Pharmaceutical Applications of Aloe vera

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ABSTRACT

Aloe vera has been used as folk medicine for a host of therapeutic indications of which the inner gel is the component extensively used and studied. Proponents of the use of this plant suggest that it is easily available, economical, and have fewer side effects compared to commercial drug compounds. However, the active constituents and their exact mechanisms have yet to be fully elucidated. This review focuses on the identification of the active constituents and their functional mechanism in the areas of anti-diabetic, anti-inflammatory, wound healing, and antibacterial. Preliminary evidence was found to support the antidiabetic effect which extended to the early stages of the disease with no adverse effects at the dosages used. Although topical application for its anti-inflammatory effect may be delayed and minute, oral administration has shown a significant response. However, too high a dose has been linked with an initial inflammatory reaction. Favorable response to the gel has also been demonstrated to support the use of A. vera in wound-healing and as an antibacterial agent, although limited to simple, uncomplicated wounds. Different active constituents such as acemannan and aloin have been suggested for the effects of the plant and this may be interpreted as synergism among different compounds rather than the action of a single compound. Until robust evidence is available, the plant should only be used as an adjunct to other well-established evidence-based treatment modalities.

Key words: A. vera; Anti-diabetic; Anti-inflammatory; Wound healing; Antibacterial

INTRODUCTION

Aloe barbadensis Miller, the botanical name of the more commonly known A. vera, is one of the approximately 420 species belonging to the family Alooaceae (Boudreau and Beland, 2006; Dagne et al., 2000). Under the same family, the Aloe genus is differentiated from the other six genera by bright yellow-coloured flowers, fleshy leaves, and stamens that are as long as or longer than the perianth (Akinyele and Odiyi, 2007). Of the many species, A. vera, Aloe arborescens, and Aloe ferox are among the more extensively studied species. The use of A. vera has sustained the passage of time, which dates back to 1750 B.C. in which there is evidence to suggest that the plant has been used as medicinal treatment in Mesopotamia (Shelton, 1991). Originating from South Africa, they are now found widespread and thrive in the dry climates of subtropics and tropics, including Malaysia (Boudreau and Beland, 2006).

Figure 1. Aloe vera plant.

The triangular fleshy leaves are lined with spines and are arranged in a rosette pattern (Figure 1) (Cole and Heard, 2007; Morton, 1961; Shelton, 1991). Each leaf is being made up of three distinct layers (Figure 2) and as follows: 1 The outermost layer is a thick rind of 15-20 cells in which proteins and polysaccharides such as highly-acetylated glucomannans are produced (Rahman et al., 2017; Shi et al., 2017). 2 The
middle layer which contains the yellow sap exuded by peripheral bundle sheath cells covers the gel surface and has anthraquinones and glycosides as its constituents. 3 The innermost layer that originates from the clear central mucilaginous pulp is made up mainly of water (Rahman et al., 2017; Shelton, 1991). Initially, the yellow latex of the plant was collected and used as a bitter cathartic, then, an array of other medicinal uses involving the inner clear gel were later discovered (Morton, 1961).

![Figure 2. Cross-section of Aloe vera leaf.](image)

The plant has been used for its wound healing, ultraviolet (Veerasubramanian et al. 2018) protective, anti-inflammatory, laxative, antiviral and antitumour, moisturising and anti-aging, and antiseptic effects (Surishe et al., 2008). However, as the use of A. vera is further studied, conflicting results pertaining to its effects are discovered. This is further compounded by the lack of understanding of the biochemical components of the plant and their mechanism of action. Scientific research as such has been intensified for a better understanding on these aspects, however; results have been inconsistent, suggesting that perhaps it is not only one active biochemical compound responsible for the effects but a result of the interplay of many active components within the plant. Therefore, this review focuses on establishing the active constituents and their functional mechanism in areas where A. vera has been extensively studied (i.e. anti-diabetic, anti-inflammatory, wound healing, and antibacterial) (Figure 3, 4, 5 and 6).

