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Review Article

Aloe Vera Gel Research Review

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ABSTRACT

Aloe vera, commonly known as Barbados or Curaçao Aloe, is an herbal medicine with a long tradition of use by a variety of cultures. The succulent plant grows in arid and subtropical climates and is best known for 2 distinct preparations: the clear mucilaginous gel that is widely used for the treatment of minor burns, especially sunburns, and the thick sap of the leaves that turns yellow-brown and has strong laxative effects that caution its use. The traditional uses of the clear mucilaginous gel are manifold, ranging from topical applications to reduce perspiration to oral dosing for diabetes and a range of gastrointestinal ailments. The efficacy of aloe vera gel to treat burn wounds, genital herpes, and seborrheic dermatitis have been shown in clinical trials, but other indications such as psoriasis or internal application for the treatment of type 2 diabetes remain inconclusive. The main limitation of the current clinical knowledge about aloe vera gel is small clinical studies that often lack rigorous methodology. Several clinical trials are being conducted to further evaluate the use of aloe vera gel for a variety of disorders, as well as to further confirm traditional uses of the plant extract.

INTRODUCTION

Aloe vera (syn. Aloe barbadensis Mill., Fam. Liliaceae), also known as Barbados or Curaçao Aloe, has been used in traditional and folk medicines for thousands of years to treat and cure a variety of diseases. Although the plant is native to northern parts of Africa, it has rapidly spread across the world because its cultivation is easy. An important distinction has to be made between the

strongly laxative and purgative latex derived from the bundle-sheath cells and the clear mucilaginous gel. The plant has been used by Egyptians, Assyrians, and Mediterranean civilizations, as well as in Biblical times. A variety of aloe species are still used in folk medicines of Africa and Asia. Hunters in the Congo reportedly rub their bodies in the clear mucilaginous gel to reduce

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perspiration; some African tribes apply the gel for chronic conjunctivitis; the gel is used in India for the treatment of asthma.1 Aloe vera gel is used as an ethnomedicine in Trinidad and Tobago for hypertension.2 The most common folk use of aloe has been for the treatment of burn wounds and specifically to aid in the healing process, reduce inflammation, and tissue scaring. The gel was described by Dioscorides and used to treat wounds and mouth infections, soothe itching, and cure sores.3 The use of aloe vera gel as a household remedy in the United States was triggered by reports of its beneficial effect on radiation dermatitis4followed by a boom in cultivation in the 1930s; it remains a common plant and for burns and abrasions.1,5 Important contemporary uses of the gel exist in traditional medicines of India, China, and Mexico, as well as Middle America and the West Indies. Mexico is producing roughly 47% of aloe worldwide with a total sales volume of \$123.5 million US dollars as of 2008.6 Despite its widespread popularity, scientific evidence on the aloe vera gel remains sparse. Aloe vera gel is regarded as safe if applied topical with only a few allergic reactions being reported.7 The efficacy of aloe vera gel to treat burn wounds, genital herpes, and seborrheic dermatitis have been shown in clinical trials, but other indications such as psoriasis or internal application for the treatment of type 2 diabetes remain inconclusive. The major application of aloe vera gel remains as a skin moisturizer in cosmetics and as an après treatment for sunburns, for which it has proven its effectiveness.8.9



Description

Aloe vera is a succulent plant with thick, fleshy, serrated, lanceolate-shaped leaves of greengreyish color. Aloe vera inner gel is obtained from the lower leaves of the plant by slicing the leaf open. The gel is clear, odorless, and tasteless and should be free of leaf skin or yellow parts. No consistent standardization has been established, but the International Aloe Science Council (IASC), a trade association of internationally based aloe producers and marketers, requires adherence to certain specifications for the product to be certified.10 Other preparations include a hydrophilic cream containing 0.5% aloe vera gel and an emulsion consisting of 30% aloe vera gel.

