Original Article

Comparative Metabolic Properties of Aloe Vera Extracts and Sitagliptin in Diabetic Rats

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Author's Contribution

[1] Conception of study
[1] Experimentation/Study conduction
[1] Analysis/Interpretation/Discussion
[1] Manuscript Writing
[1,2] Critical Review
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Abstract

Introduction: Diabetes Mellitus, a global epidemic affecting millions of people is pretty challenging to cure as all the available antidiabetics have various health hazards, especially, in long-term administration. So, a safe alternative is always desired.

Objective: To compare the metabolic (hypoglycemic and hypolipidemic) effects of Aloe Vera extracts with novel anti-diabetic medicine, "Sitagliptin" on diabetic rats.

Materials and Methods: The study design was a Randomized Control Trial. The study was conducted in the Pharmacology department of Islamic International Medical College, Rawalpindi in collaboration with NIH, Islamabad, Pakistan, from September 2019 to August 2020. Adult, fifty Albino rats were taken and randomly grouped into A and B. After induction of type 2 diabetes with low dose streptozotocin, group B was subdivided; GroupB1 (Diabetic Control), Group B2 (Aloe Vera whole leaf treated), GROUP B3 (Aloe Vera gel treated), and Group B4 (Sitagliptin treated). Fasting blood sugar (FBS), Hemoglobin A1c (HbA1c), and triglycerides were measured. Statistical Analysis was done by SPSS version 25. A one-way ANOVA test was used for assessing any difference in the mean values. Post-hoc Turkey analysis was conducted to compare any inter-group mean differences. A p-value of <0.05 was considered significant.

Results: On completion of study, Fasting blood sugar in Group A was 82.40mg/dl, Group B1 498.40 mg/dl, Group B2 89.30 mg/dl, Group B3 95.70 mg/dl, Group B4 93.00mg/dl; HbA1c in Group A was 3.71%, Group B1 11.84%, Group B2 4.02%, Group B3 4.17%, Group B4 3.73%; Serum triglycerides in Group A 125.40mg/dl, Group B1 221.00 mg/dl, Group B2 112.50 mg/dl, Group B3 129.70 mg/dl, Group B4 125.00 mg/dl respectively, showing significant improvement in Diabetes Mellitus in study subjects.

Keywords: Aloe Vera gel, Sitagliptin, diabetes, glycated haemoglobin.

Introduction

The major pandemic hitting the world today is Diabetes Mellitus, with serious catastrophes on health and the economy across the globe.[1] Its burden has quadrupled in the preceding three decades owing to accelerated growth in obesity, physical inactivity, high caloric food consumption, and population ageing.[2] In spite of the global utilization of the enormous glucose-lowering agents, the clinical outcome is not adequate, rather, dubious.[3] We are moving towards an era of treating diabetes with alternative medicine. Many compounds of plant origin have been used since ancient times for curing hyperglycemia. Aloe Vera is one of these herbs with good antidiabetic potential along with numerous health benefits for mankind.[4]

The oral hypoglycemic agents are quite a large group including metformin, sulfonylureas, glitazones, and the various new classes used for curing diabetes mellitus.[5] Orally administered Dipeptidyl-Peptidase-IV inhibiting drugs are a recent development in diabetes treatment with the potential of enhancing the incretin hormones by preventing their inactivation by the dipeptidyl peptidase-4 enzyme.[6] Sitagliptin, the 1st orally available DPP-IV inhibitor is launched in 2006 for diabetes treatment and is proving very effective, especially for the elderly and those with coexistent cardiovascular diseases. By inhibiting the DPP-IV enzyme this drug increases the level of two hormones namely, Glucagon-like Peptide-1 (GLP-1) and Glucose-Dependent Insulinotropic Polypeptide (GIP). The serum levels of these hormones remain elevated for several hours followed by enhanced Insulin release from pancreatic beta cells and positive anabolic effects on metabolism.[7]

Aloe Vera is a perennial herb with draught-resistant, dragger-shaped lancet leaves for water storage.[8] *Aloe Vera* has an unremitting history of use dating back to 1750 B.C. when it was used as a medicinal treatment in Mesopotamia.[9] It contains almost 75 biologically active ingredients in its inner mucilaginous gel, consisting of polysaccharides, proteins, phytosterols, vitamins, and minerals. It is successfully being used for curing diabetes mellitus because of the synergistic activity of the multiple biological agents present in it.[8] According to some studies, *Aloe Vera* contains calcium which stimulates pancreatic beta cells to release insulin, and appreciable amounts of Cr, Zn, and Mn present in *Aloe Vera* may be responsible for potentiating insulin action.[10]

We compared the metabolic effects of Aloe Vera whole leaf and *Aloe Vera* gel extracts with the novel hypoglycemic agent, Sitagliptin on Streptozotocin-induced type 2 diabetic rats in this research trial. As far as we know, no such comparative studies were done before.

