PRE-CLINICAL STUDY **OPEN ACCESS**

The Anti-Diabetic, Anti-Oxidative and Hepatorenal Protective Effects of Citrullus Lanatus Seed Oil Against Toxicity Caused by Alloxan in Wistar Rats

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ABSTRACT

Background:

Diabetes Mellitus (DM) is a disorder of metabolism represented by persistent hyperglycaemia due to the non-secretion or insensitivity of insulin. Pancreatic beta cells are responsible to release insulin and maintain blood glucose level. Alloxan is a cytotoxic glucose analogue that is experimentally used to damage pancreatic beta cells of rats for the creation of pancreatitis, oxidative stress and Diabetes. Watermelon seed oil (WMSO) is a reservoir of antioxidants and has been shown to produce defence against oxidative damage. Since oxidative stress is the primary cause of alloxan-induced pancreatic beta cell damage therefore the purpose of this study was to determine the anti-diabetic, anti-oxidative, and hepatorenal protective activities of WMSO on rats with alloxan-induced pancreatic beta cell damage.

Methodology:

In this experimental study, eighteen healthy age-matched male Wistar rats of 150-200g were used and randomly allotted into three experimental groups (n=6). A-Group: (control-untreated), B-Group: (Alloxan-treated), C-Group: (Alloxan + WMSO treated) each containing Six rats. Following overnight fasting, an intra-peritoneal-injection of Alloxan 120mg/kg dissolved within 0.9% saline was given in group B & C rats whereas WMSO was additionally provided to group C rats in a dose of 2.5gm/kg daily via oral gavage for 21-days. Bodyweights were observed weekly and on 22nd-day, animals were sacrificed for biochemical assessments.

Results:

The bodyweights were well maintained in group A whereas reduced in group B & C. Alloxan treatment in group B has been shown to cause beta cell damage evidenced by hyperglycaemia and decreased serum insulin levels. Alloxan also has caused impaired renal and hepatic functions in group B and indicated by significantly higher ($p<0.05$) levels of AST, ALT, ALP, urea, creatinine and BUN whereas significantly lower ($p<0.05$) levels of antioxidant enzymes SOD, CAT, and GSH in comparison to group A. WMSO treatment in group C rats along with alloxan resulted in drop of hepatorenal and oxidative stress markers as endorsed by a significant ($p<0.05$) decline in AST, ALT, ALP, urea, creatinine and BUN while increase ($p<0.05$) in antioxidant enzymes SOD, CAT, and GSH when compared with group B.

Conclusion:

The study proves ameliorative effects of WMSO against alloxan induced pancreatic beta cell damage in rats. WMSO also has been shown promising hepatorenal protective effects via reducing oxidative stress thereby endorsing its anti-diabetic and antioxidant potential.

Keywords: Diabetes mellitus (DM), Hepatorenal, Hyperglycaemia, Oxidative stress, Water melon seed oil (WMSO).

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INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by chronic hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The number of people living with diabetes rose from 200 million in 1990 to 830 million in 2022. According to Global Burden of Disease Collaborative Network, 2024, prevalence has been rising more rapidly in low- and middle-income countries than in high-income countries. According to International Diabetes Federation 2024, there is 31.4% prevalence of diabetes in adults in Pakistan.

Insulin is needed to manage sugar from entering into cells to make energy as a fuel source. As the principal source of insulin, pancreatic beta cells are essential for preserving glucose homeostasis. These cells are responsible for producing, storing, and releasing insulin, which is strictly controlled in response to variations in the body's metabolic state.

