

## REVIEW

### Chemical Constituents, Biological Activity and Agricultural Cultivation of *Aloe vera*

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(Received: 8 August 2012;

Accepted: 16 May 2013)

AJC-13505

*Aloe vera* is a perennial, drought-resisting and succulent plant belonging to the Liliaceal family, which historically has been used for a variety of medicinal purposes. Scientific investigations on *A. vera* have gained more attention the last several decades due to its reputable medicinal properties. After describing *Aloe* in a botanical point of view, the papers relating with the chemical composition of skin and gel of *Aloe*, particularly describes the gel of *Aloe*. The chemical analysis reveals that *A. vera* contains various carbohydrate polymers, notably glucomannans, along with a range of other organic and inorganic components. The heterogeneous nature of *Aloe* products may contribute to the diverse biological and therapeutic activities that have been observed including promotion of wound healing, antifungal activity, hypoglycemic or antidiabetic effects, antiinflammatory, anticancer, immunomodulatory and gastroprotective properties etc. On the other hand, different factors also affecting the chemical composition of the gel, such as species and variety, climatic and soil conditions, cultivation methods and stress adaptation are enumerated and discussed. In this review, the historical uses, the botany, the chemistry, pharmacological activity and clinical trial, adverse effects and agricultural cultivation of *A. vera* will be described. This paper concludes that it still remains uncertain as to which of the component(s) is responsible for these physiological properties, more researches are needed to confirm the therapeutic and beneficial effects and to definitively clarify the myth surrounding *Aloe vera*. In addition, promoting its large-scale cultivation such as beach planting and seawater irrigation is also a meaty theme to study and debate.

**Key Words:** *Aloe vera*, Chemical constituent, Biological activity, Agricultural cultivation.

## INTRODUCTION

The *Aloe vera* plant has been known and used for its health, beauty, medicinal and skin care properties since 6000 years B.C. Its applications have been recorded in several cultures for millennia: India, Egypt, Greece, Rome and China<sup>1</sup>. In biblical times the Egyptians hailed *A. vera* as the plant of immortality. Ancient Egyptian papyrus and Mesopotamian clay tablets described *aloe* as useful in curing infections, treating skin problems and as a laxative<sup>2</sup>. *Aloe* was used by Hippocrates and Arab physicians and was carried to the Western Hemisphere by Spanish explorers. Further, historians have recorded that Alexander was persuaded by Aristotle to conquer the island of Socotra in east Africa, to obtain *aloe* which was known by Greeks as a wound healing agent for his soldiers<sup>3</sup>. *A. vera* still has an important role in the traditional medicine of many contemporary cultures. The Chinese call it their elixir of youth and describe *aloe*'s skin and the inner lining of its leaves as a cold, bitter remedy which is downward draining and used to clear constipation due to accumulation of heat; the gel is

considered cool and moist<sup>4</sup>. In Ayurvedic medicine, the traditional medicine of India, *aloe* is used for a variety of conditions, particularly for their cathartic, stomachic, emmenagogic and anthelmintic properties<sup>5,6</sup>; it is used topically, often in combination with licorice root, to treat eczema or psoriasis. In Arabian medicine, the fresh gel is rubbed on the forehead as a headache remedy or rubbed on the body to cool it in case of fever, as well as being used for wound healing, conjunctivitis and as a disinfectant and laxative<sup>7</sup>. In all these countries *A. vera* is an introduced species, but has been rapidly adopted as an essential part of local material medica. The first reference to *A. vera* in English was a translation by John Goodyew in A.D. 1655 of Dioscorides' Medical treatise *De Materia Medica*<sup>8</sup>. By the early 1800s, *A. vera* was used as a laxative in the United States, but in the mid-1930s, a turning point occurred when it was successfully used to treat chronic and severe radiation dermatitis<sup>8</sup>.

Currently, *A. vera* gel was widely used species both commercially and for their therapeutic properties. In 2008 Americans have spent almost 40 billion dollars on functional

foods, drinks and supplements for the improvement of their appearance as well as in providing energy and added nutrition to handle health issues such as hypercholesterolemia and diabetes. *A. vera* products are among the popular ones for these applications<sup>9</sup>. Today, the *A. vera* industry is flourishing and the gel is used in many products such as fresh gel, juice and other formulations for health, medicinal and cosmetic purposes<sup>10</sup>. 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. Simultaneity, it is essential to establish the relationships between the phytochemical of *A. vera* and its agricultural cultivation. However, many authors' reviews<sup>2,3,5,6,9-20</sup> describe the phytochemical and pharmacological of *A. vera* gel, few researchers focus on the chemical constituents and biological activities of *A. vera* skin and its agricultural cultivation. Therefore, this review addresses the following aspects: (1) The analysis essentially deals with the botany; (2) Chemical composition of the skin and gel of Aloe; (3) Pharmacological activity of *A. vera* skin and gel; (4) Agricultural cultivation and (5) Concluding remarks.

The review aims to provide a succinct resume of information regarding *A. vera* to serve as a reference for further investigations about this potential ingredient to develop an effective method for exploring of *A. vera* leaf. Besides, agronomy of *A. vera* was described in this paper providing technology information for researchers who concentrate on the accumulation of the active ingredients and agricultural cultivation.

**Botany:** Aloes are members of the Liliaceae which are tropical plants easily grown in hot and dry climates and are mostly succulents with a whorl of elongated, pointed leaves and the genus Aloe comprises 548 accepted species and sub-species, of which at least one-third are documented as having some utilitarian value<sup>21</sup>. However, *A. vera* is the most widely domesticated and commercially cultivated<sup>19</sup>.

