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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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 attempt 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 arborescens, 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 Vuure, 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 ethnomedical and 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 Aloe 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 arborescens, 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, glugogalactomannan, 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*.

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

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 \textit{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 \textit{Aloe} species and these are known to contribute to the bitter taste of \textit{Aloe}. Feralodial is a coumarin which has been reported to be present in \textit{A. ferox} (Speranza et al., 1993), while dihydroiscoumarin is present in \textit{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 \textit{Aloe} gel with antioxidant properties include naringenin, apigenin, myrcetin, quercetin, 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 \textit{Aloe} species are campesterol, \textit{β}-sitosterol, lophenol, cycloartenol, 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 wound 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 leaf part are Aloin, \textit{Aloe} emodin, aloeasaponarin, chrysophanol, and isoxanthorhine (Reynolds and Dweck, 1999). The concentration of aloin and \textit{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. Barbaloine is one of the first anthrones to be isolated from \textit{A. vera}. \textit{Aloe ferox} leaves are also reported to have higher amounts of anthrone (around 30%) (van Wyk et al., 1995). From \textit{Aloe marlothi}, anthrones such as homonataloin and nataloin have been extracted (Dagne et al., 2000). The anthrones are also known to have strong antioxidant properties.

**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, Aloesorin A, and Aloesorin 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 \textit{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 \textit{A. vera} gel (Cock, 2015). Some lectins have also been isolated from \textit{A. vera}. Most of the glycoproteins from \textit{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 \textit{A. vera} and their therapeutic potential, including anti-inflammatory, anti-diabetic, and immunomodulation, has been studied (Das et al., 2011; Siripetawee 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). \textit{Aloe vera} also contains alkaloids, benzene derivatives, and furan derivatives (Cock, 2015).

These are some of the bioactive components which are present in the \textit{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 \textit{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 \textit{Aloe} genus, most of the constituents (sterols, polyphenols, saccharides, proteins, glycoproteins, and minerals) have been reported either from \textit{A. vera}, \textit{A. ferox}, or \textit{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, cycloartenol, and 24-methylene cycloartenol) 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 cycloartenol) 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 hizaeensis 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-hypoglycemic 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 rhamnose 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
A 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

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

<table>
<thead>
<tr>
<th>Components/ Constituents</th>
<th>IUPAC Name</th>
<th>Property/ Condition</th>
<th>Dose</th>
<th>Period of the study</th>
<th>Model</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polyphenols</strong></td>
<td>Aloe ([(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-dodecahydرو-pH-1H-cyclopenta[a]phenanthren-3-yl] acetate)</td>
<td>Hypoglycemic</td>
<td>181.7 mg g^-1 Aloe</td>
<td>4 weeks</td>
<td>ICR</td>
<td>(Pérez et al., 2007)</td>
</tr>
<tr>
<td><strong>Anthraquinones</strong></td>
<td>Aloe emodin</td>
<td>Hypoglycemic, Increase adiponectin levels, improves insulin sensitivity</td>
<td>200 mg kg^-1</td>
<td>12 weeks</td>
<td>C57BL/6J</td>
<td>(Yimam et al., 2014)</td>
</tr>
<tr>
<td><strong>Chromones</strong></td>
<td>Aloe ([(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-dodecahydرو-pH-1H-cyclopenta[a]phenanthren-3-yl] acetate)</td>
<td>Hypoglycemic</td>
<td>100 mg kg^-1 of Aloe</td>
<td>100 mg kg^-1 Aloeemodin</td>
<td>Mice</td>
<td></td>
</tr>
<tr>
<td><strong>Phytosterols</strong></td>
<td>Lophenol, 24-methyl lophenol, 24-ethyl lophenol, Cycloartenol, 24-methyl cycloartenol</td>
<td>Anti-diabetic</td>
<td>1 µg each</td>
<td>28 days</td>
<td>Lepr (db/db)</td>
<td>(Tanaka et al., 2006)</td>
</tr>
<tr>
<td><strong>Polysaccharide and Glycoprotein</strong></td>
<td>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-dodecahydرو-pH-1H-cyclopenta[a]phenanthren-3-yl] acetate)</td>
<td>Hypoglycemic and hypolipidemic</td>
<td>25 µg kg^-1</td>
<td>28 days</td>
<td>Zucker diabetic fatty rats</td>
<td>(Misawa et al., 2008)</td>
</tr>
<tr>
<td><strong>Mineral elements</strong></td>
<td>Magnesium</td>
<td>Carbohydrate metabolism, glucose and insulin homeostasis</td>
<td>90 mg/kg bw</td>
<td>30 days</td>
<td>Wistar Rats</td>
<td>(Rajasekaran, Sivagnanam and Subramanian, 2005)</td>
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<td></td>
<td>Zinc</td>
<td>Increases insulin effectiveness</td>
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<tr>
<td></td>
<td>Potassium</td>
<td>Release of insulin</td>
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<td></td>
<td>Calcium</td>
<td>Stimulation of insulin</td>
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<td></td>
<td>Copper</td>
<td>Insulin binding</td>
<td></td>
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<tr>
<td></td>
<td>Chromium</td>
<td>Carbohydrate metabolism</td>
<td></td>
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<tr>
<td></td>
<td>Vanadium</td>
<td>Lipid metabolism</td>
<td></td>
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</tbody>
</table>

