Review

# Aloe Barbadensis Miller (Aloe Vera)

## Pharmacological activities and clinical evidence for disease prevention

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**Abstract:** Aloe Barbadensis Miller (Aloe Vera, AV) is a widely recognized for its diverse health-promoting, skin care, and medicinal properties. This narrative review provides a comprehensive overview of AV's bioactive compounds, pharmacological activities, potential applications, its toxic and adverse effects, as well as the clinical evidence supporting AV's efficacy in disease prevention. AV contains over 200 bioactive compounds, with the inner clear gel of the leaves containing the majority of these compounds. These include phenolic acids (274.5–307.5 mg/100 g), flavonoids. (3.63–4.70 g/kg), polysaccharides (3.82–6.55 g/kg), saponins, alkaloids, terpenoids, and anthraquinone derivatives. Findings from clinical studies involving both humans and animals highlight the therapeutic potential of AV across diverse health domains. The studies demonstrate AV's efficacy in reducing blood glucose levels, exhibiting antioxidant and immunomodulatory effects, inducing apoptosis in cancer cells, protecting the liver from damage, and displaying antimicrobial properties. In the fields of dermatology and dentistry, AV has also been observed to promote skin and oral health. However, it is imperative to acknowledge potential risks, adhere to recommended dosages, and seek guidance from healthcare experts before employing AV as a natural therapeutic option. Moreover, considering safety concerns, further well-designed randomized controlled trials are necessary to substantiate the potential benefits of AV and comprehensively assess any associated risks.

**Keywords:** Aloe Barbadensis Miller, Aloe Vera, healing plant, medicinal plant

## Introduction

The importance of ancient medicinal plants has been a topic of interest in nutrition research for many years. *Aloe Barbadensis Miller*, also known as *Aloe Vera* (AV), is renowned for its remarkable properties in promoting health, skin care, and medicinal benefits. The word "Aloe" is originated from an Arabic word "Alloeh", which means "shining bitter substance," while "Vera" is derived from the Latin word, meaning "true" [1]. For over 2000 years, AV has been revered as a healing herb in traditional medicine worldwide, especially in India, China, the West Indies, and Japan [2]. AV is available in different forms including fresh whole leaf, fresh gel (pulp), juice (sap and extract), and dried gel. It contains over 200 biologically active substances, such as anthraquinones (barbaloin, isobarbaloin, anthranols, aloetic acid), hydrosoluble and liposoluble vitamins, minerals, enzymes, polysaccharides, phenolic compounds, and organic acids [3, 4, 5, 6, 7]. These components exhibit diverse effects such as lipid-lowering, antibacterial, antimicrobial, anti-inflammatory, antioxidant, anti-obesity, anti-diabetic, immunomodulatory, antihypertensive, and cardioprotective effects. Consequently, AV has found extensive applications in the cosmetic, pharmaceutical and food industries [8, 9, 10]. Overall, this narrative review aims to summarize the published evidence relating to the history, botanical aspects, phytochemistry, pharmacological properties, safety and toxicity of AV.

### Ancient history

In the late 19th century, archaeologists traced back the origin of AV to 2200 B.C.E. through Sumerian clay tablets, where it was known as "Sibaru". Additional evidence of its usage was found in the ancient Egyptian medical document, the Ebers Papyrus, from 1552 B.C.E. The knowledge of AV spread from Egypt to Greece, leading to its documentation in pharmacopoeias. In AD 41–68, a Greek physician, Pedanius Dioscorides, compiled his findings on the medicinal properties of aloe in "De Materia Medica." In 600 B.C., Arab traders introduced AV to Persia, India and the Far East. The knowledge of aloe was also found in the sacred Hindu text from ancient India, The Rigveda. By the 15$^{th}$ century, European maritime powers (Spain, France and Britain), brought AV to their nations through expeditions and explorations. Spanish Physician, Diego Alverez Chanca,

described the use of aloes in a letter to Christopher Columbus during his second voyage to America in 1494. The plant eventually reached Southern California through Spanish sailors and the mission system. English botanist, Philip Miller, named it "*Aloe Barbadensis Miller*" on the Caribbean Island of Barbados about 200 years later. In ancient times, AV was used for various purposes, including treating skin conditions, wounds and diseases. It also had significant roles in longevity, religious rites and acupuncture [1, 11].

### Botanical description

AV, the most biologically active species among more than 500 species in the *Aloe* genus, is an evergreen succulent perennial plant belonging to Liliaceae family. Some botanists, included it in the Aloaceae family, a subdivision of the Liliaceae family, although this classification is not widely accepted [12, 13]. AV is known by various synonyms, including: *Aloe (A.) vera (L.) Burm. f. Barbados aloe; A. chinensis Bak; A. elongata Murray; A. indica Royle; A. officinalis Forsk; A. perfoliata L; A. rubescens DC; A. vera L. var. littoralis Konig ex Bak; A. vera L. var. chinensis Berger; and A. vulgaris Lam* [14].

### Geographical distribution

Due to its extensive cultivation worldwide, the exact natural occurrence of the AV plant remains uncertain. However, historical evidence suggests that it originated in the southern half of the Arabian Peninsula, and spread through North Africa, Sudan and neighbouring countries. It is also found in the Canary Islands, as well as temperate and tropical regions of Australia, Barbados, Belize, Nigeria, Paraguay and the United States. Nowadays, AV is cultivated in Europe, North America, South America, the Middle East, China, India, Pakistan and Australia. While most species of aloe occur in mainland Africa, some are specific to Madagascar or the Indian Ocean islands [11, 15].

### Ecology

AV, belonging to the Asparagales order, is a crassulacean acid metabolism plant known for its ability to thrive in arid and semi-arid environments with drought tolerance. It grows wild in tropical and subtropical regions, preferring well-drained sandy loam soil with an adequate sunlight and organic matter. Although aloe plant can survive hot, humid conditions and high rainfall, it does not thrive in freezing temperatures, shady environments, water stagnation or with the use of fertilisers [11, 16].

