The phytochemical constituents and therapeutic uses of genus Aloe: A review

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Abstract

Aloe, the largest genus in the Asphodelaceae family, comprises 548 species, with A. vera, A. arborescens and A. ferox being among the most widely studied species. Aloe species originated in arid climates and cover various habitats, from sea level up to 2700 m, and from desert to closed-canopy forests. For human health, Aloe species are the richest natural sources. The biological activity of Aloe sp. constituents covers a wide spectrum. Most of the indications come from traditional, folkloric use and several have been verified by in vitro or in vivo studies. Emodin, the main phenolic component, has shown anti-neoplastic, anti-inflammatory, anti-angiogenic and toxicological potential for use in pharmacology. Polysaccharides, with acemannan being the most important, are present in high abundance in Aloe gels. Acemannan has been reported to have applications in oral, metabolic and cardiovascular diseases, oncology, dentistry and wound healing. The effectiveness of Aloe sp. constituents on colon, liver, duodenum, skin, pancreas, intestine, lungs and kidneys cancers was highly studied with remarkable findings. Regarding the metabolic syndrome, Aloe sp. can be used as an antidiabetic and reduces cholesterol and total body fat. Constituents of Aloe sp. are nontoxic in experimental acute oral studies and are widely used in cosmetology and as bitter agents or consistence modifiers in food and beverages. Traditional Aloe remedies cover most human diseases; however, in order to gain legitimacy, the Aloe-derived drugs must have a well-established composition, with thoroughly investigated adverse effects and conventional drug interactions.

Keywords: Aloe; antidiabetic; antimicrobial; cancer; healing

Introduction

Aloe, the largest genus in the Asphodelaceae family, bears its name from the Arabic word “Alloeh,” meaning shining bitter substances (Sánchez et al., 2020). The genus Aloe L. comprises 548 accepted species, with at least one-third having some commercial importance (Grace et al., 2009). A. vera, A. arborescens and A. ferox are among the most widely studied Aloe species. The Egyptians called Aloe the “Plant of Immortality” because they can live and even bloom without soil (Mukesh et al., 2010). The plant was widely used by the
Assyrians, Egyptians and Mediterranean civilizations (Moein et al., 2017). Dried leaf exudate is the principal medicinal product. Dioscorides used *A. vera* as a purgative, to treat mouth infections, wounds and other dermatological conditions (Grindlay and Reynolds, 1986). The purpose of this review is to highlight the characteristics of Aloe Plants with their compounds and pharmacological activities.

The *Aloe* genus comprises monoecious, perennial species with shallow roots. *Aloe* species thrive in arid climates in Africa (from where it probably originates) and India. Its adaptability, conditioned by temperature, rainfall, soil moisture and fire tolerance, allows *Aloe* species to cover various habitats, from sea level up to 2700 m, and from desert shrub lands to closed-canopy forests (Salehi et al., 2018).

The most appropriate soil is a loamy mixture with pH 7.0-8.5, but some species (*A. vera*) prefer acidic soils. Well-drained sandy soil or rocky sites are preferred, but many *Aloe* species can grow in almost any soil type. Several *Aloe* species may act as nurse plants, ameliorating harsh conditions in barren landscapes and increasing soil binding and stabilization in degraded rangeland (King and Stanton, 2008). The optimal growth temperatures range between 4-21 °C. The blooming time is in May-June and the colour may vary depending on the soil mineral composition.

Most of the *Aloe* species are diploids (2n=14). Polyploidy is uncommon in *Aloe* and is not uniform in its geographical distribution. The only known case of hexaploidy (2n = 42) in the entire genus is *A. ciliaris* var. *ciliaris*, whereas several other varieties of *A. ciliaris* are tetraploid (2n = 28). The tetra- and hexaploids appear naturally as intraspecific autopolyploids, and the morphological differences between the varieties are quantitative rather than qualitative (Riley, 1959). There are reports of triploidy in *Aloe* (2n = 21), with sterile but vegetatively vigorous individuals (Brandham et al., 1994).