Materials and Methods

Randomized Control Trial, conducted in the Pharmacology department of Islamic International Medical College in collaboration with the National Institute of Health (NIH) Islamabad from September 2019 to August 2020. Male, 2 months old, healthy Sprague Dawley rats, of 200-250 g weight were procured from the animal house of NIH and housed in standard cages under standard laboratory conditions. The care and handling of subjects were in harmony with the internationally accepted standard guidelines. After 1 week of acclimatization, the rats were randomly distributed into two main groups; 10 rats in group A and the remaining (40) in experimental group B. Group A was labelled as Normal Control and took normal saline and normal standard diet while Group B received high fat (HFD) standard diet for two weeks (prepared at NIH as standard food pellets. Rats in group B were found to have a significant increase in body weight after two weeks of HFD. Streptozotocin catalogue number 4191002-1(714986), CAS No. 18883-66-4, Brand bio world the USA, bought from the commercial supplier was set just before use and injected within 5 min of dissolution in citrate buffer. Overnight fasted rats were given a single intraperitoneal injection of streptozotocin at the dose of 35 mg/kg body weight.[11] Fasting blood glucose was recorded, after 3 days of streptozotocin administration to confirm diabetes. Rats with fasting blood glucose equal to and above 250mg/dl were considered diabetic.[12]

Research grade Sitagliptin, Batch No: M-20191010-D05-M06-01, supplied by CCL Pharmaceuticals, Lahore, Pakistan, and given orally at a dose of 10mg/kg body weight/day for 40 days.[13] Fresh 2 -3 years old, healthy *Aloe Vera* brought from a local nursery and plant material identification was done by Department of Plant Sciences of Pakistan, Quaid-e-Azam University, Islamabad, Accession Number 132644 and Voucher Specimen Number 125, preserved at the Herbarium. *Aloe Vera* leaves were thoroughly washed under tap water, thorny edges were removed along with the yellow sap. Thin slices of the whole leaf were made and put for 5 days in the sun to get dried.[14] The leaf powder was made after grinding them carefully, and stored in a tightly closed glass jar, under

cool, dry, and dark conditions. Fresh *Aloe Vera* gel was extracted from leaves and scooped into an electric blender and then homogenized to obtain the gel extract. Both these extracts were later given orally to rats, mixed in feed (food pellets), at a calculated dose (300mg/kg body weight/day) for 40 days.[15] Terminal sampling was done on Day 60, to measure FBS, HbA1c, and serum triglycerides. Fasting blood glucose was measured through the glucose oxidase method and serum triglycerides determination was done after enzymatic splitting with lipoprotein lipase Microlab 300, a chemical analyzer was used for these procedures. For HbA1c measurement, Quo–Lab analyzer was used.

Statistical analysis was done by applying the statistical package for Social Sciences version 25 (SPSS 25). Results were documented as mean+_SEM. Comparisons of quantitative parameters among the five groups were analyzed by using one-way ANOVA (post hoc turkey test). A p-value of less than 0.05 was considered significant.

Results

At Day Zero, all parameters were within the normal range in all rats. Type 2 diabetes mellitus was induced well in all rats of group B.

FBS was measured to assess the progress of the study (on Day 32). At day 60, final sampling was carried out through cardiac puncture to assess fasting serum sugar, HbA1c along with Serum Triglycerides, and the following results were seen.

Fasting blood sugar in Group A (Figure 1) was 82.40mg/dl, Group B1 498.40 mg/dl, Group B2 89.30 mg/dl, Group B3 95.70 mg/dl, Group B4 93.00mg/dl; HbA1c (Figure 2) in Group A was 3.71%, Group B1 11.84%, Group B2 4.02%, Group B3 4.17%, Group B4 3.73%; Serum triglycerides (Figure 3) in Group A 125.40mg/dl, Group B1 221.00 mg/dl, Group B2 112.50 mg/dl, Group B3 129.70 mg/dl, Group B4 125.00 mg/dl respectively.

