Topical Effect of Aloe with Ribonucleic Acid and Vitamin C on Adjuvant Arthritis*

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Rheumatoid arthritis is a serious, painful, and potentially crippling systemic disease. Adjuvant-induced arthritis in rats closely resembles rheumatoid arthritis in humans and provides a good experimental model for studying the disease. The authors' previous work showed that, individually, ascorbic acid, aloe extract, and ribonucleic acid (RNA) have varying degrees of systemic antiarthritic as well as anti-inflammatory activity. The anti-inflammatory and antiarthritic topical activity of combined ascorbic acid, aloe extract, and RNA in hydrophilic cream were evaluated i. this study. The results may provide an effective topical treatment for rheumatoid arthritis.

Rheumatoid arthritis is a serious, painful, and potentially crippling systemic disease. It is characterized by an inflammation at peripheral joints. There are no ideal animal models for rheumatoid arthritis; however, Sprague-Dawley rats provide the best experimental tool for studying the disease. The induction of adjuvant arthritis by injection of *Mycobacterium butyricum* in mineral oil is well known.[1] The adjuvant arthritis closely resembles rheumatoid arthritis in its pathologic and clinical manifestations.[2] Also, the drug effect seems to parallel those observed in human disease, especially rheumatoid arthritis.[3] Denaturation of collagen occurs at the site of injection. The denatured collagen acts as an antigen and stimulates antibodies. Antibodies then circulate throughout the body, attacking normal collagen and causing systemic immunologic response.

The animal model presents a sequence of events which stereotypes adjuvant arthritis. Following injection of *M. butyricum* with mineral oil into a hind paw, an immediate inflammatory response is seen at the injection site. Within 7 to 14 days, edema is observed throughout the body. This body reaction represents the immunologic phase of the arthritis.

In this study, therapeutic agents against adjuvant arthritis may be classified as preventive or immunosuppressive agents. Preventive agents prevent inflammation at the injection site, and immunosuppressive agents prevent the systemic and immunologic aspects of the disease by reducing the arthritis in the non-injected paw.

In this particular study, topical *Aloe vera*, ascorbic acid, and RNA (salt) in hydrophilic cream were used against adjuvant arthritis. These agents systemically possess both anti-inflammatory and immunosuppressive activity.[4,5] Many studies have shown that ascorbic acid enhances the development of collagen. Ascorbic acid plays an essential role in the formation of collagen by hydroxylation of proline to hydroxyproline.[6] Ascorbic acid promotes aggregation of ribosomes in the endoplasmic reticulum to facilitate collagen synthesis.[1,5] The authors believe that high levels of ascorbic acid applied topically might prevent excessive collagen break-

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down. Immunosuppressive corticosteroid stimulation by ascorbic acid can have a delayed suppressive effect on secondary inflammation.

The authors found that RNA type II-S exerts strong anti-inflammatory and immunosuppressive activity.[4] Ribonucleic acid can combine with antigenic fragments invading an animal's immunologic system.[7] It may unite with the antigen on the surface of *M. butyricum*. As a result, the host's immunologic system may not recognize the antigens as foreign, or the host may recognize the foreign complex but be unable to respond to it.

The aloe plant (*Aloe africana*) in this study has a long history of healing effects. It breaks down dead tissue as it regenerates the new tissue. It has no known side effects and, in the commercial or prepared form, aloe can be taken internally.[8,9] The cosmetic industry has demonstrated over the years the possible therapeutic activity of aloe against sunburn, small wounds, and athletic injuries.[9] The authors' previous study on natural substances showed aloe to be an effective treatment for adjuvant arthritis.[5] It inhibited the immunologic response and the inflammation. The present study attempts to determine the topical antiarthritic activity of aloe, RNA, and ascorbic acid when given in hydrophilic cream. Both the prevention and regression of the disease were considered.

Materials and Methods

The preparation used against adjuvant arthritis was a hydrophilic cream base containing a 5% concentration of homogenized *Aloe africana* leaves, RNA sodium salt, and L-ascorbic acid-sodium salt. The preparation was made fresh every other day and kept refrigerated.

At the beginning of the experiment, six groups of male Sprague-Dawley rats (175 to 200 g, 10 to 12/group) were injected with 0.1 ml of heat-killed *M. butyricum* suspended in light mineral oil at a 5 mg/ml concentration. Two other groups were injected with the oil alone into the plantar aspect of the left hind paw while the rats were under ether anesthesia.

