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Bioactive constituents of the genus *Aloe* and their potential therapeutic and pharmacological applications: A review

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ABSTRACT

The therapeutic and pharmacological properties of plant bioactive constituents still continue to be the subject of many researches. Species of the *Aloe* genus have a history in folklore medicine and they have gained more attention over the years due to their various medicinal properties. Phytochemical studies have revealed that the *Aloe* species contain a number of constituents, such as polyphenols, phytosterols, polysaccharides, proteins, amino acids, chromones, and mineral elements. A comprehensive evidence-based review on the different constituents of *Aloe* species is needed in order to understand the benefits imparted by them. This review presents an overview of the bioactive components of the *Aloe* genus with emphasis on their anti-diabetic potential and other pharmacological benefits. This information will be beneficial for the advancement of new strategies of *Aloe* formulations with therapeutic and economical value in the near future. Furthermore, the potential applications and constraints have also been discussed so as to provide a wider prospect for research in this field for the benefit of the society.

INTRODUCTION

Efforts are being undertaken over the last few decades to develop efficient therapies for diseases such as diabetes, cancer, arthritis, cardiovascular diseases, etc. The medications available for treatment are costly and are associated with some side effects. Hence, it is prudent to search for options in herbal medicine. Herbal medicine or phytomedicine has been the oldest form of healthcare known to mankind. It is based on the usage of plant products as medication and it has been associated with different traditional medicine systems spread across the geo-cultural spheres in the world (David *et al*., 2015). The natural products have been used to isolate active constituents and some of these active leads have also been taken up for clinical trials (David *et al*., 2015; Fabricant and Farnsworth, 2001). Hence, in the past decade, there has been a resurgence of interest in the investigation of natural resources as a source of potential drug substance.

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The *Aloe* species has been used for centuries for its health, beauty, medicinal, and skin care properties. *Aloe barbadensis* Miller commonly called as *Aloe vera* belongs to the family Liliaceae and is a cactus-like plant (Ahlawat and Khatkar, 2011). *Aloes* are perennial succulents or xerophytes which are around 60–100 cm tall; as such, they are adaptable to habitats with low or erratic water availability and are characterized by the capacity to store large volumes of water in their tissue. *Aloes* have in common green fleshy leaves covered by a thick cuticle or rind and an inner clear pulp. The concentration of *Aloe* latex in the rind depends on the leaf part, age, position of the leaf on the plant, leaf orientation, and season of collection. The latex in the plant is used as defense strategy to deter it from being consumed. The gel consists of about 99.5% water and the remaining 0.5–1% is solid material (Eshun and He, 2004). The dry weight solid material consists of a range of compounds, including water-soluble and fat-soluble vitamins, minerals, enzymes, mono (Femenia *et al*., 1999) and polysaccharides, lignin, proteins, polypeptides, phenolic compounds, and organic acids (Boudreau and Beland, 2006; Hamman, 2008).

The genus *Aloe* contains over 400 different species, among which *A. barbadensis* Miller (*A. vera*) is widely used compared to other species, like *Aloe arborescens* Mill, *Aloe ferox*

Mill, for their therapeutic properties (Radha and Laxmipriya, 2015). The *Aloe* preparations have been used to treat frostbite, burns, radiation dermatitis, ulcers, psoriasis, wounds, skin infections, cancer, arthritis, and diabetes (Boudreau and Beland, 2006).

The phytochemistry of *A. vera* gel has reported the presence of more than 200 bioactive chemicals. The main constituents are monosaccharide, polysaccharides, amino acids, enzymes, chromones, anthraquinones (aloin and emodin), lignins, minerals, vitamins, salicylic acid, saponins, and sterols. The biological activities of several *Aloe* species have been reviewed by Reynolds and Dweck (1999) and their relationship between the components and biological effects have been reported by Choi and Chung (2003). Since then, further pharmacological activities of the components of *A. vera* have been reported. This review aims to provide updated information on bioactive components, their pharmacological properties, recent advances, and side effects of species of the genus *Aloe*.

METHOD

This review was prepared with the help of articles collected using databases such as Google Scholar, PubMed, Science Direct, and other peer reviewed journals. The Plant List (www.theplantlist.org), The International Plant Name Index (www.ipni.org), and Tropicos® (www.tropicos.org) were used for understanding the differences between the species from *Aloe* genus. ChemDraw Ultra 12 was used for drawing of the structures.

ETHNOMEDICAL USES OF THE GENUS *ALOE*

As mentioned earlier, the *Aloe* species are succulent, stem less xerophytes. The leaves are succulent and are usually greenish or greyish green in color. The flowers usually bloom in the months of October and January (Manvitha and Bidya, 2014). The flower grows around 90 cm, often being pendulous and consists of yellow tubular corolla around 2–3 cm (Babu *et al*., 2019). The *Aloe* plants are mostly used as decorative plants and are widely used in cosmetic industries. However, the *Aloe* species have a broad range of medicinal properties. Mostly, the gel portion of the plant is used for the treatment of diseases and disorders (Reynolds and Dweck, 1999). *Aloe barbadensis* Miller, commonly referred to as *A. vera*, is the most commonly used species of *Aloe*, followed by *Aloe arborenscens*, *A. ferox*, and *Aloe chinensis*. These are the species which are present in abundance geographically and also have therapeutic potential. The Indian Ayurveda medicine system uses the epidermis part of the *A. vera* for its anti-helminthic property and digestive system problems (Sandeep and Yadav, 2014). The Mexicans use *A. vera* for the treatment of burns and skin problems. Other medicinal properties of *A. vera* include treatment for rheumatoid arthritis, diabetes, cancer, and as an immunomodulatory agent (Cock, 2015).

The traditional use of *A. arborescens* involves the use as a topical agent to treat wounds and burns (Mabona and Van Vuuren, 2013). The Japanese use this species for the treatment of intestinal ailments and also as an antiseptic agent. Apart from that, it is also used as an immunomodulatory and chemo-preventive agent and it also has anti-diabetic and anti-inflammatory properties. *Aloe chinensis* is used for its antioxidant and immunomodulatory potential (Wu *et al*., 2006).

Aloe ferox is predominantly found in the African region, and according to folklore, it was used as a laxative and anti-purgative agent in the African medicine system. Scientific reports are available, which report the use of this species for treating wounds, psoriasis treatment, eczema, and melanoma. It has also been used for the treatment of infectious diseases such as syphilis and candida. The latest reports that have been published credit *A. ferox* for having anti-diabetic, anti-cancer, anti-microbial, and anti-inflammatory properties (Kambizi and Afolayan, 2008; Loots *et al*., 2011; Mwale and Masika, 2014).

Species native to the Arabian nations also have a history of therapeutic properties. Among these, *Aloe perryi* Baker has wider usage due to its medicinal properties. It has been used to treat skin and eye infections and intestinal disorders (Al-Fatimi *et al*., 2005). It is also used in treatment of malaria and has anti-bacterial property (Mothana *et al*., 2009). Other species belonging to this region are *Aloe inermis*, *Aloe officinalis*, and *Aloe tomentosa*, which have been known for their antioxidant and anti-microbial properties (Cock, 2015).

Apart from these species, other species of *Aloe* have narrow geographical distributions and in turn, their ethno-pharmacological benefits are also less. These include *Aloe africana* (used as a laxative), *Aloe marlothii* (used to treat microbial infections and respiratory disorders), and *Aloe variegata* (used as a laxative). More than 400 species of *Aloes* have been reported and most of these species have some or other medicinal benefits. Most of the work has been carried out using *A. barbadensis* Miller, *Aloe arborescenes*, and *A. ferox* (Cock, 2015). Table 1 lists out some of the species of *A. vera* that have been studied for its beneficial properties, while Figure 1 shows some of the important species of the genus *Aloe*.

BIOACTIVE CONSTITUENTS PRESENT IN THE GENUS *ALOE*

The gel of *A. vera* consists of around 200 active constituents such as saccharides, polyphenols, flavonoids, glycoproteins, minerals, vitamins, anthraquinones, lipids, amino acids, and enzymes (Hamman, 2008). In this section, we discuss the components of the gel and the epidermis of *A. vera* with some important chemical structures (Fig. 2).

Saccharides

Saccharides form the major component of the *Aloe* gel. Acemannan and mannose-6-phosphate are major constituents of the carbohydrates. Acetylated mannan, also called as acemannan, is considered to be one of the important bioactive polysaccharides present in the *Aloe* gel, which has been known for its therapeutic properties such as anti-diabetic and immunomodulation. It is made up of mannosyl residues that have been acetylated at C-2 and C-3 positions and the C-6 position consists of a side chain, which is usually galactose (Femenia *et al*., 1999). Other polysaccharides such as arabinan, arabinorhamnogalactan, galactan, galactogalacturan, glucogalactomannan, galactoglucoarabinomannan, and glucuronic acid containing polysaccharides have been reported to exist in the *A. vera* inner leaf gel part (Ni *et al*., 2004). Aloeride contains glucose (37.2%), galactose (23.9%), mannose (19.5%), and arabinose (10.3%). It is reported to have a molecular weight between 4 and 7 Million Dalton (Pugh *et al*., 2001). The saccharides are known to

Table 1. Medicinal properties of different species of the genus *Aloe*.

