

*Aloe vera (Aloe barbadensis Miller) is a perennial succulent belonging to the Liliaceal family, and is called the healing plant or the silent healer. As a result of its use as folk medicine, it is claimed that aloe vera has wound and burn healing properties, and anti-inflammatory, and immunomodulatory effects. Aloe vera is used in a variety of commercial products because of these therapeutic properties. It is being used as a whole extract, however, and the relationship between the components of the extract and its overall effect has not been clarified. A more precise understanding of the biologic activities of these is required to develop aloe vera as a pharmaceutical source. Many attempts have been made to isolate single, biologically active components, to examine their effects, and clarify their functional mechanism. This review focuses on the relationship between the isolated aloe vera components (ie, glycoproteins, anthraquinones, saccharides, low-molecular-weight substances) and their presumed pharmacologic activities.*

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# A REVIEW ON THE RELATIONSHIP BETWEEN ALOE VERA COMPONENTS AND THEIR BIOLOGIC EFFECTS

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## INTRODUCTION

**A**loe vera (*Aloe barbadensis Miller*) is a perennial succulent belonging to the Liliaceal family. It is a cactus-like plant that grows in hot, dry climates. In nature, it may be damaged physically by ultraviolet (UV) irradiation or by insects. Perhaps its survival in a harsh environment encourages people to believe that aloe vera has wound-healing and antibiotic effects. It is, therefore, less than fortuitous that aloe vera has been reported to possess immunomodulatory, antiinflammatory, UV protective, antiprotazoal, and wound- and burn-healing promoting properties.<sup>1</sup> However, previous treatments of such diseases and conditions with aloe vera gel have been empirical rather than theoretical. Therefore, the clarification of the modes of action of the biochemical components of aloe vera is important in the determination of the most efficient way of using such active species effectively and developing their applications. It is essential to establish the relationships between the components of aloe vera and their pharmacologic effects. Many attempts have been made to isolate single, active components to examine their effects and clarify their functional mechanisms. Reynold's review<sup>1</sup> describes the biologic activ-

ities of several aloe species. Since then, further pharmacologic activities of the components of aloe vera have been reported. Therefore, this review focuses on establishing the relationship between the components of aloe vera and their effects based on published reports and more recent findings.

### BIOLOGIC ACTIVITIES OF ALOE VERA GEL

The whole gel extract of aloe vera has been reported to have various pharmacologic properties, specifically to promote wound, burn, and frost-bite healing, in addition to having antiinflammatory, antifungal, hypoglycemic, and gastroprotective properties.<sup>1</sup> Of those claims, aloe vera's antiinflammatory and wound healing has been the most extensively studied.

Wound healing is considered to be composed of three overlapping events: (1) inflammation, (2) new tissue formation, and (3) matrix remodeling.<sup>2</sup> In the case of whole gel extracts, many clinical trials have been performed on animal models. Protein factors related to wound healing have been investigated, such as growth factors, cell-migration related factors, matrix-forming factors, and matrix-degradation factors. Aloe vera gel extract stimulated fibroblast growth in a synovial model and also enhanced wound tensile strength and collagen turnover in wound tissue.<sup>3-5</sup> In another trial, topical application of aloe vera gel stimulated fibroblast activity and collagen proliferation, in addition to increasing the content of granulation tissue and tissue crosslinking by increasing the aldehyde content and decreasing the acid solubility.<sup>6,7</sup> The aloe vera gel also increased levels of hyaluronic acid and dermatan sulphate in granulation tissue.<sup>8</sup> In terms of the formation of new tissue, angiogenesis is essentially required to provide oxygen and metabolites to the tissues. An increase in the blood supply was observed after aloe vera gel treatment,<sup>9</sup> and it has been suggested that an increased oxygen access is one of the factors enhanced by aloe vera gel.<sup>10</sup> Aloe vera gel was found to contain an angiogenic component.<sup>11</sup> The aloe vera gel extract permitted faster healing of burns, and reestablished the vascularity of burn tissue of a guinea pig.<sup>12,13</sup> Although many reports support the promotion of wound healing by the whole gel extract, several reports have mentioned inhibitory effects. A delay in wound healing was

observed when a wound was treated with aloe vera gel.<sup>14</sup> In another trial, aloe vera gel hindered wound healing in an experimentally induced second-degree burn.<sup>15</sup> Different results should be expected, however, given the fact that the composition of the aloe vera gel varies and that even within the same species the plant depends on source, climate, region, and the processing method. Nevertheless, as more factors involved in the wound healing process are discovered, data accumulates *supporting* the enhancing effect of whole gel.

Other aspects of the pharmacologic activity of aloe vera gel are presented by its antiinflammatory and immunomodulatory effects. Antiinflammation is the first step in the wound healing process. Based on the fact that aloe vera gel effectively enhances wound healing, whole gel was examined for antiinflammatory activity. The whole gel extract was found to have antiinflammatory activity on carrageenan-induced edema in rat paws.<sup>16</sup> Moreover, it was found to enhance wound tensile strength and antiinflammation.<sup>4</sup> Topically administered aloe vera preparations inhibited inflammation in the croton oil-induced edema assay.<sup>9</sup> In terms of the mechanism involved, the inhibitory action of aloe vera gel on the arachidonic acid pathway via cyclooxygenase has been suggested.

