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Review Article

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 showed 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

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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 peripheric 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)

Aloe structural components	Class	Compounds	Source	Pharmacological Activities
The outer green epidermis	Glycosides			
	Anthraquinones Pre-anthraquinones	aloe-emodin emodin	Aloe spp.	Purgative, cell proliferation, anticancer,antiprotozoar, antibacteria, antioxidant, genotoxicity
		aloetic acid aloin anthranol isobarbaloin ester of cinnamic acid		
The outer pulp region		barbaloin	Aloe spp.	Purgative
	Anthrones	Aloe barbendol	Aloe barbadensis	
		Aloe-emodinanthrone	Aloe spp.	
	Flavonoids	Apigenin Naringenin Isovitexin	Aloe spp.	
	Chromones	Aloeresin C, D, E, F Isoaloesin	Aloe spp. Cape aloe Aloe vera	
	Coumarins	Feralolide Dihydroisocoumarin glucoside	Cape aloe Aloe hildebrandtii	
	Pyrones	Aloenin (Aloecarbonoside) Aloenin acetal Aloenin aglycone	Aloe nyeriensis Aloe arborescens	
	Miscellaneous	Acemannan	Aloe vera	Immunomodulation Antimicrobiol effect Antitumor
The inner leaf pulp	Proteins	lectins lectin-like substance		
	Vitamins	B1 B2 B6 C β-carotene choline folic acid α-tocopherol		
	Minerals			
	Enzymes	amylase carboxypeptidase catalase cyclooxydase lipase oxidase		

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 leafs. 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 acemannnan 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 protoplasts 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 paraprilosis, Candida krusei and Candida albicans* (Das *et al.*, 2011).

A film containing *Aloe vera* used for coating sliced fruit prolonged the shelf-life of the merchandise by controlling fungal contamination(Benítez *et al.*, 2015; Sánchez *et al.*, 2020).

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 Coxsackievirus (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 G1G1M1DI2, 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 (Salehi *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, thus reducing the necessary doses for radiotherapy from 3.4 to 2 Gy (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 *A. vera* extracts from both leaves and flowers are good natural antioxidant sources (López *et al.*, 2013). A study performed on several *Aloe* sp. concluded that the most active antioxidant may be found in *A. pillansii* along with *A. broomii* and *A. spinosissima*, comparable to the better known *A. arborescens* and *A. vera* (Sazhina *et al.*, 2016). A study on healthy volunteers receiving 250 mL of *A. vera* gel extract daily demonstrated a significant increase in the plasma total antioxidant capacity (TAC)(Prueksrisakul *et al.*, 2015).

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

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

Antidiabetic effects

The empirical use of *Aloe* sp. as an antidiabetic has been supported by several studies (Grindlay and Reynolds, 1986). A study by Froldi *et al.* (2019) demonstrated that both the methanolic and the hydroalcoholic *A. arborescens* extracts led to the inhibition of glycation and free-radical persistence, without any cytotoxic activity, thus supporting the traditional use of *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 *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 *et al.*, 2015). In a randomized double-blind placebo-controlled clinical trial, Huseini *et al.* (2012) demonstrated that *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 *et al.* (2012) significant differences were observed between cholesterol levels in rats fed a high-cholesterol diet combined with *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 *A. vera*.

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

Huseini *et al.* (2012) noted that *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 *et al.* (2012) have shown that *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 *A. vera* gel extract Tada *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 mannan intake were independent of changes in blood glucose levels (Best *et al.*, 2015).

The ameliorating effect of aqueous extract of *A. vera* leaves against cartap and malathion toxicity could be used to protect non-target animals from the adverse effects of pesticides (Gupta *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 topic 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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