

## ORIGINAL ARTICLE

### Animal models for inducing inflammatory bowel diseases: an integrative review

*Modelos animais de indução das doenças inflamatórias intestinais: revisão integrativa*

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#### KEYWORDS

Animal disease models  
Inflammatory bowel diseases  
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#### ABSTRACT

**Objective:** To identify and describe comparatively the chemical models of the induction of inflammatory bowel diseases (IBD) in rodents most used and that best mimic the pathogenesis in humans.

**Methods:** Based on an integrative review in the Medline and LILACS databases, it was investigated which experimental induction models were most cited in articles published from 2004 to 2020, with the descriptors "Colitis/CI", "Colitis model ulcerative" and "Intestinal inflammation model." All empirical articles that addressed one or more inflammation models in rats or mice were included.

**Results:** 239 articles were identified; of these, only ten empirical articles were selected. The most used models were colitis induced by TNBS acid, DSS, and colitis induced by acetic acid (AA).  
**Conclusion:** It was possible to identify the most used models to promote the induction of intestinal inflammation in rats, and both models proved to be effective according to the limitations observed in the models described, suggesting the need for new works that use more well-defined protocols and that more fully represent the pathophysiological complexity of the disease.

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**PALAVRAS-CHAVE**

Colite ulcerativa  
Doenças inflamatórias  
intestinais  
Modelos animais de  
doenças

**RESUMO**

**Objetivo:** Identificar e descrever de forma comparativa os modelos químicos de indução das doenças inflamatórias intestinais (DII) em roedores mais utilizados e que melhor mimetizam a patogênese em humanos.

**Métodos:** a partir de uma revisão integrativa nas bases de dados Medline e LILACS, investigou-se quais os modelos de indução experimental mais citados nos artigos publicados no período de 2004 a 2020, com os descritores “Colite/CI”, “Modelo de colite ulcerativa” e “Modelo de inflamação intestinal”. Foram incluídos todos os artigos empíricos que abordassem um ou mais modelos de inflamação em ratos ou camundongos.

**Resultados:** 239 artigos foram identificados; destes, somente dez artigos empíricos foram selecionados. Os modelos mais utilizados foram o de colite induzida por ácido TNBS, por DSS e colite induzida por ácido acético (AA).

**Conclusão:** Foi possível identificar os modelos mais utilizados para promover a indução da inflamação intestinal em ratos e ambos os modelos se mostraram eficazes de acordo com seu protocolo de indução. Ficaram claras as limitações observadas nos modelos já descritos, sugerindo a necessidade de novos trabalhos que utilizem protocolos mais bem definidos e que representem de forma mais integral a complexidade fisiopatológica da doença.

**INTRODUCTION**

Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal tract's mucosa, caused by the interaction between genetic, immune, and environmental factors<sup>1</sup>. Crohn's Disease (CD) and Ulcerative colitis (UC) are the two main presentations of this group and, despite the shared similarities, they have different pathophysiological mechanisms. The clinical picture of both can range from intestinal manifestations - such as chronic diarrhea, abdominal pain, and low digestive bleeding – as well as extraintestinal – articular, cutaneous and ocular. CD can reach any segment of the gastrointestinal tract transmurally, leading to severe anatomical complications, such as fistulas and strictures. The UR, in turn, is limited to the specific involvement of the colon mucosa. Both are associated with substantial impairment of quality of life, being potentially lethal in some patients<sup>2,3</sup>.

Several mechanisms have been described as the cause of these diseases, ranging from psychogenic to immunological factors, with no consensus among authors<sup>4</sup>. Due to environmental factors, an atypical intensified immune response is triggered in the intestine but capable of spreading to other tissues and organs, inducing extraintestinal reactions, namely, joint, ophthalmic, dermatological, urological, hepatobiliary, pulmonary involvement<sup>5</sup>. Once installed, they can evolve independently of intestinal disease, as is the case with primary sclerosing cholangitis causing liver cirrhosis<sup>6</sup>.