The experiment contained two separate studies. In one study, the authors attempted to prevent the symptoms of adjuvant arthritis. In the other study, the authors attempted to cause regression of the already established disease. The change in hind paw edema was measured with a mercury plethysmograph, which was used to monitor the disease's progress. Each study contained an oil control, an adjuvant control, and a cream control group. These control groups were not given the aloe, RNA, and ascorbic acid treatment. This was in order to ascertain the preparation's therapeutic effectiveness by comparison.

In the prevention study, treatment rats received 2.5 g of aloe, RNA, and ascorbic acid daily for 13 days, beginning on the day they were injected (day 0). The cream control group received daily applications of 2.5 g of hydrophilic cream. Both the cream and the aloe, RNA, and ascorbic acid treatment were smeared over the entire surface of both hind paws below the anatomical hairline.

In the regression study, the rats were left undisturbed for 21 days after having been injected with *M. butyricum* in light mineral oil or mineral oil alone, according to which group they were in. The symptoms of adjuvant arthritis usually take 1 to 21 days to develop.[10] Treatment of the rats began on day 21 and stopped after day 33 (a total of 13 treatments). Again, the aloe, RNA, and ascorbic acid therapy groups and cream control groups received the same treatment program as the prevention experiment, after an initial 21-day delay.

Since the left hind paws of the rats (inflammatory paw) were injected, edema in the right hind paws was considered an immunologic response. In other words, any edema in the right paw must be due to an immunologic phenomenon because this paw was not injected.[11,12] Six hours after the injections, day 0 measurements of hind paw edema were taken. Hind paw volumes were measured by inserting them into a mercury-filled cell up to the anatomical hairline. Units of edema were calculated by subtracting day 0 volumes from the subsequent measurements for the prevention experiment. Measurements for this study were taken on days 0, 7, 14, and 21. Day 21 volumes were considered zero units of edema for the regression experiment. Measurements for this study were taken on days 0, 21, 28, 35, and 38. Body weights were also recorded on all measurement days. All rats were killed on day 21 (prevention) or day 38 (regression), and their hind paws were severed at the anatomical hairline. These paws were weighed, and the relative paw weight was calculated to rule out any variation in paw volume as a result of changes in body weight. This value is calculated by dividing the paw weight by the body weight and multiplying the product by 100.

The right hind paws of representative rats were photographed on day 21 (prevention) and day 38 (regression) with a CU-5 Medical Land Camera.[®1]

[®1] Polaroid Corporation, Cambridge, MA.

Xeroradiographs were also made on the same days to demonstrate soft tissue and bone changes. Standard errors were determined by using the formula:[13]

$$SE = \sqrt{d^2/n\ (N-1)}\ .$$

At the end of each study, blood samples were obtained from several rats. A rheumatoid antibody test kit was used to determine whether adjuvant arthritis induced the formation of rheumatoid antibodies. Several swollen rats and control rats which showed less edema were tested.

Results and Discussion

Prevention of Arthritis. The test preparation was administered at the same time the arthritis was developing in an attempt to prevent or inhibit the disease. The experiment was started by injecting the left hind paws of adult, male Sprague-Dawley rats with 0.1 ml of *M. butyricum* suspended in mineral oil (5 mg/ml). Swelling occurred in both hind paws and continuously increased. The left hind paw increased from −4.69 ± 1.79 units of edema on day 7 (relative to day 0 measurements) to 15.00 ± 3.86. The right paws of the adjuvant controls increased from −1.75 ± 0.14 units to 10.60 ± 2.52 units. Thus, the inflammatory increase was 1969% and the arthritis increase was 1235% (Table 1; Fig. 1). These responses represent the inflammatory and arthritic response against which the aloe, RNA, and ascorbic acid must work. It is a maximum response for *M. butyricum*.

The cream controls received topically 2.5 g of hydrophilic cream daily on days 0 through 12. Hind paw edema increased from −3.63 ± 1.74 units to 14.63 ± 7.54 units (1826% increase) in the inflammatory paw, and from −1.70 ± 0.36 to 9.94 ± 1.94 units (1164% increase in the immune paws) (Table 1). The progress of adjuvant arthritis in animals receiving cream alone was similar to that observed in untreated adjuvant animals.

The oil control animals given mineral oil alone were included to ascertain whether the oil itself caused swelling. No significant change in volume occurred in these rats. Aloe was used in this experiment because of its performance in previous work on prevention and regression of adjuvant arthritis.[5] A 48% inhibition of inflammation and a 72% inhibition of arthritis was recorded for 150 mg/kg daily subcutaneous aloe injections. This is one of the largest responses recorded for a prevention study.