*A. vera* is a shrubby or arborescent, perennial succulents plant of liliacea family with turgid pea-green leaves joined at the stem in a rosette pattern and are characterized by stemless large, thick, fleshy leaves that are lance shaped and have a sharp apex and a spiny margin<sup>14</sup>. The name, Aloe, is derived from the Arabic word "Alloeh" or Hebrew "halal" meaning bitter shiny substance, while "vera" in Latin means "true"<sup>9,16</sup>. But the nomenclature of *A. vera* has been very confused, most reference books regard *Aloe barbadensis* Mill as correct species name and *Aloe vera* (L.) Burm f. as a synonym. However, according to the International Rules of Botanical Nomenclature, *Aloe vera* (L.) Burm f. is the legitimate name for this species<sup>22-24</sup>. The genus Aloe has also been placed taxonomically in a family called Aloaceae<sup>25</sup>. Nowadays, *Aloe vera* is popularly known as *Aloe barbadensis* by taxonomists.

*A. vera* is a spiky cactus like xerophytes with fleshy leaves arising in a rosette from a short stem. In young plants the leaves appear at ground level, but the stem can grow up to 25 cm long in older plants. There may be 15-30 leaves per plant, the young leaves more or less erect and the older, lower ones more spreading. And the leaves are a kind of bright green colour, with irregular whitish spots on both sides. The leaves are

covered with thick cuticle, beneath which epidermis and mesophyll are present. Later is differentiated in upper chlorenchyma and lower parenchyma. The inflorescence is a dense raceme borne on a peduncle some 30-50 cm long arising from the centre of the leaf rosette. The flowers are pendent, with a tubular yellow perianth around 2 cm long. As the rosette mature, the leaves are up to 0.5 m long and 8-10 cm across at the base, tapering to a point, with saw-like teeth along their margins. In transverse section the leaves are slightly concave on their adaxial surface, while the lower, abaxial surface is markedly convex, successive leaves have fewer whitish spots and grey-greenish in colour<sup>5,10</sup>. As the plant matures when it is *ca.* 4 years old and has a life span of *ca.* 12 years, thick fibrous root which produces large basal leaves, usually 12-16 per plant, weighing up to 1.5 kg<sup>9,10</sup>. The flower stalk grows up to 1.5 m in height. The fruit is a triangular capsule containing numerous seeds<sup>9</sup>.

The epidermis of the leaves has a thick cuticle and beneath is a zone of chlorenchyma, which is differentiated into chlorenchyma cells and thinner walled cells, known as parenchyma. The central bulk of the leaf contains the colourless mucilaginous pulp, made up of large thin-walled mesophyll cells containing the *A. vera* gel itself<sup>5</sup>. The vascular bundles with inner bundle sheath cells contain the yellow sap, which exudes from the leaves when they are cut.

Thus, there are broadly three distinct portions of the *A. vera* leaves<sup>10,16,26</sup>: (1) Aloe gel is a clear jelly-like substance that is obtained from the thin walled sticky cells of the inner portion of the leaf, which contains 99 % water and rest is made of glucomannans, amino acids, lipids, sterols and vitamins. (2) The middle layer of Aloe latex (or juice) is obtained from the cells beneath the plant's skin and contains laxative anthraquinones latex and has a bitter taste. (3) The outer thick layer of 15-20 cells called as rind which has protective function and synthesizes carbohydrates and proteins. Inside the rind are vascular bundles responsible for transportation of substances such as water (xylem) and starch (phloem).

**Chemical constituents:** Cosmetic and some medicinal products are made from the mucilaginous tissue in the centre of the *A. vera* leaf and called *A. vera* gel. The peripheral bundle sheath cells of *A. vera* produce an intensely bitter, yellow latex which is due to the presence of aloin, aloe-emodin and related compounds. Many compounds about 200 different types of molecules with diverse structures have been isolated from both the central parenchyma tissue of *A. vera* leaves and the exudate arising from the cells adjacent to the vascular bundles<sup>8,17</sup>.

The aloe parenchyma tissue or pulp has been shown to contain proteins, lipids, amino acids, vitamins, enzymes, inorganic compounds and small organic compounds in addition to the different carbohydrates. The raw pulp of *A. vera* contains *ca.* 98.5 % water, while the mucilage or gel consists of about 99.5 % water<sup>10</sup>. The remaining 0.5-1.5 % solid material consists of a range of compounds including water-soluble and fat-soluble compounds<sup>27</sup>. On dry matter basis aloe gel consists of polysaccharides (55 %), sugars (17 %), minerals (16 %), proteins (7 %), lipids (4 %) and phenolic compounds (1 %) (Fig. 1) with some seasonal fluctuation<sup>9,28</sup>.

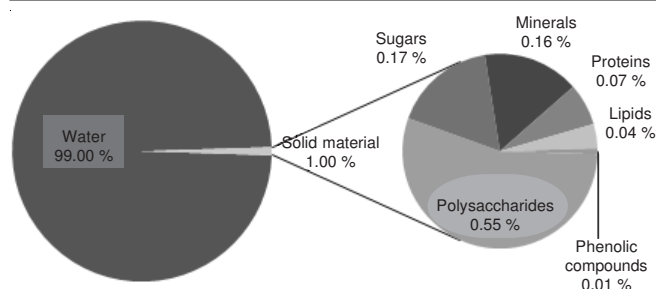


Fig. 1. Chemical composition of *Aloe vera* gel

The large fluctuations in carbohydrates composition of *A. vera* fillet as found in the literature has been explained by the fact that the mannosyl residues are contained in a reserve polysaccharide with a significant seasonal influence, as well as large variations between cultivars in terms of the quantities of mannose-containing polysaccharides within the parenchyma cells<sup>29</sup>. The chemical constituents of *A. vera* leaves including the gel and exudate are given in Table-1<sup>2,3,5,6,9,12,14,16-21,30-32</sup>.

Now, the processing of *A. vera* gel, derived from the leaf pulp of the plant, has become a big industry worldwide due to the application in the pharmaceutical and cosmetic industries. However, more and more aloe skin was discarded as waste. Less is known about the bioactive substances in *A. vera* skin and the potential use of aloe skin in industry as well.

