PHYTOCHEMISTRY, PHARMACOLOGY AND TOXICITY OF Aloe vera: A VERSATILE PLANT WITH EXTENSIVE THERAPEUTIC POTENTIAL

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(Date of Receiving: 22-06-2023; Date of Acceptance: 28-09-2023)

ABSTRACT

Aloe vera, with its immense potential has a rich history of traditional medicine and cosmetic use, addressing various health issues from digestion to dermatological conditions. Its therapeutic versatility arises from a different pharmacological activities, encompassing anti-inflammatory, antibacterial, wound healing, antioxidant, laxative, immunomodulatory, anti-diabetic, skin protective, and potential anti-cancer effects. These effects are attributed to its bioactive compounds ranging from tannins, saponins, flavonoids, terpenoids, alkaloids to triterpenoids, glycosides, glucomannans, chromones, anthraquinones, and anthrone derivatives primarily located in the latex layer of the outer leaf. However, A. vera’s toxicity varies with form, with some products exhibiting low toxicity, while others posing risks at high doses.

Keywords: Aloe vera, pharmacology, phytochemistry, traditional, anthraquinones, toxicity.

Introduction

As per World Health Organization (WHO) about 75–80% of the global population depends on the plant based healthcare products including dietary supplements. The beliefs in the herbal remedies over allopathic treatments have escalated over the years. The importance of herbal medicine lies in its historical significance, cultural acceptance, and effectiveness, particularly in regions with limited access to modern healthcare resources (Sam, 2019). The genus Aloe is native to Arabian Peninsula and has since undergone substantial diversification, resulting in the diversity of Aloe species we see today (Sung, 2006; Grace et al., 2015). Aloe vera, sometimes known as the ‘Plant of Immortality,’” has a long history that dates back thousands of years. It was utilized for therapeutic and healing purposes in ancient Egypt, Greece, and Sumeria (Mehta, 2017). In sanskrit, A. vera is referred to as “Ghrit Kumari”. It is also known as Aloe barbadensis belonging to the family Asphodelaceae and has a long history of topical and oral therapeutic use, with its gel and latex derived from its leaves containing a variety of constituents with potential biological and toxicological effects (Boudreau and Beland, 2006). Thus, A. vera is traditionally employed for medicinal and cosmetic purposes, taken internally to address digestive issues, asthma, diabetes, and periodontal diseases, and applied externally to treat skin conditions, burns, and promote healthy skin (Shrestha et al., 2015; Lanka, 2018). The traditional usage of A. vera for skin injuries and stomach disorders, based on its anti-inflammatory (Langmead et al., 2004; Yagi et al., 2002) antibacterial (Nejatzadeh-Barandozi, 2013; Danish et al., 2020), and wound healing (Davis et al., 1989; Maenthaisong et al., 2007) characteristics, has evolved into modern medicine through substantial research (Sánchez et al., 2020).

A key compound in A. vera, well-documented is anthraquinones (Ravi et al., 2011; Ali et al., 2012; Logaranjan et al., 2013), recognized for its bitter taste and laxative properties, primarily located in the outer leaf, specifically the latex layer just beneath the skin (Ramachandra and Rao 2008; Riaz et al., 2021; Borges-Argáez et al., 2019). Although A. vera features various other bioactive compounds, anthraquinones stands out historically for its laxative use. The current article concentrates on bioactive compounds anthraquinones in A. vera and its pharmacological activity emphasizing its potential therapeutic benefits and the need for more research.

Botany

Aloe vera (L.) Burm.f. (syn. Aloe barbadensis Miller), is a perennial plant of the Asphodelaceae (Lily) family. The species is native to Oman and has a bushy look and a lush pea-green colour. A gel-like material is found in the inner section of its leaves (Fig. 1). A. vera looks like a spiky cactus and has thick leaves. It is a small, stemless plant that often grows in clusters, creating dense groups. Its succulent leaves grow upright, forming a compact rosette. These leaves are grayish-green, reaching lengths of about 50 cm, and they have pinkish margins adorned with numerous small spines. Sometimes, the leaf surfaces have white flecks or spots. The plant produces yellow, tubular flowers that can grow up to 3 cm in length, with anthers and stigma sticking out. These flowers are arranged in tall, branching clusters called racemes, which can reach heights of up to 90 cm.
Traditional use

