

Four-Week Safety and Acceptability Study of 15% Bromelain Topical Lotion: An Open Label, Non-Comparative, Triple-Arm Study

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ABSTRACT

Pruritus is a common and distressing skin disorder and treatment of itch is a daily problem for millions of people. Available therapies are ineffective and there is an urgent need for new topical treatments to relieve itch. Studies were undertaken to identify the optimal concentration of a natural therapeutic for the relief of itch and to assess the safety of this agent in dermal application with six volunteers. In the initial study, six volunteers with self-diagnosed atopic dermatitis applied a lotion containing concentrations ranging from 5 to 25 weight percent of 1200 Gelatin Dissolving Units (GDU) bromelain to their skin and noted any discomfort caused to the area and the amount of symptomatic relief that was obtained. Based on this study, 15 weight percent of 1200 GDU bromelain suspended in lotion was selected for further testing. For the safety study, a total of thirty subjects were randomized into three pools and participants in each pool applied the lotion to their arms, backs, or legs on a daily basis. After four weeks, all the participants had completed the study and none had reported an adverse event. The lotion was found to be safe and effective when applied topically on a daily basis.

Keywords: Pruritus, Bromelain, Safety Study, Efficacy Study.

INTRODUCTION

Pruritus or itch is defined as an unpleasant subjective sensation which leads to the desire to scratch, which leads to new irritation of the skin and this in turn induces pruritus, creating a vicious cycle. The treatment of itch is a problem for millions of people and is important not only for dermatology practices but also for all other medical specialties. The currently available topicals for pruritus, such as the antihistamines, steroids, astringents, and plant-based oils, are known to have only limited efficacy [1,2] and with many patients, these agents have been shown to further sensitize the skin. Therefore, there is an urgent need to find new, effective treatments to relieve itching.

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As a folk remedy, meat tenderizer products containing active enzyme preparations of bromelain and papain have been reported to be highly effective in relief of pain and swelling associated with mosquito bites, bee stings, nonpoisonous spider bites, and jellyfish stings when applied as a paste in water for short periods. It has been proposed that the proteolytic action of bromelain and papain quickly digests the proteinaceous venom components (e.g. melletin) responsible for the stinging pain and associated swelling. Based upon its reported use for treating jellyfish stings and venomous insect bites, Kiss My Itch Goodbye initiated studies to explore the use of bromelain for the immediate and extended relief from itching and irritation associated with contact dermatitis, insect bites, idiopathic itching, hives, psoriasis, seborrhea, eczema and cracked fingertips, skin abrasions, cuts and minor burns as well as other indications. Initial studies were conducted to assess the safety of dermal application of lotions containing bromelain and their effectiveness in relieving itch.

Bromelain is a well-known compound. Several therapeutic, industrial and other applications have been reported for stem bromelain [3-7] and the Food and Drug Administration, USA, has categorized bromelain as a food additive that is among the substances that are generally accepted as safe (FDA Code of Federal Regulations Title 21 Sec. 184.1024 Bromelain). Bromelain also is an accepted phytotherapeutic agent [8-10] that is sold in the form of a powder, cream, tablet, or capsule, and it may be used alone or in combination with other ingredients. It is not a licensed medical product and thus it is freely available to the general public in health food stores and pharmacies in the USA and Europe.

The use of bromelain has been reported as an agent to remove damaged tissue from wounds or second/third degree burns (debridement) [11-13], however the topical use of bromelain to relieve itch and to treat other skin conditions has not been reported. The objective of this work is to determine the optimal concentration of bromelain in lotion that will enable the safe, prolonged application to skin and to conduct initial efficacy studies directed to the relief of itch. The successful conclusion of this work will enable further development of a novel therapeutic agent for the treatment of chronic itch, which is an underserved area of medicine.

MATERIALS AND METHODS

The aim of the first study was to determine the initial concentration of bromelain to be used in lotion for the four-

week safety study. The upper level for the concentration of bromelain was set at the 35-weight percent which has been reported by Houck [12] to be an effective debriding agent. Based upon this work, samples of KMIG lotion were made using a commercial base lotion to which 5, 10, 15, 20 and 25 weight percent of bromelain (assay strength 1200 GDU) was added. Test sets for participants were assembled using lotions prepared at each of these concentrations and these then were placed into individual bottles labeled with the concentration of the lotion.

