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Rauwolfia Serpentina Ameliorates Hyperglycemic, Haematinic and Antioxidant Status in Alloxan- Induced Diabetic Mice

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ABSTRACT

To investigate the effect of methanolic root extract (MREt) of *Rauwolfia serpentina* on hyperglycemic, haematinic and antioxidative dysfunction associated with alloxan-induced diabetes. Mice were divided into normal and alloxan-induced diabetic groups, the second group was sub-divided into three MREt (10, 30 & 60mg/kg) treated test groups and three diabetic (distilled water 1ml/kg), negative (0.05% dimethyl sulphoxide 1ml/kg) and positive (glibenclamide 5mg/kg) control groups. Each treatment was done orally for 14 days. The MREt significantly reduced blood glucose level by improving the body weights, glycosylated hemoglobin (HbA1c) to total hemoglobin (Hb) ratio, red blood cell (RBC) & white blood cell (WBC) counts, packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) in test groups. Beside this, extract decreases the percent inhibition of catalase (CAT) & superoxide dismutase (SOD) enzymes and restores the liver function by recovering the total protein concentration and normalizing the levels of alanine transaminase (ALT), aspartate transaminase (AST) & alkaline phosphatase (ALP) in test mice. Therefore, MREt ameliorates hyperglycemic, haematinic and antioxidant status in alloxan-induced diabetic mice. Further work is still required to find out the active principle in same extract involved in antidiabetic activity.

INTRODUCTION

A significant contribution from herbal medicines has been reported from all over the world for the treatment of diabetes and its endocrine disturbance. These medicines are gaining fame in both developing and developed countries due to person's lack of accessibility towards commercially available expensive treatments and their side effects (Aggarwal and Shishu, 2011). In spite of this, there is still an upsurge in discovering a new drug from natural sources for curing number of diseases including diabetes due to their cost effective nature with no / fewer harmful impacts. Internationally it has been estimated that above 400 million people are living with diabetes and greater than 86% increase is expected in current figure till 2030 (Azmi and Qureshi, 2012a). Diabetes not only alters the glucose utilization but also destabilizes protein and lipid metabolism in the body. Hyperglycemia, the characteristic symptom of diabetes causes protein glycation and induce oxidative stress by producing reactive oxygen species (ROS) that may leads to lipid peroxidation which sooner or later associated with micro- and macrovascular complications like cardiovascular diseases (CVDs), neuropathy, retinopathy and nephropathy, etc (Chueh and Lin, 2011).

Among the vast range of medicinal plants, *Rauwolfia serpentina* Benth (family: *Apocynaceae*), is therapeutically famous in the treatment of high blood pressure and psychological disorders (Qureshi and Udani, 2009). Variety of antihypertensive alkaloids has been reported from the roots of this plant, of which reserpine is the most well-known (Azmi and Qureshi, 2012b). Likewise, the curative effectiveness of same plant against breast cancer and intestinal disorders were already reported (Dey and De, 2011). Leaf extract of same plant was also reported for its *in-vitro* antimicrobial and antioxidant activities (Harisaranraj *et al*., 2009). Recently this plant becomes target for evaluating its antidiabetic potential in order to validate its briefly described hypoglycemic activities in scientific literature (Cazzaroli and Dall'Oglio, 1958; Cohen *et al.*, 1959; Chatterjee *et al.*, 1960). In this regard, antidiabetic potential of methanolic root extract of *R.serpentina* have been reported in alloxan-induced diabetic rats (Qureshi *et al.*, 2009).

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Its glucose tolerance activity with therapeutic dose selection objective (Azmi and Qureshi, 2012b) and long-term antidiabetic investigation with qaulitative and quantitative phytoconstituents analysis have been done (Azmi and Qureshi, 2012a). Moreover, two computational studies have also been published to support the antidiabetic aspect of this plant (Ganugapati *et al.,* 2012; Pathania *et al.,* 2013).

