Journal of Traditional and Complementary Medicine 5 (2015) 21–26

HOSTED BY

Contents lists available at ScienceDirect

Journal of Traditional and Complementary Medicine

journal homepage: http://www.elsevier.com/locate/jtcme

Review article

Evaluation of biological properties and clinical effectiveness of *Aloe vera*: A systematic review

Maharjan H. Radha, Nampoothiri P. Laxmipriya*

Biochemistry Department, Faculty of Science, The M S University of Baroda, Vadodara, Gujarat, India

ARTICLE INFO

Article history:
Received 4 June 2014
Received in revised form
7 July 2014
Accepted 24 July 2014
Available online 23 December 2014

Keywords:
Aloe vera
biological properties
phytocomponents
review
clinical effectiveness

ABSTRACT

Aloe vera (蘆薈 lú huì) is well known for its considerable medicinal properties. This plant is one of the richest natural sources of health for human beings coming. The chemistry of the plant has revealed the presence of more than 200 different biologically active substances. Many biological properties associated with *Aloe* species are contributed by inner gel of the leaves. Most research has been centralized on the biological activities of the various species of *Aloe*, which include antibacterial and antimicrobial activities of the nonvolatile constituents of the leaf gel. *Aloe* species are widely distributed in the African and the eastern European continents, and are spread almost throughout the world. The genus *Aloe* has more than 400 species but few, such as *A. vera*, *Aloe ferox*, and *Aloe arborescens*, are globally used for trade. *A. vera* has various medicinal properties such as antitumor, antiarthritic, antirheumatoid, anticancer, and antidiabetic properties. In addition, *A. vera* has also been promoted for constipation, gastrointestinal disorders, and for immune system deficiencies. However, not much convincing information is available on properties of the gel. The present review focuses on the detailed composition of *Aloe* gel, its various phytocomponents having various biological properties that help to improve health and prevent disease conditions.

1. Introduction

Aloe barbadensis Miller (蘆薈 lú huì), commonly referred to as *Aloe vera*, is one of more than 400 species of *Aloe* belonging to family Liliaceae that originated in South Africa, but have been indigenous to dry subtropical and tropical climates, including the southern USA.[1] Recently, only a few species of *Aloe* have been considered for commercial importance, of which *A. vera* is considered the most potent and, thereby, the most popular plant in the research field.[2] *A. vera* has been used in folk medicine for over 2000 years, and has remained an important component in the traditional medicine of many contemporary cultures, such as China, India, the West Indies, and Japan.[3]

A. vera is a succulent plant. Succulents are xerophytes, which are adapted to living in areas of low water availability and are characterized by possessing a large water storage tissue. The main feature of the *A. vera* plant is its high water content, ranging from 99–99.5%.[4] The remaining 0.5–1.0% solid material is reported to contain over 75 different potentially active compounds including water- and fat-soluble vitamins, minerals, enzymes, simple/complex polysaccharides, phenolic compounds, and organic acids. In compositional studies on the structural components of the *A. vera* plant leaf portions, the rind was found to be 20–30% and the pulp 70–80% of the whole leaf weight. On a dry weight basis, the percentages of the rind and pulp represented as lipids (2.7% and 4.2%) and that as proteins (6.3% and 7.3%) only accounted for a minor fraction.[5] However, the nonstarch polysaccharides and lignin represented the bulk of each leaf fraction and were found to be 62.3% and 57.6% of the dry weight of the rind and pulp, respectively. *A. vera* gel polysaccharides consist of linear chains of glucose and mannose molecules, of which mannose is more concentrated than glucose, thereby the molecules are referred to as polymannans.[6] These are linear chains ranging in size from a few to several thousand molecules.[7] The major polysaccharide, acemannan, is composed of one or more polymers of various chain lengths with molecular weights ranging from 30 kDa to 40 kDa or greater, and consisting of repeating units of glucose and mannose in a 1:3 ratio.[5,8]

In western societies, especially in the USA, *A. vera* has been grown mainly to supply the latex component of the leaf to the pharmaceutical industry.[9] However, over the last decade, various *Aloe* species have gained popularity as therapeutic botanicals and consequently a

* Corresponding author. Biochemistry Department, Faculty of Science, The M S University of Baroda, Sayajigunj, Vadodara-390 002, Gujarat, India.
E-mail address: lnampoothiri@gmail.com (N.P. Laxmipriya).
Peer review under responsibility of The Center for Food and Biomolecules, National Taiwan University.

http://dx.doi.org/10.1016/j.jtcme.2014.10.006

large industry has developed utilizing biological properties of *A. vera*.[1] Many investigators have endeavored to establish the active principles in *A. vera* gel. It has been used for many centuries for its curative and therapeutic properties and although over 75 active ingredients from the inner gel have been identified, therapeutic effects have not been correlated well with each individual component.[10] Many of the medicinal effects of *Aloe* leaf extracts have been attributed to the polysaccharides found in the inner leaf parenchymatous tissue.[6] However, it is believed that these biological activities should be assigned to a synergistic action of the compounds contained therein rather than a single chemical substance.[11] 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.[4]

The species of *Aloe* selected for commercial exploitation or selected by the traditional healer, would be based on its local availability and distribution. In South Africa, the most widely distributed *Aloe* species are *Aloe greatheadii* var. *davyana* (Asphodelaceae) and *Aloe ferox* Mill. (Asphodelaceae). *A. greatheadii* grows wild in the northern parts of South Africa, whereas *A. ferox* grows wild primarily in the Eastern and Western Cape provinces. Monosaccharides of both *A. ferox* and *A. vera* released after hydrolysis showed a potential for gel fingerprinting and allow for a distinct property. *A. ferox* contains various combinations of glucose and galactose as main monosaccharides, while *A. vera* yields only mannose.[12] Various extracts of these *Aloe* species are traditionally used and their application used to cure arthritis, skin cancer, burns, eczema, psoriasis, digestive problems, high blood pressure, and diabetes.[13] As different *Aloe* species would have varying phytochemical contents due to interspecies variation and varying climate and soil conditions, direct correlation of biological activity would be inaccurate.

