Revista Brasileira de Farmacognosia
https://doi.org/10.1007/s43450-022-00231-3

REVIEW

Aloe vera and Streptozotocin-Induced Diabetes Mellitus

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Received: 15 November 2021 / Accepted: 12 January 2022

Abstract

Diabetes mellitus is defined as prolonged hyperglycemia, which can harm the eyes, kidneys, and cardiovascular and neurological systems. Herbal agents and their derived supplements have been used for treatment of diabetes mellitus as a part of integrated complementary medicine for centuries. Numerous studies have considered *Aloe vera* (L.) Burm.f, Xanthorrhoeaceae, as an alternative medicine due to its abundant bioactive chemicals, such as alkaloids, anthraquinones, and enthrones, with therapeutical properties including antioxidant, anti-inflammatory, neuro-protective, and anti-diabetic effects. *Aloe vera* has received considerable attention in traditional medicine for the treatment of several diseases including diabetes mellitus. Numerous studies have investigated the effects of herbal agents on diabetes mellitus using a streptozotocin-induced diabetic model. Thereby, this article reviews the effects of *Aloe vera* prescription on streptozotocin-induced diabetes mellitus to provide a clear insight into the role of this medicinal plant in several biological functions, such as antioxidant, wound healing, anti-inflammatory, anti-hyperglycemic, and anti-hyperlipidemic in diabetic models.

Keywords Phytocomponents · Biological properties · Side effects · Pathophysiology · Biochemical parameters

Introduction

Herbal medicines have been applied in the treatment of diseases for millenia (Petrovska 2012; Hardy 2021). Approximately 25% of pharmaceutical drugs are produced from plants (Choudhury et al. 2018). Numerous studies have explored *Aloe vera* (L.) Burm.f., Xanthorrhoeaceae, as an alternative medicine due to its abundant bioactive chemicals, such as alkaloids, anthraquinones, saponins, and salicylic acid derivatives, *inter alia*, with significant therapeutic properties as antioxidant, anti-inflammatory, neuro-protective, and anti-diabetic natural agents (Langmead et al. 2004; Lanka 2018). Moreover, no chronic toxic effects have been reported for sub-chronic oral administration of *Aloe vera* (Hęś et al. 2019). Nowadays, this medicinal plant is frequently used in the field of cosmetology.

Diabetes mellitus (DM) is a metabolic disorder classified into different types based on primary causation. Type I diabetes mellitus (TIDM), also identified as insulin-dependent diabetes or juvenile-onset diabetes, is caused by inadequate secretion of insulin by the pancreas β-cell (Bilous et al. 2021; Hill-Briggs et al. 2021). Patients with T1DM are vulnerable to ketoacidosis and require regular insulin administration to keep the amount of glucose in their blood under control. It accounts for just 5–10% of the overall number of people with diabetes, mostly infants and adolescents. Type 2 diabetes, which affects mostly adults and develops when the body grows resistant to insulin or does not produce enough of it, is the most prevalent (Saikat et al. 2021) Figs. 1 and 2.

Streptozotocin (STZ, **1**) (2-deoxy-2-(3-methyl-3-nitrosourea)-1-D-glucopyranose) is a naturally occurring alkylating antineoplastic agent that is particularly toxic to the insulin-producing β-cell of the pancreas in mammals. It is a mixture of α- and β-stereoisomers with molecular weight of

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Published online: 10 March 2022

