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An Evidence-Based Systematic Review of *Aloe vera* by the Natural Standard Research Collaboration

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ABSTRACT. An evidence-based systematic review including written and statistical analysis of scientific literature, expert opinion, folkloric precedent, history, pharmacology, kinetics/dynamics, interactions, adverse effects, toxicology, and dosing.

KEYWORDS. Adverse effects, aloe, *Aloe vera*, dosing, evidence based, interactions, pharmacodynamics, pharmacology, pharmacokinetics, systematic review

SYSTEMATIC AGGREGATION, ANALYSIS, AND REVIEW OF THE LITERATURE

Search Strategy

To prepare each Natural Standard review, electronic searches are conducted in nine databases, including AMED, CANCERLIT, CINAHL, CISCOM, the Cochrane Library, EMBASE, HerbMed, International Pharmaceutical Abstracts, Medline, and NAPRALERT. Search terms include the common name(s), scientific name(s), and all listed synonyms for each topic. Hand searches are conducted of 20 additional journals (not indexed in common databases), and of bibliographies from 50 selected secondary references. No restrictions are placed on language or quality of publications. Researchers in the field of complementary and alternative medicine (CAM) are consulted for access to additional references or ongoing research.

Selection Criteria

All literature is collected pertaining to efficacy in humans (regardless of study design, quality, or language), dosing, precautions, adverse effects, use in pregnancy/lactation, interactions, alteration of laboratory assays, and mechanism of action (*in vitro*, animal research, and human data). Standardized inclusion/exclusion criteria are utilized for selection.

Data Analysis

Data extraction and analysis are performed by healthcare professionals conducting clinical work and/or research at academic centers, using standardized instruments that pertain to each review section (defining

inclusion/exclusion criteria, and analytic techniques, including validated measures of study quality). Data are verified by a second reviewer.

Review Process

A blinded review is conducted by multidisciplinary research-clinical faculty at major academic centers with expertise in epidemiology and biostatistics, pharmacology, toxicology, CAM research, and clinical practice. In cases of editorial disagreement, a three-member panel of the editorial board addresses conflicts, and consults experts when applicable. Authors of studies are contacted when clarification is required.

Update Process

Natural standard regularly monitors scientific literature and industry warnings. When clinically relevant new data emerge, best efforts are made to update content immediately. In addition, regular updates with renewed searches occur every 3 to 18 months, variable by topic.

Synonyms/Common Names/Related Substances:

- Acemannan, *Aloe africana*, *A. arborescens* Miller, *A. barbadensis*, *A. barbadesis*, *A. capensis*, *A. ferox*, *A. latex*, *A. mucilage*, *A. perfoliata, A. perryi Baker, A. spicata, A. vulgari*, Barbados aloe, bitter aloe, burn plant, Cape aloe, Carrisyn, hirukattali, Curaçao aloe, elephant's gall, first-aid plant, Ghai kunwar (Indian), Ghikumar (Indian), Hsiang-Dan (Chinese), jelly leek, kumari, lahoi, laloi, lily of the desert, Lu-Hui, medicine plant, Mediterranean aloe, miracle plant, mocha aloes, musabbar, natal aloes, nohwa, plant of immortality, plant of life, rokai, sabilla (Spanish), Savila, Socotrine aloe, subr, true aloe, Venezuela aloe, Za'bila (Swahili), Zanzibar aloe.
- *Combination products (example):* Mepentol Leche (an emulsion based on hyper-oxygenated fatty acids, A. barbadensis, and Mimosa tenuiflora).

CLINICAL BOTTOM LINE/EFFECTIVENESS

Brief Background

- Transparent gel from the pulp of the meaty leaves of *A. vera* has been used topically for thousands of years to treat wounds, skin infections,

burns, and numerous other dermatologic conditions. Dried latex from the inner lining of the leaf has traditionally been used as an oral laxative.

- There is strong scientific evidence in support of the laxative properties of aloe latex, based on the well-established cathartic properties of anthroquinone glycosides (found in aloe latex). However, aloe's therapeutic value compared with other approaches to constipation remains unclear.
- There is promising preliminary support from *in vitro*, animal, and human studies that topical aloe gel has immunomodulatory properties that may improve wound healing and skin inflammation.

Scientific Evidence for Common/Studied Uses

See Table 1 for scientific evidence for common/studied uses.

Natural Standard Evidence-Based Validated Grading Rationale™

- Grades reflect the level of available scientific evidence in support of the efficacy of a given therapy for a specific indication.

TABLE 1. Scientific evidence for common/studied uses.

Indication	Evidence Grade
Constipation (laxative)	A
Genital herpes	B
Psoriasis vulgaris	B
Seborrheic dermatitis	B
Aphthous stomatitis	C
Cancer prevention	C
Diabetes (type 2)	C
HIV infection	C
Skin burns	C
Ulcerative colitis	C
Infected surgical wounds	D
Mucositis	D
Pressure ulcers	D
Radiation dermatitis	D

- Expert opinion and folkloric precedent are not included in this assessment, and are reflected in a separate section of each review ("Strength of Expert Opinion and Historic/Folkloric Precedent").
- Evidence of harm is considered separately; the grades shown in Table 2 apply only to evidence of benefit.

Historical or Theoretical Uses Which Lack Sufficient Evidence

- Alopecia (hair loss), Alzheimer's disease, antioxidant,[1–3] arthritis (osteoarthritis and rheumatoid arthritis), asthma,[4] bacterial skin infections,[5] candidal skin infections,[6] chronic fatigue syndrome, chronic leg ulcers,[7] congestive heart failure,[8] corneal abrasions/ulcers,[9] coronary artery disease prevention,[10] diabetic ulcers,[11] duodenal ulcer, dry skin (aloe gel gloves),[12] frostbite,[13,14] functional bowel disorders, gastric acid reduction (hyperacidity), gastric ulcer, helminthic infections, hepatitis,[15] human papilloma virus[16] hyperlipidemia, inflammatory bowel disease, lichen planus,[17] Parkinson's disease, peptic ulcer,[18] periodontal surgical rinse,[19] postdermabrasion wound healing,[20] radioprotection,[21] sunburn,[22] systemic lupus erythematosus, tic douloureux,[23] untreatable advanced solid neoplasms,[24] urolithiasis (bladder stones), vaginal contraceptive.[25]

Expert Opinion and Historic Precedent

- Topical aloe first gained popularity in the United States in the 1930s with reports of its success in treating x-ray burns.[26–30] Today, *A. vera* gel is an ingredient in hundreds of skin lotions and sun blocks,[31] and the gel's use in cosmetics has been boosted by claims that it possesses antiaging effects similar to vitamin A derivatives.[32]
- Aloe is popular in traditional Chinese and Ayurvedic medicine. The Chinese literature describes the skin and the inner lining of aloe leaves as a "cold, bitter remedy" that can be "downward draining" and used to clear constipation due to accumulation of "heat" (fire). The gel is considered "cool and moist." In Ayurvedic medicine (the traditional medicine of India), aloe is used internally as a laxative, anthelminthic, hemorrhoid remedy, and uterine stimulant (menstrual regulator); it is also used topically, often in combination with licorice root, to treat eczema or psoriasis. In Arabian medicine, the fresh gel is rubbed on the forehead as a headache remedy, rubbed on the body to cool

TABLE 2. Natural Standard Evidence-Based Validated Grading Rationale™.

Level of Evidence Grade	Criteria
A (strong scientific evidence)	Statistically significant evidence of benefit from > 2 properly randomized trials (RCTs), or evidence from one properly conducted RCT and one properly conducted meta-analysis, or evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit and with supporting evidence in basic science, animal studies, or theory.
B (good scientific evidence)	Statistically significant evidence of benefit from 1–2 properly randomized trials, or evidence of benefit from ≥1 properly conducted meta-analysis OR evidence of benefit from >1 cohort/case-control/nonrandomized trials, and with supporting evidence in basic science, animal studies, or theory.
C (unclear or conflicting scientific evidence)	Evidence of benefit from ≥1 small RCT(s) without adequate size, power, statistical significance, or quality of design by objective criteria,* or conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, or evidence of benefit from ≥1 cohort/case-control/nonrandomized trials and without supporting evidence in basic science, animal studies, or theory, or evidence of efficacy only from basic science, animal studies, or theory.
D (fair negative scientific evidence)	Statistically sig0nificant negative evidence (i.e., lack of evidence of benefit) from cohort/case-control/nonrandomized trials, and evidence in basic science, animal studies, or theory suggesting a lack of benefit.
F (strong negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from ≥1 properly randomized adequately powered trial(s) of high-quality design by objective criteria.*
Lack of evidence†	Unable to evaluate efficacy due to lack of adequate available human data.