Many beneficial effects of this plant have been attributed to the polysaccharides present in the pulp. The clear pulp which is also known as gel is widely used in various medical, cosmetic, and neutraceutical applications.[4] Studies have noted higher antioxidative activities present in its rind.[14] *A. vera* has been used externally to treat various skin conditions such as cuts, burns and eczema.[15] These *Aloe* species are currently listed in the pharmacopoeia of many countries in form of main *Aloe*, extract and powder.[16]

A. vera is also known for useful secondary metabolites.[1,17] Anthraquinones, tricyclic aromatic quinines are the major secondary metabolites that are abundantly present. Among the naturally occurring anthraquinone derivatives, *Aloe* emodin and chrysophanol are the major compounds.[18] The tricyclic aromatic quinines of *Aloe* have been proposed to be synthesized via the type III polyketide biosynthesis pathway. Recently, novel plant-specific type III polyketide synthases (PKS), octaketide synthase, PKS4, and PKS5 were isolated from *Aloe arborescens* and their functions examined in *E. coli*.[19] These novel plant enzymes might potentially be associated with biosynthesis of natural tricyclic aromatic quinines in *Aloe*, but it remains unclear whether these enzymes produce end products such as *Aloe*-emodin and chrysophanol *in vivo*.[20] Aloesin, aloin and *Aloe*-emodin (oxidative product of aloin) are the most important secondary metabolites found in *A. vera* gel. Many secondary metabolites in plants have reported potent anti-inflammatory, lipid lowering, and antioxidant activities.[21] However, no reports have elucidated complete entire secondary metabolites present in the plant species.

2. Clinical efficacy and mechanism of action

2.1. Burn wound healing effect

Aloe is known as *the healing plant*. *A. vera* has been used for traditional medical purposes in several cultures.[22] *In vitro* extracts of *A. vera* stimulate the proliferation of several cell types. Many studies have shown that treatment with whole *A. vera* gel extracts resulted in faster healing of wounds.[23,24] *A. vera* may have a direct effect on the wound healing process as a whole, which is manifested by increase in rate of contraction of wound area[25] and has confirmed the effect of *A. vera* on increasing wound contraction and collagen synthesis. This property is attributed to the mannose-6-phosphate known to be present in *A. vera* gel.[26] Polysaccharides from *Aloe* promote both the proliferation of fibroblasts and the production of hyaluronic acid and hydroxyproline in fibroblasts, which play important roles in extracellular matrix remodeling during wound healing.[27] Acemannan, significantly increases periodontal ligament cell proliferation, upregulation of growth/differentiation factor 5, type I collagen and alkaline phosphatase activity in primary human periodontal ligament cells.[27] In a clinical study, to check the efficacy of *A. vera* gel compared with 1% silver sulfadiazine cream as a burn dressing for the treatment of superficial and partial thickness burns, healing of burn wounds were remarkably early in *A. vera* treated patients than those patients treated with 1% silver sulfadiazine.[28] Polysaccharides isolated from *A. vera* induce matrix mellatopeptidase (MMP)-3 and metallopeptidase inhibitor-2 gene expression during the skin wound repair of rat, which directly helps to regulate the wound healing activity of *A. vera* gel.[29]

2.2. Immunomodulatory effect

A. vera gel has strong immunomodulatory activity wherein it downregulates lipopolysaccharide-induced inflammatory cytokine production and expression of NLRP3 (NACHT, LRR, and PYD domain-containing protein 3) inflammasome in human macrophages.[30] *A. vera* could inhibit the inflammatory process following burn injury, as characterized by the reduction of leukocyte adhesion, as well as proinflammatory cytokines.[31] Liu et al have shown that *Aloe* polysaccharides pretreatment can attenuate the cerebral ischemia and reperfusion injury in severe traumatic–hemorrhagic rats by first entering high altitude through inhibiting systemic inflammatory response and leukocyte aggregation and lipid peroxidation in the brain.[32] Administration of *A. vera* has been universally demonstrated to result in marked increase in phagocytic and proliferative activity of the reticuloendothelial system.[33] *A. vera* directly inhibits the cyclooxygenase pathway and reduces prostaglandin E2 production,[35] which plays an important role in inflammation. *Aloe* also contains anthraquinones and chromone in the inner gel, which possess strong anti-inflammatory effects as shown in murine macrophages.[34,35] This report suggests that *Aloe* as a whole has anthraquinones (aloin) and chromone (aloesin) components, and *Aloe* gel has pharmacological activity to alleviate inflammatory responses in inflammatory bowel disease.[36] A recent report of a clinical study evaluated the therapeutic effect of *A. vera* gel wherein 2% oral gel is not only effective in decreasing the pain score and wound size in recurrent aphthous stomatitis patients but also decreasing the aphthous wound healing period.[37]

2.3. Intestinal absorption

Aloe material has been used for drug absorption enhancement for drugs with low bioavailability due to extensive efflux.[38] *Lactobacillus brevis* strains were isolated from naturally fermented *A. vera* gel which inhibited the growth of many harmful enteropathogens without restraining most normal commensals in the gut and hence were named POAL (probiotics originating from *Aloe* leaf) strains; these and exhibit discriminative resistance to a wide range of antibiotics.[39] Aloin, present in the gel, is metabolized by the colonic flora to reactive *Aloe*-emodin, which is responsible for

the purgative activity. *Aloe*-emodin isolated from *A. vera* inhibits colon cancer cell migration by downregulating MMP-2/9 and also inhibits *ras a* homolog family member B and vascular endothelial growth factor (VEGF) via reducing DNA binding activity of nuclear factor κ-light-chain-enhancer of activated B cells.[40] *A. vera* gel has been shown to contain five phytosterols, which are able to reduce visceral fat accumulation, and influences the metabolism of glucose and lipids in animal model experiments, where they reduced large-sized intestinal polyps and ameliorated reduction in plasma. High molecular weight adiponectin levels in adenomatous polyposis coli gene-deficient multiple intestinal neoplasia mice fed high-fat diet. Further, an *in vitro* study has shown that *A. vera* gel and whole leaf extract were able to reduce significantly the transepithelial electrical resistance of the Caco-2 cell monolayers and thereby showed the ability to open tight junctions between adjacent cells. Hence, *A. vera* gel and whole leaf extract solutions significantly enhanced the transport of insulin across the Caco-2 cell monolayers.[41]

