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REVIEW ARTICLE

Antidiabetic Potential of *Aloe barbadensis* Miller

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ABSTRACT

Background: Diabetes mellitus (DM) is a metabolic disease of the endocrine system, characterized by chronic hyperglycemia, resulting either from insulin resistance or defective insulin production due to dysfunction of pancreatic β-cells. Approximately 80% of diabetic patients live in developing and underdeveloped countries. Pakistan is ranked on 7th position regarding the prevalence of DM. In developed nations, DM is the 4th leading reason for death. Several conventional and traditional methods i.e., allopathic medicines, herbal and medical plants have being used to treat DM and its complications for several decades. Diet-based approaches are considered safe, economical, and sustainable by individuals suffering from various health disorders.

Objectives: The current review has been generated to highlight and compare the utilization of various conventional and traditional methods i.e., allopathic medicines, herbal and medical plants as an alternative source to treat DM and its complications.

Methodology: Existing relevant literature (both research / review articles) published in last many years was looked over numerous sources like Google Scholar, Medline, PubMed, Research Gate, Science Direct, Scopus and Web of Science.

Results: Complementary and Alternative Medicine (CAM) is considered a holistic approach for the treatment of Diabetes that combines the use of dietary supplements with herbs. Worldwide, approximately 30% of DM patients and 50% in Pakistan are using CAM. *Aloe vera* (AV) is known as a "miracle plant" and extensively used in commercial products. AV contains numerous bioactive components such as vitamins, saponins, salicylic acid, minerals, lignin, enzymes, anthraquinones, and amino acids which are responsible for health-promoting activities in the body. Isolated bioactive components have extensively been employed in nutraceuticals and pharmaceutical items and claimed to have antioxidant potential. Phytosterol compounds such as phenol and cycloartenol have claimed to downregulate the synthesis of fatty acid and increases the oxidation in the liver that in results decrease in lipid deposition.

Conclusion: From the above analysis, it is therefore concluded that the utilization of herbaceous plants as medicine can be encouraged to treat and prevent numerous health problems.

Keywords	*Address of Correspondence	Article info.
Aloe vera, Diabetes, Gel, Herbal medicine, Leaf, Latex.	*makkia.saleem@yahoo.com*	*Received: June 08, 2020* *Accepted: March 12, 2021*

Cite this article *Saleem M, Sharif MK, Saleem R. Antidiabetic Potential of Aloe barbadensis Miller. RADS J Biol Res Appl Sci. 2021; 12(1):81-89.*

INTRODUCTION

The therapeutic claim of *Aloe vera* covers a wide range of conditions. The first case for topical use of AV was reported in 1935 by Collins and Collins[1]. Extract of AV's leaf was claimed to have quick relief from the burning sensation and itching due to dermatitis followed by skin regeneration. Several successive reports have explored the topical use of AV's gel in dermatological problems including wound healing, dermatitis, oral mucositis, and psoriasis. The oral intake of AV leaf, gel, and latex are promoted as a remedy with chemotherapy of ameliorating disorders such as Diabetes mellitus (DM), constipation, and infection, a certain type of cancer, colitis, and inflammation[2]. Health-promoting claims encouraged the use of AV in the management of various diseases, such as varicose veins,

sclerosis, hepatitis, hemorrhoids, glaucoma, depression, and alopecia[3].

Utilization of *Aloe Vera* for Treating Diabetes Mellitus

In various countries, AV is used as traditional therapy for preventing and treating DM for decades, such as the Arabian Peninsula[4] and Latin America[5]. The number of evidences both in animals and humans subjects suggested that AV has the potential to improve characteristic disorders of diabetes such as chronic hyperglycemia and can disturb lipid concentration that is the chief cause of cardiovascular, hepatic, and renal complications. However, researches covering human's subjects provided pilot data that support the useful effects of AV in DM and other related diseases. The anti-diabetic potential was confirmed through controlled clinical trials that were randomized and double-blind. The antidiabetic potential of different part of plant and their mode of action is summarized in Table **1**.

Table 1. Utilization of Aloe Vera for Treating Diabetes Mellitus.