Type-1 DM (T1DM) called as JDM *(*juvenile diabetes) or DID (diabetes insulin-dependent), is distinguished by reduced β-cell function and mass that cause pancreatic insulin make-up little or stop which requires regular insulin administration.[1] Type 2 diabetes mellitus is characterized by the presence of insulin resistance with an inadequate compensatory increase in insulin secretion.[2]

DM has been associated with increased formation of reactive oxygen species (ROS), protein glycosylation, glucose autoxidation, and inflammatory mediators that cause insulin resistance and its complications.[3] Increased concentrations of extracellular and intracellular sugar lead to oxidative stress (OS) and cellular damages.[4] Hyperglycaemia increases the production of free radicals, age-rage interactions, protein glycation, glucose autoxidation, polyol pathway. Superoxide anion, OH^-

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radical, and H_2O_2 radicals are main endogenous sources of ROS of physiological significance while the exogenous sources are ozone pollution, Ionizing radiation, and heavy metal ions.[5] ROS may be produced from Neutrophils, platelets metabolism, mitochondrial cytochrome-oxidase, xanthine-oxidase, and by the Arachidonic acid metabolism. OS causes persistent inflammation because ROS production is not easy to avoid due to cellular metabolic mechanisms.[6]

There are various methods for experimental induction of Type 1 or insulin-dependent Diabetes Mellitus in rats among which alloxan is very significant in doing so. The organic compound Alloxan (5,5-dihydroxyl pyrimidine-2,4,6-trione) is a cytotoxic glucose analogue and has been widely used by researchers for the destruction of pancreatic beta cells thereby causing deficiency of insulin and resultant hyperglycaemia in rats. The mechanism of action of alloxan on beta cells involves its penetration via the GLUT2 glucose transporter protein and generation of reactive oxygen species (ROS). Beta cells are deficient in antioxidant enzymes and hence susceptible to necrosis caused by ROS through DNA fragmentation.[7]

Seeds of fruits and vegetables are often discarded as waste despite of being enriched with enhanced nutritional and medicinal components. The seed oils may be harnessed and consumed for various purposes and their medicinal properties can be investigated by researches to verify its safe consumption as food and preventative agent. Watermelon (Citrullus lanatus) is one of those fruits whose seeds are often wasted.

Watermelon (Citrullus lanatus) has potent hypoglycaemic nature is categorized as a Cucurbitaceae or Gourd family member.[8] Watermelon seed oil (WMSO) has anti-Plasmodial, anti-prostatic hyperplasia, anti-giardia, analgesic, anti-ulcerogenis, anti-diarrhoeal activities and treats many metabolic syndromes by its phytochemical constituents.[9] As alloxan induced pancreatic beta cell damage is principally caused by generation of oxidative stress and WMSO has been reported to produce defence against oxidative damage therefore the aim of this study was to find out the anti-diabetic, anti-oxidative and hepatorenal protective activities of WMSO on rats with pancreatic beta cell damage induced by alloxan.

METHODOLOGY

All the ethical principles and methods used in this experimental study are according to an internationally recognized laboratory-usage ethics and caution in an animal-based experiment that followed the Health Research Extension Act (HREA) of 1985 and the Ethical-instructions of the International-ERB. Ethical approval from Departmental Research Committee (DRC) was taken prior to the commencement of study.

Watermelon Seed Oil (WMSO) Hydraulic Press Extraction: Fresh watermelons were purchased from local market located in Saddar Bazar Karachi. Remove the rinds and flesh from watermelon to collect seeds, then washed and sun-dried them. Seeds contained about 46.7% oil and 10% moisture content. The Oil extraction was carried out in Cold Hydraulic press machine. Between each run, all press devices were cleaned and dried. This extracted oil was centrifuged to separate extra solid particles to obtain pure extracted oil and stored in a glass bottle for experimental usage.[10]

Study Procedure:

For this research study, all rats were purchased from the ICCBS (International Centre for Chemical and Biological Sciences) University Of Karachi). Water and the standard (Sugar-Free) Diet were provided through-out the experiment formulated according to their daily requirements. All the rats were acclimatized for 1-2 weeks.

Study Design:

18 age and weight matched male Wistar rats were randomly divided in to three groups (n=6)

Group A: Control group; did not receive any treatment.