Carl Linnaeus was the first to describe *Aloe vera* in 1753 as *Aloe perfoliata* var. *vera*, followed by Nicolaas Laurens Burman as *Aloe vera* on April 6, 1768 and by Philip Miller as *Aloe barbadensis* some ten days after Burman (LE, 1979). Considering this, the correct binomial name is *Aloe vera* (L.) Burm.f (Grindlay and Reynolds, 1986).

**Characteristics of Aloe Plants**

*A. vera* is a perennial succulent xerophyte green herb growing up to 100 cm, with 15-30 fleshy leaves per plant ranged in a rosette from a short stem that can reach 25 cm with age (Figure 1). The young leaves are central and straighter than the older, the peripheral ones, which are lower and more spreading. The leaves may be 0.5 m long and 10 cm wide at the base, with teeth like a saw along their margins (serrated margins). In young plants, the leaves and pups that arise from the base are bright green, with irregular whitish spots on both surfaces, adaxial, concave and abaxial, convex. With time, successive leaves have fewer spots and disappear in older leaves (Figure 2). The inflorescence is a raceme fixed on a peduncle 30-50 cm long, arising from the centre of the leaf rosette. The flowers are pendent, with a tubular yellow perianth approximately 2 cm long (Grindlay and Reynolds, 1986). Arbuscular mycorrhizal (AM) symbiosis has been shown to increase nutrient uptake and growth of Aloe (Pareek et al., 1999; Tawaraya et al., 2007).

*Aloe arborescens* Miller, native to central-southern Africa, is a traditional medicinal plant that is quite popular in South Africa, Asia, Russia, and Japan. *A. arborescens* is characterized by a central woody stem that can reach several meters. The branches have bushy shrubs, and the grey-green leaves are long, thin and spiny. The natural habitats of *A. arborescens* are mountainous regions of southern Africa (Salehi et al., 2018). *A. arborescens* is also grown as a source for medicinal, cosmetic, and food use in various countries (China, Israel, Italy, Japan, Crimean Peninsula). As pot plants, they reach only modest dimensions (Glatthaar-Saalmüller et al., 2015). The large colourful flower spikes are borne in profusion during May-July. The most common colour is deep orange, but there are also pure yellow forms, and an unusual bi-coloured form of deep orange (almost red) and yellow (Leistner, 2000; Heinrich, 2001).
**Figure 1.** *Aloe vera*

**Figure 2.** *Aloe vera* grown in the Green House (a - young leaves, b - mature leaves)
*Aloe ferox* Mill. (= *A. candelabrum* A. Berger), commonly known as the bitter *Aloe* or *Cape aloe*, is a polymorphic species indigenous to the Western Cape region of South Africa. It has a single, tree-like stem with succulent leaves protected by reddish spines; hence, the name *ferrox* (Latin for fierce). Six to twelve branches are present at *A. candelabrum*, and the flowers have their inner petals tipped with white. The flowers are carried in a large candelabra-like flower-head. There are usually between five and eight branches, each carrying a spike-like head of many flowers (*Schmid et al.*, 1998).

**Phytochemical Constituents of Aloe Plants**

*Aloe* leaves, the most commonly used medicinal parts, can be divided into the following structural components: outer green epidermis, consisting of a thick cuticle and under a zone of chlorenchyma (1); outer pulp region, under the epidermis, containing vascular bundles with bitter sap (latex) that exudes from the leaves when they are cut (2); inner leaf pulp, containing large thin-walled parenchyma cells filled with the colorless mucilaginous gel (containing the aloe gel) (3) (*Grindlay and Reynolds*, 1986; *Salehi et al.*, 2018). Description of the inner central part of the aloe leaf may sometimes be confusing, due to the different terms that are used interchangeably such as inner pulp, mucilage tissue, mucilaginous gel, mucilaginous jelly, inner gel and leaf parenchyma tissue. Technically, the term ‘pulp’ or ‘parenchyma tissue’ refers to the intact fleshy inner part of the leaf including the cell walls and organelles, while ‘gel’ or ‘mucilage’ refers to the viscous clear liquid within the parenchyma cells (*Hamman*, 2008). It is important to differentiate between the two medicinal components of *A. vera* leaves: gel and exudates.

