Antioxidant and Hepato-protective effect of Desmodium gangeticum (L.) DC. ethanolic extract in Streptozotocin induced rat model of diabetes mellitus

Abstract:

Ethno-pharmacological relevance: Desmodium gangeticum (L.) DC.(DG) is well explored and well documented traditional Indian medicinal plant used to treat various ailments like neurological imbalances, anti-diabetic, anti-leishmanial, anti-inflammatory etc.
Aim of the study: To evaluate the hepato-protective and antioxidant effects of whole plant ethanolic extract of Desmodium gangeticum (L.) DC. (DGE) in Streptozotocin induced diabetic rats.

Materials and methods: The DGE was administered in diabetic rats at varied doses. Glibenclamide was used as positive control. The oxidative stress was measured in the liver by the level of antioxidant markers i.e. lipid peroxidation (indicated by MDA), superoxide dismutase (SOD), reduced glutathione (GSH), glutathione peroxidase (GPx) and catalase (CAT) and the hepatic enzyme marker levels i.e. serum glutamic pyruvic transaminases (SGPT), serum glutamic oxaloacetic transaminases (SGOT) and alkaline phosphatase (ALP) were determined in diabetic control and treated rats.

Results: Oral administration of DGE at doses of 100,200,400 mg/kg, significantly (p˂0.05) increased CAT, GPx, GSH and SOD in hepatic tissues in diabetic rats. The increased level of MDA was found to get reverted back to near normal. DGE extract also showed reduction of SGPT, SGOT and ALP levels in diabetic rats.

Conclusion: The results clearly suggest that DGE exerted hepato-protective and antioxidant effects in the treated groups at dose dependent manner.

KEY WORDS: Desmodium gangeticum, Hepato-protective, antioxidant, antidiabetic , Streptozotocin.

Graphical abstract:

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder that is getting transformed into a deadly disease as projected by the Recent World Health Organization (WHO) diabetes statistics. According to the statistics, worldwide, the number of people with diabetes has substantially increased between 1980 and 2014, rising from 108 million to 422 million that is nearly four times higher. (WHO REPORT)

DM occurs whenever there is damage /exhaustive deterioration of β-cell function wherein body is unable to produce or properly use insulin, as per the demand leading to prolonged and severe hyperglycemia (Gerich, 2003).Hyperglycemia which is regarded as the most significant attribute to diabetes is mainly due to body’s impaired ability to maintain glucose homeostasis and is indicated by elevated fasting blood glucose (FBG) levels. (Elham Ghanbari, and Lezek 2011). DM involves multiple organs and multiple pathways. Hence uncontrolled diabetes ultimately results in end organ damage along with several micro and macro vascular complications like retinopathy, nephropathy, peripheral neuropathy, hypertension etc(Beckmann et al.,2002).

Substantial evidence in the literature indicates that among various pathways that contribute to DM and its complications, the main culprit is chronic hyperglycemia induced oxidative stress. This oxidative stress is due to overproduction of free radicals, especially reactive oxygen species (ROS) and an inferior antioxidant defense, (Fatmah A Matough,et ,al.2012)(Liu 2017).via over activity of the hexosamine pathway (Brownlee, 2001)increased flux of glucose through the polyol pathway (Chung et al., 2003), increased production of advanced glycation end products (AGEs) (Prabakaran,D. Ashok kumar,N), and increased activation of protein kinase C (PKC) (Noh and King, 2007). An overdrive of the electron transport chain, resulting in overproduction of superoxide radical, hydrogen peroxide (H2O2) and hydroxyl radical anions . (Dave and Kalia, 2007). Maher M Al-Enazi). Glucose autoxidation (Maritim et al., 2003),