### Morphology

AV, taxonomically classified under class Equisetopsida and subclass Magnoliidae, is a stemless or short-stemmed plant (up to 30 cm long) belonging to the Aloe Acauleas category. It forms a rosette pattern with 12–20 fleshy, tapered, and spiny leaves, ranging from grey to green. The leaves can grow up to 40–50 cm long and 6–7 cm wide, containing a clear gel in the central mucilaginous pulp. During spring, AV produces yellow to red tubular flowers in simple or double raceme inflorescences. As a monoecious plant, it reproduces through propagation or mobile pollinators. AV has short, fibrous underground roots and bears loculicidal capsules with dark brown, winged seeds (about 7 mm long). The mature plant can reach a height of approximately 160 cm and is ready for harvest within 3 years. The leaves can be periodically cut for gel production every 12 weeks. The outer pulp of the leaf contains bitter anthraquinones, contributing to disease resistance and pest repellence. AV has a lifespan of up to 25 years or more, depending on growing conditions. Previous research suggests that factors such as salinity stress, vermicompost composition, irrigation levels, and nitrogen fertilization can influence AV's morphological and physiological traits [17, 18, 19, 20].

### Karyotype

Despite having an equal number of diploid chromosomes (n=7), aloe species exhibit karyotypic variations. The chromosomes in this monocot species demonstrate a bimodal nature. The haploid set of the genome consists of 3 pairs of small sub-metacentric and 4 pairs of long sub-telocentric chromosomes. The karyotype is asymmetrical, following the formula $6S_m+8S_t$, with the nucleolar region located in the 1$^{st}$ and 4$^{th}$ pairs of sub-telocentric chromosomes [21].

### Phytochemistry

The AV leaf consists of three layers. The inner, clear gel or mucilaginous layer, is primarily composed of water (99–99.5%) with a pH of 4.5. The remaining solid material (0.5–1.0%) contains potentially active compounds like polysaccharides, vitamins, amino acids, lipids, and sterols. The middle layer having bitter yellow sap or aloe latex, contains anthraquinones or anthracene (10% to 40%) and their glycosides. The outer thick layer, called the rind, synthesizes carbohydrates (about 25%) and proteins. However, the chemical composition of AV can vary based on plant species, climate, growing conditions, and geographical factors [1].

### Nutritive value

The proximate composition of AV is shown in Table 1. The summary of chemical compounds found in AV is presented in Table 2.

### Proximate composition

Proximate analysis of AV leaves revealed that they are highly nutritious containing crude fibre, ash, protein, crude fat, ascorbic acid, organic acids, minerals, monosaccharides, and polysaccharides [22, 23, 24]. Additionally, AV powder is characterized by its abundant carbohydrates content [25], whereas, AV flowers exhibit a higher percentage

**Table 1.** Proximate composition of Aloe Vera

| AV part | Moisture | Ash | Crude Fibre | Protein | Fat | Carbohydrate | References |
|---|---|---|---|---|---|---|---|
| Leaves[1] | – | 16.88 (0.44) | 73.35 (0.30) | 6.86 (0.06) | 2.91 (0.09) | – | [22] |
| Leaves[2] | – | 14.9 | 23.8 | 7.7 | 2.2 | – | [23] |
| Leaves[3] | – | 19.50 | – | 10.50 | 1.83 | 56.27 | [24] |
| Powder[4] | 11.71 (0.02) | 2.36 (0.01) | 7.84 (0.01) | 4.73 (0.01) | 0.27 (0.01) | 73.08 (0.04) | [25] |
| Dried flower[5] | 8.45 | 8.07 | 12.65 | 11.75 | 2.30 | – | [26] |
| Fresh Gel[6] | 98.93 (0.06) | 0.16 (0.02) | 0.12 (1.20) | 0.12 (0.01) | 0.01 (0.02) | 0.66 (BD) | [27] |
| Powder[7] | 7.65 (0.12) | 19.83 (0.78) | 16.25 (1.25)* | 22.2 (0.21) | 0.59 (0.001) | 49.7* (BD) | [134] |

Figures in parentheses represent standard deviations; BD: by difference. [1,3]Values are percentages on dry matter basis. [4,5,*]Values are percentages. [2,6]Values are g/100 g on dry matter basis. [7]Values are percentages on wet basis.