The immunomodulatory activity of aloe vera gel has also been widely studied. The topical application of aloe vera gel extract to the skin of UV-irradiated mice improved UV-induced immune suppression.<sup>17</sup> Topical application inhibited contact hypersensitivity and delayed type hypersensitivity suppression by UV radiation in mice. It preserved the number and morphology of irradiated Langerhans and dendritic epidermal cells in skin. Lissoni et al<sup>18</sup> demonstrated that the administration of aloe vera with pineal indole melatonin enhances the therapeutic results in patients with advanced solid tumors. The percentage of nonprogressing patients and the percentage of 1-year survival was significantly higher in the group treated with aloe vera plus melatonin than in the melatonin-only group. It is possible that aloe vera activates anticancer immunity and produces therapeutic benefits in terms of stabilization of disease and survival in patients with advanced solid tumors.<sup>18</sup>

Aloe vera gel also showed hypoglycemic activity on insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus rats,

though it was found to be more effective in non-insulin dependent diabetes.<sup>19</sup> The acute and chronic effects of aloe vera gel were studied on the plasma glucose levels of alloxan-diabetic mice and was found to reduce plasma glucose levels.<sup>20</sup> Aloe vera gel has also been found to have antifungal activity and is believed that aloe vera likely contains antibiotic substances to help to prevent infection.<sup>21</sup>

Studies *in vitro*, using crude gel extracts, are difficult to perform and the results are difficult to interpret because of the active substances' complexity. For example, since aloe vera gel contains both inhibitory and stimulatory systems with respect to inflammatory and immune responses,<sup>22,23</sup> it is possible that several activities operate separately and each has with its own part to play in the overall effect. Therefore, the clarification of the modes of action for each individual components of aloe vera is the most efficient way to develop applications for the components of aloe vera.

### COMPONENTS OF ALOE VERA

**B**ox 1 summarizes the components of aloe vera, which are primarily glycoproteins, anthraquinones, saccharides, and low-molecular-weight substances. Polysaccharides are largely glucomannans of various compositions; some are acetylated while others are not. Galactose and galactouronic acid polymers are also frequently found. Different investigators have reported different polysaccharide structures, which may be due to different geographical origins or to the use of different varieties or subspecies. Acetylated mannan has a range of interesting biologic activities as described below. Recently glycoproteins with cell proliferation-promoting activity have been reported.<sup>24,25</sup> Aloe-specific anthraquinones are also present and include aloin, aloe-emodin, barbaloin, isobarbaloin, and others. In addition to these, low-molecular-weight substances are reported, such as aloe-sin,  $\beta$ -sitosterol, diethylhexylphthalate, vitamins, and beta-carotene. Apart from technical differences and inconsistencies, it appears that the types and levels of components present in aloe gel vary according to geographic origin or variety, therefore, the identification of the active components of aloe vera is important for the effective use of the plant.

### **Glycoproteins**

Compared to the other components the glycoproteins have not been extensively studied, especially with respect to wound healing. However, there have been a consistent number of reports regarding biologically active glycoproteins from aloe vera.<sup>1</sup> Several of these reports point to the wound-healing effect of glycoproteins and have attempted to isolate glycoprotein components and found that glycoproteins stimulate cell proliferation.<sup>24,25</sup> Fractions prepared from aloe vera gel contain lectin-like substances that promote the growth of normal human cells like human fibroblasts.<sup>26</sup> Yagi et al<sup>24</sup> reported on the cell-proliferating activity of a 29 kDa glycoprotein composed of two 14 kDa subunits. This was found to enhance the proliferation of baby hamster kidney cells and normal human dermal fibroblasts.

Recently, Choi et al<sup>25</sup> reported on the proliferation and wound healing effect of a 5.5 kDa glycoprotein. This glycoprotein was isolated by activity-guided sequential fractionation from aloe vera gel and was found to enhance keratinocyte proliferation. The cell-proliferating effect of the glycoprotein was confirmed by accelerated closure of a scratch made on a monolayer of human keratinocytes. Moreover, when this glycoprotein was tested on a three-dimensional raft-culture, it dose-dependently stimulated the formation of epidermal tissue. Furthermore, at the immunohistochemical level, epidermal growth factor receptor, fibronectin receptor, fibronectin, and keratin 5/14 were noticeably expressed. This glycoprotein fraction was found to enhance wound healing in hairless mice by 8 days after injury with significant cell proliferation. This glycoprotein is linked to saccharides, 70% of which is mannose. Due to a lack of information regarding the amino-acid sequence of glycoproteins isolated from aloe vera, it is not yet known whether the 5.5 kDa glycoprotein is a fragment of longer glycoproteins. Nevertheless, this experiment systematically showed how the 5.5 kDa glycoprotein affects cell proliferation and wound healing both *in vivo* and *in vitro*.

Lectin has mitogenic activity and a wound healing effect.<sup>27-30</sup> Winters et al<sup>31</sup> reported that lectins are present in the gel portion of aloe vera leaves. Koike et al<sup>32</sup> isolated a 35 kDa lectin from aloe aborescence, which was presumed to be either a trimeric or tetrameric form composed of identical subunits with a molecular mass of about 9 kDa. It was also found to be a mannose-binding lectin

with hemagglutination and mitogenic activities. However, no studies have been conducted regarding the amino sequences of active lectins of aloe vera. Mannose is linked to the active 5.5 kDa glycoprotein at a high percentage, may be a kind of lectin. Another possibility is that the mannose exhibit the wound-healing activity when linked to the protein as suggested by Davis et al.<sup>33</sup>

Davis et al<sup>33</sup> tried to determine whether mannose-6-phosphate is the active ingredient in aloe vera for wound healing and antiinflammation, and whether binding to a protein is necessary to initiate a growth response. Experiments showed that mannose-6-phosphate dose-dependently promotes wound healing. Mannose-6-phosphate linked to a protein, thereby forming a mucopolysaccharide, may produce even greater wound-healing effects.<sup>34</sup> It is possible that the binding of a ligand at one binding site is capable of influencing ligand binding at another binding site of the same receptor; binding of mannose-6-phosphate to its binding site preferentially increases the affinity of insulin-like growth factor II to its binding site.<sup>35,36</sup> Then insulin growth factor is delivered to cells and increases fibroblast activity and the wound's healing response. Therefore, the wound healing activity of the reported glycoproteins should be further investigated as protein with and without mannose bound.