Therefore this study is the continuation of same idea that helps to elaborate the antidiabetic potential of this plant by investigating the effect of methanolic root extract of *R.serpentina* on hyperglycemic, haematinic and antioxidative dysfunctions associated with alloxan-induced diabetes in animal model.

MATERIALS AND METHODS

Plant sample and its methanolic extract preparation

The roots of *R.serpentina* (voucher specimen: KU/BCH/SAQ/02) were purchased, authenticated and grinded into fine powder which was used to prepare methanolic root extract (MREt) by using rotary evaporator (Qureshi *et al.,* 2009).

Chemicals and their usage

Single intra-peritoneal injection of alloxan monohydrate of Sigma chemicals in a dose of 150 mg/kg was used to induce diabetes in overnight fasted mice. Commercially available glibenclamide (*Daonil*) of Sanofi-aventis Pakistan Ltd in a dose of 5mg/kg used as positive control while 0.05% diluted dimethyl sulphoxide (DMSO) of Fisher Scientific (UK) used as medium for administrating the doses of MREt in test mice.

Experimental animals and procedure

Wistar male albino mice (25 - 30 g) were bought from the animal house of DUHS (Dow University of Health Sciences), Karachi and kept in hygienic environmental condition with temperature at 22 ± 2.0 ^{0}C. Standard laboratory diet and water *ad libitum* were given to them. After 1 week, mice were categories into seven (07) groups (n=6/group).

Group I represented normal control group treated with 1 ml distilled water. Group II and III were alloxan-induced diabetic and negative controls treated with 1ml each distilled water and 0.05% DMSO respectively. Group IV was alloxan-induced diabetic positive control treated with glibenclamide 5mg/ kg. Rest of the alloxan-induced diabetic mice in group V, VI and VII were constituted the experimental test groups treated with MREt in doses of 10, 30 and 60 mg/kg respectively. The mode of treatment was oral in fasting state consecutively for 14 days. On final day of trial, mice were decapitated to collect whole blood, serum and organs.

Percent glycemic and body weight change

The blood glucose levels and body weights of mice in all groups were measured at first and final day of treatment by using glucometer and weighing balance respectively. Finally, percent glycemic and body weight change was determined as described by Azmi and Qureshi (2012a).

Hepatic and antioxidant biomarkers

Hepatic biomarkers *viz.,* total protein (TP), alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP) were qauntitated in serum by using commercially available assay kits (Randox, United Kingdom) while antioxidant enzymes *viz.,* catalase (CAT) and superoxide dismutase (SOD) were measured in liver homogenate by conducting manual methods (Pari and Latha, 2004; Naskar *et al.,* 2010).

Complete blood profile

Complete blood profile including total hemoglobin (Hb), red blood cells (RBC), white blood cells (WBC), packed cell volume or hematocrit (PCV), haemoglobin concentration (Hb), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) was evaluated by using Automated Analyzer Sysmex (*XS-1000i*). However, glycosylated haemoglobin (HbA1c) was determined by commercially available Nycocard kit, USA.

Statistical Analysis

Results are expressed as mean ± standard error mean (SEM) and analyzed through *one way* ANOVA and LSD (least significant difference) test at $p < 0.05$ by using SPSS (statistical package for social sciences) version 18.

RESULTS

Effect of MREt on percent change in body weights

A noticeable reduction in body weights was found in diabetic (group II) and negative (group III) controls after 14 days. However, these changes were much improved significantly in MREt treated mice in group V, VI and VII especially in last group treated with MREt in a dose of 60mg/kg ($p<0.0001$). Glibenclamide also showed an evident ($p<0.05$) increase in body weights of group IV (Figure 1).

Effect of MREt on percent glycemic change

A significant percent glycemic ($p<0.0001$) reduction was observed in group IV, V, VI and VII treated with glibenclamide (5mg/kg) and MREt (10, 30 and 60 mg/kg) as compared to group II and III (Figure 1). Especially three of the MREt treated groups showed almost same blood glucose levels that was also found in normal control mice in group I (Figure 1).

