*Review Article*

# Phytoconstituents and biological consequences of *Aloe vera*: A focused review

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**Abstract**

*Aloe vera* (*Aloe barbadensis* Miller) is a perennial leaf succulent belonging to the Liliaceae family, and is called the silent healer. It is use as folk medicine, it is claimed that *Aloe vera* has wound and burn healing properties, and immunomodulatory effects. Also it is used in a commercial products because of these therapeutic attributes. 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 elucidated. A 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. The present review focuses on the detailed composition of *Aloe vera*, its various phytocomponents having various biological properties that help to improve health and prevent disease conditions.

***Keywords:*** *Aloe vera,* Aloe emodin, biological properties, phytoconstituents

## Introduction

The *Aloe* genus contains 581 accepted species, *Aloe vera* (*Aloe barbadensis Miller*) is a perennial leaf succulent xerophytes belonging to the Liliaceae family. It is cactus-like plant that grows in hot dry climates. In nature, it damaged physically by ultraviolet (UV) irradiation or by insects. 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 antiprotozoal, UV protective, immunomodulatory and wound and burn-healing promoting properties (Reynolds and Dweck, 1999). The modes of action of the biochemical constituents of *Aloe vera* is important for the determination of the most effective way of using such active species effectively and developing their applications. It is essential to lay down the relationships between the pharmacologic effects and components of *Aloe vera*. In compositional studies on the structural components of the *Aloe vera* plant leaf portions, the pulp 70-80% and the rind was found to be 20-30% of the whole leaf weight. The percentages of the rind and pulp presented as lipids (2.7% and 4.2%) and that as proteins (6.3% and 7.3%) on the basis of dry weight.

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## Biological activities of *Aloe vera*

The whole gel extract of *Aloe vera* has been represented to have various pharmacologic properties, specifically to encourage wound, burn, and frost-bite healing, in addition to having anti-inflammatory, hypoglycemic, and gastro-protective properties of those claims, *Aloe Vera*'s anti-inflammatory and wound healing has been the most extensively studied. Wound healing is studied to be composed of three overlapping actions: inflammation, new tissue formation, and matrix remodeling (Dunphy, 1974). 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, matrix-forming factors cell-migration related factors, and matrix-degradation factors (Davis et al, 1992). *Aloe vera* gel extract enthused fibroblast growth in a synovial model and also enhanced wound tensile strength and collagen turnover in wound tissue (Davis et al, 1994; Chithra et al, 1998). The *Aloe vera* gel also stimulates the levels of hyaluronic acid and sulphate in granulation tissue (Chithra et al, 1998). 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 (Davis et al,

1989), and it has been suggested that an increased oxygen access is one of the factors enhanced by *Aloe vera* gel (Lee et al, 1995). *Aloe vera* gel was found to contain an angiogenic component (Lee et al, 1998). The *Aloe vera* gel extract permitted faster healing of burns, and reestablished the vascularity of burn tissue of a guinea pig (Rodriguez-Bigaset et al, 1988; Heggers et al, 1992). 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 (Schmidt and Green spoon, 1991). Other aspects of the pharmacologic activity of *Aloe vera* gel are presented by its anti-inflammatory and immunomodulatory effects. Inflammation suppression 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 anti-inflammatory activity. The whole gel extract was found to have anti-inflammatory activity on carrageenan induced edema in rat paws (Vazquez et al, 1996). Moreover, it was found to enhance wound tensile strength and antiinflammation. Topically administered *Aloe vera* preparations inhibited inflammation in the croton oil-induced edema assay. 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 (Strickland et al, 1994). 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 1998). It is demonstrated that the administration of *Aloe vera* with pineal indole melatonin enhances the therapeutic results in patients with advanced solid tumors. *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 (Okyar et al, 2001). 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 (Ajabnoor, 1990). 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 (Davis et al, 1991; Davis et al, 1991). 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*.

**Elements of *Aloe vera***

Table 1 summarizes the components of *Aloe vera*, which are primarily glycoproteins, anthraquinones, and saccharides. 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 (Yagi et al, 1997; Choi et al, 2001). 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 aloesin, β-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.

**Table 1.** Major components of *Aloe vera*

| Saccharides | Anthraquinones | Enzymes | Vitamins |
|---|---|---|---|
| Cellulose | Barbaloin | Carboxypeptidase | B-carotene |
| Glucose | Isobarbaloin | Catalase | Choline |
| Mannose | Emodin | Cyclooxydase | folic acid |
| Aldopentose | Ester of Cinnamic Acid | Lipase | α-tocopherol |

