Myth, Magic, Witchcraft, or Fact? *Aloe vera* Revisited*

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The beneficial effects of Aloe vera *extract have been examined experimentally. In order to ascertain the distribution of the chemical constituents present in* Aloe vera *that may exhibit these beneficial effects, a complete chemical analysis was first performed. Inorganic substances (eg, sodium, potassium, chloride, calcium, and inorganic phosphorus) along with organic compounds (eg, glucose, protein, cholesterol, triglycerides, and salicylic acid) were found to be present. Trace metal analysis revealed that magnesium and zinc were also present. The bactericidal effects of the extract were also examined. Concentrations as low as 60% were found to be bactericidal against nine of the 12 species of organisms tested. These were* Citrobacter *sp.,* Serratia marcescens, Enterobacter cloacae, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus agalactiae, *and* Candida albicans. *The remaining three species,* Escherichia coli, Streptococcus faecalis, *and* Bacillus subtilis, *all exhibited some resistance to the 60% concentration. However, all of these were susceptible to concentrations of 80% and 90%. A cream base containing 70% of* Aloe vera *extract was found to be most effective in preserving the dermal microcirculation after thermal injury. This compound was demonstrated to inhibit some of the products of arachidonic acid metabolism such as thromboxane B_2 and to limit the production of prostaglandin $F_2\alpha$, thus preventing progressive dermal ischemia. These experimental data clearly show that the effects elicited by the* Aloe vera *extract are truly beneficial in a burn wound.*

The results in the treatment of burn patients attributed to *Aloe vera* are so miraculous as to seem more like myth than fact. However, the recurring myths about this tropical cactus have persisted since the 4th century BC.[1,2] Mention of the beneficial effects of *Aloe vera* are contained in the Ebers Papyrus and the writings of Hippocrates and Alexander the Great.[1-6] Processors of the gel, armed with biblical references and anecdotal testimonials from laymen, laboratories, and physicians continually seek recognition for their products. As pointed out by Morton,[4] exploitation of Aloe preparations has been accompanied too often by misinformation and exaggerated claims in commercially inspired articles.

In 1959, Hamit[7] stated that no real scientific data or conclusive proof had been presented that any of the numerous preparations of *Aloe vera* had any therapeutic value in the treatment of thermal burns and, indeed, may be deleterious when used for this purpose. Despite this, the rumors and myths persist.

Several known properties of *Aloe vera* could theoretically be of benefit to the burn patient. It is said to penetrate tissue and to anesthetize the tissue when applied to the traumatized area.[2,3,6,8] It has been shown by some investigators to be bactericidal, virucidal, and fungicidal.[5,6,9,10] It is said to have anti-inflammatory properties similar to those of a steroid and to be able to dilate capillaries, thus increasing the blood supply to the area to which it is applied.[11]

Experimental studies using prostanoid inhibitors such as methylprednisolone, indomethacin, aspirin, imidazole, methimazole, or dipyridamole appear to have a beneficial effect in preventing progressive dermal ischemia after burning.[12-15] Since many of the properties attributed to *Aloe vera* are similar to those of antiprostanoid agents, we attempted to identify their presence and to prove or disprove the beneficial effects of the "miraculous" plant in the treatment of thermal injuries.

MATERIALS AND METHODS

The following studies were performed to evaluate the potential efficacy of *Aloe vera* for treatment of burn wounds. A detailed chemical analysis of 99.5% pure *Aloe vera* extract was carried out using inorganic and organic spectroscopy and trace metal analysis. In vitro antimicrobial assays were performed, and experimental animal burn tissue was examined for antiprostanoid activity after treatment.

Chemical Analysis of *Aloe vera* Extract

Liquid *Aloe vera* extract (Dermaide Aloe) was assayed biochemically with a Simultaneous Multiple Analyzer-Computerized (SMAC). Assays were conducted for glucose, sodium, potassium, chloride, inorganic phosphorus, uric acid, salicylic acid, creatinine, alkaline phosphatase, creatine phosphokinase, cholesterol, triglyceride, and total protein.

