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MULTIPLE BIOLOGICAL ACTIVITIES OF *Aloe barbadensis* (ALOE VERA): AN OVERVIEW

Shilpi Agarwal* , T.R.Sharma

Faculty of Pharmacy, R.P.E.T.G.I, Karnal Haryana, India

ABSTRACT

In ayurveda, a tradional system of medicine, aloe vera (Aloe Barbadensis) is commonly used in sunburn, minor cuts, insect bites and used as wound healing, anti-inflammatory, antiviral, antitumor, laxative and in the treatment of frostbite and psoriasis. The whole plant as well as its specific parts (leaves, roots), plant extracts and its active constituent mucopolysaccharides [MPS] (long chain sugars) have been widely used as antiseptic, anti-inflammatory, anti-viral, anti-tumor and immunomodulator. Several epidemiological, clinical and experimental studies have demonstrated the multiple biological activities of aloe vera. This review summarizes the most interesting studies on the various biological activities of aloe vera.

Keywords: Mucopolysaccharides, Immunomodulator

***Corresponding Author's E-mail: -** agarwalgshilpi@yahoo.com

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INTRODUCTION

Aloe barbadensis Miller (also known as Aloe vera), a member of the family Liliacae, The genus *Aloe (*Asphodelaceae), with nearly 420 species confined mainly to Africa.

***Aloe Vera* Taxonomy:**

Kingdom: Plantae
Order : Asparagales
Family : Asphodelaceae
Genus : *Aloe*
Species : *Aloe vera*

Aloe has been used medicinally for several thousands of years in many cultures—from ancient Egypt, Greece, and Rome to China and India. The plant has many common names and is often referred to as aloe vera, burn plant, first-aid plant, or medicine plant. Its name is most likely derived from the Arabic word Alloeh, meaning "shining bitter substance.[1] Aloes are thought to have originated in tropical Africa but are now cultivated in warm climate areas of Asia, Europe, and America. Aloe has been extensively cultivated in the Caribbean islands and in Mexico since the early 1800s.[2] In the U.S., it is grown commercially in the Rio Grande valley of Texas, southern California, and Florida. Aloe plants can withstand high temperatures and long periods of drought, due to their ability to store water in their succulent leaves. On the other hand, they are very sensitive to freezing temperatures, which can damage or kill the plants.[3,4]

CHEMICAL COMPOSITION AND ACTIVE CONSTITUENTS

The aloe plant is the source of two herbal preparations: aloe gel (AG) and aloe latex. Aloe gel is often called "aloe vera and refers to the clear gel or mucilaginous substance produced by parenchymal cells located in the central region of the leaf. Diluted aloe gel is commonly referred to as "aloe vera extract. The gel is composed mainly of water (99%) and mono- and polysaccharides (25% of the dry weight of the gel). The most prominent monosaccharide in AG is mannose-6-phosphate, and the most common polysaccharides are called gluco-mannans (beta-(1,4) acetylated mannan). They are long-chain sugars containing glucose and mannose. A prominent gluco-mannan named acemannan has been isolated and is being marketed as Carrisyn. Recently a glycoprotein with antiallergic properties, called alprogen, was isolated from AG. In addition, a novel anti-inflammatory compound, C-glucosyl chromone, has recently been isolated from AG.[5]

Aloe gel also contains lignan, salicylic acid, saponins, sterols, and triterpenoids. The fresh gel contains the proteolytic enzyme carboxypeptidase (which breaks down bradykinin), glutathione peroxidase, as well as several isozymes of superoxide dismutase.[6] The gel also contains vitamins A, C, E, B12, thiamine, niacin and folic acid, as well as the minerals sodium, potassium, calcium, magnesium, manganese, copper, zinc, chromium, and iron.[7,8]

PHARMACOLOGICAL ACTIVITIES

The various effects of aloe vera are documented in traditional as well as in recent scientific literature. It is widely used in sunburn,minor cuts, scrapes, moisturizer,psoriasis,shingles, and others associated with itching; in addition, cuts, abrasions and burns are said to be benefited from topically applying it.

WOUND HEALING

Aloe gel has long been used both externally and internally for its beneficial effects in the wound-healing process.[9, 10] It is most often included in topical formulations (ointment, cream, or lotion), but evidence also supports its effectiveness when taken orally. At least part of AG's beneficial effect on the skin likely is due to its moisturizing effect. Also, it may leave a protective layer on the skin after drying, possibly providing some protection to the wound. Both topical and oral AG have been shown to significantly stimulate collagen synthesis in experimental dermal wounds in rats[11]. Aloe gel not only increased collagen content of the wound but also changed collagen composition (more type III).