Aloe has been used to treat various skin conditions in many ancient civilizations.[14] Antipyretic and anti-inflammatory activity has been demonstrated in aloe, and aloe contains ascorbic acid, a nutrient. Leaves have been successfully used to treat x-ray burns.[15] The authors used the entire leaf to make aloe extract because the therapeutic properties have been found in the pulp and the rind.[16]

Ascorbic acid caused a 29% inhibition of edema in prevention, and a 55% inhibition in regression

Table 1. Prevention of Adjuvant Arthritis with Topical Aloe, RNA, and Vitamin C

Group	Oil	Adjuvant	Cream	Treatment
No. of rats	12	12	12	12
Treatment			2.5 g of Hydrophilic cream daily	2.5 g of Aloe, RNA, and ascorbic acid treatment daily
Average body weight (g)				
Day 21	296.5 ± 4.7	237.8 ± 12.1	248.5 ± 9.48	250.2 ± 8.56
Units of edema ± SE				
Day 7 L paw	−3.21 ± 0.280	−4.69 ± 1.79	−3.63 ± 1.74	−3.13 ± 0.900
R paw	−1.25 ± 0.270	−1.75 ± 0.140	−1.71 ± 0.360	−1.42 ± 0.400
Day 14 L paw	1.23 ± 2.28	3.08 ± 4.65	2.42 ± 3.91	4.21 ± 1.50
R paw	2.54 ± 1.44	5.68 ± 2.68	2.69 ± 1.59	3.58 ± 0.860
Day 21 L paw	0.413 ± 1.29	15.00 ± 3.86	14.63 ± 7.54	10.29 ± 1.82
R paw	0.47 ± 0.470	10.60 ± 2.52	9.94 ± 1.94	7.93 ± 2.23
% Volume inhibition *versus* adjuvant				
Day 21 L paw				31.40%
R paw				25.19%
$\frac{\text{Hind paw weight} \times 100}{\text{Mean body weight}}$				
Day 21 L paw	0.746	0.781	1.702	1.737
R paw	0.697	1.226	1.105	1.037
% Weight inhibition				
Day 21 L paw				2.470%
R paw				15.416%

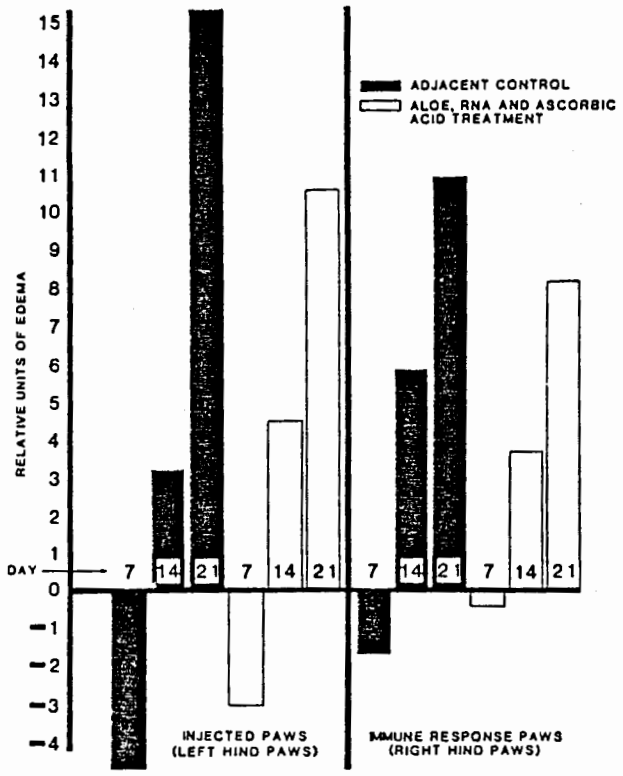

Figure 1. Prevention of adjuvant arthritis with topically administered aloe, RNA, and vitamin C *versus* adjuvant controls.

in previous studies.[5] The authors included ascorbic acid in this study in an attempt to improve regression more than prevention. However, one cannot anticipate the effects of synergy and antagonism when other substances are involved. Ribonucleic acid was effective in both prevention and regression of adjuvant arthritis.[17] Ribonucleic acid sodium salt was used because it has been shown by Davis et al[4] to work better than the acid. They showed that RNA injections caused an immunosuppressive action in treating adjuvant arthritis. Aloe, RNA, and ascorbic acid have all demonstrated excellent inhibition of edema in both inflamed and immune response paws. This indicates that each ingredient individually exhibits therapeutic activity against inflammation and arthritis. It was deemed reasonable to combine all three substances in a cream and apply it topically in a search for activity. A topical preparation for arthritis would be very useful for the podiatrist.