Species	Properties	Dose	Reference
A. barbadensis Miller	Anti-diabetic	300 mg/kg bw	(Noor *et al*., 2008)
	Hypoglycemic	300 mg/kg bw	(Rajasekaran *et al*., 2004)
	Wound healing	30 mg	(Chithra *et al*., 1998)
	Immunomodulation	400 mg/kg bw	(Halder *et al*., 2012)
Aloe Arborensces Miller	Chemopreventive	1% and 5%	(Furukawa *et al*., 2002)
	Immunomodulatory	1.2–4.8 mg/ml	(Picchietti *et al*., 2013)
	Anti-diabetic	500 mg/kg bw	(Ajabnoor, 1990)
	Anti-inflammatory	250 mg/kg bw	(El Sayed *et al*., 2016)
Aloe chinensis	Anti-oxidant	IC-50-22 µg/ml	(Wu *et al*., 2006)
	Microphage activation	5 mg/ml	(Liu *et al*., 2006)
A. ferox	Anti-helminthic	200 mg/kg bw	(Mwale and Masika, 2014)
	Anti-microbial	0.5 mg/ml	(Kambizi and Afolayan, 2008)
	Anti-diabetic	300 mg/kg bw	(Loots *et al*., 2011)
	Anti-inflammatory	250 mg/kg bw	(El Sayed *et al*., 2016)
Aloe greatheadii	Anti-diabetic	300 mg/kg bw	(Loots *et al*., 2011)
Aloe littoralis	Anti-inflammatory	2.5 and 5 ml/kg	(Hajhashemi *et al*., 2012)
	Wound healing	500 mg	(Hajhashemi *et al*., 2012)
Aloe macaluta	Anti-plasmodial	>100 µg/ml	(Clarkson *et al*., 2004)
A. marlothii	Anti-plasmodial	74 µg/ml	(Clarkson *et al*., 2004)
A. perryi	Hypoglycemic	2 mg/kg bw every 16 hours for 54 hours study	(Ibegbulem and Chikezie, 2013)
	Anti-bacterial	>8 mm inhibition zones against Gram-positive bacteria	(Ali *et al*., 2001)
Aloe saponaria	Anti-inflammatory	10%	(Silva *et al*., 2013)

Figure 1. Some important species of the genus *Aloe.*

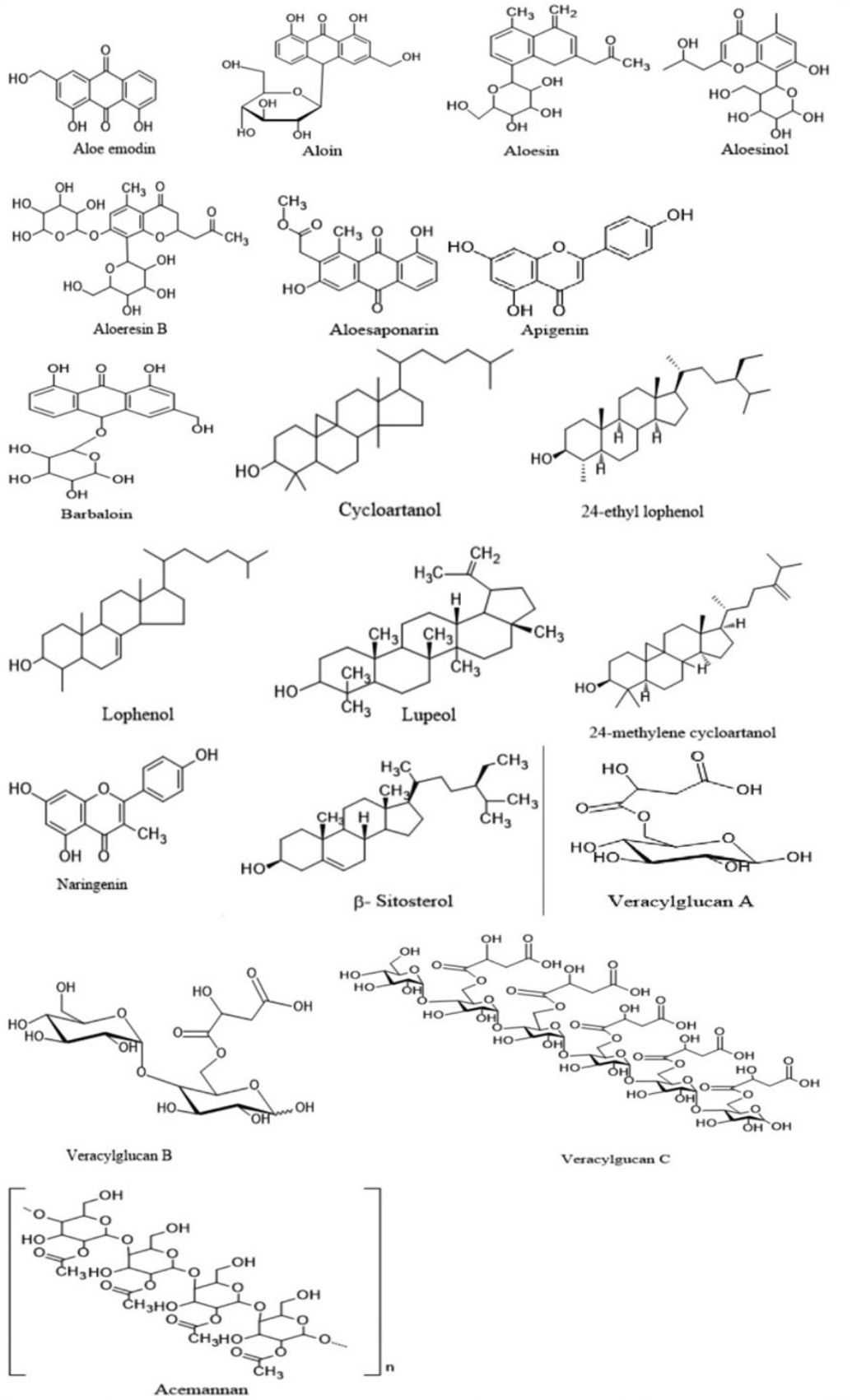

Figure 2. Chemical structures of some of the bioactive constituents present in the genus *Aloe.*

have wound healing properties, anti-diabetic properties, and anti-inflammatory properties (Cock, 2015).

Polyphenols

The polyphenols are known to exert their effect through their antioxidant properties. Apart from that, polyphenols from *Aloe* species have been reported to possess anti-diabetic potential, anti-inflammatory properties, and wound healing properties (Babu *et al*., 2019).

Coumarins, a class of polyphenols, are mostly found in the leaf of *Aloe* species and these are known to contribute to the bitter taste of *Aloes*. Feralolide is a coumarin which has been reported to be present in *A. ferox* (Speranza *et al*., 1993), while dihydroisocumarin is present in *Aloe hildebrandtii* (Veitch *et al*., 1994), which is known to stimulate the macrophages for fluid reabsorption in edema patients (Casley-Smith *et al*., 1993).

Flavonoids

The flavonoids that are present in the *Aloe* gel with antioxidant properties include naringenin, apigenin, myrcetin, quercitine, and cinnamic acid (Dagne *et al*., 2000), and are known to have inhibitory activity on platelets (Fuhrman and Aviram, 2001).

Sterols

Sterols are present in the leaf as well as the gel portion of the plant. Some of the important sterols which are known to be present in *Aloe* species are campesterol, β-sitosterol, lophenol, cycloaretonol, and lupeol (Dagne *et al*., 2000). These are said to have cell proliferative activities of endothelial cells. They are also reported to have a role in angiogenesis and hence are used in would healing process (Awad *et al*., 2007; Reynolds and Dweck, 1999).

Anthraquinones

Anthraquinones are usually present in the epidermis of the plant. Some of the anthraquinones present in the lead part are Aloin, *Aloe* emodin, aloesaponarin, chrysophanol, and isoxanthorin (Reynolds and Dweck, 1999). The concentration of aloin and *Aloe* emodin determines the antioxidant property. It is interesting to note that emodin acts as an antioxidant at high concentrations and at lower concentrations it acts as a prooxidant (Cock, 2015). Whereas aloin not only acts as a prooxidant at higher and lower levels, but it also acts as an antioxidant agent (Tian and Hua, 2005).

Anthrones

Anthrones are another set of compounds which are usually found in the leaf epidermis of the plant. These are the compounds which usually have purgative effects and are hence used as laxatives. Barbaloin is one of the first anthrones to be isolated from *A. vera*. *Aloe ferox* leaves are also reported to have higher amounts of anthrone (around 30%) (van Wyk *et al*., 1995). From *Aloe marlotthi*, anthrones such as homonataloin and nataloin have been extracted (Dagne *et al*., 2000). The anthrones are also known to have strong antioxidant properties. Yen *et al*. (2000) have suggested that the structures of anthrones determine their electrophilic nature and this enables them to have antioxidant potential. As mentioned earlier, the concentration of anthraquinones determines whether they can act as an antioxidant or a prooxidant.

