiotics due to eradication of the commensal microbiota, antibiotics administered after the use of NSAIDs proved to be harmful, precisely due to the elimination of the adapted microbiota[18].

In view of all these changes, there are currently therapeutic strategies aimed at mitigating the harmful intestinal effects of nonsteroidal anti-inflammatory agents. For instance, a study was conducted in which healthy patients were exposed to aspirin (ASA) for 6 weeks associated with the use of *Bifidobacterium breve* Bif195. It was then found that the co-treatment objectively provided protection against ASA-induced small bowel lesions, in addition to not interfering with the COX inhibition cascade and reduced prostaglandins and thromboxanes, suggesting that the interference of Bif195 in the specific cardioprotective effects of aspirin is unlikely. In this sense, a possible alternative treatment for enteropathy arises in patients who chronically use aspirin[19].

Some other alternatives can be listed among such treatment strategies evaluated for correcting dysbiosis and preventing enteropathy associated with this group of anti-inflammatory drugs. Colucci et al.[7](2018) demonstrated that administration of antibiotics such as rifaximin did not cause lesions when associated with diclofenac, unlike the isolated use of diclofenac, which resulted in multiple ulcerative lesions. Rifaximin also acted to counterbalance the damage caused by the reduction of *Lactobacillus* by diclofenac when administered together[7,20]. Diet and stress (previously mentioned as aggravating factors), are shown to be potential approaches dependent on patient behavior (balanced diet low in fat and stress control). In the case of stress, it was also proven that its harmful effects were blocked by administration of a glucocorticoid receptor antagonist. All of these possibilities, in addition to the use of probiotics in an attempt to rebalance the composition and quantity of the intestinal microbiota, can be used to mitigate the harmful impact of NSAIDs on intestinal flora and homeostasis[10,11].

CONCLUSION

In view of the results obtained and the literature analyzed

during this study, we can infer that although the changes observed in the microbiome varied according to the NSAID in question, administration of this therapeutic class is in fact linked to the symbiotic breakdown of our enteric microbiota, triggering dysbiosis, meaning an imbalance of the intestinal flora.

Although some observed patterns are not fully elucidated, they include a generalized increase in Gram-negative microorganisms associated with a significant decrease in the abundance of Gram-positive microorganisms, which may be related to the enteropathy caused by such drugs. In this sense, there is room for complementary therapies which include the use of probiotics, especially Gram-positive strains, in an attempt to enhance the intestinal barrier and mitigate the dysbiotic effects of these medications.

Finally, it is noted that scientific production and work conducted within this theme are still scarce, and in most cases, inconclusive. Therefore, there is a clear need for greater encouragement for future related studies in order to further elucidate the real impacts of this pharmacological class and the consequences of the resulting dysbiosis on the human organism and development of certain diseases, so that these drugs can be used with greater rationality and success in therapy.

Authors' contribution: Danilo Saragiotto Ferreira de Mello (main author): responsible for preparing the project, selecting and analyzing materials and data, writing the article, critical review of the work, approval of the final manuscript and publication of the article; Anderson Benegas Mendes (co-author): participated in the development and critical review of the work, in addition to the approval of the final manuscript; Aline Namie Tanimaru (co-author): participated in the development and critical review of the work, in addition to the approval of the final manuscript; Fabiana Gaspar Gonzalez (advisor): provided guidance from suggestion of the theme and idealizing the project, critical review of the work until the approval of the final version for publication; Celine de Furtado Carvalho (co-advisor): provided guidance from suggestion of the theme and idealizing the project, critical review of the work until the approval of the final version for publication.

All authors declare that they had sufficient participation in the work to assume responsibility for its full content.

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