The authors gave 2.5 g of topical aloe, RNA, and ascorbic acid daily from day 0 through day 12. The edema in the left hind paws of these rats only increased from -3.13 ± 0.90 units to 10.29 ± 1.82 units (Table 1; Fig. 1). On day 21, the treatment rats had 31.40% less edema than the adjuvant controls in their inflammatory paws, and 25.19% less edema in their immune hind paws. This response was reflected in the paw weight (Table 1; Fig. 1). The relative hind paw weights of all the prevention study animals were calculated on day 21. The inflammatory hind paws of the adjuvant controls were 2.470% heavier than those of the aloe, RNA, and ascorbic acid treatment rats. The immune hind paws were 15.416% heavier than the treatment paws (Table 1). If a response such as this could be obtained in the clinic, podiatrists would have a good tool for treating rheumatoid arthritis.

Inhibition of injected paw edema of 0.86% and 29% in immune response paws was achieved by Hanley et al.[5] They accomplished this by using subcutaneous injections of ascorbic acid. Using aloe extract injections, they obtained 72% and 48% inhibition of edema in immune and inflammation paws, respectively.

Forst and Davis[17] found that RNA injections inhibited edema 88% in arthritic paws and 35% in inflamed paws. Both of these earlier experiments were similar to the prevention part of the present experiment in duration and course of therapy. The present work attempts to show effectiveness by the topical route of administration. The average inhibition obtained by using aloe, RNA, and ascorbic acid individually was 69.68% in the antiarthritic response, and 27.95% for the anti-inflammatory activity. The superior activity recorded in these studies was due to the systemic route of administration that was used. The authors decided to test topically the combined aloe, RNA, and ascorbic acid in hydrophilic cream because of the ease with which it can be administered to human patients. A topical preparation for the treatment of arthritis would be welcomed by the podiatrist, and the patient could more easily participate in the therapy.

Figure 2 contains photographs of the right (immune response) hind paws of representative animals from each group. The second photograph demonstrates the absence of any swelling in oil control rats. The third photograph clearly illustrates the inflammation caused by the adjuvant injection. Notice the similarity of this paw to that of the cream control animals. A rat treated with aloe, RNA, and ascorbic acid is depicted in the first frame. One can clearly see the inhibition of edema.

Xeroradiographs of the same animals are recorded in Figure 3. The adjuvant and cream controls exhibit severe degeneration of bone and marked soft tissue inflammation. This is in striking contrast to the oil control and the aloe, RNA, and ascorbic acid treatment animals, which are free of