Effect of MREt on HbA1c to Hb ratio

MREt and glibenclamide significantly lowered and improved the HbA_{1c} to Hb ratio ($p<0.0001$) in group IV, V, VI and VII whereas much elevated levels of same ratio were observed in group II and III (Figure 2).

Table. 1: Effects of MREt on hepatic biomarkers.

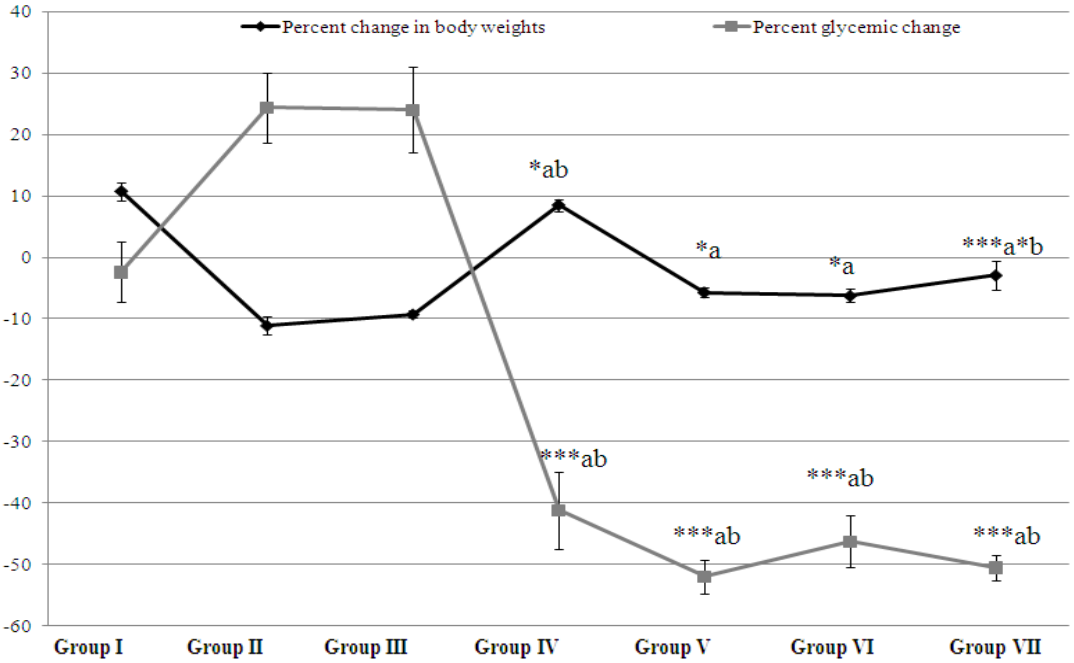
Groups	Treatments	ALT (U/L)	AST (U/L)	ALP (U/L)	TP (g/dL)
Group I	Distilled water(1 mL/ kg)	51.08 ± 2.56	35.66 ± 3.12	77.89 ± 4.93	7.13 ± 0.47
Group II	Alloxan (150 mg/kg)	100.7 ± 7.87	107.36 ± 4.62	187.75 ± 7.04	4.3 ± 0.75
Group III	Alloxan (150 mg/kg)+ DMSO (0.05%)	108.11 ± 18.12	120.05 ± 7.1	177.25 ± 11.58	4.56 ± 0.56
Group IV	Alloxan (150 mg/kg)+ Glibenclamide(5 mg/kg)	46.98 ± 4.75^{***ab}	46.39 ± 2.93^{***ab}	99.32 ± 4.56^{***ab}	6.53 ± 1.04
Group V	Alloxan (150 mg/kg)+ MREt (10 mg/kg)	52.97 ± 2.35^{***ab}	54.64 ± 6.34^{***ab}	95 ± 8.35^{***ab}	5.65 ± 0.46
Group VI	Alloxan (150 mg/kg)+ MREt (30 mg/kg)	48.14 ± 2.89^{***ab}	45.45 ± 4.84^{***ab}	90 ± 7.38^{***ab}	6.32 ± 0.42^{*a}
Group VII	Alloxan (150 mg/kg)+ MREt (60 mg/kg)	38.71 ± 4.61^{***ab}	40.25 ± 2.2^{***ab}	81 ± 7.58^{***ab}	6.48 ± 0.45^{*ab}