The over production of free radicals like molecular oxygen are responsible for interacting with biological macromolecules such as lipids, proteins and DNA, and causing structural and functional abnormalities in them ,hence lead to development of diabetic complications (Yavuz O, Cam2003. Yavuz O, Cam), also influence the signal transduction pathways, boosting of immunity against invading microorganisms and gene expression to the promotion of growth or death (Lee J.).
Liver is the main effector organ responsible for performing array of functions like glucose, lipid hemostasis and gluconeogenesis (Adewole & S. Indradevi). This involvement of liver makes it more vulnerable to diseases especially in patients with metabolic disorders like DM. (Rigobello). There is enormous evidence indicating liver disease to be one of the major causes of mortality in patients with DM (Gilson Teles Boaventura, year). Virtually the entire spectrum of liver disease is seen in patients with type 2 diabetes. It also includes Non-alcoholic fatty liver disease (NAFLD), cirrhosis, hepatocellular carcinoma, and acute liver failure (Ali Akbar Abolfathiet al). The association of liver disease with diabetes is also confirmed from the Insulin resistance Atherosclerosis study (IRAS) which proves that the liver function markers like the SGOT and SGPT are predictors of incident diabetes. (Haney et al., 2004) The biomarkers of oxidative stress are elevated in the liver at an early stage (Stadler et al., 2003) this elevation is the direct reflection of the alterations in the hepatic structural integrity (Elham Ghanbari).

Streptozotocin (STZ), an antibiotic produced by Streptomyces achromogenes, is frequently used to induce DM in experimental animals through its toxic effects on pancreatic β-cells. The cytotoxic action of STZ is associated with the generation of ROS causing oxidative damage (T. Szkudelski,)

The use of synthetic oral anti-diabetic agents and insulin is declining because of the various side effects associated with them like hypoglycemia, and weight gain. As evidenced from literature review antioxidant enzymes like Vitamin C, Vitamin D, SOD, CAT, GPX, GST etc. (Budin et al., 2009) are impaired in DM. Antioxidant compounds taken either through diet or as supplements could reduce the risk of DM and its complications hence prove beneficial (Rangkadiolk et al., 2007) In view of the poorly controlled diabetes through synthetic agents and the role played by oxidative stress in progression of DM and its complications, many of the diabetic patients, healthcare professionals, shifted their focus from allopathic to complementary and alternative medicine (Grover et al., 2002) i.e. towards natural substances with superior antioxidant properties and antidiabetic properties. Clinical research has confirmed the efficacy of several plants and its active compounds. Of the various phytochemical constituents Flavonoids and polyphenols are known to have powerful antioxidant activity that could play a protective role in oxidative stress-mediated diseases. (Maher M Al-Enazi)

According to WHO, almost 70% of the diabetic patients use plants as a primary source of anti-diabetic agents in order to satisfy their principal health needs (Bailey and Day, 1989). This is because the herbal component is associated with diverse mechanism and good efficacy. More than 800 plants have been reported to have anti-hyperglycemic effects with less adverse effects and low toxicity as compared to synthetic compounds (Kirithikar and Basu, 1995; Nadkarni, 1976).

Desmodium gangeticum (L.) DC. (DG) (Family: Fabaceae) commonly known as Shalaparni is an important species of the genus Desmodium. It is an erect, semi-woody herb or under shrub up to 2m high seen on damp sites. It is found in tropical and sub-tropical climatic conditions. It is extensively practiced as traditional medicine in India because of its therapeutic potentiality. Used in Ayurvedic preparations like ‘Dashmoolarishta’ and ‘Dashmoolakwaath’ recommended for post-natal care to avoid secondary complications. (Kamidi VK, 2012.) Moreover, pharmacological studies reveal the potentiality of DG extract and its active principles viz. desmodin, hordenine and gangetin as anti-amnesic, immunomodulator, anti-diabetic, antioxidant, cardio-protective, hepatoprotective, anti-inflammatory drug, Antibacterial, etc., (Atano battachaterjee).

