

**Evaluation of the anti-inflammatory activity of gel with *Matricaria recutita*  
L. using a permeation enhancer**

Avaliação da atividade anti-inflamatória de gel com *Matricaria recutita* L. usando um promotor de permeação.

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## **RESUMO**

### **Avaliação da atividade anti-inflamatória de gel com *Matricaria recutita* L. usando um promotor de permeação.**

*Matricaria recutita* L. (Asteraceae), conhecida como camomila, apresenta várias atividades, sendo uma delas a atividade anti-inflamatória. Com base nessa atividade, o trabalho teve como objetivo preparar um extrato etanólico de camomila e um extrato bruto de camomila para avaliar a atividade anti-inflamatória por via tópica. Concentrações de 3,0% e 5,0% desses extratos foram utilizadas em formulações gelificantes de 1,0% de carbopol<sup>®</sup> 940. Utilizou-se o lauril sulfato de sódio como promotor de permeação nas formulações gelificantes. As formulações foram aplicadas na pele de ratos Wistar com edema de pata induzido por carragenina. A ação anti-inflamatória das formulações foi avaliada, porém não se observou resultados significativos. O controle positivo, gel de diclofenaco de sódio 1,0%, também não reduziu significativamente o edema. Concluiu-se que neste tipo de preparação utilizando o extrato de camomila não houve ação anti-inflamatória significativa mesmo quando o promotor de permeação foi utilizado.

**PALAVRA-CHAVE:** Camomila, Administração tópica, diclofenaco de sódio.

**ABSTRACT**

**Evaluation of the anti-inflammatory activity of gel with *Matricaria recutita* L. using a permeation enhancer.**

*Matricaria recutita* L. (Asteraceae), known as chamomile, has several activities, one of which the anti-inflammatory activity. Based on this activity, the study aimed to prepare an extractive ethanolic chamomile solution (EECS) and the raw ethanolic chamomile extract (RECE) to evaluate the anti-inflammatory activity topically. Concentrations of 3.0% and 5.0% of extracts were used in gelling formulations of 1.0% Carbopol® 940. It was used sodium lauryl sulfate (SLS) as the permeation enhancer in gelling formulations. The formulations were applied to the skin of the Wistar rats with paw edema induced by carrageenan. The anti-inflammatory action of the formulations was evaluated, but no significant results were observed. The positive control, diclofenac sodium gel 1.0%, did not significantly reduce the edema. It was concluded that in this type of preparation using chamomile extract had no anti-inflammatory action even when the permeation enhancer was used.

**KEYWORDS:** Chamomile, Topical administration, diclofenac sodium.

## INTRODUCTION

Focus on the medicinal plant research has been increasing all over the world. People are turning to natural products; predominantly those derived from plants for their health care, due to the growing recognition that these natural products are mainly non-toxic, have lesser side effects than synthetic drugs, and are accessible at affordable prices (Petronilho *et al.*, 2012). Studies on plant pharmacological activity and the development of phytotherapeutic products are often based on plants used in traditional and folk medicine. According to the World Health Organization (WHO), in the beginning of the 1990s it was estimated that 80% of the population in developing countries relied primarily on medicinal plants to treat a variety of diseases and symptoms (Veiga-Jr, 2008).

Recently, there has been an increase in the incorporation of plant extracts in dermatological and cosmetic products. Since standards must be established for these extracts, detailed studies of the composition of the original plant or plants are required. The raw plant material extracted may be solid, such as dry extracts and powders; semi-solid, such as soft extracts; or liquid, such as the extractive solutions used in many solvent systems (Sonaglio *et al.*, 2007).

One of the most common herbs used for medicinal purposes is Chamomile whose standardized tea and herbal extracts are prepared from dried flowers of *Matricaria* species. Chamomile is one of the oldest, most widely used and well documented medicinal plants in the world and has been recommended for a variety of healing applications (Raal *et al.*, 2012; Srivastava *et al.*, 2010)

*Matricaria recutita* L., popularly known as Chamomile, belonging to the Asteraceae family, is one of the many plant species of medicinal interest. Its floral capitula have been used in traditional medicine for centuries, due to their anti-inflammatory, spasmolytic, sedative, anti-bacterial and anti-fungal properties (Heidari *et al.*, 2012; Mazokopakis *et al.*, 2005; Lucena *et al.*, 2009). Chamomile is known to have a variety of active flavonoids, as well as its volatile oil, which is rich in terpenoids, such as alphasisabolol, azulene, matricine and chamazulene. These components provide the anti-inflammatory, antispasmodic and antibacterial activity of the Chamomile (Batista *et al.*, 2014; Lins *et al.*, 2013).