**ANTI-DIABETIC**

Diabetes mellitus is a non-communicable disease characterized by chronic hyperglycemia and other metabolic derangements. Mainly the body’s resistance to insulin, as well as the reduced pancreatic output of the hormone causes it. If not treated, symptoms such as polydipsia, lethargy, polyuria, weight loss, blurred vision, and slow-healing wounds may appear. As the disease continues to deteriorate without being arrested, complications will then develop; this can be divided into macrovascular (cerebrovascular, cardiovascular, peripheral vascular diseases) and microvascular (nephropathy, neuropathy, and retinopathy) complications (Ministry of Health Malaysia, 2015). In Malaysia, the disease has been on an increasing trend, and the most recent prevalence, both reported and unknown, has reached 17.5% (617, 715 respondents) in those aged 18 years and above as reported by the National Health and Morbidity Survey (NHMS) 2015. Of the above figure, more than a quarter (25.1%) of known diabetics claimed that they were on insulin (Institute for Public Health, 2015).

*A. vera* is among the many plants that have been used as traditional remedies for diabetes mellitus, such as Iranian plant *Amygdalus lycioides* (Moezi et al., 2018), Cuban plant *Allophylus cominia* (Semaan et al., 2018), tea plant *Camellia sinensis L.* (Fan et al., 2018), perennial herbs *Anoectochilus roxburghii* and *Anoectochilus formosanus* (Tang et al., 2018), and *Cichorium intybus L.*, a vegetable (Ferrare et al., 2018). However, the scientific community is divided on whether *A. vera* is indeed effective in the treatment of diabetes mellitus as new research findings become available. Some studies were in support of this claim (Cárdenas-Ibarra et al., 2017; Devaraj et al., 2013; Huseini et al., 2012), while others negated this claim and have even demonstrated that *A. vera* may lead to hyperglycemia (Beppu et al., 2006; Okyar, et al., 2001). In an investigation by Okyar and colleagues, they have concluded that the leaf pulp extract exerted hyperglycaemic effect in Type II diabetic rats as opposed to the gel extract which demonstrated hypoglycemic effect (Okyar et al., 2001). It is however, important to note that gel and pulp are essentially the same part of the plant, which is the inner parenchymal tissue (Turner et al., 2004). Based on the preparation method, the leaf pulp extract and the leaf gel extract were both derived from the liquid fraction of the parenchymal tissue. However, the doses used for the two groups were different and are not directly comparable:
A dosage of leaf pulp extract was based on the weight of a lyophilized concentrate while dose of leaf gel extract was based on the volume of a diluted gel. Therefore, the hyperglycaemic effect seen with the gel extract may be simply due to the much lower dose of *A. vera* that may be insignificant in lowering blood glucose. Meanwhile, in another report, administration of *A. vera* leaf pulp did not significantly alter the blood sugar levels of diabetic mice. This was attributed to the high content of monosaccharides and polysaccharides in the freeze-dried pulp powder that increased the workload of the beta cells of the pancreatic islets (Beppu *et al*., 2006). Similarly, the dosing regimen used in this study may be flawed: dose was set at a concentration of 2% of the mice’s feed, instead of being determined on the basis of body weight.

On the other hand, the hypoglycaemic effects of the plant were not accompanied by any adverse effects when administered in a randomized, double-blind, placebo-controlled clinical trial. Analysis of blood sugar levels revealed small but significant reductions in fasting blood glucose and glycosylated haemoglobin (HbA1c) levels (Huseini *et al*., 2012). On the basis of such promising results, efforts have been initiated in developing a concentrate of the active compounds found in the plant. A concentrated form may better demonstrate the efficacy, of which a patented concentrated 5:1 *A. vera* by total process has shown a higher hypoglycemic effect than the corresponding gel (Cárdenas-Ibarra *et al*., 2017). The observed hypoglycaemic effect may also be beneficial in conditions of prediabetes. Impaired fasting glucose and impaired glucose tolerance could be reverted with administration of a standardized gel preparation, UP780 containing 2% aloesin as shown in another double-blind, placebo-controlled study. Parameters such as fasting blood glucose, HbA1c, fructosamine, and homeostasis model assessment (HOMA), a marker for insulin resistance were significantly improved with treatment. This finding may support the use of *A. vera* as an addition to therapeutic lifestyle changes in the early stages of the disease, in which initiation of treatment is not yet indicated (Ministry of Health Malaysia, 2015).

