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ORIGINAL ARTICLE

Effect of Aloevera Whole Leaf Extract in Combination with Rosiglitazone on Oxidative Stress and Lipid Profile Levels in Type-2 Diabetic Rats

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ABSTRACT

Objective: To measure the synergistic effects of Aloevera and Rosiglitazone on plasma glucose, oxidative stress and lipid profile in Type-2 Diabetic Sprague-Dawley rats.

Subjects and Methods: A Randomized control trail was carried out in Physiology department of Army Medical College, Rawalpindi. Twenty healthy rats were made diabetic according to Srinivasan model. After confirmation of type 2 Diabetes, they were randomly segregated into two equal groups. Groups were named as diabetic control group and Diabetic treatment group. Control group was injected normal saline and treatment group was given 150 mg/kg body weight of Aloevera extract and 2.5mg/kg body weight of rosiglitazone. It was half of the effective doses which were calculated through pilot study.

Results: Plasma glucose, Malondialdehyde and lipid profile were significantly reduced ($p<0.000$) in diabetic treatment group as compared to diabetic control group.

Conclusion: A significant reduction in plasma glucose, oxidative stress and lipid profile was obtained in diabetic treatment group although half of the effective doses were used. It would also be help in reducing side effects associated with use of rosiglitazone.

Key words: Aloevera, Diabetes Mellitus type 2, Oxidative Stress, Rosiglitazone.

Author`s Contribution
[1] Conception, synthesis, planning of research and manuscript writing Interpretation and discussion
[2] Data analysis, interpretation and manuscript writing, [3] Active participation in data collection.

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Article info.
Received: September 15, 2017
Accepted: July 12, 2018

Cite this article. *Gul M, Moazzam S, Adil I. Effect of Aloevera whole leaf extract in combination with rosiglitazone on oxidative stress and lipid profile levels in Type-2 diabetic rats. JIMDC.2018; 7(3):159-164*

Funding Source: *Nil*
Conflict of Interest: *Nil*

Introduction

Diabetes Mellitus (DM), the third killer of the mankind, is increasing with alarming rate throughout the world especially in developing countries.[1] DM is a continuous source of oxidative stress to the body. Oxidative stress is an imbalance between production of free radical generation and scavenging system[2]. It is relevant to the both types of diabetes and its associated complications. The increased production of free fatty acid (FFAs) in Diabetes can directly increase reactive oxygen species (ROS) via lipid peroxidation reactions and mitochondrial production.[3] Chronic hyperglycemia causes oxidative stress by degrading antioxidant defense system and oxidation of glutathione pool.[4] Malondialdehyde (MDA) is considered as an adequate indicator of lipid peroxidation caused by free radicals and its level is increased in diabetes.[5] The amount of MDA is then determined by thiobarbituric acid (TBARS) levels.[6] To protect themselves against harmful effects of ROS, cells may reduce the

formation of ROS and/or enhance ROS removal.[7]

Managing Diabetes is difficult due to its chronic nature and number of side effects associated with drugs used for its treatment. Complementary and alternative medicine (CAM) for the treatment of diabetes mellitus is becoming popular. It is claimed that dietary supplements and herbal remedies are safer than conventional drugs. Studies have revealed that Aloevera is rich in polysaccrides and flavonoids and can be used effectively against diabetes.[8] Clinical trials have indicated that supplementation with antioxidant is associated with reduction in the incidence of chronic disease morbidity and mortality. Previous results revealed Aloevera as hypoglycemic and antilipidemic in its gel extract, which may also contribute to its antioxidant potential. Aloevera whole leaf has about three to five times more constituents than gel.[9]

Rosiglitazone is a known antidiabetic drug of thiazolidinediones family. It works by binding to peroxisome proliferators activated receptor gamma (PPARγ), nuclear regulatory protein and regulate glucose and fat metabolisms by improving insulin sensitivity in muscles and liver. These drugs decrease plasma triglyceride (TG) levels but are associated with weight gain, an increased in low density lipoprotein (LDL)-cholesterol levels, congestive heart failure and left ventricular dysfunction.[10] Literature survey does not reveal work on antidiabetic effect of *Aloevera* whole leaf extract, used in combination with rosiglitazone. Therefore, in present study *Aloevera* whole leaf extract was used in combination with rosiglitazone in half of its effective dose to overcome the side effects associated with drug and to look for its synergistic effects.