*Aloe vera* has traditionally been used for skin healing, as it soothes burns, irritations, and cuts, possesses bactericidal properties, and has anti-aging potential due to its nutrient-rich composition (Nirala et al., 2020). In addition, it has also been used for detoxifying and immune-boosting qualities, digestive improvement, because of rich content of vitamins and amino acids (Rajeswari et al., 2012). Furthermore, *A. vera* has traditionally been used for a wide range of medicinal purposes, including treating ailments like mild fever, wounds, burns, gastrointestinal disorders, diabetes, sexual vitality and fertility issues, cancer, immune modulation, AIDS, and various skin diseases (Manvitha and Bidya, 2014).

Phytochemistry of *Aloe vera*

*Aloe vera* is rich in a diverse range of phytochemical compounds including tannins, saponins, flavonoids, terpenoids, alkaloids, carbohydrates, steroids, triterpenoids, glycosides, glucomannans, chromones, anthraquinones, and anthrone derivatives, benzene and furan derivatives, coumarins, phytosterols, pyrans and pyrones (Arunkumar and Muthuselvam, 2009; Patel et al., 2012; Raphael, 2012; Mukherjee et al., 2014; Cock, 2015). The leaves of *A. vera* have high moisture content, ash, crude fibre, crude protein, and crude lipid, as well as trace amounts of ascorbic acid, while enzymatic activities (superoxide dismutase, peroxidase, catalase, and amylase) and sugar content (total soluble and reducing sugars) vary within the plant with bacteriostatic properties (Lorenzetti, 1964; Ahmed and Hussain, 2013). The phenolic compounds traditionally recognized as laxatives can be found in the bitter reddish-yellow exudates situated beneath the plant's outer leaf. These compounds include anthraquinones and their derivatives (Fig. 2), such as barbaloin, aloemodin-9-anthrone, isobarbaloin, anthrone-c-glycosides, and chromones (Sharma et al., 2014). However, the barbaloin, barbaloin (S)-isomer, barbaloin beta-D-isomer, barbaloin monoglucoside, and isobarbaloin are all the synonyms of Aloin (NCBI, 2023). Jawade and Chavan (2013) extracted Aloin from *A. vera* using ultrasound-assisted extraction (UAE) with methanol as the solvent, followed by quantification using HPLC. Aloin is a bitter-tasting chemical with laxative qualities found largely in the plant's outer leaf, notably the latex layer just beneath the epidermis (Ramachandra and Rao 2008; Riaz et al., 2021). While *A. vera* contains a number of additional chemicals with medical and aesthetic qualities, Aloin is most well-known for its historic usage as a laxative. Aloin is represented by the chemical formula C_{33}H_{52}O_{9} and its molecular weight is 418.4 g/mol (NCBI, 2023). In the study conducted by Ravi et al. (2011), *A. vera* leaf gel products were examined, showing that processed samples had low Aloin content (below 0.1 mgL^{-1}), while unprocessed ones contained over 10 mgL^{-1}, and Aloin A at low concentrations protected cells from hydrogen peroxide-induced toxicity. In addition, the anthraquinones present in *A. vera* include aloesaponarin-I and aloesaponarin-II, along with their derivatives obtained through methylation, acetylation, and O-glycosylation reactions, as well as a new Tetra-O-acetyl-β-d-glucopyranosyl derivative from aloesaponarin-II (Borges-Argáez et al., 2019).

Pharmacological Properties

*Aloe vera* exhibits various pharmacological properties (Table 1), such as anti-inflammatory (Langmead et al., 2004; Yagi et al., 2002) antibacterial (Nejatzadeh-Barandozi, 2013; Danish et al., 2020), and wound healing (Davis et al., 1989; Maenthaisong et al., 2007), antioxidant (Hu et al., 2003; Hêş et al., 2019), laxative (Manvitha and Bidya, 2014; Surjushe et al., 2008), immunomodulatory (Madan et al., 2008; Kwon et al., 2011), anti-diabetic (Tanaka et al., 2006; Atanu et al., 2018), skin protective (Foster, 1999; Gao et al., 2019) and potential anti-cancer effects (Karpagam et al., 2019; Ali et al., 2020; Murugesan et al., 2021) making it a versatile plant with medicinal potential. It has been employed in the pharmaceutical industry to manufacture topical drug products, ointments, gel preparations, tablets, and capsules (Manvitha and Bidya 2014).

