PharmacologyOnLine December 30, 2015

Archives • 2015 • vol.3 • 123-130

TOPICAL EFFECTS OF *CHAMOMILLA RECUTITA* IN SKIN DAMAGE: A LITERATURE REVIEW

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Abstract

To identify the available evidence in the literature on topical effect of *Chamomilla recutita* to prevent and/or treat skin damages. This is a literature review which search was conducted in the following bibliographic databases: The Cochrane Library, PubMed, LILACS, CINAHL, and Web of Science. A total of 11 comparative clinical studies used chamomile in different skin conditions: erythema, pityriasis alba, similar to eczema lesions, peristomal injury, contact dermatitis, phlebitis, atopic eczema, radiodermatitis, induced contact dermatitis, wound healing, and eczema. It is necessary to develop comparative clinical studies that tests standard formulas and the outcomes need to be measure by validated scales to encourage the use and reproducibility of pharmaceutical preparations containing *Chamomilla recutita* in clinical practice.

Keywords: Chamomile, Matricaria, Skin diseases, Review.

Introduction

Among the wide variety of medicinal herbs the *Chamomilla recutita* (*C. recutita*), Asteracea family plant, stands out and it has one of the most common uses of the herbal therapeutic forms. Its anti-inflammatory properties has been widely described such as antioxidant activity [1], antispasmodic, sedative, anti-microbial, anti-allergic, anti-hyperglycaemic and antimicrobial, justifying the recognized use as medicinal herb [2].

C. recutita has different components including coumarins, flavonoids and sesquiterpenes. Apigenin is a flavonoid found in larger quantities in chamomile flowers and contributes to the pharmacological properties described [3]. The use of *C. recutita* has been described for different skin conditions, such as eczema and skin irritations [4]. The search for herbal products to control skin damage is significant, especially considering the interest in measures causing minor side effects when compared to pharmacological therapies [5]. Interest in the topical effect of chamomile already ranks among other publications, among them a systematic review [6]. However, the article is published in Danish, which reduces the scope of the information described. In addition, the article includes studies in vitro and in vivo and suggests lack of evidence about the dermatological effects of chamomile. Thus, considering the different actions described in *C. recutita* and its use in skin damage, we sought to identify the available evidence in the literature on the topical effect of *C. recutita* to prevent and / or treat skin damage in comparative studies.

Methods

This is a literature review. This is a literature review. The guiding question constructed by PICO strategy (7) was “What the topical effect of C. recutita to prevent and / or treat skin damage?". Publications were considered only in Portuguese, English, Spanish and German, with no limit to publication date. Reviews, letters to the editor, expert opinions, case reports and preclinical studies were excluded. Search strategies were developed for each of the following bibliographic databases: The Cochrane Library, PubMed, LILACS, CINAHL, and Web of Science. The crossing of the descriptors and keywords, obtained by prior knowledge articles that addressed the topic studied, was performed for each database. For the databases The Cochrane Library, PubMed, CINAHL, and Web of Science, the following search strategy was applied: (matricaria OR chamomile OR chamomilla OR chamomilla recutita OR camomile) AND (skin OR skin care OR skin lesions OR skin disease OR dermatitis OR dermatologic agents OR skin manifestations OR skin reactions OR skin healing OR wound OR wound dressing). The strategy applied to the base LILACS was matricaria OR camomila OR manzanilla [words]. The strategy applied to the base LILACS was: matricaria chamomile OR OR manzanilla [words]. The searches in electronic databases were held in February 2015. After the search, duplicates have been removed. To select the articles, two reviewers assessed independently, the titles and abstracts of all references obtained through search in the databases. At this stage, all the items that did not meet the selection criteria were excluded. The differences were evaluated by a third reviewer. After the initial selection, the articles were read in full by the first two reviewers, applying the inclusion criteria again. Considering that abstracts some could present sufficient information to apply the selection criteria, at this stage the third reviewer was consulted again if there was any disagreement on the selection of items. Two reviewers extracted data independently, to conduct a cross between all the information extracted from articles. Disagreements were resolved by discussion and mutual agreement between the two reviewers. Again if there was no consensus among the information collected by the first two reviewers, a third reviewer was consulted to evaluate the disagreements. For each of the selected studies, there were different data, as follows: year of publication, language, evaluated clinical situation, objective, study design, size and characteristics of the sample, evaluated intervention, strategy applied to measurement of outcomes, follow-up and product application rate, statistical analysis, and main results.