The most important constituents of Chamomile are sesquiterpenes and flavonoids. Apigenin is quantitatively the most abundant flavonoid found in Chamomile, contributing to the anti-inflammatory, anticarcinogenic, antispasmodic, antiviral and antimutagenic properties of this medicinal plant (Petronilho *et al.*, 2012; Srivastava *et al.*, 2010).

*Matricaria recutita* L. was used in an interesting case of methotrexate-induced oral mucositis in a patient with rheumatoid arthritis, who was successfully treated with wild Chamomile mouthwashes (Mazokopakis *et al.*, 2005).

Several biological effects have been attributed to *M. recutita* L., such as anti-microbial, antioxidant, anti-malarial, anti-mutagenic, anti-platelet, anti-chemotactic, anti-cancer, anti-inflammatory, anti-genotoxic, anti-spasmodic, vulnerary, mildly sedative, hypocholesterolemic, beneficial for gastrointestinal, hepatic, central nervous system and autonomic nervous system, hemodynamic, and topical properties. It was also applied topically for hemorrhoids, mastitis, leg ulcer treatments, renal colic, nausea, skin eruption, constipation, as a sedative, for the expulsion of parasitic worms, stomach complaints, and skin diseases. Chamomile cream extract has anti-inflammatory effect on skin associated with atopic dermatitis or eczemas, radiation therapy and erythema (Petronilho *et al.*, 2012).

Gels are becoming more popular due to their easy-application, better percutaneous absorption, when compared with other semi-solid preparation, and resistance to the physiological stress caused by skin flexion, blinking and mucociliary movement, adopting the shape of applied area (Barreira *et al.*, 2013). The objective of this study was to evaluate the anti-inflammatory action of chamomile extract incorporated into a semi-solid formulation containing sodium lauryl sulfate, a permeation enhancer.

## **MATERIAL AND METHODS**

### *Plant material*

Chamomile (*Matricaria recutita* L.) was donated by *Farmacotécnica* Pharmacy, Brasília - DF. They desiccated and stabilized the floral capitula in a greenhouse at 60°C by forced ventilation. The dried material (6% humidity) received was grounded in the laboratory using a food processor until a fine powder was obtained. Control samples of the material can be found in the Herbarium of the University of Brasília, under the exsiccate number UB 45515.

### *Preparation of the chamomile extract*

The floral Chamomile capitula were pulverized and then macerated at the proportion of 20g/100mL of 95% ethyl alcohol (Synth) at room temperature for 12 days (Farmacopeia Brasileira, 2010). After this period, the macerate was filtered to obtain the extractive ethanolic chamomile solution (EECS). Part of the solution was concentrated in a rotary vacuum evaporator at 600 mmHg and  $50\pm 2^{\circ}\text{C}$  to obtain the raw ethanolic chamomile extract (RECE). The extracts were kept refrigerated at  $5\pm 2^{\circ}\text{C}$  until their utilization in the preparations containing the gelling agent (carbopol<sup>®</sup>).

### *Preparation of the carbopol<sup>®</sup> 940 gels*

The 1.0% carbopol<sup>®</sup> gels were prepared by polymer dispersion in distilled water, together with the preservative and the chelant, and left to rest for 24 hours. The remaining excipients (Table 1) were added to the mixture and then homogenized in a mechanical agitator (Fisatom 175) at 200 rpm during 15 minutes. Sodium lauryl sulfate was the last excipient added. The Chamomile extract concentrations were 3.0% and 5.0%. The Chamomile extract is used between 1.0 and 10%. The pH of the preparations ranged between 6.0 and 6.5.

**TABLE 1.** Components and concentration (in %) of formulations containing hydrophilic gelling agents.

Ingredients	Supplier	G1	G2	G3	G4	G5	G6	G7	G8
Carbopol® 940	Henrifarma	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
EECS	—	3.0	5.0	—	—	3.0	5.0	—	—
RECE	—	—	—	3.0	5.0	—	—	3.0	5.0
EDTA	Volp	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Methylparaben	Vital	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Propylparaben	Vital	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Imidazolidinyl urea	Vital	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Glycerin	Merck	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
LSS	Vetec	—	—	—	—	1.0	1.0	1.0	1.0
Triethanolamine	Quimex	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Ethyl alcohol	Synth	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Distilled water	—	100	100	100	100	100	100	100	100
qsp									

G= gel; EECS= Extractive Ethanolic Chamomile Solution; RECE= Raw Ethanolic Chamomile Extract; EDTA= ethylenediaminetetraacetic acid; LSS= lauryl sodium sulfate; qsp= quantity considered sufficient.