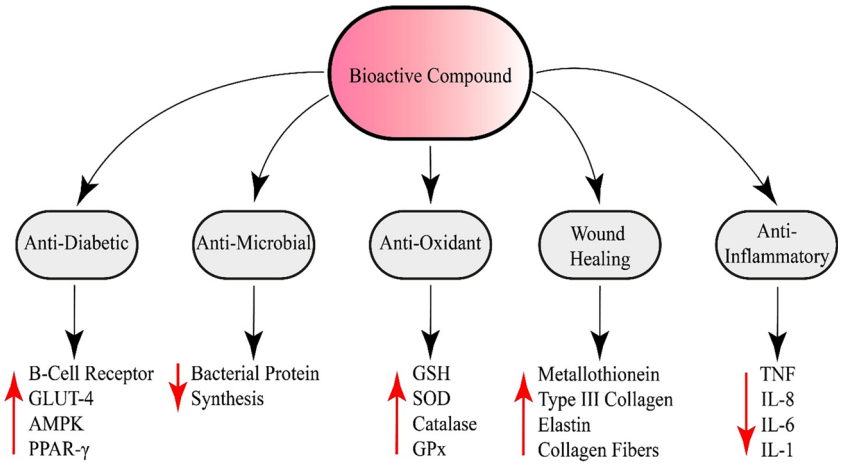


Fig. 1 Pharmacological effects of bioactive compounds from *Aloe vera*

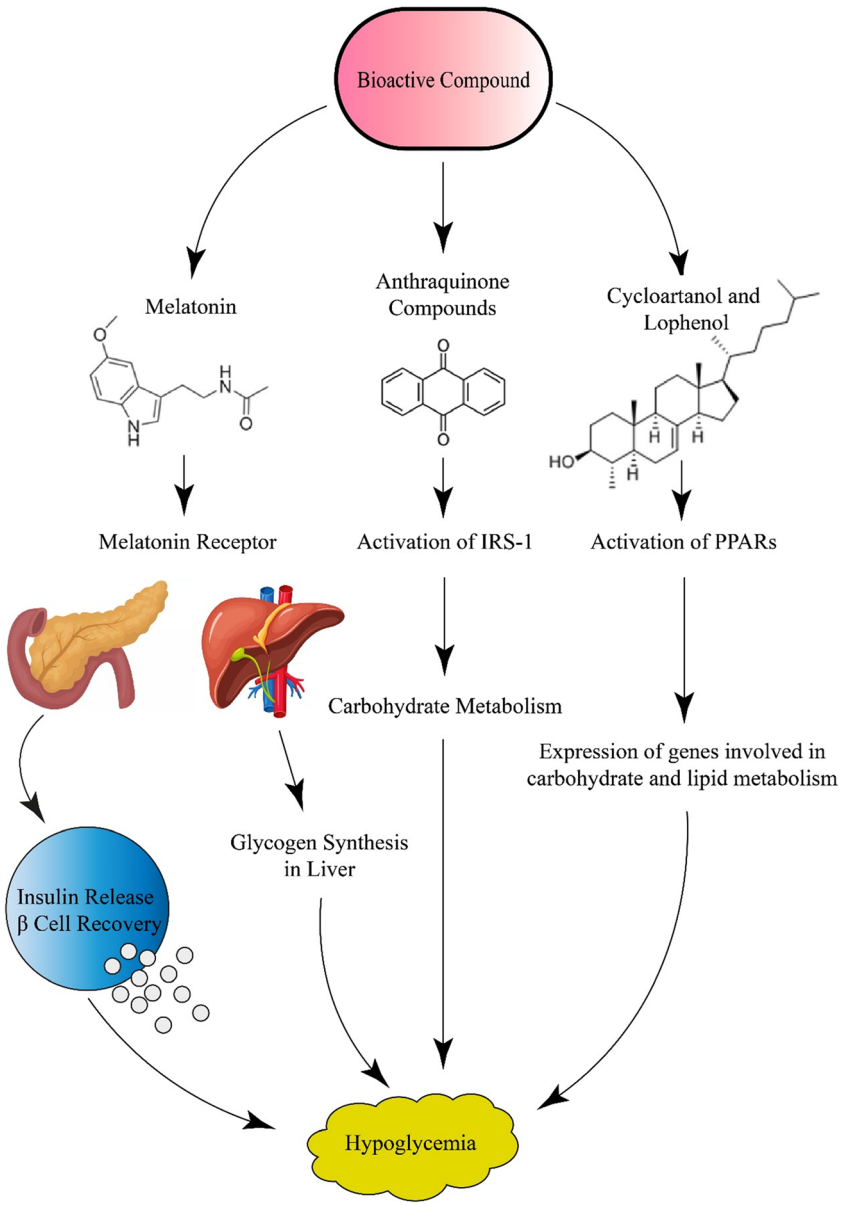
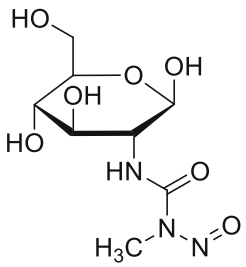


Fig. 2 Hypoglycemic effect of *Aloe vera*

265 g/mol (Eleazu et al. 2013). This cytotoxic glucose analogue is a diabetogenic compound produced by the soil bacterium *Streptomyces achromogenes* that exhibits broad spectrum of antibacterial properties (Ward et al. 2001). STZ functions as a DNA alkylating agent in both bacterial and mammalian cells (Eleazu et al. 2013). However, it is not used as the first line of treatment due to its genotoxic effects (Lenzen 2008) and β-cell-specific pancreatic cytotoxicity (Islam and du Loots, 2009). It is used in medical research to produce an animal model for hyperglycemia and Alzheimer's in a large dose, as well as type 2 diabetes or type 1 diabetes with multiple low doses (Eleazu et al. 2013). STZ disrupts β-cells of the pancreas through a dose-response pattern, leading to hyperinsulinemia, hyperglycemia, and a subsequent TIDM. It effects can be seen within 72 h after administration depending on the dose administered (Eleazu et al. 2013).



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STZ can block GLUT2 glucose transporter receptors due to its chemical structure analogue to glucose and *N*-acetyl glucosamine, β-D-(acetylamino)-2-deoxy-glucopyranose, and, therefore, it is accumulated preferentially in pancreatic β-cells. Furthermore, STZ is shown to have alkylating properties and can target pancreatic β-cells and cause immune response via releasing glutamic acid decarboxylase autoantigens, when it is prescribed in high doses (Karunanayake et al. 1976; Tjälve et al. 1976; Eleazu et al. 2013). Accordingly, the β-cells are disrupted, and hyperglycemia is induced leading to the inflammation of pancreatic islets (Böni-Schnetzler and Meier 2019).

Animal models can provide valuable information regarding the pathophysiology and treatment of diabetes. In this review study, the impact of *A. vera* administration on various aspects of STZ-induced diabetes in rat models is discussed.

Search Strategy

In this review, four main international electronic databases including PubMed, Scopus, Web of Science, and Google Scholar were comprehensively searched using the following keywords and their available MeSH terms: *Aloe vera*, *Aloe vera* gel, *Aloe vera* extract, streptozotocin, and diabetes mellitus. For this purpose, the most related *in vivo* and *in vitro* experiments evaluating the therapeutic effects of *A. vera* on the STZ-induced diabetes mellitus were reviewed with particular attention paid to the regarding mechanisms. Moreover, articles were included if they were published up to November 2021 with an available full text. On the other hand, non-English language studies were excluded from review.