**Table 2.** Summary of chemical compounds found in Aloe Vera

| Type | Compounds | References |
|---|---|---|
| Anthraquinones/Anthrones | Aloe-emodin, aloetic-acid, anthranol, barbaloin (aloin A and B), isobarbaloin, emodin, ester of cinnamic acid, chrysophanic acid, anthracene, ethereal oil | [1, 3, 4, 6, 7, 33, 39, 42] |
| Chromones | 8-C-glucosyl-(2'-O-cinnamoyl)-7-O-methyl-aloediol, 8-C-glucosyl-(S)-aloesol, 8-C-glucosyl-7-O-methyl-(S) aloesol, 8-C-glucosyl-7-O-methyl-aloediol, 8-C-glucosyl-noreugenin, isoaloeresin D, isorabaichromone, neoaloesin A | [4, 42] |
| Flavonoids | Naringenin, apigenin, dihydroisorhamnetin, isovitexin | [4] |
| Carbohydrates | Pure mannan, acetylated mannan, acetylated glucomannan, glucogalactomannan, galactan, pectic substance, arabinogalactan, galactoglucoarabinomannan, galactogalacturan, xylan | [1, 3, 7, 22, 38, 40, 98] |
| Enzymes | Bradykinase, alkaline phosphatase, oxidase, amylase, carboxypeptidase, carboxylase, catalase, cyclooxidase, phosphoenolpyruvate, cyclooxygenase, superoxide dismutase, lipase, cellulase, proteases, creatine phosphokinase | [1, 3, 6, 22, 25, 43, 98] |
| Minerals | Calcium, chlorine, phosphorous, chromium, copper, magnesium, iron, manganese, potassium, sodium, zinc, selenium | [1, 12, 24, 25, 28, 98] |
| Amino acids | Arginine, histidine, hydroxyproline, aspartic acid, glutamic acid, proline, glycine, tyrosine, alanine, isoleucine, leucine, lysine, methionine, threonine, valine, phenylalanine | [1, 3, 6, 98] |
| Proteins | Lectins, lectin-like substance | [7, 98] |
| Saccharides | Mannose, galactose, glucose, cellulose, l-rhamnose, aldopentose | [3, 5, 6, 98] |
| Vitamins | A, $B_1$, $B_2$, $B_6$, $B_{12}$, C, β-carotene, choline, folic acid, α-tocopherol | [1, 3, 5, 6, 12, 24, 25, 28, 98] |
| Lipids | Campestrol, cholesterol, β-sitosterol, lupeol, triterpenoid, arachidonic acid, γ-linolenic acid, triglycerides | [1, 3, 5, 10, 36, 37, 98] |
| Hormones | Auxin and gibberellin | [5, 98] |
| Other organic compounds | Potassium sorbate, lignins, salicylic acid, uric acid, saponins | [3, 6, 98] |

of crude fibre, compared to other nutrients [26]. When fresh AV gel (100 g) is stored after high hydrostatic pressure processing, it retains approximately 99 g moisture, 0.12 g protein, 0.01 g fat, 0.12 g crude fibre, 0.16 g ash, and 0.66 g carbohydrates. On a dry matter basis, the main sugars present are fructose (9.3 g/100 g) and glucose (25.2 g/100 g) [27]. These findings highlight the nutritional composition of AV leaves, powder, flowers, and gel, providing valuable insights into their potential health benefits and applications in various industries.

## Vitamins and minerals

AV gel contains antioxidant vitamins (Table 2) A, C, and E, as well as $B_1$, $B_2$, $B_3$, choline, folic acid, and trace amounts of vitamin $B_{12}$. It also provides 7 essential and 9 non-essential amino acids, contributing to its nutritional value. Furthermore, the extract from AV leaf skin includes β-carotene, which is a product of the isoprenoid pathway and possesses beneficial properties. Regarding minerals (Table 2), AV plant contains several essential minerals for human nutrition, including sodium, potassium, calcium, chloride, magnesium, manganese, copper, zinc, chromium, phosphorus, selenium, iron, and lead [1, 12, 24, 25, 28].

## Bioactive constituents

More than 200 bioactive compounds have been extracted in AV, with the majority (≥75) found in the inner clear gel of the leaves [3, 4, 5, 6, 7]. These bioactive compounds include phenolic acids/polyphenols, tannins, phlobatannins, saponins, mucilage, flavonoids, indoles, alkanes,

 

pyrimidines, alkaloids, organic acids, aldehydes, dicarboxylic acids, ketones, alcohols, fatty acids, phytosterols, terpenoids, cardiac glycosides, anthracene, and quinone derivatives [29, 30, 31, 32]. The peel of AV has been identified as the most promising part of the plant for the production of cosmetics products or nutraceuticals due to its high content of bioactive compounds [33].

### Organic acids and lipids

AV gel has been found to have higher content of malic acid (15.8%) and uronic acid (18.2%), while the bagasse fraction contains lignin [34]. Other compounds identified in AV extract include salicylic acid, glutamic acid, aspartic acid, gallic acid, tartaric acid, citric acid, benzoic acid, p-toluic acid, p-coumaric acid, protocatechuic acid, hydroxyphenylacetic acid, vanillic acid [1, 10, 30, 31], oleic acid, eicosadienoic acid, methyl ester, n-hexadecanoic acid, phthalic acid, butyloctyl ester, diazene, 1-heptanol, 2 propyl, diisooctyl ester, squalene, sinapic acid, syringic acid, and ferulic acid [10, 35]. Fatty acids and their metabolites identified in AV include lupeol, linolenic acid (16.6%), linoleic acid, arachidonic acid, phytol (14.4%), cholesterol, campesterol, β-sitosterol, palmitic acid (11.9%), diisooctyl phthalate (11.8%), dibutyl phthalate, 9-oxononanoic acid, 17-octadecynoic acid, and chrysophanic acid [1, 26, 30, 33]. AV flowers, on the other hand, contain myristoleic acid as the most predominant fatty acid [26], along with compounds such as vanillic acid, coumarin, gallic acid, quercetin, D-catechin, caffeic acid, naringin, naringenin, thymol, cinnamic acid, resveratrol, gentisic acid, and epicatechin [10, 36, 37].

### Carbohydrates

Under certain conditions, AV plants can synthesize total sugars, reducing sugars, soluble sugars, oligo- and polyfructans, inulin, neo-inulin, and neo-levan fructans [22, 38]. Non-starch polysaccharides and lignin constituted the majority of the dry weight of the rind and pulp, accounting for 62.3% and 57.6%, respectively [39]. Carbohydrates, including monosaccharides and polysaccharides, were the major components of AV fractions. The gel, liquid fraction, and bagasse contained 57.4 g, 40 g, and 58.5 g of carbohydrates per 100 g, respectively [34]. The main functional polysaccharides identified in AV leaf skin and gel are glucomannan (responsible for the gel's mucilaginous properties) and acemannan [1]. Trace amounts of xylose, rhamnose, galactose, arabinose, hyaluronic acid, and heparin are also present in AV [40].