Data are expressed as mean ± SEM (n= 6). *, ** & *** = $p < 0.05$, $p< 0.001$ and $p< 0.0001$ respectively when compared with group II (a) and III (b).

Table. 2: Effect of MREt on Complete blood profile.

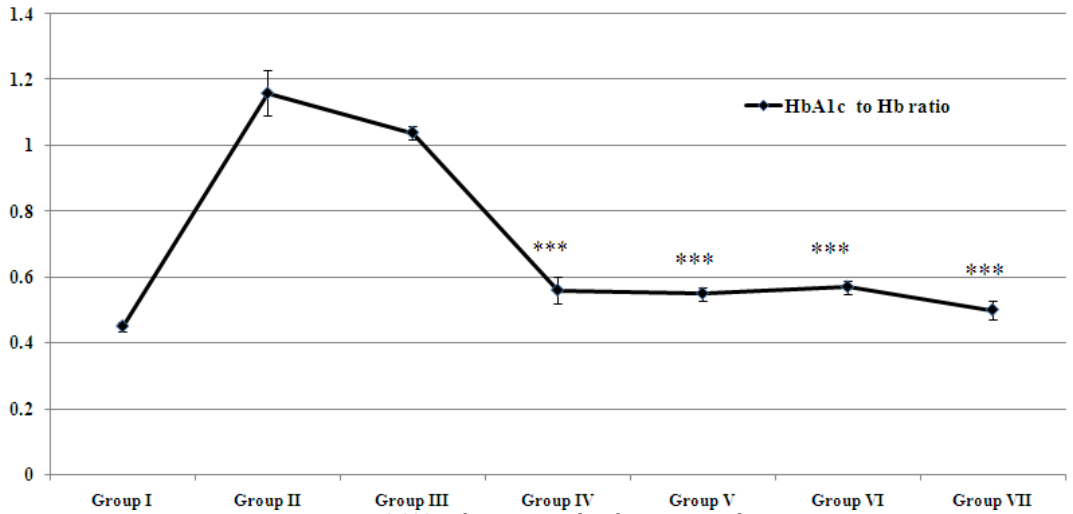
Groups	R.B.C (10^6/µL)	W.B.C (10^3/µL)	P.C.V (%)	M.C.V (fL)	M.C.H (Pg)	M.C.H.C (g/dL)
Group I	4.85 ± 0.29	3.5 ± 0.47	22.93 ± 2.64	46.20 ± 2.91	17.22 ± 1.09	34.78 ± 2.24
Group II	3.15 ± 0.39	5.08 ± 0.44	18.30 ± 2.01	36.36 ± 3.63	14.49 ± 1.05	20.21 ± 2.77
Group III	3.45 ± 0.35	5.40 ± 0.44	17.93 ± 2.80	36.15 ± 3.24	13.46 ± 1.30	22.76 ± 2.27
Group IV	3.6 ± 0.36	3.08 ± 0.30	23.28 ± 2.98	45.84 ± 1.57	17.94 ± 1.35	35.41 ± 2.25
Group V	4.38 ± 0.29^{*a}	2.88 ± 0.46^{**a***b}	23.91 ± 2.58	52.19 ± 2.98^{***ab}	16.84 ± 1.88	32.15 ± 1.84^{**a*b}
Group VI	4.68 ± 0.33^{*ab}	3.55 ± 0.52^{*ab}	28.01 ± 3.55^{*ab}	53.36 ± 2.25^{***ab}	18.02 ± 1.98^{*b}	34 ± 2.68^{***a*b}
Group VII	5.28 ± 0.33^{***a**b}	2.88 ± 0.30^{**a***b}	29.51 ± 4.31^{*ab}	55.13 ± 2.12^{***ab}	19.50 ± 1.39^{*ab}	36.89 ± 1.64^{***ab}

Data are expressed as mean ± SEM (n= 6). *, ** & *** = $p < 0.05$, $p< 0.001$ and $p< 0.0001$ respectively when compared with group II (a) and III (b).