Group B: **S**erved as Diabetic or Alloxan treated group; given 120 mg/kg bodyweight Alloxan intra-peritoneal once at day 1 of experimental phase**.**

Group C: **S**erved as a WMSO treated group; given 120 mg/kg bodyweight Alloxan intra-peritoneal once at day 1 of experimental phase along with WMSO at a dose of 2.5g/kg b.w orally via gavage for twenty-one days.

Blood glucose levels were checked at Day 1 and after 3rd day of injection of all groups via glucometer via tail pricking method. The rats in group B having fasting blood-glucose level ≥200mg/dl were considered as diabetic and then further used for this study.

Blood Collection:

At day 22 all the rats were sacrificed and blood was collected from decapitated rats in heparin and EDTA coated tubes. Serum-samples were obtained by centrifugation process at 3000rmp for 5 min, and then carefully stored at -70 to-80 °C till further analysis.

Biochemical Assessment:

1. ***Assessment of pancreatic functions:***

Blood glucose determination was done by digital glucometer. Insulin determination was carried out via prepared ELISA kit method. [11]

2. ***Assessment of Kidney functions:***

Blood Urea, [12] Blood Urea Nitrogen (BUN), Creatinine[13] were estimated to assess renal functions.

3. ***Assessment of Liver functions:***

To evaluate hepatic functions, Aspartate aminotransferase (AST), [14] Alanine aminotransferase (ALT)[15] and Alkaline phosphatase (ALP)[16] were measured calorimetrically via the above mentioned methods.

4. ***Assessment of Oxidative Stress:***

Serum antioxidants Glutathione Reductase (GSH),[17] Superoxide Dismutase (SOD)[18] and Catalase (CAT)[19] were measured to assess oxidative stress. Malondialdehyde

(MDA) was assessed by Ohkawa method to evaluate lipid peroxidation. [20]

Statistical Analysis:

Statistical evaluation employed SPSS software (version 21, IBM Corp., Armonk, NY). Data are expressed as mean ± SD. Statistical significance was determined using one-way analysis of variance (ANOVA) followed by post-hoc testing. Statistical significance threshold was established at $p < 0.05$.

RESULTS

1.Effects of WMSO on Bodyweights of Rats in Group A, B & C

Body weights of control rats were well maintained and slightly enhanced whereas gradually reduced in group B. Rats in group C also showed a very slight decrease in body weights as shown in table 1.

Table 1: Body Weight Changes in Control, Diabetic or Alloxan Treated and WMSO treated groups

	Day-1	Day-7	Day-14	Day-21
Group A	219.9±2.05	223.4±1.73	227.2±1.97	230.7±2.51
Group B[1]	201.4±1.19	185.9±2.86	179.8±3.63	166.6±0.89
Group C[2]	195.7±0.57	176.9±2.02	182.8±0.81	187.9±0.80

Values are presented as Mean ± SD

2.Effects of WMSO on Pancreatic Functions in Group A, B & C

Glucose level was well maintained throughout the study period in group A rats. Group B rats showed rapid elevation in glucose level just after alloxan treatment (day 04) which later reduced at the end of experimental phase (day 21). In group C rats after alloxan treatment (day 04), pancreatic injury caused elevation in glucose levels due to decline in insulin release which was later overcome by WMSO treatment (day 21) as shown in table 2.

Table 2: Effects Of Citrullus Lanatus On Serum Glucose Levels In Control, Diabetic Or Alloxan Treated And WMSO Treated Groups.