According to Gonçalves et al.<sup>7</sup>, CD and UC treatments are based on conventional drugs such as corticosteroids, aminosalicylates, immunomodulators, and antibiotics. However, 60%-70% of affected patients will need some surgical intervention during the follow-up and, of these, 50% will need at least a second surgery<sup>7</sup>.

In this context, the animal model presents itself as a useful tool for understanding this disease<sup>8</sup>. The models frequently used for simulation of IBDs use diluted acids or corrosive substances to induce histological changes similar to those found in the disease in humans<sup>4</sup>.

The induction of humoral and cellular immune responses against the organism's constituents is an inherent attribute of autoimmune diseases; however, its experimental induction is rarely reported.

The extrapolation of the experimental results obtained from animal species to humans is a controversial topic<sup>9</sup>, since the efficacy and safety verified in the laboratory do not guarantee that they are also in humans. For example, the antibiotic penicillin, which is generally well accepted in humans, is fatal to guinea pigs. The sedative thalidomide, historically responsible for causing malformations in children, is not associated with congenital defects in rats and many other species, except primates<sup>9</sup>.

Given the above, although animal models are susceptible to failures and errors, with deficiencies because it is an attempt to represent diseases in humans, they are recognized as useful mechanisms. Concerning IBDs, there is still no animal model that reliably represents this group of diseases. However, drugs have already been developed through preclinical models, reinforcing the importance of this study system<sup>10</sup>. Consecrated medications for treating IBD, such as mesalazine and sulfasalazine, were developed from preclinical models and validated by randomized clinical trials, which showed a statistical superiority over placebo in mild/moderate rectocolitis<sup>11</sup>.

Therefore, this integrative review describes the methods for inducing IBDs in research animals, comparing chemical substances in terms of colitis-inducing power. Consequently, it presents a description of the induction protocols most used by the scientific community. Finally, it discusses the capacity of these models to mimic aspects of pathogenesis in humans adequately.

**METHODS**

The following integrative review was conducted by searching for scientific articles that present content related to the models of induction of intestinal inflammation in rats/mice to gather in a single work

general and specific information on the topic addressed.

The search strategy descriptors were selected from the research question structured in the format of the acronym PICO: P (Population / Participants) - rats; I (Interventions) - chemical models for inducing colitis; C (Comparisons) - control group without chemical induction; O (Outcomes / Outcome) - in vivo reproduction of inflammatory human intestinal diseases. Thus, it was proposed to evaluate comparatively the capacity/efficiency of the colitis-inducing chemical models to mimic the pathophysiology of IBDs.

The survey of journals was performed on the platform of the Latin American and Caribbean Center on Health Sciences Information (BIREME – PAHO – WHO), using LILACS (Latin American and Caribbean Literature in Health Sciences) and MEDLINE databases (Medical Literature Analysis and Retrieval System Online). A series of descriptors, developed from the MeSH – Medical Subject Headings of the US National Library of Medicine (NLM), was used to construct the search string, replacing the simple search for keywords (in disuse). Thus, we selected descriptors consistent with "chemically induced colitis" and "inflammatory bowel diseases", composing the search strategy (mh:("Colitis") AND mj:("Inflammatory Bowel Diseases") AND (db:("MEDLINE "OR" LILACS))), and their Portuguese counterparts, without language restriction, year or study design (at first).

The writing process for this Integrative Review complied with the PRISMA-ScR<sup>12-16</sup> guidelines. The research was performed in duplicate, specifically by two reviewers independently. Despite being restrictive, the initial search resulted in a large number of scientific articles, often with different study themes. Therefore, a series of exclusion criteria were applied in the selection stage. The decisions were made based on the titles and abstracts of the studies and, in the impossibility of deciding due to lack of clarity, the methodological aspects needed were evaluated. All empirical articles addressing one or more inflammation models in rats or mice over 16 years (2004 to 2020) directly associated with IBD were included. Also, works not made available in full and in a language other than English and Portuguese were excluded.