Subjects and Methods

The Randomized control trial (RCT) was carried out at Physiology Department Army Medical College, Rawalpindi in collaboration with National Institute of Health (NIH) Islamabad for one year. Young *Aloevera* plant due to their high medicinal quantities was purchased from commercial nursery in Lahore. Plant material identification was carried out at Herbarium of Quaid-e-Azam University Islamabad, by the Department of Plant Sciences. Accession number 46624 and voucher specimen number 157 was obtained. A whole leaf process was employed in making the Aloe juice. Leaves were cut into sections and were pulverized into a soup like structure by placing them in a grinding unit. The filtered juice was passed through an activated charcoal column, which was prepared in a central funnel, to remove the unwanted laxative agents, aloin and aloe emodin which is a byproduct of rind and latex.[11] Pilot study was performed on a group of ten rats to find the effective dose of *Aloe vera* whole leaf extract to achieve normoglycemia in diabetic rats. It was found that *Aloe vera* whole leaf extract in the dose of 300 mg/kg body weight effectively lowered plasma glucose levels in type 2 diabetic rats. Dose of rosiglitazone was taken from literature. Half their effective doses were used in our study.

In RCT, Twenty Sprague Dawley rats, about 90 days old with average weight 220±50 grams were taken from National Institute of Health (NIH), Islamabad. Animal house facility of NIH, Islamabad was used which has a setup according to international standards for breeding and housing of experimental animals. Normal pellet diet (NPD) was `prepared at NIH according to the standard approved by the Universities Federation for Animals Welfare. High fat diet (HFD) was specially prepared at NIH according to the standard used elsewhere.[12] Twenty animals were fed with high fat diet for 2 weeks after which a single intra-peritoneal injection of streptozotocin (available as 1-gram vial, Bioworld Pharmaceutical) in the dose of 35 mg/kg body weight was given.[12] Their fasting blood glucose and MDA levels along with total lipid profile were measured after 72 hours to confirm type 2 Diabetes Mellitus (T2DM).[13]

After confirmation of T2DM, twenty Sprague Dawley rats were randomly divided into two groups as their plasma glucose and TG: High density lipoprotein (HDL) ratio was comparable to each other. Cages were labeled as control group and treatment group. Now each group having 10 rats was introduced to treatment for next 21 days. Diabetic control group was administered 0.1ml normal saline intraperitoneally (I/P) daily and diabetic treatment group was given half the effective dose of Aloevera 150mg/kg and rosiglitazone 2.5mg/kg body weight I/P. After 21 days of treatment, overnight fasted rats were anesthetized and 5 ml of intra-cardiac blood was collected to analyze plasma glucose, MDA, Lipid profile. Analysis of samples was done at Centre for Research in

Experimental and Applied Medicine (CREAM), Army Medical College, Rawalpindi, Pakistan. Estimation of glucose was done by enzymatic colorimetric (TRINDER'S) method.[14] TG, Total cholesterol and HDL were estimated simultaneously on automated chemistry analyzer (Vitalab Selectra E). LDL was calculated by using Friedewald formula and very low density lipoprotein (VLDL) by Triglyceride/5.[15] MDA levels were estimated through thiobarbituric acid reactive substances (TBARS) assay by ELISA. Data were entered into SPSS version 16.0. Mean and standard deviation was employed for all the values. Data between groups were analyzed by using independent sample t test. The p value <0.05 was considered statistically significant.

Results

At the start of study, levels of plasma glucose, MDA and lipid profile were comparable to each other in both groups. After 21 days of treatment, a marked reduction in plasma glucose, MDA and lipid profile was noted in treatment group as compared to baseline (Table 1). After treatment plasma glucose, serum TG, cholesterol, LDL and VLDL were significantly reduced in Diabetic control group as compared to Diabetic treatment group. Serum HDL levels were noted to be significantly increased in treatment group (Table 2). After three weeks, MDA level in the control group was 10.06 ± 1.07 µmol/l and in treatment group it was significantly (p<0.000) reduced i.e. 3.65 ± 0.39 µmol/L (Figure 1).

Discussion

The Srinivasan animal model of T2DM was used in this study because it closely resembled the natural course and metabolic characteristics of the disease.[12] The animal models constructed with alloxon and streptozotozin resulted in extreme insulin deficiency and overt

Table 1: Percent reduction in treatment group as compared to baseline (n=10)

Variables	percentage
Blood glucose	73
Malondialdehyde	64
Triglyceride	50
Total Cholesterol	46
High density lipoprotein	25
Low density lipoprotein	51
Very low density lipoprotein	49