Results

We identified 500 records in databases searched, among which 392 were eligible for the study. After reading the titles and abstracts, 17 studies were selected to read in full by the reviewers. Eleven were selected for qualitative synthesis of this review (Figure 1). The selected studies presented topical effect of chamomile in different skin conditions: erythema induced by UV radiation [8], pityriasis alba [9], lesions similar to eczema [9], peristomal lesion [10], contact dermatitis [11], phlebitis [12], atopic eczema [13], UV-induced erythema or removal of adhesive tape [14], acute skin reaction induced by radiation (radiodermatitis) [15], induced contact dermatitis [16], wound healing [17] and eczema [18]. Six studies were in English [9-11,13-15], four in Germany [8,16-18] and one in Portuguese [12].

The synthesis of studies is presented in Table 1, which provides information about the purpose of each selected study, the number of participants in the sample specifying the intervention groups when this information was present in the studies, how to measure the outcomes, follow-up, product application rate, some data on the statistical analysis and the main results.

Discussion

Studies involving various formulations tested *C. recutita* in acute skin reactions due to physical [8,10,14-17], chemical [12] or immunological causes [9,11,13,18]. The formulations, used were aqueous extracts and alcohol, infused, hydroalcoholic cream, and ointment containing α-bisabolol and chamazulene, that commercial name is Kamillosan®. The *C. recutita* consists of terpenes (bisabolol and chamazulene), flavonoids (apigenin and coumarins) and steroids [1,19]. Terpenes and flavonoids act by inhibiting the classical pathway of complement system and interfering with the metabolism of arachidonic acid by inhibiting prostaglandin synthesis and alleviating the enzymes cyclooxygenase pathway, which justifies the anti-inflammatory activity of the plant [1].

The erythema was the most common primary outcome among the selected studies, but showed no homogeneous measures to its measurement, with description of different scales and grades of erythema. Assessed as secondary outcomes were identified: swelling, blistering, itching, flaking and skin healing. The effect of chamomile was compared to corticosteroids in six of selected studies, with the majority (n = 4) showed superior therapeutic effect of chamomile [10, 13, 16] or similar [18]. In a study to evaluate the effectiveness of hydroalcoholic cream chamomile extract to 10% versus placebo cosmetic cream developed with 44 individuals with pityriasis alba and like eczema lesions, there was high response rate both in those receiving chamomile cream as in those who received placebo cream, with no statistically significant difference between them [9].

Effect assessment of the Kamillosan® (cream containing ethanol extract to 2% chamomile flowers) vs. almond ointment was conducted in 50 women undergoing radiotherapy that developed radiodermatitis. It was observed further development of marked erythema (31%) and moist desquamation (27%) in the group using ointment almonds. There was delay in the onset of the reactions in the group treated with Kamillosan®, which occurred between the 5th and 7th week of radiotherapy. In the group treated with ointment almonds, this range was lower, and the reactions manifested from third week [15]. Comparison between a cream containing 2% ethanol extract of chamomile flowers (Kamillosan®), hydrocortisone and placebo was performed on 72 individuals with atopic eczema [13], which was also observed higher effect of chamomile in relation to corticosteroids to reduce eczema, although the results of radiotherapy. In the group treated with ointment almonds, this range was lower, and the reactions manifested from third week [15]. Comparison between a cream containing 2% ethanol extract of chamomile flowers (Kamillosan®), hydrocortisone and placebo was performed on 72 individuals with atopic eczema [13], which was also observed higher effect of chamomile in relation to corticosteroids to reduce eczema, although the results of individuals who applied chamomile cream was similar to those who received placebo. Similar results were observed in the study [18] compared with hydrocortisone Kamillosan®, fluocortin and Bufexamac in 161 individuals with eczema on the hands, forearms and legs. It was found that the Kamillosan was as effective as hydrocortisone at 0.25% (22% vs. 18%) and higher than the fluocortin (25.5% vs. 2.2%) and the Bufexamac (53.6% vs. 14.3%).