Primary Uses

(determined by clinical trials)

External

- Mild to moderate burns11–13 as well as erythema14
- Genital herpes15,16

Post Inflammatory Erythema



Internal

Adjunct therapy of spontaneous fibrosarcomas in dogs and cats18,19



Other Potential Uses

(determined by clinical trials and/or official monographs and/or empirical use)

- Psoriasis vulgaris20
- Skin moisturizer8
- Type 2 diabetes21–23
- Malignancies and immunodeficiency viruses in cats24,25
- Oral lichen planus infections26,27
- Angina pectoris23
- Ulcerative colitis28–31
- UV-induced erythema14 Kidney stones32,33
- Alveolar osteitis34

Dosage

External

• For burns:

Clear mucilaginous gel (pure aloe vera inner gel or preparations containing 10%–70% aloe inner gel). Gel must be stabilized by pasteurization at 75–80°C for less than 3 minutes3 and applied on affected area 3 times daily.

• For seborrheic dermatitis:

30% aloe vera in a hydrophilic emulsion twice daily to affected area17

• For psoriasis and genital herpes:

Hydrophilic cream containing 0.5% aloe gel 3 times daily to affected area16,20

• Internal

• **Treatment of diabetes and angina pectoris:** recommended in humans, 100 mg of fresh inner gel each day or 1 tablespoon twice daily.23,35

- For ulcerative colitis and irritable bowel syndrome: a dose of 25–50 ml of 95% aloe inner gel is recommended 3 times daily.28
- Adjuvant therapy in feline and canine malignancies:

Acemannan Immunostimulant®, a special preparation of the clear mucilaginous gel specifically for injection, for intraperitoneal injection in cats and dogs following chemotherapy. Weekly injections over at least 6 weeks; recommended dose is 1 mg/kg body weight of animal.18,19

Duration of Administration

External administration 3–4 times daily to affected area until improvement is seen.15,17,20 No information for duration after oral application in humans is available, but generally the gel is taken as long as the symptoms persist.23

Chemistry



The fresh gel mainly consists of water (99.1%) and mesophyll cells (0.9% dry matter), which can be divided into 3 distinct fractions: cell wall, microparticles, and liquid gel [accounting for 16.2%, 0.7%, and 83.1% of dry pulp (w/w), respectively]. The predominant sugar component is mannose as mannose-6-phosphate36 in all 3 in cell wall, 32.2% fractions [20.4%] in microparticles, and 62.9% in the liquid gel (% of total sugars)], followed by other sugars in varying concentrations depending on the fraction. Overall, the 5 neutral sugars (ie, arabinose, xylose, mannose, galactose, glucose) account for 69.2% of the total sugars in the gel.37Mucopolysaccharides are mainly present as acemannan [a highly acetylated, β -1-4-linked polysaccharide (> 1kDa) made mainly of mannose] with various side chain glycosylation patterns.38 The anthraquinone content should be below 50 ppm and is considered an impurity from the leaf extract of aloe vera.7 Other ingredients include various amino acids, enzymes, and vitamins, which have not been quantified. The IASC maintains a certification program, in which "whole aloe vera leaf gel" has to adhere to the following specifications: solids (0.46%–1.31%); pH (3.5–4.7); calcium (98.2–448 mg/L); magnesium (23.4–118 mg/L; malic acid (817.8–3,427.8 mg/L); acemannan in raw materials (\geq 5% by dry weight); isocitrate (\leq 5% for inner leaf by dry weight); raw materials ash content ($\leq 40\%$); aloin (≤ 10 ppm in 0.5% aloe vera solids solution for oral consumption). Quality products should contain high amounts (95%) of pure aloe vera gel.39 One way of quantifying aloe polysaccharides is a colorimetric assay, which has been suggested for use in quality control of commercial products.40 Quality control and identification of commercial aloe vera products has also been accomplished by nuclear magnetic resonance spectrometry.41

Pharmacological Actions Note:

Information on the precise chemical composition of the aloe vera inner gel used for most of the below listed observed pharmacological activities is lacking. Therefore, results should be interpreted with caution in regard to reproducibility of the stated effect.