2.4. Antidiabetic effect

Clinical studies have suggested that *A. vera* gel may act as a safe antihyperglycemic and antihypercholesterolemic agent for type 2 diabetic patients without any significant effects on other normal blood lipid levels or liver/kidney function.[42] *In vivo* and *in vitro* studies strongly demonstrate that the water soluble fraction of *Aloe* spp. possesses glucose-lowering activities and some of its components modulate glucose transporter-4 mRNA expression.[43] In a randomized controlled trial, *A. vera* gel complex reduced body weight, body fat mass, and insulin resistance in obese prediabetes and early nontreated diabetic patients.[45] Further, in a pilot study, two *Aloe* products in patients with prediabetes over an 8-week period, tended to revert the impaired fasting glucose and impaired glucose tolerance observed in conditions of prediabetes/metabolic syndrome.[45] One study discussed the efficacy of aloe-emodin-8-*O*-glycoside isolated from *A. vera* gel in enhancing glucose transport by modulating the proximal and distal markers involved in glucose uptake and its transformation into glycogen.[46] Tanaka et al reported reductions in both fasting and random blood glucose levels of db/db diabetic mice chronically treated with the same phytosterols from *A. vera* gel.[47] Jain et al found that *A. vera* gel has significant antidiabetic and cardioprotective activity as it significantly reduced oxidative stress in streptozocin induced diabetic rats and improved antioxidant status.[48] *A. vera* gel also helps to improve the carbohydrate metabolism, with a recent report suggesting that it helps to improve metabolic condition in obese prediabetes and early nontreated diabetic patients by reducing body weight, body fat mass, fasting blood glucose, and fasting serum insulin in obese individuals.[44] Shin et al shown that dietary *Aloe* formula also reduces obesity-induced glucose tolerance not only by suppressing inflammatory responses but also by inducing anti-inflammatory cytokines in the white adipose tissue and liver, both of which are important peripheral tissues affected by insulin resistance.[49] *A. vera* also has shown improvement in the function of isolated rat pancreatic islets wherein it increased survival of the islet cells, their mitochondrial activity, and insulin levels at the same time as reducing production of reactive oxygen species.[50]

2.5. Antioxidant effect

A. vera contains substantial amounts of antioxidants including α-tocopherol (vitamin E), carotenoids, ascorbic acid (vitamin C), flavonoids, and tannins,[4] and it has been suggested that antioxidant action may be an important property of plant medicines used in treatment of various diseases. Topical *A. saponaria* treatment has shown antinociceptive and anti-inflammatory effects in ultraviolet B-induced sunburn model via its antioxidant components present in gel.[51] *Aloe* gel is able to scavenge the free radicals 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) $(ABTS)^{+\bullet}$, and nitric oxide in a concentration-dependent manner, as seen in an *in vitro* study of the radioprotective efficacy of *A. vera* gel.[52] Administration of ethanolic extract of *A. vera* gel on tissue antioxidants led to reduction in blood glucose level in diabetic rats, which helps to prevent excessive formation of free radicals through various biochemical pathways and also reduces the potential glycation of the enzymes.[53,54] *In vitro* and *in vivo* antioxidant potentials of a polysaccharide isolated from *A. vera* gel were investigated. Enzymatic extracts were prepared from *A. vera* gel using 10 digestive enzymes including five carbohydrases and five proteases. Results suggested that *Aloe* polysaccharides exhibited a protective effect against 2,2′-azobis(2-amidinopropane) dihydrochloride-induced oxidative stress and cell death in kidney epithelial cells (Vero cells) as well as in an *in vivo* zebrafish model.[39] One study determined the total phenolic content of *A. vera* leaf skin extracts and a significant correlation was established between the total phenolic content and the antioxidant capacity.[54] The methanol extracts of leaf skins and flowers of *A. vera* were also screened for their antioxidant and antimycoplasmic activities, and *in vitro* antioxidant activities of both extracts exhibited antioxidant activity, with the leaf skin extract being the most active.[55]

2.6. Hepatoprotective effect

Isolated phytosterols, namely lophenol and cycloartanol, have the ability to induce the downregulation of fatty acid synthesis and a tendency for upregulation of fatty acid oxidation in the liver, which favors the reduction in intra-abdominal fat and improvement of hyperlipidemia. Further, addition to sterol regulatory element-binding transcription factor 1/peroxisome proliferator-activated receptor (PPAR)-α ratio was decreased; metabolic syndrome-related disorders were improved and liver steatosis in *Aloe*-sterol-treated Zucker diabetic fatty rats.[56] *Aloe* formulas also suppress obesity-induced inflammatory responses by reducing levels of the proinflammatory cytokines, PPARγ/liver X receptor α, and 11β-hydroxysteroid dehydrogenase 1, and enhance anti-inflammatory cytokines in white adipose tissue and liver. The beneficial effects of *Aloe* formula with respect to obesity-induced insulin resistance and hepatic steatosis have been associated with its action on PPARγ/liver X receptor α.[50] Saito et al showed that *A. vera* gel extract prevents ethanol-induced fatty liver by suppressing mRNA expression of lipogenic genes in the liver. The combination of probiotic *Lactobacillus rhamnosus* GG and *A. vera* gel have a therapeutic potential to decrease cholesterol levels and the risk of cardiovascular diseases.[57]