*Objective criteria are derived from validated instruments for evaluating study quality, including the 5-point scale developed by Jadad et al., in which a score below 4 is considered to indicate lesser quality methodologically (Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17(1):1–12).

† Listed separately in reviews in the "historical or theoretical uses which lack sufficient evidence" section.

fevers, and is also used for wound healing, conjunctivitis, infection, and constipation.
- Some naturopaths promote aloe juice as a way to prevent and treat renal stones.[33] Recently, aloe extracts have gained popularity as a treatment for canker sores, peptic ulcers, and HIV infection. The inner leaf lining is used orally as a natural laxative.
- Many individuals keep a plant at home (thrives in bright sunlight with little care), and when faced with a minor burn, gel from a fresh leaf is applied directly to the affected skin area.
- Aloe has been cautiously approved by the expert panel, the German Commission E, for use in constipation as a second-line agent. A monograph issued by the World Health Organization has also endorsed this use.[1]
- Previously, the Food and Drug Administration (FDA) regulated the use of the laxative component of aloe as a drug, but its topical applications were not regulated or endorsed. However, because of a failure to submit further studies on its use as a laxative in 2002, the FDA recategorized any over the counter "drugs" containing aloe as misbranded as a drug. On April 29, 2002, the Federal Register ruled that aloe products (aloe extract and aloe flower extract) were reclassified as category III agents; this ruling became effective on November 5, 2002. As of 2007, there was reported use of aloe extract (*aloe* species), and an initial toxicology literature search was in progress. Aloe is not listed on the FDA's Generally Recognized As Safe list. Aloe is currently approved by the US FDA as a food flavoring agent (*A. ferox*, *A. perryi*, *A. vera*) in accordance with good manufacturing practices.

Brief Safety Summary

- Likely safe: When *A. vera* gel or extract is used topically to reduce pain and inflammation, enhance healing of skin wounds (abrasions, cuts, and ulcers), or treat psoriasis, frostbite injury, burns, and HPV I

[1]Natural Standard Monograph (www.naturalstandard.com). Copyright © 2007 Natural Standard Inc. Commercial distribution or reproduction prohibited.The information in this monograph is intended for informational purposes only, and is meant to help users better understand health concerns. Information is based on review of scientific research data, historical practice patterns, and clinical experience. This information should not be interpreted as specific medical advice. Users should consult with a qualified healthcare provider for specific questions regarding therapies, diagnosis and/or health conditions, prior to making therapeutic decisions.

infections (cold sores). Medical attention should be sought for severe burns, wounds, or frostbite.
- Possibly safe: When *A. vera* is taken orally (potential hypoglycemic properties), or when oral aloe latex is used for short term as a laxative.[34,35]
- Likely unsafe: When oral aloe latex is used as a laxative for prolonged periods, because of theoretical risk of dehydration and electrolyte imbalance. Topical aloe gel should be avoided for postoperative wounds, because of findings of delayed healing in one trial.[36]

DOSING/TOXICOLOGY

General

- Recommended doses are based on those most commonly used in available trials, or on historical practice. However, with natural products it is often not clear what the optimal doses are to balance efficacy and safety. Preparation of products may vary from manufacturer to manufacturer, and from batch to batch within one manufacturer. Because it is often not clear what the active component(s) of a product is, standardization may not be possible, and the clinical effects of different brands may not be comparable.

Standardization

- Standardized products are not widely available. Although this is likely not problematic for topical aloe gel, it may pose danger with oral aloe (because of potential hypoglycemic properties). Oral aloe preparations often contain 10–30 mg hydroxyanthracene derivatives per daily dose, calculated as anhydrous aloin.[37]
- Penalties have been enforced for illegal marketing of *A. vera* products in the United States.[38]

Adult Dosing (Age ≥18)

Topical

- *General use:* Pure *A. vera* gel is often used liberally on the skin. There are no available reports of systemic absorption leading to clinically

relevant events. Commercial preparations combined with or without other active ingredients are available.
- *Genital herpes:* Hydrophilic cream of 0.5% (by weight) of a 50% ethanol extract, combined with liquid paraffin and castor oil, three times daily on lesions for five consecutive days per week, for up to two weeks has been used.[39]
- *Psoriasis vulgaris:* Hydrophilic cream of 0.5% (by weight) of a 50% ethanol extract of aloe, combined with mineral and castor oils, three times daily for five consecutive days per week, for up to four weeks has been used.[40]

Oral

- *Constipation:* The dose often recommended is the minimum amount to maintain a soft stool, typically 0.04–0.17 g of dried juice (corresponds to 10–30 mg hydroxyanthraquinones). As an alternative, in combination with celandine (300 mg) and psyllium (50 mg), 150 mg of the dried juice/day of aloe has been found effective as a laxative.[41]
- *Diabetes (type2):* 5–15 mL of aloe juice twice daily has been used.[34,35,42] Inconclusive efficacy or safety.
- *HIV infection:* 1000 mg–1600 mg of acemannan orally in four equal doses has been used.[43,44,45] Inconclusive efficacy or safety.

Intravenous/Intramuscular

- No recommended dosage for injectable acemannan exists to date because safety has not been sufficiently evaluated. Four cases of death have been associated with *A. vera* injections under unclear circumstances.[37,46]

Pediatric Dosing (Age < 18)

Topical

- Topical use in children is common and appears to be well tolerated.
- Oral/parenteral, not recommended internally due to lack of safety data.

Toxicology

- Subchronic oral use of acemannan has been well tolerated in animals.[47] Systemic toxicity of injectable acemannan has not occurred in mice, rats, or dogs.[48]
- Although anthraquinones are believed to be genotoxic,[49] the anthraquinones in aloe, including aloe-emodin, do not appear to be well absorbed, and no detectable levels result from ingestion.[50] A low-molecular-weight fraction from aloe gel has been shown to be cytotoxic *in vitro* .[51]
- Most adverse effects appear to be mediated by potassium depletion after prolonged oral use, for which supportive care with oral or intravenous fluid/electrolyte replacement has been anecdotally reported as effective.
- The US FDA has approved *A.ferox*, *A.perryi*,*A.vera*, and certain hybrids for use as natural food flavorings.

PRECAUTIONS/CONTRAINDICATIONS

Allergy

- Avoid if known allergy to plants of the Liliaceae family (garlic, onions, and tulips).
- After prolonged use of topical aloe gel, urticaria,[52] contact dermatitis,[53,54,55]and widespread dermatitis[56] have been reported. A patch test study in 702 patients, however, showed no adverse reactions when an oily extract from the leaves, *Aloe pulvis* from the entire plant or concentrated *A. vera* gel was applied to the skin.[57]The authors suggest that aloe preparations made from the center of leaves contain mostly carbohydrates, and these products are unlikely to cause allergy.

Adverse Effects

- *Cardiovascular:* Theoretically, a risk of arrhythmia may increase with prolonged use of oral aloe latex, on the basis of anecdotal reports of potassium depletion, and on the basis of aloe's laxative properties.