Human

Mild (first degree) to moderate (second degree) burn wounds;11–13,42 genital herpes at first onset;16,20 seborrheic dermatitis;17 oral lichen planus infections;26postdermabrasion wound healing;43normalization of gastric pH;44 treatment of diabetes and angina pectoris.23

Animal

Acceleration of wound healing in mice and rats;36,45-47 reduction of radiation-induced skin reactions in irradiated mice and rats;48-50 prevention of progressive dermal ischaemia caused by burns and frostbite in rats and guinea pigs; 51-53 antidiabetic in type-2 diabetic and insulin-resistant mice;21,54-57 chemopreventive in skin papillomagenesis in mice;58,59 antiinflammatory in mice;36,60-64 enhancement of immune responsiveness in chicks and mice;65,66 amelioration of UV-induced immune suppression in mice;67 promotion of gastric ulcer healing in rats;68,69protection of alcohol dehydrogenase and reduction of blood ethanol concentrations in rats:70 reduction of salmonella-mediated inflammation in mice:71 antioxidant and cholesterol-lowering effects in aged rats.72

In vitro

Inhibits collagenase and metalloproteinase activity in Clostridium histolyticum;73 exerts cytotoxic effects in normal and malignant tissues;74 suppresses bactericidal inflammation in human leukocytes;75,76causes antioxidant activities and enhanced phagocytosis in human neutrophils;77-79 cell wall material stabilizes growth factors;80inhibits pro-inflammatory cytokines;81-83acemannan enhances T cell response through monocyte activation;84,85 induces hematopoietic and hematologic activity of carbohydrate fraction;86 acts as antifungal;87,88 stimulates cell proliferation in keratinocytes by glycoprotein fraction;47accelerates wound healing in diabetic human skin fibroblasts;89 di(2ethylhexyl)phthalate isolated from aloe vera leaves exerts antitumor activity;90 Aloe vera gel fraction on calf pulmonary artery endothelial cells has angiogenic activity.91

Proposed Mechanisms of Action

- Stimulation of macrophage and fibroblast activity, increased collagen and proteoglycan synthesis36,62,85
- Mannose-6-phosphate binds to growth factor receptor on fibroblasts and enhances their activity36,92
- Macrophage activation through increased nitric oxide synthase activity by acemannan, leading to release of fibrogenic cytokines49,93,94
- Upregulation of phagocytosis and fungicidal activity of macrophages by acemannan95
- Acemannan and other cell wall biomaterial may promote stability of growth factors and prolong stimulation of granulation tissue48,80
- Inhibition of Thromboxan A236,53
- May promote hypoglycemic effect by normalizing membrane-bound enzyme activities of phosphatases and hydrolases and increased glucose metabolism;55,56 potential active compounds include the phytosterols lophenol, cycloartenol and their alkylated derivatives21
- Anti-inflammatory effect of plant sterols like lupeol, campesterol, and β-sitosterol92 through bradikinase activation,61 prostaglandin F2 and E2, as well as thromboxane A2 inhibition45,81,96 and inhibition of IL-10 secretion83

- Inhibitory effect on release of reactive oxygen species from human neutrophils by reducing intracellular free calcium levels77
- Increase in mRNA expression of metalloproteinases and plasminogen activator may lead to angiogenic activity in endothelial cells91

Contradictions

- Known allergy against aloe vera; discontinue use if skin irritation develops or worsens97
- Pregnancy and Lactation
- It is not recommended to use aloe vera gel while during pregnancy or breastfeeding.7There is, however, no evidence that suggests a reproductive or genotoxic effect of topical aloe vera inner gel preparations. Internal use in combination with digoxin is contraindicated due to acceleration possible of potassium depletion.98

Adverse Effects

In general, topical application of aloe vera • preparations has been regarded as safe as assessed by the Cosmetic Ingredient Review Expert Panel.7 However, several case reports of the development of hypersensitivity reactions and contact dermatitis in response to topically applied aloe gel preparations have been published.99–103 This allergic reaction has been attributed in most cases to contaminations anthraquinone in the gel.97Macrophage infiltration and emesis has been observed in dogs treated intravenously with acemannan.104 Oral application of aloe vera gel may lower blood glucose levels and activity antidiabetic enhance the of treatments.23 No genotoxic effects have been observed following oral administration of an aloe vera inner leaf gel (Qmatrix® by Aloecorp, Inc., which is a standardized inner gel extract that has not been heated after extraction from the leaf) to rats after 90 days.105 An important factor for adverse effects is the purity of the aloe vera gel used, since anthraquinones like aloin might be related to the development of hypersensitivity reactions.99,106