The main classes of bioactive compounds differ among the three components. Thus, the outer green epidermis contains mostly anthraquinones, pre-anthraquinones and corresponding glycosides, while the outer pulp region consists of phenolic compounds (anthraquinones, pre-anthraquinones, flavonoids, chromones, anthrones, coumarins, and pyrones). The pulp is rich in acemannan and phenolic compounds. The *Aloe* gel from the inner leaf pulp also contains proteins, vitamins, minerals and enzymes.

Flowers of *A. vera* are a by-product with valuable bioactive compounds whose health benefits are only partially assessed. The flower can be considered as have three maturity stages: immature (1); mature (2); mature, with flowers buds opened (3) (*Martínez-Sánchez et al.*, 2020).

Immature flowers present the highest content of phenolic and antioxidant capacity. As the flower develops the content of these compounds decreases, and the content of fatty acids increases. The last maturity stage has the lowest fatty acid content. These compounds have applications in the cosmetic, nutraceutical, pharmaceutical and food industries. The harvesting period may be chosen depending on the compound of interest and, by removing the flower, the energy consumption of flowers from the plant will be lower, thus favouring plant development (*Martínez-Sánchez et al.*, 2020).

*Zapata et al.* (2013) noted that the leaf characteristics and gel chemical composition of eight *Aloe* species studied in freshly harvested leaves in three different seasons within the Mediterranean climate have differences depending of species and harvest seasons.

The biological activities of the components are the result of a combined and synergistic action rather than the added effects of single substances (*Dagne et al.*, 2005).

The anthraquinones contained by *Aloe* species are aloesaponarin, helminthosporin, aloechrysone, chrysophanol, aloesaponol, asphodelin and bianthracene (*Salehi et al.*, 2018).

The anthrone class is represented by aloin (synonym – barbaloin), homonataloin and nataloin (*Dagne et al.*, 2005). Aloin comprises two diastereomers: aloin A and aloin B. It is a C-glycoside that can be hydrolyzed in the gut to form aloe-emodin anthrone, which auto-oxidizes to quinone aloe-emodin. Emodin has numerous pharmacological effects. Both *in vitro* and *in vivo* studies have demonstrated anti-neoplastic, anti-inflammatory, anti-angiogenic and toxicological potential for use in pharmacology (*Hsu and Chung*, 2012).
Table 1. Aloe structural components with class, compounds, source and pharmacological activities (S. Choi and Chung, 2003; Dagne et al., 2005)

<table>
<thead>
<tr>
<th>Aloe structural components</th>
<th>Class</th>
<th>Compounds</th>
<th>Source</th>
<th>Pharmacological Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>The outer green epidermis</td>
<td>Glycosides</td>
<td>aloe-emodin, emodin</td>
<td>Aloe spp.</td>
<td>Purgative, cell proliferation, anticancer, antiprotozoar, antibacteria, antioxidant, genotoxicity</td>
</tr>
<tr>
<td></td>
<td>Anthaquinones</td>
<td>aloetic acid, aloin, anthrafol, isobarbaloin, ester of cinnamic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anthrones</td>
<td>barbaloin</td>
<td>Aloe spp.</td>
<td>Purgative</td>
</tr>
<tr>
<td></td>
<td>Flavonoids</td>
<td>Apigenin, Naringenin, Isovitexin</td>
<td>Aloe spp.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chromones</td>
<td>Aloeresin C, D, E, F Isoaloesin</td>
<td>Aloe spp.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coumarins</td>
<td>Feralolide, Dihydroisocoumarin, glucoside</td>
<td>Cape aloe Aloe hildebrandtii</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyrones</td>
<td>Aloenin, (Aloecarbonoside), Aloenin acetal, Aloenin aglycone</td>
<td>Aloe nyeriensis Aloe arborescens</td>
<td>Immunomodulation Antimicrobiol effect Antitumor</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous</td>
<td>Acemannan</td>
<td>Aloe vera</td>
<td></td>
</tr>
<tr>
<td>The inner leaf pulp</td>
<td>Proteins</td>
<td>lectins, lectin-like substance</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitamins</td>
<td>B1, B2, B6, C, β-carotene, choline, folic acid, α-tocopherol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minerals</td>
<td>amyrase, carboxypeptidase, catalase, cyclooxydase, lipase, oxidase</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Enzymes</td>
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The chromones, an abundant phenolic class in leaves, comprise aloesin, aloeresin A and isomeric forms, from aloeresin C to aloeresin F (Cock, 2015).