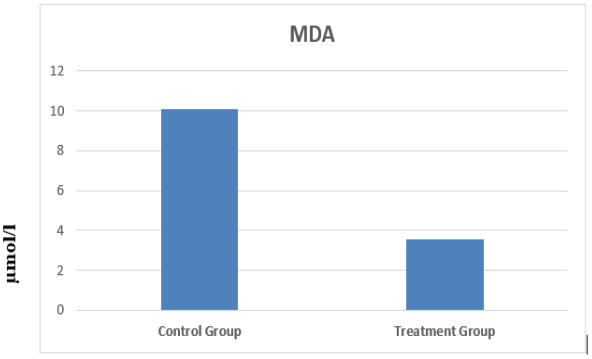

Figure-1: Effect of Aloevera and rosiglitazone on MDA levels in type 2 diabetic treatment group as compared to control group (n=20)

hyperglycemia features similar to type DM-1 than to DM-2. Models. Administration of high fat diet for 2 weeks followed by low dose of streptozotocin resulted in frank hyperglycemia, hyperinsulimemia and insulin resistance. These findings were consistent with the published data of different studies.[12] We used TG: HDL ratio of 1.8 as cut off point for presence of insulin resistance. In both groups after inducing T2DM it was more than 1.8. However, in a study by Srinivasan, *hyperinsulinemia* (467.50 ± 32.43 pmol/l) was taken as the indicator of insulin resistance in high fat fed rats.[12] *Aloevera* and Rosiglitazone combine supplementation in the present study has resulted in statistically significant (p<0.00001) reduction in plasma glucose levels when compared with Diabetic control group even when half of their effective doses were used. To latest literature, survey has revealed that no study has so far been conducted in which *Aloevera* extract and rosiglitazone are used in combination to treat type 2 Diabetes Mellitus. However, our results are encouraging when compared with studies where these drugs are used alone for T2DM.

The work of Tanka et al on Diabetic mouse strain BKS Cg-m Lepr (db/db) with *Aloe vera* gel extract resulted in significant (p<0.05) reduction in fasting plasma glucose level by 64% in diabetic mice when treated for 35 days.[16] Our study revealed 73%% reduction in plasma glucose level in combined group. The desired results in Tanka study were obtained after 35 days of treatment, while duration of our study was shorter (21 days) with much better results. This may be due to synergistic effects of Aloevera and rosiglitazone in combined group.

Table 2: After treatment comparison of Plasma glucose, MDA and Lipid profile between groups (n=20)			
Variables	**Diabetic control Group (n=10) Mean±SD**	**Treatment Group (n=10) Mean±SD**	**p value**
Plasma glucose (mmol/l)	19.05 ± 1.70	5.14 ± 0.25	<0.000
MDA (µmol/l)	10.06 ±1.07	3.65 ± 0.39	<0.000
Triglyceride (mmol/l)	3.96 ± 0.41	1.98 ± 0.14	<0.000
Cholesterol (mmol/l)	4.54 ± 0.21	2.45 ± 0.13	<0.000
HDL- cholesterol (mmol/l)	0.40 ± 0.08	0.50 ± 0.07	0.0005
LDL- cholesterol (mmol/l)	3.26 ± 0.40	1.6± 0.22	<0.0000
VLDL – cholesterol (mmol/l)	0.79 ± 0.07	0.4± 0.71	<0.000

In our study whole leaf extract rather than only gel part of *Aloevera.* was used which may also contribute towards better results in short time of 21 days rather than 35 days taken by tanka study. In their study, they also identified five phytosterol but all did not show antihyperglycemic effects, supporting the documented observation regarding the synergistic action of number of constituents rather than one component alone.[17]

In present study, oxidative stress was measured by estimating the levels of MDA in plasma. The concentration of MDA in diabetic group was 10.06 ±1.07 µmol/l which could be due to high fat diet (HFD) and streptozotocin treatment which generally induces oxidative predominance in tissue by generating reactive oxygen species.[18] The MDA levels decreased by 64% in combined group which could be due to its antioxidant properties as *Aloe vera* has been reported to have strong antioxidant potential than alpha tocopherol.[19] It has been documented that *Aloevera* extract normalized the deranged plasma glucose and lipid status and improved the antioxidant status, which may also contribute in lowering oxidative stress.[20] *Aloevera* can contribute to its antioxidant status due to presence of vitamins (C, E,) enzymes (GPx, SOD, catalase).[21] The combined group results can be attributed to its synergistic action. In a study conducted by Can et al reported the effect of *Aloevera* leaf gel and pulp extract had reduced the MDA levels by 18% and 13% respectively. They attributed the antioxidant effect to alerosin derivative present in latex.[22] Plasma MDA levels of our study were more profound than Cans' study. This may be due to the longer duration of treatment in our study design. Secondly, they had used gel and pulp of *Aloevera* separately while we used whole leaf extract. The antioxidant potency of *Aloevera* is already known which was attributed to the presence of aloe emodin present in the gel.[23] However in our study we had removed aloe emodin and still a significant (64%) decrease in MDA level was observed despite half the effective dose of drug was used. This could be due to synergistic action of *Aloevera a*nd rosiglitazone when used in combination.