	Glucose (mg/dl)			Insulin (uIU/ml)
	Day-1	Day-4	Day-21	
Group A	101.6 ± 1.90	101.7 ± 1.91	102.2 ± 2.08	2.139 ± 0.077
Group B[1]	202.54 ± 1.11	231.99 ± 1.54	202 ± 8.28*	0.215 ± 0.001*
Group C[2]	198.66 ± 1.32	229.98 ± 1.41	126 ± 2.82*	0.288 ± 0.005*

Values are presented as Mean ± SD
1= Group B compared with group A
2= Group C compared with group B
** shows significance (p<0.01)*

3.Effects Of WMSO On Kidney Functions in Group A, B & C

After alloxan treatment Urea, Creatinine and BUN levels were enhanced significantly ($p<0.05$) in group B as compared with group A whereas total proteins were reduced significantly ($p<0.05$) in comparison of group B with group A. kidney damage caused by alloxan was reverted by WMSO treatment in group C as shown by significant reduction in Urea, Creatinine and BUN levels in group C when compared with group B, as shown in table 3.

Table 3: Effects of Citrullus Lanatus on Kidney Functions in Control, Diabetic or Alloxan Treated and WMSO treated groups

	Urea (mg/dl)	BUN (mg/dl)	Creatinine (mg/dl)	Total-Protein (g/dl)
Group A	4.730 ± 2.73	2.991 ± 0.48	0.170 ± 0.02	6.596 ± 0.599
Group B[1]	23.95±3.69*	11.193±1.72*	0.525 ± 0.006*	2.532±0.297*
Group C[2]	11.013±1.39*	5.145 ± 0.65*	0.210 ± 0.06*	3.8 ± 0.218*

BUN: Blood Urea Nitrogen
Values are presented as Mean ± SD
1= Group B compared with group A
2= Group C compared with group B
** shows significance (p<0.05)*

4.Effects of WMSO on Liver Parameters in Group A, B & C

ALT, AST & ALP levels were increased significantly in group B ($p<0.05$) as compared with group A. In group C WMSO treatment caused significant reduction in ALT ($p<0.05$), AST ($p<0.05$) & ALP ($p<0.05$) level in comparison to group B indicating protection against alloxan induced hepatic injury as shown in Table 4.

Table 4: Effects of Citrullus Lanatus on Liver Functions in Control, Diabetic or Alloxan Treated and WMSO treated groups

	ALT (U/L)	AST (U/L)	ALP (U/L)
GROUP A	12.74 ± 0.675	10.4 ± 1.472	192.73 ± 1.64
GROUP B[1]	35.71 ± 1.59*	67.5 ± 16.49*	491.2 ± 46.91*
GROUP C[2]	16.87 ± 7.28*	20.4 ± 5.56*	237.3 ± 13.04*

Values are presented as Mean ± SD
1= Group B compared with group A
2= Group C compared with group B
** shows significance (P<0.05)*

5.Effects of WMSO on Antioxidant Parameters in Group A, B & C

After alloxan treatment, oxidative damages was caused and indicated by elevating MDA ($p<0.05$) or falling CAT ($p<0.05$), SOD ($p<0.05$), and GSH ($p<0.05$) levels in group B significantly when compared with group A which was overcome by WMSO treatment in group C ($p<0.05$) significantly when compared with group B as shown in Table 5.

Table 5: Effects of Citrullus Lanatus on Antioxidant Enzymes and MDA in Control, Diabetic or Alloxan Treated and WMSO treated groups

	CAT (µmol/gm tissue)	SOD (U/gm)	GSH (U/gm)	MDA (µmol/g)
Group A	15.61 ± 1.34	1.48 ± 0.087	23.28 ± 0.83	1.03 ± 0.10
Group B[1]	5.44 ± 3.10*	0.56± 0.004*	28.5 ± 1.88*	3.02 ±0.005*
Group C[2]	9.34 ± 1.183*	0.028 ± 0.21*	20.68 ±4.91*	1.16 ± 0.18*

Values are presented as Mean ± SD
1= Group B compared with group A
2= Group C compared with group B
** shows significance (p<0.05)*

DISCUSSION

The scientific community has shown a great deal of interest in the biology of beta cells because of their crucial involvement in the pathophysiology of diabetes. A deeper comprehension of the various aspects of beta cell biology may result in the creation of innovative treatments and preventative measures that can stop or slow the onset of disease.[21]

In the present study rats were selected and divided in to three groups. The control group was constructed to obtain baseline values for comparison among groups. The rats were chosen for induction of diabetes type 1 via alloxan treatment in Alloxan treated group whereas Alloxan + WMSO group rats were made diabetic via Alloxan and treated with WMSO to evaluate its anti-diabetic, anti-oxidative and hepatorenal protective effects.