- *Dermatologic:* One randomized trial reported delayed wound healing with topical aloe gel, applied following complicated gynecological surgeries.[36] Thus, topical aloe may not be advisable for the promotion of postoperative incision healing. Photodermatitis has also been reported.[58] In one case report, a 65-year-old woman who was 2 weeks postdermabrasion applied *A. vera* leaf juice to her skin, which produced stinging, induration, and erythema.[59]The patient was prescribed hydrocortisone and diphenhydramine ointment, and the dermatitis subsided over time.[59] There is also a case report of aloe-induced Henoch-Schonlein purpura.[60] In one randomized-controlled study, no serious adverse effects were recorded, although 55% of subjects reported local adverse effects mainly drying up of the skin on test areas.[61] Other symptoms reported were stinging, soreness and, in a few cases, even fissures that the authors note were probably related to the dryness. Two persons described erythema after application of *A. vera* gel, accompanied by a slight tingling sensation in one of them. Tingling and tightness of the skin was also reported after use of the placebo gel, and by-and-large there was no difference regarding the frequency of adverse effects on the two sides. The proportion of subjects with adverse effects was similar in the group with improvement and the group without.
- *Endocrine:* Hypoglycemic effects of oral aloe have been reported in two methodologically weak human trials, with purported equivalence to a sulfonylurea antihyperglycemic oral agent (glibenclamide).[34,35] Laboratory studies have documented β-cell stimulation and subsequent drops in blood glucose in mice (thus, there may be no effect in type 1 diabetics, in whom β cells have been destroyed).[62] In contrast, a small randomized trial, published only as a conference abstract, found no evidence of hypoglycemia in 16 type 2 diabetics given aloe juice (15 ml twice daily).[42] The effects of aloe on human blood glucose levels thus remain inconclusive, although caution is warranted in patients taking antihyperglycemic agents. Aloe has also been linked to thyroid dysfunction, on the basis of one case report.[63]
- *Gastrointestinal:* Occasional abdominal cramping and diarrhea with oral use have been reported anecdotally by practitioners. Using laxatives such as aloe latex for more than 7 consecutive days may aggravate constipation or cause dependency. Chronic use or abuse of anthranoid-containing laxatives for more than 1 year has been associated with increased risk of colorectal cancer, with a relative risk of 3.04 versus nonanthranoid abusers (triple the risk).[64] There is a

single case report of acute hepatitis in a 57-year-old woman taking oral aloe.[65]

- *Hematologic:* There is a poorly described single case report of excess bleeding in a surgical patient receiving the anesthetic agent sevoflurane and oral aloe.[66]
- *Musculoskeletal:* A risk of muscle weakness may increase with prolonged use of aloe latex, on the basis of anecdotal reports of potassium depletion, and on the basis of aloe's laxative properties.
- *Renal:* On the basis of the laxative properties of oral-aloe latex, prolonged use may cause potassium depletion; there are anecdotal reports of low potassium, although scant literature exists in this area. There is one report of a 27-year-old female who developed an ammonium acid urate stone because of prolonged use (12 years) of laxatives (bisacodyl, sennoside, and aloe extract).[67]

Precautions/Warnings/Contraindications

- Oral aloe products should be used cautiously in patients with diabetes or glucose intolerance, and in patients using glucose-lowering agents. Blood glucose levels should be monitored.
- Avoid oral aloe latex in patients with renal insufficiency, cardiac disease, or electrolyte abnormalities, because of theoretical risk/anecdotal reports of hypokalemia.
- Avoid use of oral aloe latex in patients with ileus, acute surgical abdomen, bowel obstruction, fecal impaction, or appendicitis.
- Avoid *A. vera* injections, which have been associated with four cases of death under unclear circumstances.[37,46]

Pregnancy and Lactation

- Although topical application is unlikely to be harmful during pregnancy or lactation,[68] internal use is not recommended because of theoretical stimulation of uterine contractility by anthroquinones. It is not known whether pharmacologically active constituents of aloe may be excreted with breast milk. Consumption of the dried juice from the pericyclic region of aloe leaves is contraindicated during lactation.

INTERACTIONS

Aloe/Drug Interactions

- *Digoxin, digitoxin*: Low levels of serum potassium (because of aloe latex laxative overuse) theoretically could interfere with cardiac glycosides or other antiarrhythmic agents.
- *Insulin:* On the basis of the laxative properties of oral aloe latex, prolonged use may cause potassium depletion and act additively with insulin to reduce serum potassium levels. Concomitant use of insulin with oral forms of aloe may increase hypoglycemic effects, based on preliminary human data.[34,35] One animal study suggests that stimulation of β cells is responsible for this effect of aloe, and thus the interaction might not apply to type 1 diabetics, in whom β cells have been destroyed.
- *Laxatives:* Theoretically, concomitant use of oral aloe latex and other laxatives may exacerbate hypokalemia, dehydration, metabolic alkalosis, or other electrolyte abnormalities.
- *Nonpotassium sparing diuretics (loop diuretics and thiazide diuretics):* On the basis of the laxative properties of oral aloe latex, prolonged use may cause potassium depletion. Hypokalemia may be exacerbated by simultaneous applications of thiazide diuretics.
- *Oral corticosteroids, oral hydrocortisone:* On the basis of the laxative properties of oral aloe latex, prolonged use may cause potassium depletion. Hypokalemia may be exacerbated by simultaneous application of steroids.
- *Oral hypoglycemic agents:* Concomitant use of glucose-lowering agents with oral forms of aloe may increase hypoglycemic effects. Hypoglycemic properties of aloe have been reported in two methodologically weak human trials, with purported equivalence to an oral hypoglycemic sulfonylurea agent (glibenclamide).[34,35] Laboratory studies have documented β-cell stimulation and subsequent drops in blood glucose in mice.[62,69] In contrast, a small randomized trial, published as a conference abstract, found no evidence of hypoglycemia in 16 type 2 diabetics given aloe juice (15 ml twice daily).[42]
- *Sevoflurane:* There is a poorly described single case report of excess bleeding in a surgical patient receiving the anesthetic agent sevoflurane and oral aloe.[66]
- *Thyroid hormones:* Aloe has been linked to thyroid dysfunction, based on one case report.[63]

- *Topical hydrocortisone:* Concomitant topical use of aloe may enhance absorption of hydrocortisone, although there is limited evidence in this area.[70]
- *Zidovudine (AZT):* Preliminary reports suggest that AZT levels may be boosted by aloe ingestion, although data remain scant in this area.[71]

Aloe/Herb/Supplement Interactions

- *Hypoglycemic agents:* Concomitant use of glucose-lowering agents with oral forms of aloe may increase hypoglycemic effects, based on preliminary human data.[34,35]
- *Laxative herbs:* Theoretically, concomitant use of oral aloe latex and other laxatives may exacerbate hypokalemia, dehydration, metabolic alkalosis, or other electrolyte abnormalities.
- *Licorice root (Glycyrrhiza glabra L):* On the basis of the laxative properties of oral aloe latex, prolonged use may result in potassium depletion. Hypokalemia may be exacerbated by simultaneous applications of licorice root.
- *Thyroid agents:* Aloe has been linked to thyroid dysfunction, based on one case report.[63]
- *Vitamins (C and E*): Aloe may slow the absorption of vitamins C and E.[72]

Aloe/Food Interactions

- *Absorption:* The high mucilage content in aloe taken orally may interfere with absorption of foods and orally administered drugs. Malabsorption may occur after prolonged oral use of aloe.

Aloe/Lab Interactions

- *Serum potassium levels:* On the basis of the laxative properties of oral aloe latex, prolonged use may cause potassium depletion, metabolic alkalosis, and dehydration.
- *Serum glucose levels:* Preliminary evidence from two poorly conducted human trials and animal data suggests that oral forms of aloe may lower blood sugar.[34,35,62]
- *Thyroid panel:* Aloe has been linked to thyroid dysfunction, based on one case report.[63]

