

Aloe vera as an antidiabetic and wound healing agent for diabetic patients

Abstract

Diabetes is a metabolic disorder that has been prevalent among the population and has been reported to rise worldwide at an alarming rate. Diabetes puts a person through a lot of risk to his or her life because of the late complications developed with time if this is not cured. It affects some metabolic processes related to lipid and glucose such that they further can lead to liver and kidney disorders. An evergreen, herbal, plant which is called aloe vera is a health remedy and in large demand these days because of its ability to cure many diseases. The present study is designed for the purpose to examine and check the efficacy of aloe vera to cure diabetes, reducing the risk of complications and also reducing the chance of liver and kidney dysfunction. The glucose level in the patient and lipid profile status is also an important part of studying effectiveness. It is also known that a therapeutic drug already is responsible to cure the disease but as it is a chemical compound, so it is important to note the side effects of the same on the patient's health, no matter how effective the drug is. To reduce this risk, the therapeutic drug in low quantity is combined with aloe vera extract to enhance effectiveness and lower down the side effects in patients. The aloe vera extract has also shown benefit in increasing the rate of the wound healing process in diabetic patients because of the problem of lack in their cell's ability to recover and heal the wound. Clinical trials have also become the evidence of proving the fact about the anti-diabetic nature of aloe vera so that in the future all the chemical drugs may get replaced by herbal plant active components to reduce health problems in most people.

Keywords: Aloe vera gel, Antidiabetic, Antioxidant, Wound healing, Rats, Insulin

1. Introduction

Various plant extracts have been used over the years to treat a wide range of diseases out of which aloe vera is the most common traditional remedy for disease treatment all over the world. Aloe vera which is also known as *Aloe barbadensis miller* is considered as an herbal plant that belongs to the Liliaceae family. Liliaceae family originated in South Africa [1]. This is one of the most popular remedial plants that is presently used for a variety of research areas. It is cultivated in large quantities due to huge demand in the market. It is a succulent cactus-like plant so it can grow in very hot and dry environmental conditions [2]. It is a xerophyte with a short stem that can grow 60-100cm in height. The leaves of this herbal plant are broad, fleshy, wide, triangular, and thorny that is made up of two parts- an inner pulp (colorless sticky gel) and an outer skin (green covering) [3]. Its leaves have the potential to retain much water so; this herbal plant can survive in drought conditions where other plants cannot survive [4].

Aloe vera consists of more than 70 active compounds comprising of phenolic compounds, important vitamins, enzymes, polysaccharides, and many organic acids [5]. It is well known that many polysaccharides present in inner pulp of aloe vera have medicinal properties such as anti-inflammatory, anti-bacterial, antioxidant, antidiabetic, healing, and anti-aging nature which are very helpful for people (Figure 1). The gel is widely used for various medical, cosmetic, and various nutraceutical applications. Studies have shown that antioxidant nature is present in the outer skin. It also has applications in treating various skins. Diabetes is one of the leading diseases which is found among the population these days. It is a chronic disorder detected via elevated level of glucose in the blood due to impaired insulin action or insulin production or both [7]. It is featured by hyperglycemia along with biochemical alterations in the metabolism processes of lipids and glucose [8]. These features are thought to be responsible for destroying the cell membranes which further elevates the production of Reactive Oxygen Species (ROS) which further decline the antioxidative defense mechanism noticed in diabetic patients which leads to the occurrence of other problems such as blindness, renal failures [9].