2.7. Anticancer activity

Aloin, an anthraquinone being a natural compound and the main ingredient of *Aloe*, has been documented for its remarkable potential therapeutic options in cancer, wherein it showed chemoprotective effects against 1,2-dimethylhydrazine-induced preneoplastic lesions in the colon of Wistar rats.[58] Aloin treatment could inhibit the secretion of VEGF in cancer cells. VEGF is one of the most important proangiogenic cytokines known and well characterized as an inducer of tumor neovascularization. Aloin treatment significantly inhibited *in vitro* VEGF-induced angiogenic response of human endothelial cells, causing an inhibition of proliferation and migration of endothelial cells.[59] *Aloe*-emodin (AE), is also a subtype of anthraquinone, a natural compound that has traditionally been found to have diverse biological activities

including anticancer functions.[60,61] AE (1,8-dihydroxy-3-hydroxymethyl-9,10-anthracenedione) is an herbal anthracenedione derivative from *A. vera* leaves. Recent reports have shown that AE possesses antiproliferation effects on some types of cancer cells, such as lung, squamous, glioma, and neuroectodermal cancer cells.[62,63] The inhibitory effect of AE on the activity and gene expression of *N*-acetyl transferase, which plays an initial role in the metabolism of aryl amine carcinogens, was found in human malignant melanoma cells.[64,65] Recently, Lin et al demonstrated that AE-induced apoptosis in T24 human bladder. Aloin, derived from *A. vera* leaves, has been shown to possess anticancer potential activities,[65] as it inhibits tumor angiogenesis and growth via blocking signal transducer and activator of transcription 3 activation, with the potential of a drug candidate for cancer therapy.[66] Anthraquinone derivatives such as emodin-like natural (emodin, rhein, and aloin) and synthetic (anthraquinone-2-sulfonic acid) anthraquinones have recently been shown to protect in models of amyloid β and τ aggregation-induced cell death through antiaggregation properties, and/or enhancing the phosphatidylinositol-3-kinase/protein kinase B survival mechanism, which suggests that anthraquinone-2-sulfonic acid could be a new neuroprotective compound and a novel caspase inhibitor.[67]

2.8. Antimicrobial activity

A. vera has been described as an antibacterial agent. The *Aloe* protein of 14 kDa from the *A. vera* leaf gel was isolated and the purified *Aloe* protein exhibited a potent antifungal activity against *Candida paraprilosis, Candida krusei*, and *Candida albicans*.[68] *A. vera* has anthraquinones as an active compound, which is structural analogue of tetracycline. The anthraquinones acts like tetracycline that inhibits bacterial protein synthesis by blocking the ribosomal A site (where the aminoacylated tRNA enters). Therefore, the bacteria cannot grow in the media containing *A. vera* extract. Pandey and Mishra established the susceptibility of Gram-positive and Gram-negative bacteria to an extract of the inner gel of *A. vera*.[10,69,70] Polysaccharides of *A. vera* gel have been attributed direct bacterial activity through the stimulation of phagocytic leucocytes to destroy bacteria.[71] *A. vera* contains pyrocatechol a hydroxylated phenol, known to have toxic effect on microorganisms.[72,73] A recent study demonstrated that the *A. vera* inner gel expresses antibacterial properties against both susceptible and resistant *Helicobacter pylori* strains and impact on the antimicrobial resistance phenomenon of *H. pylori*, proposing the *A. vera* inner gel as a novel effective natural agent for combination with antibiotics for the treatment of *H. pylori* gastric infection.[18]

2.9. Antiviral activity

Many reports have suggested that *A. vera* gel has antiviral activity that prevent virus adsorption, attachment, or entry to the host cell. An *in vitro* study has shown that crude extract of *A. vera* gel has antiviral activity against herpes simplex virus type 2 strain.[74] Anthraquinone derivatives, such as *Aloe*-emodin, emodin, and chrysophanol, reportedly exhibit antiviral activity wherein their inhibitory mechanism and effect against influenza A virus with reducing virus-induced cytopathic effect and inhibiting replication of influenza A.[75] Preliminary trials have suggested that *A. vera* consumption may be of help to HIV-infected individuals as it improves the immune system by increasing the CD4 count.[76] Many methods have been developed for the successful transformation and regeneration of *A. vera* wherein *Aloe* able to produced IFNα2. This experiment was assessed using an antiviral assay with A549 cells wherein these cells treated with extracts from both the rind and pulp fractions of the shoot and subsequently infected with the lytic *Encephalomyocarditis* virus. This experiment demonstrated that *A. vera* was capable of expressing a human protein with its biological activity namely interferon alpha 2 (IFNα2).[77]

2.10. Effect on estrogen status

Isolated emodin and aloe-emodin from *A. vera* gel specifically suppress breast cancer cell proliferation by targeting estrogen receptor-α protein stability through distinct mechanisms, which suggests a possible application of anthraquinones in preventing breast cancer cell proliferation through estrogen receptor-α inhibition.[78] *A. vera* gel also helps to maintain ovarian steroid status in polycystic ovary-like condition wherein steroidogenesis altered and disturbed estrogen:testosterone ratio.[79]

2.11. Antihyperlipidemic activity

A. vera is known for its antihyperlipidemic property wherein it has beneficial effects on the prevention of fatty streak development and may help to reduce the development of atherosclerosis through modification of risk factors.[42] *A. vera* leaf gel efficacy has been checked in hyperlipidemic type 2 diabetic patients: a randomized double-blind placebo-controlled clinical trial wherein it reduced total cholesterol and LDL levels significantly.[42] A recent study also demonstrated that administration of phytosterols isolated from *A. vera* gel reduces visceral fat mass and improves hyperglycemia in Zucker diabetic fatty rats.[80] Dried pulp of *Aloe succotrina* leaves produced significant antihyperlipidemic effect in high-fat diet- and fructose-induced hyperlipidemic rats, where it significant decreased serum levels of total cholesterol, total triglycerides, low-density lipoprotein–cholesterol, very low-density lipoprotein, and high-density lipoprotein–cholesterol.[81] Previous reports also suggested that *A. vera* gel-treated polycystic ovarian syndrome (PCOS) rats exhibited significant reduction in plasma triglyceride and LDL cholesterol levels, with an increase in high-density lipoprotein–cholesterol PCOS condition wherein hyperlipidemia is one of main consequences. The gel treatment also caused reversion of abnormal estrous cyclicity, glucose intolerance, and lipid metabolizing enzyme activities, bringing them to normal. It has phytocomponents with antihyperlipidemic effects and has shown efficacy also in management of PCOS but also the associated metabolic complications.[79,82]