Up till today, there has been a race to elucidate the active compounds involved and the mechanisms of the glucose-lowering effect. Five minor phytosterols of the lophenol and cycloartrane structural groups and a glycoside have been postulated to be the active compounds. These fractions of the plant did not result in acute hypoglycaemic conditions and other adverse side effect symptoms (M Tanaka *et al*., 2006). Meanwhile, the various inorganic elements contained in the leaf gel prepared by ashing the gel may also possess hypoglycaemic activity. Among the many
elements found in the gel ash, iron, manganese, and potassium were found at higher concentrations (Rajasekaran et al., 2005). Additionally, acemannan, a mucopolysaccharide has been identified as the responsible bioactive (Huseini et al., 2012).

It seems that A. vera addresses both the causes of diabetes: insulin resistance and reduced pancreatic output of the hormone. The effect on insulin resistance was supported by the lower levels of glucose and insulin found circulating in blood as a result of increased insulin sensitivity (Manco et al., 2004). On the other hand, preservation of insulin secretion was reflected by the bigger size and the higher number of pancreatic islets seen following administration of A. vera gel (Tanaka et al., 2006). Other mechanisms include insulinogenic activity which resulted in higher plasma insulin levels in treated rats (Rajasekaran et al., 2005) and the inhibition of pro-inflammatory state as reflected by lower levels of C-reactive protein (Cárdenas-Ibarra et al., 2017). It has been previously suggested that type II diabetes is associated with higher concentrations of inflammatory mediators that suppress insulin signal transduction. A pro-inflammatory state therefore can reduce insulin action (Dandona et al., 2004). Meanwhile, others have attributed the production of a fiber-like effect by the high molecular weight polysaccharides present in the gel. As absorption of glucose is slowed down by these polysaccharides, this prevents any blood glucose spikes as manifested by the lower blood glucose levels (Pérez et al., 2007).

**ANTI-INFLAMMATORY**

Inflammation can be defined as a pathological process that is a direct consequence from tissue injury, in which the metabolic balance is disrupted and catabolism predominates. The enhanced catabolic state can manifest as: 1) proteolysis, 2) reduction of cellular space volume, and 3) diminished oxidative metabolism over the course of the inflammation process (Stankov, 2012). The causes of inflammation are many and varied; some of the common ones include infection, external injuries, effects of chemicals or radiation, or diseases such as dermatitis. If the inflammation is severe enough, some general reactions happen in the body. The accompanying signs and symptoms include a general feeling of sickness, malaise, fever, and an increase in the number of immune defence cells (PubMed Health, 2015).

