THERAPEUTIC EFFECT OF ARNICA OINTMENT ON CICATRIZATION PROCESS OF APHTHAS AND LESIONS IN HUMAN ORAL MUCOSA

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Summary

Aphthas are small painful ulcers that appear in the mucosa of oral cavity. These ulcers can form a small lesion, in which pain is not proportional to size. With the intention of attenuating discomfort caused by these ulcerations, the present study has developed an Arnica Montana L tincture-based ointment at concentration of 30% with the purpose of verifying the anti-inflammatory and healing activity of this phytotherapeutic component in the treatment of ulceration lesions in patients' oral mucosa and observe the development of the repair process. The sample of the investigated population consisted of individuals that presented a history of recurrent oral mucosa ulceration. The patients were assessed by visual observation and answered a questionnaire, in which majority reported improvement in the inflammatory condition, which corroborates the definition of the potent anti-inflammatory and healing activity of arnica. The results proved the efficiency of the pharmaceutical preparation with arnica as the active principal, and it is a nontoxic, accessible and adequate therapeutic option.

***Keywords*:** Arnica, healing, pain, aphthas, oral mucosa.

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Introduction

The most frequent oral mucosa lesions are the aphthous ulcerations with a prevalence of 4.6 to 30.6%. (1) These can be defined as a fundamental lesion characterized by the absence of the epithelial tissue layer, which makes the subjacent conjunctive tissue unprotected and vulnerable to external aggressions. There are three main forms, the most common being the small aphtha with small, rounded, defined ulcerations that are painful and heal in 10 to 14 days. The other form of recurrent aphthous ulceration is the type of deep long Aphthas that present a grayish yellow aspect, with the same period of duration and the patient frequently presents monthly lesions. They are also called herpetiform aphthas. A third form of recurrent aphthous ulcerations are those distributed on the tongue dorsum, jugal mucosa but not in the keratinized region. All these forms cause pain, discomfort and debilitate the patient, because it makes eating difficult and aggravates the clinical condition of inflammation.

The exact reason for the appearance of these lesions remains obscure, but it may be affirmed that the contact of the oral mucosa tissues with physical agents capable of inducing trauma such as the edges of teeth, fractured crowns or defected restorations and maladapted orthodontic and prosthetic appliances or even the ingestion of acid foods represent the main causes. (2)

The form of treatment indicated can vary depending on the professional and the period of the inflammatory cycle, and as therapy, antimicrobial compounds (terramycin, neomycin), non steroid anti-inflammatory (derived from propionic acid), and steroid anti-inflammatory (triamcinolone -Oncilom-A®) (3) agents may be used.

Recently a medication named Amlexanox was released on the European market; it is a new drug capable of reducing pain and accelerating repair process of these lesions, but this drug is not available in Brazil yet.

Nevertheless, many patients that come to the dental offices with aphthas and stomatitis seek natural treatment for these afflictions. However, since the studies in this area are still at the developmental stage, an approach to prescription, posology and pharmacokinetics of these medicinal plants is needed, and this has led pharmacology, pharmacognosis, phytochemistry and microbiology entities to invest in research of new drugs with active principals of natural origin.

Arnica can be used in the form of an extract, tincture, gel or ointment. To prepare the mother tincture for external use a whole plant is used; the roots must be used only for preparation of the mother tincture for internal use (5).

There are various chemical constituents of arnica, among them terpenic acid, flavenoids, carotenoids, palmitic acid, linoleic acid and essential oils. The oleoresinous composites are the ones that have the majority of the therapeutic properties (6). When the tincture or infused oil of arnica was topically applied on injured tissues, the macrophage activity and blood circulation in the area increased, thus facilitating the removal of dead cells and accelerating the healing of the injured tissue (7).