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Trace metal analysis was performed by atomic absorption, using the Perkin-Elmer atomic absorption spectrophotometer model 303, for magnesium, zinc, copper, and calcium.[16]

Antimicrobial Assay

The antibacterial properties of the *Aloe vera* extract were evaluated using techniques of minimum inhibitory concentration (MIC) and minimum lethal concentration (MLC).[17,18] The extract was diluted in 10% increments from 100% concentration to 60% concentration using trypticase soy broth as the dilutent. One-tenth milliliter of an 18- to 24-hour culture (10^9 cfu/ml) of 12 different species of organism was selected for inoculation to each concentration of the extract. A control tube of TSB was inoculated simultaneously. An aliquot of extract was also processed as above after it had been sterilized (121 C for 15 minutes). The organisms used for inoculation were clinical isolates of *Escherichia coli, Citrobacter sp, Serratia marcescens, Enterobacter cloacae, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pyogenes* (group A), *Streptococcus agalactiae* (group B), *Streptococcus faecalis* (group D), *Bacillus subtilis,* and *Candida albicans.*

After an 18- to 24-hour incubation, tubes were examined visually to determine the MIC. More importantly, each concentration was backplated on sheep blood agar to determine the MLC. To evaluate this further in a clinical situation, the Nathan agar well[19] technique was used to test the susceptibility of some of these organisms to *Aloe vera* cream, comparing the effects to those with silver sulfadiazine (AgSD).

Antiprostanoid Activity Assay

To evaluate whether *Aloe vera* acts as an inhibitor to prostaglandins and/or thromboxanes, a 70% cream compound (Dermaide Aloe) was tested in a standard guinea pig scald model described by Zawacki.[20] Female albino Hartley strain guinea pigs received a 10% partial-thickness scald burn to their shaved, depilated backs. Histologically the depth of dermal ischemia was measured by India ink perfusion. After cannulation of the aorta, 60 ml of India ink was injected at 400 mm Hg constant pressure using a pneumatic device. At specific intervals, ie, immediately and 2, 4, 8, 24, 72, and 96 hours postburn, and after perfusion, tissue biopsies were collected. Ten biopsy specimens were removed from each guinea pig, coded, and fixed in 10% formaldehyde solution. Fixed biopsy specimens were sectioned, stained with hematoxylin and eosin (H&E), and examined under the microscope. Levels of India ink-filled vessels were noted and recorded both in terms of the percentage of filling of the total dermal thickness and in terms of the levels of India ink-filled vessels relative to levels of the general capillary plexuses within the dermis.[11-15]

Experimental groups were as follows: group 1—35 guinea pigs burned and left untreated as controls; group 2—35 guinea pigs burned and treated with methylprednisolone applied topically every 8 hours; group 3—35 guinea pigs burned and treated with the 70% cream compound, applied topically every 8 hours; group 4—35 guinea pigs burned and treated with methimazole (1 mg/kg po) every 8 hours. An additional series of guinea pigs was burned and separated into four groups comparable to those previously described, for longitudinal study. Burn wound biopsy specimens were collected at a specified time, sectioned, and stained (H&E), and the hair follicles were counted microscopically and expressed as the number per high power field (hpf). Gross observations were made for the quality of wound healing and hair distribution.

To further test the function of the cream compound as a prostanoid inhibitor, additional sections from the India ink perfusion study were examined for the presence of prostaglandins and thromboxanes using the perioxidase-antiperoxidase tech-

Table 1.—Biochemical Constituents of *Aloe vera* Extract Determined by SMAC

Constituent	Quantity
Glucose	13 mg/dl
Uric acid	0.5 mg/dl
Salicylic acid	3.6 mg/dl
Creatinine	1.9 mg/dl
Alkaline phosphatase	1 IU/L
Creatine phosphokinase	10 IU/L
Cholesterol	11 mg/dl
Triglycerides	374 mg/dl
Lactate	14.8 mg/dl
Total protein	0.2 mg/dl

Table 2.—Inorganic Constituents of *Aloe vera* Extract

Constituent	Quantity
Sodium	19.0 mEq/L
Potassium	21.5 mEq/L
Inorganic phosphorus	14.0 mg/dL
Chloride	1.0 mEq/L

Table 3.—Trace metal analysis of *Aloe vera* Extract

Constituent	Quantity
Calcium	23.5 mEq/L
Magnesium	4.6 mg/dL
Copper	0.2 mg/dL
Zinc	0.02 mg/dL