**Table 2.** Role of different constituents of *Aloe vera* in diabetes mellitus.
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 (Siripatawee 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 hemagglutinating activity and anti-proliferative activity against lung and colon cancer cell lines (Kaur et al., 2011).
The gel has been combined with biomaterials such as cellulose, chitosan, and Vitamin E for wound healing. Micro and nanoparticles have also been used as a drug delivery system due to great stability of encapsulated drug. The nano- or microparticles consisting of gel and silk fibroin showed better mechanical support, and prevention of body fluid loss. Attention has been focused on controlled release of 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).

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

<table>
<thead>
<tr>
<th>Components/ Constituents</th>
<th>IUPAC Name</th>
<th>Property/ Condition</th>
<th>Dose</th>
<th>Period of the study</th>
<th>Model</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polysaccharide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veracylgucan B</td>
<td>(3S)-3-hydroxy-4-oxo-4-[[2R,3S,4R,5R]-4,6,7-trihydroxy-3-[[2R,3R,4S,5R,6R]-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyoxan-2-yl]methoxy]β-tartaric acid</td>
<td>Anti-oxidant, cell protection for heart disease, Parkinson’s &amp; Alzheimer’s disease.</td>
<td>100–300 µg ml$^{-1}$</td>
<td>3 days</td>
<td>In vitro, rat PC12 cells</td>
<td>(Wu et al., 2006)</td>
</tr>
<tr>
<td>Polysaccharide AVP</td>
<td>Veracylgucan C:</td>
<td>Anti-cancer, anti-inflammatory,antimicrobial</td>
<td>180 µmol$^{-1}$</td>
<td>3 days</td>
<td>In vitro, cultured keratinocytes</td>
<td>(Kim et al., 1999)</td>
</tr>
<tr>
<td>Polysaccharide MAP</td>
<td>Veracylgucan C:</td>
<td>Wound healing</td>
<td>25 mg</td>
<td>30 days</td>
<td>Male wistar Rat</td>
<td>(Tabunde et al., 2014)</td>
</tr>
<tr>
<td>Maloyglucans</td>
<td>Veracylgucan B &amp; veracylgucan C</td>
<td>Immunomodulation</td>
<td>1 mg ml$^{-1}$</td>
<td>10 days</td>
<td>In vitro, RAW.264.7</td>
<td>(Im et al., 2005)</td>
</tr>
<tr>
<td><strong>Proteins/ Polypeptides</strong></td>
<td></td>
<td>Anti-oxidant, cell protection for heart disease, Parkinson’s &amp; Alzheimer’s disease.</td>
<td>100–300 µg ml$^{-1}$</td>
<td>3 days</td>
<td>In vitro, rat PC12 cells</td>
<td>(Wu et al., 2006)</td>
</tr>
<tr>
<td>14KDa Polypeptide</td>
<td>Anti-fungal</td>
<td>75 µl of 0.5 mg ml$^{-1}$</td>
<td>72 hours</td>
<td>Microbial culture</td>
<td>(Das et al., 2011)</td>
<td></td>
</tr>
<tr>
<td>5.5KD Glycopeptide</td>
<td>Wound healing</td>
<td>1 mg ml$^{-1}$</td>
<td>24 hours</td>
<td>In vitro, Human keratinocytes</td>
<td>(Choi et al., 2001)</td>
<td></td>
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<tr>
<td>Alprogen</td>
<td>Anti-allergy</td>
<td>0.5 to 10 µg ml$^{-1}$</td>
<td>72 hours</td>
<td>Keratinocytes</td>
<td>(Ro et al., 2000)</td>
<td></td>
</tr>
<tr>
<td>11.8 KD protein</td>
<td>Anti-fibrinolytic</td>
<td>0–10 µg</td>
<td>200 minutes</td>
<td>Hartley albino female guinea pigs</td>
<td>(Sintapatwee et al., 2013)</td>
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</table>

Table 3. Pharmacological activities of Aloe vera constituents
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 anthraquinones 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. 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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