The earlier studies show that Desmodium gangeticum possesses flavonoids, tannins, glycosides that are the major chemical constituents responsible for exhibiting antioxidant activity. Although all the morphological parts of the plant have been claimed to be useful in traditional medicine, no scientific studies have been carried out to establish the hepatoprotective and antioxidant effects of the plant specifically related to diabetes. Therefore the present study was undertaken to investigate the hepato-protective and antioxidant effects of ethanolic extract of whole plant of DG in diabetic rats.
2. Materials and methods

2.1. Plant material

Whole plant material of Desmodium gangeticum (L.) DC. was collected from the deciduous forest of Tirumala Hills in Andhra Pradesh, (India) in the month of October. The taxonomical identification of the collected plants was authenticated by Dr. K. Madhava Chetty, Plant Taxonomist, Department of Botany, Sri Venkateswara University, Tirupati, India. A voucher specimen has been deposited at Sri.Venkateshwara University for further reference.

2.2. Chemicals and reagents

All chemicals and reagents used in this study were obtained commercially and were all of analytical grade.

2.3. Animals

Male Wistar albino rats weighing 150-200 g were procured from Sai Animal Distributors, Musheerabad, Hyderabad (India) kept at departmental animal house of Shadan college of Andhra Pradesh (India). The animals were acclimatized by placing them at a temperature of (25 ± 2°C), 12 h light/dark cycle and 60 ± 5% relative humidity respectively for 1 week before and during the experiments and fed with commercial pelleted rats chow and water ad libitum. Animal studies were conducted according to the Institute Animal Ethics Committee regulations approved by the Committee for the Purpose of Control and Supervision of Experiments on Animals. The animals were handled gently to avoid giving them too much stress, which could result in an increased adrenal output.

2.4. Preparation of Desmodium gangeticum extract:

Dried and powdered whole plant material of Desmodium gangeticum was purchased from a commercial source (Madhav chetty). The powdered material was soaked with 70% ethanol overnight in Soxhlet thimble. The residue in the R.B flask was transferred into a beaker and was concentrated under reduced vacuum pressure to give an average yield of 70% (w/w). Solutions of the Desmodium gangeticum extract (DGE) were prepared freshly for the pharmacological studies.

2.5. Preliminary phytochemicals studies

The extract was subjected to various phytochemicals tests to determine the active constituents present in the ethanolic extracts of Desmodium gangeticum.

2.6. Acute Toxicity Study

Acute oral toxicity test for the ethanolic whole plant extract of Desmodium gangeticum was carried out as per OECD Guideline 425 425.[OECD guidelines 425].

When administered orally, the ethanolic extract of Desmodium gangeticum was found to be non-toxic up to the maximum dose of 2000mg/kg body weight. As such, the limit test at 2000 mg/kg, which required the use of only five albino rats, was performed. One–tenth and one-twentieth of the upper bound dose of the extract from the limit test was decided to be considered for the experiments.

2.7. Experimental induction of diabetes

DM was induced after 12-hour over-night fasting, the rats were given an intra-peritoneal (IP) injection of
freshly prepared Streptozotocin (STZ, Sigma, USA) at the dose of 65 mg/kg body weight (BW) in 0.1 mol/L citrate buffer (pH=4.5) (21). Since Streptozotocin is capable of producing fatal hypoglycemia as a result of massive pancreatic release of insulin, the rats were kept on 5% glucose for next 24hrs to prevent hypoglycemia (8-9). On days 3 and 7 after STZ injection, blood samples were collected from tail veins. The blood glucose level was detected by Glucose Oxidase Principle (Beach and Turner) using the one touch basic (Bayer Diagnostic) instrument and results were reported as mg/dl in order to confirm the diabetes. The rats with FBG levels >280mg/dl were considered diabetic and used for research work.

2.8. Experimental design:

Forty Rats that were procured were randomly divided into six groups (six rats in each group; n=6).

Group 1: Normal control (non-diabetic) and received normal saline

whereas the rest of the 34 rats were induced diabetes by Streptozotocin 65mg/kg/i.p. On the seventh day of the induction Blood glucose levels were estimated from the tail tip using Bayer one touch glucometer and the rats with blood glucose levels >280mg/dl were considered diabetic and used for research work.

Group 2: Diabetic control

Group 3: Diabetic + standard drug glibenclamide (600 μg/kg, p.o.).

Group 4: Diabetic + ethanolic extracts of DG at dose of 100mg/kg (p.o.)