#### *Analytical conditions*

High-Performance Liquid Chromatography (HPLC) used to assess the quality of the chamomile extract was a Shimadzu Prominence system, with an SIL-20A automatic injector fitted with a 50 µL loop, a LC-20A solvent pumping system, and a UV detector (Shimadzu Corporation, Japan). A C18 reversed phase column of 150 mm x 2.1 mm was used on 3.5 µm lab-made silica (Kromasil). The injection volume was 10 µL with a 0.2 mL/min flow, at room temperature (25 ± 1°C). Detection was performed at 254 nm and 350 nm. The mobile phase gradient with acetonitrile (ACN) HPLC grade (Fischer) and 20 mM ammonium acetate buffer (pH 6.7) started at 55% ACN, for 1.0 min., followed by 90% ACN, for 5.0 min.; and 55% ACN, for 7.0 min.

*Analytical solutions*

The standard apigenin (Sigma Aldrich® St Louis, MO, USA) and Diclofenac Sodium (*Natural Pharma*, São Paulo, Brazil) solutions were prepared individually, by transferring 10 mg of each into a 25 mL volumetric flask. About 20 mL of methanol was added to each flask, and agitated by sonication for 10 minutes. The volume was completed with methanol, to obtain 400 µg/mL solutions. The standard solutions were diluted with ACN:20 mM ammonium acetate buffer, pH 6.7 (50:50), to prepare 20 µg/mL working solutions. The EECS and RECE extracts were also prepared using this dilution system, the quantitative of the extracts was 10 mg. All samples were filtered through non-sterile Millipore® FGLP membranes, with a 0.45-µm pore size, and a 13-mm diameter (Millipore Corporation, MA, USA), before injection in the HPLC.

*Carrageenan-induced paw edema test*

Male Wistar rats (230 to 280 g) were maintained under controlled environmental conditions (22±2°C, cycles of 12-h of light and 12-h of darkness) and fed with Purina® and water *ad libitum*. The animals were trichotomized with an electrical shaver on a back skin area of approximately 10 cm<sup>2</sup> 24 hours before the tests and food and water were withdrawn two hours before the tests. One gram (1.0 g) of each one of the Chamomile gel formulations tested (groups G1 to G8; Table 1), of the extract-free gel formulation and of Diclofenac Sodium gel 1.0% was applied to the back skin (Lira *et al.*, 2007; Penzés *et al.*, 2005; Prendel *et al.*, 2005) of each animal (n=5), and the gel was rubbed 50 times to enable good distribution and penetration of the delivered drugs in the skin. One hour after the application, 0.1 mL carrageenan 1% (p/v) (Sigma®, St.Louis, MO, USA), diluted in sterile saline solution, was applied on the intraplantar region of the right hind paw of each animal, and an identical volume of saline solution 0.9% was applied on the left hind paw of each animal (Gil *et al.*, 2012; Mothana, 2011; Akdemir *et al.*, 2011; Akkol *et al.*, 2010; Semnani *et al.*, 2004).

The paws were immersed as far as the lateral malleolus (right paw first) in a simulated plethysmometer-type equipment (Santa-Cecília *et al.*, 2011; Lira *et al.*, 2007) containing a water: ethyl alcohol: tween 80 (80:20:0.05) solution and the displaced volumes (mL) were measured every hour, for 5 hours. In each test, the final reading corresponded to the difference between the volume displaced by the right paw (treated) and the left paw (control). The study also included a carrageenan group (n=5), in which the animals did not receive any gel formulation on the back skin.



This study was approved by the Animal Ethics Committee of the University of Brasilia's Institute of Biology, under the number 16632/2006.

#### *Statistical analyses*

Data were analyzed by two-way analysis of variance (ANOVA) using SPSS (*Statistical Package for the Social Sciences*), version 17.0. Differences were considered significant when  $p < 0.05$ .

## RESULTS AND DISCUSSION

The two Chamomile extracts (EECS and RECE) obtained were analyzed by HPLC to evaluate the presence of apigenin, which is the most abundant flavonoid found in *Matricaria recutita* L. The chromatographic profile of the apigenin standard and Diclofenac Sodium under the conditions used in this study is shown in Figures 1A and 1B. The presence of apigenin was confirmed in the extracts, as shown the Figures 2A and 2B, a result that was previously confirmed by thin layer chromatography (Queiroz *et al.*, 2009).