In the present study, after intake of HFD for three weeks the diabetic rats showed severe derangements in plasma lipid profile because intake of high fat diet was associated with increase in plasma triglycerides, cholesterol, LDL, VLDL and decrease in HDL levels, similar to previous studies.[24] Combined group supplementation in the present study has resulted in statistically significant ($p<0.00001$) improvement in plasma TG, cholesterol, LDL, VLDL and HDL levels when compared with diabetic control group. Combined group reduced the levels of TG's by 50%, cholesterol 46%, LDL 51%, VLDL 49% and increased HDL by 25% as compared to diabetic rats at the end study. These results were better than when *Aloevera* was used alone. No study is available, in which *Aloevera* and rosiglitazone is used in combination in half of their effective dose. However, *Aloevera* used alone showed antilipidemic effects. The findings are supported by the published data of different studies.

A study by Kim et al revealed that processed *Aloevera* gel has significantly reduced TG and raised HDL with no effects on cholesterol despite 8 weeks of treatment. They attributed this effect to reduced lipogensis and which was assessed/analyzed by the decrease in adipocyte size.[25] Our study results were much better due to usage of whole leaf extract as well as synergistic action of two drugs despite their usage in half of their effective dose. A study on *Aloe vera* gel high molecular weight fractions (AHM),

given to fifteen patients with uncontrolled T2DM.The results revealed a significant reduction in TG with no effect on cholesterol level.[26] However our study in combined group showed statistically significant results on TG, Cholestrol, VLDL and LDL while rise in HDL level. in combined group. This may be due to the fact that only a fraction from *Aloevera* gel was separated and used in this study. It has been reported that despite small solid contents of *Aloevera*, its multiple therapeutic effects of *Aloevera* are due to the synergestic effects of its components. Phenolic compounds and saponins are known to reduce hyperlipidemia in diabetes.[27] The hypoglycemic effect of *Aloevera* extract may be implicated as the major reason for the observed antihyperlipidemic effect of the extract because glycemic control is the major determinant of total cholesterol, VLDL, and triglyceride levels. Aloe chrome increases insulin sensitivity by increasing adiponectin level. Five chromones have been identified in *Aloe vera* extract.[28] Phytosterol, lophenol (Lo) and cycloartanol (Cy), may act as ligand for PPAR.[29]

Rosiglitazone is a known antidiabetic drug of thiazolidinediones family. It has been used for the treatment of type 2 DM since 1991. It increases insulin sensitivity and improves glycemic control. It also acts as a ligand for the gamma subtype of peroxisome proliferators activated receptor (PPAR- gamma), which is directly involved in the regulation of genes controlling glucose homeostasis and lipid metabolism. [30] In our study the plasma glucose levels are reduced by 73%%, TG 50%, cholesterol 46%, LDL 51%, VLDL 49% with concomitant increase in HDL by 25% despite the fact that half of its effective dose were used. These findings of combined are similar to many clinical trials carried in the past when rosiglitazone were used alone. However, no study is available in literature for using *Alevera* and rosiglitazone in combination.

In a study conducted by Atanasovska et al, rosiglitazone treatment in a dose of 5mg/kg body weight to fructose induced metabolic syndrome winstar rats resulted in a statistically significant (<0.001) decreased in plasma glucose and TG.[31] They concluded that these effects may probably involve a regulation of the enzyme lipoprotein lipase in the adipose tissue.[32] It has been reported in that a patient receiving 4mg/kg body weight of rosiglitazone showed signs and symptoms of hepatocellular injury. Discontinuation of treatment was advised to him.[33] The volume overload is responsible for heart failure associated with thiazolidines rather than direct effect on cardiac function.[34] However in our study with 2.5mg/kg body weight of rosiglitazone along with *Aloevera* in combination resulted in effective reduction in glucose lipids and MDA level. This will help in reducing the side effects associated with drug.

Conclusion

The data of our study has revealed encouraging results which could help evolve new strategy of treatment for T2DM. The use of natural herb with synthetic drug may help to lessen the financial burden associated with this disease. In addition, the side effects associated with prolong use of rosiglitazone such as myocardial infarction and heart failure due to high LDL. It has been suggested that use of lipid lowering drug may reduce this risk. Our study has beneficial effect on normalizing the oxidative stress and lipid profile, in type 2 Diabetics. It demands for a study on human T2DM patients by using *Aloevera* with rosiglitazone in half the effective dose to explore a new combination of treatment.

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