### Flavonoids and phenolic compounds

Phytochemical standardization of AV extract by HPLC showed that it has 1.9% total flavonoid and 13% phenol content [31]. Aloe leaf rind contains the highest phenolic content, with hydroxycinnamics, anthrones, and chromones being the most represented phenolics [41]. The total content of phenolic compounds in aloe's leaf skin and flowers was found to be 307.5 mg and 274.5 mg per 100 g of freeze-dried aloe material, with catechin (95.0 mg/100 g) and gentisic acid (101.0 mg/100 g) being the predominant compounds, respectively [10]. In an ethanol extract of AV flower, the total phenolic content was 17.5 mg GAE/100 g of dry mass, and the total flavonoid content was 13.2 mg catechin equivalent (CE)/100 g of dry mass [37]. Around 25 bioactive compounds, including cinnamic acids, chromones, anthracene compounds, flavonoids, and an oxylipin, have been identified in AV from the Pica, Tarapaca region in Chile. Only nine compounds were detected in the AV gel [33]. The major anthracene compounds found in AV are aloin (mixture of aloin A/barbaloin and B/isobarbaloin), aloesin, emodin, aloe-emodin-diglucoside, 10-hydroxyaloin A, and others [39, 42]. AV also contains orientin, isovitexin, isoquercitrin, berberine, catechin, rutin, myricetin, kaempferol, apigenin, cinnamic acid derivatives, and chromones [1, 10, 32, 33, 41, 42].

### Enzymes and anti-nutrients

Enzymes identified in AV include bradykinase, aliiase, cyclo-oxygenase, cellulase, carboxypeptidase, lipase, catalase, protease, peroxidase, alkaline phosphatase, superoxide dismutase, amylase and creatine phosphokinase [1, 22, 25, 43]. Regarding anti-nutrients, trace amounts of phytate (0.7 g/100 g), oxalate (0.5 g/100 g), and tannins (0.2 g/100 g) were found in AV, along with phytochemicals including saponins (5.6 g/100 g), phenols (0.2 g/100 g), alkaloids (2.5 g/100 g), and flavonoids (3.2 g/100 g) [25]. Leaf skin of AV had the highest concentration of saponin (1.2 mg/g), while other parts such as the tip, middle, bottom of the leaf, and leaf flesh had lower levels (0.2–0.8 mg/g) [44].

## Clinical evidence of biological and pharmacological activities of Aloe Vera

### Antidiabetic effect

AV has shown promising effects in reducing fasting blood glucose by 15.4% and post prandial glucose levels by 27.8% in non-insulin dependent diabetics (n=90) when supplemented with 200 mg of AV leaf gel powder for 3 months, along with nutrition counselling [45]. Additionally, a meta-analysis of nine studies involving non-insulin dependent diabetics showed significant decrease in fasting blood glucose by 46.6 mg/dL and HbA1c by 1.05% following oral AV use [46]. While some evidence suggests AV's potential for glycemic control in diabetics and prediabetics, confirming its benefits requires a high-quality, standardized

randomized trials due to existing limitations and heterogeneous results [47]. The presence of aloe-emodin-8-O-glycoside in *A. Barbadensis* is believed to contribute to its glucose-lowering action by enhancing glucose transport, uptake, and conversion to glycogen, as well as regulating the expression of GLUT4 and reducing the activity of hexokinases [48]. These human studies hold promise for AV as a natural therapeutic option in diabetes management. Furthermore, supportive evidence on beneficial effects of AV emerges from animal studies as well. In a rat study, AV leaf extract (dried powder) at doses of 200 mg/kg and 400 mg/kg, exhibited a favourable effect in reversing alloxan-induced hyperglycemia [49]. Similar benefits of AV supplementation have been observed in male obese mice, where it improved obesity-induced glucose tolerance [50]. These findings suggest that AV has the potential to complement conventional diabetes management strategies [51].

### Antioxidant effect

The antioxidant activity of aloe leaf extracts has been observed in various aloe species, although it can vary depending on factors such as agro-climatic conditions, harvesting season, growth periods, polysaccharide and phenolic content, and acetylation degree [52]. The peel of the AV plant has been found to possess the highest antioxidant activity due to its phenolic compound content, highlighting its potential as a valuable resource for antioxidant-rich extracts [33]. In hydrogen peroxide-treated BALB/c mice, ethanol (70%) extract of dried AV flowers (800 g) exhibited strong antioxidant activity by inhibiting linoleic acid oxidation and DNA damage; elevating superoxide dismutase, catalase, and glutathione peroxidase enzymes activities, which was attributed to the presence of vanillic acid [37, 53]. In vitro comparisons between leaf, gel, and flower of AV indicated that the leaf exhibits better radical scavenging activities and overall antioxidant potential [54]. These results emphasize the importance of considering the specific plant part and extraction method when evaluating the antioxidant properties of AV [55].

### Anticancer, antitumor, and cytotoxic effects

An anti-tumor potential of varying doses of AV (2.50, 7.50, and 10.45 μg/mL) and *Centella Comosum* (CC) extracts (2.5, 7.5, and 9.6 μg/mL) was evaluated in the hepatocellular carcinoma cell line (HepG2). The IC50 values for AV and CC extracts were (10.45±0.31) μg/mL and (9.60±0.01) μg/mL, respectively. These extracts significantly enhanced cytotoxicity against the HepG2 cells in a time and dose dependent manner. Furthermore, they appeared to induce apoptosis by up-regulating P53 and down-regulating Bcl-2 gene expression [56]. In an another study, an *in vitro* investigation revealed the presence of anti-proliferative effects in a human neuroblastoma cell line (IMR-32) when cultured with AV protein extract at a concentration of 0.5 μg/mL, potentially achieved through down-regulation of a cell-cycle regulator known as CCND2 [57]. Similarly, the impact of AV crude extract (ACE) alone or in conjunction with cisplatin was examined in human breast (MCF-7) and cervical (HeLa) carcinoma cell lines. The study findings revealed notable alterations in cellular morphology in response to ACE treatment, showing a dose and time-dependent pattern characterized by cell rounding, shrinkage, and detachment from the matrix in MCF-7 (40%, 50%, and 60%) and HeLa cells (30%, 40%, and 60%). Furthermore, when cisplatin was used concurrently with ACE, an anti-neoplastic effect was observed in these cancer cell lines, eliciting apoptosis and influencing the expression of key effector molecules [58]. Supporting these findings, other human studies have also demonstrated cytotoxic and genotoxic activities of AV extract against acute myeloid leukemia [59], gastric cancer [60], and colon cancer [61]. These effects are attributed to the induction of apoptosis, modulation of gene and protein expressions and the presence of aloe-emodin, an anthraquinone with potent anti-proliferative properties [55, 61]. Animal studies have further confirmed the cytotoxic and anticancer effects of AV extract and aloe-emodin through apoptosis and necrosis induction [62]. These studies highlight the potential of AV and its constituents as promising therapeutic agents for cancer research and treatments.