For the treatment of contact dermatitis induced were evaluated in 20 subjects, two formulations Kamillosan® (ointment and the ointment base) as compared with 0.1% hydrocortisone. By profilometer, skin roughness was assessed and the results indicated that the Kamillosan® ointment showed superior effect to other products evaluated in relation to the question soothing effect on the human skin [16]. The effect of chamomile was also compared to extracts of other plants such as hamamelis, aloe vera and melaleuca, among others. The anti-inflammatory activity of chamomile cream 20 mg / g was compared with formulations hamamelis 0.64 mg and hydrocortisone 1% cream in reducing the erythema induced by UV radiation in 24 individuals [14]. In this study, statistically significant results were observed with the use of witch hazel and hydrocortisone ($p = 0.0625$). However, it observed greater anti-inflammatory activity of hydrocortisone in relation to hamamelis ($p = 0.0762$) and chamomile ($p = 0.0469$).

In a study evaluating the efficacy of six plant extracts (aloe vera 10%, 1% camomile, hamamelis 5% 5% tea tree, and lemon balm 2% coriandrum 1.33%) compared to the 1% hydrocortisone, and betamethasone 0 1% to treat UV-induced erythema in 40 individuals, betamethasone was more effective

in reducing erythema within 24 hours after induction of erythema (17.7 ± 9.7). In the evaluation 48 hours, erythema lower levels were observed with the use of Aloe vera compared to the 1% hydrocortisone, and betamethasone 0.1% (p = 0.045). However, betamethasone was most effective when compared to the six extracts evaluated (p = 0.017) [8]. As compared the effects of aqueous extract of German chamomile vs. hydrocortisone application in the management of peristomal lesions by 72 colostomy patients, the results showed that healing of the injuries was faster in chamomile group (p = 0.001) [10].

Two formulations containing extracts enriched with apigenin, flavonoid constituents of *C. recutita*, one liposomal and other non-liposomal were evaluated for tolerability and clinical efficacy in 19 patients with contact dermatitis. The results demonstrated that liposomal cream was slightly more effective than the non-liposomal cream, considering the anti-inflammatory action [11]. In a study that evaluated the effect of chamomile extract vs. placebo in the healing of injuries from tattoos dermabrasion [17], a reduction of exudative wound area.

The phlebitis regression time due to peripheral intravenous infusion of chemotherapy was the main outcome assessed in the study, which examined and compared the therapeutic efficacy of different doses of the infusion *C. recutita* in 25 cancer patients. The group receiving compress with infusion of *C. recutita* in concentration of 2.5% had time to regression of lower phlebitis (29.2 hours ± 8.98), followed by the group whose concentration was 5% (38.8 hours ± 17.47) [12]. The results of the studies analyzed in this review indicate a good therapeutic potential and good tolerance of chamomile in skin damage, regardless of the formulation used. It is noteworthy that the use of complementary practices such as herbal remedies can avoid some of the side effects of conventional therapeutic interventions, also contributing to user satisfaction [20]. Because of not having a standardized measurement of the primary endpoint and a heterogeneity of clinical and therapeutic formulations situations was not possible to make a comparison of the anti-inflammatory potential of *C. recutita* between studies.

Conclusion

In this review, we identified 11 different studies testing formulations containing *C. recutita*, such as aqueous extracts and alcoholic, infusion, hydroalcoholic cream, and ointment containing α-bisabolol and chamazulene. They were used for the following skin conditions: erythema induced by UV radiation or removal of adhesive tape, pityriasis alba lesions similar to eczema, peristomal injury, contact dermatitis, phlebitis, atopic eczema, radiodermatitis, and wound healing.