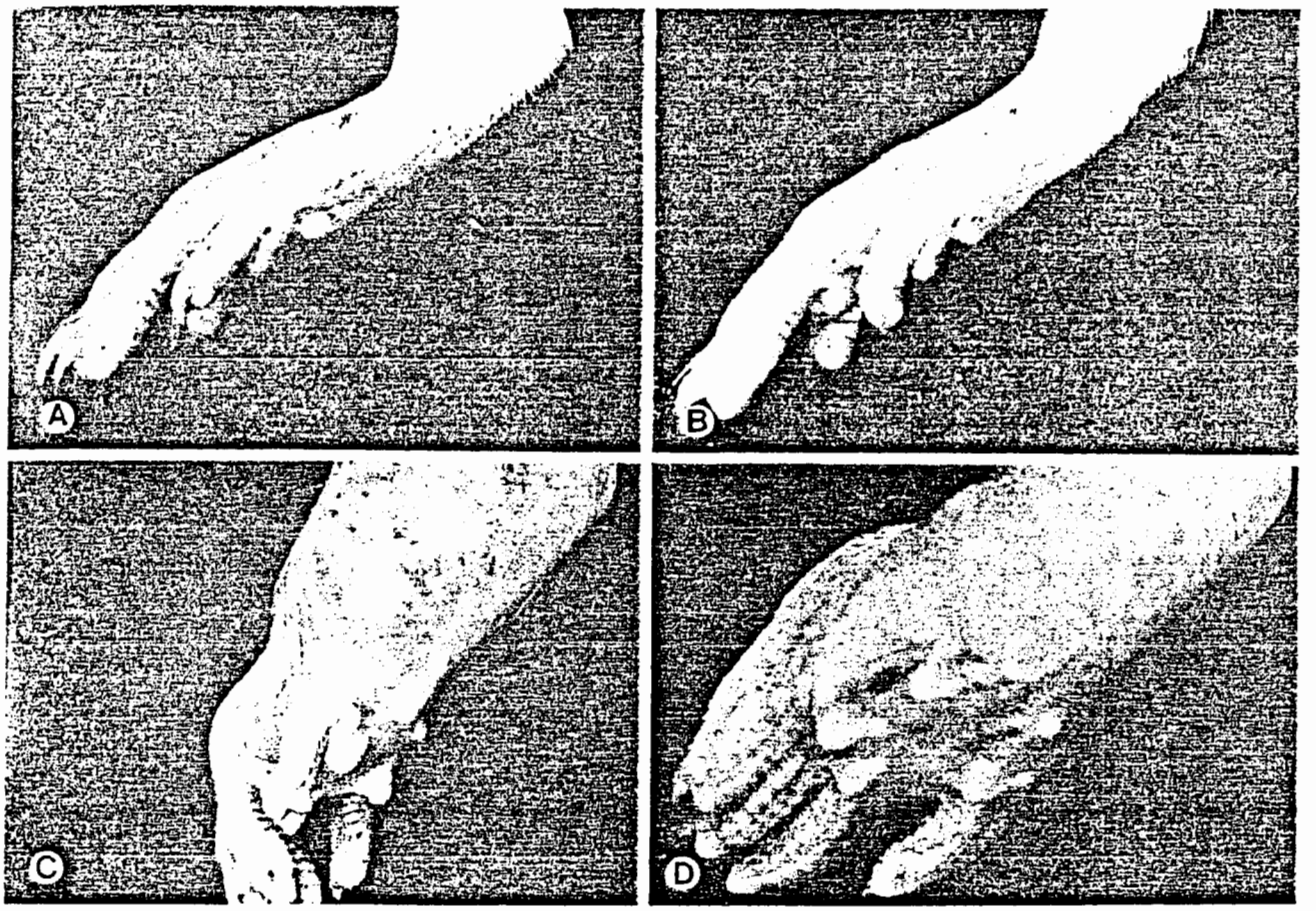

Figure 2. Photographic comparison of adjuvant arthritis treated with topically administered aloe, RNA, and vitamin C (A), *versus* oil (B), adjuvant (C), and cream (D) controls.

these changes. The combination of aloe, RNA, and ascorbic acid inhibited and caused regression of the massive arthritic changes, which can be recorded in rheumatoid arthritis.

Regression of Arthritis. Once the arthritis was fully developed, the cream with the aloe, RNA, and ascorbic acid was administered topically to reduce the already established disease. All rats involved in this portion of the experiment were injected on day 0 with 0.1 ml of *M. butyricum* suspended in mineral oil (5 mg/ml) or 0.1 ml of mineral oil only. The rats were then left undisturbed for 21 days. Currey[18] found that this amount of time is adequate for the disease to become thoroughly established. On day 21, daily applications of 2.5 g of hydrophilic cream alone were given to the cream control animals. The paws of these rats continued to swell, as did those in the adjuvant controls. Left (inflammation) hind paws increased from 0 ± 2.28 relative units of edema to 3.09 ± 2.51 units in the cream controls (Table 2). The adjuvant control rats increased 0.86 ± 0.39 units to 10.23 ± 2.71 units and from -1.45 ± 0.21 units to 6.68 ± 3.55 units in their left and right hind paws, respectively (Table 2; Fig. 1). These responses represent the maximum responses of edema over the experimental period. The oil control animals produced no significant edema in either the left or right paws.

The arthritic rats were given daily applications of 2.5 g of aloe, RNA, and ascorbic acid treatment from day 21 to day 33. Paw edema on day 28 exhibited 75.86% more edema than the adjuvant arthritic controls in the left (inflammatory) hind paws (Fig. 4). Edema was 74.14% more in the right (immune) hind paws. However, by day 35 the left hind paws of adjuvant control rats were 18.35% worse than rats receiving aloe, RNA, and ascorbic acid treatment. The inhibitory effect progressively increased as day 38 approached. Edema in the hind paws of these rats was also 19.67% (left) and 37.48% (right) less than arthritic controls on day 35. The edema in the left (inflammatory) and right (immune) hind paws was 39.11% and 45.06% less than that in the left and right hind paws of adjuvant control rats by day 38 (Table 2; Fig. 4). This represents a regression from an established arthritis