The anti-inflammatory potential of arnica by topic administration is attributed mainly to the action of its essential oil. The helenalin and the dihidrohelenalin (terpenic constituents) have shown anti-inflammatory efficacy in laboratory experiments. The mechanism is explained by the inhibition of the prostaglandin synthesis by blocking the prostaglandin-synthetase enzyme. The caffeic and chlorogenic acid esters are abundant in the family of composites, and have shown an inhibitory action on arachidonic acid (8).
The inhibition of collagen induction in platelet aggregation and thromboxin formation occurs by the action of helenalin (H) and dihidrohelenalin (DH). Both H and DH inhibit platelet formation interacting with platelet sulphydril groups probably associated with the phospholipase A2 reduction (9). By the inhibitory effect of platelet aggregation it was observed that some patients presented alterations in the parameters of coagulation and even bleeding, after the systemic administration of arnica (10).

The sesquiterpene lactones, which are one of the chemical constituents of arnica derived from terpenic acid, have been shown to have a good antieczematous effect by inhibiting the oxidative phosphorylation of the polymorphonuclear cells and their migration, at the same time as they prevent lisossomal membrane rupture (11).Furthermore, as regards the sesquiterpene lactones, it has been suggested that these inhibit transcription gene factors involved in the release of chemical mediators of the inflammatory process, especially in chronic inflammatory diseases, such as osteoarticular conditions (12).

The main objective of this study was to verify the anti-inflammatory and healing activity of *Arnica montana* in the form of an ointment for the treatment of ulcer lesions of human oral mucosa, as well as observing the development of the repair process.

Materials and Methods

1 – Ointment preparation:

The ointment with the active principle was prepared by using 70% of base ointment and 30% of arnica tincture.

The *Arnica montana* tincture used in this experiment was prepared with flowers (Schraiber – Homeopatia – São Paulo, Brazil) whose identification report reveals the physical-chemical characteristics according with the 4th edition of the Brazilian Pharmacopoeia standard.

The base ointment was prepared as follows: Nipagin, Nipazol and Propylene was heated in a clean and sterilized beaker (A) until completely dissolved, but without exceeding 70°C.At the same time, in another clean and sterilized beaker (B) BHA, Carbowax 400, Carbowax 4000 and Glycerin were heated until completely dissolved, also not exceeding 70°C.

Next, the contents of beaker A were added to the contents of beaker B, and were homogenized under continued heating. Soon after the mixture was taken off the heating it was cooled to 40°C and then saccharine was added. It was stirred until the desired consistency was obtained.

1.1- Placebo:
For the placebo, 70% of base ointment and 30% of 77°GL alcohol were used and a yellow coloring was added to simulate the color of arnica tincture, thus preventing the lack of active principle from being noticed.

2- Population
The population sample investigated in this study consisted of 31 individuals (men and women) that had presented a history of oral mucosa lesions, such as aphthas, mucositis, stomatites, cheilitis and others. The entire experimental part was performed after obtaining approval from the Research Ethics Committee of the Catholic Pontifical University of Paraná.

3- Experimental Group
The patients were divided into two groups. The first consisted of patients that had presented an ulcer and recurrent ulcer history (more than four episodes per year) (Experimental Group n=21). The arnica-based ointment was applied three times a day after oral hygiene on ulcer. The patients were duly instructed how to use the ointment and received a questionnaire to fill out during treatment, in order to observe the effect of arnica ointment.

4-Control Group
The second group also consisted of patients that had presented a history of recurrent ulceration, however, they received the ointment without the active principle, and formed the control group (n=10). The patients from the control group were also previously instructed how to use the ointment and received a questionnaire to fill out during treatment, in order to observe the effect of ointment (placebo).

5-Questionnaire
The patients returned to clinic and were assessed during a period of 7 and 14 days by visual observation and answered the questionnaire as follows:
1. Did you feel pain? Discomfort?
2. Did you have fever?
3. Were there secretions?
4. Were you able to eat adequately?
5. Were you able to brush your teeth correctly?
6. From 1 to 10, what was the level of pain and discomfort?
7. Was it better to use the ointment than other medications?
8. Were the flavor and appearance of the ointment acceptable?
9. Did the ointment have good adherence, not becoming easily detached from the place where it was applied?
10. Did you follow the posology?