All repeated articles, book chapters, course completion papers, review articles, or incomplete texts that did not address the topic were excluded. The authors excluded gray literature, editorials, opinions, comments, case reports, letters, reviews, and encyclopedias; only experimental studies were included. Also, the Agency for Healthcare Research and Quality (AHRQ) categorization was used for 'Hierarchical Classification of Evidence for Evaluation of Studies', in which the quality of evidence is classified into seven levels, namely: [i] - systematic review or meta-analysis; [ii] - randomized clinical trials; [iii] - clinical trial without randomization; [iv] - cohort and case-control studies; [v] - systematic review of descriptive and qualitative studies; [vi] - only descriptive or qualitative research; and [vii] - opinion of authorities or report of specialty committees<sup>18</sup>. Here, only studies with levels ii and iii of evidence were considered. Finally, even if they were pre-selected, those who did not fit the proposed theme were excluded in the eligibility stage after

reading in full.

The Kappa index was used to evaluate the screening effectiveness since it is widely used to describe the agreement between two or more evaluators when a nominal or ordinal evaluation of the same sample is performed. Disagreements between reviewers were resolved by consensus (see details in Landis and Koch<sup>17</sup>).

Finally, the data related to the inflammation induction models of those articles selected after screening were analyzed, discussed, and compared with the specialized literature.

## RESULTS

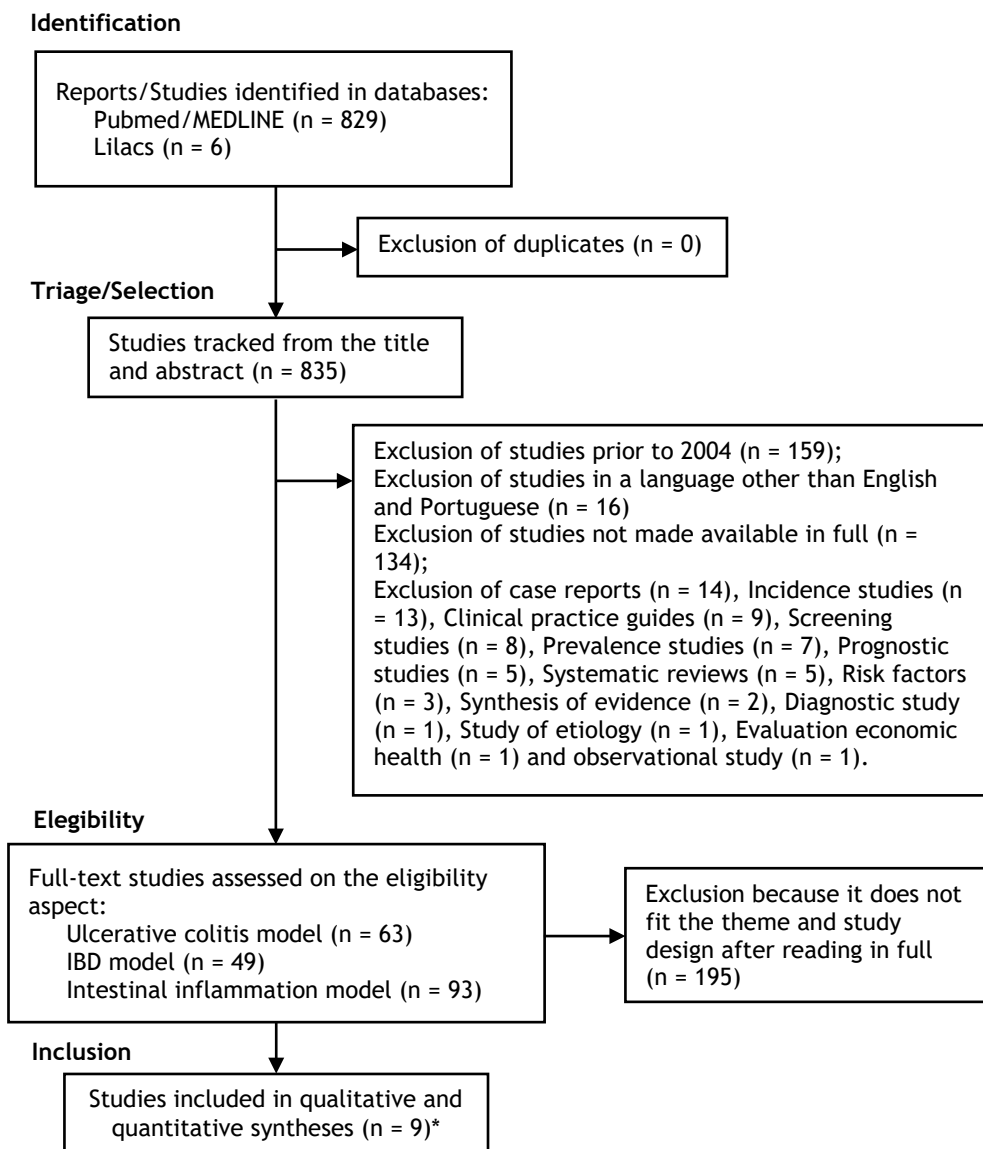
A total of 835 articles were identified from the search strategy in the LILACS (6) and MEDLINE (829) databases. After analysis by the 'Hierarchical Classification of Evidence for Evaluation of Studies', case reports (14), incidence studies (13), clinical practice guides (9), screening studies (8), prevalence studies (7), prognostic studies (5), systematic reviews (5), risk factors (3), synthesis of evidence (2), diagnostic study (1), etiology study (1), economic health assessment (1), and observational study (1) were excluded. According to the time and availability filter of the full text, 159 of 134 papers were excluded. After the selection phase, 205 studies using the IBD model (49), UC (63), and intestinal inflammation (93) were fully assessed for eligibility. Of these, only nine empirical articles were selected, systematized and discussed (Figure 1). A Kappa agreement index of 0.84 and 98.7% agreement was calculated, which indicates an "almost perfect" agreement between the reviewers.