Chromones

Chromones are mostly present in the leaf of the plant. Aloesin and Aloesinol are said to have anti-diabetic properties (Lee *et al*., 1997; Yimam *et al*., 2014). There are a number of isomeric forms of chromones present in the plant. These include aloeresin E, Aloerosin A, and Aloeresin F. Some of the chromones are present in a methylated form or are glycosylated at different positions (Dagne *et al*., 2000). These are usually said to possess antioxidant properties (Gomes *et al*., 2009); however, the levels of chromones would determine whether they would act as prooxidant or antioxidant agents (Maurya and Devasagayam, 2010).

Proteins/glycoproteins

In comparison to other constituents present in *A. vera*, not much has been reported on proteins or glycoproteins, although there have been literature reports which indicate the presence of amino acids in *A. vera* gel (Cock, 2015). Some lectins have also been isolated from *A. vera*. Most of the glycoproteins from *A. vera* are said to possess wound healing properties. Glycoproteins of different masses, such as 29KD, 5.5KD, 10KD, and 14KD, have been isolated from *A. vera* and their therapeutic potential, including anti-inflammatory, anti-diabetic, and immunomodulation, has been studied (Das *et al*., 2011; Siritapetawee *et al*., 2013; Yagi *et al*., 2009).

MINERAL ELEMENTS AND OTHER CONSTITUENTS

Trace mineral elements, such as magnesium, zinc, copper, manganese, potassium, sodium, and iron, have been reported and have been studied for their therapeutic properties (Rajasekaran *et al*., 2005). *Aloe vera* also contains alkaloids, benzene derivatives, and furan derivatives (Cock, 2015).

These are some of the bioactive components which are present in the *A. vera* plants. It can be inferred that bioactive components such as saccharides, glycoproteins, polyphenols, sterols, and mineral elements are present in the gel. The leaf or the epidermis part usually consists of a large amount of anthraquinones, anthrones, and chromones. The therapeutic potential of *A. vera* depends not only on the amount of constituents present in the plant but also on the ratio of these chemicals and their nature. The interaction of these constituents with one others may also affect the medicinal benefit imparted by this plant. It is observed that even though more than 400 species are present in *Aloe* genus, most of the constituents (sterols, polyphenols, saccharides, proteins, glycoproteins, and minerals) have been reported either from *A. vera*, *A. ferox*, or *A. arborescens*. The therapeutic potential of these bioactive constituents, such as anti-diabetic, anti-oxidant, anti-inflammatory, anti-cancer, wound healing, and immunomodulation, have been discussed in the following sections with their pre-clinical/clinical studies and their possible mechanism of action.

THERAPEUTIC PROPERTIES OF THE GENUS *ALOE* BIOCONSTITUENTS

Role of *Aloe* gel and its constituents in the alleviation of diabetes

Most of the studies have focused on the effect of the *Aloe* gel for their pharmacological actions. According to the reports, *A. vera* extract has shown not only to reduce blood sugar levels (Noor *et al*., 2008; Rajasekaran *et al*., 2004), but has also shown a protective effect on organs like pancreas, liver, and small intestine in streptozotocin-induced diabetic rats (Noor *et al*., 2008; Noor *et al*., 2017). Clinical trials have been reported wherein the patients were administered 100 g of *A. vera* gel with 20 g of *Psyllium* seed husks (Agarwal, 1985) and another clinical trial reported on the anti-hyperglycemic and anti-hypercholesterolemia effects on type 2 diabetic patients (Huseini *et al*., 2012) and lowering of blood glucose levels in diabetic patients when administered *A. vera* juice (Choudhary *et al*., 2014; Radha and Laxmipriya, 2015). The literature available on the active constituents of *A. vera* for its anti-diabetic property has been summarized in Table 2.

Anti-hyperglycemic effect of Aloe polyphenols

The polyphenols are known to exert their effect through their antioxidant properties (Pandey and Rizvi, 2009). A polyphenol-rich *A. vera* extract (350 mg/kg) containing 181.7mg/g aloin and 3.6mg/g *Aloe* emodin when administered for a period of 4 weeks to insulin-resistant mice showed a decrease in blood glucose levels (Pérez *et al*., 2007). Aloesin and Aloesinol of *A. ferox* have shown to decrease blood sugar levels in mice with an increase in adiponectin levels *in vitro* and a decrease in plasma insulin levels *in vivo* (Yimam *et al*., 2014). Phytosterols (lophenol, 24-methyl lophenol, 24-ethyl lophenol, cycloartanol, and 24-methlyene cycloartanol) have shown to reduce blood sugar levels as well as triglyceride levels (Tanaka *et al*., 2006).

Anti-hyperlipidemia effect of Aloe polyphenols

Phytosterols (lophenol and cycloartanol) have shown to reduce the serum-free fatty acid and triglyceride levels in Zucker diabetic fatty rats. Reduction in levels of PPARγ/Liver X receptor α by *A. vera* gel can lead to proper functioning of insulin and these phytosterols may be one of the compounds acting via their inhibiting activity on PPARγ/Liver X receptor α, pro-inflammatory cytokines (Misawa *et al*., 2008). Abd-Alla *et al*. (2009) reported that *Aloe hijazensis* containing flavonols and flavones help in reducing blood sugar levels and triglyceride levels, thereby ameliorate the diabetic conditions (Abd-Alla *et al*., 2009).

Anti-hyperglycemic effect and anti-hypercholesterolemic effect of Aloe saccharides

Yagi *et al*. (2009) reported the hypoglycemic effect in diabetic patients with 1,000KD polysaccharide fraction along with glycoprotein verectin (29KD) (Yagi *et al*., 2009). Acemannan, a mucopolysaccharide enriched *A. vera* extract, when given to diabetic patients showed anti-hyperglycemic and anti-hypercholesterolemic activities (Huseini *et al*., 2012).

Hypoglycemic effect by Aloe Proteins/polypeptides

A glycoprotein named verectin (29KD), along with polysaccharide fraction of 1,000KD, has shown hypoglycemic effect in patients with type 2 diabetes (Yagi *et al*., 2009). Verectin indicated anti-oxidative, anti-thromboxane A2 synthase inhibition, and cyclooxygenase-2 inhibiting activities *in vitro* and these may be correlated with vasodilatation in diabetic patients (Yagi *et al*., 2003). The mechanism of action of these constituents in alleviating diabetes is shown in Figure 3.

Insulinotropic effect by Aloe minerals

Narayanan *et al*. (2007) reported that these minerals may play a direct or indirect role in insulin secretion in a synergistic way (Narayanan *et al*., 2007). Rajasekaran *et al*. (2005) reported that the presence of these minerals in *A. vera* extract plays a role in antidiabetic activity (Rajasekaran *et al*., 2005). Magnesium is one of the important compounds which usually takes part in the metabolism of carbohydrates and fats by improving glucose and insulin homeostasis (Rumawas *et al*., 2006). Zinc enhances the effectiveness of insulin acting as a cofactor. Narayanan *et al*. (2007) reported that the presence of zinc in *A. vera* can modulate the targets for insulin activity (Narayanan *et al*., 2007). Potassium takes part in releasing insulin from beta cells, calcium in stimulation of insulin in pancreatic islets, vanadium elicits glucose levels, copper is involved in insulin binding, and chromium is essential for normal carbohydrate metabolism (Rajasekaran *et al*., 2005).

In addition to antidiabetic potential, the *Aloe* constituents also exhibit other therapeutic properties, such as anti-inflammatory, anti-allergic, anti-bacterial, anti-cancer, angiogenic, antioxidant, immunomodulation, and wound healing. The details of the findings are discussed in the following sections and are summarized in Table 3.

Antioxidant and anti-cancer properties of Aloe constituents

APS-1, a polysaccharide from *A. vera*, was shown to have both anti-oxidant property and protective effect on heart tissue (Wu *et al*., 2006), which may be due to a higher content of rhaminose and arabinose in polysaccharide fraction (Kang *et al*., 2014). *Aloe vera* polyphenols have exhibited antioxidant and anti-cancer properties (Jeon *et al*., 2011; Naqvi *et al*., 2010) with *Aloe* emodin exhibiting anti-cancer potential against hepatoma cells. Aloin has shown to exhibit anti-cancer activity by inhibiting the tumor angiogenesis by inactivating the signal transduction and activators of transcription 3 pathway (Pan *et al*., 2013). *Aloe* polysaccharides were reported for antitumor activity against sarcoma 180 cells (Liu *et al*., 2006). Another polysaccharide G2E1DS2 was shown to activate macrophages and exhibit potent anti-tumor activity when injected into mice implanted with sarcoma cells. Polysaccharides also inhibit the activity of PMA-induced tyrosine kinase activity in human leukemic cells, leading to apoptosis of leukemic cells (Kim *et al*., 1999). A glycoprotein fraction and Aloesin was found to promote cell proliferation activity in human hepatoma SK-HEP1 cell lines, while a 53KD lectin was observed to have anti-proliferative activity against colon and lung cancer cell lines (Kaur *et al*., 2011). Figure 4a shows the mechanism of action of these constituents in cancer therapy.