2.12. Antiulcer activity

A. vera is an herbal remedy widely used for a variety of illnesses; *A. vera* leaf extracts have been promoted for digestion and are used in the treatment of peptic ulcer for cytoprotective action whereby *A. vera* gel expresses antibacterial properties against both susceptible and resistant *H. pylori* strains and acts as a novel effective natural agent for combination with antibiotics for the treatment of *H. pylori* gastric infection.[37] One study demonstrated that newly formulated aloe- and myrrh-based gels proved to be effective in topical management of minor recurrent aphthous stomatitis and was superior in decreasing ulcer size, erythema, and exudation; myrrh resulted in more pain reduction in a randomized, double-blind, vehicle-controlled study.[83]

3. Discussion

Since ages, *Aloe* species have been exploited for various medicinal efficacies because of their phyto-chemical constituents.[13] Having therapeutic, rejuvenating and health enhancing properties, Aloe vera gel is widely used in food, healthcare and medicinal industries. It is seen from the literature that *A. vera* is a very

important plant for its large number of medicinal properties as well as medicinally important chemicals such as amino acids, anthraquinones, enzymes, hormones, sterols, and vitamins.[4]

Reports have shown that polysaccharides isolated from *A. vera* demonstrate various pharmacological effects, such as anti-inflammatory, wound healing, antihepatitis, antigastric ulcer, and antitumorigenicity in animals, although some side effects of *Aloe* have been found in humans. Hence, some experimental studies have been performed to confirm the upper dose of *A. vera* gel without any side effects to establish the maximal allowable daily intake of active *Aloe*. They were based on 4-week oral toxicity investigation in imprinting control region mice, which did not induce any remarkable subacute toxic effects, but decreased male kidney weights.[84] Several studies have attempted to determine whether or not *A. vera* causes toxicity in animals or humans. During a chronic 90-day study, *A. vera* leaf pulp at a dose of 100 mg/kg in the drinking water caused decreased body and vital organ weights, decreased red cell counts, a significant spermatogenic dysfunction, and a 30% lethality compared with control animals.[85] Extracts from the leaves of *A. vera* have long been used as herbal remedies and are also now promoted as a dietary supplement, in liquid tonics, powders or tablets, as a laxative, and to prevent a variety of illnesses. However, some studies have demonstrated effects of *A. vera* extract on rats and mice to identify potential toxic or cancer-related hazards.[17] Dosed water studies in mice revealed no acute toxicity of the leaf pulp at 500 mg/kg.[17] At higher doses, however, a decrease of central nervous system activity was observed. During subchronic 90-day studies, increased mortality, decreased red blood cell count, and significant sperm damage were noted, in addition to decreased central nervous system activity.[86] Hence, an upper limit of dose of *A. vera* gel plays a crucial role for the treatment of various diseases, which helps to manage disease condition without side effects.

From the whole plant, *A. vera* latex is a laxative that is regulated as a drug by the Food and Drug Administration and used as a bitter flavoring additive by the food industry; *A. vera* gel is primarily a topical agent for skin wounds and irritations but is also taken internally for the treatment of gastric ulcers and diabetes; and the whole leaf extract, which combines both the gel and latex, is popular as a dietary supplement for various systemic ailments and is promoted as a potential anticancer, anti-AIDS, and antidiabetic agent.

4. Conclusion

The plant exhibits many pharmacological activities such antioxidant, antimicrobial, immune boosting, antitumor, hypoglycemic, hypolipidemic, wound healing, and antidiabetic.[86] Many traditional uses are also reported such as burn injury, eczema, cosmetics, inflammation, and fever, which continue to be studied, and further research still has to be done. Thus, it is quite promising as a multipurpose medicinal agent so further experiments are needed to isolate and to find out the mechanism of the bioactive chemicals using modern instruments, such as high-performance liquid chromatography, high-performance thin layer chromatography, and nuclear magnetic resonance, and extended clinical trials on the road to generate novel drugs. The US Food and Drug Administration has already approved the developmental study of *A. vera* in the treatment of cancer and AIDS. In future, controlled studies are required to prove the effectiveness of *A. vera* under various conditions.

Conflicts of interest

All contributing authors declare no conflicts of interest.