Interestingly, certain plants may have anti-inflammatory activity as demonstrated by studies on these plants. Apart from A. vera, these include traditional Brazilian medicine *Cissus sicyoides* L. (Salazar et al., 2018), camphor tree *Cinnamomum camphora* (Li et al., 2018), Cordia dichotoma (Hatware et al., 2018), *Garcinia morella* fruit (Choudhury et al., 2018), and *Syzygium calophyllifolium* bark (Chandran et al., 2018). The anti-inflammatory effect of A. vera has been found comparable to two groups of compounds with established anti-inflammatory activity: NSAIDs such as indomethacin (Devaraj and Karpagam, 2011), piroxicam (et al., 2011), and diclofenac (Egesie et al., 2011), and steroids such as dexamethasone (Vázquez et al., 1996) and hydrocortisone (Hutter et al., 1996). As an inflammatory disease model, ulcerative colitis has shown a favourable response to the gel in which the histological disease activity was decreased in mild to moderate disease (Langmead et al., 2004; Park et al., 2011). However, topical administration of the gel showed a delayed anti-inflammatory effect for 48h. Although significance in the anti-inflammatory action was demonstrated afterwards, the action was similar to a hydrophilic placebo gel used as a negative control in the study even when used at a high concentration of 97.5% (Reuter et al., 2008). Despite the favourable response seen with oral administration, it should be used with caution at high dose as an initial flare in inflammation has been observed. This was seen for the first 0.5 h when 50g wet gel/kg body weight was used as compared to 25g wet gel/kg body weight that lacked such initial pro-inflammatory phase. The initial flare may be attributed to the higher cytotoxicity at higher dose as compared to the lower dose (Paul et al., 2014). The gel may have been extensively studied for its anti-inflammatory properties but even the flowers of the plant may also have such properties. A 70% ethanolic extract of the flowers has been shown to be rich in vanillic acid, postulated to be the active constituent.
The effect is achieved by scavenging activities on 2,2-diphenyl-1-pirhydrazyl (DPPH), 2,2′-azinobis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS), superoxide, and hydroxyl radicals (Debnath et al., 2017). Sterols present in the gel have been suggested as the principal component responsible for the anti-inflammatory properties as their structure is similar to the anti-inflammatory steroids (Vázquez et al., 1996). Salicylic acid is also one of the organic constituents of the plant apart from barbaloin and emodin which are precursors to aspirin-like compounds (Figure 4). These, in turn, can be broken down by the Kolbe reaction to result in salicylates which possess anti-inflammatory action (Robson et al., 1982). Also known as barbaloin, aloin is mainly found in plant exudate and has previously been used for its cathartic effect (PubChem). To suppress inflammatory responses without the presence of side effect, the safe intake level of aloin has been determined to be at 0.005 - 0.01% of diet. Although when compared to aloesin which is an aloe chromone, it was found that the anti-inflammatory effect strength the later was stronger (Park et al., 2011). Its derivatives, aleresin A (p-coumaroylaloesin) and aleresin B (feruloylaloesin) have also demonstrated anti-inflammatory effect (Yagi et al., 2002). Meanwhile, others have suggested protein (Das et al., 2011; Yagi et al., 1982), glycoprotein (Yagi et al., 1982; Yagi et al., 2003), 540 Da C-glucosylchromone (Hutter et al., 1996), and 20-100 kDa bradykininase (Bautista-Pérez et al., 2004) as the active constituent. In another research work, veracylg glucan B and veracylg glucan C which are malic acid acylated carbohydrates have also been shown to possess anti-inflammatory properties (Esua and Rauwald, 2006).

The anti-inflammatory action of A. vera may lie in the reduction of pro-inflammatory mediators: leukotriene B4 (LTB4) (Park et al., 2011) and nitric oxide (NO) (Park et al., 2009), and cytokines: tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) (Habeeb et al., 2007; Park et al., 2011). The inhibitory effect may be seen at the molecular level whereby there was reduced TNF-α and IL-1β mRNA expression (Habeeb et al., 2007; Park et al., 2011). It may also result from an inhibitory effect on the inflammatory mediators of which an antibradykinin activity has been observed (Ro Bautista-Pérez et al., 2004; Yagi et al., 1982). This is complemented by inhibitory effect on important enzymes involved in the inflammatory cascade such as lipooxygenase (LOX) and cyclooxygenase (COX) (Das et al., 2011; Vázquez et al., 1996; Yagi et al., 2003). A reduction in the levels of thromboxane A2
Yagi et al., 1996) and hence its metabolite product, thromboxane B2 (Robson et al., 1982), and matrix metalloproteinase-9 (MMP-9) (D Vijayalakshmi et al., 2012) might further contribute to the effect. Such inhibition also occurred at the molecular level whereby the inhibition of COX-2 mRNA led to reduced levels of prostaglandin E2 (Park et al., 2011). Similarly, inhibition of the expression and production of inducible nitric oxide synthase (iNOS) mRNA (Park et al., 2009) and the expression of MMP-9 mRNA has also been demonstrated (Vijayalakshmi et al., 2012).