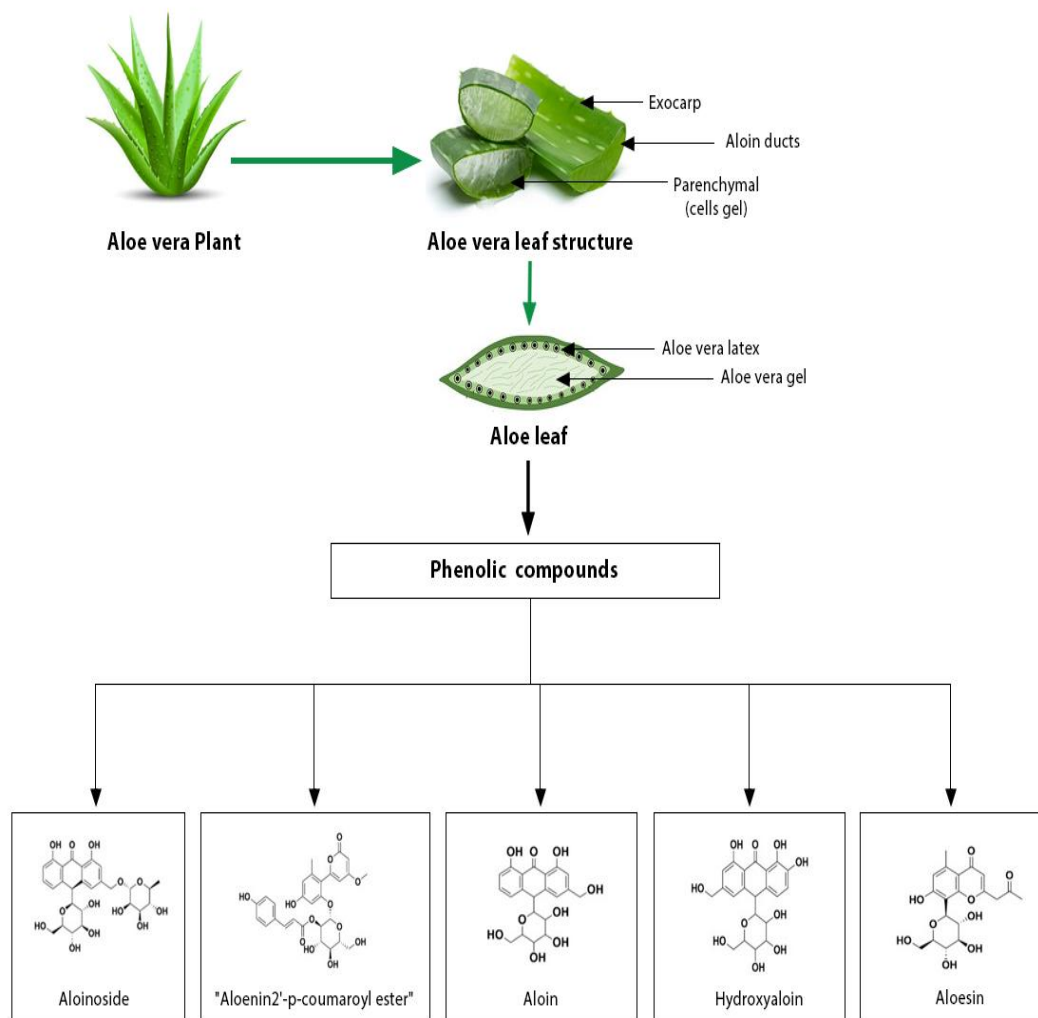


Figure 1: Aloe vera plant and the structure of its main phenolic components with medicinal properties.

To reduce this risk, control over blood glucose and lipid level is necessary. In recent years, diabetes at a younger age has become the most ruinous having a great influence on the people's wealth and wellbeing. Generally, the management procedure for controlling diabetes consists of 2 approaches- non-pharmacological (diet, surgery, physical activities) and pharmacological means (insulin or oral hypoglycemic agents) [10].

2. Antidiabetic nature and effectiveness of Aloe vera to control diabetes

2.1 Aloe vera - a cure to diabetes

The method of consuming insulin or oral medicines is expensive and also causes health risks and complications. For many years, the World Health Organization has been reinforcing traditional medicine programs by making people understand the value of medicinal plants for their health [10]. These days, a wide range of modern drugs are produced by using nature. Also, about 25% of prescriptions consist of active components present in the plants[11].