MECHANISM OF ACTION

Pharmacology

- *Aloe gel:* The gel or mucilage obtained from the flesh of the leaf is 99% water at pH 4.5. The constituent polysaccharide glucomannan is an effective human skin moisturizer, which accounts for its use in many cosmetics. Acemannan, the major carbohydrate fraction in the gel, is a water-soluble long-chain mannose polymer, which has been found *in vitro* and in animal studies to modulate immune function (particularly macrophage activation and cytokine production) and to accelerate wound healing. The macrophage stimulating principle of acemannan appears to reside in the high molecular weight polysaccharide Aloeride.[73] Acemannan has also been reported to exhibit antineoplastic and antiviral effects *in vitro*.
- Other constituents include bradykininase, which possesses anti-inflammatory properties and magnesium lactate, which has antipruritic effects.[8] A mannose-rich polysaccharide fraction of aloe gel has been shown in mice, to enhance antibody production.[74] Salicylic acid and other antiprostaglandin compounds may be responsible for aloe's local anti-inflammatory activity, possibly because of an inhibitory effect on the arachidonic acid pathway via cyclooxygenase.[75]
- Maloyl glucan compounds isolated from *Aloe babadensis Miller* include 6-O-(1-L-maloyl)-α-; β-D-Glcp (veracylglucan A); α-D-Glcp-(1–>4)-6-O-(1-L-maloyl)-α; β,-D-Glcp (veracylglucan B); and α-D-Glcp-(1–>4)-tetra-[6-O-(1-L-maloyl)-α-D-Glcp-(1–>4)]-6-O-(1-L-maloyl)-α; β-D-Glcp (veracylglucan C).[76] On the basis of *in vitro* study, veracylglucan B demonstrated potent anti-inflammatory and antiproliferative effects, while veracylglucan C exhibited significant cell proliferative and anti-inflammatory activities. Veracylglucan B and C appeared antagonistic and competitive in their effects on cell proliferation.
- Antioxidant properties have been attributed to aloesin derived from *A. vera* .[1,2,3] On the basis of cell-line research, APS-1, a polysachararide from *A. vera* var, chinesis, also showed free radical scavenging and other antioxidant properties.[77]
- Topical aloe's anti-inflammatory properties do not appear to interfere with wound healing, but rather increase wound tensile strength,[78] possibly because of the fibroblast stimulating activity of mannose-6-phosphate.[79]

- Antileukemic and antimutagenic effects of aloe *in vitro* have been attributed to di (2-ethylhexyl) phtalate.[80] Promotion of apoptosis has been reported *in vitro* as a possible antineoplastic mechanism.[81] Aloe appears to affect detoxification of reactive metabolites by liver and other organs.[2]
- Wang et al. suggested that aloe polysaccharides might have a radioprotective effect on nonmalignant cells via its ability to modulate the cell cycle.[82,83]
- Calcium isocitrate, isolated from *Aloe sponaria*, has been shown to be inotropic in rat and rabbit hearts.[8]
- Constituents of kitachi aloe leaf pulp and skin have been found to stimulate β-cells in diabetic mice, thereby lowering blood glucose levels.[62]
- *Aloe latex:* Aloe latex contains anthraquinone glycosides (aloin, aloe-emodin, and barbaloin) that act as potent stimulant laxatives.[50,84–89] These water soluble glycosides are split by intestinal bacteria into aglycones, which are believed to exert a more powerful laxative effect than other herbs, including senna, cascara, or rhubarb root. One of these compounds, aloe-emodin-9-anthrone, has been shown to increase the water content in rat large intestines.[90] This appears to be a more important cathartic mechanism than increased intestinal motility (which has also been proposed).[85,86]
- The anthraquinone glycosides have been studied for their cytotoxic effects.[91] For instance, aloe-emodin induced apoptosis in T24 human bladder cancer cells, which is thought to be mediated through the activation of p53, p21, Fas/APO-1, Bax, and caspase-3.[92] In human malignant melanoma cells, aloe-emodin inhibited NAT1 activity in intact cells in a dose-dependent manner.[93] In human lung carcinoma cells, aloe-emodin is thought to induce DNA damage through generation of reactive oxygen species.[94]
- On the basis of *in vivo* angiogenesis assays, Cárdenas et al. report that aloe-emodin may behave both as an antitumor and an antiangiogenic compound.[95] Aloe-emodin is thought to inhibit endothelial cell proliferation, but this effect is not cell specific, because aloe-emodin also inhibits tumor cell proliferation. Cell migration and invasion are not remarkably affected by aloe-emodin. On the other hand, aloe-emodin has different effects on endothelial and tumor cell gelatinases. Two main targets of the pharmacological action of aloe-emodin as an antiangiogenic compound seem to be urokinase secretion and tubule formation of endothelial cells.

Pharmacodynamics/Kinetics

- Anthraquinone glycosides, which are absorbed well only after digestion by intestinal bacteria, are eliminated in the urine, bile, feces, and breast milk.
- The half-life of aloe-emodin is approximately 48–50 hours.[96]

HISTORY

- Aloe is depicted as the "plant of Immortality" in 6000-year-old Egyptian stone carvings, and was a traditional funerary gift to the pharaohs. The ancient Egyptian Book of Remedies notes the use of aloe to cure infections, treat the skin, and prepare laxatives. The New Testament (John 19:39–40) refers to a mixture of myrrh and aloes for the preparation of Jesus' body. Alexander the Great is said to have conquered Socotra to secure control of aloe. The Greek physician Dioscorides recorded its use in 74 AD for wounds, hair loss, genital ulcers, and hemorrhoids. Arab traders found willing buyers for aloe transported to Asia in the sixth century AD, and the Spanish brought aloe to the Americas in the 16th Century. In the 1930s, topical aloe gel was hailed as a treatment of roentgen (radiation) dermatitis and has since been widely used in cosmetic and dermatologic preparations.
- Penalties have been enforced for illegal marketing of *A. vera* products in the United States.[38] See Table 3.

EVIDENCE DISCUSSION

See Table 4 for explanation of columns in natural standard evidence table.

Condition

Refers to the medical condition or disease targeted by a therapy.

TABLE 3.

Condition	Study Design	Author, Year	*N*	Statistically Significant?	Quality of Study 0–2 = poor; 3–4 = good; and 5 = excellent	Magnitude of Benefit	ARR*	NNT	Comments
Constipation	Randomized, placebo controlled, double blind	Odes, 1991	35	Yes	3	Large	NA*	NA	Efficacy for treatment of constipation in herbal combination.
Genital herpes	Randomized-controlled trial, double blind	Syed, 1997	60	Yes	3	Large	60%	2	Impressive efficacy of aloe lotion in first episode of herpes, methodologically suspicious.
Genital herpes	Randomized-controlled trial, double blind	Syed, 1996	120	Yes	2	Large	62.5%	2	Brief report in Letter to the Editor format. Found aloe hydrophilic cream superior to placebo or aloe gel.
Psoriasis vulgaris	Randomized-controlled trial, double blind	Paulsen, 2005	41	No	4	None	NA	NA	*Aloe vera* has no effect when compared with placebo
Psoriasis vulgaris	Randomized-controlled trial, double blind	Syed, 1996	60	Yes	3	Large	77%	2	Impressive efficacy of aloe lotion, methodologically suspicious.

Seborrheic dermatitis	Randomized-controlled trial, double blind	Vardyn, 1999	46	Yes	3	Large	43%	3	Impressive efficacy of aloe lotion; only known study for this indication.
Aphthous stomatitis	Randomized-controlled trial, double blind, modified crossover	Garnick, 1998	40	Yes	2	Medium	NA	NA	Combination of aloe, allantoin, and silicon dioxide vs. silicon dioxide alone.
Aphthous stomatitis	Equivalence trial, double blind	Plemons, 1994	83	Yes	2	Large	NA	NA	Acemannan (topical) accelerated oral ulcer healing vs. Orabase-Plain.
Type 2 diabetes	Placebo controlled, single-blind	Yongchaiyudha, 1996	72	Yes	1	Large	NA	NA	Poor quality design and reporting.
Type 2 diabetes	Placebo controlled, single-blind	Bunya praphatsara, 1996	72	Yes	1	Large	NA	NA	Poor quality design and reporting.
Type 2 diabetes	Randomized-controlled trial, double blind, crossover	Chalaprawat, 1997	16	No	2	None	NA	NA	Conference abstract. No effect of aloe juice on mean plasma glucose levels.