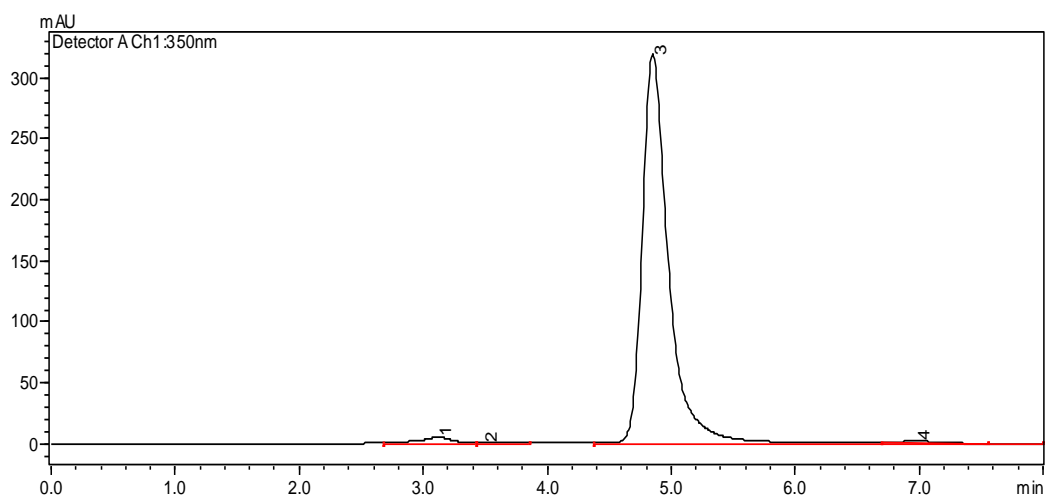


FIGURE 1A. Chromatogram of a HPLC analysis (350 nm) of the apigenin standard, at 10  $\mu\text{g/mL}$ .

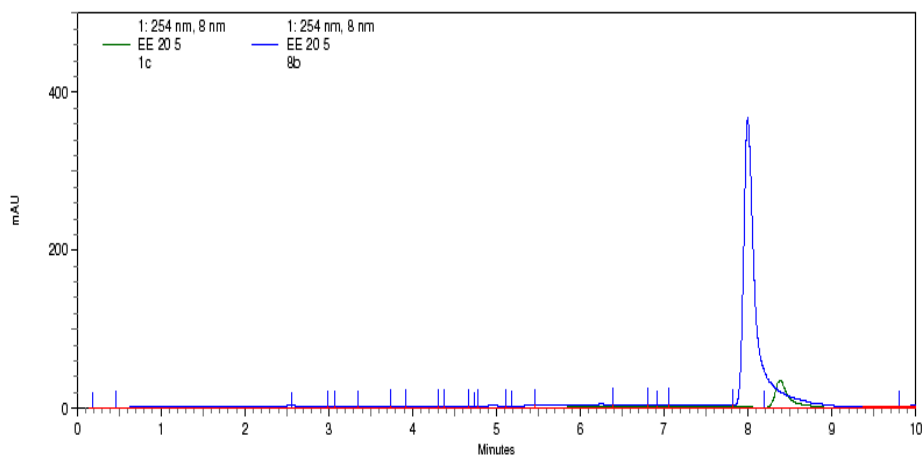


FIGURE 1B. Chromatogram of a HPLC analysis of Diclofenac Sodium.

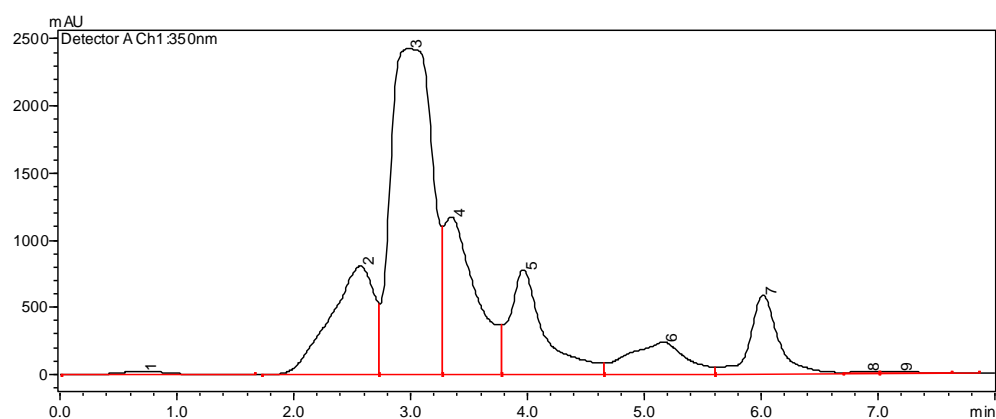


FIGURE 2A. Chromatographic Raw Ethanolic Chamomile Extract (5 µg/mL) profile obtained by HPLC (350 nm), showing apigenin at approximately 5 minutes (6).

