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Aloe Vera: The Quest For the "Curative" Missing Link

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Aloe the perennial succulent Liliaceae, aloe the USP drug, and aloe gel the cosmetic ingredient all share common aloe vera plant origins. Aloe barbadensis Miller represents one of the almost 200 species of the genus aloe. It is a particular variety of the lily family that yields rosettes of large fleshy leaves measuring as long as 30 inches and as wide as five inches at their basis. With a mature weight of about three pounds, the leaves are harvested for copious quantities of the highly prized aloe vera gel for cosmetics.

Since Biblical times use of aloe vera as a remedy has repeatedly come up in folklore, along with testimonials related to the "healing" properties of the mucilage when applied to burned or inflamed skin. But it has only been within the last several decades that scientists have begun seriously probing aloe chemistry for "non-folklore" answers to these questions: 1. What chemical ingredients of significance are really present in aloe? 2. What ingredient(s) might be responsible for the reported healing effects?

Today, there is another area of active scientific aloe inquiry: Is it feasible to establish compositional standards for cosmetic grade aloe vera gel and what analytical methodology might be utilized to achieve this end? This article reviews what we currently know (or do not know) about the composition and analysis of aloe, and examines the quest for the "curative" ingredient missing link.

It should become apparent that nomenclature confusion, compositional studies of varying source origin and species/climatic variations all currently tend to cloud a true understanding of aloe plant material composition and "functional" chemistry. It has been said that ... "Aloe vera is nonexistent and the correct name should be Aloe barbadensis."

The **USP** definition of Aloe is ... "the dried latex of the leaves of Aloe barbadensis Miller (Aloe Vera Linne) known to commerce as Curacao Aloe ..." According to the ninth edition of the **Merck Index**, aloe denotes ... "inspissated juice of leaves of Aloe perry; Baker (socotrine aloe), A. vera L. (curacao aloe), Liliacea; that for A. ferox Mill. (cape aloe) is not official." The **British Pharmacopeia** recognizes also zanzibar aloe, whereas the third edition of the **CTFA Cosmetic Ingredient Dictionary** makes no reference to particular species and considers "Aloe" as ... "a plant material derived from the leaves of one or more species of aloe."

According to Gjerstad,[2] official aloe is defined as ... "the dried juice (of the lower portion) of the leaves of any of three geographical varieties of the aloe genus" a reference to aloe the drug, recognized in the **United States Pharmacopeia** since 1820. The drug, (aloe USP) is the dried juice obtained from the pericyclic cells which are found beneath the cutinized epidermis.[3] It has an opaque, glistening blackish-brown appearance and yields, upon purification, anthraglycosides (aloin).

Aloe has long been recognized by various pharmacopeias as a purgative drug;[4] however, the "official standing" has been clouded by the fact that Aloe USP is presently included only as a constituent of compound benzoin tincture and has been deleted as a cathartic.

Aloe gel, (also erroneously called "juice") is defined by the third edition of the **CTFA Ingredient Dictionary** as ... "the mucilage obtained as the juice expressed from the leaves of Curacao aloe, aloe vera." This transparent slippery mucilage is produced by the thin-walled tubular cells found in the inner central zone (parenchyma) of the leaf. Hair-like connective matrices may be observed in the raw gel which are somewhat reminiscent of colorless gelatin in appearance (but not chemistry). It is this raw leaf mucilage consisting of 99.5 percent water, which ultimately becomes cosmetic grade aloe gel (after appropriate purification and stabilization steps.)

Aloe extracts may be obtained by extracting whole leaves or the dried pericyclic juice with appropriate solvents. It has been claimed that aloe extracts derived from aloe USP have significant compositional differences when compared to extracts prepared from aloe gel.[6]

A search of "pre-1940" scientific literature relevant to the chemistry of aloe plant materials reveals that

the emphasis appeared to be directed towards determination of aloe types and quantities of aloe bearing drugs. In this regard, Schorn[7] describes a quinoline-hydrogen peroxide reagent and a distinguishing color test for different varieties of aloe. Herissey[5] proposed a simple color reaction test for identity of tincture of aloes and Valaer[9] describes how aloes made acid and extracted with ether made subsequently alkaline with ammonia develop a red color which may be useful for ascertaining the amount of aloes or emodin-bearing drugs present. Rosenthalkr[10] attempted to differentiate commercial aloes by means of bromine water while Lestage[11] proposed a modification of the Borntrager reaction for detection of anthraquinone type products in aloe-containing preparations. Color reactions with nitric acid[12] and potassium ferricyanide[13] also have been described.