Aloe vera contains various bioactive components, enzymes, minerals, and vitamins due to which aloe vera has been reported to lower sugar levels in the blood of diabetic patients[12]. The cooperation of conditions such as cuts, burns, etc. Aloe vera is also beneficial to produce secondary metabolites in abundances such as anthraquinone and aromatic quinines [6]. Body tissues with respect to insulin has been improved by aloe vera extract that makes insulin more effective and makes aloe vera to be a natural remedy for the wide-scale treatment of all diabetic conditions[7].

With the help of an experiment different assays were performed to check the anti-diabetic activity of the aloe vera extract. It has been observed by using the experimental assays that the ethanolic mixture of gel pulp helps to inhibit the formation of unwanted free radical by many biochemical processes in order to reduce glycosylation of the enzymes[1]. In that case, when blood sugar level increases, in different organs accumulation of fructose takes place. Some products and accumulated fructose made by the process of addition of oxygen can combine with proteins to produce AGE (Advanced Glycation End-products). Protein glycosylation can take place in arginine by reactive carbonyls which further form AGE[3]. Therefore, in this way, we can prevent the complication of diabetes by inhibiting the glycation of proteins and oxidative products. The result shows the formation of arginine and methylglyoxal gets inhibited because of methanol and aloe vera mixture, thus they also restrict the glycation process of protein in Bovine Serum Albumin or glucose solution and acts as an antidiabetic agent.

2.2 Effect of Aloe vera extract on glucose level of a diabetic patient

In an experiment, the effect of aloe vera extract on glucose level has been studied which used albino rats were injected with alloxan to induce diabetes in them [10]. Table 1 represents mean blood glucose levels between different groups. A cytotoxic agent such as alloxan is having an immediate action on beta cells present in the pancreas that are responsible for

producing insulin and thus it causes diabetes mellitus in animal models sharing common characteristics with that of a human body.

Table 1: Mean blood glucose levels between different groups [10]

Group	Day 1	1st week	2nd week	3rd week	4th week	5th week
I	255±10.41	251±9.80	251.3±8.89	250.1±7.71	251.5±7.73	251.5±7.69
II	251±8.9	161.8±10.1	151.6±11.1	130±8.7	109±7.7	94±6.8
III	250±6.83	237.8±6.34	230.8±7.04	229.8±6.55	222±8.14	222.5±9.17
IV	257±9.9	210.5±7.05	170.5±4.8	143.6±2.8	120±4.2	106±3.8
V	258±9.6	176.8±2.3	159±2.8	130±2.9	91±2.5	76.6±1.8

After that five groups of rats were made from which different substitutes were given for 5 weeks. Group 1 receiving distilled water (control), Group 2 received 50mg/kg metformin (standard antidiabetic drug), aloe vera leaf extract was injected in different doses of 100, 200, 400(mg/kg) into last 3 groups of rats in order respectively. After 5 weeks, it was reported that control (Group 1) developed hyperglycemia while aloe vera extract decreased the effect of increased blood sugar level of alloxan in Group four and Group five (with high dose) while Group 3 did not show a significant reduction in blood glucose level so it is comparable.

2.3 Effect of Aloe vera extract on lipids profile status of a diabetic patient

In an experiment, the beneficial effect of Aloe vera extract on the lipid profile status of diabetic rats induced by the use of Streptozotocin has been studied. STZ induced diabetes by decrease in the number of beta cells very quickly that results in the decreased amount of insulin release [13]. The researchers used rats in four groups with 6 rats in each group- Group A were control rats (without diabetes), Group B were diabetic control rats (induced by STZ), Group C included diabetic rats which were provided with extract of aloe vera gel (300mg/kg) for

continuously 21 days, and lastly, Group D included diabetic rats which were provided with glibenclamide (600microgram/kg), a standard drug in aqueous solution for a period of 21 days.