Feralolide and dihydroisocoumarin glycoside are the coumarins contained in A. species leaves. Aloenin, aloenin aglycone, aloenin acetal and aloenin B are the pyrones identified in several Aloe species leaf exudates. The most common Aloe alkaloids are N-methyltyramine and O,N-dimethyltyramine, while γ-coniceine is only present in a few species (Cock, 2015). Protocatechuic acid, methyl-p-coumarate and pluridone are benzene derivatives frequently identified in Aloes (Salehi et al., 2018).

Naringenin, apigenin, isovitexin and dihydro-isorhamnetin are the major flavonoids detected (Salehi et al., 2018). Phytosterols are represented by cholesterol, β-sitosterol, campesterol and lupeol together with their glucosides. Polysaccharides, the non-phenolic components, with acemannan being the most important, are present in high abundance in Aloe gels. Acemannan, the main bioactive polysaccharide of A. vera, is a β-(1,4)-acetylated soluble polymannose (Liu et al., 2019). It is a storage polysaccharide in the proplasts of parenchyma cells.

Aloe acemannan content depends greatly on the species and cultivation conditions. Irrigation influenced the amount of polysaccharides. The mannose content decreased with 41% in the case of water deficit. When the aloe was irrigated with seawater, 42% seawater stress treatment only reduced the polysaccharide concentration in the base leaves, without lowering the polysaccharide concentration in the upper and middle parts (Jiang et al., 2014). Considering the age of the plant, the acemannan level reached a peak in three-year-old A. vera plants and then decreased. In addition, increased light intensity resulted in higher acemannan concentrations in A. vera and A. arborescens (Ray and Aswatha, 2013).

Acemannan has been reported to have many pharmacological and biological applications in the medical field, such as oral, metabolic and cardiovascular diseases, oncology, dentistry and wound healing (Liu et al., 2019). Acemannan, when administered orally to mammals, inhibits cholesterol absorption and induces hypocholesterolemia. Parenterally, it induces macrophage activation and interleukin-1 release, stimulates bone marrow activity, promotes wound healing, and inhibits viral replication and tumour growth. This wide range of activities promotes the mannans to potential therapeutic agents and biological response modifiers (Tizard et al., 1989).

The largest vitamin contents are in Vitamin C, B1, B2, B6, B12 and E. Gels from Aloe species contain minerals, including Mg, Zn, Ca, K, Na, Fe, P, Mn, Cu, and Mo (Vogler and Ernst, 1999; S. Choi and Chung, 2003; Dagne et al., 2005; Hamman, 2008).

**Medicinal Use of Aloe Plants**

Gastrointestinal disorders, hepatoprotective action and beneficial effects against skin problems such as wounds, injuries, and infectious diseases are among the most frequently mentioned indications in traditional medicine in connection with Aloe species (Akaberi et al., 2016). Aloe sp. dried juice is used traditionally in small doses as carminative and tonic and in larger doses, as a laxative and emmenagogue (Moein et al., 2017). The biological activity of many Aloe species covers a wide spectrum. Most of them come from traditional, folkloric use and some have been verified by in vitro or in vivo studies (Dehdari et al., 2018). The level of experimental or clinical confirmation is very variable, going from anecdotal mentioning to prospective, double-blind clinical studies.