*A. vera* skin is rich in anthraquinones and the content of aloin in leaf epidermis is significantly higher than which in the gel<sup>33</sup>. In addition, *A. vera* skin also contains a large number of polysaccharides, the polysaccharide is stored in the palisade tissue of the epidermal keratinocytes<sup>34,35</sup>. Xin-xiang *et al.*<sup>36</sup>, reported that chlorophyll in the *A. vera* skin had good tolerance for thermo-stability. The stability of the chlorophyll could be influenced by lightening. Chlorophyll was relatively stable under alkaline circumstances. Therefore, *A. vera* skin as raw material of chlorophyll, turning waste into treasure, not only improve the economic value of the *A. vera*, but also provide a new way to development and utilization of the *A. vera* skin. Besides, *A. vera* skin also includes a variety of mineral elements and calcium, iron, zinc, manganese is higher than the content of the gel<sup>37</sup>. Aloe skin is regarded as the main byproducts of processing, with a lot of quantity and high value for nutrition and health.

### Biological activity and clinical trial

**Skin of *A. vera*:** Hu *et al.*<sup>38</sup> studied the free radical-scavenging activities of extracts of *A. vera* of leaf skin by supercritical CO<sub>2</sub> extraction and solvent extraction. They found that the extracts of *A. vera* rind by supercritical carbon dioxide extraction and solvent extracts provided significantly higher free radical-scavenging activities of 33.5 and 39.7 %, respectively, than extracts of *A. vera* gel extracted by ethanol with a

TABLE-1  
MAJOR CHEMICAL COMPOSITION OF *Aloe vera* GEL AND EXUDATE

Class	Numbers	Compositions
Water/moisture	98.5-99.5 %; pH = 4-5	-
Carbohydrates	0.25% (25-50% of dry matter)	Pure mannan, acetylated mannan, acetylated glucomannan, glucogalactomannan, galactan, galactogalacturan, arabinogalactan, galactoglucoarabinomannan, pectic substance, xylan, cellulose
Sugars	93 % Mannose (3 % glucose, 3 % galactose, 1 % arabinose); 95 % free glucose (fructose, galactose)	Monosaccharides: Glucose, Fructose, Mannose, L-rhamnose and aldopentose; Polysaccharides: glucomannans/ polymannose.
Anthraquinones/ anthrones	It provides 12 anthraquinones, which are phenolic compounds traditionally known as laxatives.	Provides aloin A and B (or collectively known as barbaloin), isobarbaloin, anthranol, anthracene, ester of cinnamic acid, aloe emodin, emodin, chrysophanic acid, ethereal oil, resistannol, aloetic acid.
Proteins	0.07 %	Lectins, lectin-like substance
Enzymes	It contains 13 enzymes.	Allyase, cellulase, peroxidase, alkaline phosphatase, amylase, carboxypeptidase, catalase, cyclooxygenase, cyclooxygenase, lipase, phosphoenolpyruvate carboxylase, superoxide dismutase, bradykinase
Amino acids	Provides 20 of the 22 required amino acids and 7 of the 8 essential ones, and 20 % Arg.	Alanine, arginine, aspartic acid, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, threonine, tyrosine, valine
Vitamins		A,C,E,B,B1,B2,B6, B12, niacin, β-carotene, choline, folic acid
Essential oil		1-Tetradecyne, tridecanoic acid, phytol, oleic acid, 1-octanol, squalene, butyl heptadecyl ester, 9,12,15-octadecatrienoic acid methyl ester, allyl pentadecyl ester, eicoane, 9-octadecenal, didodecyl phthalate, 1-octadecyne, hexyl pentadecyl ester, tetracontane 1-iodo-2-methylundecane, α-tocopherol
Organic acids		n-Hexadecanoic acid, oxalic acid, 9,12-octadecadienoic acid (Z,Z), arachidonic acid, γ-linolenic acid, triglycerides, gibberillin, malic acid, lactic, acetic, succinic acids, sorbate, salicylic acid, uric acid, sulphurous acid
Saponins		Glycosides
Steroids	It provides 4 plant steroids.	Cholesterol, campesterol, lupeol, sistosterol
Hormones		Auxins and gibberellins
Minerals and trace elements	10-25% of dry matter	Minerals and electrolytes K, Cl (Na), Ca, Mg, P; trace elements Fe, Cu, Zn, Mn, Al, Se, Cr, Pb, Ni, Co, Ba
Miscellaneous	Including lignins and chromones	Alyphatics hydrocarbons/esters long chain; 8-C-glucosyl-(2-O-cinnamoyl)-7-O-methylaloediol A, 8-C-glucosyl-(S)-aloesol, 8-C-glucosyl-7-O-methyl-(S)-aloesol, 8-C-glucosyl-7-O-methylaloediol, 8-C-glucosyl-noreugenin, isoaloesol D; isorabaichromone, nealoesin A; lignins

free radical-scavenging activity of 14.2 %. Compared to BHT and  $\alpha$ -tocopherol, the extracts of *A. vera* skin, by supercritical carbon dioxide extraction and ethanol, showed stronger antioxidant activities. Components in the rind of *A. vera* are responsible for the higher antioxidant activity of *A. vera* extracts.

Xu and Damak<sup>39</sup> researched antioxidant activities of *A. vera* leaf skin extracts (AVLS) *in vitro*. They found that the chloroform-ethanol fraction of the ethanol crude extract of AVLS showed the highest total phenolics ( $40.500 \pm 0.041$   $\mu$ g gallic acid equivalents/g of extract), the highest scavenging activity and the greatest reducing power, when evaluated by the DPPH and reducing power method compared with the other fractions. Whereas the hexane extract showed the highest antioxidant capacity ( $471.300 \pm 0.013$ ) and the highest antioxidant activity coefficient by the  $\beta$ -carotene bleaching method when determined by the phosphomolybdenum and the  $\beta$ -carotene-bleaching methods.