TABLE: 1 CONSTITUENT, PROPERTIES, ACTIVITIES OF ALOE VERA

Constituents	**Number & Identification**	**Properties & Activity**	**Comment**
Amino Acids	Provides 20 of the 22 human required amino acids & 7 of the 8 essential ones	Provides the basic building blocks of proteins in the production of muscle tissue etc	The 8 essential amino acids are those the human body cannot manufacture
Anthraquinones	Provides 12 anthraquinones: Aloe emodin, Aloetic Acid, Aloin, Anthracine, Antranol, Barbaloin, Chrysophanic Acid, Emodin, Ethereal Oil, Ester of Cinnamonic Acid, Isobarbaloin, Resistannol.	In relatively small concentrations together with the Gel fraction they provide Analgesic, Antibacterial, Antifungal & Antiviral activity. In high concentration on their own they can be toxic.	Traditionally known as laxatives.The antraquinones are found in the sap. The anthraquinone derivatives (anthrones & chromones) comprise the phenolic fraction of the sap. The primary sap component is Aloin/Barbaloin anthrone derivative
Enzymes	Provides 8 enzymes: Aliiase, Alkaline Phosphatase, Amylase, Carboxypeptidase, Catalase, Cellulase, Lipase, Peroxidase	Helps breakdown of food sugars and fats aiding digestion & enhancing nutrient absorbtion	
Hormones	Auxins & Gibberellins	Wound Healing & Anti-inflammatory	
Lignin	Cellulose based substance	Thought to provide penetrating power in Aloe vera skin preparations and may act as a carrier for other components	
Minerals	Provides 9 minerals: Calcium, Chromium, Copper, Iron, Magnesium, Manganese, Potassium, Sodium, Zinc	Essential for good health and is known to work in certain combimation with each other, vitamins and other trace elements	
Salicylic Acid	Aspirin like compound	Analgesic	
Saponins	Glycosides	Soapy substance both cleansing and antiseptic	
Sterols	Provides 4 main plant steroids: Cholesterol, Campesterol, Lupeol, ß Sitosterol	Anti-inflammatory agents. Lupeol also possesses antiseptic and analgesic properties	
Sugars	Monosaccharides: glucose & fructose Polysaccarides: gluco-mannans / polymannose	Anti-inflammatory action Anti-viral, immune modulating activity of Acemannan	The long chain gluco-mannans are absorbed intact by the pinocytotic process of certain cells lining the digestive tract.
Vitamins	A, C, E, B, Choline, B12, Folic Acid	Antioxidant(A,C,E): neutralises free radicals	B's & Choline involved in amino acid metabolism, B12 required for production of red blood cells, Folic Acid in the development of blood cells

In addition, it increased the degree of collagen crosslinking.[12]Aloe gel not only increased collagen content of the wound but also changed collagen composition (more type III). In addition, it increased the degree of collagen crosslinking.[12] In an earlier study, the investigators also demonstrated an increased synthesis of hyaluronic acid and dermatan sulphate in the granulation tissue of a healing wound following oral or topical AG treatment. Both studies support an earlier trial demonstrating that both oral (100 mg/kg/day) and topical (25% AG) treatment (two months) of biopsy punch wounds in mice resulted in a significant (50%?3%) reduction in wound diameter.10 Similar beneficial effects of topical AG have been demonstrated in a skin-wound rat model. Aloe gel treatment accelerated wound contraction and increased the breaking strength of resulting scar tissue, due to increased collagen content and degree of crosslinking. In order to identify which constituents of AG are responsible for wound-healing effects, Davis and colleagues tested the effects of mannose-6-phosphate in a mouse-wound model system.[13] An oral dose of 300 mg/kg resulted in significant wound healing, similar to that seen with AG. However, not all animal studies have shown positive results. In one study, various topical agents were tested for their effects on wound contraction and rate of re-epithelialization in full-thickness excisions in a porcine mode; AG failed to show any beneficial effects.[14]

AG studies in humans are more limited, and the results generally are not as positive as those from the aforementioned animal studies. In one positive study, AG (when added to a polyethylene oxide gel wound dressing) was shown to accelerate wound healing following full-face dermabrasion. By day six, re-epithelialization was complete at the AG-treated sites. However, soon after this study a report emerged of four patients who experienced severe burning sensations and dermatitis upon application of topical aloe gel following dermabrasion. An acemannan-containing gel (Carrisyn Gel Wound Dressing) was recently shown to be no more effective than a standard saline gauze dressing in the treatment of pressure ulcers. In another study, a similar AG dermal wound gel was actually shown to significantly delay wound healing in surgical wounds following cesarean delivery or laparotomy.