**Anthraquinones**

The allegedly, pharmacologically active anthraquinones (Figure 1) of *Aloe vera* arealoin, aloe-emodin, barbaloin, and emodin (Table 1). Their therapeutic claims are a purgative action, anti-inflammatory activity, antiprotozoal action, antioxidant activity and so on (Table 2). Aloe-emodin and emodin showed synergistic effects with rheinanthrone during purgative activity in mice (Yagi and Yamauchi, 1999). The purgative action of barbaloin is induced by *Eubacterium sp,* which is capable of transforming barbaloin to aloe-emodinanthrone. Aloe-emodinquinone pretreatment reduced the acute liver injury induced by carbon tetrachloride, (Arosio et al, 2000) and aloe-emodin appears to protect against hepatocyte death and the inflammatory response that occurs subsequent to lipid peroxidation (Malterud et al, 1993). Antioxidant and

radical scavenging activity of aloe-emodin was suggested as a protection mechanism against peroxidation of linoleic acid. 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 (Camacho et al, 2000; Wang et al, 1998) *Aloe-emodin* may act like a noncompetitive inhibitor of arylamine Nacetyltransferase activity, thereby decreasing effects of arylamine carcinogens in inducing carcinogenesis (Cera et al, 1998). In addition, antibiotic factors are released by the healing tissues in response to aloe treatment. Aloe-emodinpossesses 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 (Wolfle et al, 1990). However, there are other controversialobservations. Aloe-emodin was found to have cell death or apoptosis-inducing effect in human lung squamous cell carcinoma (Lee et al, 2001; Lee, 2001) and to selectively inhibit human neuroectodermal tumor growth in an *in vivo* experiment (Pecere et al, 2000; Brusick and Mengs, 1997). In spite of these biologic activities, anthraquinones also have harmful effects, such as genotoxic, mutagenic, and tumor promoting effects (Muller et al, 1996; Grimminger and Witthohn, 1993). 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.

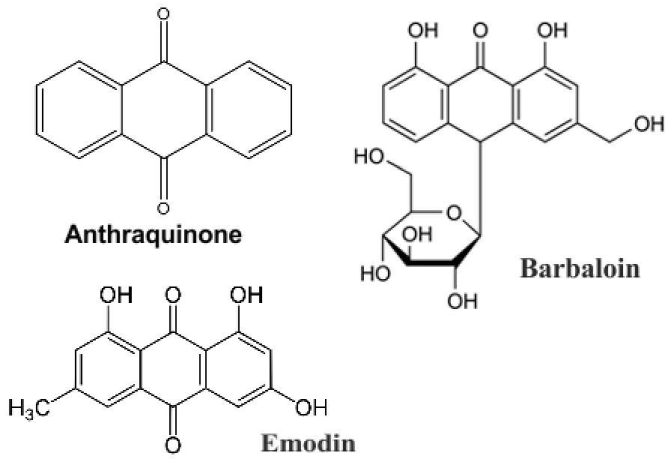


**Figure 1.** Chemical Constituents of *Aloe vera*

**Table 2.** Alleged Pharmacological Activities of *Aloe vera* Components

| Components | Alleged pharmacological activities |
|---|---|
| Barbaloin | Purgative |
| Aloe-Emodin, emodin | Purgative, cell proliferation, anticancer, antiprotozoal, antibacterial |
| Mannose-6- Phosphate | Wound healing |
| Aloesin | Inhibition of melanin synthesis |
| B-Sitosterol | Antiinflammation, angiogenesis, |
| Polysaccharide | Immunomodulation |

**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*. 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. Fractions prepared from *Aloe vera* gel contain lectin-like substances that promote the growth of normal human cells like human fibroblasts (Danof and McAnalley, 1983). Yagi and co-workers reported on the cell-proliferating activity of a 29 kDa glycoprotein composed of two 14kDa subunits. This was found to enhance the proliferation of baby hamster kidney cells and normal human dermal fibroblasts. Furthermore, at the immune histochemical 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 (Gipson et al, 1984, Yagi et al, 1985;, Heggers et al, 1996; Utsunomiya, 1998). Winters et al, 1981 reported that lectins are present in the gel portion of *Aloe vera* leaves. Koike et al, 1995 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. Davis et al, 1994 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 (Grey et al, 1991). 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 (Ro et

al, 2000). It reduced histamine release and promoted the synthesisand 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.

**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* (Davis et al, 1994). 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 anti-inflammatory ingredient in *Aloe Vera*. Mice receiving 300 mg/kg of mannose-6-phosphate had improved wound healing over saline controls. Grey et al, 1991 suggested that mannose-6-phosphate linked to a protein produce even greater wound-healing effects. The ability of *Aloe vera* to stimulate the immune system is attributed to polysaccharides present in the *Aloe vera* gel. 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 (Qiu et al, 2000) 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 (Kobayashi et al, 1993; Sakai, 1989). A high molecular weight polysaccharide (*aloe ride*) was found to have potent immune stimulatory activity, and was found to induce the expression of mRNAs encoding IL-1 β and TNF- α (Pugh et al, 2001). These polysaccharides may exhibit antitumor and antiviral activities through enhanced immune attack and immune modulation (Steinmuller et al, 1993). 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. Kim et al, 1999 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 (Davidson et al, 1990). The labile natures of factors that prevent immune suppression vary in different gel extract preparations and is possibly influenced by the manufacturing process used (Byeon et al, 1998). 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 unfractionated leaf gel from *Aloe vera*.

**Conclusion**

*Aloe vera* contains many physiologically active substances that have effective anti-inflammatory, 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*. Since ages, Aloe species have been exploited for various medicinal efficacies because of their phyto-chemical constituents. Having therapeutic, rejuvenating and health enhancing properties, *Aloe vera* gel is widely used in food, healthcare and medicinal industries. 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.

**Conflicts of interest**

**The author quotes no conflict of interest.**

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