Aloe vera gel contains a small amount of phenolics in the leaf exudates.<sup>24</sup> These phenolics be responsible for reducing the proliferative effect of lectin-like glycoproteins. In addition, conflicting activities of the proliferative glycoproteins and the inhibitory glycoproteins, in combination with phenolic substances in aloe vera gel, may cause the observed variability in the pharmacologic results and the therapeutic experiments when whole gel is used in wound healing.

Another research group recently isolated a 10 kDa glycoprotein from aloe vera gel, using an activity-based follow-up method. This glycoprotein was found to have antiallergic activity.<sup>37</sup> It reduced histamine release and promoted the synthesis and secretion of leukotrienes simultaneously in activated lung mast cells of the guinea pig. It decreased dose-dependently protein kinase C and phospholipase D activities, inhibited mass diacylglycerol and phospholipase A activity, and blocked  $Ca^{++}$  influx during mast cell activation.

<b>BOX 1.</b>	
<b>Major Components of Aloe Vera</b>	
Anthraquinones	aloe-emodin aloetic acid aloin anthranol barbaloin isobarbaloin emodin ester of cinnamic acid
Saccharides	cellulose glucose mannose aldopentose acetylated mannan (acemannan) glucomannan acetylated glucomannan galactogalacturan glucogalactomannan galactoglucoarabinomannan
Vitamins	B1 B2 B6 C $\beta$ -carotene choline folic acid $\alpha$ -tocopherol
Enzymes	amylase carboxypeptidase catalase cyclooxygenase lipase oxidase
Low-molecular-weight substances	arachidonic acid  cholesterol gibberellin lectin-like substance lignins salicylic acid $\beta$ -sitosterol steroids triglycerides uric acid

### Anthraquinones

The allegedly, pharmacologically active anthraquinones of aloe vera are aloin, aloe-emodin, barbaloin, and emodin (see Box 1). Their therapeutic claims are a purgative action, antiinflammatory activity, antiprotozoal action, antioxidant activity and so on (Table 1).

Aloe-emodin and emodin showed synergistic effects with rhein anthrone during purgative activity in mice.<sup>38</sup> The purgative action of barbaloin is induced by *Eubacterium sp.*, which is capable of

**TABLE 1.**  
**Alleged Pharmacological Activities of Aloe Vera Components**

Components	Alleged Pharmacological Activities
glycoprotein	wound healing, cell proliferation, <sup>24,25,27-30,32</sup> antiallergy, <sup>37</sup>
barbaloin	purgative, <sup>39-42,43</sup>
aloe-emodin, emodin	purgative, <sup>38</sup> cell proliferation, <sup>50</sup> anticancer, <sup>51,52,53</sup> antiprotozoa, antibacteria, <sup>47,48</sup> antioxidant, <sup>45,46</sup> genotoxicity, mutagenicity, <sup>54,55,56</sup>
mannose-6-phosphate	wound healing, <sup>33,34,35</sup>
polysaccharide	antiinflammation, <sup>33</sup> anticancer, <sup>65,66,68,69</sup> immunomodulation, <sup>22,64,67,74,75,76</sup>
acemannan	immunomodulation, <sup>57,58,59,60,62,63</sup> antimicrobiol effect, <sup>61</sup> antitumor, <sup>63</sup>
aloesin	cell proliferation, <sup>77</sup> inhibition of melanin synthesis, <sup>78</sup>
$\beta$ -sitosterol	antiinflammation, <sup>4</sup> angiogenesis, <sup>11,79</sup>
diethylhexylphthalate	anticancer, <sup>81,82</sup>
low-molecular-weight substances of 0.5~1 kDa	immunomodulation, <sup>84,85</sup>

transforming barbaloin to aloe-emodin anthrone.<sup>39-42</sup> Barbaloin inhibited rat colonic Na<sup>+</sup>, K<sup>+</sup> ATPase *in vitro*, and increased paracellular permeability across the rat colonic mucosa *in vivo*.<sup>43</sup> Isobarbaloin is decomposed to aloe-emodin-9-anthrone and barbaloin when administered orally. The cathartic effect of isobarbaloin was examined in male rats by oral administration, and its cathartic activity was found to be equal to that of barbaloin.

Regarding antiinflammatory and immunomodulatory effects of anthraquinones, one proposed mechanism involves antioxidation. Anthraquinones may act as antioxidants and radical scavengers. Reactive oxygen species and free-radical-mediated reactions are involved in inflammatory response and can contribute to liver necrosis.<sup>44</sup> Histologic analysis of liver specimens showed that inflammatory infiltration of lymphocytes and Kuffer cells was reduced in aloe-emodin treated rats. Aloe-emodin quinone pretreatment reduced

the acute liver injury induced by carbon tetrachloride,<sup>45</sup> and aloe-emodin appears to protect against hepatocyte death and the inflammatory response that occurs subsequent to lipid peroxidation.<sup>46</sup> Antioxidant and radical scavenging activity of aloe-emodin was suggested as a protection mechanism against peroxidation of linoleic acid.<sup>46</sup>

Anthraquinones, including aloe-emodin, are known to have antiprotozoal activity. Aloe-emodin elicited dose-dependent growth inhibition of *Helicobacter pylori*, which is a possible causative factor of gastric cancer.<sup>47,48</sup> Aloe-emodin may act like a noncompetitive inhibitor of arylamine N-acetyltransferase activity, thereby decreasing effects of arylamine carcinogens in inducing carcinogenesis.<sup>49</sup> In addition, antibiotic factors are released by the healing tissues in response to aloe treatment.<sup>49</sup>