Aloe constituents with anti-inflammatory, anti-allergic, and anti-fungal properties

Aloin and aloesin were shown to exhibit anti-inflammatory activities by decreasing the levels of tumor necrosis factor-α (TNF-α) and plasma leukotriene B(4) (Park *et al*., 2011). Hutter *et al*. (1996) reported an anti-inflammatory

Table 2. Role of different constituents of *Aloe vera* in diabetes mellitus

Components/ Constituents	IUPAC Name	Property/ Condition	Dose	Period of the study	Model	Reference
Polyphenols **Anthraquinones** Aloin and Aloe-emodin	**Aloin** :[(4S,5S)-17-[(5S)-5-ethyl-6-methylheptan-2-yl]-4,10,13-trimethyl-2,3,4,5,6,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a] phenanthren-3-yl] acetate ***Aloe* emodin**:1,8-dihydroxy-3-(hydroxymethyl)anthracene-9,10-dione	Hypoglycemic	181.7 mg g^{-1} Aloin 3.6 mg g^{-1} *Aloe* emodin	4 weeks	ICR Mice	(Pérez *et al*., 2007)
Chromones Aloesin and Aloesinol	**Aloesin**: 7-hydroxy-5-methyl-2-(2-oxopropyl)-8-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan--yl]chromen-4-one	Hypoglycemic, Increase adiponectin levels, improves insulin sensitivity	200 mg kg^{-1} (100 mg kg^{-1} of Aloesin 100 mg kg^{-1} Aloesinol)	12 weeks	C57BL/6J Mice	(Yimam *et al*., 2014)
Phytosterols Lophenol, 24-methyl lophenol, 24-ethyl lophenol, Cycloartanol, 24-methlyene cycloartanol	**Lophenol:**(3S,4S,5S,9R,10S,13R,14R,17R)-4,10,13-trimethyl-17-[(2R)-6-methylheptan-2-yl]-2,3,4,5,6,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a] phenanthren-3-ol **24 methyl lophenol:**3S,4S,5S,9R,10S,13R,14R,17R)-4,10,13-trimethyl-17-[(2R)-6-methyl-5-methylideneheptan-2-yl]-2,3,4,5,6,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a] phenanthren-3-ol **24 ethyl lophenol** :[(4S,5S)-17-[(5S)-5-ethyl-6-methylheptan-2-yl]-4,10,13-trimethyl-2,3,4,5,6,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a] phenanthren-3-yl] acetate	Anti-diabetic	1 µg each	28 days	BKS.Cg-$m^{+/+}$ Lepr (*db/db*) Mice	(Tanaka *et al*., 2006)
Lophenol, cycloartanol	**Lophenol** :(3S,4S,5S,9R,10S,13R,14R,17R)-4,10,13-trimethyl-17-[(2R)-6-methylheptan-2-yl]-2,3,4,5,6,9,11,12,14,15,16,17dodecahydro-1H-cyclopenta[a] phenanthren-3-ol	Hypoglycemic and hypolipidemic	25 µg kg^{-1}	28 days	Zucker diabetic fatty rats	(Misawa *et al*., 2008)
Polysaccharide and Glycoprotein 1000 KD polysaccharide fraction and 29KDa Glycoprotein (Verectin) Acemannan enriched *Aloe vera* gel extract		Hypoglycemic Anti-hyperglycemic, Anti-hypercholesterolimic	500 mg twice daily 300mg Twice daily	3 months 2 months	Human Trials 15 patients 30 patients	(Yagi *et al*., 2009) (Huseini *et al*., 2012)
Mineral elements Magnesium Zinc Potassium Calcium Copper Chromium Vanadium		Carbohydrate metabolism, glucose and insulin homeostasis Increases insulin effectiveness Release of insulin Stimulation of insulin Insulin binding Carbohydrate metabolism Lipid metabolism	90 mg/kg bw	30 days	Wistar Rats	(Rajasekaran, Sivagnanam and Subramanian, 2005)

compound called C-glucosylchromone which inhibits the cyclooxygenase pathway and reduces prostaglandin E2 production from arachidonic acid (Hutter *et al*., 1996). Veracylglucan B and Veracylglucan C have exhibited anti-inflammatory and cell proliferation activities (Esua and Rauwald, 2006). Alprogen, a glycoprotein, possessed anti-inflammatory activity (Ro *et al*., 2000). In another study carried out by Ro *et al*., 2000, alprogen was reported to have

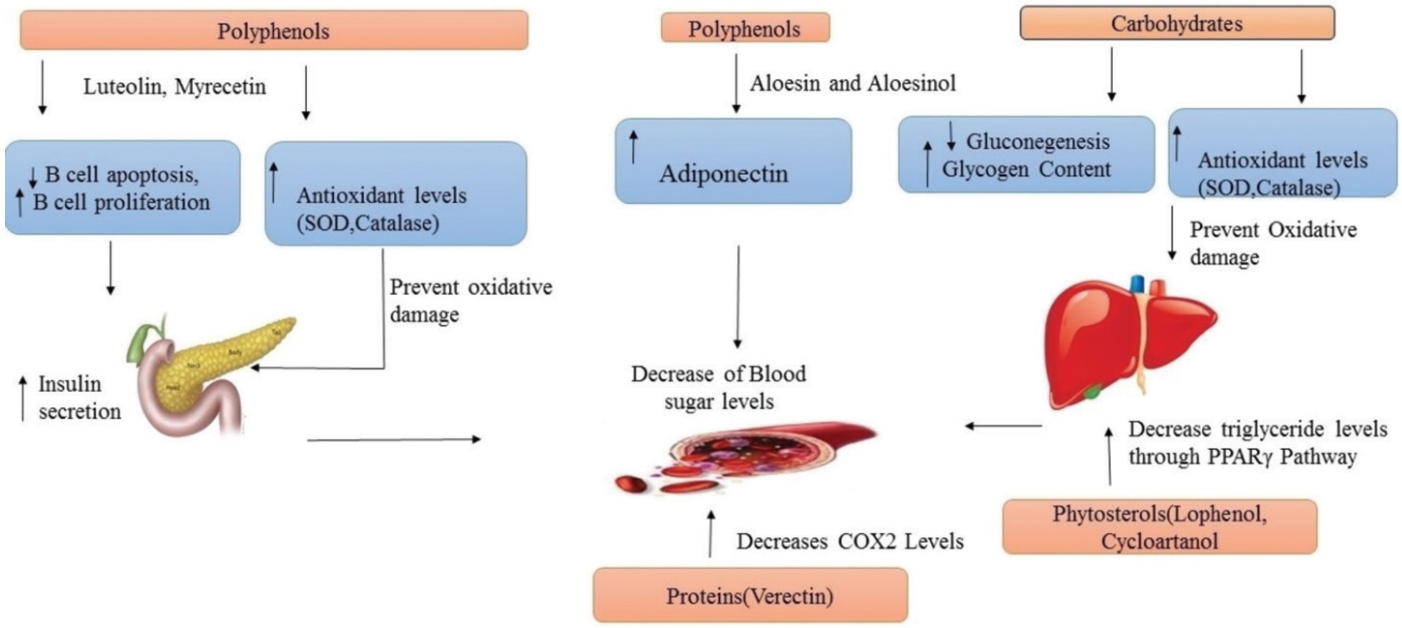

Figure 3. *Aloe* constituents' possible mechanism of action in diabetes.

anti-allergic property by inhibiting the release of histamine in allergies through blocking the calcium influx (Ro *et al*., 2000). Anti-fungal activity against the *Candida* species and anti-inflammatory properties of a protein of 14KD from *A. vera* were reported by Das *et al*. (2011). The peptide/polypeptide fraction of *A. vera* has been reported to reduce inflammation through both *in vitro* and *in vivo* studies via reduction of inflammatory mediators (Babu and Noor, 2019).The anti-inflammatory action of these constituents is shown in Figure 4b.

Aloe constituents with anti-microbial properties

The polysaccharides have shown antibacterial activity by destroying the bacteria through generation of leukocytes (Pugh *et al*., 2001). Yates *et al*. (1992) demonstrated the anti-viral activity of acemannan in a pilot study of clinically symptomatic immunodeficiency virus-infected cat (Yates *et al*., 1992). *Aloe* emodin, purified from barbaloin, was also reported to inactivate a variety of viruses, including herpes simplex virus type I and type II, varicella-zoster, and the influenza virus (Jeon *et al*., 2011). The mechanism proposed for the anti-bacterial and anti-viral effects of *Aloe* emodin is the inhibition of nucleic acid biosynthesis, thereby inhibiting protein synthesis.

Aloe constituents with angiogenic property

β-Sitosterol possesses angiogenic activity and shows an increase in the formation of new blood vessels in a dose-dependent fashion (≥500 mg/kg) in gerbil brain cells by increasing the levels of vascular endothelial growth factor, the vascular endothelial growth factor receptor fetal liver kinase-1, and blood vessel matrix laminin, which has been damaged due to ischemia (Choi *et al*., 2002) .

Aloe constituents with immunomodulation and wound healing properties

Aloe polysaccharides between 400KD and 5KD molecules were shown to have immunomodulatory activity. Acemannan acts by activating and improving the macrophage action through an increased expression of cytokines IL-6 and TNF-α and the release of nitric oxide (Im *et al*., 2005; Kang *et al*., 2014). Lu *et al*. (2012) observed that *A. vera* polysaccharides mitigate ischemia and reperfusion injury in hemorrhagic rats (Lu *et al*., 2012).