Discussion

Aloe vera

Aloe vera (L.) Burm.f. (syn. *Aloe barbadensis* Mill), Xanthorrhoeaceae, is a pea green, perennial, xerophytic, succulent, stemless, or very short-stemmed shrub growing to 60–100 cm (24–39 inches) tall, spreading by offsets that frequently grows in wild in tropical, semi-tropical, and arid climates around the world (Surjushe et al. 2008). The plant has triangular, fleshy leaves with serrated edges, yellow tubular flowers, and fruits that contain numerous seeds. Each leaf is composed of three layers: a transparent inner gel with 99% water, and 1% of glucomannans, amino acids, lipids, sterols, and vitamins. The middle latex layer is a bitter yellow juice containing glycosides and anthraquinones. The thick outer layer, namely the cortex, comprises of 15 to 20 cells with a protective function, which synthesizes carbohydrates and proteins. The crust contains vascular bundles which transport substances including phloem and xylem (Surjushe et al. 2008). The plant has been known and used for centuries for its health, beauty, medicinal, and skin care properties since ancient times. Today, *A. vera* has been used for various purposes in dermatology and applied in the production of a variety of pharmaceuticals (Eshun and He 2004; He et al. 2005).

Processing

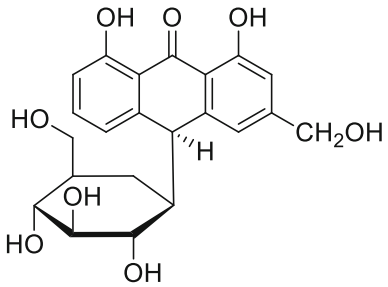
Depending on the nature of the product, *A. vera* is used in various formulations in the form of fruit juice, concentrate, or powder. *A. vera* is known as a constituent compound that maintains the ingredients in an active and unchanged manner (Eshun and He 2004). Leaves are usually soaked in an ethanol solution (commonly 15%) for 14 days in the dark. Then, the leaves are finely chopped and subjected to a mill press (Tan et al. 2013). *Aloe vera* juice is produced by grinding followed by filtering and stabilizing processes. However, *A. vera* processing steps depend on the industry and the final product quality. Traditionally, the unwanted parts of the leaf including base, upper side, sharp points, and thorns on the edge of the leaf are removed when producing juice, and the fillet is washed (Ramachandra and Rao 2008). Then, the pulper is added to the juice and the extraction is performed at low temperatures. In order to prevent the bioactivity loss of sensitive molecules, the extracted juice is stored at low temperatures (Ahlawat and Khatkar 2011). Furthermore, the juice can be

prepared by another method in which the base and tip of the leaf are removed, and the rest is ground to achieve a soup-like consistency. It is then exposed to the cellulase enzyme to release the cell components. Then, the material is passed through a series of coarse filters to remove impurities. Bioactive components in the juice obtained through this method are three times more concentrated than those in the juice prepared using the traditional method (Ramachandra and Rao 2008). Since temperature and pressure affect bioactive ingredients, *A. vera* juice is subjected to vacuum conditions (125 mm Hg) at a temperature below 50 °C for 4 min. To avoid loss of bioactivity, temperature and vacuum conditions must be controlled regularly. The juice is concentrated to the suitable consistency for a variety of food applications (Ramachandra and Rao 2008).

Aloe vera powder is obtained from dried leaves. For this purpose, leaf fillets should be washed, placed in a humid chamber at the desired temperature and relative humidity, and treated with hot air (Ahlawat and Khatkar 2011). It is shown that temperature-sensitive bioactive ingredients in *A. vera* could be adversely affected by traditional drying techniques. On the contrary, freeze-drying or lyophilization can maintain bioactivity of the ingredients, but it is not considered as a cost-effective process and, in addition, is a time-consuming method. However, novel microwave-assisted drying techniques are appropriate alternatives to conventional freeze-drying. Microwave heating followed by a conventional complete drying technique can provide an energy-efficient, inexpensive, and cost-effective method in this regard (Khan et al. 2016).

Bioactive Compounds

The potentially active ingredients in *A. vera* are presented in Table S1 (Shelton 1991; Reynolds and Dweck 1999). *Aloe vera* contains approximately 75 nutrients as well as 200 bioactive compounds including anthraquinones, vitamins, phytosterols, polysaccharides, carbohydrates, amino acids, and miscellaneous micronutrients such as minerals (Misir et al. 2014). The number of chemical compounds in different types of *A. vera* depends on factors such as growth conditions, harvest time, climate, leaf position on the stem, and *A. vera* species (Silva et al. 2010; Salehi et al. 2018; Hęś et al. 2019). *Aloe vera* contains high concentrations of anthraquinone compounds that have been used to treat burns, cathartics, purgatives, and wound healing for decades (Fox et al. 2017). Approximately 32 types of anthraquinones and their glycosidic derivatives have been identified in *A. vera*, of which aloin (**2**) (also known as barbaloin) is the most abundant bioactive compound (Kahramanoğlu et al. 2019). Other anthraquinones include aloe-emodin (**3**) and chrysophanol (**4**) (Misir et al. 2014). Numerous studies have shown that *A. vera*-isolated anthraquinones have anti-diabetic, anti-cancer, anti-microbial, hepatoprotective, and vasodilator activities (Hamman 2008; El-Shemy et al. 2010; Salah et al. 2017; Borges-Argáez et al. 2019; Kahramanoğlu et al. 2019). Anthraquinone seems to enhance the glucose tolerance and insulin sensibility via upregulation of insulin receptor substrates-1 (IRS-1) and phosphoinositide-3-kinase (PI3Ks) and modulation of metabolic-related genes (Mohammed et al. 2020). Like tetracycline, anthraquinones disrupt bacterial protein synthesis through blocking ribosomal sites-A and, consequently, exhibit antibacterial properties (Radha and Laxmipriya 2015). Furthermore, anthraquinones isolated from *A. vera* roots have shown antimalarial effects (Abdissa et al. 2017).