### Hepatoprotective effect

Oral administration of AV juice at a dosage of 20 mL twice daily over a 6-week period exhibited hepatoprotective effects in patients diagnosed with acute viral hepatitis (n=60) and drug-induced hepatitis (n=15), all aged between 15 and 65 years. These effects were evident through the restoration of normal liver function and the reduction of serum markers of liver damage, such as bilirubin, alanine aminotransferases, aspartate aminotransferase, and alkaline phosphatase levels [63, 64]. Furthermore, in an 11-week study utilizing a chronic alcohol-feeding mouse model, the hepatoprotective effects of AV gel polysaccharide (administered orally twice daily at doses ranging from 10–30 mg/kg in normal saline) were observed. This intervention demonstrated protective properties against alcoholic liver disease in the intoxicated mice (n=24), including the reduction of serum aminotransferases, lipids, and hepatic triglycerides, as well as alleviation of oxidative stress and inflammation, and restoration of antioxidant enzymes [65]. Similarly, hepatoprotective efficacy of AV gel polysaccharides was demonstrated against aflatoxin-induced hepatotoxicity in rat model. This research signifies the utilization of AV to create hepatoprotective functional food, benefiting individuals in developing countries who are chronically exposed to aflatoxins [66]. In agreement, AV has exhibited hepatoprotective properties against

 

various hepatotoxic agents in animal models [67, 68]. These findings underscore the potential of AV as a therapeutic agent for liver-related ailments and warrant further investigation into its mechanisms of hepatoprotection and potential clinical applications.

### Antibacterial, antifungal, antiviral and antimicrobial activity

A proteomic analysis of AV extract identified 15 peptides or proteins involved in stress tolerance and defense against pathogens [69]. Bioactive compounds found in AV, including dihydroxyanthraquinones, saponins, polysaccharides, pyrocatechol, lupeol, phenol, and sulphur, exert antimicrobial, antiseptic, and antibacterial effects through various mechanisms [55]. In a study performed on patients (n=20) suffering from sub gingival calculus, and periapical and periodontal abscess, AV gel (10 mL of gel mixed in 100 mL of 2% Dimethyl Sulfoxide) at higher concentration (100% and 50% concentration, p-value < 0.001) has demonstrated efficacy against oral pathogens, both gram-positive and gram-negative bacteria, *in vitro* [70]. AV also exhibits antiviral effects against influenza A virus and antifungal potential against *Aspergillus Niger*, *Candida Paraprilosis*, *Candida Krusei* and *Candida Albicans* [71, 72, 73]. Another *in vitro* study showed that both filtered fresh AV gel (15%) and food grade AV gel (50%) could be used as an edible coating for controlling post-harvest fungus on papaya fruit [74]. Additionally, commercial herbal AV gel toothpastes in the amount of 100 µL have shown antimicrobial activity against cariogenic bacterias (*S. Mutans* and *S. Aureus*) which are known to cause tooth infections [75]. These properties make AV effective against bacteria, fungi, and viruses, which highlights its potential applications in medicine, oral care, and food preservation.

### Antihyperlipidemic activity

A human study demonstrated that non-insulin dependent diabetic patients (n=60) experienced antihyperlipidemic benefits when they were supplemented with 200 mg of AV leaf gel powder daily for 3 months. This supplementation led to substantial reductions in total cholesterol, triglycerides, LDL-C, and VLDL levels, amounting to 10.1%, 12.2%, 14.6%, and 12.2% decreases, respectively, in addition to 9.4% increase in HDL levels [45]. Similarly, in an animal study, oral administration of AV extract (80% ethanol skin extract, 4%w/w) to streptozotocin-induced type 2 diabetic rats for 28 days resulted in a significant reduction in total cholesterol by 25% and LDL levels by 69%, while increasing serum HDL levels by 5%, indicating a potent hypolipidemic effect [76]. In an another study, AV gel formulation (1 mL (10 mg)/day, 30 days) also effectively managed dyslipidemia in letrozole-induced rats with polycystic ovary syndrome, normalizing estrous cycle, glucose intolerance, lipid metabolizing enzyme activities, and improving lipid profile [77]. These findings highlight the potential of AV in managing lipid disorders and associated complications.

### Antiulcer activity

AV exhibits the potential to inhibit ulcerogenic activity by reducing gastric acid secretion, protecting the gastric mucosa, and promoting gastric ulcer healing. AV has also been utilized for the prevention and treatment of skin ulcers, recurrent aphthous stomatitis, pressure ulcers, and chronic ulcers [78, 79, 80]. Processed AV gel has shown promise as a treatment for small intestinal ulcers, enhancing the mucus layer and reducing ulcer severity and bacterial translocation in the indomethacin-induced small intestinal damage mouse model, and also regulates the mucin expression in the LS174T human cell line, mainly via the extracellular-signal-regulated kinase (ERK) dependent pathway. [81]. The glycoprotein lecithin found in AV is believed to contribute to its antiulcer and acid-reducing properties by interacting with carbohydrate moieties and inhibiting certain cellular processes [55].