The growth of endothelial, epithelial, and fibroblast cells plays a critical role in wound healing processes. *Aloe* polysaccharides increased the expression of matrix metalloprotease-3 and tissue inhibitor of metalloproteinases genes, thereby accelerating the process of wound healing (Tabandeh *et al*., 2014). A 5.5KD glycoprotein of *A. vera* was reported by Choi *et al*. (2001) for wound healing property by increasing the cell proliferation with elevated levels of epidermal growth factor receptor, fibronectin receptor, fibronectin, keratin 5/14, and keratin 1/10 (Choi *et al*., 2001). Figure 4c and d shows the immunomodulation action and wound healing action of these bioactive constituents, respectively.

Aloe constituents with anti-fibrinolytic and hemagglutination properties

A protease inhibitor protein of 11.8KD was reported to have anti-fibrinolytic potential (Siritapetawee *et al*., 2013). Aloctin I and Aloctin II have been reported with hemagglutination activity (Akev and Can, 1999), while 53KD lectin Mucin was shown to have hemeagglutinating activity and anti-proliferative activity against lung and colon cancer cell lines (Kaur *et al*., 2011).

Table 3. Pharmacological activities of *Aloe vera* constituents

Components/ Constituents	IUPAC Name	Property/ Condition	Dose	Period of the study	Model	Reference
Polyphenols	*Aloe* emodin:1,8-dihydroxy-3-(hydroxymethyl)anthracene-9,10-dione	Anti-cancer	25, 50, 100 and 200 µM	3 days	*In vitro,* Human Huh cells	(Jeon *et al*., 2011)
Anthraquinones	Aloin :[(4S,5S)-17-[(5S)-5-ethyl-6-methylheptan-2-yl]-4,10,13-trimethyl-2,3,4,5,6,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl] acetate	Anti-inflammatory		28 days		(Park *et al*., 2011)
Aloe emodin		Anti-inflammatory	0.005%, 0.05%, and 0.1%	28 days	*In vivo*, Male Sprauge Dawley Rat	(Park *et al*., 2011)
Aloin		Anti-inflammatory		48 hours		(Hutter *et al*., 1996)
Chromones:	Aloesin:	Angiogenic	0.005%, 0.05%, 0.1%, and 0.5%	19 days	*In vivo*, Male	(Choi *et al*., 2002)
Aleosin	7-hydroxy-5-methyl-2-(2-oxopropyl)-8-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one		200 µg/mouse ear		SprougeDawley Rat	
C-glucosyl			500 µg kg^{-1}		Balb C mice	
Chromone	c-glucosylchromone : 8-[C-β-d-[2-O-(E)-cinnamoyl]glucopyranosyl]-2-[(R)-2-hydroxypropyl]-7-methoxy-5-methylchromone				Mongolian gerbil	
β-Sitosterol	Beta sitosterol: (3S,8S,9S,10R,13R,14S,17R)-17-[(2R,5R)-5-ethyl-6-methylheptan-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol					
Polysaccharide	Veracylglucan B:	Anti-oxidant, cell protection for heart disease, Parkinson's & Alzheimer's disease.	100–300 µg ml^{-1}	3 days	*In vitro*, rat PC12 cells	(Wu *et al*., 2006)
APS-1	(3S)-3-hydroxy-4-oxo-4-[[(2R,3S,4R,5R)-4,5,6-trihydroxy-3-[(2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl] oxyoxan-2-yl]methoxy]butanoic acid		180 µgml^{-1}	3 days		(Kim *et al*., 1999)
Polysaccharide		Anti-cancer, anti-inflammatory,antimicrobial	25 mg	30 days	*in vitro*,	(Tabandeh *et al*., 2014)
Polysaccharide AVP			and 50 mg	10 days	leukemic cells	
Polysaccharide MAP	Veracylglucan C:	Wound healing	1 mg per mouse	24 hours	Male wistar Rat	(Im *et al*., 2005)
Maloylglucans (Veracylglucan B &veracylglucan C)	(3S)-4-[[(2R,3S,4R,5R)-3-[(2R,3R,4R,5S,6R)-6-[[(2S)-3-carboxy-2-hydroxypropanoyl] oxymethyl]-5-[(2R,3R,4R,5S,6R)-6-[[(2S)-3-carboxy-2-hydroxypropanoyl] oxymethyl]-5-[(2R,3R,4R,5S,6R)-6-[[(2S)-3-carboxy-2-hydroxypropanoyl] oxymethyl]-5-[(2R,3R,4R,5S,6R)-6-[[(2S)-3-carboxy-2-hydroxypropanoyl]oxymethyl]-3,4-dihydroxy-5-[(2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl] oxyoxan-2-yl]oxy-3,4-dihydroxyoxan-2-yl]oxy-3,4-dihydroxyoxan-2-yl] oxy-3,4-dihydroxyoxan-2-yl]oxy-4,5,6-trihydroxyoxan-2-yl]methoxy]-3-hydroxy-4-oxobutanoic acid	Immunomodulation	1 mg ml^{-1} and		In vitro, RAW.264.7,	(Esua and Rauwald, 2006).
		Anti-tumor	100 µgml^{-1}		ICR Mice	
		anti-inflammatory and cell proliferation activity			*In vitro* studies-fibroblast cultures	
Proteins/		Anti-fungal	75 µl of 0.5 mg ml^{-1}	72 hours	Microbial culture	(Das *et al*., 2011)
Polypeptides		Wound healing	1 mg ml^{-1}	24 hours	In vitro, Human Keratinocytes	(Choi *et al*., 2001)
14KDa Polypeptide		Anti-allergy	0.5 to10 µg ml^{-1}	72 hours		(Ro *et al*., 2000)
5.5KD Glycoprotein		Anti-fibrinolytic	0–10 µg	200 minutes	Hartley albino female guinea pigs Calorimetric assay	(Siritapetawee *et al*., 2013)
Alprogen		Hemagglutination anti-proliferative activity	10, 30, and 100 µg	48 hours	Colon and lung cancer cell lines	(Kaur *et al*., 2011)
11.8 KD protein						
53 KD lectin						

RECENT ADVANCES ON EFFECTIVE UTILIZATION OF GENUS *ALOE*

Different formulations have been used to process *A. vera* as a commercial product. Depending on the requirement in product quality, various processing steps are followed by the industries. It is important to make sure that the constituents in *A. vera* do not lose their activity (Maan *et al*., 2018).

Research has been focused on controlled release of *Aloe* bioactive constituents. In case of wound healing, hydrogels and functional films have been developed for release of these constituents. The gel has been combined with biomaterials such as cellulose, alginate, and gelatin (Saibuatong and Phisalaphong, 2010; Silva *et al*., 2014). These formulations have prolonged drug release, better mechanical support, and prevention of body fluid loss. Attention has also been focused on tissue engineering, wherein growth factors and biomaterials have been employed for regeneration (Ikada, 2006). A nanofibrous scaffold comprising of gel and silk fibroin showed better synergistic effect in skin tissue regeneration (Suganya *et al*., 2014).

Micro and nanoparticles have also been used as a drug delivery system due to great stability of encapsulated drug. The microparticles consisting of *A. vera*, chitosan, and Vitamin E have been used for treating skin burns with better adhesive

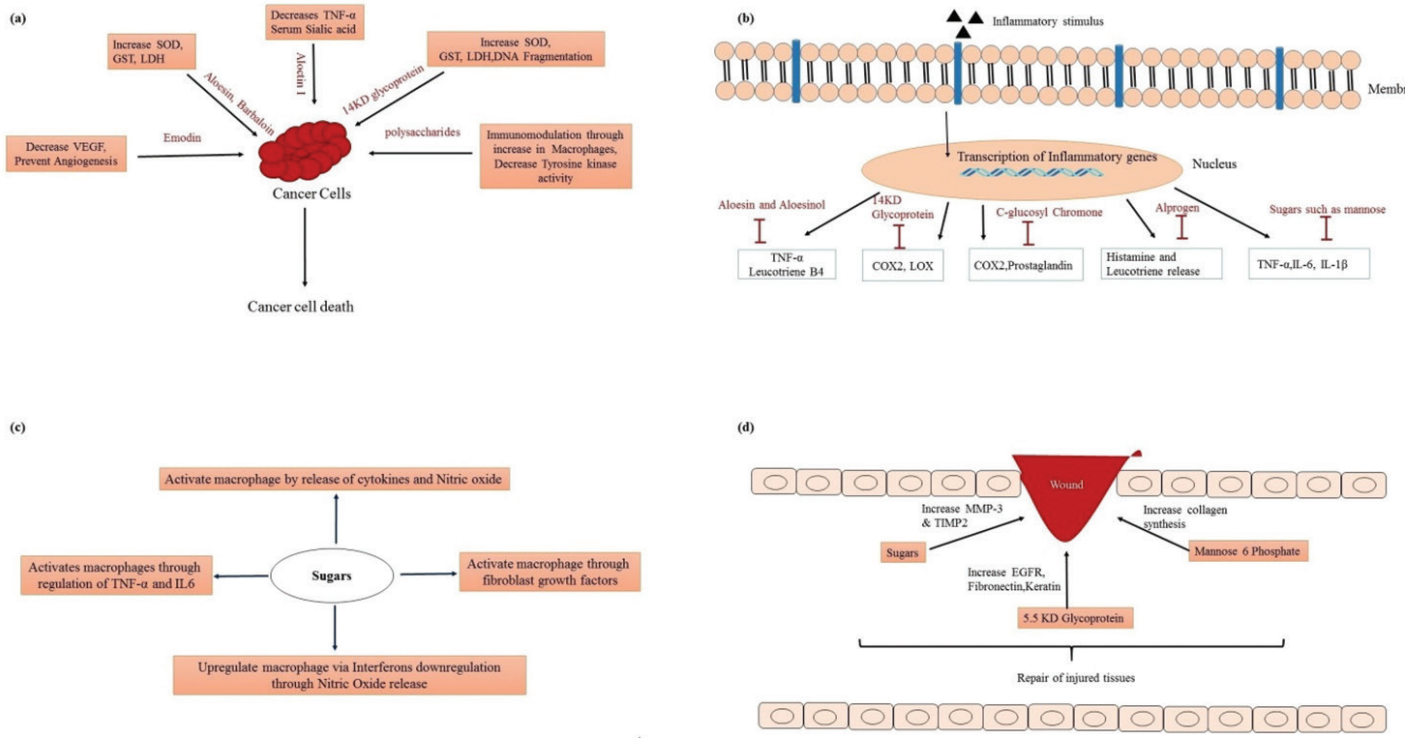

Figure 4. *Aloe* constituents' possible mechanism of action in (a) cancer, (b) inflammation, (c) immunomodulation, and (d) wound healing.