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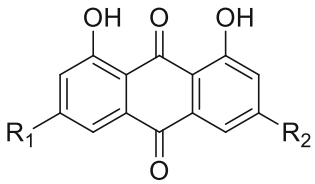
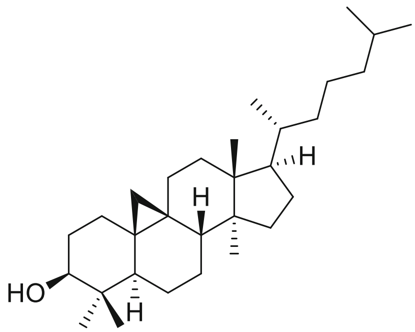


3 R_1=H; R_2=CH_2OH
4 R_1=CH_3; R_2=OH

Structurally, *A. vera* steroids are divided into two groups of compounds, lopherol and cycloartenol derived groups. To date, five steroids have been isolated from *A. vera* gel including cycloartanol (**5**), 24-methylene-cycloartanol, lophenol (**6**), 24-methyl-lophenol, and 24-ethyl-lophenol (Kahramanoğlu et al. 2019). It has been shown in mouse model investigations that oral administration of lophenol and cycloartanol can prevent metabolic disorders such as obesity and diabetes (Misawa et al. 2008; Misawa et al. 2012a; Misawa et al. 2012b; Nair et al. 2020). The *A. vera*-isolated sterols can dose-dependently activate peroxisome proliferator-activated receptors (PPAR) (Nomaguchi et al. 2011). These receptors play roles as transcription factors in regulating the expression of genes involved in carbohydrate and lipid metabolism (Chinetti et al. 2000; Bragt and Popeijus 2008). Sterols in *A. vera* have also been shown to stimulate collagen and hyaluronic acid production by skin fibroblasts and, consequently, improve skin health in humans (Tanaka et al. 2015; Tanaka et al. 2016).



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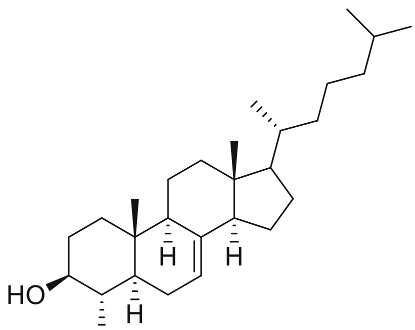

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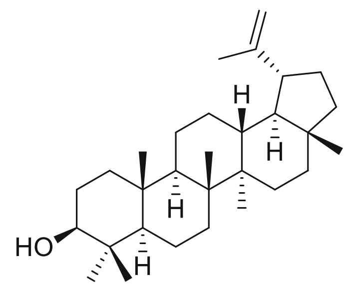
Saponins are another important ingredient in *A. vera* leaves. There is robust body of evidence for the benefits of saponins in biological activities such as antiviral and anti-diabetic properties (Choudhri et al. 2018). Saponins can increase cell membrane permeability, regulate nutrient uptake in the gut, and reduce protein digestibility. Saponins lower blood cholesterol by preventing the reabsorption of cholesterol in the gastrointestinal tract (Vinarova et al. 2015). These compounds also have anti-tumor and anti-mutagenic activities and can reduce the risk of human cancers by preventing the growth of cancer cells (Sampedro et al. 2004). In addition, saponins have been shown to protect the body against viruses and bacteria by boosting the immune system (Arunkumar and Muthuselvam 2009).

Triterpenes, which are important structural components of plant membranes whose free forms are used to stabilize phospholipid bilayers in plant cell membranes, are found in *A. vera* leaves (Saleem 2009). Lupeol (**7**), an *A. vera*-isolated pharmacologically active triterpenoid, is shown to have anti-microbial, antiprotozoal, nephroprotective, anti-diabetic, skin protective, and cardioprotective effects (Gallo and Sarachine 2009; Jäger et al. 2009; Gangadharan et al. 2019; Sharma et al. 2020). As an anti-inflammatory agent, lupeol acts primarily through the interleukin system, reducing the secretion of interleukin-4 in type 2 T-helper cells (Bani et al. 2006). In addition, lupeol has been shown to be an anti-carcinogenic compound acting through regulation of TNF-α production and angiogenesis in cancer cells (Kangsamaksin et al. 2017).



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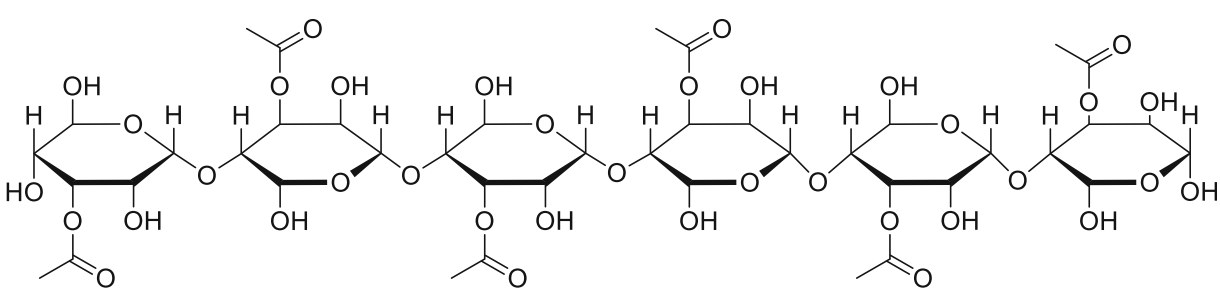
In addition, there are different forms of polysaccharides in *A. vera*, the content of which depends on the age of the plant (Femenia et al. 1999). The polysaccharides isolated from *A. vera* include mannan, galactan, arabinan, cellulose, xylan, pectic acid, and glucuronic acid. Furthermore, acemannan (**8**) is an acetylated polysaccharide derived from the *A. vera* which has anti-inflammatory, antibacterial, antiviral, anti-tumor, and wound healing properties, mainly mediating through immune system activation pathways (Sierra-García et al. 2014).