Table 1 presents the information obtained from the analysis of each selected publication, and it is possible to observe that most studies developed models of induction of intestinal inflammation. They included models of induced colitis, which were subcategorized in colitis induced by trinitrobenzene sulfonic acid (TNBS; n = 3), dextran sodium sulfate (DSS; n = 2), or acid-induced colitis acetic (AA; n = 5). One article showed results of two models simultaneously.

## DISCUSSION

Intestinal inflammation models are valuable tools that, when properly chosen, can assist in the investigation of critical pathophysiological aspects and offer the opportunity to test new therapeutic strategies, selecting the most efficient and safe treatments. However, it is essential to consider that no ideal animal model represents DII in a reliable manner<sup>18</sup>. However, a suitable animal model should allow a simplified view of the complex pathogenic characteristics found in human disease, providing a treatable and reproducible system for identifying inflammatory pathways and testing therapeutic interventions<sup>19</sup>.

There are two main categories of colitis inducers: the models induced by chemical agents and those developed spontaneously. Chemical models are



**Figure 1** – Flowchart of the processes of identification, selection and inclusion of studies. \*One article presented simultaneous data from two models.

the most used due to the rapid induction of inflammation, easy reproducibility, and low cost, which mimic some essential immunological and histopathological characteristics of IBDs in humans. Induction occurs by inserting a catheter in the animal's colon to instill a specific chemical agent, such as TNBS, DNBS, acetic acid and oxazolone. The DSS, in turn, is administered orally, diluted in water (Figure 2)<sup>20</sup>.

In this research, the chemical induction models found in the ten selected articles were DSS, TNBS and acetic acid, which are among the chemical induction models most used in practice, either for their low cost, straightforward execution, or good reproducibility<sup>21-29</sup>.