### Anti-inflammatory and immunomodulatory effect

A purified new aloe protein of 14 kDa, has demonstrated anti-inflammatory properties, inhibiting pure lipoxygenase and cyclooxygenase-2, with 84% and 73% inhibition, respectively [73]. AV leaf has shown promising immunomodulatory properties by down-regulating inflammatory cytokine production and suppressing the expression of the NLRP3 inflammasome in human macrophages [82]. Animal studies have also provided evidence of AV's (150–600 mg/kg) potential in reducing oxidative stress and inflammation associated with drug-induced nephrotoxicity [83], gastropathy [84] and hepatitis [85] when given orally. Daily supplementation of dietary aloe formulas including 100 mg/kg of processed aloe gel (PAG), 2 mg/kg of Aloesin (ALS), 100 mg/kg of PAG containing 2% ALS (Aloe QDM), and Aloe QDM plus 500 mg/kg of chromium (i.e., chromium-enriched yeast) containing 0.2% chromium (Aloe QDM complex) demonstrated an anti-inflammatory effect by reducing inflammatory phenotypes in white adipose tissue and liver, consequently improving obesity-induced insulin resistance in mice [50]. AV fermentation was shown to accelerate burn injury healing in a rat model by reducing the production of proinflammatory factors TNF-α and IL-1β ($p<0.05$) and increasing the yield of anti-inflammatory factor IL-4 in animal serum ($p<0.05$) [86]. Notably, key compounds in AV responsible for its anti-inflammatory properties include acemannan, bradykinase, lignin, aloctin, campesterol, and β-sitosterol [55].

### Role of AV in dermatology

**Wound healing:** The wound healing properties of AV are specifically attributed to glucomannan and glycoproteins found in the pulp [55, 87]. An *in vivo* study aimed to assess the impact of an AV hydrogel incorporated with allogeneic adipose stem cells (ASCs) in a rat burn wound model, where the ASCs, after isolation and culture, were mixed with 50% AV hydrogel and intradermally injected around the wound, while demineralized bone matrix (DBM) served as the dressing. The AV and DBM-AV groups demonstrated similar wound healing properties, while treatment with DBM-AV/ASCs significantly accelerated wound healing, accompanied by reduced levels of inflammatory markers like transforming growth factor-β1 (TGF-β1) and interleukin-1β on the 7th day post-injury. Additionally, the DBM-AV/ASC-treated wounds exhibited enhanced angiogenesis, re-epithelialization, higher TGF-β1 levels, and reduced scar formation compared to the other groups by the 14th day post-injury [88]. Similarly, other animal studies have consistently shown that topical application of AV gel reduces inflammation, scar tissue size, and oxidative stress markers while enhancing wound contraction, epithelialization, and collagen density [39, 89, 90]. The mechanism behind AV's efficacy in wound healing involves stimulating cell proliferation, differentiation, and the development of epidermal keratinocytes, along with upregulation of specific proteins [91, 92]. Moreover, AV gel has demonstrated the highest potential as a transdermal drug penetration enhancer compared to other Aloe species [93].

**Anti-ageing and moisturizing effect:** AV has been found to modulate skin metabolism. In a randomized, double-blind, placebo-controlled trial on women (n=28 aged $\geq$40 years), daily consumption of AV gel powder containing 40 μg aloe sterols has shown remarkable improvements in reducing facial wrinkles, enhancing skin hydration, and stimulating the production of collagen and hyaluronic acid [94]. Animal studies further support these findings, highlighting the ability of aloe sterols to counteract UVB-induced skin damage, prevent wrinkle formation, suppress collagen degradation, apoptosis, inflammation, and matrix metalloproteinases, thereby effectively combating skin photoaging [95, 96]. An aqueous extract of powdered AV whole-leaf has also exhibited photo-protective effects against UVA-induced damage, promoting membrane integrity, stability, and reducing pigmentation, wrinkles, and texture changes in human keratinocytes [97].

**Other skin conditions:** AV has been proven beneficial for various other skin conditions, aiding in the regeneration of burnt or frostbitten skin, delaying radiation-induced dermatitis, preventing cracked nipples, managing genital herpes, alleviating psoriasis and erythema, and treating mild to moderate acne vulgaris [30, 79, 98, 99, 100, 101]. A randomized controlled trial was performed on patients with mild-moderate acne severity (n=60) to compare the effectiveness of topical application of anti-acne hydrogel (containing Aloe Vera, mangosteen peel, and green tea extracts in a ratio of 50:25:1) on acne lesions twice daily for 28 days, with a 1% clindamycin gel. The study found that the hydrogel significantly reduced inflamed lesions, skin redness, and melanin levels, outperforming the clindamycin gel. However, both products were well-tolerated, with no severe side effects [102].

### Role of AV in dentistry

In a double-blind, randomized, placebo-controlled clinical study for a period of 3 months, using AV mouthwash (15 mL) twice daily for one minute was found effective in the treatment of patients (n=30) with plaque-induced gingivitis [103]. In a separate study involving 74 patients diagnosed with oral submucous fibrosis, the effectiveness of a combined systemic and topical treatment approach was evaluated, which included twice daily intake of AV juice (30 mL) before food, as well as the application of AV gel (5 mg) three times daily for a duration of 3 months. The results of this study demonstrated notable improvements in various symptoms, including a reduction in burning sensation, increased mouth opening, enhanced cheek flexibility, and improved tongue protrusion [104]. In agreement, review of human clinical trials documented similar anti-oral mucosal lesion activity of AV against oral lichen planus [105] and oral candidiasis [106]. Furthermore, a single-blind clinical trial conducted on periodontitis patients (n=20) demonstrated that the topical application of AV gel (at a concentration of 98%) may be regarded as a supplementary treatment option alongside scaling and root planning for individuals with chronic periodontitis [107]. The antibacterial, antimicrobial, and antiseptic properties of AV make it a valuable ingredient in various dental products [108]. The wide range of dental conditions in which AV has demonstrated clinical efficacy and safety highlights its potential as a versatile therapeutic option in dentistry [70]. These findings suggest that AV could serve as a beneficial alternative dental therapy, offering potential benefits for patients and expanding treatment options in dental care. However, it is advisable to conduct more extensive and extended follow-up studies with a larger sample size, to further investigate and validate these findings [104].