Chun-hui *et al.*<sup>40</sup>, isolated a polysaccharide (SAPS-1) from the skin of *A. vera* irrigated with sea water for 3.5 years through a combination of anion-exchange column chromatography and repeated gel chromatography, which was demonstrated to have strong scavenging activities against superoxide radical, moderate ferrous chelating effect, moderate scavenging activities of hydroxyl radical, moderate reductive power and moderate inhibition of lipid peroxidation, while SAPS-1 exhibited weak scavenging activity of hydrogen peroxide. Zhiliang<sup>34</sup> further studied SAPS-1, suggested that a kind of mitogen, could enhance of nowhere which was spontaneously or which was induced by Con A. SAPS-1 could well promote proliferation rate of primarily cultured and ConA induced spleen cells to be 20.04 and 25.18 % at the concentration of 20  $\mu$ g/mL. Demnification of spleen cells was remarkable under UV, 160  $\mu$ g/mL SPAS-1 was able to enhance protection and restoration of damaged spleen cells to be 26.24 and 43.56 %.

Agarry *et al.*<sup>41</sup> tested antimicrobial activities of the leaf after obtaining the gel from it by the appearance of zones of inhibition. Antimicrobial susceptibility test showed that both the gel and the leaf inhibited the growth of *Staphylococcus aureus* (18.0 and 4.0 mm, respectively), while the leaf possesses inhibitory effects on both *Pseudomonas aeruginosa* and *Candida albicans*.

In addition, El-Shemy *et al.*<sup>42</sup>, evaluated the potential anticancer properties and modulatory effect of selected *A. vera* active principles which was isolated from the leaves removed the gel *via* supercritical CO<sub>2</sub> extraction on antioxidant enzyme activities. Their experimental data suggested that the tested *A. vera* compounds (aloesin, aloemodin and barbaloin) may exert their chemo-preventive effect through modulating antioxidant and detoxification enzyme activity levels, as they were one of the indicators of tumorigenesis. Importantly they demonstrated that the tested *A. vera* active principles exhibited selectivity towards cancer proliferating cells as well as a non-toxic behaviour towards normal hematopoietic progenitor cells. This key advantage was lacking in common anticancer drugs exhibiting a non-selective mechanisms of action, with an inevitably high incidence of severe toxicity must be tolerated for effective doses to be administered. They envisaged that this finding, among others, should point to novel low-cost drug

discoveries, of natural origin, which could be afforded by developing countries.

**Gel of *A. vera*:** The whole gel extract of *A. vera* has been traditionally used worldwide as a folk remedy for various diseases because of its multiple biological activities components, mainly anthraquinones and polysaccharides (the most active is acemannan), specifically to promote wound healing, in addition to having antiinflammatory, antibacterial, antiviral, antifungal, antioxidant, laxative, immunity, hypoglycemic, gastroprotective, antitumor effects and also as a candidate for photodynamic therapy of some kinds of cancer<sup>43,44</sup>. However, approved clinical evidences are available only for promoting burn wounds, lowering low density lipoprotein (LDL), increasing high density lipoprotein (HDL), decreasing blood glucose level, treating genital herpes and psoriasis human papilloma virus, seborrheic dermatitis, aphthous stomatitis, xerosis, lichen planus, frostbite<sup>9,44-46</sup>. The topical application of *A. vera* does not seem to prevent radiation-induced skin damage<sup>47</sup>. More and better trial data are needed to define the clinical effectiveness of this popular herbal remedy more precisely.

**Skin and wound healing:** Wound healing is a dynamic process that results in the restoration of anatomic continuity and function. The use of *A. vera* in wound healing is being considered in many studies, cumulative evidence tends to support that oral administration of *A. vera* in mice is effective on wound healing in first and second burns when compared with conventional treatments<sup>15</sup>. It may be contributed to acemannan ( $\beta$ -(1,4)-acetylated polymannose)-the major polysaccharide of *A. vera* -stimulates expression of VEGF and other wound healing-related factors (*e.g.*, keratinocyte growth factor-1 and type I collagen) in gingival fibroblasts<sup>48</sup>. This can be especially beneficial in the case of oral wound healing. Thus, crude *A. vera* extract or isolated proangiogenic components may have potential pharmaceutical applications for the management of wounds<sup>49</sup>.

Khorasani *et al.*<sup>46</sup> conducted a clinical study to evaluate the efficacy of *A. vera* cream for partial thickness burn wounds and compare its results with those of silver sulfadiazine (SSD). They found that the rate of re-epithelialization and healing of the partial thickness burns was significantly faster in the site treated with aloe than in the site treated with silver sulfadiazine ( $15.9 \pm 2$  versus  $18.73 \pm 2.65$  days, respectively;  $p < 0.0001$ ). The sites treated with aloe were completely healed in less than 16 days versus 19 days for the sites treated with silver sulfadiazine. These results clearly demonstrated the greater efficacy of aloe cream over silver sulfadiazine cream for treating second-degree burns.

Eshghi *et al.*<sup>50</sup> assessed the effects of *A. vera* cream in reducing postoperative pain, postdefection pain and its promotion of wound healing after open hemorrhoidectomy in clinical trial. Patients in the topical aloe cream group had significantly less postoperative pain at hours 12, 24 and 48 h and at 2 weeks. Aloe cream reduced the pain after defecation in 24 and 48 h postsurgery ( $p < 0.001$ ). Wound healing at the end of the second postoperative week was significantly greater in the aloe group compared with the placebo group ( $p < 0.001$ ).

Delayed wound healing is a significant clinical problem in patients who have had previous irradiation. Atiba *et al.*<sup>51</sup> investigated the effectiveness of *A. vera* on acute radiation-

delayed wound healing in radiation-exposed rats compared with radiation-only and control rats. The research suggested that wound contraction was accelerated significantly by *A. vera* on days 6 and 12 after wounding. Furthermore, the inflammatory cell infiltration, fibroblast proliferation, collagen deposition, angiogenesis and the expression levels of TGF- $\beta$ -1 and bFGF were significantly higher in the radiation plus *A. vera* group compared with the radiation-only group, which showed the potential application of *A. vera* to improve the acute radiation-delayed wound healing by increasing TGF- $\beta$ -1 and bFGF production.

