Available online on 25.12.2017 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

EFFECT OF *PARTHENIUM HYSTEROPHORUS* ON OXIDATIVE STRESS IN PANCREATIC TISSUE OF DIABETIC RATS

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ABSTRACT

Increased oxidative stress and decreased endogenous antioxidant defense has been shown to be a prominent and early features in diabetes mellitus. The present study focused on investigating the possible protective role of *Parthenium hysterophorus* against free radical mediated damage in pancreatic tissue of alloxan induced diabetic rats. Diabetes was induced in rats by injecting 150 mg/kg Alloxan monohydrate IP. The results revealed that administration of 50 mg/kg & 100 mg/kg of *Parthenium hysterophorus* extract significantly increased pancreatic glutathione, superoxide dismutase, catalase level ($p<0.01$) as well as significantly reduced pancreatic total nitrate/nitrite content and lipid peroxidation ($p<0.01$) after 72 hr. In conclusion, the study suggests that *Parthenium hysterophorus* is effective in significantly reducing the oxidative stress in pancreatic tissue of diabetes rats as evidenced by the increase in antioxidant enzymes, reduction of lipid peroxidation and total nitrate/nitrite level.

Cite this article as: Patel V, Patidar A, Pagaria S, Effect of Parthenium hysterophorus on oxidative stress in pancreatic tissue of diabetic rats, Journal of Drug Delivery and Therapeutics. 2017; 7(7):223-225

INTRODUCTION:

The role of oxidative stress in both type I & type II diabetes mellitus is currently under investigation[1]. It has been established that locally produced reactive oxygen species (ROS) & nitric oxide (NO) induced after cytokine stimulation are involved in β-cell destruction through the induction of apoptosis[2]. Pancreatic β-cells are particularly susceptible to the deleterious effects of ROS because of their low level of antioxidant enzyme genes as compared to other tissue[3]. Hence the cellular antioxidant status is an important determinant of its susceptibility to oxidative damage. Reduced glutathione (GSH) is an endogenous antioxidant that acts as a first line defense system against pro-oxidant status. Depleted GSH level has been repeatedly reported in several tissues of experimental diabetes animals, including eye, aorta, kidney as well as small intestine. Lipid peroxidation, a key marker of oxidative stress is the result of a chain reaction evoked by ROS & eventually leads to extensive membrane damage & dysfunction [4]. *Parthenium hysterophorus* L. compositae, also known as Congress grass, Chatak chandani (Hindi) is light green with branching stems reaching the height of 2 m in good weeks of germination. All parts of the plant are reported to be used as a bitter tonic, febrifuge, emmenagogue, antidyscentric etc. *Parthenium hysterophorus* is a combination of biologically active flavonoids including guercetagetin & 6-hydroxykaempferol which have marked spectrum against oxygen free radicals & thus holds the promise for the prevention & treatment of variety of human disorders caused by oxidative stress [5].

The present study was thus undertaken to access the protective effect of *Parthenium hysterophorus* on oxidative damage induced by alloxan in rat's pancreatic tissue. The result could serve as a step towards the development of a mechanism based therapeutic approach for the management of diabetes & provide the basis for the usefulness of the potent antioxidants.

MATERIALS AND METHODS:

Chemicals

All the chemicals & reagents were of analytical grade & procured from E. Merck (India) Ltd.

Plant Extraction

Fresh plant of *Parthenium hysterophorus* was collected & authenticated at the plant anatomy research center, Chennai. The flowers were dried under sunlight & powdered. 20gm of the powdered drug was boiled with 100 ml of distilled water for four hours and evaporated to dryness. The yield of extract was about 2.5gm & was suspended in 5% Tween 80 & used for oral administration.

Animals

Adult albino wistar rats of either sex, weighing 150-200 gm were acclimated for a period of 10 days at room

temperature & 50% relative humidity. They were housed in a standard cage & water ad libitum. All the experimental procedures were performed after prior approval from the institutional animal ethical committee and are in accordance with the CPCSEA, India.

Induction of diabetes

Alloxan monohydrate, 150 mg/kg body wt. dissolved in normal saline & injected IP in 18 hr previously fasted animals. After 72 hr, blood glucose level of each animal was measured by glucose oxidase method & rats having blood glucose level more than 200 mg/dl were selected for study.

Experimental design

Rats were divided in to 5 groups of 6 animals each & given following drug treatment orally in a single dose. At the end of 72 hr, all animals were fasted overnight and sacrificed by cervical decapitation. Dissected pancreatic tissue was washed with normal saline. 100 mg of pancreatic tissue was dissolved in 1 ml, 0.1 M Phosphate buffer solution (pH 7.0). The homogenate was centrifuged at 10000 rpm for 20 min at 4^0c and the clear supernatant was used for biochemical analysis.

Group-1 (Normal Control) : Normal rats received 5% Tween 80 suspension only

Group-2 (Diabetic control) : Diabetic rats received 5% Tween 80 suspension only

Group-3 (Standard) : Diabetic rats received 100 mg/kg Vitamin C (ascorbic acid)

Group-4 (Test-1) : Diabetic rats received aq. extract of *Parthenium hysterophorus* 50 mg/kg

Group-5 (Test-2) : Diabetic rats received aq. extract of *Parthenium hysterophorus* 100 mg/kg

Biochemical Analysis

Serum glucose was estimated by autoanalyser using a commercial assay kit (ERBA diagnostic GmbH, Germany), according to the method described by basu. The level of TBARS, malondialdehyde (MDA) a commonly used marker for lipid peroxidation was measured spectrophotometrically by the method of uchiyama & mihara. Total glutathione (GSH) was evaluated by the method of Sedlak and Lindsay. Superoxide dismutase (SOD) was measured by using the method of Ellman. Catalase activity was evaluated using method of Claiborne. The total nitrate/nitrite content, an indicator of NO- production, was estimated in pancreatic tissue homogenate, according to the procedures of commercially available kit (R&D System UK).

