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 Aloaceae (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.

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 (Surjushe *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:

Figure . 3 Some purposed anti-diabetic active compounds of *A. vera* of sterol (Tanaka *et al.*, 2006) and carbohydrate (Huscini *et al.*, 2012)

dose 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 cycloartane 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.

Figure 4. Some purposed anti-inflammatory active compounds of *A. vera* of Carbohydrates (Esua and Rauwald, 2006), Anthraquinones (Park *et al.*, 2011; Robson *et al.*, 1982) and Chromones (Hutter *et al.*, 1996; Park *et al.*, 2011; Yagi *et al.*, 2002) and others (MC Robson *et al.*, 1982))

The effect is achieved by scavenging activities on 2,2-diphenyl-1-picrylhydrazyl (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-coumaroylaloetin) and aleresin B (feruloylaloetin) 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, veracylglycan B and veracylglycan 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-1 β (IL-1 β) (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-1 β 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 lipoxygenase (LOX) and cyclooxygenase (COX) (Das *et al.*, 2011; Vázquez *et al.*, 1996; Yagi *et al.*, 2003). A reduction in the levels of thromboxane A₂

synthase (Yagi *et al.*, 2003) 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 *Lafoesia 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 Ranjbary, 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; Hosseini-mehr *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 Veracylglycan 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 (Heggors *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

Figure 5. Some purported wound healing active compounds of *A. vera* of chromones (Wahedi *et al.*, 2017) and anthraquinone (Li *et al.*, 2017).

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 polylactico-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 Roriz* 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 satioum*. L. (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* (Pellizzoni *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 Agaoglu, 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 marescens*, *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

Figure 6. Some purported 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)

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).

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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