Group 5: Diabetic + ethanolic extracts of DG at dose levels 200mg/kg (p.o.)

Group 6: Diabetic + ethanolic extracts of DG at dose levels 400mg/kg (p.o.)

The treatment with the extract was continued once daily at 09:00a.m. for 28 days.

Blood glucose levels were estimated on the 1st, 7th, 14th, 21st and 28th day of treatment (Gupta et al., 2004).

2.9. Biochemical analysis:

At the end of experiment, blood samples were collected from the retro-orbital plexus and the sera prepared through centrifuging at 2500×g for 15 minutes at 30°C. Serum biomarkers of liver function including, serum glutamic pyruvic transaminases (SGPT), serum glutamic oxaloacetic transaminases (SGOT) alkaline phosphatase (ALP), were measured using methods described by Reitman and Frankel [yy], Kind and King respectively. Serum glutamic pyruvic transaminases (SGPT), serum glutamic oxaloacetic transaminases (SGOT) were measured to determine the concentration of intracellular hepatic enzymes that have leaked into the circulation and serve as a marker of hepatocyte injury.

2.10. Determination of Blood Glucose levels

Blood samples were obtained by needle puncture of the tail tip veins. Blood glucose concentrations were determined by means of Bayer Glucometer Elite® and compatible blood glucose test strips.

2.11. Preparation of liver homogenate:

Animals were sacrificed by cervical dislocation. The livers were carefully removed, weighed and washed in ice-cold saline to remove the blood. Liver homogenates were prepared by homogenizing the tissues in a 0.1 M phosphate buffer pH 7.4. The homogenate was centrifuged at 3000 rpm, 4°C for 10 min. The supernatant
fraction was collected and further centrifuged at 136,000 g, 4˚C for 60 min. The supernatant was separated and used for various antioxidant enzyme estimations.

2.12. Determination of the Antioxidant Enzymes levels in liver homogenate:

The levels of Malondialdehyde (MDA) indicator for the lipid peroxidation in the tissue were estimated as per the method described by Okhawa et al. (1979) based on TBA reactivity. The post-mitochondrial supernatant was used for the estimation of Superoxide dismutase (SOD) using the method described by Mc Cord and Fridvoich. The activity of catalase (CAT) was determined by the method of Aebi. H, reduced glutathione (GSH) and Glutathione peroxidase were estimated by the method described by Ellman GL, Paglia and Valentine, respectively.

2.13. Statistical analysis:

Data were expressed as mean+SEM and the data was analyzed by ANOVA, followed by Dunnet’s t- test (n=6) using WINKS SDA STAT software. Values were considered to be significant at P ≤ 0.05

3. Results

3.1. Phytochemical tests:

Preliminary phytochemical analysis of the crude ethanolic extract showed the presence of alkaloids, flavonoids, steroids, terpenoids, and volatile oil.

3.2. Acute toxicity studies:

Acute toxicity studies revealed that the administration of crude ethanolic extract (50–2000mg/kg) of Desmodium gangeticum did not produce significant changes in the behavior of the animals as observed by lack of convulsions, respiratory distress, writhing, changes to reflex activity or mortality. During first week, all animals seemed well with no observable changes in behavior or appearance. No deaths were observed up to 1 week of study.

3.3. Anti-hyperglycemic effect of Desmodium gangeticum:

Blood samples were obtained by needle puncture of the tail tip veins. Blood glucose concentrations were determined by means of Bayer Glucometer Elite® and compatible blood glucose test strips. Changes in blood glucose level in normal, diabetic and on treatment for diabetes rats with various ethanolic extract of Desmodium gangeticum and glibenclamide are presented in Table1. Ethanolic extracts of Desmodium gangeticum at concentrations of 100,200 and 400mg/kg decreased blood glucose level from 215.15 to 99.98±2.11 mg/dl, 210.15±2.86 to 89.67±3.43 and from 210.65±1.43 to 79.42±2.06mg/dl respectively. The effect was evident from the 7th day onwards. Group treated with standard drug Glibenclamide (600 μg/kg, p.o.) showed similar results and caused significant reduction (p˂ 0.01, ANOVA with Dunnett’s t-test) in blood glucose level, decreasing the mean blood glucose level from 201.03±4.36 to 78.34±2.66 mg/dl.