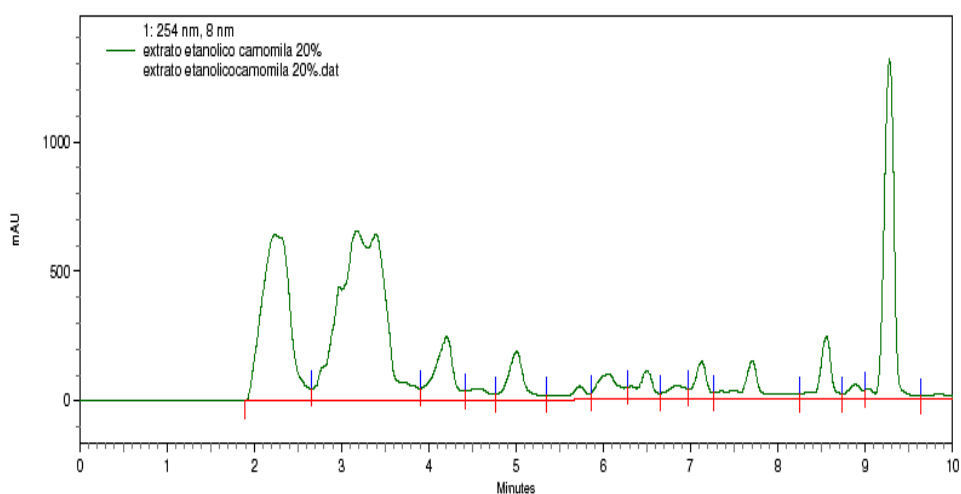


FIGURE 2B. Chromatographic Extractive Ethanolic Chamomile Solution (5 µg/mL) profile obtained by HPLC (254 nm), showing apigenin at 5 minutes.

Chamomile has been approved by the German Commission E for oral consumption and topical application in the treatment of various skin disorders and inflammatory disorders of certain mucosal surfaces, such as the oral cavity and ano-genital areas. Recent studies have demonstrated its antioxidant, hypocholesterolemic, anti-parasitic, anti-aging, and anticancer properties, supporting its longstanding traditional use for treating various human ailments (Srivastava *et al.*, 2009).

In literature, some authors mention that, after penetration and passage through the stratum corneum, the active substance may reach the dermis or even the subcutaneous layer, depending on its physical and chemical characteristics (Muggleston *et al.*, 2012; Lachman *et al.*, 2010).

The study was conducted by applying the gel formulations on the back skin of the animals according to a previously study about lapachol gel and Piroxicam from organogels (Lira *et al.*, 2007; Péntzes *et al.*, 2005). The lapachol gel and Piroxicam organogels studies were used as reference because they are topical preparations used in order to evaluate the anti-inflammatory action of each drug.

In a study, they compared comfrey root extract with a Diclofenac gel, so we decided to use the Diclofenac Sodium gel 1.0% as a parameter in our study. Diclofenac acts as a potent cyclooxygenase inhibitor. Its pharmacological properties are well documented and generally known (Predel *et al.*, 2005).

Carrageenan induces paw edema as a result of the release of mediators such as histamine, serotonin, bradykinin, substance P and platelet aggregating factors, as well as prostaglandins via cyclooxygenase (COX) (Ferreira *et al.*, 2013; Sousa *et al.*, 2009). Figures 3A-3C and 4A-4C show the results obtained in the carrageenan-induced paw edema test with the gels prepared in this study with and without the permeation enhancer, measured as the volume displaced in the simulated plethysmometer system. No significant differences were found in the extent of the edema among all tested Chamomile gels (G1 to G8) and the chamomile-free gels, indicating that the presence of the chamomile extract with or without the permeation enhancer did not have any effect on the performance of the gel over the edema. The lauryl sodium sulfate was used as permeation enhancer because it is non-ionic surfactant that does not irritate the skin and mucous.

Figures 3A and 4A show the results for the carrageenan, carbopol gel (with LSS and without LSS), and the Diclofenac Sodium gel 1.0% groups. There was evidence that the Diclofenac Sodium gel 1.0% was able to revert the edema 1 hour after the application, however this result was not statistically significant ( $p=0.054$ ). This potential anti-

inflammatory effect did not remain afterwards. In general, there were also no significant differences in the extent of the edema between the prepared gel formulation group, the carrageenan-induced edema group and the Diclofenac Sodium gel 1.0% group, at any time of the experiment. Exceptions were the groups G1 (EECS gel 3%) and G3 (RECE gel 3%) at reading time of 4 hours, where the edema was significantly larger ( $p < 0.01$ ) than that observed after the Diclofenac Sodium gel 1.0% treatment (Figures 3B and 3C).

In a study about clinical efficacy of Chamomile extract it was concluded that Chamomile extract mouthwash was effective in reducing gingival bleeding in periodontal disease suggesting that the extract has anti-inflammatory and antimicrobial actions similar to those of the chlorhexidine 0.12% (Batista *et al.*, 2014). In other study about premenstrual syndrome the Chamomile was used because it has anti-inflammatory and analgesic actions. The presence of Apigenin flavonoid present in Chamomile has anti-inflammatory, analgesic and antineoplastic effect. In fact, the results showed Chamomile is more effective than Mefenamic acid on premenstrual syndrome psychological symptoms. It may be due to presence of Flavonoid, a central nervous system stimulating molecule, and Apigenin and Luteolinin, which are antianxiety and relieving because of their binding with Benzodiazepine receptors (Sharifi *et al.*, 2014; Viola *et al.*, 1995).