Even though there are some promising results with the use of *A. vera* for diverse dermatologic conditions, clinical effectiveness of oral and topical *A. vera* is not sufficiently and meticulously explored in preventing or minimising radiation-induced injuries. Therefore, further methodologically rigorous, sufficiently powered research studies should be carried out to determine the effectiveness of *A. vera* for burn wound healing.

**Antidiabetic effects:** Vogler and Ernst's review<sup>45</sup> has demonstrated that *A. vera* gel is effective in diabetes in animal test and clinical trial. Ngo *et al.*<sup>52</sup> reviewed the available literature on the efficacy of oral *A. vera* in diabetes mellitus and dyslipidemia in humans. They concluded that the preponderance of evidence suggests a trend toward benefit from oral *A. vera* use in reducing fasting blood glucose concentration and glycosylated hemoglobin (HbA<sub>1c</sub>). Triglyceride levels also seem to be reduced, although evidence regarding changes in LDL, HDL and total cholesterol levels is conflicting. The weaknesses in study methods and inconsistency in data do not currently warrant recommendation of oral *A. vera* for the management of diabetes mellitus or dyslipidemia. Hence, more and better trial data are needed to define the clinical effectiveness of this popular herbal remedy more precisely.

Rajasekaran *et al.*<sup>53</sup> have evaluated the presence of antioxidant property in the alcoholic extract of *A. vera* leaf gel. Oral administration of *A. vera* gel extract at a concentration of 300 mg/kg to streptozotocin-induced diabetic rats significantly decreased the levels of blood glucose, glycosylated hemoglobin and increased hemoglobin. The increased levels of lipid peroxidation and hydroperoxides in tissues of diabetic rats were reverted back to near normal levels after the treatment with gel extract. The extract treatment also resulted in a significant increase in reduced glutathione, superoxide dismutase, catalase, glutathione peroxidase and glutathione-S-transferase in the liver and kidney of diabetic rats. These results clearly show a significant decrease in blood glucose levels after oral administration of the ethanol extract of *A. vera* gel in streptozotocin-induced diabetic rats was ascribed to the antioxidant effect of the extract.

Kim *et al.*<sup>54</sup> studied hypoglycemic and hypolipidemic effects of processed *A. vera* gel (PAG) in a mouse model of non-insulin-dependent diabetes mellitus. When administered orally of processed *A. vera* gel for 8 weeks reduced circulating blood glucose concentrations to a normal level in diet-induced obesity mice. The antidiabetic effects of processed *A. vera* gel were confirmed by intraperitoneal glucose tolerance testing. Processed *A. vera* gel lowered blood glucose level by decreasing insulin resistance. The administration of processed *A. vera* gel

also lowered triacylglyceride levels in liver and plasma. Histological examinations of periepididymal fat pad showed that processed *A. vera* gel reduced the average size of adipocytes. The results suggest that processed *A. vera* gel could be useful for treating non-insulin-dependent diabetes mellitus.

Mohamed<sup>55</sup> estimated the antidiabetic, antihyperlipidemic and antioxidative activity of *A. vera* gel extract in alloxan-induced diabetic and control rats. And serum glucose, total cholesterol, triacylglycerols, malondialdehyde (MDA), nitric oxide and total antioxidant capacity were evaluated. The research found that oral administration of *A. vera* gel extract resulted in a significant decrease in serum glucose, total cholesterol and triacylglycerols ( $p < 0.05$ ) in treated diabetic group as compared with diabetic control group. In addition, treatment with *A. vera* gel extract ameliorated the oxidative stress evidenced by a significant decrease in serum MDA level and a significant increase in serum nitric oxide and total antioxidant capacity ( $p < 0.05$ ) in treated diabetic group as compared with diabetic control group.

Through these documents it is clear that the glucose lowering effect could be explained by an antioxidant mechanism because it attenuated oxidative damage in the brains and reduced peroxidation levels in the kidneys of diabetic rats. Moreover, *A. vera* gel extract contained natural antioxidants (total phenols, total flavonoid, vitamins C and E) which are responsible for the antioxidative effect of this plant. Meanwhile, trace element analysis of *Aloe vera* gel extract showed that *Aloe vera* gel extract contained appreciable amount of (Cr, Mn and Zn) which potentiate the antidiabetic activity of this plant. These elements are known as hypoglycemic elements because they have a very important role in glucose metabolism. Chromium facilitates insulin binding and subsequent uptake of glucose into the cell. Supplemental chromium has been shown to decrease fasting glucose levels, improve blood glucose tolerance, decrease insulin levels and decrease total cholesterol and triacylglycerols. However, the active component(s) responsible for its antidiabetic activity have not been identified, actually. Further studies on this topic are necessary.

**Antiinflammatory effects:** Inflammation is a reaction by the body due to injury and is characterized by swelling, pain, redness, heat and loss of function, which is maybe responsible for the treatment of oral lichen planus (OLP), scabies, sepsis, wound healing, obesity, ultraviolet erythema, inflammatory bowel disease, gastric microcirculation, improves insulin sensitivity and so on.

Choonhakarn *et al.*<sup>56</sup> studied the efficacy of *A. vera* gel in the treatment of oral lichen planus which is a chronic inflammatory disease that can be painful especially in the atrophic and erosive forms by a randomized, double-blind, placebo-controlled trial. They concluded that *A. vera* gel is statistically significantly more effective than placebo in inducing clinical and symptomatological improvement of oral lichen planus with no serious side-effects. Therefore, *A. vera* gel can be considered a safe alternative treatment for patients with oral lichen planus.

Oyelami *et al.*<sup>57</sup> preliminary study of effectiveness of *A. vera* in scabies treatment compared with that of benzoate lotion among 30 patients. They found the scabietic lesions virtually disappeared in all of them. None of these patients

had any noticeable side effects. It is advised that *A. vera* gel is as effective as benzyl benzoate in the treatment of scabies.