As evident from the table the anti-hyperglycemic effect of the various ethanolic extracts of Desmodium gangeticum was comparable to that of standard drug Glibenclamide.

Figure 1: Effect of daily oral administration of various ethanolic extracts of Desmodium gangeticum and Glibenclamide on blood glucose level of STZ-induced diabetic rats.
3.4. Effect of Desmodium gangeticum on hepatic marker enzymes in normal and STZ induced diabetic treated rats

Table 2: summarized the effects of STZ on the activity of hepatic marker enzymes in serum. In the present study the levels of serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT) and alkaline phosphatase (ALP) in STZ-induced diabetic rats were elevated. Administration of the ethanolic extracts of Desmodium gangeticum at concentrations of (100,200 and 400mg/kg) significantly reduced (p˂0.01, n=6; one way ANOVA with Dunnett’s post hoc test) serum SGPT, SGOT and ALP in rats intoxicated with STZ. The restoration of hepatic enzymes was comparable to standard drug glibenclamide (p˂0.01, n=6; one way ANOVA with Dunnett’s post hoc test).

Table 2: Effect of ethanolic extract of Desmodium gangeticum (DGE) on Hepatic biomarkers of normal and STZ induced diabetic treated rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>SGPT (IU/L)</th>
<th>SGOT (IU/L)</th>
<th>ALP (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal rats</td>
<td>61.60 ± 2.56</td>
<td>57.07 ± 4.12</td>
<td>36.03 ± 0.62</td>
</tr>
<tr>
<td>Diabetic control rats</td>
<td>131.68 ± 2.25</td>
<td>146.80 ± 6.30</td>
<td>105.4 ± 0.38</td>
</tr>
<tr>
<td>Diabetic+DG 100(mg/kg)</td>
<td>100.23 ± 2.13*</td>
<td>112.43 ± 2.34*</td>
<td>66.16 ± 0.25*</td>
</tr>
<tr>
<td>Diabetic+DG 200(mg/kg)</td>
<td>77.20 ± 2.70**</td>
<td>92.43 ± 1.74**</td>
<td>52.07 ± 0.12 *</td>
</tr>
<tr>
<td>Diabetic+DG 400(mg/kg)</td>
<td>77.20 ± 2.70**</td>
<td>64.46 ± 5.05***</td>
<td>47.17 ± 0.61**</td>
</tr>
<tr>
<td>Diabetic+Glibenclamide</td>
<td>110.01 ± 2.65*</td>
<td>90.92 ± 3.46**</td>
<td>40.92 ± 0.17***</td>
</tr>
</tbody>
</table>

The data are expressed as mean ± SEM (n = number of animals in each group = 6). The comparisons were made by one way ANOVA followed by Dunnent’s test. ns non-significant, STZ – Streptozotocin.

Diabetic control rats were compared with normal control rats.
Diabetic + Desmodium gangeticum and Diabetic + Glibenclamide treated were compared with diabetic controlled rats.

*P<0.05, **P<0.01, ***P<0.001 with respect to the Diabetic Control Group (ANOVA with Dunnett’s t-test)

3.5. Effect of Desmodium gangeticum on oxidative stress parameters in normal and STZ induced diabetic (treated) rats:

Table 3 clearly illustrates the effect of DGE on the antioxidant enzymes. A marked reduction was noted in the level of superoxide dismutase (SOD), catalase (CAT), Glutathione Peroxidase (GSH-Px) and reduced glutathione (GSH) in the STZ induced diabetic rats. Administration of DGE at different doses for the 28 days to STZ induced diabetic rats significantly (p < 0.05) increased SOD, CAT, GSH-Px levels with maximum effect seen at 400 mg/kg body weight. The enhanced level of TBARS was reversed to near normal after administration of DGE. It is pertinent to note that the DGE was
found to be equipped with the antioxidant effect in a dose dependent manner (Figure 3).