It is obvious from the above results that treatment with Aloe Vera whole leaf and gel extracts resulted in a considerable decrease in the above parameters with almost similar efficacy to Sitagliptin in diabetic study rats.

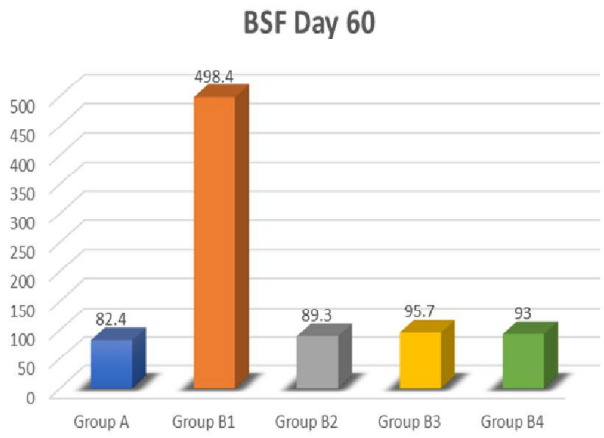

Figure 1: Graphical Representation of Mean of Fasting Blood Glucose levels (mg/dl) of all Groups on Day 60 (n = 10)

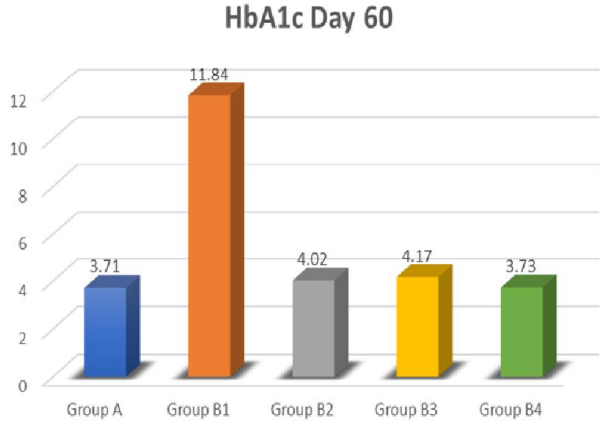

Figure 2: Graphical Representation of Mean of HbA1c (%) in Groups on Day 60 (n = 50)

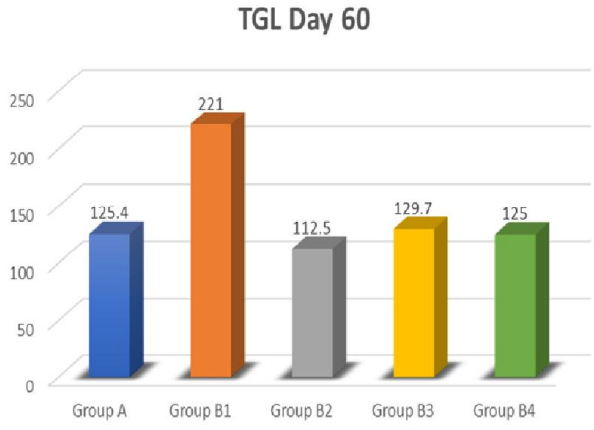

Figure 3: Graphical Representation of Mean of Serum Triglycerides (mg/dl) of all Groups on Day 60 (n=50)

Table 1: Intergroup Mean Differences in Quantitative Parameters of all Groups on Day 60

Group	Comparison Group	Difference in BSF (mg/dl)	P Value	Difference in HbA1c (%)	P Value	Mean Difference in TGL (mg/dl)	P Value
A	B1	416.00 ± 5.07	< 0.001	8.13 ± 0.20	< 0.001	95.60 ± 6.24	< 0.001
	B2	6.90 ± 5.07	0.656	0.31 ± 0.20	0.536	12.90 ± 6.24	0.252
	B3	13.30 ± 5.07	0.083	0.46 ± 0.20	0.163	4.30 ± 6.24	0.958
	B4	10.60 ± 5.07	0.243	0.02 ± 0.20	1.000	0.40 ± 6.24	1.000
B1	B2	409.10 ± 5.07	< 0.001	7.82 ± 0.20	< 0.001	108.50 ± 6.24	< 0.001
	B3	402.70 ± 5.07	< 0.001	7.67 ± 0.20	< 0.001	91.30 ± 6.24	< 0.001
	B4	405.40 ± 5.07	< 0.001	8.11 ± 0.20	< 0.001	96.00 ± 6.24	< 0.001
B2	B3	6.40 ± 5.07	0.716	0.15 ± 0.20	0.943	17.20 ± 6.24	0.061
	B4	3.70 ± 5.07	0.949	0.29 ± 0.20	0.599	12.50 ± 6.24	0.281
B3	B4	2.70 ± 5.07	0.984	0.44 ± 0.20	0.198	4.70 ± 6.24	0.943