Despite the scant description of the studies concerning the presentation of amounts arising from the application of statistical tests, it can be affirmed through a qualitative analysis, the C. recutita has the potential to be an anti-inflammatory agent as effective as steroidal anti-inflammatory drugs and non-steroidal currently marketed.

It is therefore essential to be developed comparative clinical studies testing standard formulas and outcomes measured through validated measures to promote the use and reproducibility of pharmaceutical preparations containing C. recutita in clinical practice.

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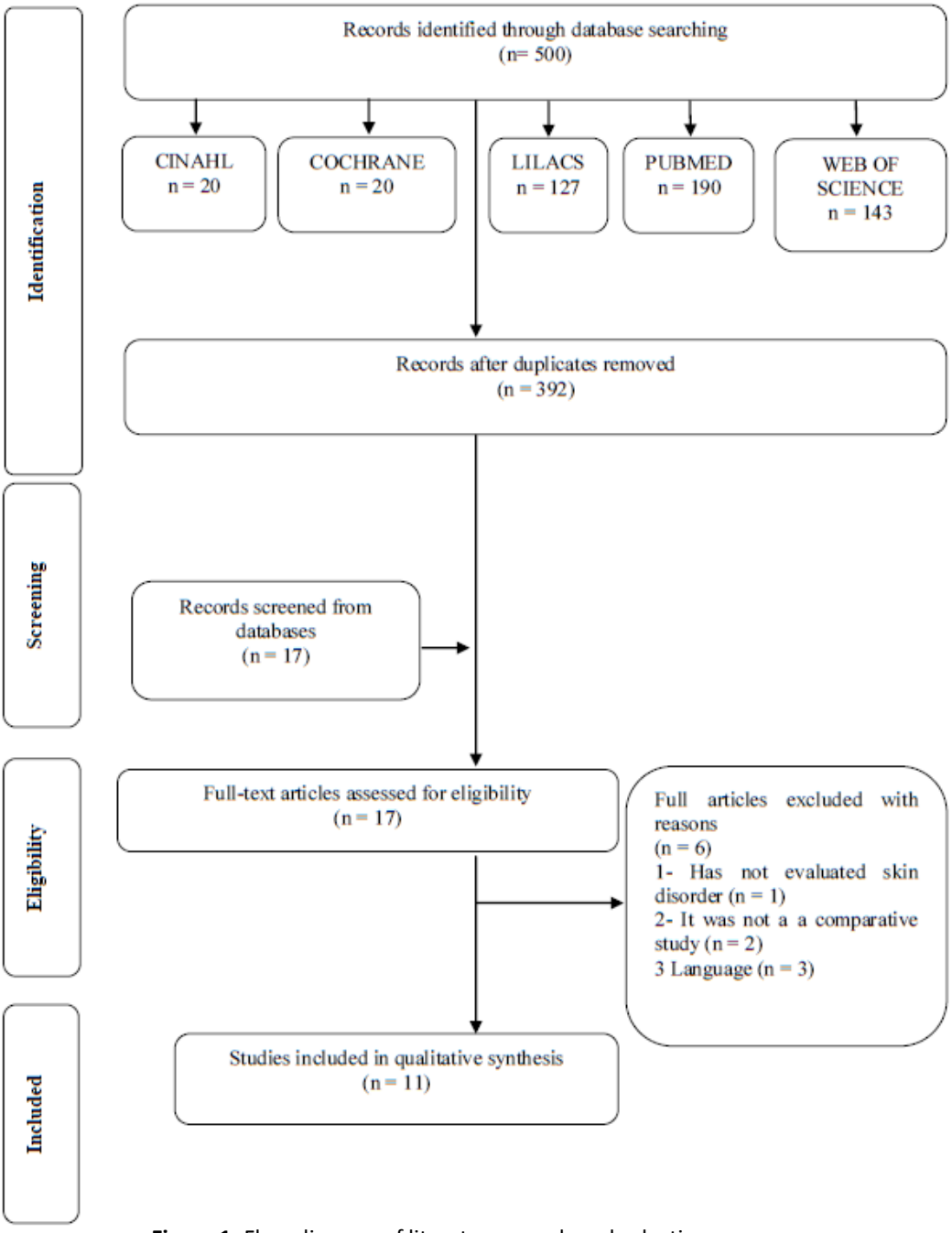