**Antimicrobial and antifungal activities**

The antimicrobial activity includes bacteria, fungi and viruses. “Smart” biohybrids containing A. vera with triiodide have excellent antifungal and promising antimicrobial activities, are cost-effective, eco-friendly and can be used against surgical site infections (SSI) and as disinfecting agents (Edis and Bloukh, 2020).
In vitro activity assessment of *Aloe barberae* demonstrated antimicrobial effects on gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) and gram-negative bacteria (*Escherichia coli* and *Klebsiella pneumoniae*). *Aloe* sap extract is more effective than leaf extract (Ndhlala et al., 2009). Another study showed that *A. vera* juice has antimicrobial activity against *M. smegmatis*, *K. pneumoniae*, *E. faecalis*, *M. luteus*, *C. albicans* and *B. sphericus*, but has no effect on *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Salmonella typhimurium* (Alemdar and Agaoglu, 2009).

*A. vera* has better therapeutic, antibacterial and anti-inflammatory effects against staphylococcal pyoderma in dogs than gentamicin (Kamr et al., 2020). A clinical study performed by Prueksrisakul et al. (2015) on healthy volunteers receiving 250 mL of *A. vera* gel extract daily demonstrated a significant decrease in the number of oral pathogenic bacteria.

Experimental studies have demonstrated that an aqueous suspension of *Aloe* polysaccharides can be used to control angular leaf spot disease (*Xanthomonas fragariae*), which acts both by its antimicrobial activity and by activating latent defence mechanisms in strawberry (Luiz et al., 2017). 

In vitro antifungal effects of *Aloe* species extract have been demonstrated also in *Candida albicans* (Ndhlala et al., 2009). The purified *Aloe* protein fraction from the *A. vera* leaf gel had potent antifungal activity against *Candida parapriosis*, *Candida krusei* and *Candida albicans* (Das et al., 2011).

*A. vera*, *A. ferox*, *A. mitriformis* and *A. saponaria* have high antifungal activity against *B. cinerea*, *P. digitatum*, *Penicillium expansum* and *P. italicum*. Measured as a percentage of infected leaves, this antifungal activity was positively correlated with aloin content (Zapata et al., 2013).

A study performed by Nidiry et al. (2011) demonstrated that aloin and aloe-emodin are the active principles against two phytopathogenic fungi *Colletotrichum gloeosporioides* and *Cladosporium cucumerinum*.

Sydiskis et al. (1991) showed that aloe emodin inactivated herpes simplex type 1 and type 2, varicella-zoster, pseudorabies and influenza but was not effective against adenovirus and rhinovirus. Electron microscopy demonstrated that the virucidal mechanism consisted of envelope disruption.

*A. arborescens* has been used for the treatment of upper respiratory tract infections in Central and Eastern European countries for many decades. In vitro study with a mixture containing *A. arborescens* extract showed a clear dose-dependent antiviral activity against human rhinovirus 14 and Coxackievirus (both non-enveloped RNA viruses). Respiratory syncytial virus and parainfluenza virus (Paramyxoviridae) were poorly blocked by the test substance, while an adenovirus was not affected by the mixture (Glatthaar-Saalmüller et al., 2015).

**Wound healing effect**

Skin healing and tissue regeneration are among the most frequently used features in both traditional and modern medicine. Empirical observations were confirmed by *in vitro* studies, followed by experimental and clinical trials.