EFFECTS ON BURNS

Several animal studies and a clinical trial have assessed the effectiveness of AG in the treatment of skin burns. One study looked at full-thickness burns in guinea pigs. Aloe gel promoted complete healing of burn wounds within 30 days, compared to 50 days in the control group. In contrast, a similar study in guinea pigs published the same year showed that AG was less effective in treating second-degree burns when compared to standard 1% silver sulfadiazine cream.[15] Wound re-epithelialization, wound contraction, and formation of granulation tissue occurred more slowly in the AG-treated animals. In another study, AG was found ineffective in treating hydrofluoric-acid induced burns in rats. In a human study, 27 patients with partial thickness burn wounds were treated with topical AG or a standard Vaseline gauze. The average healing time was 18.19 days in the Vaseline-gauze treated wounds and 11.89 days in the AG-treated wounds. Histological examination showed early epithelialization in the AG-treated skin areas.[16]

EFFECTS ON SKIN EXPOSURE TO UV AND GAMMA RADIATION

Some of the first scientific studies on the effectiveness

of AG were performed during the 1930s and involved protection of the skin against radiation damage. For the most part, these studies were inconclusive. Interestingly, recent evidence has supported a protective benefit of AG against several forms of radiation damage to the skin. An acemannan-containing topical gel was demonstrated to reduce skin damage following exposure to gamma radiation in mice. The results were best in animals who received the gel treatment for at least two weeks beginning immediately after irradiation. A protective effect also was documented in mouse skin exposed to soft x-irradiation. Investigators found that an antioxidant protein, metallothionein, was induced in the skin and liver within 24 hrs of AG administration. Following x-ray exposure, AG was found to scavenge hydroxyl radicals and prevent suppression of superoxide dismutase and glutathione peroxidase in the skin.

Several additional studies in mice and in epidermal cell culture have demonstrated an immunomodulatory effect of AG in protecting skin cells from the damaging effects of UVB radiation.[17] UVB radiation is known to suppress the ability of Langerhans cells in the epidermis to support antibody primed T-cell mitogenesis. In one study, aloe gel prevented this UVB-mediated suppression within the first 24 hrs of irradiation in murine epidermal cell culture.[18, 19] Immunomodulatory activity was found to reside in a number of low molecular weight compounds present in AG. A more recent study reports the isolation of these small immunomodulatory substances from AG.[20] Topical application of these compounds prevented UVB-induced immune suppression in mouse skin. Further work in this area has confirmed these observations and has demonstrated how AG-derived immunoprotective factors likely work. Presumably, UV-induced suppression of delayed type hypersensitivity is prevented by reducing the production and release of skin keratinocyte derived immunosuppressive cytokines, such as interleukin-10 (IL-10).[21] Another study demonstrated that AG's Treatment of Frostbite and Psoriasis prevention of UV-induced immune suppression did not involve prevention of UV-induced DNA damage or an acceleration of the repair of DNA.

Several animal studies support the clinical use of AG in treating frostbite tissue damage. Heggars and associates utilized an experimental rabbit ear model to demonstrate the effectiveness of AG, as well as that of several inhibitors of arachidonic acid metabolism (e.g., aspirin and methylprednisolone). In control animals, no tissue survival was seen. In contrast, AG treatment resulted in 28.2% tissue survival compared to 22.5% and 12.5% with aspirin and steroid, respectively. The investigators concluded that the progressive dermal ischemia occurring during frostbite could be reduced by inhibiting the production of prostaglandins and thromboxanes from arachidonic acid. A more recent study supports these observations. Systemic pentoxifylline and topical AG cream were both found to improve tissue survival in the frostbitten ears of New Zealand rabbits. Using both agents together further increased tissue survival. A recent double-blind, placebo-controlled study in 60 psoriasis patients evaluated the efficacy of treatment with topical AG.[22] PG extract (0.5% in a hydrophilic cream) was administered three times daily for five consecutive days each week for 16 weeks. At the end of the study AG had significantly reduced lesions, decreased erythema, and lowered PASI (psoriasis area and severity index) scores in 25 out of the 30 patients in the treatment group.