Plant Part	Effect	Mode of Action
Latex		
	Anti-hyperglycemic	Decrease the blood glucose Raised the insulin level
Leaf		
	Anti-hyperglycemic	Lower the blood glucose
	Anti-oxidative	Radical scavenging activity
	Hepatic-protective	Reduces the liver glycogen Reduces the lipid peroxidation Reduces the non-enzymatic glycosylation in liver tissue Reduces the enzymes like ALP, AST, and ALP Reverse the damage in hepatocytes
	Renal-protective	Reduction in creatinine and urea level
Gel		
	Anti-hyperglycemic	Decrease the blood glucose Raised the insulin level
	Hepatic-protective	Reduces the liver glycogen, lipid peroxidation, non-enzymatic glycosylation in liver tissue, ALT, AST, and ALP Reverse the damage in hepatocytes
	Pancreatic cell-protective	Improvement in Homeostatic model assessment (HOMA)
	Renal-protective	Reduction in creatinine and urea level
	Anti- cholesterolemic	Reduction in triglycerides level, cholesterol, HbA1c, VLDL, and LDL levels Improves the HDL level

Latex

The latex of *Aloe vera* plant has been checked to decrease the blood glucose levels in type II DM patients, similar to AV gel. Investigations showed that the daily intake of half a teaspoon of dried AV sap induced the anti-diabetic effect[6]. Another study performed on rodent models exposed that AV latex has a hypoglycemic effect. Both in the oral administration of 500mg/kg of body weight and intraperitoneal injection of 5mg/kg of AV latex preparations posed an anti-hyperglycemic effect[7].

Leaf

The hypoglycemic potential of AV gel extracts has been examined through the animal model in normal non-diabetic, Insulin-Dependent Diabetes mellitus (IDDM), and Non-Insulin-Dependent Diabetes mellitus (NIDDM) rats. Results revealed that the pulp extract has hypoglycemic action both in IDDM and NIDDM rats, contrary to this, gel extract exerted an anti-hyperglycemic effect only on NIDDM rats. Both extracts of AV were ineffective in lowering the glucose concentration in non-diabetic rats[8]. An experimental study using the radical scavenging method was planned to explore the antioxidant activity of leaf extract through 2,2-Diphenyl-1-picrylhydrazyl (DPPH) radical scavenging method. Results revealed that mature AV of year three contained a significant number of flavonoids and polysaccharides that exhibited antioxidant activity compared to two and four years old. The highest free radical scavenging activity was observed as 72.19% in 3-year-old AV plant, whereas 70.52% in Butylated Hydroxytoluene (BHT) and 65.20% in R-tocopherol[9].

A study by Helal *et al*. enlighted the potential effect of water extract of AV on physiological parameters related to DM through animal modeling. They found that extract has a momentous effect in reducing the blood glucose, liver glycogen and raised the insulin level in serum (hyper-insulinemic effect) as well as the body weight[10]. Results of another study by Bolkent *et al*. showed that the deteriorating changes were lessened in the kidney tissue in type II diabetic rats when treated with gel extract, whereas pulp extract doesn't show the significant protective effect on tissues of the kidney. Ingesting the gel extract exhibited betterment in the biochemical parameters such as the reduction in creatinine and urea level. On the other hand, histological analysis revealed that there was very little damage in kidney tissues[11].

The hypoglycemic potential of whole leaf, and extract of a fraction having 10KDa molecular weight compounds of AV's powder was investigated on diabetic mice. Furthermore, the absorption dynamics of AV-derived phenolic components was also studied. Three experimental trials were designed to determine alteration in blood glucose, blood insulin levels, and rates of insulitis. Firstly, mellitus one group, the mice have been fed on a basal diet supplemented with 2% whole leaf and another group was fed on 10KDa fraction powder. Results revealed that both were responsible for the suppression of elevated blood sugar and incidence of insulitis significantly. In the second trial, the inhibitory effect of the above-mentioned materials has been tested for their potential effect on the rate of glucose absorption in the intestine. Strong inhibitory action of 10KDa fraction powder was observed on intestinal glucose absorption. Thirdly, AV-derived phenol compounds were determined, followed by administration of aloe components, in blood, serum, and organs such as the liver and pancreas through HPLC. The primary component determined in the body was the same as 10KDa fraction powder[12].

Aqueous leaf extract of *Aloe vera* (L.) was verified for antioxidant action. The extract contained naturally occurring antioxidant constituents, including α-tocopherol, β-carotene ascorbic acid, flavonoids, and total phenols. The extract showed an inhibitory effect against phosphatidylcholine liposome oxidation induced by Fe^{3+}/ascorbic acid, scavenging activity against stable DPPH, ABTS (2, 2'-casino-bis-diammonium salt), and superoxide ions and works as a reducing agent. On the other hand, the AV gel didn't show any antioxidant effect[13]. The antioxidant and anti-mycoplasmic effect of methanolic extracts of AV's leaf skin having phenolic components has been investigated. About 18 phenolic elements were identified in flower and leaf. Sinapic acid, catechin, and quercitrin were concentrated in AV leaf, and quercitrin, gentisic acid, and epicatechin were the main phenolic compounds in flowers. The *in vitro* antioxidant potential determination revealed that both extracts showed free radical scavenging ability, the skin extract was more active for both as antioxidant and anti antimycoplasmic agent[14].