WOUND HEALING

The process of wound healing is initiated as soon as the normal anatomical structure and function of the skin is compromised. The continuous process may be divided into four different stages, each with their own mechanism: 1) coagulation and hemostasis partaken by endothelial cells and thrombocytes, 2) acute inflammation involving the activation of complement cascade and neutrophil infiltration into the wound site, 3) proliferation characterized by migration of fibroblasts and the deposition of a new extracellular matrix, and lastly, 4) wound remodeling with scar tissue formation (Velnar et al., 2009). A variety of plants have been used since medieval time to heal wounds. In the aloe genus, A. vera has shown higher wound healing activity than that achieved using other aloe species: Aloe ferox and Aloe marlothii (Fox et al., 2017). Apart from A. vera, other plants believed to possess wound-healing capability include the leaves of Lippia pacari A. St.-Hil, a native Brazilian tree (Pereira et al., 2018), Sanguisorba officinalis L. (Zhang et al., 2018), oat Avena sativa (Veerasubramanian et al., 2018), Artemisia khorassanica (Nowrozani and Ranjbar, 2018), and Roman chamomile Chamaemelum nobile L. (Kazemian et al., 2016).

Promising results with A. vera have been observed in different wound models. In burn wound model, second-degree burns which involve damage to the epidermis and dermis (Akhoondinasab et al., 2014; Hosseinimehr et al., 2010; Khorasani et al., 2009), and even third-degree burns which extend beyond the dermis into the deeper tissues (Akhoondinasab et al., 2014; Rodriguez-Bigas et al., 1988) have shown favorable responses. Such effects have also been demonstrated in full-thickness excisional wound model (Khan et al., 2013; Li et al., 2017; Wahedi et al., 2017), full-thickness incisional wound model (Mendonça et al., 2009; Tarameshloo et al., 2012), superficial wound model involving postdermabrasion wounds (Fulton, 1990), and internal wound model involving induced gastric ulcers (Eamlamnam et al., 2006). The potential of A. vera in wounds characterised by delayed healing such as in acute-radiation delayed wounds and diabetic wounds has also been demonstrated (Atiba et al., 2011; Atiba et al., 2011). Although most of the favourable responses were demonstrated in animal model, the effect has been supported by a prospective, randomized, double-blind, placebo-controlled trial involving post-operative patients (Eshghi et al., 2010). On the contrary, administration of the gel in addition to standard wound care has shown delayed healing of vertical incisions as compared to the group receiving standard wound care. This may indicate that the gel treatment is not suitable for those who had wound complications requiring healing by second intention (Schmidt and Greenspoon, 1991). It is also interesting to note that a more frequent administration may lead to higher healing capacity as demonstrated by twice daily topical administration of the gel as compared to once daily application (Takzare et al., 2009).

One of the active components identified as having cell-proliferation activity was a 5.5 kDa glycoprotein fraction (Choi et al., 2001), although this may be antagonized by Veracylglucan C which have shown anti-proliferative effects (Esua and Rauwald, 2006). In another study, a high molecular weight polypeptide has been suggested as the responsible constituent (Heggers et al., 1996). Aloesin (Wahedi et al., 2017) and aloin (Li et al., 2017) which are among the main constituents of A. vera exudate may also have a role to play in hastening wound healing.