HYPOGLYCEMIC AND HYPOLIPIDEMIC ACTIVITY

Processed Aloe vera gel (PAG) when administered orally for 8 weeks reduced circulating blood glucose concentrations to a normal level in diet-induced obesity mice. The antidiabetic effects of PAG were

confirmed by intraperitoneal glucose tolerance testing. PAG lowered blood glucose level by decreasing insulin resistance. The administration of PAG also lowered triacylglyceride levels in liver and plasma. Histological examinations of
periepididymal fat pad showed that PAG reduced the average size of adipocytes.[23] This shows the Hypoglycemic and hypolipidemic effects of processed Aloe vera gel.

ANTI-INFLAMMATORY EFFECTS

Several animal studies have been undertaken since 1989, clearly demonstrating the anti-inflammatory activity of AG. One study found that an aqueous extract of AG decreased carrageenan-induced edema in a rat hind-paw.[24,25,26] Further, the AG extract reduced prostaglandin E2 production from [14C] arachidonic acid via inhibition of cyclooxygenase. In a series of experiments conducted, Davis and colleagues demonstrated the anti-inflammatory action of oral and topical AG preparations in various animal models of inflammation.[27] In their earliest study they reported a 47% reduction in swelling in the croton oil-induced edema assay in rats after topical administration of AG.[28] In a later study they demonstrated an anti-inflammatory response to AG in an inflamed synovial pouch model in rats. AG reduced the vascularity and swelling in the inflamed pouch by 50%. The investigators also noted a 48% reduction in the number of mast cells in the synovial fluid of the pouch. Also of interest, they found an increased number of fibroblasts following treatment with aloe gel. C-glucosyl chromone is the anti-inflammatory compound recently isolated from AG extracts.[29] The substance was shown to be similar in potency to hydrocortisone when tested in a mouse ear bioassay.Many claims have been made throughout the years regarding AG's ability to support and enhance the immune system. Experimental evidence is now accumulating documenting immune-stimulating constituents present in AG. One of the first studies in the early 1980s demonstrated that a partially purified AG extract from Aloe vahombe acted as a nonspecific immunostimulant, protecting mice against infection from various bacteria and fungi. The AG extract had to be administered two days before exposure of the mice to the pathogenic agent to be effective. Later in the 1980s, acemannan isolated from AG was shown to increase the response of lymphocytes to antigens in an in vitro study. This helped explain the many reports of acemannan's apparent antiviral effect. In later studies, a highly purified form of acemannan derived from AG stimulated the synthesis and release of interleukin-1 (IL-1) and tumor necrosis factor from peritoneal macrophages in mice that had previously been implanted with murine sarcoma cells. These cytokines in turn initiated an immune attack on the sarcoma cells that resulted in necrosis and regression of the cancerous cells. These effects resulted in an increased survival of the sarcoma-implanted mice. In another study, acemannan stimulated the production of nitric oxide in cultures of chicken macrophages. Still another study demonstrated that several low molecular weight compounds isolated from AG are capable of inhibiting the release of reactive oxygen free radicals from activated human neutrophils. This inhibition does not appear to affect the phagocytic activity of neutrophils but may protect tissues from excessive oxidative damage from free radicals.

Early this year, a study was published reporting the isolation and partial purification of an antiallergic compound called alprogen from AG extracts. Alprogen was shown to inhibit the antigen/antibody-mediated release of histamine and leukotriene from mast cells. The postulated mechanism of this effect was via inhibition of Ca^{2+} influx into mast cells.

ANTIVIRAL AND ANTITUMOR ACTIVITY

Most of the reported antiviral and antitumor effects of AG likely are due indirectly to the stimulation of the immune system, as discussed previously. However, one study reports that anthraquinones, which are present in aloe latex, have direct virucidal effects. The anthraquinone aloin was shown to inactivate various

enveloped viruses, such as herpes simplex, varicella-zoster, and influenza. Although anthraquinones only appear in AG as a contaminant, low concentrations present in some preparations could have significant antiviral activity.[30]