Acetic acid is exclusively used for acute models of colitis, and its intrarectal administration triggers an inflammatory cascade similar to what occurs in

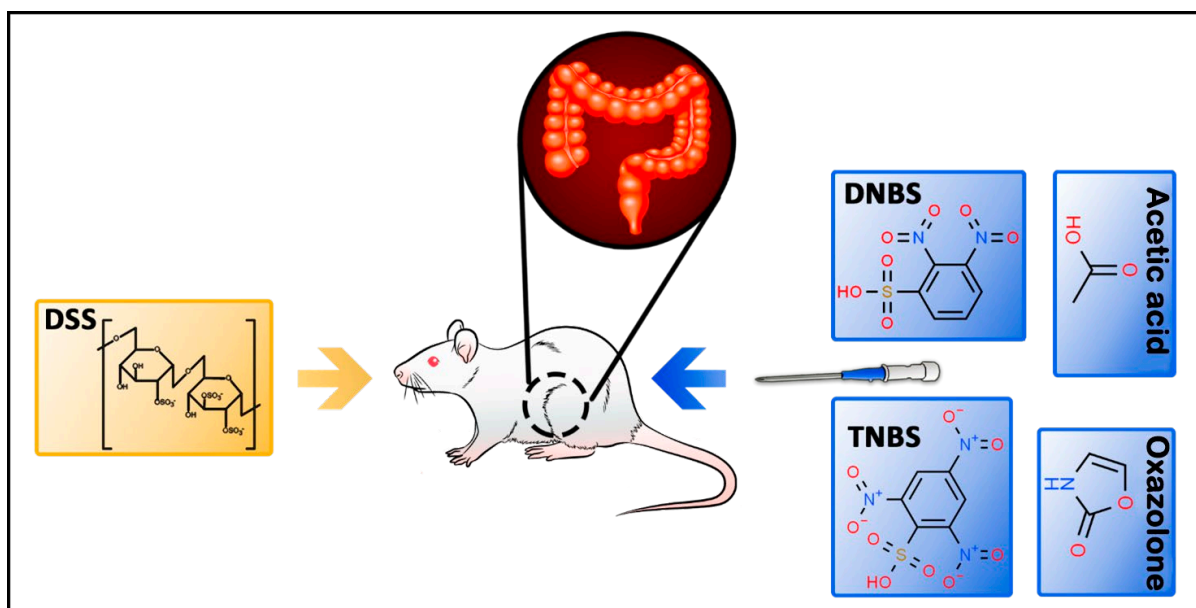
human UC, as it causes non-transmural inflammation characterized by increased infiltration of neutrophils in the intestinal tissue, massive necrosis of the mucous layers and submucosa, vascular dilation, edema and submucosal ulceration. Of the nine articles evaluated, five used acetic acid as a means of inducing inflammation, and all intended to reproduce Ulcerative Colitis through the chemical stimulus to the synthesis of pro-inflammatory cytokines such as IL-1, IL-4, IL-6, TNF- $\alpha$  and IFN- $\gamma$ , in addition to stimulating dilation and thickening of the colon walls through massive epithelial damage secondary to increased inflammatory infiltrate, reduced mucus synthesis and modulation of oxidative stress markers<sup>30</sup>.

The initial epithelial inflammatory process after acetic acid induction is not immunological in nature. Therefore, drugs designed to act on the