Chamomile inhibits prostaglandin synthesis by a mechanism similar to that induced by NSAIDs. Many phenolic compounds of plant origin, especially flavonoids, possess anti-inflammatory, anti-carcinogenic and free radical scavenging properties and the number of molecules isolated and characterized continues to increase. Previous studies have demonstrated that individual constituents of Chamomile such as chalmuzene, luteolin and apigenin are efficacious in inhibiting COX-2, iNOS and leukotrine expression in cell culture (Srivasta *et al.*, 2009).

Many factors affect the therapeutic action of a drug when it is applied to the skin, including the characteristics of the drug and its affinity with the excipient, which may delay its therapeutic action or even prevent its release. Additionally, the method used to apply the formulation may also interfere, due to the mechanical action needed to ensure even distribution. Furthermore, the physical conditions of the skin may also play a role, since skin hydration is also an important factor that may affect the formulation's potential percutaneous penetration and absorption (Muggleston *et al.*, 2012; Lachman *et al.*, 2010).

Some authors pointed out that gel-based formulations have been indicated for topical applications, since such formulations tend to release the molecules of the drug more easily

than creams or ointments, due to better viscosity, satisfactory bioadhesion and the absence of irritation or sensitivity to gels (Barreira *et al.*, 2013; Lachman *et al.*, 2010).

In this study the Chamomile gel with LSS did not show a significant reduction in paw edema induced with carrageenan. We know the potential of Chamomile in inflammation so there is necessity to investigate what happened that this sample of Chamomile did not have anti-inflammatory effect significant.

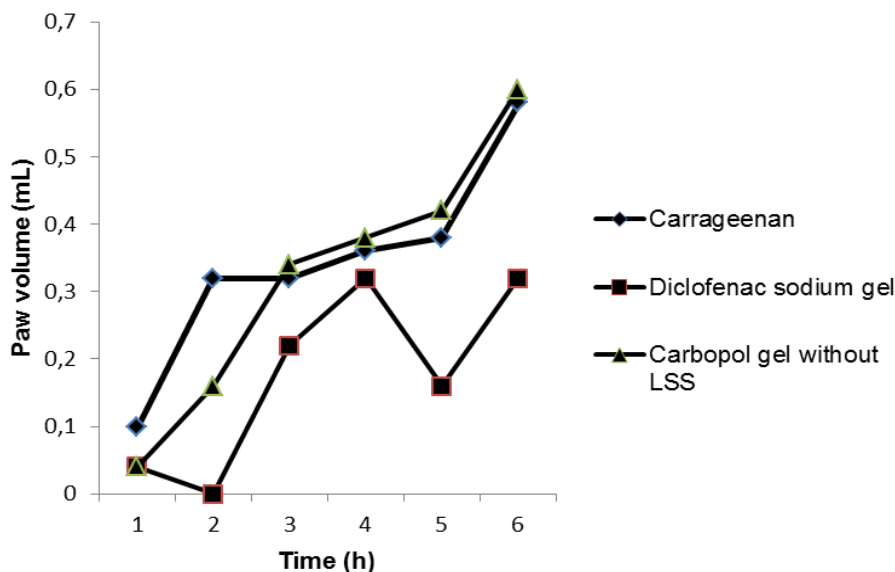


FIGURE 3A. Mean values of treatments with carrageenan, diclofenac sodium gel, and carbopol gel without permeation enhancer using (n=5) during five hours.