Figure 1. Flow diagram of literature search and selection process

Table 1. Characterization studies.

Year Study Design	Objective	Sample	Measurement of outcomes	Follow-up and product application rate	Statistical analysis	Main results
2013 RCT [8]	To assess efficacy of six plant extracts (aloe vera 10%, camomile 1%, hamamelis 5%, malaleuca 5%, melissa 2%, coriandrum 1.33%) compared to the 1% hydrocortisone, and betamethasone 0.1% to reduce UV-induced erythema	n = 40	Krutmann scale (evaluation of the intensity of erythema)	Prior to the UV radiation, 24 and 48 hours after	ANOVA	First 24 h: 0.1% betamethasone more effective in reducing erythema (9.7 ± 17.7). After 48 h: aloe showed lower levels of erythema compared to the 1% hydrocortisone, and betamethasone 0.1% ($p = 0.045$). Betamethasone was most effective when compared to extracts evaluated 7 ($p = 0.017$)
2012 RCT [9]	Evaluate safety and efficacy of hydroalcoholic cream chamomile extract to 10% compared to placebo cosmetic cream for pityriasis alba and like eczema lesions	n initial = 55 n final = 44 EG (n = 22) CG (n = 22)	Erythema, swelling, blistering and crusting. Each item was graded on a scale of 1 to 3 (0 = no injury, 1 = slight injury, 2 = moderate injury, 3 = severe injury)	Four weeks during which they were made 2 visits (D15 and D30). The cream was applied 2 times a day	$\alpha = 0.025$. Chi-square to evaluate response rate between groups. Fisher's Exact test for frequency events <5	EG: 8 (36%) patients were cured and 12 (45.5%) improved, of which six had more than 75% response. CG: high response rate
2011 RCT [10]	Compare the effects of aqueous extract of German chamomile application to topical corticosteroids in the management of peristomal lesions in patients with colostomy.	n = 72 group hydrocortisone n = 36 (Hydrocortisone ointment) group chamomile n = 36 (German chamomile solution prepared with 6g of dried flowers powder in a glass container with 150 cm^3 boiled water)	Skin appraisal included presence / absence and erythema extension, erythema and edema, erythema and papule, vesicle or wound. Size of skin damage: measured in cm using rule, determining the area in cm^2. Amount of exudate 1 = none, 2 = scarce; 3 = small; 4 = moderate; 5 = large Itching reviewed presence or absence Pain: McGill scale pain-rating scale.	Application of hydrocortisone ointment 1% 1x daily. Compress the application of German chamomile 2x a day. Lesions were assessed every three days.	To compare the mean score difference between repeated measurements was applied to the Mann-Whitney test	Healing of the lesions was significantly faster in camomile group (8.89 ± 4.89 days) than the hydrocortisone group (14.53 ± 7.6 days) $p = 0.001$.
2011 Pilot clinical study [11]	Evaluate patient acceptability, tolerability and clinical efficacy of two formulations containing extracts enriched with apigenin *C. recutita*, being a liposomal and non-liposomal another in treating contact dermatitis	n=19 The patient was his own control. Cream formulation containing liposomal not applied on the left and containing liposomal cream formulation applied on the right.	The regions were photographed to record the visible changes. Index for sizing of symptoms: 0 = no symptoms, 0.5 = mild symptoms, 1 = moderate symptoms, and 2 = severe symptoms. Cosmetic acceptability was evaluated by descriptive numerical scale. Bioengineering methods to measure the transepidermal water loss (TEWL)	The cream samples, 2 mg / cm^2 doses were applied to the affected areas of skin three times daily over a period of 2 weeks	Linear regression analysis to estimate the correlation coefficients for apigenin release rate	The study demonstrated that the liposomal cream were slightly more effective than non-liposomal formulations, whereas their anti-inflammatory action

Table 1. Characterization studies.