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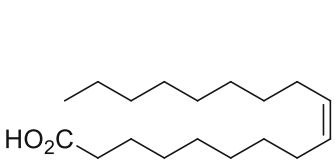
Fatty acids (FA) are bioactive compounds that form an important part of the *A. vera* chemical content. Studies show that oleic acid (omega-9 FA) (**9**) and α-linolenic acid (omega-3 FA) (**10**) are the most important fatty acids in different species of *A. vera* (Andrea et al. 2020). Omega-3 fatty acids are known as essential fatty acids since they are produced in

the body. Although not very efficient, linolenic acid can be converted into other important types of omega-3 fatty acids including eicosapentaenoic acid and docosahexaenoic acid. Omega-3 fatty acids appear to benefit the heart, immune system, and nervous system (Stark et al. 2008). Furthermore, omega-9 fatty acids only have one double bond in their structure, so that they are referred to as monounsaturated fatty acids (MUFA). Omega-9 fatty acids are not strictly "essential," as they can be produced in the body. However, omega-9 fatty acid-rich food items may have health benefits (Tutunchi et al. 2020). An experimental study showed that consuming high doses of MUFA promoted insulin sensitivity and diminished inflammation in mice. This study also discussed that humans consuming MUFA-dens diets had better inflammatory profile and more proper insulin sensitivity than those consuming diets high in saturated fat (Finucane et al. 2015). The rational intake of omega-3-enriched foods or supplements might lessen the complications in COVID-19 and might be a preventive measure (Baral et al. 2022).

Another bioactive compound identified in *A. vera* is melatonin (**11**) (Chen et al. 2003). It has been shown that there is approximately 52 μg of melatonin for every 100 g of dried *A. vera* powder (Barba et al. 2014). Melatonin is a naturally occurring antioxidant that is chemically referred to as *N*-acetyl methoxy-tryptamine. The pineal gland secretes melatonin into the bloodstream in mammals, especially during dark hours (Mohammadi et al. 2021). Melatonin can affect insulin secretion via activating the melatonin receptors (MT1 and MT2). It is shown that melatonin activates the phospholipase-C/IP3 pathway and, consequently mobilizes calcium from organelles and increases the secretion of insulin. Furthermore, animal investigations have shown that melatonin can induce production of insulin growth factor and promote tyrosine phosphorylation of insulin receptors in pancreatic β-cells, which results in more insulin secretion (Sharma et al. 2015). In addition, melatonin improves hyperglycemia through increase liver glycogen (Li et al. 2018). The consumption of foods containing melatonin can raise their physiologic concentrations in blood and, consequently, enhance antioxidant defenses, improve mood, and treat sleep disorders, depression, and anxiety (Gonçalves et al. 2021).



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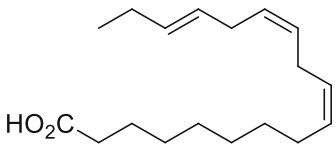

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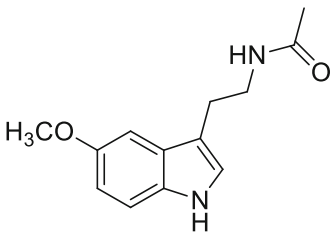

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Side Effects

Clinical trials have not reported any considerable adverse effects for *A. vera* (Foster et al. 2011), except for hypersensitivity and allergic responses (Shokraneh et al. 2016). It has been suggested that those who are allergic to plants of the Liliaceae family, garlic, onions, and tulips should avoid *A. vera* preparation or consumption (Ulbricht et al. 2007). Possible teratogenic and toxicological effects on the embryo or fetus have also been reported for the consumption of *A. vera* during pregnancy (Ulbricht et al. 2007). The consumption of *A. vera* latex for extended periods may cause watery diarrhea and consequently lead to electrolyte imbalance and hypokalemia. Thus, patients with a history of renal or cardiac problems are recommended to avoid *A. vera* latex consumption (Boudreau and Beland 2006). It seems that anthraquinone content of the products is responsible for most of allergic reactions related to *A. vera* (Bottenberg et al. 2007).

STZ-Induced Diabetes

To date, different types of diabetes have been specified, including type 1 diabetes mellitus (T1DM) caused by absolute insulin deficiency due to the β-cell destruction; type 2 diabetes mellitus (T2DM), which is related to target cells' insulin resistance; gestational diabetes mellitus (GDM) happening during pregnancy; and other types of diabetes caused by genetic abnormalities, specific drug consumption, or exocrine pancreatic diseases affecting the endocrine pancreas activities (American Diabetes Association 2014).