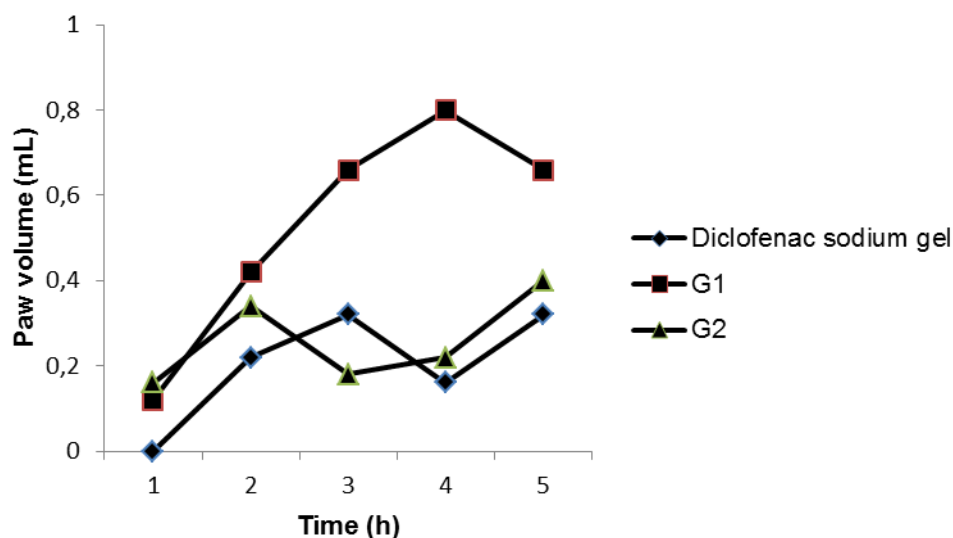


FIGURE 3B. Mean values of treatments without permeation enhancer using Extractive Ethanolic Chamomile Solution of 3.0% (G1) and 5.0% (G2) using (n=5) during five hours.

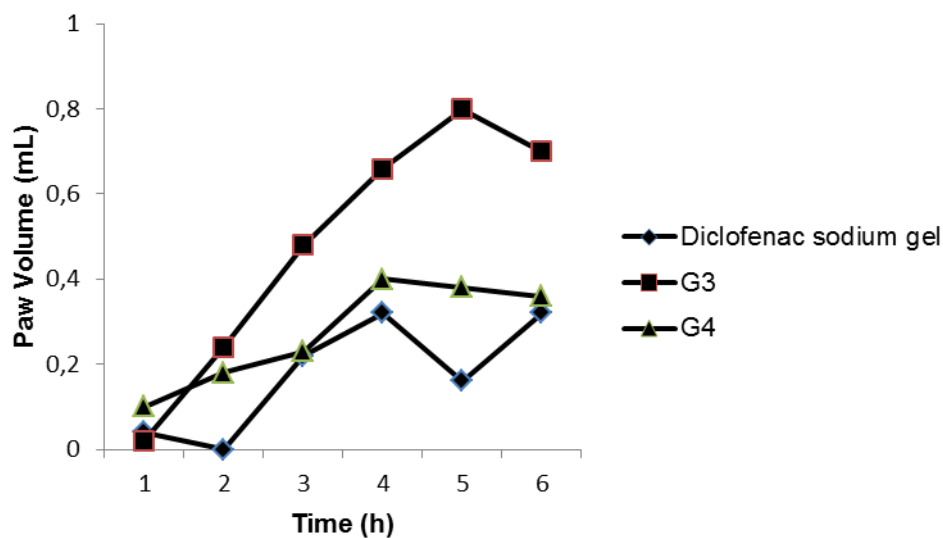


FIGURE 3C. Mean values of treatments without permeation enhancer using Raw Ethanolic Chamomile Extract of 3.0% (G3) and 5.0% (G4) using (n=5) during five hours.

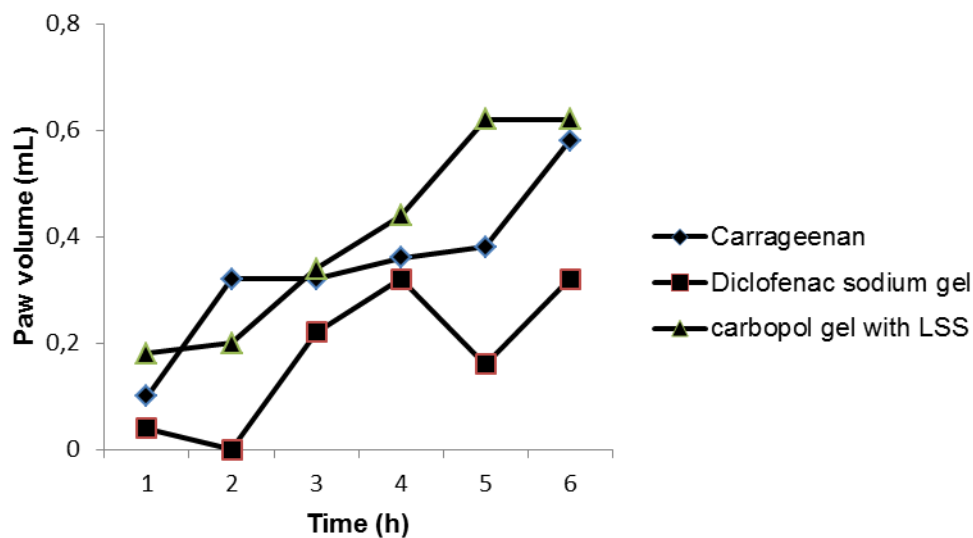


FIGURE 4A. Mean values of treatments with carrageenan, diclofenac sodium gel, and carbopol gel with permeation enhancer (LSS) using (n=5) during five hours.