Discussion

Diabetes mellitus is a broad manifestation of a group of metabolic disorders with the fundamental feature of chronic hyperglycemia, resulting from either compromised insulin secretion or diminished insulin efficacy or, most frequently, together.[16] Such defective insulin mechanisms progress to imbalances of the supervisory system involved in storing and utilizing metabolic fuels, namely, the breakdown of proteins, lipids, and carbohydrates, culminating in disease complications.[17] Over five hundred medicinal herbs have shown anti-oxidant activities for overcoming the oxidative strain and cell damage of hyperglycemia. Aloe Vera is used since prebiblical times for treating various diseases as well as for beauty enhancement. The phytochemical analysis of *Aloe Vera* revealed the existence of tannin, saponins, steroids, cardiac glycosides, and anthraquinones. It is successfully being used for diabetes cure due to the synergistic activity of its numerous constituents including zinc, chromium, magnesium, and manganese through enhancing the efficacy of insulin.[18] The current RCD aims to fetch ***Aloe Vera***'s tremendous metabolic (serum glucose and triglyceride lowering) effects in diabetes control under the limelight.[19]

In the present study, we found that treatment with *Aloe Vera* whole leaf as well as *Aloe Vera* gel extracts significantly decreased FBS, HbA1c, and triglycerides with almost similar efficacy to each other as well as to Sitagliptin in male diabetic albino rats. Similar to our work, Ayesha Noor, et.al conducted a study to evaluate the role of *Aloe* extract in enhancing insulin release from Beta cells of the pancreas in Streptozotocin-induced diabetic Wistar rats and found that *Aloe Vera* extracts at 300mg/kg/d for three weeks, resulted in normalizing blood glucose and increasing insulin level as well. They found a tremendous rise in the number, length, and bulk of the pancreatic islets in their study animals.[20]

Bhaskar Sharma et al administered *Aloe Vera at* 300 and 500 mg/kg body weight orally daily to a mice model of Alloxan-induced diabetes mellitus for a period of 21 days and noticed a significant reduction in serum glucose level along with the hepatoprotective effect at both doses of *Aloe Vera* in the mice under study.[21]

Louay Labban and Zeina Malek, conducted an experimental study on type 2 diabetic patients in 2019 to identify the glucose and lipid-lowering effects of *Aloe Vera* at 100 mg and 200 mg daily dose and found noteworthy diminution ($p<0.05$) in the HbA1c, total cholesterol, triglycerides, low-density lipoprotein cholesterol, and a substantial rise in HDL in patients who received *Aloe Vera* at 200mg daily dose compared to patients who received 100mg *Aloe Vera* powder extracts and to those who did not take any treatment.[22]

Results of all these studies are in consistence with the findings of our study where a significant decrease in FBS, HbA1c, and triglycerides is noticed (P value <0.001) with Aloe Vera whole leaf as well as Aloe Vera gel extracts (at the same 300mg/kg daily dose) to Streptozotocin-induced type 2 diabetic rats.

Limitations

Owing to time limits, cost, and accessibility issues complete lipid profiles, serum insulin levels, and histopathological studies of the pancreas are not performed.

Conclusion

Aloe Vera whole leaf, as well as Aloe Vera gel, extracts significantly lowered hyperglycemia, HbA1c, and serum triglycerides with almost similar efficacy to each other as well as to Sitagliptin with minor statistically insignificant differences (P value > 0.05) in controlling metabolic changes in HFD-STZ – T2DM rat model. Therefore, both *Aloe Vera* whole leaf and *Aloe Vera* gel extracts can be used interchangeably in the treatment of type 2 diabetes mellitus and assist in achieving ideal readings of blood glucose, HbA1c, and triglycerides via reliable, effortlessly available, eco-friendly means.

Recommendations

Further exploration of the active constituents of *Aloe Vera* leaf needs to be done to establish their individual hypoglycemic role. Comparative effects of different doses and different routes of administration of various *Aloe Vera* extracts should be investigated. Combined effects of *Aloe Vera* extracts with sitagliptin as well as with other oral hypoglycemics should be explored.

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