properties and prolonged release of the constituents (Pereira *et al*., 2014). Nanoparticles along with *A. vera* gel led to improved antiviral property along with high loading efficiency (Joshy *et al*., 2016). Co-encapsulation of *A. vera* along with curcumin has enhanced the antioxidant property of the phytoconstituents (Kitture *et al*., 2015). Liposomes of 200 nm with Mannose-6-phosphate have shown anti-inflammatory potential and are used for collagen synthesis and growth of skin cells (Conte *et al*., 2017; Takahashi *et al*., 2009). The use of liposomes, biomaterials, and micro and nano encapsulation studies on these constituents for their other therapeutic potential needs to be explored further.

SIDE EFFECTS/TOXICOLOGICAL STUDIES OF THE GENUS *ALOE*

Most of the studies on *A. vera* and their constituents have been reported to be safe. But some side effects have also been mentioned. Application of *A. vera* to skin may cause redness, burning, or stinging sensations due to the presence of anthraquinones like aloin and barbaloin (Ferreira *et al*., 2007; Reider *et al*., 2005). It is also reported that prolonged use of *Aloe* latex or the *Aloe* epidermis region can increase the risk of arrhythmia (Ulbricht *et al*., 2008) due to its laxative property, leading to depletion of potassium. Based on our literature survey, most of the side effects reported are mainly because of the latex which has been poorly described (Kato *et al*., 2004).

Most of the works reported have used the *Aloe* plant or the gel portion alone. It can be inferred that the use of the entire plant or only the gel portion of *Aloe* can prevent these side effects. The presence of constituents, such as saccharides, proteins, and polyphenol minerals, in the gel may mask the effects of the *Aloe* latex which is usually rich in antharquinones such as aloin and barbaloin.

CONCLUSION

The genus *Aloe* consists of many species and the most prominent is the *A. barbadensis* Miller plant, commonly known as *A. vera*. There is no wonder in considering *A. vera* as the 'Miracle plant' as there is untapped potential in it for the management of therapeutic uses, and this review seeks to create more interest in screening of as many constituents as possible. Potential biological activity of constituents may be affected by the climate, season, harvesting, processing, storage conditions, and geographical origin which may bring about change in constituents, which may result in variations. Therefore, careful assessment of these constituents, their ecological and seasonal variation, metal contents, and toxicology studies need to be carried out to keep the toxic components, if any, at very low or permissible levels. The pharmacokinetic parameters, such as dose, its absorption and release and its metabolism also need to be studied. The action and the desired activity of these constituents, the time duration, and the therapeutic window need to be analyzed and validated through proper clinical trials. In addition to this, the route of delivery of the constituents needs to be studied. Studies regarding the usage, efficacy, safety of liposomes, polymers, bioadhesives, and nanoparticles to deliver these phytoconstituents need to be carried out. The bioactive constituent's role in the clinical applications may help in development of new formulations, wherein these constituents may be used as an alternate source for treating various ailments. Therefore, it is considered that studies on the genus *Aloe*

and its constituents should be expanded significantly to enable improvement in healthcare.

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CONFLICT OF INTEREST

Authors declared that they do not have any conflicts of interest.

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REFERENCES

Abd-Alla HI, Shaaban M, Shaaban KA, Abu-Gabal NS, Shalaby NMM, Laatsch H. New bioactive compounds from *Aloe hijazensis*. Nat Prod Res, 2009; 23(11):1035–49.

Agarwal OP. Prevention of atheromatous heart disease. Angiology, 1985; 36(8):485–92.

Ahlawat KS, Khatkar BS. Processing, food applications and safety of *Aloe vera* products: a review. J Food Sci Technol, 2011; 48(5): 525–33.

Ajabnoor MA. Effect of aloes on blood glucose levels in normal and alloxan diabetic mice. J Ethnopharmacol, 1990; 28(2):215–20.

Akev N, Can A. Separation and some properties of *Aloe vera* L. leaf pulp lectins. Phytother Res, 1999; 13(6):489–93.

Al-Fatimi M, Friedrich, Jenett-Siems K. Cytotoxicity of plants used in traditional medicine in Yemen. Fitoterapia, 2005; 76(3–4):355–8.

Ali NAA, Jülich WD, Kusnick C, Lindequist U. Screening of Yemeni medicinal plants for antibacterial and cytotoxic activities. J Ethnopharmacol, 2001; 74(2):173–9.

Awad AB, Chinnam M, Fink CS, Bradford PG. beta-Sitosterol activates Fas signaling in human breast cancer cells. Phytomedicine, 2007; 14(11):747–54.

Babu S, Noor A. *Aloe barbadensis* Miller peptide/polypeptide fraction alleviates inflammation through inhibition of proinflammatory cytokines and mediators *in vitro* and in rats with Freund's adjuvant-induced hind paw edema. Asian Pac J Trop Biomed, 2019; 9(12):524–30.

Babu SN, Govindarajan S, Vijayalakshmi MA, Noor A. Evaluation of *In vitro* anti-diabetic and anti-oxidant activities and preliminary phytochemical screening of gel, epidermis and flower extract of *Aloe vera*. Res J Pharm Technol, 2019; 12(4):1761–8.

Boudreau MD, Beland F. An evaluation of the biological and toxicological properties of *Aloe barbadensis* (miller), *Aloe vera*. J Environ Sci Health C, 2006; 24(1):103–54.

Casley-Smith JR, Wang CT, Casley-Smith JR. Zi-hai C. Treatment of filarial lymphoedema and elephantiasis with 5,6-benzo-alpha-pyrone (coumarin). BMJ, 1993; 307(6911):1037–41.

Chithra P, Sajithlal GB, Chandrakasan G. Influence of *Aloe vera* on the healing of dermal wounds in diabetic rats. J Ethnopharmacol, 1998; 59(3):195–01.

Choi S, Chung MH. A review on the relationship between *Aloe vera* components and their biologic effects. Semin Integr Med, 2003; 1(1):53–62.

Choi S, Kim KW, Choi JS, Han ST, Park YI, Lee SK, Kim JS, Chung MH.. Angiogenic activity of beta-sitosterol in the ischaemia/reperfusion-damaged brain of Mongolian gerbil. Planta Med, 2002; 68(4):330–5.

Choi SW, Son BW, Son YS, Park YI Lee SK, Chung MH. The wound-healing effect of a glycoprotein fraction isolated from *Aloe vera*. Br J Dermatol, 2001; 145(4):535–45.

Choudhary M, Kochhar A, Sangha J. Hypoglycemic and hypolipidemic effect of *Aloe vera* L. in non-insulin dependent diabetics. J Food Sci Technol, 2014; 51(1):90–6.

Clarkson C, Maharaj VJ, Crouch NR, Grace OM, Pillay P, Matsabisa MG, Bhagwandin N, Smith PJ, Folb PI. *In vitro* antiplasmodial activity of medicinal plants native to or naturalised in South Africa. J Ethnopharmacol, 2004; 92(2–3):177–91.

Cock IE. The genus *Aloe*: phytochemistry and therapeutic uses including treatments for gastrointestinal conditions and chronic inflammation. Prog Drug Res, 2015; 70:179–235.

Conte R, Marturano V, Peluso G, Calarco A, Cerruti P. Recent advances in nanoparticle-mediated delivery of anti-inflammatory phytocompounds. Int J Mol Sci, 2017; 18(4): E709.

Dagne E, Bisrat D, Viljoen A,Van Wyk BE. Chemistry of *Aloe* species. Curr Org Chem, 2000; 4(10):1055–78.

Das S, Mishra B, Gill K, Ashraf MS, Singh AK, Sinha M, Sharma S, Xes I, Dalal K, Singh TP, Dey S. Isolation and characterization of novel protein with anti-fungal and anti-inflammatory properties from *Aloe vera* leaf gel. Int J Biol Macromol, 2011; 48(1): 38–43.