Drug Interactions

- When aloe vera gel is administered topical, it is generally regarded as safe.7 Aloe gel might enhance the ability of hydrocortisone to reduce swelling if applied topically.107 If ingested, it might lead to increased hypoglycemia in conjunction with oral antidiabetics or insulin.97 The American Pharmaceutical Association rates aloe vera gel for external use in category 2, meaning that "according to a number of well-designed studies and common use, this substance appears to be relatively effective and safe when used in recommended amounts."39Aloe vera inner gel may significantly increase the absorption of vitamins C and E after oral application.108 Aloe vera gel for systemic application is not recommended in combination with antidiabetic, diuretic, or laxative drugs; sevoflurane; or digoxin.107 In general, a 2-hour time period is recommended between oral drug application and aloe vera ingestion due to increased intestinal motility and reduced drug absorption.98 If aloe vera gel is used with any other prescription drug, the patient should inform the physician and/or pharmacist.
- Clinical Review
- Clinical data on aloe vera gel is sparse, which might be in part due to the many possible indications for the gel. The table outlines 18 clinical trials on a total of 7,297 subjects conducted for various types of aloe gelderived preparations on numerous indications. The design of the clinical studies evaluated ranges from placebo-controlled, double-blind,

multicenter studies to equivalence investigations. One of the most important factors is the composition of the aloe vera preparation used, which in most cases is a certain purity aloe vera gel without further elucidation of compound quantity. This discrepancy complicates a direct comparison of the studies.

- Three randomized studies on the efficacy of radiation-induced aloe vera gel for dermatitis109-111 reported either a delayed onset of skin changes if aloe vera gel was applied in addition to mild soap against mild soap alone111 or no efficacy of the gel against a placebo gel or aqueous cream.109,110 A review of aloe vera for radiation-induced skin damage concluded that there is no evidence for a protective effect of the gel and that more research with well-designed studies is needed to evaluate potential benefits.112 Similar results were obtained from a clinical study evaluating the use of aloe vera gel for the treatment of radiation-induced oral mucositis with no significant differences from the placebo group.113
- The historical application of aloe vera gel for the treatment of wounds has been evaluated in surgical wounds and the randomized study concluded that there was a significant delay in complete wound healing for the aloe vera gel compared to standard treatment.114
- The use of aloe vera gel for the treatment of lichen planus lesions was examined in 2 clinical trials with small sample sizes. One study examined the use of aloe vera gel (containing 70% mucilage) in oral lichen planus lesions compared to placebo over 8 weeks and found a significant improvement in 88% of patients versus 4% in the placebo group.26 Another study used a similar design but with unspecified composition of the aloe vera gel and reported significant improvement

in 82% of patients versus 5% in the placebo group over a period of 8 weeks.115

- Three clinical trials on the effect of aloe vera • gel for the treatment of psoriasis vulgaris were inconclusive. One study reported a significant beneficial effect of aloe vera extract 0.5% in hydrophilic cream compared to hydrophilic cream alone in reducing psoriatic plaques and inflammation,20 while the other study did not find a significant benefit of 98% pure aloe vera gel versus placebo after 12 weeks.116 A third study compared aloe vera cream containing 70% mucilage to 0.1% triamcinolone acetonide cream over the course of 8 weeks and found it to be equally effective.117
- One study evaluated the effect of aloe vera 0.5% in hydrophilic cream and aloe vera gel versus placebo for the treatment of genital herpes15 and concluded that aloe vera in hydrophilic cream is more effective than aloe vera gel, but that both resulted in faster healing times compared to placebo.
- An aloe vera emulsion showed significant benefits for the treatment of seborrheic dermatitis in a double-blind, randomized study compared to placebo,17 but the placebo formulation was different from the base used for the emulsion.
- A randomized, double-blind clinical trial evaluated the effectiveness of a prepared 70% aloe vera gel for the treatment of oral lichen planus infections compared to the base gel alone and reported a significant improvement of symptoms in the aloe vera group.26
- The use of aloe vera gel in the traditional medicine of India has triggered an observational, inter-patient control study using fresh aloe vera inner gel in addition to adding psyllium (Plantago ason, Plantaginaceae) seeds to the daily diet of 5,000 patients diagnosed with angina pectoris.