Several recent studies have demonstrated direct inhibitory effects of AG on both tumor initiation and promotion. A polysaccharide fraction of AG inhibited the binding of benzopyrene to primary rat hepatocytes and thus prevented the formation of potentially cancer-initiating benzopyrene-DNA adducts. This effect was also demonstrated in vivo, where adduct formation was reduced in various organs. A follow-up study published in 1999 by the same investigators showed that several other plant-derived polysaccharides were also able to block benzopyrene-DNA adducts. They also reported in this study an induction of glutathione S-transferase and an inhibition of the tumor-promoting effects of phorbol myristic acetate by AG. These two studies suggest a possible benefit of using aloe gel in cancer chemoprevention. to be similar in potency to hydrocortisone when tested

ANTITUMOR AND ANTIOXIDANT ACTIVITY

The active principles of A.vera exhibited significant inhibition on Ehrlich ascite carcinoma cell (EACC) number, when compared to control group, in the order arbaloin>aloe-emodin > octapeptide > aloesin. In trypan blue cell viability assay a significant concentration-dependent cytotoxicity against acute myeloid leukemia (AML) and acute lymphocytes leukemia (ALL) cancerous cells. In MTT cell viability test, aloe-emodin was found to be active against two human colon cancer cell lines (i.e. DLD-1 and HT2), with IC(50) values of 8.94 and 10.78 microM,. Treatments of human AML leukemic cells with active principles (100 microg ml(-1)) resulted in varying intensities of internucleosomal DNA fragmentation, hallmark of cells undergoing apoptosis. Treatment of EACC tumors with active principles resulted in a significant elevation activity of key antioxidant enzymes (SOD, GST, tGPx, and LDH). This results proves the antitumor and antioxidant properties of Aloe vera.[31]

LAXATIVE EFFECTS OF ALOE LATEX

Anthraquinones present in aloe latex function as potent stimulant laxatives. Aloe latex is typically sold as an incapsulated dried powder. The substance is still listed in the U.S. Pharmacopoeia and is recognized by the FDA, as well as in several other European countries, as an effective laxative. Studies in rats have shown that aloe latex increases intestinal water content, stimulates mucus secretion, and increases intestinal peristalsis. Long-term use of the substance could result in electrolyte imbalances, especially depletion of potassium salts.

USES Moisture

Moisture is important for keeping the collagen network supple. It is the condition of the skin's collagen, NOT the facial muscles that cause lines and wrinkles. With age, the collagen network tends to weaken, to lose moisture and resiliency, thus causing the skin to lose its tone and suppleness. It is therefore very important to start caring for the skin at a young age. Ageing skin needs extra care and nourishment.

Elasticity

To determines the condition of the skin to a large extent. Wrinkles and sagging occur when the skin loses its elasticity. To test the elasticity of your skin do the following:-

(i)take a small portion of the facial or neck skin between the thumb and forefinger,

(ii) give the skin a slight outward pull, and

(iii) if the skin returns immediately to its normal shape, the elasticity is good, if not, you need help.

Regeneration

Regeneration occurs continuously as dead skin is shed and is replaced by new cells pushed to the surface. The quicker the process, the quicker the skin regenerates. Just below the skin's outer layer lies the dermis which carries nourishment to the skin. Recent test results have shown Aloe Ferox gel to have a rapid vasodilatory effect. The more nutrients, the quicker the skin regenerates.

MODE OF ACTION

It is surprising that the evident healing effects of aloe vera can be produced by such a small quantity of solid material. Some people believe that there is a synergistic action between all the component ingredients, giving a result which is greater than the sum of the individual actions. The combined action of all herbal preparations taken from whole stems, roots, leaves or fruits containing huge numbers, but very small amounts of phyto-chemicals, stretches the boundaries of the conventional medicinal paradigm.

In all allopathic (orthodox) medicine, the practice is to isolate, in a chemically pure form, the biologically active substance of the constituent ingredients. These extracted drugs must be uniform in their composition in order to demonstrate a consistent physiological effect. Perhaps there is some truth in an ancient Ayurvedic text from India: 'Extracting drugs from a part of the plant is taking out the intelligence and throwing away the wisdom.' Whole plant preparations; though less potent, are generally considered to be safer with fewer side effects.

The evidence suggests that the primary sites of action for aloe vera are:

- Epithelial tissues — the epithelium is the layer of cells which covers the surface of the body or lines a cavity that communicates with the surface. The skin, the largest organ of the body, is also the largest epithelial surface — but other epithelial tissues line the nose, sinuses, lungs, mouth, oesophagus and alimentary tract, as well as the genital tract. This action on surfaces and membranes, rather than solid organs, may account for some of the healing properties of aloe vera.