Liang et al. (2020) suggested that adding gel to the wound dressing could be a simple and standardized way to use *A. vera*. Inflammation is a normal component of healing, yet, the anti-inflammatory effects of *Aloe* sp. seem to boost tissue healing (Park et al., 2009). The *in vitro* study demonstrated anti-inflammatory effects of *Aloe* sp., indirectly confirmed by the effect of aloe-emodin, comparable to that of kaempferol and quercetin (Ndhlala et al., 2009). The effect of G1G1M1D12, a glycoprotein fraction isolated from *A. vera*, on cell migration was confirmed by the accelerated healing of a monolayer of human keratinocytes. It promoted the formation of epidermal tissue in raft culture. Thus, this glycoprotein fraction promotes wound healing by both cell proliferation and migration (Choi et al., 2001). Other healing effects include increased cell phagocytic effect, more rapid wound area contraction rate and collagen synthesis, all due to the mannose contained in *A. vera*. The polysaccharides present in *A. vera* induce fibroblast proliferation, hyaluronic acid and
hydroxyproline production, which play an important role in extracellular matrix remodeling (Salchi et al., 2018). A. vera green-synthesized silver nanoparticles photobiomodulated by irradiation with laser led to an increase in cell migration in normal wounded and diabetic wounded fibroblast cells (Kumar et al., 2020). An experimental study in rats with eight Aloe species (A. arborescens, A. brevifolia (Figure 3), A. eru, A. ferox, A. grandidentata, A. perfoliata, A. saponaria, and A. vera) demonstrated a significantly accelerated healing in the topical application of leaf methanol extracts on diabetic wounds (El Sayed et al., 2016). Oryan et al. (2016) showed that A. vera modulated inflammation, increased wound contraction and epithelialization, decreased scar tissue size, and increased alignment and organization of the regenerated scar tissue. The lesions also demonstrated improved modulus of elasticity, maximum load and ultimate strength. Oral administration of A. vera promotes healing by increasing collagen content and improving angiogenesis and chemotaxis in rats (Ali et al., 2020). Patients with thermal burns dressed with A. vera gel showed advantages compared to those dressed with sulfadiazine regarding early wound epithelialization, earlier pain relief and cost-effectiveness (Shahzad and Ahmed, 2013). Aloe sp. are also efficient in preventing and improving hypertrophic scars (Duansak et al., 2003; Surakunprapha et al., 2020). A. vera may have an anti-inflammatory effect in burn injuries due to the reduction in leukocyte adhesion and pro-inflammatory cytokines. A meta-analysis performed by Guo et al. (2016) concluded that A. vera may be used both as an alternative and integrative way to reduce symptom severity in the wound healing process at the mucocutaneous level.

Figure 3. Aloe brevifolia

Aloe effects on digestive system

The favourable effects on the digestive system begin with the traditional use as a laxative and cover almost every aspect or organ. Significant antiulcer and gastroprotective activities were observed after the administration of Aloe-containing preparations (Akaberi et al., 2016; Eamlamnam et al., 2006). An interesting direction was provided by a study that noted that the A. vera gel has antibacterial properties against both susceptible and resistant Helicobacter pylori strains. Thus, a combination of A. vera gel with antibiotics may improve the results of H. pylori eradication (Cellini et al., 2014). A study on rats that deal with the effect of A.
vera on gastric microcirculatory changes, cytokine levels and gastric ulcer healing showed that A. vera treatment reduced leukocyte adherence and TNF-alpha levels, elevated IL-10 levels and promoted gastric ulcer healing (Eamlamnam et al., 2006).

A study with a A. ferox extract on constipated rats led to improved intestinal motility, increased fecal volume and normalized body weight, confirming the empiric use as a laxative in South Africa (Wintola et al., 2010). A similar effect is targeted in sheep diets containing A. vera extract to reduce enteric methane emission and boost productivity (Akanmu et al., 2020). A recent study has confirmed that acemannan has the advantage of inducing intestinal growth in bacteria such as Bifidobacterium and Lactobacillus (Quezada et al., 2017). A. vera gel had a dose-dependent inhibitory effect on reactive oxygen metabolite production in incubated colorectal mucosal biopsies, which indicated a therapeutic effect in inflammatory bowel disease (Langmead et al., 2004). Aloe extract and a number of its compounds have been shown to ameliorate inflammation and improve clinical and histopathological colitis symptoms in animal models (Akaberi et al., 2016). Any prolonged treatment for chronic inflammatory bowel disease should maintain a high awareness of cancer risk (Harris et al., 2020).

Prospective, randomized, double-blind, placebo-controlled trials in proctology consisted of the application of A. vera cream on the surgical site. The results were similar and demonstrated that the treatment is effective in reducing postoperative pain both at rest and during defecation, healing time, and analgesic requirements (Gaj and Crispino, 2009; Eshghi et al., 2010).