Table 4.—Antimicrobial Effects of *Aloe vera* Extract

Organisms	(CFU/ml/conc. of extract) 100%	90%	80%	70%	60%
Gram negative					
E. coli	≤4	≤4	≤4	2.4×10^3	8.0×10^4
Citrobacter sp.	≤4	≤4	≤4	≤4	≤4
S. marcescens	≤4	≤4	≤4	≤4	≤4
Enterobacter sp.	≤4	≤4	≤4	≤4	20
Klebsiella sp.	≤4	≤4	≤4	≤4	≤4
P. aeruginosa	≤4	≤4	≤4	≤4	12
Gram positive					
S. aureus	≤4	≤4	≤4	≤4	1.5×10^2
S. pyogenes, group A	≤4	≤4	≤4	28	40
S. agalactiae, group B	≤4	≤4	≤4	≤4	≤4
S. sp., group D	≤4	≤4	10^4–10^5	5.5×10^6	7.2×10^6
B. subtilis	2.2×10^4	2.5×10^4	2.2×10^4	1.9×10^4	2.8×10^4
Yeast					
C. albicans	≤4	≤4	≤10^3	2.9×10^3	2.7×10^6

nique.[21] Specific antiprostaglandin (PGE_2 and $PGF_2\alpha$) and antithromboxane (TxB_2) antibodies were reacted with tissue biopsies from groups 1, 2, 3, and 4. Then, as described by Heggers et al,[21] goat anti-rabbit immunoglobulin and horseradish peroxidase were utilized to demonstrate the actual presence of prostanoid metabolites in tissue.

RESULTS

The composition of 99.5% *Aloe vera* extract (Dermaide Aloe) is listed in Tables 1–3. In addition to acetysalicylic acid, there are organic compounds such as emolin, barbaloin, and emodin that can be broken down by the Kolbe reaction to salicylates. The presence of fatty acids such as cholesterol and triglycerides (374 mg/dl) was also demonstrated. Triglycerides as well as cell membrane phospholipids are precursors of the arachidonic acid cascade.

Table 4 shows the antimicrobial effects of the extract. When gram-negative organisms were assayed, the extract was effective as a bactericidal agent to concentrations as low as 60% for all organisms except *E. coli*. *E. coli* was able to grow to 2.4×10^3 colony-forming units per milliliter at the 70% concentration, whereas the 60% concentration was bactericidal for the remaining gram-negative organisms tested. At concentrations of 70% or greater, most of the gram-positive organisms' growth did not exceed the critical level of 10^5/ml. For *S. aureus, S. pyogenes, S. agalactiae*, the extract was effective at inhibiting growth at concentrations as low as 60%. However, for *S. faecalis*, the concentration most effective was 90%. The *B. subtilis* was not significantly inhibited even with the 100% concentration of the extract. Growth of *C. albicans* was almost totally inhibited at the 90% concentration. Only at the 60% concentration level did greater than 10^5 colony-forming units per milliliter of *C. albicans* emerge.

The antimicrobial effects, as demonstrated by the Agar well diffusion assay, are comparable to those of AgSD (Table 5).

In the dermis there are two general capillary plexuses—the subpapillary and the dermal. Immediately beneath the dermis is a subdermal plexus within the subcutaneous tissue layer. In the normal injected, unburned guinea pig, India ink has been shown to fill to the subpapillary plexus and higher. Thus, at least 95% of the dermal thickness is perfused. In the present experiment, this was also the case immediately after burning in all of the groups. By 2 hours postburn, sections from untreated burn controls demonstrated India

Table 5.—Antimicrobial Effects of *Aloe vera* Extract in Cream Base Compared to Silver Sulfadiazine in Agar Well Diffusion (Zone Sizes Measured in mm)

Organisms	*Aloe vera*	AgSD
Gram negative		
E. Coli	16	12
Enterobacter cloacae	14	12
K. pneumoniae	14	6*
P. aeruginosa	17	12
Gram positive		
S. aureus	18	12
S. pyogenes	16	12
S. agalactiae	16	12
S. faecalis	6	11
B. subtilis	19	14

*Agar well is 6 mm in diameter.

ink filling to 80% of the dermal thickness, and by 8 hours, filling only to the level of the dermal plexus (40% of dermal thickness), suggesting a progressive decrease in the level of dermal perfusion. At 24 hours, sections from untreated burn controls showed India ink only within the subdermal plexus, the dermis now being devoid of India ink-filled vessels.