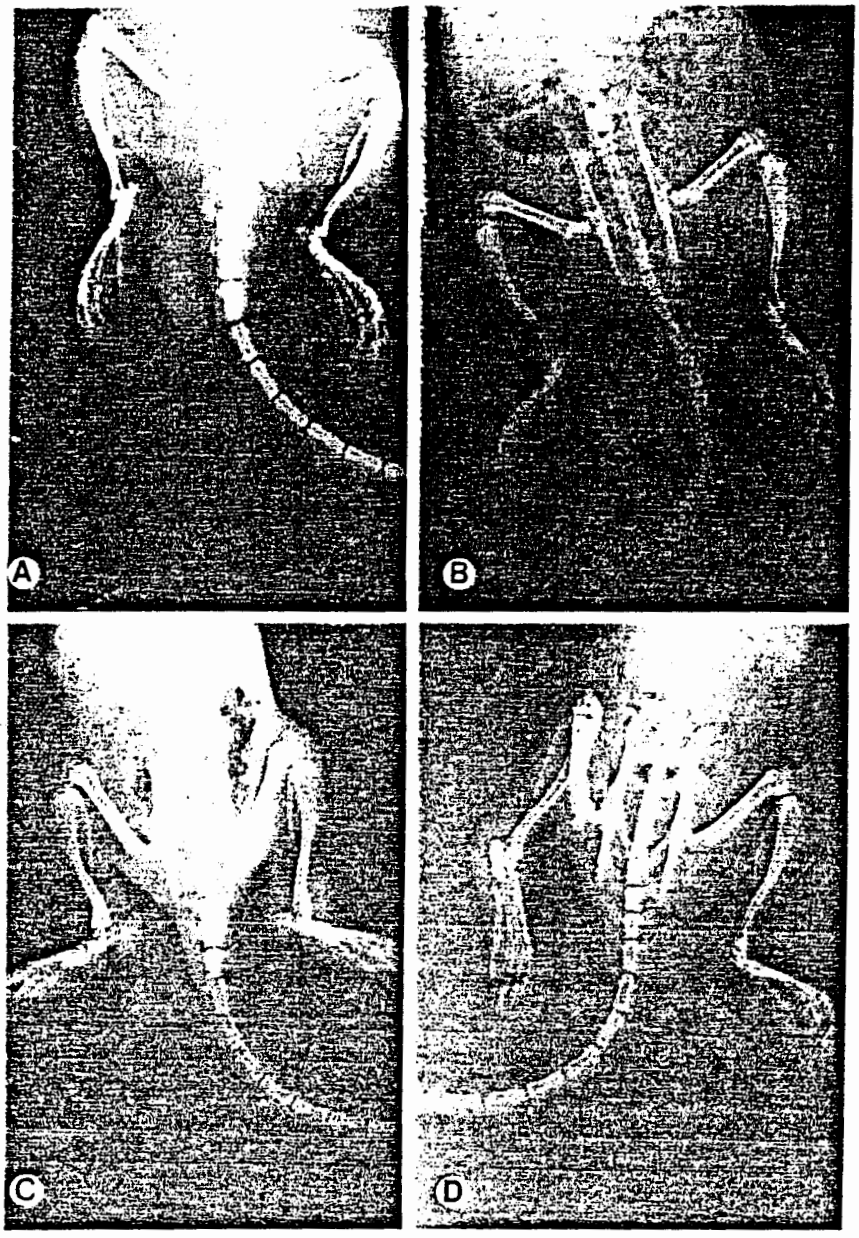

Figure 3. Xeroradiographic comparison of adjuvant arthritis treated with topically administered aloe, RNA, and vitamin C (A), *versus* oil (B), adjuvant (C), and cream (D) controls.

by natural substances given topically. To the authors' knowledge, this type of response has not been recorded in the past.

On day 38, the relative paw weights of adjuvant control rats were compared to those of aloe, RNA, and ascorbic acid-treated rats. The adjuvant control rats left hind paws weighed 19.55% more than the aloe, RNA, and ascorbic acid treatment groups. The right hind paws of adjuvant control rats weighed 29.68% more (Table 2). These weights compared favorably with edema volumes, but are less responsive as a parameter. Hanley et al[5] were able to produce inhibition of adjuvant arthritis by injecting ascorbic acid into rats that had been given *M. butyricum* 21 days before. Values of 55% for the immune response paws and 31% in the inflammation paws were obtained. Aloe extract injections were used to produce 26% inhibition in the immune response paws and 16% in the injected paws. These data reveal the effectiveness of natural substances in the prevention and regression of arthritis.

No data are currently available concerning the regression of adjuvant arthritis as a result of using RNA injections. The average inhibition obtained previously using aloe or ascorbic acid injections was 40.50% for the antiarthritic response, and 23.50% was recorded for anti-inflammatory activity. Using aloe, RNA, and ascorbic acid in hydrophilic cream topically, the authors achieved 45.06% inhibition against arthritis and 39.11% anti-inflammatory activity.