The bitter latex of Aloe ferox is used as a laxative in Africa and Europe and is considered to have tonic, antioxidant, anti-inflammatory, antimicrobial and anticancer properties (Chen et al., 2012).

**Hepatoprotective effects**

A. vera and A. arborescens have hepatoprotective activities (Singab et al., 2015). Thus, polysaccharides exert a protective effect against chronic alcohol-induced liver injury (Cui et al., 2014), toxic solvents such as carbon tetrachloride (Chandan et al., 2007), and aflatoxins (Cui et al., 2017). The hepatoprotective effect appears to be associated with antioxidant capacity and the ability to accelerate lipolysis and inhibit inflammatory response, improve excretory capacity and stimulate bile flow secretion. However, its use in gallbladder conditions that are at risk for carcinogenesis should be discouraged (Puia and Puia, 2013).

Aloe may be used for intestinal drug absorption enhancement in drugs with low bioavailability due to extensive efflux (Josias et al., 2013).

**Anticancer activity**

A review performed by Singab et al. (2015) mentioned several studies with findings about the effectiveness of Aloe sp. on various cancers affecting several organs, including the colon, liver, duodenum, skin, pancreas, intestine, lungs and kidneys. Aloe is thought to be a potential agent for the treatment of gastrointestinal cancers. Qin et al. (2006) noted that the inhibitory effect of aloe-emodin on the proliferation and migration of gastric tumour cell lines is dose-dependent. Pan et al. (2013) showed that aloin inhibits tumour angiogenesis and growth by blocking STAT3 activation. Aloe-emodin and emodin demonstrated anticancer activities in the human gastric cancer MKN45 cell line (Chihara et al., 2015). Emodin also induces apoptosis and cell death in human lung squamous carcinoma cells in vitro (Lee et al., 2001). Aloin can be used to radio-sensitize HeLaS3 human cervical carcinoma cells in vitro (Nićiforović et al., 2007). Paraneoplastic venous thrombosis affects many patients. Fan et al. (2018) demonstrated in vitro that protein and phenolic extracts of four Aloe species have good thrombolytic and fibrinolytic activities. Adding this clot lytic quality to the known anticancer effects may open a new direction in the use of Aloe sp. in oncological treatment (Fan et al., 2018).
Antioxidant activity

In vitro studies have demonstrated that \textit{A. vera} extracts from both leaves and flowers are good natural antioxidant sources (López \textit{et al.}, 2013). A study performed on several \textit{Aloe} sp. concluded that the most active antioxidant may be found in \textit{A. pillansii} along with \textit{A. broomii} and \textit{A. spinosissima}, comparable to the better known \textit{A. arborescens} and \textit{A. vera} (Sazhina \textit{et al.}, 2016). A study on healthy volunteers receiving 250 mL of \textit{A. vera} gel extract daily demonstrated a significant increase in the plasma total antioxidant capacity (TAC) (Prueksrisakul \textit{et al.}, 2015).

In a study performed in India on plants harvested from various regions, \textit{A. vera} extracts from colder climatic regions showed good antiplasmodial activity. There was a significant correlation between the quantities of aloin and \textit{aloe}-emodin and the antiplasmodial effect (Kumar \textit{et al.}, 2020). Homonataloin, belonging to the anthrone group, seems to be the most efficient component against chloroquine-resistant \textit{Plasmodium falciparum} strains (van Zyl \textit{et al.}, 2002).

Maphosa \textit{et al.} (2010) provided evidence that \textit{A. ferox} extract has in-vitro anthelminthic activity, thus encouraging use in the treatment of GI helminthosis.