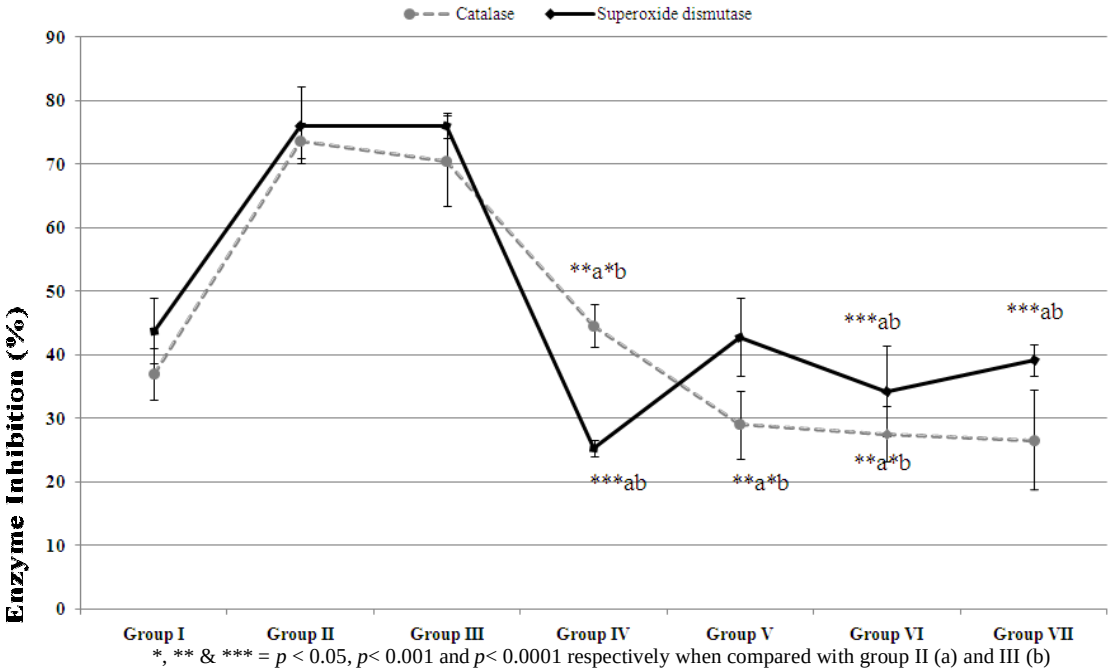
* & *** = $p < 0.05$ and $p< 0.0001$ respectively when compared with group II (a) and III (b).

Fig. 1: Effect of MREt on percent glycemic and body weight change .



*** = $p< 0.0001$ when compared with group II and III

Fig. 2: Effect of MREt on HbA_{1c} to Hb ratio .



*, ** & *** = $p < 0.05$, $p < 0.001$ and $p < 0.0001$ respectively when compared with group II (a) and III (b)

Fig. 3: Effect of MREt on percent inhibition of antioxidant enzymes .

Effect of MREt on hepatic biomarkers

Elevated levels of ALT, AST and ALP were found in both diabetic and negative control groups while glibenclamide and MREt recover ($p<0.0001$) the levels of these enzymes in their respective groups (Figure 3). On the other hand, decreased content of total protein was found in diabetic control groups which was also considerably improved ($p<0.05$**)** in groups from IV to VII (Table 1).