Figure 5 contains xeroradiographs demonstrating that adjuvant and cream control animals display severe osseous changes and marked soft tissue

Table 2. Regression of Adjuvant Arthritis with Topical Aloe, RNA, and Vitamin C

Group	Oil	Adjuvant	Cream	Treatment
No. of rats	12	12	12	12
Treatment			2.5 g of Hydrophilic cream daily	2.5 g of Aloe, RNA, and ascorbic acid treatment daily
Average body weight (g)				
Day 38	379.8 ± 16.6	278.0 ± 22.7	330.2 ± 18.5	302.2 ± 17.1
Units of edema ± SE				
Day 28 L paw	4.08 ± 1.08	0.864 ± 0.390	0 ± 2.28	3.58 ± 2.21
R paw	4.83 ± 1.40	−1.45 ± 0.2130	1.05 ± 1.46	−0.375 ± 1.29
Day 35 L paw	4.46 ± 0.506	9.59 ± 3.680	2.64 ± 2.07	7.83 ± 1.35
R paw	4.83 ± 0.483	−1.00 ± 2.860	5.64 ± 1.73	5.87 ± 2.03
Day 38 L paw	4.38 ± 0.970	10.23 ± 2.71	3.09 ± 2.51	6.29 ± 2.69
R paw	4.88 ± 1.050	6.68 ± 3.55	5.59 ± 1.54	3.67 ± 1.53
% Volume inhibition *versus* adjuvant				
Day 38 L paw				39.11%
R paw				45.06%
Hind paw weight × 100 / Mean body weight				
Day 39 L paw	0.705	2.020	1.590	1.625
R paw	0.616	1.388	1.105	0.976
% Weight inhibition				
Day 38 L paw				19.55%
R paw				29.68%

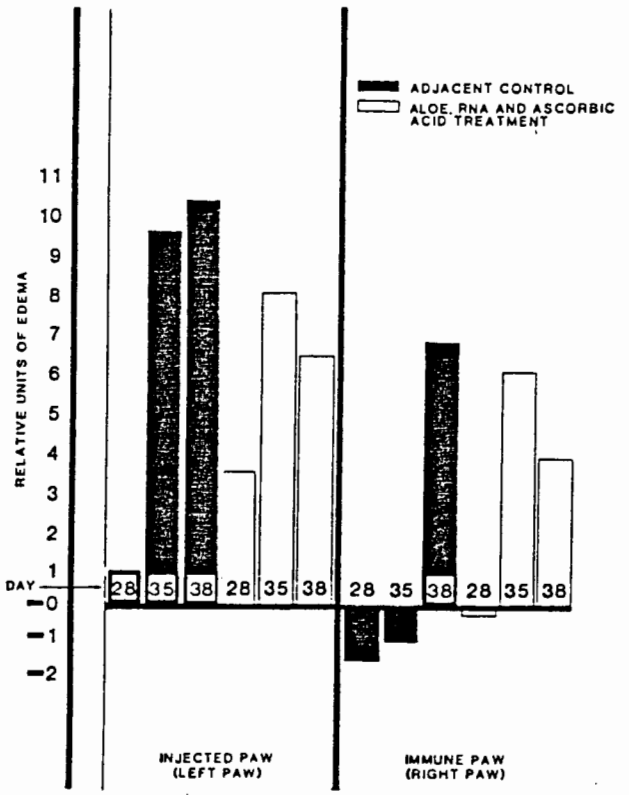

Figure 4. Regression of adjuvant arthritis with topically administered aloe, RNA, and vitamin C *versus* adjuvant controls.

swelling. The aloe, RNA, and ascorbic acid treatment appears to eliminate the changes produced by the adjuvant. Since the edema in the aloe, RNA, and ascorbic acid treatment animals was progressively eliminated, the authors feel that this indicates that bone has actually been remodeled (Fig. 4). These changes produced by aloe, RNA, and ascorbic acid represent major dramatic changes.

On day 38, blood samples were drawn from animals in each group. These samples were tested for the presence of rheumatoid antibodies. None of the samples gave positive results. This merely means that the adjuvant does not induce the formation of identical antibodies seen in the human disease. A serum containing antibodies needs to be developed for the adjuvant arthritis model. Topical administration of combined aloe, RNA, and ascorbic acid in hydrophilic cream needs to be tested on rheumatoid arthritis patients. A stabilized form of aloe must be used to prevent breakdown, or the material will have to be obtained from the plant source daily. Based on previous experience with other nonsteroidal substances, the authors feel that this preparation will prove to be active against inflammation as well as arthritis. Future studies must include further evaluation of aloe regarding its active ingredients and longevity of action. This work attempts to provide the podiatrist with a nontoxic treatment for inflammation and arthritis which can be applied topically.