Results and Discussion

This study was composed of a total of 31 patients, and after the treatment for 14 days, they answered the questionnaire. We observed aspects clinical of the patients received the base ointment and the majority (71%) reported improvement of the inflammatory condition in general. Moreover, the (52%) that received the arnica ointment perceived a faster ulcer lesion healing process in the oral mucosa, and (45%) reported an analgesic action. Surprisingly most of the patients observed an anesthetic effect from the arnica ointment which helped the patient to keep a

healthy diet and good oral cavity hygiene. None of these results were observed in the patients that used only the control ointment, and some patients (48%) stopped using it because they did not notice any improvement. This data is very important to show that it was not the lubrication of the base ointment that caused the pharmacological effect, which proves the therapeutic activity of arnica.

In this study, the patients that used the arnica ointment reported that the cicatrisation period was faster when compared with other treatments and the ointment reduced the discomfort caused by the lesion. This corroborates with findings of Merfort (12) that considered the sesquiterpene lactones the most important constituents of arnica, capable of preventing genic transcription factors involved in the syntheses of the chemical mediators of the inflammatory process, thus interfering in the formation of prostaglandin, prostacyclin and other mediators suppressing the inflammatory process and preventing lesion from becoming chronic. Convergent with the findings of the present study, since the lesions present rapid improvement accelerating repair process, clinical findings have shown reduction in lesion size, diminishment of the hyperemic state and burning.

Aphthous lesions are characterized particularly by pain that frequently is not proportional to size of the ulceration (13). An important result in this study was the anesthetic action caused by the arnica ointment, as patients reported a feeling of anesthesia. Arnica has various chemical constituents, among them the following are pointed out: terpenic acid, flavenoids, carotenoids, palmitic acid, linoleic acid and essential oils. The oleoresinous composites are the ones that have the majority of therapeutic properties (6). It is suggested that the anesthetic action of arnica must be by means of interaction of these chemical constituents, since they all present a pharmacological activity in the inflammatory process, reducing the pain caused by these lesions. That is to say, the anesthetic action of *Arnica montana* is of the utmost importance and further pharmacological trials must be conducted to prove this finding.
Another relevant finding of arnica is the analgesic action. The chemical mediators involved in the inflammatory process are also responsible for algesia; they cause pain. Helenalin and dihidrohelenalin have been shown to have anti-inflammatory properties through inhibition of prostaglandins syntheses, by blocking the prostaglandin-synthetase enzyme. This property is reinforced by the presence of carotenoids, flavenoids and magnesium salts which, by inhibiting the production of these chemical mediators, inhibit the painful feeling (8).

Studies have proved the pharmacological activity of amlexanox in the repair process and have also compared its activity with the extract of glycyrrhiza, which like arnica, also has flavenoids and terpenoids (3).

As active principles, Glycyrrhiza has flavenoids, terpenoids and essential oils and it has many pharmacological effects, such as increase in macrophage function, anti-inflammatory action and cicatrisation. The application of the glycyrrhiza-based extract reduced the duration, size and pain of lesions (3). These findings are in agreement with the present study that has proved the therapeutic action of arnica on these variables, and furthermore, the phytochemical constitution of these bioactive agents have elements that are equipotent.

According to this study, *Arnica montana* has presented pharmacological relevance in the repair process of oral mucosa lesions, by activating cicatrisation, reducing the

pain process. Moreover, patients that received arnica because they presented lesions of an infectious nature also reported a significant improvement in the infection. Among these findings, 2 patients that presented lip herpes and angular cheilitis are outstanding. The pharmacological action of the arnica ointment was surprising by reducing the period of lip herpes cycle and also in angular cheilitis lesions (*Candida albicans*). Patients that used the ointment for treatment of these lesions presented less painful sensitivity, did not report fever and were able to eat without difficulties. Thus, the antimicrobial and anesthetic activity of arnica was proved. There are also reports in literature of the antimicrobial action of arnica, particularly against the gram positive bacteria and *Staphylococcus aureus* (14) as well as antiviral action (15).