Aloe-emodin possesses contradictory activities on cell growth. It was found to stimulate the growth of primary rat hepatocytes and caused a 2.5-fold increase of DNA synthesis in primary rat hepatocytes.<sup>50</sup> However, there are other controversial observations. Aloe-emodin was found to have cell death or apoptosis-inducing effect in human lung squamous cell carcinoma<sup>51,52</sup> and to selectively inhibit human neuroectodermal tumor growth in an *in vivo* experiment.<sup>53</sup> Biochemical evidence for the apoptotic action of aloe-emodin is that aloe-emodin-treated CH27 cells showed activation of caspase-3, caspase-8, and caspase-9 and increased relative abundances of cytochrome c in the cytosolic fraction.<sup>51</sup> This cytochrome c increase resulted in mitochondrial death and finally CH27 cell death.

In spite of these biologic activities, anthraquinones also have harmful effects, such as genotoxic, mutagenic, and tumor-promoting effects.<sup>54-56</sup> Therefore, caution should be exercised with regard to the anthraquinones, and further studies need to be undertaken to more accurately define the activities of each component.

### Saccharides

Aloe is a rich source of polysaccharides and has various carbohydrate constituents, for example, polysaccharides, acemannan, and mannose-6-phosphate, of which mannose-6-phosphate and acemannan are major constituents of the carbohydrates of aloe vera.<sup>33</sup> Since mannose-6-phosphate is the major sugar in aloe vera gel, it was studied to determine whether it is an active

wound-healing and antiinflammatory ingredient in aloe vera. Mice receiving 300 mg/kg of mannose-6-phosphate had improved wound healing over saline controls. Grey et al<sup>34</sup> suggested that mannose-6-phosphate linked to a protein produce even greater wound-healing effects.

Acemannan (ie, aloe polymannose, a polydispersed  $\beta$ -(1,4)-linked acetylated mannose-containing complex carbohydrate) was found to have immunomodulatory activity.<sup>57</sup> It was reported to activate macrophages; enhance cytokine release; stimulate interactions between macrophages, T-lymphocytes and B-lymphocytes; and enhance the generation of cytotoxic T-lymphocytes. Acemannan was also found to potentiate antibody production against coxsackie virus and reduce radiation-induced skin reactions in C3H mice.<sup>58</sup> Acemannan enhanced the allo-responsiveness of human lymphocytes<sup>59</sup> and induced the phenotypic and functional maturation of immature dendritic cells.<sup>60</sup> It also upregulated phagocytosis and the candidicidal activity of macrophages.<sup>61</sup> Regarding its mechanism, acemannan induced *no* synthesis, which was mediated by macrophage mannose receptors in chickens,<sup>62</sup> stimulated the synthesis of monokines, and initiated immune response.<sup>63</sup> It also showed inhibitory effects on tumor growth, that is, murine sarcoma implanted in mice regressed after acemannan treatment, which was probably due to an immune attack and enhanced immunomodulation.<sup>63</sup>

The ability of aloe vera to stimulate the immune system is attributed to polysaccharides present in the aloe vera gel.<sup>22</sup> There has been some disagreement concerning the identities of the active materials, thus, the optimal form and composition of the aloe polysaccharides has been investigated to maximize immunomodulatory activity and stability. In one study the immunomodulatory activity of aloe vera was found to be caused by a 15 kDa polysaccharide,<sup>64</sup> while modified aloe polysaccharide with an average molecular weight of 80 kDa showed the highest protective activity against UVB irradiation-induced immune suppression. The native polysaccharide is of 2000 kDa with a mannose:galactose:glucose ratio of 11:0.2:1, whereas the active form is of 80 kDa with mannose:galactose:glucose ratio of 40:1.4:1. The active polysaccharide is composed of mannose at a high ratio. Polysaccharides are also known to possess antitumor effects.<sup>65,66</sup> A high molecular weight polysaccharide (aloeride) was found to have potent immunostimulatory activity, and

was found to induce the expression of mRNAs encoding IL-1  $\beta$  and TNF- $\alpha$ .<sup>67</sup> These polysaccharides may exhibit antitumor and antiviral activities through enhanced immune attack and immunomodulation.<sup>68</sup>

Carcinogenesis induced by DNA adduct formation was shown to be inhibited by a polysaccharide-rich aloe gel fraction in an *in vitro* rat hepatocyte model.<sup>69</sup> Kim et al<sup>69</sup> reported on the chemopreventive effect of aloe polysaccharide isolated from aloe vera noting that oxidative DNA damage assessed by 8-hydroxyguanosine was significantly reduced by the polysaccharide, which also inhibited benzo[a]pyrene-DNA adduct formation by interfering with benzo[a]pyrene-DNA absorption *in vivo*. This may be due to the inhibition of carcinogen activation systems or to the induction of detoxifying enzymes.<sup>70</sup>

Cutaneous exposure to high doses of UVB radiation induces the systemic suppression of contact hypersensitivity responses to hapten applied to non-irradiated sites and of delayed-type hypersensitivity responses to infectious agents.<sup>71</sup> UVB radiation contributes to the growth of highly antigenic skin cancers by suppressing T-cell mediated immune responses.<sup>72</sup> Therefore, susceptibility to UV-induced immune suppression of contact hypersensitivity responses may be a risk factor for the development of skin cancer in humans.<sup>73</sup> Therapeutic intervention to prevent immune suppression may reduce the risk of skin cancer.<sup>74</sup> Aloe oligosaccharides and polysaccharides were found to inhibit UV-induced immune suppression and interleukin-10 production.<sup>75</sup> Aloe oligosaccharides may prevent UV-induced suppression of delayed-type hypersensitivity by reducing keratinocyte derived immunosuppressive cytokines.<sup>74</sup> It is also suggested that aloe oligosaccharide protects against delayed type hypersensitivity response indirectly by inducing immunostimulatory cytokines, such as interleukin-12.<sup>76</sup>

The labile natures of factors that prevent immune suppression vary in different gel extract preparations and is possibly influenced by the manufacturing process used.<sup>74</sup> Variable activities in the reported experiments possibly result from the degradation of polysaccharide resulting from bacterial contamination or endogenous enzyme activity in aloe vera gel. These explain some of the difficulties that investigators have experienced in terms of result reproducibility when using unfraktionated leaf gel from aloe vera.