Anti-inflammatory

The species has broad-spectrum anti-inflammatory effects, primarily due to anthraquinones (Davis et al., 1989). Aloin and Aloe-Emodin, two of its components, also exhibit anti-inflammatory properties (Park et al., 2009), making *A. vera* a potential therapeutic option for reducing inflammation. It works by inhibiting the production of reactive oxygen metabolites, prostaglandin E2, and interleukin-8, as shown in *in-vitro* assays, suggesting its potential use in inflammatory bowel disease (Langmead et al., 2004). Moreover, *A. vera*‘s anti-inflammatory effects,
including the reduction of inflammation, may be linked to components such as mannose-6-phosphate, as observed in mouse studies (Davis et al., 1994).

**Antimicrobial effects**

Aloins exhibit pharmacological potential by inhibiting microbial and human metalloproteinases, including *Clostridium histolyticum* collagenase (ChC) and granulocyte matrix metalloproteinases (MMPs), and their inhibitory effects are structurally similar to antimicrobial tetracyclines (Barrantes and Guinea 2003).

**Wound healing**

Aloin has been studied for its potential role in wound healing (Davis et al., 1987; Maenthaisong et al., 2007; Liang et al., 2021). *A. vera* is known to improve wound healing, as demonstrated by studies involving mice where it enhanced the healing process compared to control groups. This wound-healing effect is likely due to its various beneficial components, including mannose-6-phosphate (Davis et al., 1994). The wound healing properties of *Aloe vera* gel in the study are attributed to its optimized formulation with Carbopol 934, which improved spreadability and consistency, leading to faster wound healing and reduced inflammation (Khan et al., 2013).

**Antioxidant**

Superoxide dismutase activity in *A. vera* plants, whether *in-vitro* generated or conventionally propagated, appears to be similar, possibly indicating a contribution from Aloin (Gantait et al., 2011). Aloin was examined for its antioxidant properties, with ethanolic extracts from different *A. vera* accessions showing significant free radical scavenging capabilities, which can help protect tissues from oxidative damage caused by reactive oxygen species (ROS) (Anima et al., 2012).

**Laxative effects**

*A. vera* appears to improve bowel movements and alleviate symptoms in patients with irritable bowel syndrome (IBS) based on a meta-analysis of randomized controlled trials. It showed a significant reduction in IBS symptom severity, a higher response rate, and no adverse effects, suggesting its potential as a safe and effective remedy for IBS (Hong et al., 2018).

**Immune system support**

Aloin-containing *A. vera* products are used by some individuals to boost immune system function (Huang et al., 2019). *A. vera* supplementation in the diet of rainbow trout improved their growth, immune responses, and resistance against a pathogenic oomycete, *Saprolegnia parasitica*, suggesting its supportive role in enhancing the fish’s immune system and overall health (Mehrabi et al., 2019). It appears to have an immunomodulatory effect by reducing cell-mediated immune responses (such as hypersensitivity reactions) while simultaneously enhancing humoral immunity, particularly the production of antibodies (Halder et al., 2012).

**Antidiabetic activity**

Aloin A, a component found in *A. vera*, exhibits antidiabetic activity (Aldayel et al., 2020). Oral administration of *A. vera* juice twice a day for at least 2 weeks in diabetic patients led to a reduction in blood sugar and triglyceride levels, indicating the potential of *Aloe vera* juice as an antidiabetic agent (Yongchaiyudha et al., 1996). *A. vera* methanol extract (AVM) was found to significantly reduce the formation of advanced glycation end products (AGEs) and inhibit enzymes like α-amylase and α-glucosidase, suggesting its potential in preventing diabetes complications associated with AGEs (Muñiz-Ramirez et al., 2020).

**Skin health**

Aloin was observed to induce melanin aggregation in tadpole melanophores, suggesting its potential as a safe melanolytic agent for treating hyperpigmentation by stimulating alpha adrenergic receptors and promoting skin lightening (Ali et al., 2012).