### AV and gut health

In vitro research investigating the prebiotic properties of AV polysaccharides found that AV fructans were more effective in boosting bacterial growth compared to commercial fructo-oligosaccharides (FOS) known as inulin. AV fructans also resulted in higher production of short-chain fatty acids and increased the population of Bifidobacterium species. On the other hand, Acemannan, induced bacterial growth

 

**Table 3.** Maximum allowable safe levels and contraindications for Anthraquinone or Aloin present in Aloe Vera-based products

| AV component/product | Industry-established safe levels | References |
|---|---|---|
| Cosmetics (accepted industry standards) | | |
| Non-medicinal and topical usage | ≤50 ppm | [123, 125] |
| Oral consumption | <10 ppm | |
| Food stuffs | | |
| Food supplements and herbal products (in 0.5% aloe vera solution for oral consumption) | <10 ppm | [123] |
| Food and drinks (for flavouring purposes) | <0.1 ppm | [123] |
| Liquid consumer products | <1 ppm | [123] |
| Solid or semi-solid products | May be 10–100 times higher | [123] |
| Usual consumption as traditional foodstuff in a normal diet | 0.1 mg/kg | [123] |
| Aloe juice | <30–40 mL/day | [120] |
| **Contraindications (Avoid Aloe gel or latex)** | | |
| • Pregnancy & breast-feeding<br>• Young children aged <12 years<br>• Pre-surgery<br>• Individuals living with diabetes, heart or kidney problems, Crohn's disease, ulcerative colitis or obstruction, and hemorrhoids | | [123] |

to a lesser extent than fructans but comparable to commercial FOS. Acemannan supplementation significantly increased acetate concentrations. These findings suggest that AV polysaccharides have potential prebiotic properties that can contribute to improving gastrointestinal health [109, 110]. An investigation carried out with 25 schizophrenic patients aged 50–60 years revealed positive outcomes associated with AV consumption (4-weeks supplementation), particularly in relieving constipation [111]. Similarly, a meta-analysis of 3 prospective randomized controlled trials involving a total of 151 study participants indicated that a short-term treatment with AV (1 month) demonstrated therapeutic effectiveness in controlling symptoms of constipation-predominant Irritable Bowel Syndrome or functional constipation [112]. This effect can be attributed to the presence of anthraquinones, specifically aloins A and B, found in the plant's latex [113]. Incorporating AV gel cubes in probiotic yogurt has been found to be an effective carrier of probiotic bacteria, increasing bacterial counts beyond recommended levels [114]. In an *in vitro* study, AV supernatant fermentation fermented by *Lactobacillus (L) Plantarum* has been shown to positively modify gut microbiota by increasing beneficial bacteria like *Lactobacillus* (L) and reducing pathogenic bacteria. These findings suggest the potential utility of AV and its fermented products as a functional food or cosmetic product aimed at safeguarding human intestinal well-being, slowing down the aging process, and mitigating chronic diseases [115].

## Anti aggregatory effect

Protein aggregation plays a significant role in the development of various physiological diseases such as Huntington's disease, Alzheimer's disease, and diabetes mellitus. Aloe-emodin, derived from AV, act as an inhibitor of hemoglobin aggregation [116]. An 8-week double-blind, placebo-controlled study was undertaken to assess the effect of a dietary supplement containing Aloe gel, grape juice, *Polygonum Cuspidatum*, and vitamins on Platelet-activating factor (PAF) actions and metabolism in healthy individuals. Supplementation with plant extracts and vitamins has been shown to mitigate platelet aggregation, primarily targeting PAF and, to a lesser extent, adenosine diphosphate. It also enhances the breakdown of PAF by increasing PAF-acetyl hydrolase activity in healthy individuals [117]. These findings indicate that AV has potential therapeutic applications in reducing protein aggregation and platelet activation, contributing to the management of certain inflammation-related conditions and diseases.

## Safety, toxicity, adverse effects and drug interaction

Table 3 provides information regarding maximum allowable safe levels and contraindications for anthraquinones or aloin present in AV-based products.

Although AV has shown therapeutic effects in several human and animal studies, it is important to note that some aloe species can have adverse side effects, partly attributed to high levels of aloe-emodin and other dihydroxyanthraquinones in it [118, 119]. Excessive ingestion of AV has been associated with strong laxative effects, stomach pain, muscle weakness, electrolyte imbalance, kidney dysfunction, and even potential carcinogenic and hepatotoxic effects [120, 121, 122, 123, 124]. These toxic reactions are primarily linked to the intake of aloe latex rather than aloe gel. Therefore, it is important to differentiate AV gel from aloe juice or latex, as the latter two contain anthraquinones, known for their laxative effects. The intake of AV for

internal use should be discouraged due to potential adverse effects and a lack of conclusive clinical data. There have been cases of fatalities among cancer patients who received AV injections. To address safety concerns, the US Food and Drug Administration (FDA) has mandated warning labels for non-pasteurized AV products [123].