The underlying mechanisms of the enhanced wound-healing process are likely to start from the second phase of the wound-healing process (inflammation) (Guo and DiPietro, 2010). At this stage, higher levels of neutrophils and macrophages were seen in the treated group (Takzare et al., 2009; Wahedi et al., 2017) which then decreased on Day 7 (Wahedi et al., 2017). The higher number of neutrophils
enhanced the removal of microbes and cellular debris in the wound but at the same time, neutrophils also produce chemical substances that may cause some damage such as reactive oxygen species and proteases. Meanwhile, macrophages function to promote the inflammatory response by releasing cytokines and also inducing and clearing apoptotic cells including neutrophils as the wound enters the proliferative phase (Guo and DiPietro, 2010).

Subsequently, the proliferative phase was found to be enhanced yet still occurring in a controlled manner. The enhanced cell proliferation resulted from a shortening of the Gap 0 (resting phase) / Gap 1 (interphase) of the cell cycle, and thus an extension of the S phase (DNA synthesis) (Li et al., 2017). The enhanced proliferation was also contributed by the faster migration of fibroblasts mediated through phosphorylation of Cdc42 and Rac1, and upregulation of α-P-21 activated kinase (α-PAK) which are migration-related proteins (Li et al., 2017; Negahdari et al., 2017; Wahedi et al., 2017). With a high number of fibroblasts, higher levels of extracellular matrix (ECM) components such as glycosaminoglycan (GAG), hyaluronic acid, proteoglycan, and dermatan sulfate could be synthesised (Chithra et al., 1998). Higher amounts of collagen, another component of the extracellular matrix were also produced and the newly-formed collagen fibres showed superior alignment compared to untreated wounds which may prevent the formation of a scar tissue (Li et al., 2017; Oryan et al., 2010; Wahedi et al., 2017).

On the contrary, in another research work, such a proliferative effect on fibroblasts was not observed but the fibroblasts were more matured and better aligned (Oryan et al., 2010). The levels of glycohydrolases in wound granulation tissue were also found to be elevated in A. vera treated groups. The few glycohydrolases studied include beta-glucuronidase, N-acetyl glucosaminidase, beta-glucosidase, and beta-galactosidase which are implicated in the turnover of the extracellular matrix (Chithra et al., 1998). Furthermore, Smad (an abbreviation from the fusion of Caenorhabditis elegans Sma genes and the Drosophila Mad, Mothers against decapentaplegic) and mitogen activated protein kinase (MAPK) signaling proteins which are key players in cell migration, angiogenesis, and tissue development were also activated (Wahedi et al., 2017).

Angiogenesis, the generation of new capillaries from existing vasculature in granulation tissue was found enhanced with A. vera treatment, consistent with the upregulation of angiogenic growth factors (Li et al., 2017; Ucuzian et al., 2010; Wahedi et al., 2017). The higher expression of the following growth factors might also have a role: vascular endothelial growth factor (VEGF) (Atiba et al., 2011; Oryan et al., 2010; Tarameshloo et al., 2012), transforming growth factor -1 (TGF-β-1) (Atiba et al., 2011; Hormozi et al., 2017; Wahedi et al., 2017), and basic fibroblast growth factor (bFGF) (Atiba et al., 2011; Hormozi et al., 2017). The effect of A. vera on the expression of TGF-β-1 and bFGF in particular, was found to be dose- and time-dependent in which the expression decreased significantly after 24h. This seems like a feedback mechanism to prevent the overproduction of these growth factors as it may lead to an accumulation of matrix proteins and hence, the formation of a hypertrophic scar (Hormozi et al., 2017). In the final phase of the wound-healing process, the collagen fibres were characterised by a higher degree of cross-linking, resulting in enhanced wound strength (Chithra et al., 1998).
As such, researchers have attempted to incorporate A. vera into formulations in order to develop functional wound dressings. In particular, electrospinning has been used to produce nanofibrous dressings with polylactic-co-glycolic acid (PLGA) (Garcia-Orue et al., 2017) or polyvinyl alcohol (Sirima et al., 2017) as the polymeric matrix. Loading of recombinant human Epidermal Growth Factor (rhEGF) into these dressings was then carried out, which together with A. vera, enhanced fibroblast proliferation, demonstrating the synergistic effect of these two compounds was not affected by the electrospinning process. Incorporation of A. vera extract also increased the viscosity and conductivity of the polymeric solution, which facilitated the electrospinning process (Sirima et al., 2017). In addition, it provided greater elasticity and tensile strength to the membranes (Garcia-Orue et al., 2017). Incorporation into different types of matrices resulted in different release rate of A. vera owing to the different mechanisms involved. In electrospun films, an inverse trend between the content of A. vera and the release rate was observed. This was attributed to the increasing fibre diameter with increasing A. vera content and hence, a reduction in the surface area of the films. On the contrary, a higher content in hydrogel films led to higher release rates. As A. vera content increased, pore expansion was enhanced which facilitated water entry into the hydrogel films (Sirima et al., 2017). Meanwhile in another research work, chitosan-alginate (CA) and chitosan-xanthan (CX) membranes loaded with aloin have also been developed as wound dressings. CA membranes have the characteristics of being more stable in liquid media and showed higher values of elongation at break while CX membranes showed sustained release of aloin up to 5 h which resulted from the cross-linking process with calcium ions (Bierhalz et al., 2017).