Type 1 diabetes mellitus can be induced *in vivo* using STZ (**1**) (Furman 2021). Usually, in rats or mice, a single dose in the range of 50 to 65 mg/kg is used most frequently (Goyal et al. 2016; Wang-Fischer and Garyantes 2018). Also in some studies, a single dose of nicotinamide (110 mg/kg) along with STZ (55 mg/kg) was used to induce DM in rats (Arigela et al. 2021), while the administration of a low dose (40 mg/kg) of STZ along with a high-fat diet can develop a metabolic

syndrome model (Suman et al. 2016; Ameer and Salman 2021). GLUT-2 is a plasma membrane glucose transporter through which STZ enters and accumulates in pancreatic β-cell (Tjälve et al. 1976; Damasceno et al. 2014). However, previous investigations have shown that GLUT-1-expressing islets are completely resistant to the toxic effects of STZ (Hosokawa et al. 2001). STZ causes DNA fragmentation and damage via DNA-alkylating properties of its methyl nitrosourea (Murata et al. 1999). Fragmented DNA activates poly (ADP-ribose) synthetase, which causes the depletion of cellular NAD^+ and ATP (Sandler and Swenne 1983). In this pathway, more substrates for xanthine oxidase are produced through dephosphorylation, which elevates hydrogen peroxide/hydroxyl radicals and leads to oxidative stress and ATP synthesis suppression (Szkudelski 2001). Moreover, mitochondrial function is impaired due to the *N*-methyl-*N*-nitrosourea presence, which can release nitric oxide and inhibit aconitase activity (Friederich et al. 2009). Although the precise mechanism of STZ cytotoxicity on pancreatic β-cell remains ambiguous, it could be partially attributed to apoptotic and necrotic cell deaths. Furthermore, the reactive oxygen species (ROS) and the reactive nitric oxide species (NO/RNS) production, as well as the induction of inflammatory responses, are assumed to play roles in STZ cytotoxicity (Van Dyke et al. 2008; Raza and John 2012). However, the validity of STZ-induced diabetes protocol seems to be doubtful due to the physiochemical characteristics and associated toxicities of STZ (Goyal et al. 2016). In addition, lack of appropriate dose use of STZ was associated with high mortality rates and animal suffering (Wang-Fischer and Garyantes 2018).

Aloe vera and STZ-Induced Diabetes

Wound Healing Effects

Both endogenous factors (pathophysiological) and exogenous factors (microorganisms) can adversely affect would healing (Bowler 2002). Wound healing comprises a set of coordinated interactions between cells in the dermis and the epidermis. Microbial colonization of wounds cannot be prevented, but endogenous bacteria, which can be potentially pathogenic in the wound environment, predominate in most cases (Banerjee et al. 2021).

Mucopolysaccharides in *A. vera* help moisture to penetrate the skin. *Aloe vera* stimulates fibroblasts, which consequently causes the production of collagen and elastin fibers, reducing wrinkles. It also softens the skin through its cohesive effect on superficial epidermal cells (West and Zhu 2003). *Aloe vera* also improves the wound healing process by having essential amino acids and several inorganic electrolytes such as iron, potassium, and magnesium (Alven et al. 2021). *Aloe vera* stimulates wound healing and prevents scars by releasing growth factors, stimulating cell production, and supporting the regeneration process in the deepest layers of the skin (Bozzi et al. 2007; Tarameshloo et al. 2012). *Aloe vera* gel consumption can be used in the treatment of stomach ulcers through a number of mechanisms (Suvitayavat et al. 2004). Mansour et al. (2014) reported that *A. vera* and myrrh gels could reduce ulcer size, erythema, and exudation. *Aloe vera* could heal skin ulcers, such as mouth ulcers, at a concentration of about 80% (Mansour et al. 2014).

Aloe vera is effective in the healing of STZ-induced diabetic ulcers. In 1989, Davis and Maro (1989) showed that *A. vera* improves wound healing via inhibiting inflammation and adjuvant-induced arthritis. To evaluate the anti-inflammatory activity of *A. vera*, the inhibition of polymorphonuclear leukocyte infiltration in STZ-induced diabetic mice was assessed (Davis and Maro 1989). In DM induced by STZ, newly synthesized collagen is degraded, or reduced biosynthesis diminishes the skin's collagen content. Chithra et al. (1998) showed that *A. vera* improved wound healing in a rat model. Inpanya et al. (2012) showed that the combination of fibroin and *A. vera* gel improved wound healing in STZ-induced diabetic rats through the proliferation and attachment of skin fibroblasts. Daburkar et al. (2014) reported that both oral and topical use of *A. vera* gel ethanolic extract improved wound ulcer healing through decreasing blood glucose, improving plasma insulin, and upturning DNA and glycosaminoglycans (GAGs). Another effect of *A. vera* is healing diabetic wounds caused by reduced oxidative stress. Hotkar et al. (2015) reported that the administration of a combination of *A. vera* and carbopol 974p (1%) in diabetic rats accelerated wound healing. Gharaboghaz et al. (2020) reported that *A. vera* gel and *Teucrium polium* hydroethanolic extract combination curtailed the inflammatory phase and elevated cell proliferation and collagen deposition. The cream formulations of *A. vera* extract can be used for diabetic wounds infected with *Staphylococcus aureus* (Prakoso et al. 2019).

Antioxidant Effects

The imbalance between radical-generating and radical scavenging systems causes oxidative stress, which is the underlying cause of diabetes and its associated complications. Antioxidant activity of *A. vera* secondary metabolites has been confirmed (Rajasekaran et al. 2005c). *Aloe vera* has beneficial effects in a dose-dependent manner for treating several diseases due to having antioxidant agents such as α-tocopherol, carotenoids, and ascorbic acid (Aburjai and Natsheh 2003; Eshun and He 2004; Radha and Laxmipriya 2015). It has been noted that hydrochloride-induced oxidative stress and cell death in kidney epithelial cells can be reduced a polysaccharide found in *A. vera* gel (Kang et al. 2014). In addition, antioxidant activity and total phenolic contents of ethanolic skin extract of *A. vera* are high (Moniruzzaman et al. 2012).