**Table 1** – Summary methods to induce experimental inflammatory bowel disease using chemical agents.

Author; year	Induction compound	Quantity, type and weight of the animal model	Disease	Induction method
Gheibi S et al.; 2018 <sup>24</sup>	Acetic acid (AA)	70 Wistar Rats, 160-200g	Ulcerative colitis	1 ml of intracolonic acetic acid was administered to rats and they were kept tilted for 30 s to keep the acid within its rectum.
Necklaces JR et al.; 2016 <sup>23</sup>	Acetic acid (AA)	25 male Wistar rats, 300 g	Ulcerative colitis	The animals received intracolonic administration of 4% acetic acid in a volume of 4 mL per enema.
Oliveira LG et al.; 2014 <sup>28</sup>	Dextran sodium sulfate (DSS)	* Male Wistar rats (6-8 weeks)	Ulcerative colitis	Oral administration of 5% dextran sodium sulfate for seven days
Perera LMS et al.; 2009 <sup>29</sup>	Trinitrobenzene sulfonic acid (TNBS)	* Male Sprague-Dawley rats, 200-220 g	Ulcerative colitis	10 mg of TNBS dissolved in 0.25 ml of 50% (v/v) ethanol were supplied through a Teflon cannula inserted 8 cm into the anus.
Perera LMS et al.; 2009 <sup>29</sup>	Acetic acid (AA)	* Wistar rats, 180-200 g	Ulcerative colitis	1 mL of 4% acetic acid using an intracolonic cannula.
Zhong et al.; 2010 <sup>20</sup>	Dextran sodium sulfate (DSS)	* Female BALB / c albino dong	Does not specify	Oral administration of dextran sodium sulfate 4%
Karatepe et al.; 2012 <sup>25</sup>	Trinitrobenzene sulfonic acid (TNBS)	28 Male Wistar rats, 250-300g	Does not specify	TNBS dissolved in 50% ethanol was instilled in the colon through the cannula (10 mg in a 0.25 ml volume).
Moura et al.; 2016 <sup>27</sup>	Acetic acid (AA)	40 Wistar Rats, 350g	Colitis	Intracolonic administration by enema with 4% AA solution
Marcelino et al.; 2015 <sup>26</sup>	Trinitrobenzene sulfonic acid (TNBS)	* # Wistar rats	Does not specify	TNBS 40 mg / mL solution in 50% (v / v) ethanol. Induction was performed by intracolonic administration of 0.25 mL of TNBS solution at a point 8 cm from the rectum.
Bertevello PL et al.; 2005 <sup>22</sup>	Acetic acid (AA)	39 Wistar rats, 250-300g	Colitis	Rectal injection of 0.5 mL of 10% acetic acid through a polyethylene catheter.

\* Number of animals used in the experiment was not specified by the authors; # Weight of animals not specified.



**Figure 2** – Chemical models of colitis induction in animals orally (orange) and insertion of a catheter in the colon (blue). Source: the authors.



immune system must be tested after a minimum interval of 24 h from the beginning of the process<sup>25</sup>, which is in accordance with Colares et al. (2016)<sup>23</sup>, Gheibi et al. (2018)<sup>24</sup> and Moura et al. (2016)<sup>27</sup>.

Of the ten articles selected in this review, three used the TNBS model to induce colitis<sup>24,25,28</sup>. Although the type of disease was not specified in these studies, their methodology show more remarkable similarity with CD due to the increased production of pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$ , increased production of MPO and infiltration of neutrophils and high levels of malondialdehyde (MDA) and nitric oxide (NO). Additionally, it elicited a predominantly Th1 immune response, severe and intense transmural inflammation or necrosis, inflammatory granulomas, and neutrophil infiltration. Clinically, they demonstrated progressive weight loss, bloody diarrhea, rectal prolapse, and thickening of the colon wall<sup>14</sup>. The TNBS colitis model has been useful in studying many essential aspects of intestinal inflammation, including patterns of cytokine secretion, mechanisms of tolerance, cell adhesion and immunotherapy<sup>31</sup>.

DSS resembles morphologically and symptomatically ulcerative colitis in humans, as it causes erosion with complete loss of surface epithelium due to its direct toxic effect on epithelial cells. Also, the rise in TNF- $\alpha$  levels is considered the hallmark of DSS-induced colitis. Eventually, changes in the profile of Th1/Th2 cytokines may occur over time, in addition to changes in the levels of IL-1 $\beta$ , IL-6, IL-10 and IL-17, and activity of IL-17 and MPO<sup>30</sup>.

Two of the articles analyzed used the DSS as a model for inducing colitis, but only one specified its study for UC. In the study by Oliveira et al. (2014), the UC was established, observing a series of clinical manifestations characteristic of the disease, namely diarrhea, presence of rectal bleeding, weight reduction of the animals, direct destruction of epithelial cells, with a change in the expression of matrix metalloproteinases extracellular (MMP), in addition to increased levels of MPO<sup>27,29</sup>.