Effect of MREt on antioxidant enzymes

All three doses of MREt significantly decreased the percent inhibition of CAT and SOD in group V, VI and VII as compared to group II and III ($p<0.0001$, $p<0.001$ & $p<0.05$) that showed increase in precent inhibition of these enzymes. Similar significant effect was also observed by glibenclamide in group IV on these antioxidant enzymes (Figure 3).

Effect of MREt on complete blood profile

The RBC count was gradually improved ($p<0.0001$, $p<0.001$ & $p<0.05$**)** in group V, VI and VII treated with MREt when compared with group II and III where reduce levels of same count was found. In contrast, WBC count was decreased significantly ($p<0.0001$, $p<0.001$ & $p<0.05$**)** in same three MREt treated groups. Similarly, other hematological parameters including PCV, MCV, MCH and MCHC levels were found better ($p<0.0001$, $p<0.001$ & $p<0.05$**)** in test groups (Table 2).

DISCUSSION

The present study is actually the continuation of our previous study, which describes that MREt of *R.serpentina* has noteworthy potential in lowering the blood glucose levels in alloxan-induced diabetic mice (Qureshi *et al.*, 2009). Beside this, the same extract was found effective in normalizing the alterations exist in lipid profile due to alloxan-induced hyperglycemia and improved the cardio-protective indices, thereby minimizing the risk of cardiovascular problems (Azmi and Qureshi, 2012a). Similarly, in this study, the doses of MERt (10-60mg/kg) showed significant percent reduction ($p<0.0001$) in blood glucose levels in all three test groups. The reproducibility of this result confirms the antidiabetic ability of MREt of *R.serpentina* which was previously described that it might due to extra-pancreatic action of extract (Azmi and Qureshi, 2012b). Interestingly, this concept is more strengthen by a recent computational study which describes that few alkaloids including ajmalicine, yohimbine, reserpine, ajmaline, etc of *R.serpentina* may serve as activators of insulin receptors (Ganugapati *et al.*, 2012). These are well-reported alkaloids from roots of this plant (Azmi and Qureshi, 2012b) and presence of alkaloids was also detected in MREt in our last paper (Azmi and Qureshi, 2012a). In the same manner, extra-pancreatic mode of action of glibenclamide has already been reported (Kaku *et al.*, 1995) and this known antidiabetic drug also showed significant percent glycemic reduction in alloxan-induced diabetic mice.

Another noticeable feature of present study is the gradually improved body weights of mice found in three test groups treated with 10, 30, and 60 mg/kg of MREt ($p<0.05$ & $p<0.0001$) and this improvement is exponential with increase in doses hence extract may also helps to restores body tissue proteins. The hypoglycemic action of extract was more supported by observing a prominent decrease in HbA_{1c} to Hb ratio in all test groups ($p<0.0001$). HbA_{1c} is the non-enzymatic glycosylated (glycated) hemoglobin and its increase levels are normally appeared in diabetic patients which not only tell the severity of

hyperglycemia to physicians but it also affect the total Hb content in patients. Anemia has also been reported in more than 25% diabetic patients and unfortunately there are few antidiabetic drugs like thiazolinedione can induce anemia as their side effects (Thomas *et al.,* 2003). Therefore, an effective antidiabetic drug should recover the total Hb content and decrease the percentage of HbA_{1c}, this actually improves the HbA_{1c} to Hb ratio in patients as the glibenclamide (positive control) did in this study. Amazingly, extract has done the same and HbA_{1c} to Hb ratio found in test groups was as same as observed in normal control group.

One of the drawbacks of hyperglycemia is the production of ROS which become the prime cause of chronic complications of diabetes as well as reducing the half-life ($t_{1/2}$) of RBCs (the normal is 120 days) by disturbing the osmotic fragility of these cells via generating superoxide radicals due to increased xanthine oxidase activity and these free radicals then involved in oxidation of RBC's membrane proteins and lipids that makes them susceptible to hemolysis (Saba *et al.,* 2010). In addition, impaired production of erythropoietin from kidney in diabetic condition also alters the process of erythropoiesis that results in decrease RBC count (Thomas, 2008).