Comparison of sections from burned, untreated controls with those from guinea pigs treated topically with the 70% cream showed remarkable similarities to those animals treated with methylprednisolone and methimazole. As noted previously, all groups showed India ink perfusion to the level of the subpapillary plexus immediately after burn. However, at 2 hours, the treated groups showed 90% of dermal thickness filling. At 8 hours, when untreated controls showed perfusion only to the level of the dermal plexus (40% of thickness), the treated groups maintained perfusion to the subpapillary plexus, 90% and 90%, respectively. By 24 hours, when complete dermal ischemia existed in the control group, sections from the treated groups showed perfusion continuing to the level of the subpapillary plexus (Fig 1). Dermal filling was present to about 90% for groups 2, 3, and 4. In addition, sections from the treated groups at 72 and 96 hours showed a persistent India ink filling above the level of the dermal plexus.

Fig 1.—Treated animal with perfusion to dermal plexus and higher at 24 hours (*arrow* indicates India ink perfusion).

Three weeks after burning, gross observation of the burn wound showed almost total absence of hair in the healed, untreated burn, whereas the burned, treated guinea pigs showed a luxuriant hair growth after healing (Fig 2). Burned, untreated guinea pigs showed a mean of only 2.5 follicles/hpf while treated groups showed a mean of 18 follicles/hpf.

As can be seen in Table 6, the Aloe cream compound was effective in preventing the formation of some of the arachidonic acid metabolites in burned tissue. In the control animals, TxB_2 began to be formed at 2 hours postburn. It increased through 72 hours postburn. Conversely, in the cream-treated animals, no TxB_2 was demonstrated in the burned tissue. Similarly but to a lesser degree, *Aloe vera* appeared to inhibit the formation of $PGF_2\alpha$. At 8 hours, 24 hours, and 72 hours, there was increased $PGF_2\alpha$ in the control animals compared to that in treated animals.

DISCUSSION

Certainly the label of a panacea or old wives' tale is deserved for a plant that lessens general debility, enhances sexual excitement, promotes menstruation, develops mammary glands, relieves headaches, heals injuries, and acts as a purgative.[1-6] However, stranger properties were once attributed to the foxglove plant. Only with a systematic experimental approach can the claims for a product be verified or discarded.

The results of the chemical analysis in Table 1 have been verified by Bouchey and Gjerstad.[22] None of the compounds identified in *Aloe*

vera extract would affect the burn wound except salicylic acid, magnesium, and the fatty acids. In addition, the known organic constituents of *Aloe vera* can be converted to salicylates by the Kolbe reaction[23] (Fig 3). One can postulate that since the extract contains an aspirin-like compound capable of causing analgesia, coupled with the high magnesium content, it may be capable of relieving pain, as so frequently reported.

The antimicrobial effects of the extract have been controversial. Previous investigators used concentrations below 50% showing a wide diversity of reactions.[9] Barbaloin has been quoted as the effective agent against *Mycobacterium*.[6] Experimentally, concentrations of 60% or greater effect a lethal action against gram-negative and gram-positive organisms alike, with a few exceptions.[18] Therefore, a concentration of the extract at 70% or greater, when combined with a cream base, becomes an effective topical antimicrobial against those organisms most frequently isolated as etiologic agents of burn wound sepsis. This product in its cream base proved to be comparable to AgSD in these experiments.

Because it contained aspirin-like compounds or their precursors, eg, emolin, barbaloin, and emodin,[6,24] it was thought that the anti-inflammatory, edema-relieving, and wound-healing properties attributed to the extract might be due to an anti-prostanoid effect. Some of the prostaglandins and the thromboxanes can elicit platelet aggregation, leukocyte sticking, and vasoconstriction.[25,26] Obviously these can be, and often are, detrimental to the burn wound. If *Aloe vera* blocks the formation of all or some of these products of the arachidonic acid cascade, the detrimental processes might be obviated. Using the guinea pig-India ink injection burn model, the extract proved to be comparable to or better than other known anti-prostanoids tested, resulting in a 90% maintenance of dermal perfusion after a 10% partial-thickness burn. Brasher et al[11] have reported that *Aloe vera* is an anti-inflam-

Fig 2.—Treated animal with near-normal distribution of hair 3 weeks after burning.