Parihar et al. (2004) reported that *A. vera* extract could inhibit the hippocampal and cortical cell degenerations caused by STZ-induced oxidative stress as demonstrated in both lipid peroxidation and protein carbonyl. Rajasekaran et al. (2005c) revealed that the ethanolic extract of *A. vera* could significantly lower fasting blood glucose, reactive substances of thiobarbituric acid, α-tocopherol, glutathione, insulin, and hydroperoxides in the plasma of diabetic rats. In another study by Rajasekaran et al. (2005a), the consumption of *A. vera* gel extract increased hemoglobin and lowered the levels of blood glucose and glycosylated hemoglobin. In addition, *A. vera* extract turned the elevated levels of lipid peroxidation and hydroperoxides to normal (Rajasekaran et al. 2005a). In 2008, results reported by Ozsoy et al. (2008) suggested that *A. vera* reduces the impact of oxidative damage in the skin and heart tissue due to DM through its antioxidant properties. *Aloe vera* at the doses of 150 and 300 mg/kg reduces lipid peroxidation by increasing superoxide dismutase activity and glutathione levels (Mohapatra et al. 2013). In STZ-induced diabetic rats, oxidative factor and catalase (CAT) level increased significantly, while superoxide dismutase (SOD) and glutathione decreased (Rajasekaran et al. 2005a). Jain et al. (2010) revealed that *A. vera* gel diminished the oxidative and cardiotoxicity effects of STZ in diabetic rats via its antioxidative property (Jain et al. 2010). *Aloe vera* was found to increase SOD, CAT, glutathione peroxidase (GPX), and glutathione reductase (GR) activity levels of a diabetic rat model (Mohapatra et al. 2013; Rajasekaran et al. 2005a). Also, some histological changes in the kidney and regenerative activity in the liver were noted in this model (Can et al. 2004; Ramachandraiahgari et al. 2012; Desrini and Kadek, 2018).

Glutathione levels and antioxidant enzymatic activities (SOD and CAT) were also found to increase in diabetic rats treated with *A. vera* extract (Christijanti et al. 2019a). DNA fragmentation and the intracellular concentration of 8-oxo-2′-deoxyguanosine were also increased significantly in diabetic patients (Shin et al. 2001; Rama Raju et al. 2012). *Aloe vera* extract significantly reduces the level of 8-oxo-dG and DNA fragmentation in STZ-induced diabetes (Christijanti et al. 2017; Christijanti et al. 2019b). Haritha et al. (2014) reported that oxidative stress was lowered by the oral administration of *A. vera* gel extract at a dose of 300 mg/kg body weight. Tabatabaei et al. (2017) suggested that *A. vera* gel can protect hippocampal neurons and improve behavioral deficits in diabetic rats due to its antioxidative and hypoglycemic properties.

Anti-lipizemia Effect

Hyperlipidemia has been found to be closely associated with nephropathy progression in diabetic patients (Loots et al. 2011; Chen and Tseng 2013). *Aloe vera* gel has been claimed to have an anti-hyperlipidemic effects, and it could be an effective treatment for patients who do not respond to nutritional measures (Mulay 2014). A study reported by Kumar et al. (2013) also showed that the combination of *A. vera* gel and *Lactobacillus rhamnosus* was an effective treatment for hypercholesterolemic rats and could lower the incidence of cardiovascular diseases. A study recently performed also confirmed that *A. vera* could diminish nephropathy progression through its effects on lipid alteration and renal oxidative stress (Arora et al. 2019). Also, *A. vera* juice supplementation affected GPx, SOD, and MDA in the kidneys of a diabetic rat model (Salehi et al. 2019). Rajasekaran et al. (2006) in a study on the impact of *A. vera* on STZ-induced diabetes reported significant antilipidemic effects.

Anti-diabetic Effect

DM is a chronic disease characterized by depletion of β-cells of the endocrine pancreas and/or reduced sensitivity to insulin in target cells (Balaji et al. 2019). Studies have shown that *A. vera* lowers the blood sugar level due to its increased metabolism, while leaving the normal blood lipid level and liver/kidney function intact (Hamman 2008; Huseini et al. 2012). Devaraj et al. (2013) delineated that *A. vera* impacts diabetes through reducing the body weight and enhancing insulin (Devaraj et al. 2013). In addition, *A. vera* gel could positively impact diabetic patients due to its antioxidant properties (Yongchaiyudha et al. 1996; Jain et al. 2010).

Aloe vera gel is an effective anti-hyperglycemic in STZ-induced diabetic models (Barmak et al. 2013; Fakharzadeh et al. 2014; Meena et al. 2015). In 2004, researchers reported that *A. vera* extract can improve diabetes through regulating the carbohydrate-metabolizing enzymes (Rajasekaran et al. 2004). Beppu et al. (2006) showed that *A. vera* has compounds that inhibit the methyl radical derived from STZ from destructing Langerhans islets. On the other hand, *A. vera* extract could normalize the activity of enzymes metabolizing carbohydrate (Kumar et al. 2011). In another study, daily administration of *A. vera* extract (300 mg/kg) daily could drop blood glucose levels in an STZ-induced diabetic rat model (Noor et al. 2017). In addition, oral administration of *A. vera* extract could improve renal and hepatic function in STZ-induced diabetic rats (Rajasekaran et al. 2007). Finally, *A. vera* has been suggested to inhibit the absorption of glucose in the jejunum of rats and protect pancreatic β-cells in them (Beppu et al. 2006).