Statistical analysis

The results were analyzed by one-way ANOVA test followed by Dennett's test. Graph pad prizm 3.0 software used. The results were expressed as mean ± S.E.M., n=6. P-value <0.05 were considered to be significant.

RESULT AND DISCUSSION:

As shown in table1, Alloxan produced a significant increase in pancreatic MDA level. The administration of *Parthenium hysterophorus* L. extract significantly reduced the pancreatic MDA level compared to diabetic control group at 72 hr ($p<0.01$).

Table 1: Effect of *Parthenium hysterophorus* Linn. on lipid peroxidation, Pancreatic nitrate/nitrite, and antioxidant's level in normal and diabetic rats

S. No.	Treatment	Lipid Peroxidation (MDA) (µM/g)	GSH (mM/g)	CAT (µM of H_2O_2 consumed /mg protein)	SOD (µM/mg protein)	Pancreatic nitrate/nitrite µM /l
1	Normal control	0.16±0.01**	0.110±0.01*	3.51±3.11**	4.91±0.28**	219.43±7.9**
2	Diabetic control	0.32±0.0	0.058±0.02	1.13±1.21	2.78±0.15	501.11±9.89
3	Vitamin C	0.15±0.03**	0.39±0.99**	4.79±2.71 **	4.92±0.27**	201.34±1.8**
4	*P. hysterophorus* Extract 50 mg/kg	0.24±0.01**	0.28±0.05**	1.17±1.07*	3.14±0.85*	199.38±9.5**
5	*P. hysterophorus* Extract 100 mg/kg	0.19±0.01**	0.31±0.01**	2.77±0.90**	4.10±0.14**	151.7±8.9**

The values are mean ± SEM. (n=6). *p<0.05 & **p<0.01; when compared with diabetic control group

Table 1 illustrate that alloxan treatment consistently reduced pancreatic GSH, CAT and SOD content as compared to control group. Administration of *Parthenium hysterophorus* L. extract significantly elevated the pancreatic antioxidant's level ($p<0.05$) and reached maximum level at 72 hr. Such effect was more obvious ($p<0.01$) with high dose of *Parthenium hysterophorus* i.e. 100 mg/kg.

Alloxan caused a significant increase in total nitrate/nitrite content. However Diabetic animal treated with *Parthenium hysterophorus* L. extract showed significant reduction in the pancreatic total nitrate/nitrite level as shown in table1. Such effect was obvious at both doses used following 72 hr.

Alloxan induced diabetes is a well documented model of experimental diabetes. This compound causes severe necrosis of pancreatic β-cells. The sensitivity of β-cells to oxidative stress has been attributed to their low levels of antioxidants compared with other tissue. Accordingly, maintenance of β-cell oxidant status and

their protection against oxidative damage might delay the onset of diabetes as well as the development of its complications.

The current study revealed that alloxan significantly induced hyperglycemia. Such effect might be explained by the possible pancreatic damage caused by observed significant rise in lipid peroxidation as well as total nitrate/nitrite content. Interestingly *Parthenium hysterophorus* restored the oxidant status of pancreatic tissue; such result suggests a protective effect of *Parthenium hysterophorus* against alloxan action.The observed increase in the level of lipid peroxides in alloxan treated rats might be due to the increased generation of different radical species. These radicals have been documented to stimulate degradation of DNA, lipids, and carbohydrates leading to hyperglycemia and related glucose auto-oxidation. These results are in accordance with previous findings whereby alloxan treated rats showed marked increase in pancreatic cells lipid peroxidation.

Alloxan treated rats showed significant elevation of total pancreatic nitrate/nitrite levels. Such finding coincide with the previously published studies that proved the production of NO by β-cells in presence of alloxan, has been implicated in the development of diabetes. NO reacts with the superoxide radical to form the noxious peroxynitrite that contributes in the pathogenesis of diabetes complications. The data presented reveled marked protective effect of *Parthenium hysterophorus* against alloxan induced elevation of total nitrate/nitrite level in pancreatic tissue. Whereby, concurrent treatment with *Parthenium hysterophorus* normalized the pancreatic NO levels.

Alloxan treatment leads to depletion of pancreatic GSH content, which significantly affects the overall Redox potential of the cell. In the current study, the depletion of pancreatic GSH, CAT and SOD effect was reversed by the administration of *Parthenium hysterophorus.* A possible explanation of this effect is that these compound function as free radical scavengers and therefore increase the available free GSH which detoxify the reactive intermediary oxygen product of lipid peroxidation induced by alloxan. In summary, *Parthenium hysterophorus* possess potent protective effect on the induction of diabetes by alloxan. The data provided suggest that the mechanism underlying such protection is mediated via prevention and restoration of pancreatic antioxidant defense system.

CONCLUSION

Based on the oxidative stress hypothesis of alloxan action it was considered as an adequate model for investigating the role of free radicals in the pathology of diabetes mellitus. The present study demonstrates that *Parthenium hysterophorus,* a potent antioxidant can exert anti-diabetic effect by preserving pancreatic β-cell function.

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