Over the course of 5 years, patients were observed and blood cholesterol, glucose, and triglyceride levels evaluated. A cofounding variable was the influence of aloe vera gel on diabetes mellitus. Aloe vera gel had a significant influence on normalizing blood parameters and relief of angina pectoris symptoms, as well as diabetic symptoms.23 In many patients, the continued use of aloe vera gel daily led to the discontinuation of prescription medications. An important drawback of the study is the absence of a control group and no chemical definition of the aloe vera gel used in the study.

- The widespread use of aloe vera gel as moisturizer and for the treatment of xerosis was evaluated in two studies.8,118 The moisturizing effects of aloe vera resulted in increased water content in the stratum corneum after short-term and long-term application of a hydrophilic cream containing various concentrations of freeze-dried aloe vera concentrate compared to the base cream alone.8 A partially blinded, non-placebo study suggests a benefit of freeze-dried aloe vera gel on the inner side of a glove to dry skin, although this study lacks both control and complete blinding.118
- In addition, aloe vera gel lotions are popular for the treatment of sunburn (UV-induced erythema). One randomized, double-blind, placebo-controlled trial compared the antiinflammatory effect of 97.5% pure aloe vera gel to 1% hydrocortisone and a placebo gel. Aloe vera gel, if applied under an occlusive bandage for 2 days following UV exposure, significantly reduced inflammation compared to placebo gel or 1% hydrocortisone in placebo gel, but was less effective than 1% hydrocortisone cream. The authors suggest that aloe vera gel might be useful for the treatment of inflammatory skin conditions.14

- Two studies evaluated beneficial effects of aloe vera gel on irritable bowel syndrome30and ulcerative colitis,28 which resulted in no significant effect for either indication, although a patient-evaluated improvement was seen for the treatment of ulcerative colitis after 1 month.
- Based on its immunomodulatory effect, acemannan was evaluated for the adjunct treatment of HIV infections in addition to standard treatment (either zidovudine or didanosine).119 The one-year, double-blind, placebo-controlled, randomized trial concluded that there were no differences in CD4 count or survival after 48 weeks between acemannan capsules and placebo.
- A non-controlled trial reported a positive influence of nutritional dietary supplements partially containing aloe vera on fibromyalgia and chronic fatigue syndrome, but failed to differentiate between the various supplements.
- Since acemannan has been shown to stimulate macrophage activation and enhances wound healing, 1 study evaluated the use of acemannan hydrogel in a patch for the treatment of alveolar osteitis after oral surgery.34 Acemannan significantly reduced the incidence and severity of the inflammatory process compared to clindamycin Gelfoam patches. Although the study lacks a complete clinical design, the comparison between the treatment groups showed an impressive advantage of acemannan in the prevention of alveolar osteitis in a large patient collective (n=1,194).
- One randomized, double-blind, placebocontrolled study investigated the use of aloe vera inner leaf gel for its anti-hyperglycemic and anti-hypercholesteremic effects in a small study population and found a slight decrease in fasting blood glucose, HbA1C, total

cholesterol, and LDL levels, although this may be attributed to a restricted diet that patients in both groups were prescribed.120

- Two promising clinical trials with fresh aloe • healthy adult33 vera gel in and pediatric32volunteers showed increased calcium and oxalate urinary secretions, which might confirm the traditional use of aloe vera gel in the treatment of kidney stones.1 However, confirmation through clinical studies for this indication in patients suffering from kidney stones is lacking to date.
- A non-controlled trial reported a positive influence of nutritional dietary supplements partially containing aloe vera on fibromyalgia and chronic fatigue syndrome, but failed to differentiate between the various supplements.121

CONCLUSION

In conclusion, the use of aloe vera gel or its components for the treatment of a variety of conditions and diseases needs further clinical evidence through well-designed studies with defined aloe extracts and matching placebo controls. Currently (June 2012), 5 national and international clinical studies are listed by the United States National Institutes of Health clinical trial database with a major emphasis on the use of aloe vera in the treatment of wounds.122 This indicates the scientific significance of aloe vera gel and the need to establish it as a valid treatment option for wounds. However, the use of aloe vera gel in topical applications has widely been confirmed in the clinical studies as safe.

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