After 21days, rats were killed and the plasma from blood was separated and the kidney and liver were to Group 1. Standard drug metformin showed a highly significant reduction in blood glucose level in Group 2 which is comparable to high-dose aloe vera containing rats [10]. So, the hyperglycemic effect of Aloe vera extract was because of the efficient metabolism rate of glucose and thus glucose level has been proved to be managed by Aloe vera extract showing equal effectiveness as the standard drug [13]. Taken out and homogenized, the total lipids were extracted from tissue homogenate.

Further, the cholesterol content, triglycerides, free fatty acids, total phospholipid content, and fatty acid composition analysis were done. As a result, the level of triglycerides, cholesterol, phospholipids, free fatty acids, low density lipoproteins, and very low-density lipoproteins were elevated by a significant amount while the level of HDL-cholesterol was lowered in rats having diabetes compared to control rats.

Table 2: Showing blood glucose and plasma insulin levels in control and experimental groups of rats [14]

Group of rats	Blood glucose (mg/dL)	Plasma insulin (μU/mL)
Control (Group A)	85.81 \pm 5.20	15.86 \pm 1.38
Diabetic		
Control (Group B)	332.27 \pm 20.80	5.12 \pm 0.68
+300 mg/kg Aloe vera (Group C)	96.80 \pm 5.30	14.12 \pm 1.48
+600 μ g/kg Glibenclamide (Group D)	118.46 \pm 6.56	12.52 \pm 0.69

While the rats of Group C and D showed effects similar to control rats. Even the constituents of fatty acid increased in amount in the case of Group B rats but remained normal in the case of Group C and group D rats with Aloe vera extract and standard drug respectively (Table 2) [14]. The cure of hyperglycemic rats using Aloe vera extract leads to some beta-cells getting stimulated and thus giving rise to the state of production of insulin. So, in this manner, the aloe vera extract stimulates insulin secretion from beta cells. Normalization of saturated fatty acid composition with aloe vera extract was due to a decline in the amount of plasma lipids which results as a consequence of extract that reduces the production of fatty acids

(Table 3) [14]. The antioxidants in aloe vera for example- saponins and phenolic compounds could be responsible for reducing hyperlipidemia in diabetes.

Table 3: Showing concentrations of Plasma cholesterol, triglycerides, phospholipids, free fatty acids and lipoproteins in control and experimental groups of rats [14]

	Control (Group A)	Diabetic Control (Group B)	Diabetic + 300 mg/kg Aloe vera (Group C)	Diabetic + 600 µg/kg Glibenclamide (Group D)
Cholesterol (mg/dL)	92.6 ± 5.7	228.3 ± 15.1	98.3 ± 8.5	106.2 ± 7.0
Triglycerides (mg/dL)	73.5 ± 5.2	229.3 ± 16.1	79.2 ± 5.2	83.4 ± 5.8
Phospholipids (mg/dL)	80.5 ± 5.7	163.8 ± 11.1	85.7 ± 5.8	88.8 ± 6.7
Free fatty acids (mg/dL)	58.3 ± 3.6	145.2 ± 10.5	64.7 ± 4.1	66.1 ± 4.6
VLDL-C (mg/dL)	19.3 ± 1.2	58.6 ± 4.5	21.8 ± 1.6	24.7 ± 1.6
LDL-C (mg/dL)	45.1 ± 2.9	139.2 ± 10.3	48.5 ± 3.1	53.4 ± 3.4
HDL-C (mg/dL)	26.5 ± 1.7	21.6 ± 1.6	23.4 ± 1.5	22.03 ± 1.42