The efficiency trial of dietary complements of AV on oxidative stress and hepatic cholesterol in aged rats was planned by another researcher group. They validated that the AV supplemented rats group exhibited about a 30% reduction in the hepatic cholesterol content. They also concluded suggested that life-long AV intake has increased anti-oxidant effect contrary to peroxidation of lipid *in vivo*, as supported through the reduction in the concentration of the hepatic hydroperoxide and phosphatidylcholine[15]. The hepatic protective effect of extracts of gel and pulp has been validated in the type II diabetic animal model. In AV gel extract-treated group, the oxidative stress marker such as glutathione was increased, and a momentous reduction in lipid peroxidation and non-enzymatic glycosylation in liver tissue. Enzymes like serum alanine transaminase and alkaline phosphatase showed a reduction in their activities. Histological examination of liver tissues also showed a reduction in the damage to the hepatocytes[16].

The extract of AV leaves has hepatic protective potential against the hepatotoxicity induced by carbon tetrachloride. The hepatic protective action was marked by the rebuilding of alkaline phosphatase, triglycerides, bilirubin, and transaminases. It was further confirmed by the restoration of glucose-6-phosphatase, lipid peroxidation, glutathione, amidopyrine N-demethylase, and microsomal aniline hydroxylase towards normal. Afterward, histopathological analysis of the liver supported the findings. Results also revealed that the aqueous extract has the potential to improve the integrity of hepatic cells that was supported by upgrading physiological parameters such as an increase in hepatocytes excretory capacity and bile secretion[17].

Other scientists evaluated the anti-atherogenic activity and hypoglycemic capacity of leaf extract in hyperglycemic rabbits. Results showed that oral intake of the extract significantly decreases fasting glucose, triglycerides level, cholesterol, HbA1c, and LDL levels. Furthermore, a concomitant rise in high-density lipoprotein cholesterol levels was reported. The heart-protective potential of AV was confirmed by decreased atherogenic index in the extract-treated group[18].

Gel

Anti-Hyperglycemic and Anti-lipidemic Effect

An experiment was modulated to check the hypoglycemic action of AV extract in both healthy and diabetic rats. Outcomes showed that oral ingestion of AV extract improved the tolerance of glucose significantly and reverted elevated concentration of urea and glycogen to normal. The effect of treatment is more noticeable in diabetic rats than in healthy animals treated with AV. The transformed activities of enzymes such as reduced action of hepatic hexokinase and increased efficiency of lactate dehydrogenase, fructose-1,6-bisphosphatase, and glucose-6-phosphatase also returned to normal level in the diabetic model[19].

The minerals content of AV's gel was analyzed and evaluated for their function in diabetic rats. The oral dose of ash content of 90mg/kg leaf gel (Avg-ash) on the body weight for 30 days showed the hypoglycemic effect. Biochemical test results revealed that blood and urine glucose level, glycosylated hemoglobin (HbA1c), and urea concentration were significantly reduced. The altered activity of enzymes like hepatic hexokinase and fructose-1,6-bisphosphatase and glucose-6-phosphatase reverted to normal in diseased subjects after the administration of Avg-ash[20].

The alcoholic extract of AV gel was tested for the antioxidant property. Oral intake of extract at 300mg/kg dose, lower the level of HbA1c and glucose and improved the Hb pointedly in the diabetic animal model. Diabetic rats treated with gel extract showed normalization in their higher levels of hydroperoxides and peroxidation of lipid. Results also revealed a significant rise in glutathione-S-transferase, glutathione, glutathione peroxidase, reduced catalase, and superoxide in the kidney as well as the liver. AV extract was more effective to restore these parameters than the Glibenclamide[19]. An experimental study on db/db mice has been designed to evaluate the effect of isolated phytosterols components from *Aloe barbadensis* Miller to evaluate the anti-hyperglycemic potential. Administration of the isolated five phytosterols including lophenol and cycloartenol expressively decrease the fasting glucose by 28-64% and HbA1c levels by 15-18%. On the other side, severe diabetic mice revealed a little reduction in weight[21].

AV has several inorganic elements that have their direct or indirect action for the management of hyperglycemia, glucose tolerance, and anti-inflammatory disorders. Elements such as zinc, copper, magnesium, calcium, chromium, iodine, and sodium are present in AV and studies revealed that the optimal intakes of these elements

can reduce diabetes-related risk factors. Magnesium and potassium are necessary for the proper metabolism of carbohydrates and the steady release of insulin in the blood. As diabetic patients have a hypo concentration of magnesium, potassium, and zinc, AV may a good source of them as they present in more quantity compare to others[22].