References

1. Reynolds T, Dweck AC. *Aloe vera* gel leaf: a review update. *J Ethnopharmacol*. 1999;68:3–37.
2. Eshun K, Qian H. *Aloe vera*: a valuable ingredient for the food, pharmaceutical and cosmetic industries—a review. *Crit Rev Food Sci Nutr*. 2004;44:91–96.
3. Foster M, Hunter D, Samman S. Evaluation of the nutritional and metabolic effects of *Aloe vera*. In: Benzie IFF, Wachtel-Galor S, eds. *Herbal Medicine: Biomolecular and Clinical Aspects*. 2nd ed. Boca Raton: CRC; 2011.
4. Hamman JH. Composition and applications of *Aloe vera* leaf gel. *Molecules*. 2008;13:1599–1616.
5. Femenia A, Sanchez ES, Simal S, Rossello C. Compositional features of polysaccharides from *Aloe vera* (*Aloe barbadensis* Miller) plant tissues. *Carbohydr Polym*. 1999;39:109–117.
6. Ni Y, Turner D, Yates KM, Tizard I. Isolation and characterization of structural components of *Aloe vera* L. leaf pulp. *Int Immunopharmacol*. 2004;4:1745–1755.
7. Hutter JA, Salman M, Stavinoha WB, et al. Antiinflammatory C-glucosyl chromone from *Aloe barbadensis*. *J Nat Prod*. 1996;59:541–543.
8. Chow JT-N, Williamson DA, Yates KM, Goux WJ. Chemical characterization of the immunomodulating polysaccharide of *Aloe vera* L. *Carbohydr Res*. 2005;340:1131–1142.
9. Lee KY, Weintraub ST, Yu BP. Isolation and identification of a phenolic antioxidant from *Aloe barbadensis*. *Free Radic Biol Med*. 2000;28:261–265.
10. Habeeb F, Shakir E, Bradbury F, et al. Screening methods used to determine the anti-microbial properties of *Aloe vera* inner gel. *Methods*. 2007;42:315–320.
11. Avijgan M, Mahboubi M, Moheb Nasab M, Ahmadi Nia E, Yousefi H. Synergistic activity between *Echinophora platyloba* DC ethanolic extract and azole drugs against clinical isolates of *Candida albicans* from women suffering chronic recurrent vaginitis. *J Mycol Med*. 2014;24:112–116.
12. O'Brien C, van Wyk BE, van Heerden FR. Physical and chemical characteristics of *Aloe ferox* leaf gel. *S Afr J Botany*. 2011;77:988–995.
13. Hossain MS, Mamun-Or-Rashid ANM, Towfique NM, Sen MK. A review on ethnopharmacological potential of *Aloe vera* L. *J Intercult Ethnopharmacol*. 2013;2:113–120.
14. Miladi S, Damak M. *In vitro* antioxidant activities of *Aloe vera* leaf skin extracts. *J Soc Chim Tunisie*. 2008;10:101–109.
15. Serrano M, Valverde JM, Guillen F, Castillo S, Martinez-Romero D, Valero D. Use of *Aloe vera* gel coating preserves the functional properties of table grapes. *J Agric Food Chem*. 2006;54:3882–3886.
16. Park YI, Jo TH. Perspective of industrial application of *Aloe vera*. In: Park YI, Lee SK, eds. *New Perspective on Aloe*. New York: Springer Verlag; 2006:199–200. ISBN 0387317996.
17. Boudreau M, Beland F. An evaluation of the biological and toxicological properties of *Aloe barbadensis* (Miller), *Aloe vera*. *J Environ Sci Heal*. 2006;C 24:103–154.
18. Tan Z, Li F, Xing J. Separation and purification of *Aloe* anthraquinones using PEG/salt aqueous two-phase system. *Sep Sci Technol*. 2011;46:1503–1510.
19. Mizuuchi Y, Shi SP, Wanibuchi K, et al. Novel type III polyketide synthases from *Aloe arborescens*. *FEBS J*. 2009;276:2391–2401.
20. Lee YS, Ju HK, Kim YJ, et al. Enhancement of anti-inflammatory activity of *Aloe vera* adventitious root extracts through the alteration of primary and secondary metabolites via salicylic acid elicitation. *PLoS One*. 2013;8:e82479.
21. Rajasekaran S, Ravi K, Sivagnanam K, Subramanian S. Beneficial effects of *Aloe vera* leaf gel extract on lipid profile status in rats with streptozotocin diabetes. *Clin Exp Pharmacol Physiol*. 2006;33:232–237.
22. Grace OM, Simmonds MS, Smith GF, Wyk AE. Therapeutic uses of *Aloe* L. (Asphodelaceae) in southern Africa. *J Ethnopharmacol*. 2008;119:604–614.
23. Tarameshloo M, Norouzian M, Zarein-Dolab S, Dadpay M, Mohsenifar J, Gazor R. *Aloe vera* gel and thyroid hormone cream may improve wound healing in Wistar rats. *Anat Cell Biol*. 2012;45:170–177.
24. Liu C, Leung MYK, Koon JCM, et al. Macrophage activation by polysaccharide biological response modifier isolated from *Aloe vera* L. var. chinensis (Haw.) Berg. *Int Immunopharmacol*. 2006;18:1634–1641.
25. Subramanian S, Kumar DS, Arulselvan P. Wound healing potential of *Aloe vera* leaf gel studied in experimental rats. *Asian J Biochem*. 2006;1:178–185.
26. Liu LY, Chen XD, Wu BY, Jiang Q. Influence of *Aloe* polysaccharide on proliferation and hyaluronic acid and hydroxyproline secretion of human fibroblasts *in vitro*. *Zhong Xi Yi Jie He Xue Bao*. 2010;8:256–262 [in Chinese].
27. Chantarawaratit P, Sangvanich P, Banlunara W, Soontornvipart K, Thunyakitpisal P. Acemannan sponges stimulate alveolar bone, cementum and periodontal ligament regeneration in a canine class II furcation defect model. *J Periodontal Res*. 2013;49:164–178.
28. Shahzad MN, Ahmed N. Effectiveness of *Aloe vera* gel compared with 1% silver sulphadiazine cream as burn wound dressing in second degree burns. *J Pak Med Assoc*. 2013;63:225–230.
29. Tabandeh MR, Oryan A, Mohammadalipour A. Polysaccharides of *Aloe vera* induce MMP-3 and TIMP-2 gene expression during the skin wound repair of rat. *Int J Biol Macromol*. 2014;65:424–430.
30. Budai MM, Varga A, Milesz S, Tőzsér J, Benko S. *Aloe vera* downregulates LPS-induced inflammatory cytokine production and expression of NLRP3 inflammasome in human macrophages. *Mol Immunol*. 2013;56:471–479.
31. Duansak D, Somboonwong J, Patumraj S. Effect of *Aloe vera* on leukocyte adhesion and TNF-α and IL-6 levels in burn wounded rats. *Med Biochem Biophys*. 2009;29:239–246.