2.4 Effectiveness of Aloe vera extract in combination with a therapeutic drug (herb-drug interaction)

Herb-drug interaction is the type of interaction that occurs between herbal medicine and conventional drugs. In a study, the herb-drug interaction of aloe vera gel (herbal ingredient) with glimepiride (the antidiabetic drug) has been demonstrated because both are known to cure diabetes. In the experiment, the action and effectiveness of Aloe vera gel and glimepiride are observed by using Streptozotocin as an agent to induce diabetes in rats [15]. The different doses of Aloe vera gel and glimepiride were individually injected inside the rats (Also using one

group of rats to control that is given 0.1M NaOH). Apart from this, lower and higher doses of glimepiride were given in combination with Aloe vera gel extract with constant quantity (400mg/kg) to the respective 2 other groups. The blood samples of each group were taken out at different hours (0,1,2,3,4,6,8,10,12,16,24) on the first day and the 8th day of performing the experiment. This is done for the detection of serum glucose levels and their percentage reduction. By the use of the chemiluminescence immunoassay method, the change in insulin level was observed.

The results interpreted that out of all the groups, the rats of the group which was given a higher dose of glimepiride in combination with Aloe vera gel (400mg/kg) had the highest percentage reduction in serum glucose level, also from chemiluminescence results the same group with a higher dose of glimepiride combined with Aloe vera gel (400mg/kg) showed maximum increase in serum insulin level. Pancreatic endocrine cells are reported to have the ability to proliferate after diabetes induction. It is also known that glimepiride affects the beta cells and also it increases the secretion of insulin [16]. Therefore, serum insulin level increases then one's treatment with glimepiride prove that the extra increase in insulin is due to Aloe vera only. It also indicates that combining Aloe vera and glimepiride could help to reduce the dose of glimepiride which may minimize adverse effects caused by therapeutic drugs alone.

3. Benefits of aloe vera for promoting wound healing process in case of Diabetic patients

3.1 Unhealed wounds in diabetes

Skin is a protective and flexible outer tissue covering the body. A dangerous condition caused by diabetes which is widely known in patients is delayed wound healing and the occurrence of increasing sensitivity in patients for chronic non-healing wounds. It is related to steady inflammatory status, an increase in pro-inflammatory cytokines, and poor expression of growth factors. Healing of wounds occurs in three different steps: - Thrombosis and inflammation, tissue proliferation, and formation, the last one is tissue retrieval. In this disease, hyperglycemia slows down the healing of wounds because of rise in the free radicals in the patient's body causing oxidative imbalance and lowering down of biosynthetic metabolism and expression of growth factors of insulin [17].

Growth factors are the major element of the study because factors such as fibroblast growth factor, epidermal growth factor can cure unhealed wounds very quickly [18]. The compound that is insulin is found to be responsible for inhibition of the components causing inflammation in people [19]. The insulin-like growth factors or IGFs stimulate mitogenic fibroblasts and angiogenesis (a stage of formation of blood vessels involved as a phase for wound healing). Also, they are responsible for an increase in the width of both the layers of aloe vera leaf: outermost layer that is epidermis and middle layer that is dermis. The hypoglycemic effect is correlated with some biochemical and anti-inflammatory reactions and the small effort to inhibit inflammation can help to cure this disease[20]. Medicinal plants such as Aloe vera are the safe agents to be used for healing wounds, especially for diabetic conditions.

3.2 Effectiveness of Aloe vera for wound healing

The mucilage of the Aloe vera plant has been proved to be effective for efficient recovery of all types of wounds. This herbal plant is known to have antioxidant and anti-inflammatory effects because of some glycoproteins and polysaccharides present in the extract and pulp of this plant. Aloe vera have also been compared with conventional creams for recovery from injury and one of them is sulfadiazine cream but the patient's heat-burns those are dressed with aloe vera gel have found to give early recovery than the cream [21]. The other scientists used Aloe vera extract and Teucrium polium extract (also an herbal plant). After the induction of diabetes, round wounds were found to be formed in animals of all the 6 groups created by them. Two types of ointments were prepared - One was Teucrium polium extract ointment (TPEO) and the other was Aloe vera gel ointment (AVGO). For the 14 days, all different groups were given these which are mentioned in the table 4.