**ANTIBACTERIAL**

Bacteria are microscopic unicellular organisms characterized by the lack of a membrane-bound nucleus and other organelles, therefore ranked together with prokaryotes, which are single-celled organisms (K Rogers, 2010). Bacteria are then further categorized into Gram-positive and Gram-negative based on the results of Gram stain, a classification system based on morphology. Gram-negative microorganisms possess an outer lipid-rich membrane above the peptidoglycan layer as opposed to the single peptidoglycan layer in Gram-positive microbes, which allows the use of Gram stain to distinguish between them (Amyes, 2013; Beveridge, 1999). The emergence of multidrug resistant bacteria has rendered some antibiotics ineffective and the antibacterial activity of naturally-occurring antimicrobials can potentially contribute to the discovery of novel antibiotics. The antibacterial effect of a number of plants has been demonstrated; these include hardy kiwifruit leaves, Actinidia arguta (Almeida et al., 2018), vine shoot extracts of Tinta Raríz variety (Moreira et al., 2018), garden sage Salvia officinalis L. (Wei et al., 2018), Beach spider lily Hymenocallis littoralis (Nadaf et al., 2018), and even the common garlic Allium sativum. I. (Cavallito and Bailey, 1944).

A. vera has also exhibited a broad range of antibacterial activity, although with varying susceptibility (Robson et al., 1982). Bacilli, were particularly susceptible to the antibacterial effect, which has been demonstrated in Bacillus cereus (Pelizzzoni et al., 2012), Bacillus subtilis (G Yebpella et al., 2011), Bacillus megaterium (Subramanian et al., 2006), Bacillus sphaericus, and Mycobacterium smegmatis. Other susceptible Gram-positive microbes include, Enterococcus faecalis, Micrococcus luteus (Alemdar and Agioolu, 2009), Staphylococcus aureus (Salah et al., 2017), Methicillin-resistant S. aureus (MRSA) (Banu et al., 2012), Staphylococcus epidermidis (Garcia-Orue et al., 2017), and Streptococcus pyogenes (Nejatzadeh-Barandozi, 2013). Meanwhile, Gram-negative microbes that are susceptible include: Escherichia coli (Salah et al., 2017), Salmonella typhi (Lawrence et al., 2009), Salmonella paratyphi (Lorenzetti et al., 1964), Shigella flexneri (Ferro et al., 2003), Alcaligenes faecalis, Aeromonas hydrophilia, Citrobacter freundii, Serratia marcescens, Enterobacter aerogenes (Cock, 2008), Klebsiella pneumoniae, Proteus mirabilis (Dahiya and Purkayastha, 2012), Proteus vulgaris, Agrobacterium tumefaciens (Subramanian et al., 2006), Pseudomonas fluorescens (Cock, 2008), Pseudomonas aeruginosa (Salah et al., 2017), and Vibrio cholera (Mehrotra and rivastava, 2010). Although the antibacterial properties were demonstrated mostly in *in-vitro* studies, topical application of A. vera dressing on patients with non-healing, infected leg ulcers has also shown...
favorable responses except in cases of poorly controlled blood glucose (Banu et al., 2012). Albeit the antibacterial effect by A. vera was confirmed, Gram-negative microorganisms were less susceptible, which can be attributed to structural differences (Lawrence et al., 2009; Pellizzoni et al., 2012).