32. Liu Z, Ge X, Lu Y, Dong S, Zhao Y, Zeng M. Effects of chitosan molecular weight and degree of deacetylation on the properties of gelatine-based films. *Food Hydrocolloids*. 2012;26:311–317.
33. Im SA, Oh ST, Song S, et al. Identification of optimal molecular size of modified Aloe polysaccharides with maximum immunomodulatory activity. *Int Immunopharmacol*. 2005;5:271–279.
34. Picchietti S, Bernini C, Belardinelli MC, et al. Immune modulatory effects of *Aloe arborescens* extract on the piscine SAF-1 cell line. *Fish Shellfish Immunol*. 2012;34:1335–1344.
35. Park MY, Kwon HJ, Sung MK. Evaluation of aloin and aloe-emodin as anti-inflammatory agents in aloe by using murine macrophages. *Biosci Biotechnol Biochem*. 2009;73:828–832.
36. Langmead L, Makins RJ, Rampton DS. Anti-inflammatory effects of *Aloe vera* gel in human colorectal mucosa *in vitro*. *Aliment Pharmacol Ther*. 2004;19:521–527.
37. Babaee N, Zabihi E, Mohseni S, Moghadamnia AA. Evaluation of the therapeutic effects of *Aloe vera* gel on minor recurrent aphthous stomatitis. *Dent Res J (Isfahan)*. 2012;9:381–385.
38. Carien B, Alvaro V, Josias H. Modulation of drug efflux by aloe materials: an *in vitro* investigation across rat intestinal tissue. *Pharmacogn Mag*. 2013;9:44–48.
39. Kang MC, Kim SY, Kim YT, et al. *In vitro* and *in vivo* antioxidant activities of polysaccharide purified from *Aloe vera* (*Aloe barbadensis*) gel. *Carbohydr Polym*. 2014;99:365–371.
40. Suboj P, Babykutty S, Valiyaparambil Gopi DR, Nair RS, Srinivas P, Gopala S. *Aloe* emodin inhibits colon cancer cell migration/angiogenesis by downregulating MMP-2/9, RhoB and VEGF via reduced DNA binding activity of NF-κB. *Eur J Pharm Sci*. 2012;45:581–591.
41. Chen W, Lu Z, Viljoen A, Hamman J. Intestinal drug transport enhancement by *Aloe vera*. *Planta Med*. 2009;75:587–595.
42. Huseini HF, Kianbakht S, Hajiaghaee R, Dabaghian FH. Anti-hyperglycemic and anti-hypercholesterolemic effects of *Aloe vera* leaf gel in hyperlipidemic type 2 diabetic patients: a randomized double-blind placebo-controlled clinical trial. *Planta Med*. 2012;78:311–316.
43. Kumar R, Sharma B, Tomar NR, Roy P, Gupta AK, Kumar A. *In vivo* evaluation of hypoglycemic activity of *Aloe* spp. and identification of its mode of action on GLUT-4 gene expression *in vitro*. *Appl Biochem Biotechnol*. 2011;164:1246–1256.
44. Choi HC, Kim SJ, Son KY, Oh BJ, Cho BL. Metabolic effects of *Aloe vera* gel complex in obese prediabetes and early non-treated diabetic patients: randomized controlled trial. *Nutrition*. 2013;29:1110–1114.
45. Devaraj S, Jialal R, Jialal I, Rockwood R. A pilot randomized placebo controlled trial of 2 *Aloe vera* supplements in patients with pre-diabetes/metabolic syndrome. *Planta Med*. 2008;74:SL77.
46. Anand S, Muthusamy VS, Sujatha S, et al. *Aloe* emodin glycosides stimulates glucose transport and glycogen storage through PI3K dependent mechanism in L6 myotubes and inhibits adipocyte differentiation in 3T3L1 adipocytes. *FEBS Lett*. 2010;584:3170–3178.
47. Tanaka M, Misawa E, Ito Y, et al. Identification of five phytosterols from *Aloe vera* gel as anti-diabetic compounds. *Biol Pharm Bull*. 2006;29:1418–1422.
48. Jain N, Vijayaraghavan R, Pant SC, Lomash V, Ali M. *Aloe vera* gel alleviates cardiotoxicity in streptozocin-induced diabetes in rats. *J Pharm Pharmacol*. 2010;62:115–123.
49. Shin E, Shim KS, Kong H, et al. Dietary *Aloe* improves insulin Sensitivity via the suppression of obesity-induced inflammation in obese mice. *Immune Netw*. 2011;11:59–67.
50. Rahimifard M, Navaei-Nigjeh M, Mahroui N, et al. Improvement in the function of isolated rat pancreatic islets through reduction of oxidative stress using traditional Iranian medicine. *Cell J*. 2013;16:147–163.
51. Silva MA, Trevisan G, Hoffmeister C, et al. Anti-inflammatory and antioxidant effects of *Aloe saponaria* Haw in a model of UVB-induced paw sunburn in rats. *J Photochem Photobiol B*. 2014;133:47–54.
52. Saini DK, Saini MR. Evaluation of radioprotective efficacy and possible mechanism of action of Aloe gel. *Environ Toxicol Pharmacol*. 2011;31:427–435.
53. Rajasekaran S, Sivagnanam K, Subramanian S. Modulatory effects of *Aloe vera* leaf gel extract on oxidative stress in rats treated with streptozotocin. *J Pharm Pharmacol*. 2005;57:241–246.
54. Kammoun M, Miladi S, Ben Ali Y, Damak M, Gargouri Y, Bezzine S. *In vitro* study of the PLA2 inhibition and antioxidants activities of *Aloe vera* leaf skin extracts. *Lipids Health Dis*. 2011;10:30.
55. Lopez A, de Tangil MS, Vega-Orellana O, Ramirez AS, Rico M. Phenolic constituents, antioxidant and preliminary antimycoplasmic activities of leaf skin and flowers of *Aloe vera* (L.) Burm. f. (syn. *A. barbadensis* Mill.) from the Canary Islands (Spain). *Molecules*. 2013;18:4942–4954.
56. Misawa E, Tanaka M, Nomaguchi K, et al. Oral ingestion of *Aloe vera* phytosterols alters hepatic gene expression profiles and ameliorates obesity-associated metabolic disorders in Zucker diabetic fatty rats. *J Agric Food Chem*. 2012;60:2799–2806.
57. Kumar M, Rakesh S, Nagpal R, et al. Probiotic *Lactobacillus rhamnosus* GG and *Aloe vera* gel improve lipid profiles in hypercholesterolemic rats. *Nutrition*. 2013;29:574–579.
58. Hamiza OO, Rehman MU, Khan R, et al. Chemopreventive effects of aloin against 1,2-dimethylhydrazine-induced preneoplastic lesions in the colon of Wistar rats. *Hum Exp Toxicol*. 2014;33:148–163.