Anti-inflammatory Effects

Aloe vera gel contains anthraquinones and chromones, which are the main reason for its anti-inflammatory effects, which are helpful in relieving joint pain. Oral ingestion of *A. vera* gel (2%) in aphthous stomatitis patients reduced the pain level and the size of the wound (Radha and

Laxmipriya 2015). The production of bradykinin (a mediator of inflammation) causes painful inflammation in the body, and *A. vera* can reduce inflammation due to an enzyme, bradykinase, which breaks down bradykinin; it can also be an effective treatment for inflammation caused by prostaglandin synthesis and leukocyte infiltration (Peng et al. 1991). The results of various studies indicated that *A. vera* could reduce inflammatory responses in STZ-induced diabetic model (Davis and Maro 1989; Noor et al. 2008; Inpanya et al. 2012; Hotkar et al. 2015; Prakoso et al. 2019; Gharaboghaz et al. 2020; Babu et al. 2021). Furthermore, *A. vera* could diminish *C*-reactive protein, polymorphonuclear leukocyte infiltration, interleukin-1β, TNF-α, and interleukin-6 in STZ-induced diabetic models (Davis and Maro 1989; Inpanya et al. 2012; Prakoso et al. 2019; Gharaboghaz et al. 2020; Babu et al. 2021).

Anti-microbial Effects

As mentioned before, *A. vera* contains anthraquinones and lectin, which have antiviral effects and prevent cytomegalovirus proliferation (Kahlon et al. 1991; Saoo et al. 1996). Emodin is effective against several infectious viruses such as herpes simplex virus (Sydiskis et al. 1991; Saoo et al. 1996). A study demonstrated antifungal properties of *A. vera*, as it gradually inhibited the growth of *Malassezia furfur* and *Candida albicans* (Rezazadeh et al. 2016). Also, *A. vera* was found to decrease the growth of *Rhizoctonia solani* and *Colletotrichum coccodes* (De Rodrıguez et al. 2005). *Aloe vera* inhibits food spoilage through reducing the growth of various microorganisms (Eshun and He 2004).

Studies show that alcoholic extract of *A. vera* not only reduces inflammatory responses, but also promotes wound healing in patients infected with methicillin-resistant *Staphylococcus aureus* (Prakoso et al. 2019). *Aloe vera* gel contains immunomodulatory polysaccharides, and the administration of process *A. vera* gel (PAG) in normal mice could significantly reduce the growth of *Candida albicans*. However, it did not increase ovalbumin-specific cytotoxic T lymphocyte generation, suggesting the immunomodulatory activity of PAG (Im et al. 2010).

Other Effects

Diabetes causes retinopathy through impairing glucose metabolism, leading to dysfunction in the neural retina, and damaging nonvascular cells, leading to the loss of ganglion cells, horizontal cells, amacrine cells, and photoreceptors (Cheung and Wong 2008). Prolonged treatment with *A. vera* gel could be used in the treatment of diabetic retina (Saberi and Gholami 2012; Gholami and Saberi 2015).

Administration of *A. vera* gel in diabetic rats could reduce hyperglycemia and modulating nerve growth factor expression and P75 and TrkA receptors (Mahabady et al. 2021). In addition, it inhibited hippocampal and cortical cell degeneration in diabetic mice (Parihar et al. 2004). Induction of diabetes by STZ also affects kidney function. *Aloe vera* gel extract could promote histological and biochemical parameters and lower serum urea, oxidative stress, and creatinine levels in STZ-induced diabetic rats (Bolkent et al. 2004; Rajasekaran et al. 2004; Rajasekaran et al. 2005b; Ramachandraiahgari et al. 2012; Arora et al. 2019).

Perspectives and Future Directions

Results assembled in this review showed that *Aloe vera* has antioxidant, anti-microbial, immune-boosting, anti-carcinogenic, hypoglycemic, anti-hyperlipidemic, wound healing, and anti-diabetic properties. However, *A. vera* is plant product nowadays frequently used in the field of cosmetology. Though there are various indications for its use, further pharmacological studies and controlled clinical trials are needed to determine its real efficacy and health benefits, with special attention to its probable side effects for humans.

Conclusion

Aloe vera was effective in the healing of STZ-induced diabetic ulcers through decreasing blood glucose, improving plasma insulin, and reducing oxidative stress and can stimulate the production of collagen and elastin fibers. Furthermore, *A. vera* can inhibit oxidative stress through increasing activities of antioxidant enzymes and glutathione levels. *Aloe vera* reduces inflammatory responses in STZ-induced diabetic model by suppressing the production of inflammatory mediators. *Aloe vera* acts as an antioxidant, anti-hyperlipidemic, anti-diabetic, and anti-microbial agent in toxic responses induced by STZ. In conclusion, *A. vera* is an easy-to-use and a cost-effective local drug delivery system with limited adverse effects in animal models.

Author Contribution AGB and MRA conceived the concepts and searched the electronic databases, separately. MRA and FH cooperated in the assessment of papers' relevancy and data extraction. AGB, SM, and MRA cooperated in the interpretation of the findings. All authors actively participated in the literary and scientific editing of the manuscript to provide the article final draft.

Declarations

Conflict of Interest The authors declare no competing interests.

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