Topical and oral administration of aloe gel is generally safe, but occasional skin reactions such as burning, itching, and contact dermatitis may occur [121, 122, 123]. Purified extracts of AV are carefully processed to remove hydroxyanthraquinones, ensuring contaminant levels are below 50 ppm and even less than 1 ppm [123]. The International Aloe Science Council Standard provides guidelines for the permissible levels of aloin content in aloe-derived materials (Table 3). During pregnancy or breastfeeding, it is recommended to avoid aloe gel or latex as it may potentially lead to miscarriage or pose a risk of birth defects. AV is also considered potentially unsafe for: young children under the age of 12; individuals with scheduled surgeries, and those suffering from chronic diseases [123].

Regarding aloe-drug interaction, a major interaction has been observed between aloe (latex) and the cardiac glycoside Digoxin (Lanoxin). Aloe also exhibits a moderate interaction with cytochrome P450 substrates, glyburide, and diuretics. During topical application, AV has shown interactions with hydrocortisone and sevoflurane [123]. Some studies have reported that AV gel and whole leaf materials enhance the absorption of drugs in vitro, particularly with solid oral dosage forms of aloe [126, 127, 128, 129]. In humans, the co-administration of AV liquid preparations has been found to increase the bioavailability of vitamins [130]. Other studies have demonstrated that AV gel enhances the buccal absorption of the antiretroviral drug, inhibits the efflux of cimetidine, improves ketoprofen diffusion across dermatomed skin, and alters pharmacokinetic parameters by inhibiting indinavir metabolism in an in vitro LS180 cell model [93, 131, 132, 133].

### AV-extract market's global trends, European recognition, and regulatory challenges

The global recognition of AV's potency has surged significantly, driven by its widespread use in health-related products [134]. Global forecast indicates significant growth in the AV extract market, from $2.65 billion in 2023 to $4.55 billion by 2030 [135]. In 2018, the largest market segment was liquid products, accounting for 63.8% of the market share, with cosmetics being the leading category at 41.9%. The Asia Pacific region was the dominant market in 2018, with a 30.6% market share, primarily driven by China and India as key revenue contributors [136].

AV has gained a strong reputation globally due to its extensive application in health products (beverages, foods, and dietary supplements), as manufacturers increasingly focus on using natural ingredients in their products [137]. In certain cases, AV gel is incorporated into commercial jellies. Additionally, AV is utilized as a natural alternative to conventional synthetic preservatives. In the United States, aloe-based products are available as dietary supplements. Unlike pharmaceutical companies, supplement manufacturers are not obligated to provide the FDA with evidence of the safety and efficacy of their supplements unless they make specific claims regarding the prevention, treatment, or cure of particular disease [123].

In Europe, AV is well-recognized among both buyers and health product manufacturers for its diverse properties and applications [137]. European regulations classify new foods or novel food ingredients as those not widely consumed by European consumers before May 15, 1997 [138]. According to these regulations, powdered gel from *A. Macroclada Baker* leaf extract is deemed substantially similar to AV gel extract and can be used as a food supplement [139]. Therefore, AV can be categorised as a novel food or novel food ingredients [138]. Worldwide, AV has been employed in developing various novel functional foods and beverages [140].

In 2013, EFSA raised concerns about potential risks associated with hydroxyanthracene derivatives (HADs) found naturally in botanicals such as AV, advising against long-term use. In 2019, EFSA concluded that HAD derivatives in AV extracts could harm DNA and that whole-leaf aloe extracts demonstrated carcinogenic properties. In 2020, the European Commission put forth a draft regulation proposing a ban on several AV compounds (aloe emodin, emodin, aloe species leaves containing HAD derivatives, danthron, and all related extracts) due to severe health risks. AV extracts containing these substances may be included in Regulation (EC) No 1925/2006, which lists prohibited substances in food. The regulation's outcome remains uncertain and may affect the AV supply chain to Europe. However, this legislation does not extend to herbal and medicinal products. Furthermore, the prohibition would not encompass aloe extracts that have undergone processing to eliminate disputed components, allowing their ongoing use in food products [137].

In 2022, Europe emerged as the largest market for AV extract, with a value of USD 843 million [135]. However, safety concerns surrounding AV have impeded its growth in the European market, potentially leading to bans or restrictions on certain substances. Various AV gel extracts are available in Europe, including whole leaf extract/juice, decolorized whole leaf extract, and dried AV latex. AV is used in herbal medicinal products, primarily as dried, and concentrated leaf juice (latex). In food supplements, AV gels, extracts, and latex are generally allowed, with some exceptions for latex usage [137]. Regulations governing the safe use of AV vary among countries, with Italy permitting

 

aloe latex for all species and Germany only allowing AV extracts and gels. Some European countries, such as Germany, Belgium, France, and Italy under the BELFRIT project, have established lists of six approved aloe species for use in food supplements. Notably, the BELFRIT list does not specify maximum aloin levels for food supplements, as these are determined by individual EU Member States' food safety authorities. Consequently, European supplement manufacturers often use aloes with minimal aloin content [141]. Despite regulatory variations, AV continues to be utilized in diverse applications, highlighting its significance in the global market.

## Conclusion

Aloe Vera is a plant with a long-standing reputation for its various health, skincare, and medicinal benefits. Extensive research has identified several phytochemicals and bioactive components in AV that exhibits diverse pharmacological activities, including antidiabetic, antioxidant, anticancer, hepatoprotective, antibacterial, antifungal, antiviral, antihyperlipidemic, antiulcer, anti-inflammatory, and immunomodulatory effects, emphasising its potential as a valuable natural therapeutic agent. Although AV's global significance remains prominent, driven by its diverse applications in various industries, regulatory concerns persist, possibly impacting its usage and market growth. Hence, it is crucial to be aware of its potential risks, follow proper dosages, and consult with healthcare professionals before use. Additionally, more research is necessary to better understand the AV's mechanisms of action, optimal dosage forms, and potential side effects to fully exploit its benefits and ensure its safe and effective usage.

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**History**
Received September 2, 2022
Accepted October 8, 2023
Published online November 2, 2023

**Conflict of interest**
The authors declare that there are no conflicts of interest.

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