**Anti-hyperlipidemic**

*Aloe vera* gel when administered alongside standard diabetes medications, has shown promise in reducing fasting blood glucose, HbA1c, total cholesterol, and LDL levels in hyperlipidemic type-2 diabetic patients, making it a potential safe option for managing both blood sugar and cholesterol levels (Huseini et al., 2011). Aqueous extract of *Aloe vera* leaves displayed notable oral hypoglycemic effects in diabetic rats, especially at a dose of 500.00 mgkg⁻¹, and also exhibited antihyperlipidemic properties by lowering serum cholesterol levels, indicating its potential as a treatment for both diabetes and hyperlipidemia (Hasan et al., 2020).

**Gastroprotective**

*A. vera*’s gastroprotective properties are linked to its low molecular-weight gel fraction (lgfAv), which effectively reduces alcohol-induced gastric lesions in mice by inhibiting the activity of matrix metalloproteinase-9 (MMP-9), thus protecting the gastric mucosa (Park et al., 2017). *A. vera* drink, known as Masfon, was investigated for its gastroprotective effects in rats. It increased basal gastric acid output but reduced acid output when histamine was administered, suggesting potential cytoprotective properties on the gastric mucus (Oka et al., 2014).

**Antifungal**

In some studies, *A. vera* has exhibited antifungal activity against certain fungi, which could have implications for the treatment of fungal infections (Rosca-Casian et al., 2007; Danish et al., 2020; Bajwa, 2012).

**Anticancer properties**

Preliminary research has explored the potential anticancer effects of *A. vera* although more studies are needed to establish its efficacy in cancer therapy. *A. vera*’s chief bioactive compounds have shown promise in pre-clinical studies for their potential anticancer effects, making *A. vera* a subject of interest in cancer prevention and treatment research due to its diverse mechanisms of action (Majumder et al., 2019). The plants active compounds, such as anthraquinones (barbaloin, aloesin, aloe-emodin) and an octapeptide, exhibited significant anticancer effects by prolonging animal lifespan, inhibiting tumor growth, inducing cytotoxicity in leukemia and colon cancer cells, and promoting apoptosis (El-Shemy et al., 2010). The ethanolic leaves extract displayed potent anticancer activity against liver, cervical, and lung cancer cell lines, suggesting its potential as a source of anticancer agents that require further characterization (Karpagam et al., 2019).
Antiviral properties

An extract of A. vera gel exhibited antiviral activity against HSV-2 at different stages of virus replication, suggesting its potential as a natural source for developing antiviral drugs against HSV-2 with a favorable selectivity index (Zandi et al., 2007). A. vera molecules were subjected to molecular docking studies with the main protease (3CLpro) responsible for coronavirus replication, revealing three potential enzyme inhibitors, with ligand 6 showing the highest binding energy and adhering to Lipinski’s rule of five, indicating their potential as antiviral agents against SARS-CoV-2, the virus responsible for COVID-19 (Mpiana et al., 2020). Anthraquinones present in A. vera were evaluated for their antiviral activity against influenza virus AH1N1 strains (Borges-Argáez et al., 2019).

Toxicity

Aloe vera gel toxicity against Aliivibrio fisheri was assessed with values ranging from 0.03 to 0.09 mg mL⁻¹, indicating varying toxicity, with some samples having low toxicity (Kaparakou et al., 2021). Wu et al., (2021) found that A. vera soft capsules had no harmful effects at high doses in animal tests, and there was no evidence of genetic damage. This suggests that A. vera soft capsules is safe for use as a laxative and health food. Some study indicates that A. vera green rind and whole leaf extracts are safe at high doses for short periods. However, extended and high-dose use of whole leaf extract may lead to kidney issues, so caution is advised in such cases (Nalimu et al., 2022). Moughbel et al., (2007) tested A. vera cream for healing second-degree burn wounds in 30 patients. It showed superior wound healing (90.6%) compared to silver sulfadiazine (29.8%) by day 10. Importantly, A. vera didn’t cause skin issues, suggesting it’s a promising option for burn wound management. Some findings also suggest that A. vera can help counteract arsenic-induced oxidative stress without changing arsenic concentrations in organs (Gupta and Flora 2005).