David B, Wolfender JL, Dias DA. The pharmaceutical industry and natural products: historical status and new trends. Phytochem Rev, 2015; 14(2):299–315.

El Sayed AM, Ezzat SM, El Naggar MM, El Hawary SS. *In vivo* diabetic wound healing effect and HPLC–DAD–ESI–MS/MS profiling of the methanol extracts of eight *Aloe* species. Braz J Pharmacogn, 2016; 26(3):352–62.

Eshun K, He Q. *Aloe vera*: a valuable ingredient for the food, pharmaceutical and cosmetic industries–a review. Crit Rev Food Sci Nutr, 2004; 44(2):91–6.

Esua MF, Rauwald JW. Novel bioactive maloyl glucans from *Aloe vera* gel: isolation, structure elucidation and *in vitro* bioassays. Carbohydr Res, 2006; 341(3):355–64.

Fabricant DS, Farnsworth NR. The value of plants used in traditional medicine for drug discovery. Environ Health Perspect, 2001; 109(Suppl. 1):69–75.

Femenia A, Sánchez ES, Simal S, Rosselló C. Compositional features of polysaccharides from *Aloe vera* (*Aloe barbadensis* Miller) plant tissues. Carbohydr Polym, 1999; 39(2):109–17.

Ferreira M, Teixeira M, Silva E, Selores M. Allergic contact dermatitis to *Aloe vera*. Contact Dermatitis, 2007; 57(4):278–9.

Fuhrman B, Aviram M. Flavonoids protect LDL from oxidation and attenuate atherosclerosis. Curr Opin Lipidol, 2001; 12(1):41–8.

Furukawa F, Nishikawa A, Chihara T, Shimpo K, Beppu H, Kuzuya H, Lee IS, Hirose M. Chemopreventive effects of *Aloe arborescens* on N-nitrosobis(2-oxopropyl)amine-induced pancreatic carcinogenesis in hamsters. Cancer Lett, 2002; 178(2):117–22.

Gomes A, Neuwirth O, Freitas M, Couto D, Ribeiro D, Figueiredo AGPR, Silva AMS, Seixas RSGR, Pinto DCG, Tomé AC, Cavaleiro JaS, Fernandes E, Lima JLFC. Synthesis and antioxidant properties of new chromone derivatives. Bioorg Med Chem, 2009; 17(20):7218–26.

Hajhashemi V, Ghannadi A, Heidari AH. Anti-inflammatory and wound healing activities of *Aloe littoralis* in rats. Res Pharm Sci, 2012; 7(2):73–8.

Halder S, Mehta AK, Mediratta PK. Augmented humoral immune response and decreased cellmediated immunity by *Aloe vera* in rats. Inflammopharmacology, 2012; 20(6):343–6.

Hamman JH. Composition and applications of *Aloe vera* leaf gel. Molecules, 2008; 13(8):1599–616.

Huseini H, Kianbakht S, Hajiaghaee R, Dabaghian FH. Anti-hyperglycemic and anti-hypercholesterolemic effects of *Aloe vera* leaf gel in hyperlipidemic type 2 diabetic patients: a randomized double-blind placebo-controlled clinical trial. Planta Med, 2012; 78(4):311–6.

Hutter J, Salman M, Stavinoha WB, Satsangi N, Williams RF, Streeper RT, Weintraub ST. Antiinflammatory C-glucosyl chromone from *Aloe barbadensis*. J Nat Prod, 1996; 59(5):541–3.

Ibegbulem CO, Chikezie P. Hypoglycemic properties of ethanolic extracts of *Gongronema* latifolium, *Aloe perryi*, *Viscum* album and *Allium sativum* administered to alloxan-induced diabetic albino rats (*Rattus norvegicus*). Pharmacogn Commun, 2013; 3(2):12–6.

Ikada Y. Challenges in tissue engineering. J R Soc Interface, 2006; 3(10):589–601.

Im SA, Oh ST, Song S, Kim MR, Kim DS, Woo SS, Jo TH, Park YI, Lee CK. Identification of optimal molecular size of modified *Aloe* polysaccharides with maximum immunomodulatory activity. Int Immunopharmacol, 2005; 5(2):271–9.

Jeon W, Jeon YK, Nam MJ. Apoptosis by aloe-emodin is mediated through down-regulation of calpain-2 and ubiquitin-protein ligase E3A in human hepatoma Huh-7 cells. Cell Biol Int, 2011; 36(2):163–7.

Joshy KS, Sharma CP, Kalarikkal N, Sandeep K, Thomas S, Pothen LA. Evaluation of *in-vitro* cytotoxicity and cellular uptake efficiency of zidovudine-loaded solid lipid nanoparticles modified with *Aloe vera* in glioma cells. Mater Sci Eng C, 2016; 66(9):40–50.

Kambizi L, Afolayan AJ. Extracts from *Aloe ferox* and Withania somnifera inhibit Candida albicans and *Neisseria* gonorrhoea. Afr J Biotechnol, 2008; 7(1):012–5.

Kang MC, Kim SY, Kim YT, Kim E, Lee SH, Ko SC, Wijesinghe WAJP, Samarakoon KW, Kim YS, Cho JH, Jang HS, Jeon YJ. *In vitro* and *in vivo* antioxidant activities of polysaccharide purified from *Aloe vera* (*Aloe barbadensis*) gel. Carbohydr Polym, 2014; 99(1):365–71.

Kato Y, Hou K, Saga Y, Yamaguchi S, Yachiku S, Kawakami N. Ammonium acid urate stone due to laxative abuse: a case report. Hinyokika Kiyo, 2004; 50(11):799–803.

Kaur M, Singh J, Kamboj SS, Saxena K. Purification and characterization of a lectin from leaf pulp of *Aloe vera* (L.) BURM. F. J Pharm Res, 2011; 4(7):2441–6.

Kim HS, Kacew S, Lee BM. *In vitro* chemopreventive effects of plant polysaccharides (*Aloe barbadensis* miller, *Lentinus* edodes, *Ganoderma* lucidum and coriolus versicolor). Carcinogenesis, 1999; 20(8):1637–40.

Kitture R, Ghosh S, More PA, Date K, Gaware S, Datar S, Chopade BA, Kale SN. Curcumin-loaded, self-assembled *Aloe vera* template for superior antioxidant activity and trans-membrane drug release. J Nanosci Nanotechnol, 2015; 15(6):4039–45.

Lee KY, Park JH, Lee YJ, Lee SK, Chung MH, Park YI, Kim KW, Lee YJ, Lee SK. Aloesin up-regulates cyclin E/CDK2 kinase activity via inducing the protein levels of cyclin E, CDK2, and CDC25A in SK-HEP-1 cells. IUBMB Life, 1997; 41(2):285–92.

Liu C, Leung MYK, Koon JCM, Zhu LF, Hui YZ, Yu B, Fung KP. Macrophage activation by polysaccharide biological response modifier isolated from *Aloe* vera L. var. *chinensis* (Haw.) Berg. Int Immunopharmacol, 2006; 6(11):1634–41.

Loots DT, Pieters M, Islam MS, Botes L. Antidiabetic effects of *Aloe ferox* and *Aloe greatheadii* var. Davyana leaf gel extracts in a low-Dose streptozotocin diabetes rat model. S Afr J Sci, 2011; 107(7–8):46–51.

Lu ZQ, Deng YJ, Lu JX. Effect of *aloe* polysaccharide on caspase-3 expression following cerebral ischemia and reperfusion injury in rats. Mol Med Rep, 2012; 6(2):371–4.

Maan AA, Nazir A, Khan MKI, Ahmad T, Zia R, Murid M, Abrar M. The therapeutic properties and applications of *Aloe vera*: a review. J Herb Med, 2018; 12(6):1–10.

Mabona U, Van Vuuren SF. Southern African medicinal plants used to treat skin diseases. S Afr J Bot, 2013; 87:175–93.

Manvitha K, Bidya B. *Aloe vera*: a wonder plant its history, cultivation and medicinal uses. J Pharmacogn Phytochem, 2014; 2(25):85–8.

Maurya DK, Devasagayam TPA. Antioxidant and prooxidant nature of hydroxycinnamic acid derivatives ferulic and caffeic acids. Food Chem Toxicol, 2010; 48(12):3369–73.

Misawa E, Tanaka M, Nomaguchi K, Yamada M, Toida T, Takase M, Iwatsuki K, Kawada T. Administration of phytosterols isolated from *Aloe vera* gel reduce visceral fat mass and improve hyperglycemia in Zucker diabetic fatty (ZDF) rats. Obes Res Clin Pract, 2008; 2(4):239–45.

Mothana RA, Lindequist U, Gruenert R, Bednarski PJ. Studies of the *in vitro* anticancer, antimicrobial and antioxidant potentials of selected Yemeni medicinal plants from the Island Soqotra. BMC Complement Altern Med, 2009; 9:7; doi:10.1186/1472-6882-9-7

Mwale M, Masika PJ. *In vivo* anthelmintic efficacy of *Aloe ferox*, agave sisalana, and gunnera perpensa in village chickens naturally infected with Heterakis gallinarum. Trop Anim Health Prod, 2014; 47(1):131–8.

Naqvi S, Ullah MF, Hadi SM. DNA degradation by aqueous extract of *Aloe vera* in the presence of copper ions. Indian J Biochem Biophys, 2010; 47(3):161–5.