2011 Dose response curve study [12]	Analyze and compare the efficacy of different doses of the infusion of *C. recutita*, as to its anti-inflammatory effect in patients with cancer who had phlebitis due to peripheral intravenous infusion of antineoplastic chemotherapy and evaluate the toxicity of this infusion in humans.	n = 25 Group A (n = 5): Compress infused with 1.25% Group B (n = 5): A dressing infused with 2.5% Group C (n = 5): Compress infused with 5.0% Group D (n = 5): Compress infused with a 10.0% GC (n = 5): Compress with warm water. Temperature set at 38 °C in all groups.	Erythema was chosen as the parameter for evaluation of regression of the inflammatory process. To measure the erythema, it was used in centimeters squared transparent paper, from which the erythema area was calculated with great precision. Toxicity was investigated by means of visual assessment of the application site, looking for some sign that would indicate any reaction to the infusion and symptoms of research.	The intervention was applied on phlebitis three times daily (morning, afternoon and night) for 20 minutes for all groups, being exchanged every 5 minutes. The treated area was assessed daily, in three different moments: 8, 13 and 19h. The intervention was performed until there is complete disappearance of erythema.	Analysis of variance One-way ANOVA followed by the multiple comparison test - Bonferroni test. α = 5%.	The phlebitis regression time was shorter for the group with concentration 2.5% (mean = 29,2h, SD = 8.98) followed by the group with concentration 5% (mean = 38,8h, SD = 17, 47). Practically local toxicity was not observed.
2000 RCT [13]	To assess efficacy and tolerance of cream containing 2% ethanol extract of chamomile flowers (Kamillosan®) compared to hydrocortisone cream to placebo and 0.5% (cream) in individuals with atopic eczema	n = 72 Group 1: hydrocortisone vs. Kamilosan Group 2: vs. kamilosan placebo Group 3: Hydrocortisone Vs. Kamillosan Group 4: Placebo vs. Kamillosan	Pruritus, and erythema were evaluated separately by 4-point scale (0 = no, 1 = weak, 2 = clear, 3 = severe), and through summation with scores ranging from 0-9, with 0 being no eczema and 9 severe eczema. Global assessment of efficacy and tolerance used 4-point scale: very good / good, satisfactory, inadequate and inaccessible.	2 weeks, during which were made three visits. Patients used a first product (left arm) for 7 days and the second product (right arm) for 7 days. There was no mention frequency of use per day	Unlike the average of individual scores and sum of scores (α = 5%) For other parameters we used descriptive statistics. It does not present confidence interval and p value	44/72 patients (61%) had a score sum> 7 points (moderate to severe eczema). The difference between the average scores suggest that Kamillosan was superior to hydrocortisone, but similar to placebo. Global assessment of efficacy as the very good / good item: kamillosan (49.3%), hydrocortisone (19.4%), placebo (48.5%); Tolerance: kamillosan (92.8%), hydrocortisone (77.8%) and placebo (84.8%)
1993 RCT [14]	Compare the anti-inflammatory activity of three preparations of hamamelis (Hamamelis ketone 0,64mg / 100g emulsion with or without phosphatidylcholine -PC; hamamelis ketone 2,56mg / 100g) with cream 1% hydrocortisone cream and lotion 20 mg / g erythema induced by UV radiation (UV lamp 800, 1.5 MED - minimal erythema dose, positioned 50 cm from the skin) or removal of adhesive tape (Tesafilm)	Radiation Group (n = 24) Tape Group (n = 24) 1 - witch hazel cream 0,64mg and chamomile cream 2 - hydrocortisone cream and witch hazel cream 0,64mg / 2,56mg	Radiation-induced erythema and removal of tape. Erythema reduction was quantified by visual score and cromametria. Effect of preparations compared between themselves and with control área. Erythema (0 - intense erythema, no effect; 1 - marked erythema, but no maximum; 2 - mild residual erythema; 3 - complete regression of erythema. Skin color - visual 5-point scale (0 - very intense erythema 1 - Intense erythema 2 - Moderate erythema 3 - mild residual erythema, 4 - no erythema, skin coloring equal to intact skin	Subjects undergoing UV radiation were evaluated after 24 and 48 h Subjects underwent removal of adhesive tape were evaluated after 4, 8 and 24 hours Product Application often not described	Average of the values assigned to the erythema and the control area were compared using the Wilcoxon-Pratt test, where p ≤ 0.05 / 0.10 was considered to indicate significant difference	Radiation: reduction of erythema compared to the control area only with the use of hamamelis 0.64 mg with PC and hydrocortisone 1% (p = 0.0625). Results suggest superiority of hydrocortisone on hamamelis (0,64mg) (p = 0.0762) and chamomile (p = 0.0469). Cromametria indicated no statistically significant difference. Tape: There were differences in visual score