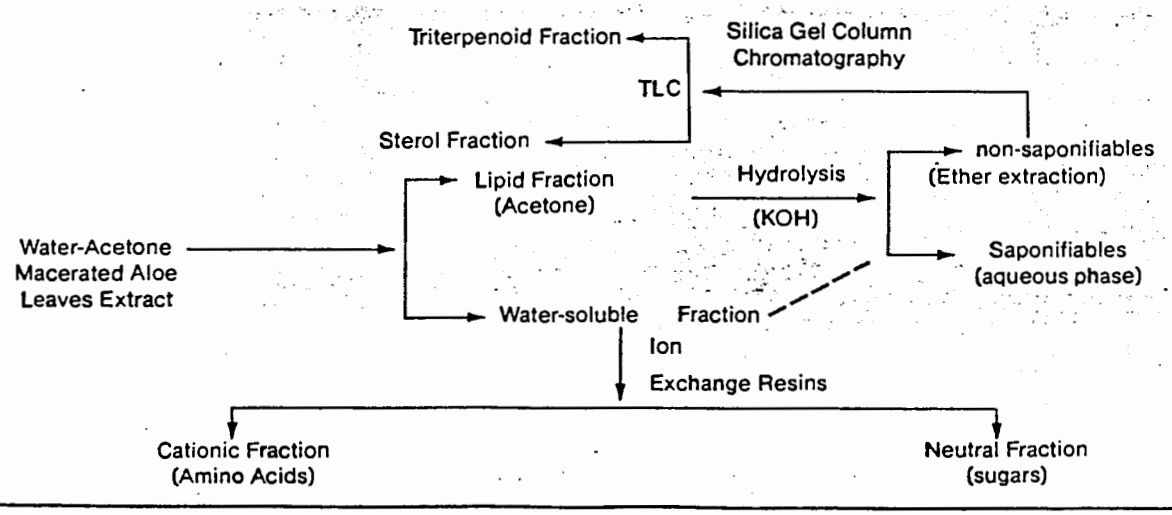
The composition of aloe plant materials has been investigated intermittently over the past 40 years. It appears, however, that relatively few of these published studies have been well controlled or verified by other investigators. There also appears to be some ambiguity in the reporting of certain compositional findings, in that substances found in one part of the leaves (eg. pericyclic juice) may become muddled with components in another part (eg. parenchyma mucilage).

The Relevance of Anthraquinones

Homologs of 1,8 Dihydroxyanthraquinone have been said to be a common ingredient of the natural product aloe. Gjerstad[15] has pointed out that "aloe vera juice does not respond to the Borntrager anthranol test, indicating its distinct difference from aloe USP". Brody et.al.[16] have discussed the results of a chromatographic study of the anthraquinone derivatives of Curacao aloe. In this 1950 investigation, a magnesia-Celite mixture was employed to separate isoemodin, aloe-emodin and anthranols by a chromatographic technique, from chloroform extracts of aloe powder.

Ruggieri[17] utilized a potentiometric titration in a water-free medium to determine the hydroxyanthraquinone content of socotrine aloe. Hydroxyanthraquinone was said to be present partially free and partially as glucosides. Leung[18] has pointed out that the "gel which is mostly responsible for the reputed common uses of aloe vera, normally does not contain an-

Table I Analytical Scheme for Macerated "Whole-Leaf" Analysis
(Waller, et. al. Proc. Okla. Acad. Sci.: 58:69-76, 1978



responds to about 0.013 percent in the commercial aloe gel product.[27]

At least six enzymes have been claimed to be present:[28] cellulose, carboxypeptidase, bradykinase, catalase, anylase and an oxidase. The bradykinase activity of an aloe extract has been reviewed by Fujita, et.al. Existence of any anti-inflammatory activity action **in-vivo** remains to be shown.

Structural studies of polysaccharides found in aloe vera gel have indicated that the mucilagenous jelly is composed of at least four different partially acetylated glucomannans[30] which are linear polymers with no branching[31] containing 1-4 glycosidic linkages in the ratio of glucose and mannose 1:2.8.

Uronic acid was obtained by extraction of aloe vera leaves, which upon fermentative hydrolysis with pectinase, yielded galacturonic acid and oligosaccharides.[32] Gjerstad[33] has reported that aloe vera juice carbohydrates consist of glucose and a polyuronide consisting of a high molecular weight glucose-mannose polyose (MW up to about 2.75×10^5) and hexuronic acids which upon hydrolysis yield glucose and mannose, as well as traces of galactose, arabinose and xylose. Gjerstad found no uronic acids in the course of his analysis.

Mineral constituents of lyophilized A. barbadensis juice have been examined by neutron activation analysis. It was concluded[34] that the concentration of C1 and K appeared to be excessive for most plant productions whereas the sodium content was less than average. Meadows[35] has pointed out that . . . "as for minerals, they will vary largely, depending on the rains and terrain."

Pitfalls in Compositional Analysis

Henry[36] points out "that all species do not contain the same amount of the same components, and that seasonal climate causes variations in the anthraquinones present." Mepedova, et.al.[37] also found compositional variations in various species of aloe, in that only 12 species contained flavanoids, hydroxy anthraquinones and coumarin of the 22 species which were investigated by thin-layer chromatography.