Table 6.—Immunohistochemical Analysis of Aloe and Methimazole Treated Tissue Compared with Untreated Burn Tissue

Prostanoid derivative	*Aloe vera* (Time [hr])			Methimazole (Time [hr])			Control (Time [hr])		
	8	24	72	8	24	72	8	24	72
PGE_2	3+	4+	3+	4+	4+	3+	2+	2+	1+
$PGF_2\alpha$	2+	2+	2+	2+	1+	1+	3+	4+	3+
TxB_2	0	0	0	1+	0	0	3+	4+	3+
Normal rabbit serum control	0	0	0	0	0	0	0	0	0

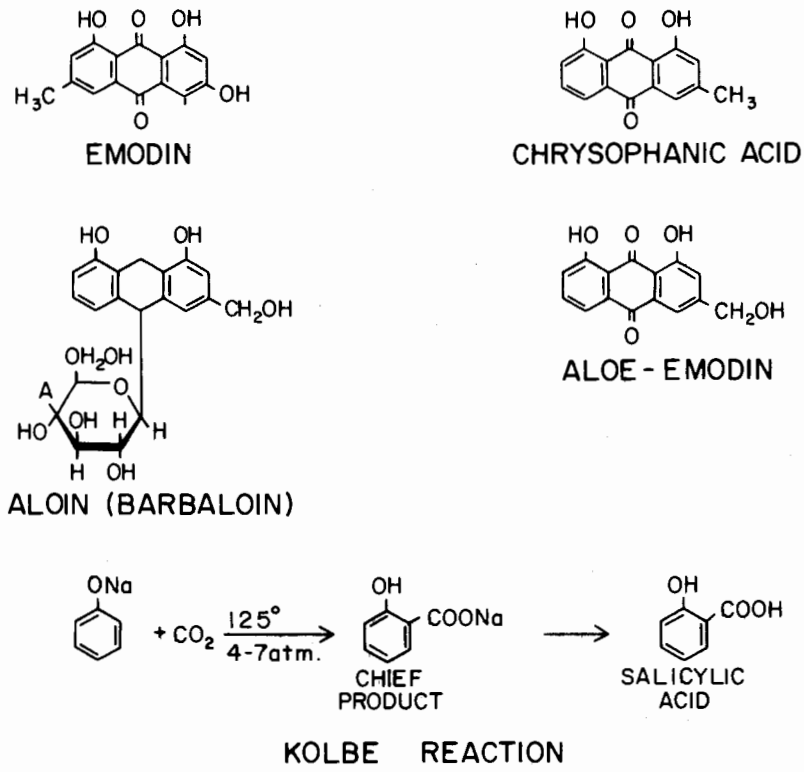

Fig 3.—Organic constituents of *Aloe vera* and the Kolbe reaction for salicylate conversion.

matory agent similar to prednisolone and indomethacin. They also found it less toxic to tissue culture cells than other prostaglandin inhibitors.

The immunohistochemical demonstration of prostaglandins and thromboxanes in burned tissue has been useful in elucidating the mechanism of action of various prostanoid inhibitors. This study suggests that the extract has multifactoral action: (1) among its chemical constituents, it contains products that yield an anesthetic reaction; (2) these chemical constituents are bactericidal; and (3) the constituents exhibit an antithromboxane effect.

Aloe vera, therefore, has three major properties that are most beneficial in thermal injury: (1) Either due to the aspirin-like effect or the high Mg^{2+} content or possibly both, acting synergistically, it can potentiate an anesthetic effect; (2) it has a broad-spectrum antimicrobial effect, especially against agents frequently responsible for burn wound sepsis; and (3) it has an antiprostanoid or, more specifically, an anti-thromboxane effect. This latter property may be due to its biochemical configuration, which allows the compound to act as an enzymatic substrate competitor. *Aloe vera* has an abundance of fatty acids, which probably supply the necessary nutirnets required for normal tissue maturation. Fitzpatrick and Gorman[25] have stated that PGE_2 and $PGF_2\alpha$ exist in a steady state in order to maintain membrane equilibrium. Therefore, although *Aloe vera* inhibits thromboxane production by competitive inhibition through stereochemical means, it also supplies the necessary precursors to initiate the arachidonic cascade, giving the cell the important constituents (PGE_2 and $PGF_2\alpha$) to maintain cellular integrity.[27] These experimental data clearly suggest that a 70% concentration extract of *Aloe vera* can be therapeutically beneficial in a burn wound. ■

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