Table 4: Aloe vera extract and Teucrium polium extract treatment for diabetes

S.No.	Group no.	Received
1.	1	Mupirocin (Standard drug)
2.	2	5% TPEO
3.	3	10% TPEO

4.	4	5% AVGO
5.	5	10% AVGO
6.	6	5% TPEO + 5% AVGO

By the use of different analyses and assay techniques, the wound recovery results have been found which showed that the mean wound area for a mixture of AVGO + TPEO was much less as compared with a standard drug for the 1st control group. The mean wound area for mupirocin, 5% TPEO, 5% AVGO, 10% TPEO, 10% AVGO, and mix of AVGO + TPEO are found to be 20.2, 17.3, 18.3, 13.2, 14.1, 10.2 mm square respectively. This proved that the TPEO+AVGO mixture is more effective to decrease wound area in comparison to others. Also, serum analysis proved that the level of IL-1 β and TNF- α reduced in TPEO and AVGO treated groups in comparison to mupirocin. The TPEO +AVGO treated groups had a remarkable rise in GLUT-1, VEGF and IGF-1 positive cells. TPEO and AVGO are antioxidants in nature and have synergistic interaction. Therefore, it helps to boost antioxidant and anti-inflammatory characteristics. In AVGO, TPEO treated cells the healing process is improved because of GLUT-1 that is responsible for cell viability.

A condition of hypercortisolemia (large amount of cortisol in the body) in the case of diabetes is responsible to inhibit and cease the IGF-1 machinery that leads to unhealed wounds [22]. Whereas diabetes leads to a change in GLUT-1 expression, so the healing process slows down. IGF-1 promotes fibroblasts proliferation and migration to the wound area. Aloe vera gel consists of beta-sitosterol and acemannan that are too responsible for promoting angiogenesis [23]. The synthesis of collagen has been known to initiate in the area of wound injury because of the presence of mannose-6-phosphate in the gel extract [24]. Therefore, it can be said that Aloe vera gel is a very important herb to be beneficially used for the wound healing process either individually or with a combination but the clinical effectiveness has been enhanced for healing especially in the case of diabetes.

4. Clinical effectiveness of aloe vera extract

A clinical trial was carried out by a group of researchers in which different age groups women were selected that had diabetes. Aloe vera juice was prepared by adding preservatives and was given to the women with diabetes for 42 days. While on the other hand control groups

received no treatment with aloe vera gel but were given a placebo. Blood samples were taken from those women every week and triglyceride and cholesterol levels were also estimated. As a result, control groups were not found to have any significant change in blood glucose, cholesterol, or triglyceride levels. But on the other hand, the groups which were provided with the juice of aloe vera expressed a significant decrease in blood glucose level and triglycerides from the first week itself up to the completion of the experiment. But cholesterol amounts of aloe vera treated groups have not shown any change. Because of already present diabetic complication (which is ketosis) a single patient out of all other 40 patients was eliminated from the trial experiment but all other patients showed such significant decrease in sugar and lipid content that proved that aloe vera is an antidiabetic agent that cures disease through its active ingredients including some polysaccharides and glycoproteins present in its gel and extract [25]. Apart from this, at a large scale for the cure some jellies made by the combination of aloe vera and honey can be employed as a future approach because of hypoglycemic properties of both [7].

5. Conclusion

The present study concluded that the Aloe vera plant is such an amazing medical health remedy that exhibits many pharmacological activities including antioxidant, antidiabetic, hypoglycemic, and with a foremost role in wound healing. The aloe vera inhibits the glycation pathway for reducing glucose levels in the blood. The antioxidants such as phenolic compounds and saponins inside extract of aloe vera gel helped in the reduction of hyperlipidemia. The herb-drug combination was helpful to reduce the content of chemical drugs because of limitations but increasing effectiveness towards disease control in a better way. The mixed operation of TPEO and AVGO produced a more genuine wound healing effect in diabetes because of the enhanced proliferation of tissues. Thus, it is a promising medicinal agent which can be replaced by chemical drugs in the coming years.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and

country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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