### Other Low-Molecular-Weight Components

In addition to the aforementioned components, low-molecular-weight components, such as aloe-sin,  $\beta$ -sitosterol, diethylhexylphthalate, and immunomodulatory substances have been examined. Aloe-sin, a chromone derivative isolated from aloe vera, was found to enhance cell proliferation by upregulating cyclin E/CDK2 kinase activity via inducing cyclin E, CDK2, and CDC25A, in SK-HEP-1 cells.<sup>77</sup> Aloe-sin and arbutin were found to inhibit mushroom-tyrosinase activity *in vitro* in a synergistic manner, which is an important element in melanin synthesis.<sup>78</sup> They inhibit tyrosinase activity via different mechanisms in the SK-Mel-1 cell line; aloe-sin inhibits human tyrosinase activity via a noncompetitive inhibition mechanism, whereas arbutin works via a competitive inhibition mechanism.<sup>78</sup>

Based on the wound-healing effect of aloe vera, the angiogenic component was isolated using an activity-guided fractionation from aloe vera gel.<sup>10,11,79</sup> A low-molecular-weight component from the dichloromethane extract of freeze-dried aloe vera gel was shown to stimulate blood vessel formation in a chick chorioallantoic membrane.<sup>10</sup> Moreover, a methanol-soluble fraction of the gel stimulated the proliferation of artery endothelial cells in an *in vitro* assay, and induced them to invade a collagen substrate.<sup>11</sup> The active component was found to be  $\beta$ -sitosterol, which showed a dose dependent angiogenic effect in a chick embryo chorioallantoic membrane assay.<sup>79</sup>  $\beta$ -sitosterol enhanced new vessel formation in Mongolian gerbil brain damaged by ischaemia/reperfusion, especially in the cingulate cortex and septal areas.<sup>79</sup> It also enhanced the expression of proteins related to angiogenesis, namely the von Willebrand factor, vascular endothelial growth factor (VEGF), and VEGF receptor Flk-1.<sup>79</sup> Morisaki et al<sup>80</sup> suggested that sterol structure be responsible for the angiogenic activity.  $\beta$ -sitosterol was also found to have significant anti-inflammatory effects in wounded mice.<sup>4</sup> Taking into account its unique activity,  $\beta$ -sitosterol can be viewed as another component that contributes to the wound-healing effect of aloe vera.

Diethylhexylphthalate isolated from aloe vera induced apoptosis and was found to possess antileukemic and antimutagenic effects.<sup>81,82</sup> CD95-mediated apoptosis is supposed to be a major effect pathway by diethylhexylphthalate, but this detailed mechanism has not been widely studied.<sup>83</sup>

Aloe vera gel contains low-molecular-weight immunomodulators (ie, G1C2F1), which restore UVB-suppressed accessory cell function of epidermal Langerhans cells both *in vitro*<sup>84</sup> and *in vivo*.<sup>85</sup> Exposure of the shaved abdominal skin of mice to UVB irradiation resulted in suppression of contact sensitization through the skin. Although treatment with G1C2F1 prevented UVB-induced suppression of contact sensitization in a dose-dependent manner, the irradiated skin of G1C2F1-treated groups showed similar levels of sunburn when examined on the day of sensitization.<sup>85</sup> This may indicate that G1C2F1 prevent UVB-induced elimination or functional alteration of epidermal Langerhans cell through a mechanism that does not alter the initial inflammatory response and release of proinflammatory cytokines.<sup>85</sup>

### CONCLUSION

Aloe vera contains many physiologically active substances that have effective antiinflammatory, immunomodulatory, and wound-healing effects. The active ingredients, whether acting alone or in concert, include glycoproteins, anthraquinones, polysaccharides, and low-molecular-weight species. Moreover, the fact that biologically active components in aloe vera may be labile, varied, or modified explain some of the difficulties that investigators have reported in reproducing results using unfractionated materials from aloe vera. In light of the many pharmacologic activities of the components of aloe vera, each active component has several interacting factors, each of which may be affected by another substance(s). Thus, a further understanding of these individual components and of their effects is essential if aloe vera is to be successfully developed for therapeutic purposes.