(Continued on Next Page)

TABLE 3. *(Continued)*

Condition	Study Design	Author, Year	*N*	Statistically Significant?	Quality of Study 0–2 = poor; 3–4 = good; and 5 = excellent	Magnitude of Benefit	ARR*	NNT	Comments
Advanced HIV Infection	Randomized-controlled trial, double blind	Montaner, 1996	63	No	5	None	NA	NA	Acemannan ineffective against HIV.
Skin burns	Randomized-controlled trial, double blind	Puvabanditsin, 2005	20	No	2	None	NA	NA	70% *A. vera* cream had no suntan or sunburn protection and no efficacy in sunburn treatment.
Skin burns	Non-blinded, not controlled	Visuthikosol, 1995	27	Yes	2	Large	NA	NA	Study used "within subject" controls.
Skin burns	Equivalence trial	Heck, 1981	18	NA	1	Medium	NA	NA	Faster healing with aloe vs. silvadene.
Ulcerative colitis	Placebo- controlled trial	Langmead, 2004	44	Yes	3	Medium	23%	4	Clinical improvement in 30% of patients treated with oral aloe, but no changes on sigmoidoscopy. Small study.
Infected surgical wounds	Randomized-controlled trial, nonblinded	Schmidt, 1991	21	Yes	4	Negative	NA	NA	Significant delay in wound healing by second intention after gynecological laparotomy.
Mucositis (radiation induced)	Double-blind, placebo-controlled phase II study	Su, 2004	58	No	3	None	NA	NA	No improvements in mucositis symptoms with oral aloe gel during radiation therapy for head and neck cancers.

ressure ulcers	Randomized-controlled trial	Thomas, 1998	30	No	2	None	NA	NA	No effect of acemannan on pressure ulcers.
Radiation induced dermatitis	Systematic review	Richardson, 2005	7 trials	No	NA	None	NA	NA	No effect.
Radiation induced dermatitis	Comparison trial	Bosely, 2003	45	Yes	2	None	NA	NA	Aloe gel less effective than 1% anionic phospolipid-based cream in prevention and treatment of radiation dermatitis in children.
Radiation induced dermatitis	Randomized-controlled trial, double blind	Williams, 1996	194	No	4	None	NA	NA	No prevention of radiation dermatitis by aloe gel.
Radiation induced dermatitis	Randomized-controlled trial, double blind	Heggie, 2002	225	Yes	3	None	NA	NA	Aloe gel less effective than aqueous cream for prevention of pain or desquamation from radiation therapy for breast cancer.
Radiation induced dermatitis	Randomized-controlled trial, partially blinded	Olsen, 2001	70	Yes	1	Medium	NA	NA	Delay in development of radiation-associated skin changes.
Multiple indications	Systematic review	Vogler, 1999	10 studies	NA	NA	NA	NA	NA	10 studies of various indications analyzed.

*ARR, absolute risk reduction; NA, not applicable.

TABLE 4. Explanation of Columns in Natural Standard Evidence Table

1	2	3	4	5	6	7	8	9	10
Condition	Study Design	Author, Year	*N*	Statistically Significant?	Quality of study 0–2 = poor; 3–4 = good; and 5 = excellent	Magnitude of Benefit	Absolute Risk Reduction	Number Needed to Treat	Comments
	Study Design	Author, Year	*N*	Statistically Significant?	Quality of study 0–2 = poor; 3–4 = good; and 5 = excellent	Magnitude of Benefit	Absolute Risk Reduction	Number Needed to Treat	Comments

Study Design

Common Types Include

- *Randomized-controlled trial (RCT)*: An experimental trial in which participants are assigned randomly to receive either an intervention being tested or placebo. Note that Natural Standard defines *RCTs* as being placebo controlled, whereas studies using active controls are classified as equivalence trials (see below). In RCTs, participants and researchers are often blinded (i.e., unaware of group assignments), although unblinded and quasi-blinded RCTs are also often performed. True random allocation to trial arms, proper blinding, and sufficient sample size are the basis for an adequate RCT.
- *Equivalence trial:* An RCT that compares two active agents. Equivalence trials often compare new treatments to usual (standard) care, and may not include a placebo arm.
- *Before and after comparison:* A study that reports only the change in outcome in each group of study, and does not report between-group comparisons. This is a common error in studies that claim to be RCTs.
- *Case series:* A description of a group of patients with a condition, treatment, or outcome (e.g., 20 patients with migraine headache underwent acupuncture and 17 reported feeling better afterwards). Case series are considered weak evidence of efficacy.
- *Case-control study:* A study in which patients with a certain outcome are selected and compared with similar patients (without the outcome) to see if certain risk factors/predictors are more common in patients with that outcome. This study design is not common in the complementary and alternative medicine literature.
- *Cohort study:* A study that assembles a group of patients with certain baseline characteristics (for example, use of a drug), and follows them forward in time for outcomes. This study design is not common in the complementary and alternative medicine literature.
- *Meta-analysis:* A pooling of multiple trials to increase statistical power (often used to pool data from a number of RCTs with small sample sizes, none which demonstrates significance alone but in aggregate can achieve significance). Multiple difficulties are encountered when designing/reviewing these analyses; in particular, outcomes measures or therapies may differ from study to study, hindering direct comparison.
- *Review:* An author's description of his or her opinion on the basis of personal, nonsystematic review of the evidence.

- *Systematic review:* A review conducted according to prespecified criteria in an attempt to limit bias from the investigators. Systematic reviews often include a meta-analysis of data from the included studies.
- *P* : Pending verification.

Author, Year

Identifies the study being described in a row of the table.

"N"

The total number of subjects included in a study (treatment group plus placebo group). Some studies recruit a larger number of subjects initially, but do not use them all because they do not meet the study's entry criteria. In this case, it is the second, smaller number that qualifies as *N*. *N* includes all subjects that are part of a study at the start date, even if they drop out, are lost to follow-up, or are deemed unsuitable for analysis by the authors. Trials with a large number of dropouts that are not included in the analysis are considered to be weaker evidence for efficacy. (For systematic reviews the number of studies included is reported. For meta-analyses, the number of total subjects included in the analysis or the number of studies may be reported.) P = pending verification.

Statistically Significant?

Results are noted as being statistically significant if a study's authors report statistical significance, or if quantitative evidence of significance is present (such as *P* values). P = pending verification.

Quality of Study

A numerical score between 0 and 5 is assigned as a rough measure of study design/reporting quality (0 being weakest and 5 being strongest). This number is based on a well-established and validated scale developed by Jadad et al. (Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17(1):1–12). This calculation does not account for all study elements that may be used to assess quality (other aspects of

TABLE 5. Jadad score calculation.

Item	Score
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer generated, etc)?	0/1
Was the study described as double blind?	0/1
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0/−1
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/−1

study design/reporting are addressed in the "evidence discussion" sections of reviews).

- A Jadad score is calculated using the seven items in the table below. The first five items are indications of good quality, and each counts as one point towards an overall quality score. The final two items indicate poor quality, and a point is subtracted for each if its criteria are met. The range of possible scores is 0 to 5 (see Table 5).

Magnitude of Benefit

This summarizes how strong a benefit is: Small, medium, large, or none. If results are not statistically significant "NA" for "not applicable" is entered. To be consistent in defining *small*, *medium*, and *large* benefits across different studies and reviews, Natural Standard defines the *magnitude of*

benefit in terms of the standard deviation (SD) of the outcome measure. Specifically, the benefit is considered

- *Large:* if >1 SD
- *Medium:* if 0.5 to 0.9 SD
- *Small:* if 0.2 to 0.4 SD

P = pending verification.

In many cases, studies do not report the SD of change of the outcome measure. However, the change in the SD of the outcome measure (also known as effect size) can be calculated, and is derived by subtracting the mean (or mean difference) in the placebo/control group from the mean (or mean difference) in the treatment group, and dividing that quantity by the pooled SD (effect size = [mean treatment — mean placebo]/SD *P*).

Absolute Risk Reduction

This describes the difference between the percent of people in the control/placebo group experiencing a specific outcome (control event rate), and the percent of people in the experimental/therapy group experiencing that same outcome (experimental event rate). Mathematically, absolute risk reduction (ARR) equals experimental event rate minus control event rate. Absolute risk reduction is better able to discriminate between large and small treatment effects than relative risk reduction, a calculation that is often cited in studies ([control event rate — experimental event rate]/control event rate). Many studies do not include adequate data to calculate the ARR, in which cases "NA" is entered into this column. P = pending verification.