Summary

The effects of topical application of natural nonsteroidal substances in treatment of adjuvant arthritis were studied. The natural nonsteroidal sub-

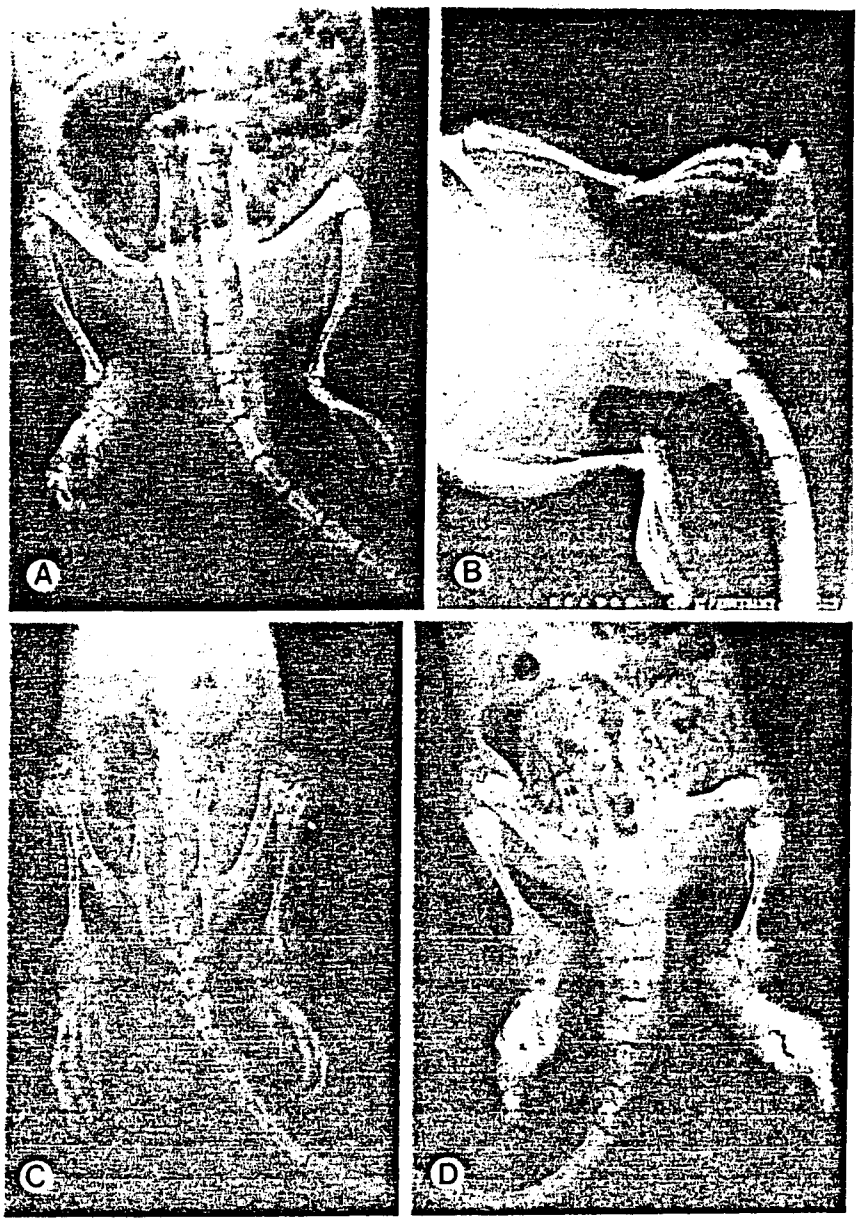

Figure 5. Xeroradiographic comparison of regression of adjuvant arthritis treated with topically administered aloe, RNA, and vitamin C (A), *versus* oil (B), adjuvant (C), and cream (D) controls.

stances were *Aloe vera*, RNA (salt), and ascorbic acid. Sprague-Dawley rats were injected on day 0 with *M. butyricum* to cause adjuvant arthritis. Prevention animals received topical aloe, RNA, and ascorbic acid daily from day 1 to day 13. A 31.4% inhibition of inflammation and a 25.19% reduction in arthritis were recorded. The regression animals received topical treatment from day 21 to day 35 daily. The inhibition of inflammation and arthritis was 39.11% and 45.06%, respectively. These data show significant inhibition of adjuvant arthritis and inflammation in the animal model. The authors hope that this work may lead to the development of an effective treatment for rheumatoid arthritis.

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