### REFERENCES

1. Reynolds T, Dweck AC: Aloe vera leaf gel: a review update. *J Ethnopharmacol* 68:3-37, 1999
2. Dunphy JE: Modern biochemical concepts on the healing of wounds: Wound healing. Baltimore, MD, Williams and Wilkins, 1974, pp 22-31
3. Davis RH, Stewart GJ, Bregman PJ: Aloe vera and the inflamed synovial pouch model. *J Am Podiatr Med Assoc* 82: 140-148, 1992
4. Davis RH, DiDonato JJ, Johnson RW, et al: Aloe vera, hydrocortisone, and sterol influence on wound tensile strength

- and anti-inflammation. *J Am Podiatr Med Assoc* 84:614-621, 1994
5. Chithra P, Sajithlal GB, Chandrakasan G: Influence of Aloe vera on collagen turnover in healing of dermal wounds in rats. *Indian J Exp Biol* 36:896-901, 1998
  6. Thompson JE: Topical use of aloe vera derived allantoin gel in otolaryngology. *Ear Nose Throat J* 70:56, 1991
  7. Chithra P, Sajithlal GB, Chandrakasan G: Influence of Aloe vera on collagen characteristics in healing dermal wounds in rats. *Mol Cell Biochem* 181:71-76, 1998
  8. Chithra P, Sajithlal GB, Chandrakasan G: Influence of Aloe vera on the glycosaminoglycans in the matrix of healing dermal wounds in rats. *J Ethnopharmacol* 59:179-186, 1998
  9. Davis RH, Rosenthal KY, Cesario LR, et al: Processed Aloe vera administered topically inhibits inflammation. *J Am Podiatr Assoc* 79:395-397, 1989
  10. Lee MJ, Yoon SH, Lee SK, et al: In vivo angiogenic activity of dichloromethane extracts of Aloe vera gel. *Arch Pharm Res* 18:332-335, 1995
  11. Lee MJ, Lee OH, Yoon SH, et al: In vitro angiogenic activity of Aloe vera gel on calf pulmonary artery endothelial (CAPE) cells. *Arch Pharm Res* 21:260-265, 1998
  12. Rodríguez-Bigas M, Cruz NI, Suarez A: Comparative evaluation of Aloe vera in the management of burn wounds in guinea pigs. *Plast Reconstr Surg* 81:386-389, 1988
  13. Hegggers JP, Pelley RP, Hill DP, et al: Wound healing with aloe substances. *Academic/Industry Joint Conference* p 41, 1992
  14. Schmidt JM, Greenspoon JS: Aloe vera dermal wound gel is associated with a delay in wound healing. *Obstet Gynecol* 78:115-117, 1991
  15. Kaufman T, Kalderon N, Ullmann Y, et al: Aloe vera gel hindered wound healing of experimental second-degree burns: A quantitative controlled study. *J Burn Care Rehabil* 9:156-159, 1988
  16. Vazquez B, Avila G, Segura D, et al: Antiinflammatory activity of extracts from Aloe vera gel. *J Ethnopharmacol* 55:69-75, 1996
  17. Strickland FM, Pelley RP, Kripke ML: Prevention of ultraviolet radiation-induced suppression of contact and delayed hypersensitivity by Aloe barbadensis gel extract. *J Invest Dermatol* 102:197-204, 1994
  18. Lissoni P, Gianni L, Zerbini S, et al: Biotherapy with the pineal immunomodulating hormone melatonin versus melatonin plus aloe vera in untreatable advanced solid neoplasms. *Nat Immun* 16:27-33, 1998
  19. Okyar A, Can A, Akev N, et al: Effect of Aloe vera leaves on blood glucose level in type I and type II diabetic rat models. *Phytother Res* 15:157-161, 2001
  20. Ajabnoor MA: Effect of aloes on blood glucose levels in normal and alloxan diabetic mice. *J Ethnopharmacol* 28:215-220, 1990
  21. Ali MI, Shalaby NM, Elgamal MH, et al: Antifungal effects of different plant extracts and their major components of selected aloe species. *Phytother Res* 13:401-407, 1999
  22. Davis RH, Parker WL, Samson RT, et al: Isolation of a stimulatory system in an aloe extract. *J American Podiatric Medical Assoc* 81:473-478, 1991
  23. Davis RH, Parker WL, Samson RT, et al: The isolation of an active inhibitory system from an extract of aloe vera. *J American Podiatric Medical Assoc* 81:258-261, 1991
  24. Yagi A, Egusa T, Arase M, et al: Isolation and characterization of the glycoprotein fraction with a proliferation-promoting activity on human and hamster cells in vitro from Aloe vera gel. *Planta Med* 63:18-21, 1997
  25. Choi S, Son BW, Son YS, et al: The wound-healing effect of a glycoprotein fraction isolated from aloe vera. *Br J Derm* 145:535-545, 2001
  26. Danof IE, McAnalley W: Stabilised Aloe vera: Effect on human skin cells. *Drug & Cosmetic Industry* 133:105-106, 1983
  27. Gipson IK, Kiorpes TC, Brennan SJ: Epithelial sheet movement: Effects of tunicamycin on migration and glycoprotein synthesis. *Dev Biol* 101:212-220, 1984
  28. Yagi A, Machii K, Nishimura H, et al: Effect of aloe lectin on deoxyribonucleic acid synthesis in baby hamster kidney cells. *Experientia* 41:669-671, 1985
  29. Hegggers JP, Kucukcelebi A, Listengarten D, et al: Beneficial effect of Aloe on wound healing in an excisional wound model. *J Altern Complement Med* 2:271-277, 1996
  30. Utsunomiya T: A histopathological study of the effects of low-power laser irradiation on wound healing of exposed dental pulp tissues in dogs, with special reference to lectins and collagens. *J Endod* 24:187-193, 1998
  31. Winters WD, Benavides R, Clouse WJ: Effects of aloe extracts on human normal and tumor cells in vitro. *Economic Botany* 35:89-95, 1981
  32. Koike T, Beppu H, Kuzuya H, et al: A 35 kDa mannose-binding lectin with hemagglutinating and mitogenic activities from "Kidachi Aloe" (*Aloe arborescens* Miller var. *natalensis* Berger). *J Biochem (Tokyo)* 118:1205-1210, 1995
  33. Davis RH, Donato JJ, Hartman GM, et al: Anti-inflammatory and wound healing activity of a growth substance in Aloe vera. *J Am Podiatr Med Assoc* 84:77-81, 1994
  34. Grey V, Rouyer-Fessard C, Gammeltoft S, et al: Insulin-like growth factor II/mannose-6-phosphate receptors are transiently increased in the rat distal intestinal epithelium after resection. *Mol Cell Endocrinol* 75:221-227, 1991
  35. MacDonald R: Mannose-6-phosphate enhances cross-linking efficiency between insulin-like growth factor-II (IGF-II) and IGF-II/mannose-6-phosphate receptors in membranes. *Endocrinology* 128:413-421, 1991
  36. Roth RA: Structure of the receptor for insulin-like growth factor II: the puzzle amplified. *Science* 239:1269-1271, 1988
  37. Ro JY, Lee BC, Kim JY, et al: Inhibitory mechanism of aloe single component (alprogen) on mediator release in guinea pig lung mast cells activated with specific antigen-antibody reactions. *J Pharmacol Exp Ther* 292:114-121, 2000
  38. Yagi T, Yamauchi K: Synergistic effects of anthraquinones on the purgative activity of rhein anthrone in mice. *J Pharm Pharmacol* 51:93-95, 1999
  39. Yamauchi K, Shinano K, Nakajima K, et al: Metabolic activation of sennoside C in mice: Synergistic action of anthrones. *J Pharm Pharmacol* 44:973-976, 1992
  40. Ishii Y, Tanizawa H, Takino Y: Studies of aloe. IV: Mechanism of cathartic effect. (3). *Biol Pharm Bull* 17:495-497, 1994
  41. Ishii Y, Tanizawa H, Takino Y: Studies of aloe. V: Mechanism of cathartic effect. (4). *Biol Pharm Bull* 17:651-653, 1994
  42. Akao T, Che Qm, Kobashi K, et al: A purgative action of barbaloin is induced by *Eubacterium* sp. strain BAR, a human intestinal anaerobe, capable of transforming barbaloin to aloe-emodin anthrone. *Biol Pharm Bull* 19:136-138, 1996
  43. Ishii Y, Tanizawa H, Takino Y: Studies of aloe. III.