Reuter *et al.*<sup>58</sup> explored the antiinflammatory potential of a highly concentrated *A. vera* gel in the UV erythema test by 40 volunteers with skin types II and III were included in the randomized, double-blind, placebo-controlled, phase III monocenter study. In this study after 48 h the *A. vera* gel (97.5 %) displayed some anti-inflammatory effects superior to those of 1 % hydrocortisone in placebo gel. The *A. vera* gel tested here might be useful in the topical treatment of inflammatory skin conditions such as UV-induced erythema.

Sepsis is an acute life-threatening clinical condition and remains the major cause of death in intensive care units. The primary pathophysiologic event central to the septic response is an overwhelming activation of the inflammatory system and countervailing response from the antiinflammatory system. Yun *et al.*'s research<sup>59</sup> elucidated the cause of this perturbation. They reported that the administration of *A. vera* ameliorated the multiple organ dysfunction syndrome (MODS), as evidenced by the serum levels of biochemical parameters and histological changes containing the levels of the cytokines, tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1b and IL-6, which were determined by ELISA at various time points. The increases in the levels of TNF- $\alpha$ , IL-1b and IL-6 were attenuated by *Aloe vera*. *In vivo* administration of *A. vera* also markedly enhanced bacterial clearance. Their findings suggest that *A. vera* has potent therapeutic effects in polymicrobial sepsis by decreasing pro-inflammatory cytokines associated various cytokine cascades in sepsis pathogenesis and ultimately leading to the alleviation of MODS. Thus, *A. vera* is a potential therapeutic medication for the care of clinical septic patients. Prabjone *et al.*<sup>60</sup> investigated antiinflammatory effects of *A. vera* on leukocyte-endothelium in the gastric microcirculation of *Helicobacter pylori*-infected rats. Treatment with *A. vera* gel reduced the leukocyte adhesion and TNF- $\alpha$  significantly ( $p < 0.05$ ). They found *H. pylori* enhanced leukocyte-endothelium interaction in the posterior stomach area markedly. This enhancement in leukocyte-endothelium interaction could be improved by the treatment of *A. vera*, associated with reduction in TNF- $\alpha$  level.

Langmead *et al.*<sup>61</sup> assessed the effects of *A. vera* gel *in vitro* on the production of reactive oxygen metabolites, eicosanoids and interleukin-8, all of which may be pathogenic in inflammatory bowel disease. They reported that *A. vera* gel had a dose-dependent inhibitory effect on reactive oxygen metabolite production; 50 % inhibition occurred at 1 in 1000 dilution in the phycoerythrin assay and at 1 in 10-50 dilution with biopsies. *A. vera* inhibited the production of prostaglandin E<sub>2</sub> by 30 % at 1 in 50 dilution ( $p = 0.03$ ), but had no effect on thromboxane B<sub>2</sub> production. The release of interleukin-8 by CaCo<sub>2</sub> cells fell by 20 % ( $p < 0.05$ ) with *A. vera* diluted at 1 in 100, but not at 1 in 10 or 1 in 1000 dilutions. The results provide support for the proposal that it may have a therapeutic effect in inflammatory bowel disease.

Shin *et al.*<sup>62</sup> established that dietary aloe formula reduces obesity-induced glucose tolerance not only by suppressing inflammatory responses but also by inducing antiinflammatory cytokines in the white adipose tissue (WAT) and liver, both of which are important peripheral tissues affecting insulin

resistance. The effect of Aloe QDM complex in the WAT and liver are related to its dual action on peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) and 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1) expression. They demonstrated that Aloe QDM was a useful dietary phytochemical for improving not only obesity-induced inflammation but also obesity-related metabolic disorders.

Park *et al.*<sup>63</sup> compared the antiinflammatory effects of aloin and aloe-emodin with other polyphenols. Their results demonstrated that aloe-emodin dose-dependently inhibited inducible nitric oxide synthase (iNOS) mRNA expression and nitric oxide (NO) production at 5-40  $\mu$ M. In addition, the levels of cyclo-oxygenase-2 (COX-2) mRNA and prostaglandin E<sub>2</sub> production were suppressed by 40  $\mu$ M aloe-emodin. Aloin also suppressed the production NO at 5-40  $\mu$ M, although it did not suppress prostaglandin E<sub>2</sub> production. The results indicated that aloin and aloe-emodin possibly suppress the inflammatory responses by blocking iNOS and COX-2 mRNA expression. Thus, aloe-emodin is a possible key constituent responsible for the antiinflammatory activity of aloe.

It is conceivable that the anthraquinones (aloin, aloe-emodin, *e.g.*) may be responsible for the antiinflammatory effect. In terms of the mechanism involved, the antiinflammatory activity of *A. vera* gel may be due to reduce prostaglandin E<sub>2</sub> production by inhibition of the arachidonic acid pathway or reduce the leukocyte adhesion and TNF- $\alpha$  level through blocking iNOS and COX-2 mRNA expression and also relate to its dual action on peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) and 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1) expression.

**Anticancer effect:** Aloe extracts have been tested in the treatment of cancer and positive effects have been observed. In recent studies, the two fractions from aloes that are claimed to have anticancer effects include glycoproteins (lectins) and polysaccharides, specifically acemannan has been investigated in many *in vitro* models as well as in different animal species in terms of reduced tumour burden, tumour shrinkage, tumour necrosis and prolonged survival rates. In addition to these effects, *A. vera* gel has also shown chemopreventative and antigenotoxic effects on benzo[ $\alpha$ ]pyrene-DNA adducts<sup>27</sup>. One mechanism of action that was proposed for these anti-cancer effects of aloe polysaccharides is stimulation of the immune response<sup>14</sup>. However, some researchers<sup>64</sup> suggested that aloe-emodin, which involved disruption of mitochondria membrane potential, cytochrome c release and activation of caspase 3, could be a promising candidature for the research and development of new antitumor drugs.