59. Pan Q, Pan H, Lou H, Xu Y, Tian L. Inhibition of the angiogenesis and growth of aloin in human colorectal cancer *in vitro* and *in vivo*. *Cancer Cell Int*. 2013;13:69.
60. Lin SY, Lai WW, Ho CC, et al. Emodin induces apoptosis of human tongue squamous cancer SCC-4 cells through reactive oxygen species and mitochondria-dependent pathways. *Anticancer Res*. 2009;29:327–335.
61. Muto A, Hori M, Sasaki Y, et al. Emodin has a cytotoxic activity against human multiple myeloma as a Janus-activated kinase 2 inhibitor. *Mol Cancer Ther*. 2007;6:987–994.
62. Lin ML, Lu YC, Su HL, et al. Destabilization of CARP mRNAs by aloeemodin contributes to caspase-8-mediated p53-independent apoptosis of human carcinoma cells. *J Cell Biochem*. 2011;112:1176–1191.
63. Masaldan S, Iyer VV. Exploration of effects of emodin in selected cancer cell lines: enhanced growth inhibition by ascorbic acid and regulation of LRP1 and AR under hypoxia-like conditions. *J Appl Toxicol*. 2014;34:95–104.
64. Lin CC, Kao ST, Chen GW, Chung JG. Berberine decreased N-acetylation of 2-aminofluorene through inhibition of N-acetyltransferase gene expression in human leukemia HL-60 cells. *Anticancer Res*. 2005;25:4149–4155.
65. Lin JG, Chen GW, Li TM, Chouh ST, Tan TW, Chung JG. Aloe-emodin induces apoptosis in T24 human bladder cancer cells through the p53 dependent apoptotic pathway. *J Urol*. 2006;175:343–347.
66. Jackson TC, Verrier JD, Kochanek PM. Anthraquinone-2-sulfonic acid (AQ2S) is a novel neurotherapeutic agent. *Cell Death Dis*. 2013;4:e451.
67. Das S, Mishra B, Gill K, et al. Isolation and characterization of novel protein with anti-fungal and anti-inflammatory properties from *Aloe vera* leaf gel. *Int J Biol Macromol*. 2011;48:38–43.
68. Pandey R, Mishra A. Antibacterial activities of crude extract of *Aloe barbadensis* to clinically isolated bacterial pathogens. *Appl Biochem Biotechnol*. 2010;160:1356–1361.
69. Ferro VA, Bradbury F, Cameron P, Shakir E, Rahman SR, Stimson WH. *In vitro* susceptibilities of *Shigella flexneri* and *Streptococcus pyogenes* to inner gel of *Aloe barbadensis* Miller. *Agents Chemother*. 2003;47:1137–1139.
70. Lawless J, Allan J. The clinical composition of *Aloe vera*. In: *Aloe vera: Natural Wonder Cure*. London: Thorsons Publishing Ltd; 2000:161–171.
71. Pugh N, Ross SA, ElSohly MA, Pasco DS. Characterization of Aloeride, a new high molecular weight polysaccharide from *Aloe vera* with potent immunostimulatory activity. *J Agric Food Chem*. 2001;49:1030–1034.
72. Kametani S, Yuasa AK, Kikuzaki H, Kennedy DO, Honzawa M, Yuasa M. Chemical constituents of Cape Aloe and their synergistic growth inhibiting effect on Ehrlich ascites tumor cells. *Biosci Biotechnol Biochem*. 2007;71:1220–1229.
73. Cowan MM. Plant products as antimicrobial agents. *Clin Microbiol Rev*. 1999;12:564–582.
74. Cellini L, Di Bartolomeo S, Campli E, Genovese S, Locatelli M, Di Giulio M. *In vitro* activity of *Aloe vera* inner gel against *Helicobacter pylori* strains. *Lett Appl Microbiol*. 2014;59:43–48.
75. Li SW, Yang TC, Lai CC, et al. Antiviral activity of *Aloe*-emodin against influenza A virus via galectin-3 up-regulation. *Eur J Pharmacol*. 2014;27:125–132.
76. Olatunya OS, Olatunya AM, Anyabolu HC, Adejuyigbe EA, Oyelami OA. Preliminary trial of *Aloe vera* gruel on HIV infection. *J Altern Complement Med*. 2012;18:850–853.
77. Lowther W, Lorick K, Lawrence SD, Yeow WS. Expression of biologically active human interferon alpha 2 in *Aloe vera*. *Transgenic Res*. 2012;21:1349–1357.
78. Huang PH, Huang CY, Chen MC, et al. Emodin and *Aloe*-emodin suppress breast cancer cell proliferation through ERα inhibition. *Evid Based Complement Alternat Med*. 2013;2013:376123.
79. Maharjan R, Nagar PS, Nampoothiri L. Effect of *Aloe barbadensis* Mill. formulation on Letrozole induced polycystic ovarian syndrome rat model. *J Ayurveda Integr Med*. 2010;1:273–279.
80. Dana N, Javanmard SH, Asgary S, Asnaashari H, Abdian N. The effect of *Aloe vera* leaf gel on fatty streak formation in hypercholesterolemic rabbits. *J Res Med Sci*. 2012;17:439–442.
81. Dhingra D, Lamba D, Kumar R, Nath P, Gauttam S. Antihyperlipidemic activity of *Aloe succotrina* in rats: possibly mediated by inhibition of HMG-CoA reductase. *ISRN Pharmacol*. 2014;2014:243575.
82. Desai BN, Maharjan RH, Nampoothiri LP. *Aloe barbadensis* Mill. formulation restores lipid profile to normal in a letrozole-induced polycystic ovarian syndrome rat model. *Pharmacognosy Res*. 2012;4:109–115.
83. Mansour G, Ouda S, Shaker A, Abdallah HM. Clinical efficacy of new *Aloe vera*- and myrrh-based oral mucoadhesive gels in the management of minor recurrent aphthous stomatitis: a randomized, double-blind, vehicle-controlled study. *J Oral Pathol Med*. 2014;43:405–409.
84. Kwack SJ, Kim KB, Lee BM. Estimation of tolerable upper intake level (UL) of active *Aloe*. *J Toxicol Environ Health A*. 2009;72:1455–1462.
85. Shah AH, Quereshi S, Tariq M, Ageel AM. Toxicity studies on six plants used in the traditional Arab system of medicine. *Phytother Res*. 1989;3:25–29.
86. Boudreau MD, Beland FA, Nichols JA, Pogribna M. Toxicology and carcinogenesis studies of a noncolorized whole leaf extract of *Aloe barbadensis* Miller (*Aloe vera*) in F344/N rats and B6C3F1 mice (drinking water study). *Natl Toxicol Program Tech Rep Ser*. 2013:1–266.