- Mechanism of cathartic effect. (2). *Chem Pharm Bull (Tokyo)* 38:197-200, 1990
44. Gressner AM: Liver fibrosis: Perspectives in pathobiochemical research and clinical outlook. *Eur J Clin Chem Clin Biochem* 29:293-311, 1991
45. Arosio B, Gagliano N, Fusaro LM, et al: Aloe-emodin quinone pretreatment reduces acute liver injury induced by carbon tetrachloride. *Pharmacol Toxicol* 87:229-233, 2000
46. Malterud KE, Farbrot TL, Huse AE, et al: Antioxidant and radical scavenging effects of anthraquinones and anthrones. *Pharmacology* 47(suppl 1):77-85, 1993
47. Camacho MR, Kirby GC, Warhurst DC, et al: Oxoaporphine alkaloids and quinines from *Stephania dinklagei* and evaluation of their antiprotozoal activities. *Planta Med* 66:478-480, 2000
48. Wang HH, Chung JG, Ho CC, et al: Aloe-emodin effects on arylamine N-acetyltransferase activity in the bacterium *Helicobacter pylori*. *Plant Med* 64:176-178, 1998
49. Cera LM, Hegggers JP, Robson MC, et al: The therapeutic efficacy of aloe vera cream (Dermaide Aloe) in thermal injuries: Two case reports. *J Am Anim Hosp Assoc* 16:768-772, 1980
50. Wolffe D, Schmutte C, Westendorf J, et al: Hydroxyanthraquinones as tumor promoters: Enhancement of malignant transformation of C3H mouse fibroblasts and growth stimulation of primary rat hepatocytes. *Cancer Res* 50:6540-6544, 1990
51. Lee HZ, Hsu SL, Liu MC, et al: Effects and mechanisms of aloe-emodin on cell death in human lung squamous cell carcinoma. *Eur J Pharmacol* 431:287-295, 2001
52. Lee HZ: Protein kinase C involvement in aloe-emodin and emodin-induced apoptosis in lung carcinoma cell. *Br J Pharmacol* 134:1093-1103, 2001
53. Pecere T, Gazzola MV, Mucignat C, et al: Aloe-emodin is a new type of anticancer agent with selective activity against neuroectodermal tumors. *Cancer Res* 60:2800-2804, 2000
54. Brusick D, Mengs U: Assessment of the genotoxic risk from laxative senna products. *Environ Mol Mutagen* 29:1-9, 1997
55. Muller SO, Eckert I, Lutz WK, et al: Genotoxicity of the laxative drug components emodin, aloe-emodin and danthron in mammalian cells: Topoisomerase II mediated? *Mutat Res* 371:165-173, 1996
56. Griminger W, Witthohn K: Analytics of senna drugs with regard to the toxicological discussion of anthranoids. *Pharmacology* 47(suppl 1):98-109, 1993
57. Womble D, Helderman JJ: The impact of acemannan on the generation and function of cytotoxic T-lymphocytes. *Immunopharmacol Immunotoxicol* 14:63-77, 1992
58. Roberts DB, Travis EL: Acemannan-containing wound dressing gel reduces radiation-induced skin reactions in C3H mice. *Int J Radiat Oncol Biol Phys* 32:1047-1052, 1995
59. Womble D, Helderman JH: Enhancement of allo-responsiveness of human lymphocytes by acemannan (Carrisyn). *Int J Immunopharmacol* 10:967-974, 1988
60. Lee JK, Lee MK, Yun YP, et al: Acemannan purified from *Aloe vera* induces phenotypic and functional maturation of immature dendritic cells. *Int Immunopharmacol* 1:1275-1284, 2001
61. Stuart RW, Lefkowitz DL, Lincoln JA: Upregulation of phagocytosis and candidicidal activity of macrophages exposed to the immunostimulant acemannan. *Int J Immunopharmacol* 19:75-82, 1997
62. Karaca K, Sharma JM, Nordgren R: Nitric oxide production by chicken macrophages activated by Acemannan, a complex carbohydrate extracted from *Aloe vera*. *Int J Immunopharmacol* 17:183-188, 1995
63. Peng SY, Norman J, Curtin G, et al: Decreased mortality of Norman murine sarcoma in mice treated with the immunomodulator, acemannan. *Mol Biother* 3:79-87, 1991
64. Qiu Z, Jones K, Wylie M, et al: Modified *Aloe barbadensis* polysaccharide with immunoregulatory activity. *Planta Med* 66:152-156, 2000
65. Kobayashi H, Matsunaga K, Fujii M: PSK as a chemopreventive agent. *Cancer Epidemiol Biomarkers Prev* 2:271-276, 1993
66. Sakai R: Epidemiologic survey on lung cancer with respect to cigarette smoking and plant diet. *Jpn J Cancer Res* 80:513-520, 1989
67. Pugh N, Ross SA, Elsohly MA, et al: Characterization of aloeride, a new high-molecular weight polysaccharide from *Aloe vera* with potent immunostimulatory activity. *J Agric Food Chem* 49:1030-1034, 2001
68. Steinmuller C, Roesler J, Grottrup E, et al: Polysaccharides isolated from plant cell cultures of *Echinacea purpurea* enhance the resistance of immunosuppressed mice against systemic infections with *Candida albicans* and *Listeria monocytogenes*. *Int J Immunopharmacol* 15:605-614, 1993
69. Kim HS, Kacew S, Lee BM: In vitro chemopreventive effects of plant polysaccharides (*Aloe barbadensis* Miller, *Leontodon edodes*, *Ganoderma lucidum* and *Coriolus versicolor*). *Carcinogenesis* 20:1637-1640, 1999
70. Davidson NE, Egner PA, Kensler TW: Transcriptional control of glutathione S-transferase gene expression by the chemopreventive agent 5-(2-pyrazinyl)-4-methyl-1,2-dithiol-3-thione (oltipraz) in rat liver. *Cancer Res* 50:2251-2255, 1990
71. Toews GB, Bergstresser PR, Streilein JW: Epidermal Langerhans cell density determines whether contact hypersensitivity or unresponsiveness follows skin painting with DNFB. *J Immunol* 124:445-453, 1980
72. Fisher MS, Kripke ML: Systemic alteration induced in mice by ultraviolet light irradiation and its relationship to ultraviolet carcinogenesis. *Proc Natl Acad Sci USA* 74:1688-1692, 1977
73. Yoshikawa T, Rae V, Bruins-Slot W, et al: Susceptibility to effects of UVB radiation on induction of contact hypersensitivity as a risk factor for skin cancer in humans. *J Invest Dermatol* 95:530-536, 1990
74. Byeon SW, Pelley RP, Ullrich SE, et al: *Aloe barbadensis* extracts reduce the production of interleukin-10 after exposure to ultraviolet radiation. *J Invest Dermatol* 110:811-817, 1998
75. Strickland FM, Darvill A, Albersheim P, et al: Inhibition of UV-induced immune suppression and interleukin-10 production by plant oligosaccharides and polysaccharides. *Photochem Photobiol* 69:141-147, 1999
76. Aragane Y, Riemann H, Bhardwaj RS, et al: IL-12 is expressed and released by human keratinocytes and epidermoid carcinoma cell lines. *J Immunol* 153:5366-5372, 1994
77. Lee KY, Park JH, Chung MH, et al: Aloesin up-regulates cyclin E/CDK2 kinase activity via inducing the protein levels of cyclin E, CDK2, and CDC25A in SK-HEP-1 cells. *Biochem Mol Biol Int* 41:285-292, 1997
78. Jin YH, Lee SJ, Chung MH, et al: Aloesin and arbutin