**Immunomodulatory effects:** Most studies examined their immunomodulatory activity *in vivo*, Im *et al.*<sup>65</sup> provide the first clear evidence for the immunomodulatory activity of orally administered *A. vera* gel; Vahedi *et al.*<sup>66</sup> demonstrated that oral administration of *A. vera* affects various aspects of the immune system, including the effects on the composition of lymphocyte subsets and serum immunoglobulins, which may stimulate both cellular and humoral immune responses after immunization. The gel of *A. vera* was performed their immunomodulatory activity, which is possible due to components such as aloctin A and acemannan.

**Other beneficial effects:** In addition, there are other beneficial effects that are attributed to diverse extracts of *A. vera*. In several studies<sup>32,67-71</sup>, beneficial effects at antioxidant and antimicrobial have been found after tested. Besides, the effect of Aloe gel on the human absorption of vitamins C and E was reported<sup>72</sup>. On the other hand, it was observed that gel of *A. vera* solutions significantly enhanced the transport of insulin across the Caco-2 cell monolayers compared with the control, which suggests that these plant products have a high potential to be used as absorption enhancers in novel dosage forms for drugs with poor bioavailabilities when administered orally<sup>73</sup>. The hydro alcoholic extract of the gel has also been used in antidepressant compared with the fluoxetine-treated and the control samples by FST and OFT tests on the animal model (mouse) for the first time<sup>74</sup>.

**Adverse effects:** Scientific evidences suggest that *A. vera* gel is safe for external use, but it also may cause redness, burning, stinging sensation and rarely generalized dermatitis in sensitive individuals<sup>14,16,45</sup>. Allergic reactions are mostly due to anthraquinones, such as aloin and barbaloin. However, there was no subchronic toxicity or genotoxic activity using aloesin *in vitro* and *in vivo*<sup>75,76</sup>. The results support potential use of aloesin which does not share the presumed toxicity profile of Aloe anthraquinones, as a functional food ingredient. In oral, abdominal cramps, diarrhea, red urine, hepatitis, dependency or worsening of constipation were reported<sup>16,19,77</sup>. Laxative effect may cause electrolyte imbalances (low potassium levels). Although, all adverse effects were reversible and *A. vera* was generally very well tolerated, it is recommended that aloe products should not be used internally during pregnancy or lactation period by women and by persons suffering from abdominal pain, appendicitis or intestinal obstruction.

**Agricultural cultivation:** Historical records indicate that it may have originated from Egypt or the Middle East, but the geographical origin of *A. vera* is not known for sure, since it has been introduced and cultivated in other areas with different climatic conditions, throughout most of the tropics and warmer regions of the world, including the West Indies and Bahamas, southern USA, Mexico, Central America, Arabia and India and other parts of Asia, due to the numerous beneficial effects attributed to Aloe gel and due to its medicinal properties. However, large differences in the nutritional content of *A. vera* gel due to cultural conditions and there is a scarcity of information about its agronomic management. Therefore, the *A. vera*'s agronomy research is particularly important.

**Influential factors in the chemical composition of Aloe gel:** There are many factors that can influence the chemical composition of *A. vera* gel which could explain the differences in the results observed in the literature. A first factor to consider is the different species/subspecies or varieties of *A. vera* used in the investigation<sup>78,79</sup>. Other investigators have also pointed out that other factors decisively influence the composition of the Aloe gel, such as the annual seasons, exposed to irradiance levels, harvest date, the climate and the land and cultivation methods<sup>5,80-82</sup>.

In addition, the irrigation of the plant affects physiological and ecological characters. Rodríguez-García *et al.*<sup>83</sup> researched *A. vera*'s physiological, growth and yield responses under

different irrigation regimes. The results suggested that the low leaf temperature increased stomatal resistance, decreased plant and leaf growth rates. This behaviour is opposite to other crassulacean acid metabolism (CAM) species in semiarid. Jin *et al.*<sup>84</sup> found that in spite of membrane injury in these two cultivars (F0 and F50) caused by salt stress, both F0 and F50 may ensure the normal growth through the absorption and accumulation of inorganic cations in stems and roots. Therefore, *A. vera* can be planted in saline soil and irrigated with saline water and under salt stress the main osmotic adjustment form of *A. vera* is accumulating inorganic cations in root and not accumulating low molecular weight organic solutes such as soluble sugars. Silva *et al.*<sup>85</sup> evaluated the effect of different irrigation rates on the growth and water use efficiency (WUE) for the production of leaves biomass and gel. The results show that *A. vera* is a promising crop for arid zones, with high yield of leaf biomass production and thus a high gel production, associated with a high WUE and low water requirements. This report contributed to the understanding of the key factors of potential yield and WUE; they concluded that in the case of *A. vera*, these factors are not mutually exclusive, but rather are complimentary if the total system is considered. Mean while, Delatorre-Herrera *et al.*<sup>86</sup> determined the effect of water restriction on the WUE and osmotic adjustment (OA) of *A. vera* under different water treatments. The results showed that the plants irrigated with 75 % of FC (Water treatments/%) presented the best WUE in terms of dry mass and amount of gel produced by a litre of supplied water. The degree of polymerization also appeared to increase in *A. vera* plants treated with 25 % of FC. It is probable that the increase in soluble and total sugars, the increase in the degree of polymerization of oligo and polyfructans, the change in structure from inulin type to neofructan type fructans and the moderate increase in proline will provide the osmotic adjustment for *A. vera* plants when there is a water stress.

The age of the plant is an additional and decisive factor that needs to be considered. Hu *et al.*<sup>38</sup> suggest that the maturity of the plant plays an important role in the antioxidant capacity of the gel. It has also been proven that the phenolic compounds can vary depending on the part of the leaf that is analyzed<sup>87</sup>. On the other hand, there is a decrease of the biological activity as a result of these physicochemical modifications, therefore it is fundamental to use adequate preservation methods to maintain the therapeutic activity of the products<sup>10</sup>. The chemical composition of the derivative products of the Aloe can also be affected during the post-harvest, especially for the time and temperature used in the dehydration process used in the preparation of commercial extracts<sup>18</sup>.