Six healthy volunteers who were between 50 and 75 years of age were recruited for this study. The study was conducted with three males and three females who reported no current health problems but who stated that they were afflicted with idiopathic itch. After obtaining written informed consent, study participants were asked to apply a specific sample of lotion to their arms, legs or backs twice daily over a period of one week and to report any reactions to the lotion as well as any relief from itching that the lotion afforded. After a 2-day washout period, participants were asked to then apply the next sample in the test set and the same protocol was then used to test the third, fourth and fifth samples. Feedback was collected via telephone interviews and the data was entered into an Excel spreadsheet for analysis. The subject number values for each participant were created using a random number generator written in the php programming language and the statistical analysis of the data was conducted using built-in Excel functions.

The second study that was conducted following the initial range finding was a randomized, open label, non-comparative study conducted at the participants' homes. Participants were selected for inclusion if they were between 25 and 85 years of age and had the need to resolve itching caused by insect bites, contact dermatitis, allergies, stings, psoriasis, eczema, idiopathic, or other itch. Thirty participants age 50-85 were randomly enrolled in one of three treatment groups. The formulation that was tested in all groups was a lotion containing 15% bromelain by weight which was manufactured by Kiss My Itch Goodbye (Washington, DC) according to the company's manufacturing and stability testing SOPs.

After obtaining written informed consent, ten male and twenty female volunteers were enrolled who were in good health, had no current medical conditions, and agreed to participate in the study. The allocation values for each participant were

created using a random number generator written in the php programming language. Participants in Group 1 applied the lotion once daily during 28 consecutive days (Table 2), Group 2 applied the lotion twice daily for 28 days (Table 3), and Group 3 applied the lotion three or more times daily for 28 days (Table 4). The primary safety outcome was the absence of any self-reported skin irritations at the site of application during the study period and for one week after the termination of the application period. Efficacy was evaluated by the time to relief after application and the duration of the relief obtained.

RESULTS

Range finding Study

The protocol for the study instructed participants to apply the lotion supplied to them and to immediately record the occurrence of any adverse events. As reported in Table 1, no adverse effects were reported in groups 1-3. In group 4, 75% of participants reported low to moderate levels of unwanted

itching, burning and discomfort. At 25 weight percent, 100% of the participants reported moderate to significant levels of discomfort and two (33%) reported the need to wash the lotion off to stop an unpleasant burning sensation on their skin. There was no significant difference in reported events between male and female participants. Based on these results, the 15% equivalent weight of 1200GDU bromelain in lotion was selected for evaluation of efficacy against itch.

At 5 weight percent bromelain, participants reported that while there were no side effects, there was also no relief from itch (p 0.005). Reports for the 10 percent bromelain lotion indicated that minor relief was obtained by 50% of the participants and that no side effects were observed (p 0.005). The optimal balance between itch relief and the absence of side effects for 100% of the participants was noted at 15 weight percent (p 0.005) and this was the concentration of bromelain selected for the follow-on safety studies.

Table 1. Range Finding Study

ID	Weight % Bromelain	Gender	Adverse Event	Relief from Itch
5	5%	Female	None	None
9	5%	Male	None	None
13	5%	Female	None	None
22	5%	Male	None	None
31	5%	Female	None	None
54	5%	Male	None	None
5	10%	Female	None	None
9	10%	Male	None	None
13	10%	Female	None	Minor
22	10%	Male	None	Some
31	10%	Female	None	Minor
54	10%	Male	None	None
5	15%	Female	None	Significant
9	15%	Male	None	Significant
13	15%	Female	None	Significant
22	15%	Male	None	Significant
31	15%	Female	None	Significant
54	15%	Male	None	Significant
5	20%	Female	None	Significant
9	20%	Male	Slight Discomfort	Significant

13	20%	Female	Slight Discomfort	Significant
22	20%	Male	Discomfort	Significant
31	20%	Female	None	Significant
54	20%	Male	Discomfort	Significant
5	25%	Female	Significant Discomfort	N/A
9	25%	Male	Significant Discomfort	N/A
13	25%	Female	Discomfort	N/A
22	25%	Male	Discomfort	Significant
31	25%	Female	Slight Discomfort	Significant
54	25%	Male	Significant Discomfort	N/A

Efficacy Study

During the safety study, all participants self-applied the lotion for the period specified and noted the development of any adverse conditions; defined as redness or swelling, itch or

burning sensations, dry or peeling skin or other changes in the area of application. As shown in the following tables, the application of the lotion over a four-week period did not result in any sustained adverse events regardless of the number of daily applications ($p < 0.005$).