An experiment was designed to identify and quantify the phytochemical contents and then compared the antioxidant action and antibacterial activity of Lyophilized AV Gel (LGE) and Ethanolic Gel Extract (EGE). EGE was nearly 345 times more concentrated in phytochemicals than LGE. Many alcohols, aldehydes, alkaloids, alkanes, di-carboxylic acids, fatty acids, indoles, ketones, organic acids, phytosterols, pyrimidines, and phenolic acids/polyphenols were isolated and quantified. Because of indoles, antioxidant, alkaloids, and polyphenols, AV gel showed antioxidant capacity, which was promising in preventing or alleviating the symptoms linked with diabetes and cardiovascular diseases[23].

Antidiabetic action of AV extract **v**alidated in hyper and normal glycemic rats. Oral intake (500mg/kg BW) of AV extract showed a noteworthy drop in plasma glucose levels in hyperglycemic subjects. However, in the normal glycemic rats, AV extract triggered diarrhea and a drop in body weight but no change in plasma glucose level resulted[24]. A meta-analysis conducted to assess the AV potential on glycemic control in prediabetes and type II diabetes patients. In pre-diabetics fasting plasma glucose was improved significantly with no change in HbA1c, whereas in type II diabetes, results revealed little change in glycemic level and more development in HbA1c[25].

Hepatic-Protective and Renal-Protective Effect

The effect of AV gel extract on lipid levels was clarified in diabetics. Results showed that a daily oral intake of 300mg/kg BW for 21 days significantly reduced glucose, triglycerides, cholesterol, and LDL. On the other hand, hepatic enzymes such as transaminases (ALT, AST) were restored to the normal level and plasma LDL and VLDL, and insulin were improved. Also, fatty acid levels in the kidney and liver were restored to normal[26]. An experiment enlightened the potential of ethanolic extract of AV gel on phosphatases enzyme and lysosomal hydrolases in diabetic animal subjects. Results bared that daily consumption of gel extract improved the diabetes-related deteriorated function of the membrane and intracellular metabolism. The activity of membrane-bound phosphatases such as ATPase, Na^+-K^+ ATPase, Ca^+ ATPase, and Mg^+ ATPase normalized in both kidney and liver of diabetic rats. There was a significant decrease in the action of hepatic and renal lysosomal hydrolases such as beta-D-glucuronidase, beta-D-N-acetyl glucosaminidase, cathepsin-D, and acid phosphatase[22].

Anti-Cholesterolemic Effect

The effect of intake of minor phytosterols isolated from the gel on glucose concentration and visceral fat mass was studied. Phytosterols such as cycloartanol and lophenol repressed the blood glucose levels by 37.2%. Triglyceride levels, free fatty acid and accumulated visceral fat in the phytosterol treated group reduced significantly. These observed results suggested that phytosterols derived from AV have the potential to recover hyperlipidemia and hyperglycemia[27]. The preventive effect of Processed Gel (PAG) on diet-induced diabetes and related symptoms has been validated through animal modeling. They found that oral intake of PAG exhibits positive effects in lowering the blood glucose concentration, insulin level, and triglyceride in both plasma and liver. The anti-diabetic effects of PAG further confirmed by histological examinations of the peri epididymal fat pad and there was a significant decrease in the size of the adipocytes[28]. Another scientist found that gel extract has antioxidant potential, anti-hyperlipidemic, and anti-diabetic activity. Results revealed that the oral intake of extract lowered the glucose, cholesterol, and triglycerides both in diabetic and normal rats. Moreover, the AV gel extract-treated group ameliorated the oxidative stress that was verified by the significant reduction in serum Malondialdehyde (MDA) level and rise in total antioxidant capacity and serum nitric oxide level[29].

The AV extracts effects in alleviating the hyperlipidemia in diabetics were studied by using different extracts, such as Ethanolic Gel (Gel-Et) extract and ethanolic skin extract of AV. Skin's extract showed the highest antioxidant potential by lowering Malondialdehyde (MDA) levels in plasma as it has the maximum concentration of total phenolic and flavonoids. The oral administration of Gel-Et significantly lowers the fasting glucose. The groups treated with extracts showed a reduction in total cholesterol and LDL by

11-25% and by 45-69%, respectively[30]. A randomized controlled trial was planned to determine the effects of different doses of AV extract powder on lipid and glucose concentration in pre-diabetic patients. Results revealed that the dose of 300mg meaningfully lowered the mellitus fasting glucose and HbA1c level but no change in lipid profile. On the other hand, the dose of 500mg showed improvement in the lipid profile[31].