The decrease in RBC count is also the reflection of low Hb content in diabetic patients (Thomas *et al.,* 2003). On the other hand, increased WBC count observed in diabetic control groups which may be due to the pancreatic assault associated with alloxan-induced diabetes (Tanko *et al.,* 2011). In the present study, doses of MREt significantly improve ($p< 0.05$) the RBC count and normalize the WBC count in all three test groups.

The gradual improvement in RBC count in test groups in dose-dependent manner also significantly recover ($p<0.001$) the other parameters of complete blood profile like PCV, MCV, MCH and MCHC in test groups while normal levels of WBC indicates the decrease in pancreatic inflammation or necrosis. PCV is also referred as erythrocyte volume fraction (EVF) and provides an information about the volume of blood occupied by RBC while MCV is the average RBC volume that use to report the types of anemia in pure anemic condition or in anemia secondary to other pathological problems like diabetes (Hoffman *et al.,* 2005). The MCH and MCHC represent the mean Hb concentration per erythrocyte and per given volume of packed red blood cells respectively, both are also serve indicators of anemia as these severely affected by low levels of total Hb in patients (Hoffman *et al.,* 2005).

Therefore, the beneficial impact of MREt in improving the haematinic profile in alloxan-induced diabetic mice may be due to reducing the oxidative stress in body thus establishes the osmotic fragility of RBC and restoring the total Hb concentration in blood. The oxidative stress reducing ability of MREt is more evident by observing the significant decrease in percent inhibition of antioxidant enzymes viz., CAT and SOD in livers of MREt treated test mice as compared to both diabetic control groups that showed marked increase in percent inhibition of both these enzymes. On the basis of function, SOD and CAT work together as SOD converts superoxide anion into hydrogen peroxide, which then decomposes by CAT into water and oxygen thereby preventing the body cells or tissues from toxic effects of free radicals (Mao *et al.,* 1993). Therefore, MREt positively involve in elevating the antioxidant status of alloxan-induced diabetic test mice. This observation is strongly supported by a computational study which described that few indole alkaloids of *R.serpentina* act as inhibitors of aldose reductase, the rate-regulatory enzyme of polyol pathway, an alternate pathway of glucose metabolism in diabetic condition which leads to the production of ROS (Pathania *et al.,* 2013).

The chances of toxicity associated with oral administration of MREt were completely diminished by observing the normal serum levels of liver-specific enzymes including ALT, AST and ALP in test mice while their elevated levels observed in diabetic control groups which was possibly due to the oxidative damage produced by alloxan in hepatocytes. This is another proof that supports the antioxidant potential of extract. Glibenclamide was also found effective in this regard.

Liver is the chief site where orally administrated drugs have their first pass metabolism and any alteration in this tissue made by the subjected pharmacological agent reflects in the elevated levels of specific enzymes of this tissue *viz.*, ALT, AST and ALP (Azmi and Qureshi, 2012a; Bishop *et al.,* 2010). Determination total protein in serum also one of the ways to assay liver function as 90% of total proteins except immunoglobulins are synthesized in liver and any damage in liver will decrease the synthesis of total proteins.[24] In this study, MREt also confirms its role in restoring the function of liver by observing normal levels of total proteins in test mice while decrease levels of same parameter were observed in diabetic and negative control groups ($p<0.05$). The normal level of serum total protein ranging from 6-8g/dl (Bishop *et al.,* 2010) and interestingly almost same was observed in test mice in present study.

CONCLUSION

The results of present work conclude that MREt of *R.serpentina* not only improves hyperglycemic but also haematinic status of alloxan-induced diabetic mice by significantly up-grading the antioxidant enzyme system. Work is still required to evaluate the antidiabetic potential of this plant in different fractions of MREt which will help to isolate and characterize the active ingredient involve in this activity.

CONFLICT OF INTEREST

The authors affirm no conflict.

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