Table 2. Treatment Group 1–Once Daily Application 15 Weight Percent Bromelain Lotion

ID	Redness or Swelling	Itch or Burning	Dryness or Peeling	Other	Minutes to Relief
3	No	No	No	No	5
31	No	No	No	No	10
35	No	No	No	No	1
50	No	No	No	No	3
52	No	No	No	No	2
61	No	No	No	No	1
63	No	No	No	No	1
67	No	No	No	No	5
68	No	No	No	No	1
83	No	No	No	No	10

Table 3. Treatment Group 2–Twice Daily Application 15 Weight Percent Bromelain Lotion

ID	Redness or Swelling	Itch or Burning	Dryness or Peeling	Other	Minutes to Relief
1	No	No	No	No	1
7	No	No	No	No	2
9	No	No	No	No	1
10	No	No	No	No	1
12	No	No	No	No	4
13	No	No	No	No	5
54	No	No	No	No	5
66	No	No	No	No	1
89	No	No	No	No	7
93	No	No	No	No	1

Table 4. Treatment Group 3-Three Times or More Daily Application 15 Weight Percent Bromelain Lotion

ID	Redness or Swelling	Itch or Burning	Dry or Peeling	Other	Minutes to Relief
2	No	No	No	No	1
6	No	No	No	No	8
15	No	No	No	No	1
16	No	No	No	No	5
18	No	No	No	No	3
41	No	No	No	No	10
45	No	No	No	No	3
49	No	No	No	No	1
53	No	No	No	No	5
82	No	No	No	No	5

DISCUSSION AND CONCLUSION

Numerous over-the-counter lotions are available for the treatment of itch; however, none offer long lasting relief and many fail to break the itch-scratch cycle. Clearly, new approaches to the treatment of pruritus are needed. The aim of the present study was to evaluate potential adverse events that arise from the daily application of a potential new approach to treating itch, a lotion containing 15 weight percent of stem bromelain. This formulation was developed by examining the application of a series of bromelain concentrations suspended in a commercial base lotion to the back, arms and legs of a small number of volunteers with idiopathic itch.

Participants in all of the arms of the safety study reported that over a period of four weeks, the daily use of this lotion did not cause any skin irritations regardless of the number of times that the lotion was applied to the affected area. All of the participants also reported that the lotion improved their skin tone and relieved their chronic itch. After completion of the study, over 90% of the participants continued to use the lotion and after 12 months they reported the lack of

any adverse outcomes (Table 5) as well as continued relief from itch. All of the participants completed the study and no adverse events were reported that would limit the use of this lotion or constitute intolerability. Participants stated that the bromelain-based lotion was significantly better (92%, p 0.004) or better (6%, p 0.004) than other anti-itch products they had used and that relief from itch occurred less than five minutes after the application of the lotion (83%, p <0.003). Based on these results, we conclude that a 15-weight percent of bromelain suspended in oil in water lotion is safe to use as an antipruritic on a daily basis [14].

We have demonstrated that a new approach to treating pruritus using a lotion containing stem bromelain has a significant potential to improve this condition. While these studies are observational, they inform the basis for further studies that will elucidate the mechanism of action for this novel therapeutic and expand its use to other skin conditions.

CONFLICTS OF INTEREST

This work has been self-funded and the authors identify no conflicts of interest.

Table 5. Twelve Month Application of Kiss My Itch Goodbye 15 Weight Percent Bromelain Lotion

ID	Use (Days)	Frequency	Redness or Swelling	Itch or Burning	Dry or Peeling	Other
9	400	2x Daily	No	No	No	None
50	400	2x Daily	No	No	No	None
67	330	As Needed	No	No	No	None
82	330	1x Daily	No	No	No	None
83	400	2x Daily	No	No	No	None
89	400	As Needed	No	No	No	None
91	330	2x Daily	No	No	No	None
93	400	1x Daily	No	No	No	None

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