Table 3: Effect of ethanolic extract of Desmodium gangeticum (DGE) on oxidative stress parameters in liver of normal and STZ induced diabetic treated rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Oxidative stress Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SOD (units/mg protein) CAT</td>
</tr>
<tr>
<td>Normal rats</td>
<td>10.49 ± 0.68 71.25 ± 2.17 9.38 ± 0.91 129.67 ± 2.66 0.78 ± 0.51</td>
</tr>
<tr>
<td>Diabetic control rats</td>
<td>4.65 ± 0.17 38.67 ± 1.92 5.19 ± 0.88 74.23 ± 1.51 1.59 ± 0.11</td>
</tr>
<tr>
<td>Diabetic + DG 100(mg/kg)</td>
<td>7.27 ± 1.01 * 46.23 ± 2.36* 6.11 ± 0.74 99.76 ± 4.32 * 1.26 ± 0.18*</td>
</tr>
<tr>
<td>Diabetic + DG 200(mg/kg)</td>
<td>9.71 ± 1.22 ** 63.21 ± 3.69*** 7.27 ± 1.36* 107.97 ± 1.97* 1.01 ± 0.23*</td>
</tr>
<tr>
<td>Diabetic + DG 400(mg/kg)</td>
<td>9.80 ± 1.67 ** 65.31 ± 2.56*** 9.17 ± 0.88** 118.67 ± 2.54** 1.02 ± 0.08**</td>
</tr>
<tr>
<td>Diabetic + Glibenclamide</td>
<td>10.90 ± 0.14 *** 70.22 ± 1.24*** 9.24 ± 0.61*** 128.67 ± 1.41*** 0.81 ± 0.21***</td>
</tr>
</tbody>
</table>

The data are expressed as mean ± SEM (n = number of animals in each group = 6). The comparisons were made by one way ANOVA followed by Dunnent’s test. ns non-significant, STZ –Streptozotocin.

4. Discussion:

Traditional usage of plant medicines is as old as the mankind. Plant medicines are used throughout the world for a range of diabetic complications. The Ayurveda of Indian traditional medicine has enormous usage of plant drugs for treatment of DM. Unfortunately only few of them could be scientifically scrutinized. Plant
drugs are frequently considered to be less toxic and free of side effects than synthetic ones (). The research that involves plant drugs might offer a solution to unlock a diabetologist's pharmacy for the future. The present research was done to evaluate the protective effects of Desmodium gangeticum (L.) DC. whole plant ethanolic extract on antioxidant status and its protective effects against hepatic injury. Drug-induced diabetes is one of the most commonly used experimental diabetic models that has provided considerable physiological and biochemical insight to the diabetic state (Sakata N). STZ diabetic model is one of the important and most widely accepted and utilized method to induced diabetes comparable to human diabetes. In the present study diabetes was induced in rats by intra-peritoneal injection of streptozotocin(65 mg/kg b.w).

Streptozotocin enters the pancreatic β-cells through one of the important glucose transporter known as GLUT 2. It damages the β-cells of pancreas by generating excess ROS and Carbonium ion (CH3+) which finally leads to DNA alkylation causing tissue damage by oxidative stress and hyperglycaemia. (Parminder Nain, 2012; Moradi-Afrapoli et al. 2012). Furthermore, the damage is also done by the production of superoxide radicals, formation of nitric oxide free radicals. Therefore, free radicals play an important role in the development of diabetes mellitus by causing the partial destruction of β-cells [Santini SA]. In view of that, we hypothesized that free radicals scavenging properties of a compound can ameliorate the diabetic conditions.

As a result of the STZ action, pancreatic β-cells undergo destruction by necrosis (Szkudelski, 2001). In STZ induced diabetic rats, the elevation in fasting blood glucose along with decrease in liver glycogen levels may be due to lower levels of plasma insulin The continuous treatment of diabetic rats with DGE for a period of 28 days produced a significant (p<0.05) decrease in blood glucose levels as reported in our previous study, which shows that DGE showed a hypoglycemic effect on diabetic rats (Yasmeen et al, 2010) which is comparable to that of the standard drug Glibenclamide and the diabetic control group. Several other studies have shown the benefits of this plant extract in the management of Diabetes Mellitus, the hypoglycemic effect of DGE (p<0.001) was also reported by (Rekha Bisht and 2S. Bhattacharya).