Number Needed to Treat

This is the number of patients who would need to use the therapy under investigation, for the period of time described in the study, in order for one person to experience the specified benefit. It is calculated by dividing the ARR into 1 (1/ARR). P = pending verification.

Comments

When appropriate, this brief section may comment on design flaws (inadequately described subjects, lack of blinding, brief follow up, not intention-to treat, etc.), notable study design elements (crossover, etc.),

dosing, and/or specifics of study group/subgroups (age, gender, etc). More detailed description of studies is found in the evidence discussion section that follows the "Evidence Table" in Natural Standard reviews.

Constipation

- *Summary:* Few clinical studies have been conducted to evaluate the laxative effect of aloe latex in humans. However, the laxative effect of anthraquinone glycosides found in aloe, such as aloin, aloe-emodin, and barbaloin, is well established scientifically.[50,84,85,86,87,88,89] The question of whether aloe latex may offer a reasonable approach to treating constipation remains to be answered. Further study is warranted to establish dosing, and to compare efficacy and safety with commonly used laxative agents.
- *Evidence:* Chapman and Pitelli compared the laxative effect of aloin (1 grain [=0.0648 g] once) with phenolphtalein (2 grain once), phenolphtalein + aloin (1 grain and 0.5 grain, respectively), and placebo in 28 healthy adults.[97] Study subjects were randomly allocated to different treatment sequences; stool frequency and transit time were compared for all treatments. Aloin had a laxative effect (compared with placebo), which was reported as stronger than phenolphtalein and slightly weaker than the combination. However, no statistical analysis was presented in the article.
- A randomized double-blind placebo-controlled study found that aloe (in combination with celandine and psyllium) was an effective laxative in patients suffering from chronic constipation.[41] Thirty-five such patients were randomly allocated to either celandine + aloe + psyllium (starting with one 500mg capsule per day containing these ingredients in ratios 6:3:1 and increasing up to three capsules per day as required) or placebo. Three subjects in the placebo group dropped out because of lack of effect, whereas all subjects in the celandine + aloe + psyllium group remained in the study. All indicators of constipation improved in the experimental group versus placebo with statistical significance. The mean number of stools increased to 7.9 in the aloe group versus 4.3 in the placebo group. Stool consistency scores (1 = soft/liquid, 2 = normal, 3 = hard) improved to 1.6 and 2.4, respectively. The number of capsules taken was a third lower in the experimental group versus placebo (10.1 and 15.8, respectively). Pain scores remained unchanged in both groups. Although this study demonstrated the efficacy of an herbal combination containing aloe

as a laxative, the effect of aloe cannot be separated from the other ingredients.

Genital Herpes

- *Summary:* Limited evidence suggests that 0.5% extract from *A.vera* in a hydrophilic cream is an effective treatment of genital herpes in men (superior to both aloe gel and placebo). The best available study (Syed, 1997), although seemingly well designed and reported, reports a high degree of efficacy that is suspicious from a methodological standpoint. Additional research is warranted in this area.
- *Evidence:* Syed et al. randomized 60 men with a first episode of genital herpes to receive topical aloe or placebo.[39] Aloe treatments consisted of three daily applications of a 0.5% cream for five days versus applications of a cream without active ingredients. Two-thirds were cured of lesions in the aloe group after one week compared with only 2/30 in the placebo group ($P < .001$). It is unlikely that this strong effect was accounted for by flawed randomization or blinding procedures (neither was disclosed in the paper). From methodological and clinical perspectives, such highly effective results in an isolated study are suspicious. However, without further evaluation in a follow-up randomized trial, a firm conclusion cannot be made.
- In a prior published Letter to the Editor, Syed et al. described a randomized, double-blind controlled trial in 120 men in Pakistan, in which 0.5% topical aloe extract gel or cream, or placebo, was applied to male patients with first episode of genital herpes.[98] Treatment was administered three times/day, for five consecutive days/week, for two weeks. Aloe in hydrophyllic cream was noted to significantly shorten the duration of lesions versus gel or placebo (4.8 days, 7.0 days, and 14.0 days respectively). With cream, 70% of patients were cured, versus 7.5% in placebo. Although promising, the abbreviated format of this publication neither describe blinding, randomization, and method of statistical analysis, nor measurement criteria for classifying lesions. Therefore, the evidence remains inconclusive.

Psoriasis Vulgaris

- *Summary:* Evidence from one randomized trial suggests that 0.5% extract from *A.vera* in a hydrophilic cream is an effective treatment

of psoriasis vulgaris. Although well designed and reported, the high degree of efficacy in this study is suspicious from a methodological standpoint. Additional research is warranted in this area.

- *Evidence:* Paulsen et al. conducted a randomized, double-blind, placebo-controlled, and right/left comparison study to assess the effects of a commercial, preserved, but otherwise untreated *A. vera* gel in the treatment of psoriasis.[61] Forty-one patients (at least 18 years of age) with stable plaque psoriasis were included. Patients were excluded if they were pregnant, expectedly noncompliant, had received systemic antipsoriatic treatment recently, had known allergy to any ingredients of the gels, or had severe concomitant disease, demanding the use of immunosuppressive or immunomodifying drugs. Certain medication use also qualified as exclusion criteria. Subjects were administered a commercial Aloe Vera Gel® (Aloe Vera Group ApS, Søborg, Denmark), which consisted of 98% *A. vera* leaf gel, with less than 100 p.p.m. of anthraquinones, and the additives xanthan gum, potassium sorbate, sodium benzoate, sodium sulphite, and citric acid. The placebo gel contained the same ingredients except that the liquid *A. vera* gel was replaced by water. There was a two-week washout period followed by a four-week treatment period with two daily applications and follow-up visits after one and two months. Statistical analysis included all randomized patients with at least two post start-of-treatment measurements ($N = 40$). The difference between the changes on the two sides was assessed with Wilcoxon's matched-pairs signed-ranks test and the level of significance chosen at 5%. There was one drop out in this study, but the authors did not state a reason for dropping out. No serious adverse effects were recorded, although 55% of subjects reported local adverse effects mainly drying up of the skin on test areas. The score sum of erythema, infiltration, and desquamation decreased in 72.5% of the *A. vera*-treated sites compared with 82.5% of the placebo-treated areas from week 0 to week 4, which was statistically significant in favor of the placebo treatment ($P = 0.0197$). Overall, this was a well-designed study, but the description of randomization was unclear. The lack of observed effect may be attributable to the small sample size of the study; furthermore, it is unclear whether the large placebo response can be explained by the short duration of the study; longer studies would help clarify this limitation.
- Syed et al. randomized 60 patients with long-standing psoriasis to receive aloe treatment or placebo.[40] Aloe treatments consisted of three daily topical applications of a 0.5% cream for four weeks versus

applications of a cream without active ingredients. Patients were followed over eight months and compared in terms of proportion cured and proportion of plaques cured. More than 80% of plaques and patients were cured in the treatment group versus < 10% in the placebo group (for both comparisons, $P < .001$). It is unlikely that such a strong effect is attributable to flawed randomization or blinding. The high degrees of efficacy and compliance reported in this study, and lack of reporting of blinding or randomization, raise questions about the accuracy of these results. However, no firm conclusion can be made without further study.

Seborrheic Dermatitis

- *Summary:* Preliminary evidence from one randomized trial supports aloe's efficacy in the treatment of seborrheic dermatitis. Corroboration by studies from independent groups is warranted before a strong recommendation can be made.
- *Evidence:* Vardyn et al. examined the efficacy of aloe emulsion for the treatment of seborrheic dermatitis.[99] Forty-six patients were randomly allocated to treatment with 30% *A. vera* emulsion topically twice per day or to placebo for 4–6 weeks. At the end of the treatment period, global improvement was seen in the aloe group (58% and 62% according to dermatologist and patient ratings scales, respectively) versus placebo (15% and 25%, respectively). This study was well designed and reported, and the dramatic results are unlikely because of bias. However, because this is an isolated study, further evaluation is warranted to provide additional support.