Antidiabetic effects

The empirical use of \textit{Aloe} sp. as an antidiabetic has been supported by several studies (Grindlay and Reynolds, 1986). A study by Froldi \textit{et al.} (2019) demonstrated that both the methanolic and the hydroalcoholic \textit{A. arborescens} extracts led to the inhibition of glycation and free-radical persistence, without any cytotoxic activity, thus supporting the traditional use of \textit{A. arborescens} leaf extracts against hyperglycemic conditions. Five phytosterols evaluated for their anti-hyperglycemic effects in type 2 diabetic mice led to a decrease in fasting blood glucose levels between 28% and 64% compared to the control levels (Tanaka \textit{et al.}, 2006). A double-blind randomized controlled trial on 72 patients with pre-diabetes symptoms demonstrated that fasting blood glucose and HbA1C levels improved after 8 weeks (Alinejad-Mofrad \textit{et al.}, 2015). In a randomized double-blind placebo-controlled clinical trial, Huseini \textit{et al.} (2012) demonstrated that \textit{A. vera} gel lowered fasting blood glucose and HbA1c levels significantly without affecting any liver/kidney function tests.

Antihyperlipidic effects

In an experimental study performed by Dana \textit{et al.} (2012) significant differences were observed between cholesterol levels in rats fed a high-cholesterol diet combined with \textit{A. vera} and a high-cholesterol diet alone. The formation of fatty streaks in the aorta was also significantly lower in the same animals under the influence of diet with \textit{A. vera}.

A clinical study showed the effectiveness of \textit{A. vera} in improving total cholesterol, LDL-C, HDL-C and triglycerides after 4-8 weeks of intake (Alinejad-Mofrad \textit{et al.}, 2015).

Huseini \textit{et al.} (2012) noted that \textit{Aloe} gel has a favourable effect on total cholesterol and LDL levels and no adverse effects, thus promoting it as a safe anti-hypercholesterolemic agent for hyperlipidemic patients.

The research of Misawa \textit{et al.} (2012) have shown that \textit{A. vera} gel powder combined with a high-fat diet induces in rats only a modest decrease of body weight but, much more important, reduces significantly subcutaneous, visceral and total body fat. In an experimental study meant to decipher the anti-obesity mechanism of \textit{A. vera} gel extract Tada \textit{et al.} (2020) showed that brown adipose tissue activation contributes to weight loss.

Other favourable effects

Placebo-controlled studies have shown that the consumption of mannans improves cognitive performance in middle-aged patients with mental fatigue. Improvements in memory performance following mannans intake were independent of changes in blood glucose levels (Best \textit{et al.}, 2015).

The ameliorating effect of aqueous extract of \textit{A. vera} leaves against cartap and malathion toxicity could be used to protect non-target animals from the adverse effects of pesticides (Gupta \textit{et al.}, 2020).
In cosmetology, *Aloe* sp. are used in toothpaste, creams, shampoos and soap production. Industrial applications as bitter agents or consistence modifiers include beverages, ice cream or food supplements.

A panel of experts established that *Aloe* is not toxic in experimental acute oral studies but can cause significant sperm damage, be abortifacient or produce skeletal abnormalities. Aloin had no carcinogenic effects on mice. Case reports in humans included acute eczema, contact urticaria, and dermatitis, but no phototoxicity in topical use (Andersen, 2007).

A major obstacle in introducing *A. spp* derived products on a large scale in medicine is the lack of standardization regarding the components and their concentration (Moein *et al*., 2017).

**Conclusions**

Many species of the *Aloe* genus have been in use for a long time in folk medicine and, more recently, as components of food and beverages. Its adaptability led to a worldwide spontaneous or cultivated growth that made *Aloe* available at a reasonable cost. Traditional *Aloe* remedies cover most human diseases; however, in order to gain legitimacy, the derived drugs must have a well-established composition, with thoroughly investigated adverse effects and conventional drug interactions.

**Authors’ Contributions**

Conceptualization: AP, CP, MF; Data curation: EM, FG and AF; Supervision: CP; Validation: AP, CP, EM, FG, AF, MF; Visualization: AP, CP, EM, FG, AF, MF; Writing - original draft: AP and CP; Writing - review and editing: AP, CP, EM, FG, AF, MF. All authors read and approved the final manuscript.

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**Conflict of Interests**

The authors declare that there are no conflicts of interest related to this article.

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