This model is particularly useful for drug screening studies and for exploring the mechanisms of epithelial regeneration, the impact of innate immunity on mucosal homeostasis, and the role of inflammation in promoting intestinal dysplasia and developing adenocarcinoma<sup>32</sup>. According to the studies evaluated here, the model of acute colitis by DSS would also stand out in studies of the contribution of the innate immune mechanisms of colitis, especially for promoting ulceration and infiltration of granulocytes, in addition to dysplasia similar to the clinical course of human and proportional UC to the concentration of the inducing chemical.

Thus, DSS-induced colitis has some advantages compared with others (TNBS) since acute, chronic colitis or models of recurrence of the disease can be

easily reproduced only by changing the administered DSS concentration. There are, however, some disadvantages to the DSS model, including variation in the DSS concentration required to induce colitis in different animal facilities, as well as inconsistent water absorption by rats and, therefore, irregular exposure to DSS, resulting in variation in the degree, extent and distribution of mucosal damage and ulceration in the colon<sup>33</sup>.

Some crucial differences were evidenced between the protocols used in each work. Among them, we highlight the variability between dosage, concentration, and duration of administration of the inducing agent, strains used, and percentage of ethanol. Such factors need to be better defined, and careful standardization is essential when planning a new experiment and interpreting the obtained results.

The chemical models of colitis are mostly used to test diseases' immunological mechanisms or test new therapeutic alternatives<sup>21,27</sup>. The relative ease and speed of establishing inflammation by chemically induced models make them more useful for studying the immunogenic effects of small, short-lived therapeutic molecules. In addition to the need for less material, pharmacokinetic and pharmacodynamic assessments tend to be simpler using these models<sup>33</sup>.

An advantage of using animal models to study the pathogenesis of IBDs is the ability to separate the different stages of the inflammatory process experimentally and analyze the mechanisms from the beginning to the disease's late events, which cannot be done in patients. This makes it possible to separately examine the mechanisms related to the disease's progress and clarify the events of the acute and chronic phases distinctly. However, chemical models are especially interesting for studies that address the physiology of acute attacks of IBDs, wound healing, and resolution of acute inflammation, since chemical damage to the epithelial barrier leads to self-limited inflammatory activity to the detriment of chronic disease<sup>18</sup>.

None of the models presented so far would represent a recurrent chronic presentation, characteristic of most presentations of IBDs, in addition to not being associated with the classic extraintestinal manifestations that can be observed in this group of diseases<sup>34</sup>. Besides, most models imitate the Th1 profile, similar to what occurs in DC. Regarding the lesion location, most models only affect the large intestine and not the small intestine - a frequent site of CD involvement. Thus, at the current level of understanding, these models generally focus on particular abnormalities of intestinal inflammation<sup>34</sup>.

Indeed, the existing models are only incompletely similar to IBDs, not reflecting all aspects of these diseases, especially the immunopathology of the colon mucosa. However, over the decades, this

model has helped us to understand how the mucosal immune system orchestrates the maintenance of intestinal homeostasis, which pathogenic mechanisms are responsible for the initiation and maintenance of IBDs, the importance of intestinal integrity for the establishment of inflammation, nature of the regulatory T response, in addition to the genetic aspects of protectors and predisposition<sup>35</sup>.

Analyzing the results presented by the studies listed in this integrative review, it was noticed that the pro-inflammatory induction was established, despite the peculiarities of each one regarding the applied induction method. A more detailed discussion about the comparative effectiveness of such models in terms of histochemistry, level of cellular stress, quantification of granulocyte infiltrates, and cytokine dosage will be the objective of a later study, which will collect data from SciELO (Scientific Electronic Library Online), one of the most prestigious electronic libraries for scientific dissemination, covering journals published by institutions and Academies in Ibero-American countries and South Africa.

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