- The immune system — here, aloe vera exerts an effect on the cytokine system, resulting in immunomodulation (Green 1996, Marshall et al 1993, Winters 1993). In the US, the polymannose sugar has been extracted by Carrington Laboratories and its product, Carrisyn, has been licensed to treat the onchogenic retroviral infection which causes leukaemia in cats. It is currently being tn-aIled in human retroviral infection (AIDS) where it has been found to be synergistic with Zidovudine.

BURNS AND LEG ULCERS

Aloe vera appears to speed up the healing of damaged epithelial tissue in burns and leg ulcers by:

- Providing essential micronutrients
- An anti-inflammatory effect
- An antimicrobial effect
- The stimulation of skin fibroblasts (Danhoff and McAnally 1983).

Medicinal Uses

The Plant is bitter, sweet, cooling, anthelmintic, aperient, carminative, deobstruent, depurative, diuretic, stomachic, emmenagogue, ophthalmic and alexeteric. The juice is used in dyspepsia, amenorrhoea, burns, colic, hyperadenosis, hepatopathy, splenopathy, skin diseases, constipation, spanomenorrhea, vitiated conditions of vata and pitta, abdominal tumours, dropsy, carbuncles, sciatica, lumbago and flatulence.

The aloe is also used for helminthiasis in children and is a purgative, anthelmintic and emmenagogue. It is used for local application in painful inflammations, chronic ulcers and catarrhal and purulent ophthalmia.

COSMETIC USES

Aloe Vera has unique, anti-aging formulations to maintain healthy, fresh-looking skin. The aloe plant's healing powers are most widely touted for being able to treat skin conditions. These conditions include psoriasis, shingles, and others associated with itching; in addition, cuts, abrasions and burns are said to benefit from topically applying the leaf's gel to the affected areas.[32]

The uses of aloe vera -- that is, its efficacy -- stem from its active ingredients. These substances harbor anti-inflammatory properties, which may explain why it has been reported to alleviate the pain and swelling associated with itches and burns. Aloe Vera has unique, anti-aging formulations to maintain healthy, fresh-looking skin. Its Cosmetic action is antinflammatory, soothing, toning, moisturizing, and protective.[33]

During the end of the seventies Aloe vera gel became very popular in the USA as a moisturizing ingredient in cosmetics and its popularity has grown to such an unprecedented extent that it is now the most widely used ingredient in skin care products and can be found on the ingredient list of virtually all cosmetic products. Even dog or cat creams contain Aloe and you can now buy tissues impregnated with Aloe.

Also in the Far East Aloe is a popular ingredient in skin care products as well as in health drinks. Now its popularity is also coming to Europe where more and better known companies have started to add Aloe to their established products and also introduced special Aloe vera product lines.

The great success of Aloe as a commodity for use in nutritional foods and cosmetics is due to the proper stabilizing procedures that enable processors to store and ship the Aloe Gel without fear of spoilage throughout the market places of the world. Research conducted around the world leaves little doubt that certain biochemical properties of Aloe will be proven facts. Such attributes as moisturizing and penetrating properties are known, but the attributes such as its healing abilities and analgesic action to bacterial activity has not been clearly defined and documented through properly controlled scientific research and testing.

The gel stimulates cell growth and as such enhances the restoration of damaged skin. It moisturizes the skin because it has a water holding capacity. This moist on the skin also has a cooling effect. As a drink it protects the mucous membrane of the stomach especially when irritated or damaged. Aloe Vera Gel consists for 99.3% of water. The remaining 0.7% are the solids that consist for a large part of polysaccharides of the glucose and mannose type. Together with the enzymes and amino-acids in the gel they give the gel the special properties as a skin care product.[34,35]

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TOXICITY AND ADVERSE REACTIONS

Aside from occasional allergic skin reactions in a small number of people, AG used topically has few if any side effects.[37] Several patients who applied AG topically following dermabrasion reported burning sensations and development of dermatitis on the face. Because of possible contamination by anthraquinones, oral AG may cause symptoms of abdominal cramps and diarrhea. There have also been several reports of AG lowering plasma glucose levels in laboratory animals and in humans. It was postulated in one study that this hypoglycemic effect was mediated through the stimulation and release of insulin from the beta-cells of the pancreas.[38] Therefore, caution should be exercised when using oral AG in patients with diabetes.

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