**Stress adaptation:** Accumulation of polysaccharides and anthraquinones in aloe leaf plays a very important role in the ability to adapt to adversity. Because aloe mucopolysaccharide can significantly increase the osmotic potential of leaf water storage cells and promote root absorption of water to transport to the leaves and the leaf absorption the water that can be used near the ground moist air. In particular, which can enhance the antidehydration and water retention of leaves, which is the reasons why the vitality of the whole plant is extremely tenacious.

The accumulation of anthraquinones *in vivo* for the physiological meanings of Aloe is mainly manifested in two aspects: (1) Resist the animal feeding, pests and diseases. While *Aloe vera* leaves are damaged, the aloin is oxidized to aloe emodin, which is more prominent in resisting animal feeding, pests and diseases due to its special bitter. (2) The leaf tissue in massive accumulation of phenolic compounds which can effectively absorb the ultraviolet rays in sunlight, thereby reducing or avoiding the damage caused by the strong solar radiation on plants.

In the recent 10 years, Chinese scholars has studied the relationship between the structure of *A. vera* leaves, the bioactive ingredients and low temperature stress, drought stress, UV stress, salt stress and gas pollution, *etc.*, which deepened human's understanding of basic theory about aloe cultivation and promoted the level of the scientific cultivation of Aloe.

Lin *et al.*<sup>88</sup> studied the ultra structures of one year old aloe mesophyll cells which were simulated with salt stress, low temperature stress and drought stress. It was found that all the three kinds of environmental stress could damage membrane system, organelle structure stabilities, mitochondria structure and nucleus structure of aloe in various degrees and many vesicles appeared around the chloroplasts, which resulted in the cellular endomembrane system falling into disorder and the organelles becoming destabilized; under salt stress, the Golgi bodies disintegrated in the cytoplasm; under both salt stress and low temperature stress, there appeared a phenomenon that the mitochondria and chloroplast membranes fused and as a result the mitochondria embedded in the chloroplasts. In addition, the study found that salt stress and low temperature stress damaged cellular membrane of aloe more severely than drought stress, *i.e.*, water stress showed less severe damage to the cellular membrane of aloe and this indicated aloe performed better in drought resistance than in salt resistance. Qing-Song *et al.*<sup>89</sup> found that *A. vera* is the greater adaptation to water stress than to iso-osmotic salt stress. However, Aloe seedlings also showed some specific adaptations to 0.44-0.88 NaCl stress. Although the aloe's drought resistance is stronger than salt tolerance and cold hardiness, cultivation should pay attention to overcome drought stress or control in the moderate range. Drought stress increased the activation of secondary metabolites of aloe, while significantly reducing its economic value.

Recently, some researches on aloe involved the relationship between the aloe active ingredients with different light quality. Chuan-ying *et al.*<sup>90</sup> found that the soluble protein and the soluble polysaccharide contents of *A. vera* under blue light reduced 33 and 27 %, respectively compared to white light, but the anthraquinones content of *A. vera* increased 44 % in this condition. It is concluded the blue light was beneficial to the accumulation of anthraquinones secondary metabolites. Therefore, the study of ultraviolet radiation on secondary metabolites of anthraquinones from aloe is significance guiding for greenhouse cultivation of *A. vera*.

In short, the formation, storage and distribution of Aloe leaf structure and *in vivo* anthraquinones, polysaccharides and glycoproteins and other important bioactive substances had a close relationship between the two major categories of substances with aloe to adapt to the adversity. The situation of

moderate stress could promote the accumulation of bioactive ingredients of aloe. Improving the light, temperature and moisture conditions maybe improve the mineral nutrition of N and P, Si significantly, which will enhance the adaptability of aloe on the face of adversity and promote the production of biological activity in leaves. Understanding of the aloe these rules and characteristics was significant for the use of commercial production and scientific guidance of aloe.

## Conclusion

The present study shows the traditional, pharmacological and phytochemical properties of various bioactive compounds present in *A. vera* including glycoproteins, anthraquinones, polysaccharides and low-molecular-weight species. Reported therapeutic benefits of *A. vera* products are numerous such as anti-inflammatory, anticancer, antioxidant, antimicrobial immunomodulatory and wound-healing effects, minimizing frost bite damage, protection against skin damage from X-rays, lung cancer, intestinal problems. However, approved clinical trial data support its effectiveness for promoting burn wounds, lowering LDL, increasing HDL, decreasing blood glucose level, treating genital herpes and psoriasis human papilloma virus, seborrheic dermatitis, aphthous stomatitis, xerosis, lichen planus, frostbite. In light of the many pharmacologic activities of the components of *A. 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 their effects is essential if *A. vera* is to be successfully developed for therapeutic purposes. Meanwhile, large differences exist in the nutritional content of *A. vera* gel due to cultural conditions and there is a scarcity of information about its agronomic management. Therefore, the *A. vera*'s agronomy research is particularly important. With technological developments in the field of analytical chemistry and agriculture cultivation, it is expected that more information in this regard will become available in the future at a faster rate. Therefore, it would be worthwhile embarking on an intensive scientific experimentation and investigation on this apparently valuable medicinal agent and to promote its large-scale cultivation such as beach planting and seawater irrigation. What's more, the fast expanding *A. vera* industry urgently needs reliable testing protocols to assess the quality and quantity of bioactive chemicals present in the final products. The product claims must be tested by intensive clinical trials, verified and certified by the Government regulatory authorities to build consumer confidence and to ensure safety of the *Aloe vera* products.

## ACKNOWLEDGEMENTS

The authors acknowledged the document supply of Analytical and Testing Center of Hainan University. This article is supported by National High Technology Research and Development Program 863-No. 2007AA021500 and supported by the State key subject of Botany at Hainan University (071001).

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