Aphthous Stomatitis

- *Summary:* There is equivocal evidence from two studies that treatment of recurrent aphthous ulcers with aloe gel reduces pain and prolongs ulcer-free intervals. Further study is warranted.
- *Evidence:* Garnick et al. examined the effectiveness of a gel containing aloe, in addition to silicon dioxide and allantoin, on the healing of recurrent aphthous ulcers (100). First, a gel containing aloe, allantoin, and silicon dioxide was compared with a gel containing only silicon dioxide in 40 patients. The mean duration of lesion-free intervals was five days in the experimental group versus 18 days in the silicon dioxide group. However, this trend was not statistically significant.

When comparing the experimental treatment with a control gel ($N = 18$), mean intervals were 9 versus 2 days ($P = .0335$). Because of the multiple agents involved in this study, it is not possible to draw conclusions about the efficacy of aloe itself.

- Plemons et al. randomized 53 patients suffering from recurrent oral ulcers to topical treatment with either the aloe constituent acemannan (Carrisyn Gel Wound Dressing®, modified for oral lesion use) or Orabase-Plain® (oral analgesic) four times daily. A third group was treated with freeze-dried acemannan (Carrisyn Gel Wound Dressing® cut into small pieces). The average healing time was shorter in the acemannan groups (5.7 days) than in the control group (7.8 days; $P = .0031$), whereas other parameters (erythema and discomfort) were only marginally affected. These results suggest that topical acemannan accelerates the healing of ulcers in aphthous stomatitis, but interpretation of the results must take methodological weaknesses into account (randomization inadequately reported, blinding methods inappropriate).

Cancer Prevention

- *Summary:* There is preliminary evidence from a small case-control study that aloe consumption may reduce the risk of developing lung cancer. Further evidence is warranted in this area to clarify whether it is aloe itself or other factors that mediate this benefit.
- *Evidence:* In a multi-center Japanese case-control study of 192 subjects (1 case per 2 controls), a questionnaire was administered to determine the potential correlations between lung cancer incidence, smoking, and consumption of 17 different types of plants.[101] Odds ratios were calculated via an established method (Mantel-Haenszel analysis). A subgroup of 132 subjects (44 "pairs") was analyzed specifically for plant food intake, and it was determined that the odds ratio for the aloe species *Aloe arborescens Miller* was 0.5 ($P < .1$), suggesting half the incidence of cancer in regular consumers of aloe versus nonaloe consumers. Although compelling, the methodological difficulties of case-control studies apply to this report. The possible effect of confounders not detected by the study questionnaire is prominent. For example, aloe/plant eaters may be more likely to exercise than nonplant eaters, which may exert an independent effect on outcome. In addition, it is not clear whether this effect is generalizable to other species of aloe.

Diabetes (Type 2)

- *Summary:* Laboratory studies have documented β-cell stimulation by aloe, as well as drops in blood glucose in mice.[62] Results from two poorly conducted human trials suggest that oral aloe gel may be effective in lowering blood glucose levels, although a third, smaller study found no effect. More definitive studies are needed to explore efficacy and safety of aloe in diabetics.
- *Evidence:* Two nonrandomized studies conducted by the same group concluded that aloe gel might be as effective as glibenclamide (a sulfonylurea antihyperglycemic oral agent) to lower blood glucose in type 2 diabetes mellitus.[34,35] However, methodology, statistics, and results were incompletely described. Thus, firm conclusions cannot be drawn.
- In a randomized double-blind placebo-controlled crossover study published only as a conference abstract, Chalprawat found no hypoglycemic effect of aloe juice (15mL twice daily) in 16 type 2 diabetics.[42] Although the statistical power of this study was low, a large hypoglycemic effect is unlikely given the results.
- Oral dried aloe gel was studied in five patients with type 2 diabetes.[102] Half a teaspoon of aloe was administered daily over 4–14 weeks, after which time fasting glucose was noted to have fallen from a mean of 273 to 151 ($P < .05$). In a simultaneous mouse study, both glibenclamide (10 mg/kg twice daily) and aloe (500 mg/kg twice daily) were found to induce hypoglycemia after five days (blood sugar reduced by 40%). However, only glibenclamide was effective after three days. Although compelling, this study is too preliminary and methodologically weak (small, no controls, and poor description of methods) to be of direct relevance to clinical practice.

HIV Infection

- *Summary:* Acemannan, the major carbohydrate fraction in aloe gel, has been shown *in vitro* to possess immunostimulant and antiretroviral activities. Preliminary data from human trials are equivocal; because of methodological weaknesses of available studies, firm conclusions are not possible. Without further human trials, the evidence cannot be considered compelling either in favor or against this use of aloe.

- *Evidence:* Montaner et al. conducted a randomized double-blind study to evaluate the efficacy of acemannan as an adjuvant antiretroviral agent for HIV.[43] In this trial, 63 patients were randomized to receive either 400 mg oral acemannan four times daily or placebo. No difference in CD4 counts, CD4/CD8 ratios, P24 antigen, β_2-microglobulin concentration, or viral load was found between the two treatment groups. Although these results are discouraging, because no power calculation was performed, it is not clear that the sample size was adequate to properly measure differences between groups. Descriptions of blinding and randomization are limited.
- Two non-randomized studies evaluating the efficacy of oral acemannan in the treatment of HIV infection have been published as conference abstracts.[44,45] Both studies found clinical improvement and large increases in circulating monocytes/macrophages. The observational character of these reports provides compelling, albeit preliminary, support.
- In a case report, McDaniel and McAnalley found improvement in several serologic and clinical indicators of HIV infection in eight patients treated with acemannan (Carrisyn®) for 90 days (unclear if subjects received four doses of 250 mg or 250 mg in four divided doses).[44] Benefits included decline in HIV core antigen, elimination of diarrhea, fever, diaphoresis, and "loss of culturability."
- In a nonrandomized controlled study, McDaniel et al. found circulating monocytes/macrophages to be significantly more numerous in 14 HIV patients treated with 800 mg acemannan per day (365 per smear) than in 35 patients not receiving acemannan (68 per smear, $P = .00027$).[45] These surrogate serologic endpoints require clinical correlation.

Skin Burns

- *Summary:* Preliminary evidence suggests that aloe may be effective in promoting healing of partial thickness skin burns. However, the existing studies are small and poor in quality, and therefore no clear conclusion can be drawn. Further study is warranted in this area.
- *Evidence:* Puvabanditsin et al. conducted a double-blind, randomized, placebo-controlled study to assess the efficacy of *A. vera* cream in prevention of burn and tan from ultraviolet light.[103] Patients were excluded from this study if they were pregnant or taking photosensitizing medications. Twenty volunteers were included in this study,

who were at least 18 years of age with no history of sun sensitivity or skin cancers in the family. Patients were randomized to received 70% *A. vera* cream on the test sites 30 minutes before, immediately after, or both before and after then the serial ultraviolet UVB 40,50,60,70,80 mj were radiated. The minimal erythema dose reading was taken at 24 hours for sunburn evaluation, and both erythema and pigmentation were evaluated using a visual grading 1–4 score. The *A. vera* cream application was continued at the test sites twice daily for the next three weeks. Twenty volunteers completed with study, although the results suggested that that the *A. vera* cream has no sunburn or suntan protection and no efficacy in sunburn treatment when compared with placebo ($P > .05$). The *A. vera* cream had no bleaching effect either. It is unclear whether the study size was large enough to produce statistically significant results. Limitations of this study include an incomplete description of randomization and blinding.

- Visukitosol et al. examined the effect of a topical aloe gel preparation on skin burns in comparison to Vaseline® gauze.[104] They found in 27 patients with partial thickness skin burns that the mean healing time was 12 days with aloe gel treatment versus 18 days with Vaseline® gauze. Although the findings from this trial are suggestive, the lack of true controls (only the distal part of each wound was treated with aloe) or blinding prohibits firm conclusions.
- Heck et al. topically treated 18 patients with second-degree burns (2%–12% of total body surface area) with either aloe extract or with Silvadene®[105]. The average wound healing time was 13 days with aloe versus 16 days with Silvadene®. No statistical analysis was presented and results were not stratified by burn severity. Therefore, a definitive conclusion cannot be made.
- In a poorly described study, silver sufladiazine cream was found to be more effective than aloe in the treatment of experimental second degree burns, with a suggestion that aloe may in fact disrupt the healing process.[106] These conflicting results cannot be considered conclusive, but must be considered.