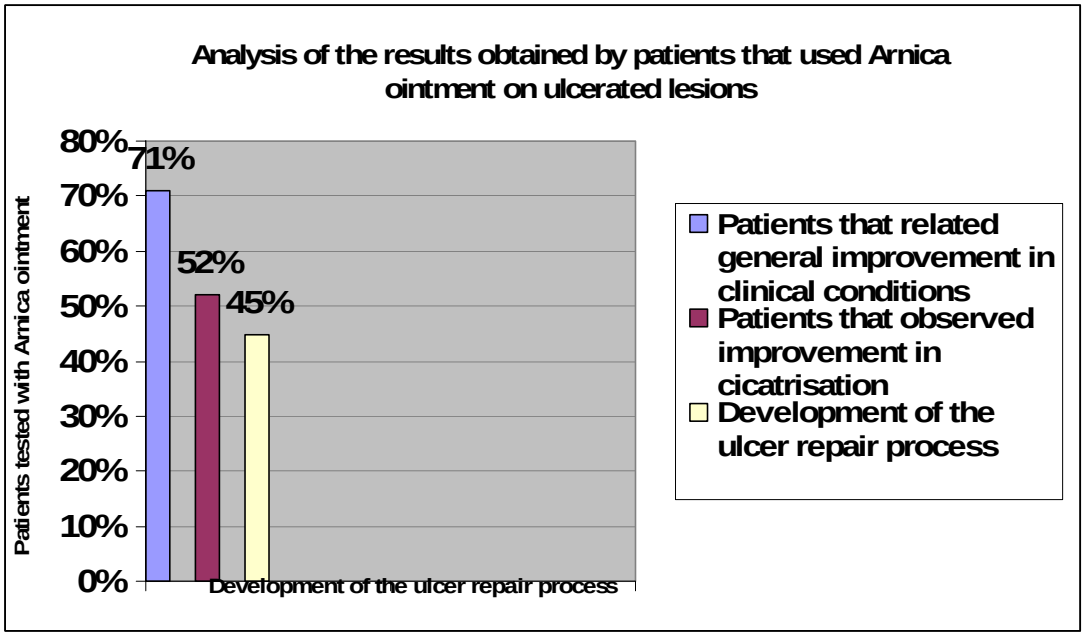
Moreover, arnica was efficient for treating ulcer lesions in the oral mucosa of a patient that was an isotretinoin user (retinoic acid derivative – anti-acne action). This proves the great anti-inflammatory potential of the arnica ointment, because the patients that used these anti-acne drugs reported xerostomia and xerophthalmia, and furthermore, they can cause mouth lesions. Thus, because arnica has resinous oil constituents it was capable of diminishing inflammatory process of oral mucosa caused by these drugs.

During the inflammatory process, chemotaxis occurs in some cells, such as mastocytes, macrophages, neutrophils and, at a second stage, in lymphocytes. The appearance of these cells in different stages accelerate or inhibit the repair process of tissue lesion; that is, each of these cells have a specific physiopathological role in inflammation. By means of experiments with animals, GREGIO et al (16). verified an increase in number of some of these cells in oral mucosa ulcers in rats treated with arnica, among these cells, the presence of neutrophils and macrophages is outstanding in order to phagocyte and to digest the inflammation faster. In a second phase, there was a fibroplasia guaranteeing a rapid tissue re-epithelization. These findings corroborate the present research, which verified a reduction in the period of inflammation in patients that used the arnica ointment. This effect was particularly notable in treatment of lesions of an infectious nature, suggesting a chemotaxis for the phagocytic cells that combated this process.

The sesquiterpene lactones evidenced a good antieczematous effect by inhibiting the oxidative phosphorylation of polymorphonuclear cells and their migration, at the same time as they prevented lisossomal membrane rupture (11).The phagocytic activity of arnica was observed by COHEN, et. al (7) (particularly macrophages) facilitating removal of foreign bodies and accelerating injured tissue healing. Similar results were observed in studies of CHATONET (17) and RAMELET (18).

Conclusion

All the results found in this study reinforce the potent anti-inflammatory and cicatrisation activity of arnica on the repair process of lesions in oral mucosa, and suggest that pharmacological preparations containing arnica facilitate this process, and are an adequate, accessible and non toxic therapeutic option, since patients that participated in this study did not report presence of undesirable adverse effects.



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