Conditions of leaf storage also may effect compositional analysis results. Joshi and Bartakke[38] found that malic or citric acid may be present in the leaves at concentrations which vary, depending upon whether the leaves were stored in light or darkness. Leung[39] emphasized the importance of considering seasonal, climatic and soil variations in research of aloe vera chemistry, since all these factors may have significant effects on composition of the gel.

Mahabnle and Kamble[40] determined the percentage of aloin in 10 aloe species and found that there were considerable variations between certain species. McCarthy[41] found that the quantity of aloin in two different Aloe species fluctuates markedly throughout the year. The summer months produced

the highest percentage of aloin in the dried leaf juice of both species tested.

In addition to species, climatic and seasonal variations, age of the plant also must be considered. Janik[42] determined the aloin content of Aloe arborescens and found that both the aloin and aloe emodin anthrone content increased simultaniously with age of the plant. Most significant increase was found in plants 2-3 years old.

De Leo and Cararrone[43] investigated distribution of ascorbic acid in various parts of flowers and fruits during development in some species of aloe. This study indicated that amount of ascorbic acid present in the whole fruit decreases with development of the fruit. Ascorbic acid content also was found to vary from species to species.

Mahabnle and Kamble[44] studied the amino acid composition of 10 different species of aloe. Although L-Asparagine, Aspartic acid, DL-threonine and L-tryptophan were common to all species tested, alanine, DL-phenylalanine, DL-Leucine and DL-valine were represented selectively.

Thus, current efforts to impose aloe vera gel purity standards[45] must be carefully defined with respect to the natural product variations tó be expected, including species, climatic, seasonal, plant maturity and conditions of storage.

Aloe Extract vs. Aloe Gel

Robson[46] recently published the results of a detailed chemical analysis of "99.5 percent pure Aloe vera extract," which was carried out using a combination of spectroscopy and trace metal analysis. Objective of this work was to ascertain distribution of the chemical constituents present in aloe vera that may exhibit certain "beneficial effects," especially with regard to preservation of dermal microcirculation after thermal injury.

The commercial aloe vera extract assayed by Robson contained salicylic acid, leading him to the hypothesis . . . "that since the extract contains an aspirin-like compound capable of causing analgesia, coupled with the high magnesium content, it may be capable of relieving pain, as so frequently reported."

An antiprostanoid effect was proposed whereby certain "anti-inflammatory, edema-relieving and wound-healing" constituents of aloe vera block the formulation of all or some of the detrimental products of the arachidonic acid cascade (Anti-thromboxane effect). Relationship of the Robson commercial aloe extract to aloe vera gel was not defined. It is also unclear as to what constitutents (including salicylic acid) may have been additives (or artifacts) in the course of the commercial extract preparation.

It has been theorized[47] that the active aloe vera gel principle for promoting healing may be mucopolysaccharides, which may act synergistically in some unknown manner with sulfur derivatives and nitrogen compounds which are also present. Leung[45] pc out that . . . "it is commonly believed that the m turizing, emollient and healing properties of aloe are due to the polysaccharides present . . . It is pr able that the gel's beneficial properties are not du the polysaccharide alone, but rather from a syner tic effect of these compounds with other substan present in the gel." Waller, et.al[47] observes that "as in the case of many other folk medicines, the e cacy of A. barbadensis remains uncertain and sc potentially physiologically active constituents are unidentified."

Mucopolysaccharides are essential component many tissues, where they are generally present cc bined with protein as mucoproteins. The term glyc protein has been used to include the mucoprote and carbohydrate-containing proteins. Lectins are group of sugar-binding proteins which are ubiquitc in plants. This particular type of glycoprotein known to have cell-agglutinating properties.

Recently, a glycoprotein, termed "Aloctin A" w isolated from aloe.[51] This material was determined have a molecular weight of 1.8×10^4 and a ratio protein to sugar of 8.2 by weight. It was also dete mined that the aloe glycoprotein has binding reactiv ty with some serum proteins . . . and may be useful f the treatment of some serum proteins . . . and may b useful for the treatment of certain types of cancer, Ir flammations and skin diseases.

Another glycoprotein (Alcotin B) isolated from alc arborescens, was found to contain greater than 5 percent by weight sugars (Molecular weight = 2.4 10^4). Anticancer activity in-vitro against accute lym phocytic leukemia has been claimed.[52,53]

Could glycoproteins hold the secret to an aloe derived curative ingredient missing link?

One cannot rule out the possibility that the alo vera gel curative ingredient missing link may be un definable by the tools of modern day chemical analy sis. How do you analyze the chemistry of folklor belief, which with use may yield bonafide consume benefits? □

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