Ulcerative Colitis

- *Summary:* There is promising preliminary evidence from a small randomized placebo-controlled trial in 44 individuals suggesting that oral *A. vera* gel (100 mL twice daily for 4 weeks) is beneficial in the

management of ulcerative colitis.[107,108] Clinical improvement ("remission") was seen in 30% of aloe patients compared with 7% of placebo patients (i.e., one patient), although no sigmoidoscopic improvements were seen in either group. Comparisons to standard therapies have not been conducted, and additional research is warranted in this area before a firm conclusion can be drawn.

Infected Surgical Wounds

- *Summary:* In one study, topical aloe gel was found to prolong wound-healing time following gynecological or obstetrical laparotomy. Further study is warranted, because wound healing is a popular use of topical aloe.
- *Evidence:* Schmidt et al. examined the effect of aloe gel on the healing of complicated surgical wounds (healing by second intention).[36] In this study, 21 women with complicated wounds after gynecological or obstetric surgery were stratified according to incision type and randomized to either standard treatment (debridement and irrigation), or standard treatment plus aloe gel. Wounds in the experimental group healed in 83 days on average versus 53 days with standard treatment ($P = .003$). Because of the clearly prolonged healing in the group treated with aloe, patient recruitment was terminated before the desired sample size ($n = 114$) was reached. This otherwise well-designed trial was not placebo-controlled. However, the effect of size was unlikely because of a placebo effect. Further study of aloe's role in the healing of wounds of varying severity may be warranted before this traditional use can be strongly discouraged, although use in complicated surgical wounds may not be advisable in light of these results.
- *A. vera* rinses have also been used on periodontal surgical sites.[19]

Mucositis

- *Summary:* There is preliminary evidence from a double-blind placebo-controlled phase II trial in 58 patients with head-and-neck cancers suggesting that oral *A. vera* gel does not improve radiation induced mucositis.[109] No improvements were observed in soreness, tolerance of therapy, or overall well-being.

Pressure Ulcers

- *Summary:* One well-designed randomized trial found no benefit of topical acemannan hydrogel (the major carbohydrate fraction in aloe gel) in the treatment of pressure ulcers.
- *Evidence:* Thomas et al. conducted a randomized-controlled trial in which 30 patients with pressure ulcers were randomly allocated to receive either acemannan hydrogel (daily dressings with 0.25-inch layer) or saline dressing.[110] Ulcers were evaluated weekly for 10 weeks or until ulcers healed. Both the proportion of healed ulcers (63% versus 64%) and the mean time to healing (5.3 vs. 5.2 weeks) were similar in the two groups. This study had sufficient (80%) power to detect a 25% difference between treatment arms. These results suggest that acemannan hydrogel may not be effective in the treatment of pressure ulcers.

Radiation Dermatitis

- *Summary:* Reports, during the 1930s, of topical aloe's beneficial effect on postradiation dermatitis triggered widespread use in dermatological and cosmetic products.[26,27,28,29,30] Aloe gel is currently recommended by some practitioners for radiation-induced dermatitis. However, preliminary scientific evaluation suggests that topical aloe may not significantly improve pain or desquamation related to radiotherapy, and may be inferior to topical aqueous gel. Additional well-designed studies are necessary before a firm conclusion can be drawn.
- *Systematic review:* Richardson et al. conducted a systematic review to assess the effectiveness of *A. vera* gel for radiation-induced skin reactions.[111] Major biomedical databases, specialist CAM databases, and unpublished and ongoing research were searched. Seven trials were found. The authors conclude that there is no evidence from clinical trials to suggest that topical *A. vera* is effective in preventing or minimizing radiation-induced skin reactions in cancer patients. Further methodologically rigorous, sufficiently powered research studies should be conducted to evaluate the effectiveness of currently used and novel therapies for the prevention, minimization, and management of radiation-induced skin reactions.
- *Evidence:* Olsen et al. prospectively studied 70 cancer patients receiving radiation doses greater than 2000cGy.[112] Patients were

randomized to either pure *A. vera* gel (applied liberally to the irradiated skin area throughout the day) or no specific topical treatment. All patients were instructed to wash the irradiated skin area with mild soap. Skin changes were evaluated by a clinician, blinded to the treatment, at weekly intervals. The only statistically significant difference found between treatment arms was skin texture, which at a cumulative dose below 2700cGy was rare in the nontreated group than in the aloe group ($P < .012$). No significant differences were seen for erythema, itching, or tanning. However, in a subgroup receiving higher cumulative radiation doses, onset of skin changes was significantly delayed in the aloe group. Although this study found some beneficial effects of aloe on radiation-associated skin changes, lack of patient blinding or placebo weakens the results.

- Williams et al. conducted a randomized trial addressing the efficacy of aloe gel for radiation-induced dermatitis.[113] In this study, 184 women undergoing treatment for breast cancer were stratified according to age, planned target radiation dose, dose fraction, and skin complexion. Subjects were randomized in a double-blind manner to topical aloe (applied twice/day on the treatment field) versus placebo (inert gel). No difference was found between groups or within strata. Although this was a fair-sized trial, no power calculation was performed at the onset, and description of methodology was limited. Nonetheless, these results are discouraging.
- Heggie et al. conducted a randomized-controlled trial (phase III) in 225 women undergoing radiation therapy for breast cancer.[114] Subjects received either topical *A. vera* gel or aqueous cream three times per day throughout radiotherapy and for two weeks following therapy. Assessments were made by nursing staff at weekly visits. The authors report that patients receiving aqueous cream experienced significantly less pain and desquamation compared to aloe patients. These results suggest that aqueous gel may be a superior choice in such patients, although because of lack of use of validated evaluation instruments and incomplete reporting of analysis, these results cannot be considered definitive. Comparison of aloe to a nonactive intervention would provide additional information about the efficacy of aloe.
- Bosley et al. conducted a randomized-controlled trial (phase III) comparing a 1% anionic phospholipid-based cream with an *A. vera*-based gel in the prevention and treatment of radiation dermatitis in 45 pediatric patients treated with radiation therapy.[115] The mean age of subjects was 11 years with Hodgkin's disease being the most common diagnosis, and the thorax being the most common treatment

field. Chemotherapy was either used before or during radiation treatment. Patients were excluded if they had received prior irradiation for their disease, had coincident dermatological conditions, or if there was planned use of other topical products. Treatments were applied topically, symmetrically, and adjacent within the field of irradiation once daily after radiation treatment. Skin comfort was evaluated by a questionnaire and dermatological assessments were made using a 15-item score on a 4-level scale before and weekly during treatment, and up to six weeks after radiation. The authors reported statistically significant results favoring the cream-on-skin assessment variables such as dryness ($P = .002$), comfort ($P = .002$), erythema ($P = .002$), and peeling ($P = .008$). Limitations of the study include a lack of description of randomization, lack of blinding, and the lack of reported mean duration of treatment between the two treatment groups. In addition, the skin comfort assessment was based on subjective data.

PRODUCTS STUDIED

Brands Used in Statistically Significant Clinical Trials

- Carrisyn® (internal preparations have been used in HIV with unproven efficacy); Carrisyn Gel Wound Dressing® (preparation of acemannan, the major carbohydrate fraction of aloe gel, found efficacious for oral aphthous ulcers/stomatitis).

Brands Shown to Contain Claimed Ingredients Through Third-Party Testing

- *Consumer Lab: Recalls and warnings*—Marketers of Seasilver Ordered to Pay Almost $120 Million (Posted: 7/24/2006); Aloe Producer Recalls Product Due to Toxic Levels of Vitamin D (Posted: 4/1/2004); Federal Trade Commission Charges Marketers of Seasilver with False and Deceptive Claims (Posted: 6/20/2003).
- Consumer Reports: NA. last accessed 6/1/07.
- Natural Products Association: NA. last accessed 6/1/07.
- NSF International: NA. last accessed 7/30/07.
- U.S. Pharmacopeia (February 2005): In an expert committee meeting summary, aloe was assigned a class 1 safety rating.

U.S. Equivalents of Most Commonly Recommended European Brands

- Not applicable.

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