The metabolic effect of the gel complex obtained from AV (Aloe QDM complex) on obese pre-diabetic subjects was validated. Results revealed that intervention introduction helped to lower the fasting blood glucose, body fat mass along with the reduction of the body weight. The homeostasis model of assessment for insulin resistance showed an elevation of resistance by the cells and normalization in the level of fasting serum insulin[32]. In another study, the supplement of AV leaf gel was evaluated for their effect on metabolic syndrome in pre-diabetics. A double-blind, placebo-controlled study pilot showed a formulation of a 500mg dose of AV gel powder in form of a capsule that resulted in a significant reduction in total and LDL cholesterol, glucose, and fructosamine. On the other hand, supplements of gel powder standardized with 2% aloesin helped to reduce blood glucose, HbA1c, fructosamine, insulin, F2-isoprostanes in urine, and HOMA[33]. A clinical trial was directed on 5000 patients for 5 years having angina pectoris. Researchers found that including AV gel along with Isabgol husk in the diet produced a remarkable reduction in fasting and post-prandial blood sugar, triglycerides, and total cholesterol[34].

The hypoglycemic impact of *Aloe vera* L. fractions having high molecular weight molecules has enlightened on type II diabetic patients. Results showed that fractions containing bioactive components such as polysaccharide and barbaloin having a molecular weight of almost 1000 kDa along with glycoprotein, and ivermectin having a molecular weight of 29 kDa has the potential to reduce the blood glucose and triglyceride level in the blood significantly[35]. The non-insulin-dependent diabetic subjects were treated with the different dose concentrations of AV gel powder to check their effect on the diabetes-related complications. They found that the level of fasting blood glucose was reduced by 15.4%, postprandial glucose by 27.8% followed by a momentous decrease in cholesterol by 10%. The triglycerides, LDL, and VLDL levels were lower by 12.2%, 14.6%, 12.2%, respectively. The intervention has improved the HDL level in blood almost by 9.4%[36]. Supplementation of AV in pre-diabetic and non-treated but early diabetic patients showed better control of glycemic levels. A noteworthy decrease was observed in the levels of glucose, HbA1c, triglyceride, cholesterol, and LDL and an increase in the serum HDL in treated groups[37].

A WAY TO INCREASE THE UTILIZATION OF *ALOE VERA*

To enhance the utilization of any bioactive compound, daily foods are the most common way to increase its intake. The unique properties of AV such as watery and colorless makes it easy to blend in different food products such as in bakery items as fat replacers[38], beverages[39], confectionery[40], dairy items[41], food supplements[42], and preservatives[43].

CONCLUSION

Herbaceous plants and vegetables can be utilized as a medicine to treat and prevent numerous health problems. Since, these plants are already a part of daily cuisine in most of the countries therefore, no difficulties shall be faced to increase their consumption and utilization to derive specific health benefits. Because of the unique bioactive compound's composition, which is responsible for controlling diabetes and its related complications, increased utilization of AV should be promoted worldwide.

CONFLICTS OF INTEREST

None.

FUNDING SOURCE

None.

ACKNOWLEDGMENTS

None.

LIST OF ABBREVIATIONS

ABTS	2, 2'-casino-bis-diammonium salt
ALP	Alkaline Phosphatase
ALT	Alanine transaminase
AST	Aspartate Aminotransferase

ATPase	Adenosine Triphosphatase
AV	Aloe vera
Avg-ash	*Aloe vera* gel Ash
BHT	Butylated hydroxytoluene
BW	Body Weight
Ca^{+}	Calcium
CAM	Complementary and Alternative Medicine
DM	Diabetes mellitus
DPPH	2,2-Diphenyl-1-picrylhydrazyl
EGE	Ethanolic Gel Extract
Gel-Et	Ethanolic Gel Extract
Hb	Hemoglobin
HbA1c	Glycosylated hemoglobin
HDL	High-Density Lipoproteins
HOMA	Homeostatic Model Assessment
IDDM	Insulin-Dependent Diabetes Mellitus
K^{+}	Potassium
KDa	KiloDalton
Kg	Kilogram
LDL	Low-Density Lipoproteins
MDA	Malondialdehyde
mg	Milligram
Mg^{+}	Magnesium
Na^{+}	Sodium
NIDDM	Non-Insulin-Dependent Diabetes Mellitus
PAG	Processed Gel
VLDL	Very Low-Density Lipoproteins

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