Many of the plant and their extracts have shown to exert hypoglycemic action through stimulation of insulin release [52,53]. The hypoglycemic action of the DGE is comparable to the conventional sulfonylurea i.e. Glibenclamide that is reported to enhance the insulin release from the beta cells of pancreas though their activation.

It was also reported that D. gangeticum extract caused a significant increase in insulin secretion from MIN6 cells grown as monolayers and as pseudoislets, indicating that the antidiabetic activity may be as a result of increased insulin secretion (Govindarajan).

In the present study elevation in biomarker enzymes like SGPT, SGOT and ALP was observed which could be attributed to cytotoxicity by STZ. This was in accordance with the reports from several investigations that have shown that the liver cells are irreversibly destroyed in STZ-induced diabetic rats and the hepatocellular damage was indicated by the elevation of hepatic biomarker enzymes levels like SGPT, SGOT and serum ALP in the blood of diabetic rats. (Daisy et al., 2008). Gluconeogenesis and ketogenesis complications associated with DM might be due to elevated transaminase activity. (Ghosh and Suryawanshi, 2001). The ethanolic extract of Desmodium significantly lowered the SGPT, SGOT and ALP levels the hepatic damage was restored and integrity of hepatocytes was maintained. Form this point of view DGE may act as hepatoprotective agent.

The liver damage caused by diabetes is probably due to lipid peroxidation subsequent to free radical production. Reactive Oxygen Species (ROS) produced due to the oxidative stress are highly toxic and are capable of unleashing the Lipid peroxides and hydroperoxides (Karthikesan et al 2012). Measurement of plasma thiobarbituric acid reactive substances (TBARS) indicated by MDA levels serves as an index of lipid peroxidation and also used to assess the extent of tissue damage that is done. Several studies have reported increased lipid peroxidation in plasma and various tissues like liver and kidney both in clinical and experimental diabetes. (Singh & Kakkar 2009) The treatment with flavonoid fraction of DG reduced MDA.
levels in liver of Carrageenan-induced Inflamed Rats (govindrajan et al, 2007). Also, Kurian et al have reported that treatment with DG extract reduced MDA levels in ischemic reperfusion injury by oxidative stress in rat and showed cardio protection. The result of the present study shows that treatment with DGE significantly (p<0.05) decreases the MDA levels and hence lowered the risk of hepatic damage.

Antioxidant enzymes that form the first line of defense against ROS include SOD, CAT, GPx and GST, which play an important role in scavenging the toxic intermediate of incomplete oxidation. Antioxidant capacity is reduced significantly in the plasma of STZ-induced diabetic rats, which can increase the deleterious effects of free radicals. The two major free radical scavenging enzymes are SOD and CAT. The decreased activity of endogenous antioxidant enzymes (SOD and CAT) leads to overproduction of the superoxide anion and hydrogen peroxide (H2O2) radical resulting in LPO and tissue damage. SOD is the major enzyme that protects tissues against oxygen free radicals by scavenging the superoxide radical. Catalase detoxifies H2O2 and protects the tissues from hydroxyl radicals. Reduction in CAT activity may be due to inactivation of the enzyme by glycation. Therefore removing O2 and OH is probably one of the most effective defenses against diseases (Sankaranarayanan and Pari, 2011). Reduction in the SOD and CAT activities in diabetic rats is supported by the results of Elham ghanbari. Also studies by Govindarajan et al , Kurian et al have indicated that DG extracts caused a significant elevation in the activities of GSH-Px, SOD and CAT of liver and spleen tissue in Carrageenan-induced Inflamed Rats and in cardiac tissue of rats under oxidative stress due to ischemic reperfusion injury. In the present study, a decrease in the SOD and CAT activity suggested that oxidative stress was increased in diabetic rat, and a significant elevation of SOD and CAT levels were observed in the DG-treated diabetic rats which is likely due to its free-radical-scavenging activity.