The A. vera extracts in which different solvents were used (acetone, ethanolic, hexane, chloroform, methanolic, and aqueous) have varying potency of antibacterial effects (Dahiya and Purkayastha, 2012; Irshad et al., 2011; Stanley et al., 2014). The aqueous extract, in particular, showed little or no antimicrobial activity (Dahiya and Purkayastha, 2012). As water is a polar solvent, the aqueous extract may only extract polar active constituents while the use of semi-polar solvents such as alcohols and ketones may induce a certain degree of polarity in non-polar compounds. Therefore, polar and a fraction of non-polar compounds may be found in these semi-polar solvents as opposed to the presence of only polar compounds in water (Abarca-Vargas et al., 2016).

The antibacterial action of A. vera may result from the synergism of the many active constituents present. Anthraquinones, aloin (Pellizzoni et al., 2012) and aloe-emodin, and chromones, aloeresin D and isoaloeresin D (Cock, 2008) are among the active constituents responsible for the antimicrobial effect. Acemannan, a major polysaccharide found in A. vera gel has also demonstrated such an effect (Salah et al., 2017). Meanwhile, pyrocatechol and cinnamic acid which are phenolic compounds, p-coumaric acid, and ascorbic acid have been suggested as active antibacterial compounds (Lawrence et al., 2009). A phytochemical screen also identified saponins, glycosides, alkaloids, and flavonoids (Yebpella et al., 2011) as the active compounds. The antiMRSA activity may however, be the action of tannins present in the extract (Dahiya and Purkayastha, 2012) (Figure 6).

Exposure to A. vera extract reduced the number and size of bacteria apart from shape distortion which may be the result of changes to cell wall structure. The phenolic compound, pyrocatechol is known to denature proteins and disrupt cell membrane (Lawrence et al., 2009). Modification of the physiological properties of the bacterium may also contribute to the antibacterial effect. This involves the diminished ability of the bacterium to consume tryptophan, lactose, and glucose, in addition to the loss of motility and the capability to produce acid and gas (Kargaran et al., 2017; Kouassi and Shelef, 1998).

![Figure 6. Some proposed antibacterial active compounds of A. vera on the Anthraquinones (Pellizzoni et al., 2012), Chromones (Cock, 2008), Carbohydrate (Salah et al., 2017) and Miscellaneous (Lawrence et al., 2009)](image-url)
CONCLUSION

There is promising preliminary evidence to support the use of A. vera that exhibits impressive functions in the areas of anti-diabetic, anti-inflammatory, wound healing, and antibacterial. The antidiabetic effect extends to the early stages of the disease with no presence of side effects at the dosages used. Although topical application for its anti-inflammatory effect may be delayed and minute, oral administration has shown a significant response. However, caution should be practiced as too high a dose has led to an initial inflammatory reaction. Favorable response to the gel has also been demonstrated to justify the use of A. vera in wound-healing and as an antibacterial agent, although it should only be used on simple, uncomplicated wounds. A number of different active constituents such as acemannan and aloin have been suggested for its effects and this may be interpreted as an interaction among different compounds rather than the action of a single compound. Currently, there is an increase in the development of processed formulations of A. vera to obtain a concentrate of the active compounds; however, the impact of these processing steps should be studied to prevent the degradation of the active compounds and a loss of the desired effect. Further study should be directed in this direction amidst the growing applications of A. vera in many aspects.

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