Table 1: Compounds found in A. vera with its pharmacological significance

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Pharmacological activities</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthraquinones</td>
<td>Anti-inflammatory</td>
<td>Yagi et al. (2002); Langmead et al. (2004).</td>
</tr>
<tr>
<td></td>
<td>Antibacterial</td>
<td>Nejatzadeh-Barandozi, (2013); Danish et al. (2020).</td>
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<tr>
<td></td>
<td>Wound healing</td>
<td>Davis et al. (1989); Maenthaisong et al. (2007).</td>
</tr>
<tr>
<td></td>
<td>Antioxidant</td>
<td>Hu et al. (2003); Heš et al. (2019).</td>
</tr>
<tr>
<td></td>
<td>Laxative</td>
<td>Surjushe et al. (2008); Manvitha and Bidya (2014).</td>
</tr>
<tr>
<td></td>
<td>Immunomodulatory</td>
<td>Madan et al. (2008); Kwon et al. (2011).</td>
</tr>
<tr>
<td></td>
<td>Anti-diabetic</td>
<td>Tanaka et al. (2006); Atanu et al. (2018).</td>
</tr>
<tr>
<td></td>
<td>Skin protective</td>
<td>Foster (1999); Gao et al. (2019).</td>
</tr>
<tr>
<td></td>
<td>Anti-Hyperlipidemic</td>
<td>Huseini et al. (2011); Hasan et al. (2020).</td>
</tr>
<tr>
<td></td>
<td>Gastroprotective</td>
<td>Oka et al., 2014; Park et al., 2017.</td>
</tr>
<tr>
<td></td>
<td>Antifungal</td>
<td>Rosca-Casian et al. (2007); Bajwa, (2012); Danish et al. (2020).</td>
</tr>
<tr>
<td></td>
<td>Anticancer</td>
<td>Karpagam et al. (2019); Ali et al. (2020); Murugesan et al. (2021).</td>
</tr>
<tr>
<td></td>
<td>Antiviral</td>
<td>Zandi et al. (2007); Borges-Argáez et al. (2019); Mpiana et al. (2020).</td>
</tr>
<tr>
<td>Polysaccharides</td>
<td>Immune-modulating</td>
<td>Yu et al. (2009).</td>
</tr>
<tr>
<td></td>
<td>Anti-inflammatory</td>
<td>Tomerno-Martínez et al. (2022).</td>
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<tr>
<td>Phytosterol</td>
<td>Cholesterol-lowering</td>
<td>Pothuraju et al. (2016).</td>
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<tr>
<td></td>
<td>Anti-inflammatory</td>
<td>Conte et al. (2017).</td>
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<tr>
<td>Saponins</td>
<td>Antimicrobial</td>
<td>Yebpella et al. (2011); Berniyanti and Mahmiyah (2015).</td>
</tr>
<tr>
<td></td>
<td>Anti-inflammatory</td>
<td>Das et al. (2011); Paul et al. (2014).</td>
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<tr>
<td>Flavonoids</td>
<td>Antioxidant</td>
<td>Gorsi et al. (2019); Heš et al. (2019).</td>
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<td></td>
<td>Anti-inflammatory</td>
<td>Kumar et al. (2020); Mir and Masodi (2020).</td>
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<td>Anticancer</td>
<td>Jose et al. (2014).</td>
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<tr>
<td>Enzymes</td>
<td>Anti-inflammatory</td>
<td>El-Shemy et al. (2010).</td>
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<tr>
<td>Vitamins</td>
<td>Nutritional support</td>
<td>Nagpal et al. (2012).</td>
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</table>

Conclusion

Aloe vera, known as the "Plant of Immortality," has been traditionally used for its medicinal and cosmetic properties, with applications ranging from digestive issues to skin conditions. It possesses various pharmacological activities, including anti-inflammatory, antibacterial, wound healing, antioxidant, laxative, immunomodulatory, anti-diabetic, skin protective, and potential anti-cancer effects, largely attributed to its bioactive compound anthraquinones primarily found in the outer leaf's latex layer. The species possess laxative phytochemical compounds, including anthraquinones like Aloin, predominantly found in the outer leaf and the latex layer. These compounds have notable laxative properties and can vary in concentration depending on processing methods. A. vera exhibits a range of toxicity levels depending on its form, with some products showing low toxicity, while others may pose risks at high doses, particularly in the case of unprocessed whole leaf extracts. Concurrently, A. vera demonstrates potential wound healing benefits and protective effects against arsenic-induced oxidative stress. Nevertheless, further research is needed to explore its therapeutic potential fully through modern scientific methods.

References