Glutathione is a tripeptide, which acts as an intracellular antioxidant and functions as free radical scavenger, co-substrate for peroxide detoxification by glutathione peroxidases and protects the cellular system against the deleterious effects of LPO. (Ananthan et al., 2004). During the present study in diabetic rats, it was observed that there is a significant decrease in GSH levels in liver tissue. The induced alteration/decrease in GSH content in whole blood and plasma reflect the increased utilization for neutralizing free radicals due to oxidative stress in diabetic rats. This finding is in consistent with the results of (Venkateswaran and Pari, 2003 and Sudhakara et al.) [47]. Treatment with the DGE extract resulted in elevation of the GSH levels, which protects cellular proteins and the cell membrane against oxidation through the glutathione redox cycle and also directly detoxifies reactive oxygen species generated from exposure to STZ (parsley extract).

GPx, an enzyme with selenium and works together with Glutathione, catalyzes the reduction of hydrogen peroxide and other hydroperoxides to non-toxic compounds at the expense of reduced glutathione. (Hygrophilia auriculata). In the present study, decrease in the GPx enzymes levels in liver tissue of streptozotocin-induced animals was observed and the treatment with DGE helped in attainment of increased levels of GPx which indicates that oxidative stress elicited in hepatic tissue of diabetic rats had been nullified due to the effect of the extract.

The results of the present study demonstrate that daily treatment of diabetic rats by DGE extract markedly improves antioxidant status in liver tissue, and serum biomarkers of liver tissue injury. It is therefore likely that DGE extract could be effectively used to treat DM its complications and ameliorates diabetic hepatopathy through its antioxidant potential. On the other hand, there is a need to determine whether the diabetic complications are due to Hyperglycemia induced oxidative stress or direct glycemic injury of liver. The use of this plant DG in diabetes is then well studied and supported but the precise active substance(s) in it, and cellular and molecular mechanism(s) of its pharmacological effect are still to be determined.

5. Conclusion:

Based on our findings, we conclude that STZ treatment is associated with oxidative stress in hepatic tissues, and that Desmodium gangeticum whole plant ethanolic extract has a beneficial effect on hyperglycaemia and possesses antioxidant activity which is able to inhibit and/or prevent hepatic oxidative damage produced by
STZ treatment. Active phytoconstituents such as flavonoids, sterols, terpenoids, phenols, are responsible for antihyperglycaemic, and antioxidant properties of DGE. In addition, the hepatoprotective effect of DGE is demonstrated by the significant reduction of serum levels of ALT, AST, and ALP in the diabetic treated rats. It can be concluded that DGE possesses hepatoprotective and antioxidant effects in streptozotocin-induced diabetic rats. However, further studies are necessary for the isolation and purification of bioactive compounds from DGE and to elucidate the exact mechanism by which DGE elicits its modulatory effects; this could be a limitation of the study. Identification of the potent bioactive compounds with specific chemical moieties might provide a new therapeutic strategy for the treatment and management of diabetes and its complications.

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39. Paglia and Valentine


41. Parminder nain, 2012


44. Szkudelski, 2001

45. Yasmeen et al, 2010

46. 1Rekha Bisht and 2S. Bhattacharya


53. Singh & Kakkar 2009.

54. govindrajan et al, 2007).

55. Also, Kurian et al

56. Sankaranarayanan and Pari, 2011

57. Ananthan et al., 2004

58. Venkateswaran and Pari, 2003

59. Sudhakara et al.

60. Hygrophilia auriculata

61. 28..


Abbreviations:

STZ: Streptozotocin

GSH: Glutathione

SOD: Superoxide dismutase

CAT: Catalase

GPx: Glutathione peroxidase

ROS: Reactive oxygen species

TBARS: Thiobarbituric acid reactive substances

ALP: Alkaline phosphatase

ANOVA: Analysis of variance

LPO: Lipid peroxidation
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