inhibit tyrosinase activity in a synergistic manner via a different action mechanism. *Arch Pharm Res* 22:232-236, 1999

79. Choi S, Kim KW, Choi JS, et al: Angiogenic activity of  $\beta$ -sitosterol in the ischaemia/reperfusion-damaged brain of Mongolian gerbil. *Planta Med* 68:1-6, 2002

80. Morisaki N, Watanabe S, Tezuka M, et al: Mechanism of angiogenic effects of saponin from Ginseng *Radix rubra* in human umbilical vein endothelial cells. *Br J Pharmacol* 115: 1188-1193, 1995

81. Lee KH, Hong HS, Lee CH, et al: Induction of apoptosis in human leukaemic cell lines K562, HL60 and U937 by diethylhexylphthalate isolated from *Aloe vera* Linne. *J Pharm Pharmacol* 52:1037-1041, 2000

82. Lee KH, Kim JH, Lim DS: Anti-leukaemic and

anti-mutagenic effects of di(2-ethylhexyl)phthalate isolated from *Aloe vera* Linne. *J Pharm Pharmacol* 52:593-598, 2000

83. Friesen C, Herr I, Krammer PH, et al: Involvement of the CD95(APO-1/FAS) receptor/ligand system in drug-induced apoptosis in leukemia cells. *Nat Med* 2:574-577, 1996

84. Lee CK, Han SS, Mo YK, et al: Prevention of ultraviolet radiation-induced suppression of accessory cell function of Langerhans cells by *Aloe vera* gel components. *Immunopharmacology* 37:153-162, 1997

85. Lee CK, Han SS, Shin YK, et al: Prevention of ultraviolet radiation-induced suppression of contact hypersensitivity by *Aloe vera* gel components. *Int J Immunopharmacol* 21:303-310, 1999

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