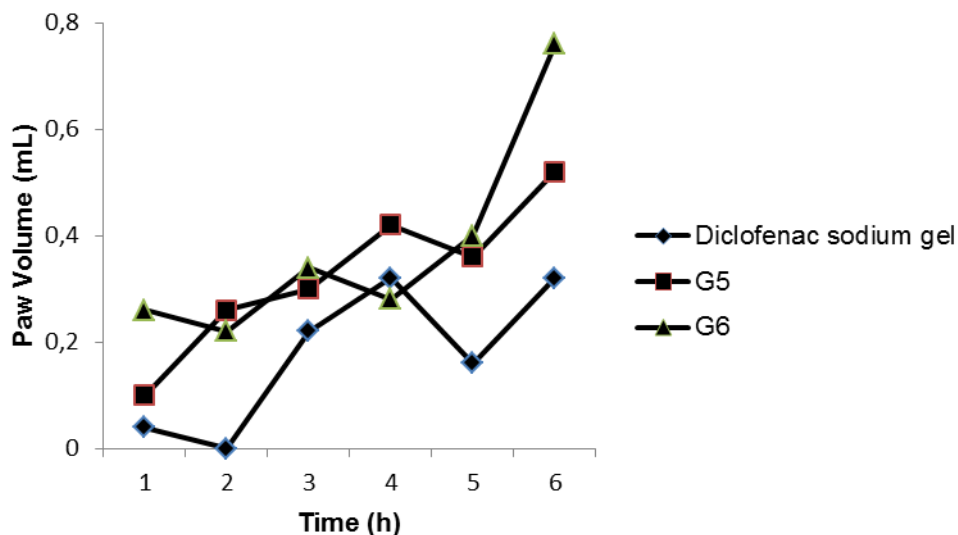


FIGURE 4B. Mean values of treatments with permeation enhancer (LSS) using Extractive Ethanolic Chamomile Solution of 3.0% (G5) and 5.0% (G6) using (n=5) during five hours.

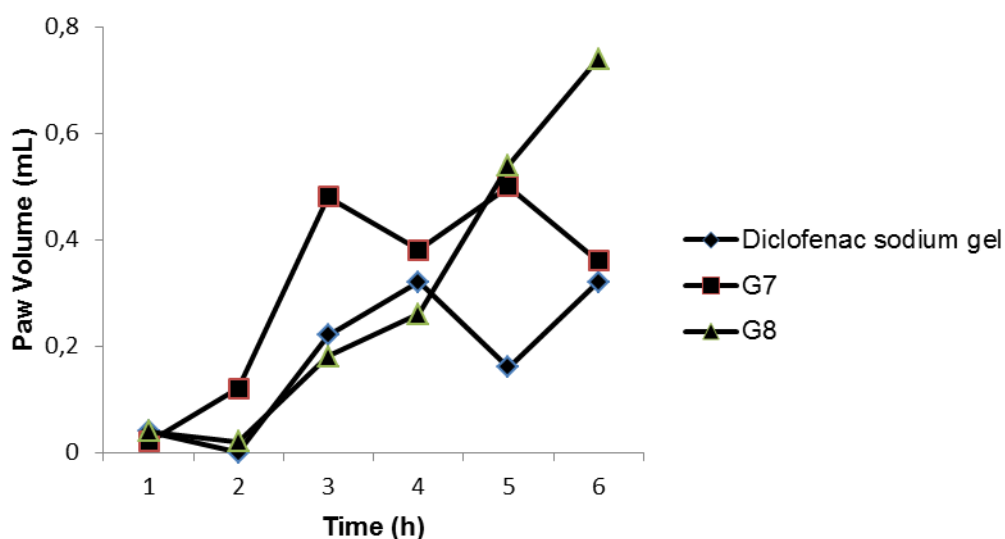


FIGURE 4C. Mean values of treatments with permeation enhancer (LSS) using Raw Ethanolic Chamomile Extract of 3.0% (G7) and 5.0% (G8) using (n=5) during five hours.

## CONCLUSION

This study showed that hydrophilic carbopol® gels containing Chamomile extracts were not able to induce anti-inflammatory action when applied on the back skin of animals with carrageenan-induced paw edemas. However, under the same conditions, Diclofenac Sodium gel 1.0% did not show significant anti-inflammatory action over the induced edema.

We believe that the administration site, far from the edema, was critical to the absence of anti-inflammatory activity. Moreover, the use of a permeation enhancer did not improve the penetration of the formulation and produce the expected result. More studies should be conducted with another gel formulation and permeation enhancer to have more certainty as to affirm the action of anti-inflammatory Chamomile extract in topical gel.

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