Table 1. Characterization studies.

1991 RCT [15]	Effect of and tolerance Kamillosan® vs ointment almonds in patients undergoing radiation therapy that presented radiodermatitis	50 women who underwent surgical resection of breast and radiated plastron (two discontinued) Each patient was his own control, and randomized the areas that received radiotherapy in the region plastron EG = 48 Kamillosan CG almonds = 48	Skin reaction, according to the scale: 0 = no change, 1 = mild erythema, 2 = marked erythema, 3 = moist desquamation	The patients were followed for seven weeks and evaluated once a week Preparations were applied by the nurse daily after each radiation session	Descriptive statistics (frequency)	Mild erythema 100% of the irradiated áreas marked erythema: EG = 11 (23%), GC = 15 (31%), moist desquamation EG = 4 (8%), CG = 13 (6%). There was delay in the onset of the reactions treated Kamillosan (took place between 5th and 7th week), the treated areas with almonds, reactions manifested from the 3rd week.
1988 RCT [16]	To evaluate the effect Kamillosan® ointment, Kamillosan® ointment base, 0.1% hydrocortisone acetate in the treatment of contact dermatitis	n=20	Structural changes in the skin surface were analyzed by profilometry	Evaluated skin roughness parameters	Teste t de Student	Results indicate that Kamillosan ointment demonstrates marked superiority to other reference product with respect to its soothing effect on the human skin
1987 CT [17]	Compare effect of chamomile extract to a placebo in healing of injuries from the tattoo dermabrasion	n=14	The objective parameters evaluated were related to epithelial effect and drying the area exudative wound after tattoo dermabrasion	Chamomile application three times a day. The applied chamomile extract is standardized to 3 mg chamazulene, 50 mg of α-bisabolol	To objective parameters applied to analysis of variance for the subjective used to Mantel-Haenszel test	The reduction of the wound area and the reduction of the amount of secretions were statistically significant
1985 CT [18]	Evaluate the efficacy of hydrocortisone vs. Kamillosan®, fluocortin and Bufexamac in maintenance therapy of eczema	n=161 patients with eczema in hands, forearms and legs	Extension of efflorescence and the severity (assessed by observation of vesicles, papular vesicles, erythema with infiltration, erosion or incipient ulceration)	Three to four weeks after the acute phase (until day 14) The preparations were aplicadadas three times daily	Descriptive statistics (frequency)	Kamillosan® was as effective as hydrocortisone at 0.25% (22% vs. 18%) and was superior to the fluocortin 0.75% (25.5% vs. 2.2%) and the Bufexamac (53, 6% vs. 14.3%)