Narayanan V, Gnanavel I, Campus G, Care L, Remedies P. Study on the analysis of trace elements in *Aloe vera* and its biological importance. J Appl Sci Res, 2007; 3(14):1476–8.

Ni Y, Turner D, Yates KM,Tizard I. Isolation and characterization of structural components of *Aloe vera* L. leaf pulp. Int Immunopharmacol, 2004; 4(14)1745–55.

Noor A, Gunasekaran S, Soosai Manickam A, Vijayalakshmi MA. Antidiabetic activity of *Aloe vera* and histology of organs in streptozotocin-induced diabetic rats. Curr Sci, 2008; 94(8):1070–6.

Noor A, Gunasekaran S, Vijayalakshmi MA. Improvement of insulin secretion and pancreatic β-cell function in streptozotocin-induced diabetic rats treated with *Aloe vera* extract. Pharmacognosy Res, 2017; 9(5):99–104.

Pan Q, Pan H, Lou H, Xu Y, Tian L. Inhibition of the angiogenesis and growth of Aloin in human colorectal cancer *in vitro* and *in vivo*. Cancer Cell Int, 2013; 13(1):69–78.

Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev, 2009; 2(5):270–8.

Park MY, Kwon HJ, Sung MK. Dietary aloin, aloesin, or aloe-gel exerts anti-inflammatory activity in a rat colitis model. Life Sci, 2011; 88(11–12):486–92.

Pereira GG, Santos-Oliveira R, Albernaz MS, Canema D, Weismüller G, Barros EB, Magalhães L, Lima-Ribeiro MHM, Pohlmann AR, Guterres SS. Microparticles of *Aloe vera*/vitamin E/chitosan: microscopic, a nuclear imaging and an *in vivo* test analysis for burn treatment. Eur J Pharm Biopharm, 2014; 86(2):292–300.

Pérez YY, Jiménez-Ferrer E, Zamilpa A, Hernández-Valencia M, Alarcón-Aguilar FJ, Tortoriello J, Román-Ramos R. Effect of a polyphenol-rich extract from *Aloe vera* gel on experimentally induced insulin resistance in mice. Am J Chin Med, 2007; 35(6):1037–46.

Picchietti S, Bernini C, Belardinelli MC, Ovidi E, Taddei AR, Guerra L, Abelli L, Fausto AM. Immune modulatory effects of *Aloe arborescens* extract on the piscine SAF-1 cell line. Fish Shellfish Immunol, 2013; 34(5):1335–44.

Pugh N, Ross SA, ElSohly MA, Pasco DS. Characterization of aloeride, a new high-molecular-weight polysaccharide from *Aloe vera* with potent immunostimulatory activity. J Agric Food Chem, 2001; 49(2):1030–4.

Radha MH, Laxmipriya NP. Evaluation of biological properties and clinical effectiveness of *Aloe vera*: a systematic review. J Tradit Complement Med, 2015; 5(1):21–6.

Rajasekaran S, Sivagnanam K, Ravi K, Subramanian S. Hypoglycemic effect of *Aloe vera* gel on streptozotocin-induced diabetes in experimental rats. J Med Food, 2004; 7(1):61–6.

Rajasekaran S, Sivagnanam K, Subramanian S. Mineral contents of *Aloe vera* leaf gel and their role on streptozotocin-induced diabetic rats. Biol Trace Elem Res, 2005; 108(1–3):185–95.

Reider N, Issa A, Hawranek T, Schuster C, Aberer W, Kofler H, Fritsch P, Hausen BM. Absence of contact sensitization to *Aloe vera* (L.) Burm. f. Contact Dermatitis, 2005; 53(6):332–4.

Reynolds T, Dweck C. *Aloe vera* leaf gel: a review update. J Ethnopharmacol, 1999; 68(1–3):3–37.

Ro JY, Lee BC, Kim JY, Chung YJ, Chung MH, Lee SK, Jo TH, Kim KH, Park YI. Inhibitory mechanism of *aloe* single component (alprogen) on mediator release in guinea pig lung mast cells activated with specific antigen-antibody reactions. J Pharmacol Exp Ther, 2000; 292(1):114–21.

Rumawas ME, McKeown NM, Rogers G, Meigs JB, Wilson PWF, Jacques PF. Magnesium intake is related to improved insulin homeostasis in the framingham offspring cohort. J Am Coll Nutr, 2006; 25(6):486–92.

Saibuatong O, Phisalaphong M. Novo *Aloe vera*-bacterial cellulose composite film from biosynthesis. Carbohydr Polym, 2010; 79(2):455–60.

Sandeep K, Yadav JP.Ethnobotanical and pharmacological properties of *Aloe vera*: a review. J Med Plants Res, 2014; 8(48):1387–98.

Silva MA, Trevisan G, Klafke JZ, Rossato MF, Walker CIB, Oliveira SM, Silva CR, Boligon AA, Flores FC, Silva CB, Athayde ML, Ferreira J. Antinociceptive and anti-inflammatory effects of *Aloe saponaria* haw on thermal injury in rats. J Ethnopharmacol, 2013; 146(1):393–401.

Silva SS, Oliveira MB, Mano JF, Reis RL. Bio-inspired *Aloe vera* sponges for biomedical applications. Carbohydr Polym, 2014; 2(4):264–70.

Siritapetawee J, Sojikul P, Soontaranon S, Limphirat W, Thammasirirak S. A protein from *Aloe vera* that inhibits the cleavage of human fibrin(ogen) by plasmin. Appl Biochem Biotechnol, 2013; 170(8):2034–45.

Speranza G, Manitto P, Cassara P, Monti D. Feralolide, a dihydroisocoumarin from cape aloe. Phytochemistry, 1993; 33(1):175–8.

Suganya S, Venugopal J, Ramakrishna S, Lakshmi BS, Dev VRG. Naturally derived biofunctional nanofibrous scaffold for skin tissue regeneration. Int J Biol Macromol, 2014; 68(7):135–43.

Tabandeh MR, Oryan A, Mohammadalipour A. Polysaccharides of *Aloe vera* induce MMP-3 and TIMP-2 gene expression during the skin wound repair of rat. Int J Biol Macromol, 2014; 65:424–30.

Takahashi M, Kitamoto D, Asikin Y, Takara K, Wada K. Liposomes encapsulating *Aloe vera* leaf gel extract significantly enhance proliferation and collagen synthesis in human skin cell lines. J Oleo Sci, 2009; 58(12):643–50.

Tanaka M, Misawa E, Ito Y, Habara N, Nomaguchi K, Yamada M, Toida T, Hayasawa H, Takase M, Inagaki M, Higuchi R. Identification of five phytosterols from *Aloe vera* gel as anti-diabetic compounds. Biol Pharm Bull, 2006; 29(7):1418–22.

Tian B, Hua Y. Concentration-dependence of prooxidant and antioxidant effects of aloin and aloe-emodin on DNA. Food Chem, 2005; 91(3):413–8.

Ulbricht C, Armstrong J, Basch E, Basch S, Bent S, Dacey C, Dalton S, Foppa I, Giese N, Hammerness P, Kirkwood C, Sollars D, Tanguay-Colucci S, Weissner W. An evidence-based systematic review of *Aloe vera* by the natural standard research collaboration. J Herb Pharmacother, 2008; 7(3–4):279–323.

van Wyk BE, van Rheede van Oudtshoorn MC, Smith GF. Geographical variation in the major compounds of *Aloe ferox* leaf exudate. Planta Med, 1995; 61(3):250–3.

Veitch NC, Simmonds MSJ, Blaney WM, Reynolds T. A dihydroisocoumarin glucoside from *Aloe hildebrandtii*. Phytochemistry, 1994; 35(5):1163–6.

Wu JH, Xu C, Shan CY, Tan RX. Antioxidant properties and PC12 cell protective effects of APS-1, a polysaccharide from *Aloe vera* var. *chinensis*. Life Sci, 2006; 78(6):622–30.

Yagi A, Hegazy S, Kabbash A, Wahab EAE. Possible hypoglycemic effect of *Aloe vera* L. high molecular weight fractions on type 2 diabetic patients. Saudi Pharm J, 2009; 17(3):209–15.

Yagi A, Kabash A, Mizuno K, Moustafa SM, Khalifa TI, Tsuji H. Radical scavenging glycoprotein inhibiting cyclooxygenase-2 and thromboxane A2 synthase from *Aloe vera* gel. Planta Med, 2003; 69(3):269–71.

Yates KM, Rosenberg LJ, Harris CK, Bronsta DC, King GK, Biehle GA, Walker B, Ford CR, Hall JE, Tizard IR. Pilot study of the effect of acemannan in cats infected with feline immunodeficiency virus. Vet Immunol Immunopathol, 1992;35(1–2):177–89.

Yen GC, Duh P Der, Chuang DY. Antioxidant activity of anthraquinones and anthrone. Food Chem, 2000; 70(4):437–41.

Yimam M, Zhao J, Corneliusen B, Pantier M, Brownell L, Jia Q. Blood glucose lowering activity of *aloe* based composition, UP780, in alloxan induced insulin dependent mouse diabetes model. Diabetol Metab Syndr, 2014;6(1):61–79.

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