The body weights of rats were well maintained in the present study throughout the experimental period whereas declined considerably in Alloxan treated and slightly in Alloxan +WMSO treated groups (Table 1). The decline of weight in group B & C rats is because the pancreas plays a vital role in maintaining the body homeostasis by its enzyme and hormone which are responsible to break food for providing energy by shifting glucose from blood to cell, but pancreatic cell dysfunction due to alloxan causes weight loss because body starts to utilize muscles, fats, and tissues because in T1DM, the ER stress, ROS, mitochondrial dysfunction become increased that can increase apoptosis and decreased regeneration so β cell mass becomes reduced.

The serum insulin concentration was found to be decreased significantly in Alloxan treated ($p<0.05$) and Alloxan +WMSO ($p<0.05$) treated groups in comparison to control group that reflects the necrotic effects of alloxan on pancreatic beta cells (Table 2). Another study has also reported the decline in insulin levels after alloxan administration[22] because alloxan shows a tri-phasic response and causes physiological acute inhibitory effects for glucose-stimulating insulin release and pancreatic disruptions. [23]

The current study also assessed renal functionality of rats in the presence of alloxan and WMSO administration. Alloxan is specific in action for causing pancreatic beta cell damage without harming liver and kidney functions[24] but some current studies have shown that it may cause tubulointerstitial nephritis which may lead to nephrotoxicity.[25] In our study alloxan dose has caused renal impairments and resulted in significantly higher levels of serum urea ($p<0.05$), creatinine ($p<0.05$) and BUN ($p<0.05$) in group B as compared with group A (Table 3). The treatment of rats with WMSO of group C rats resulted in improvements of renal functions as indicated via decline in serum in urea ($p<0.05$), creatinine ($p<0.05$) and BUN ($p<0.05$) in group C as compared with group B (Table 3). There is no specific study to date which has evaluated the effects of WMSO against alloxan induced toxicity in rats. One study has revealed that consumption in higher doses may cause nephrotoxicity in rats.[26]

In the present study alloxan administration in rats of group B showed significantly enhanced liver enzymes ALT ($p<0.05$), AST ($p<0.05$) & ALP ($p<0.05$) when compared with control group. Alloxan accumulation is 20-times higher in renal and hepatic cells but causes selective-cytotoxicity of pancreatic beta-cells, yet some studies suggest hepatic functional alterations in rats evidenced by increased levels of their liver enzymes [27]. On the other hand liver enzymes of rats treated with both alloxan and WMSO in group C significantly declined ($p<0.05$) when compared with group B (Table 4). Another study has also evaluated the therapeutic potential of WMSO in rats against carbon tetra chloride induced hepatotoxicity[28] but the present study is unique that it has evaluated therapeutic potential of WMSO against alloxan induced hepatic toxicity.

The present study also demonstrated significantly decreased level of CAT ($p<0.05$), SOD ($p<0.05$), GSH ($p<0.05$), whereas increased MDA ($p<0.05$) in group B in comparison to group A.

WMSO has been observed to reduce oxidative stress via enhancing the activity of CAT ($p<0.05$), SOD ($p<0.05$), GSH ($p<0.05$), and decreasing hepatic lipid peroxidation such as MDA ($p<0.05$) significantly in group C when compared with group B (Table 5). Oxidative stress is a root of T1DM via apoptosis of pancreatic β cells. It is widely understood that an inconsistency between ROS scavenging and developing processes disrupt the pancreatic-acinar corpuscles, inducing auto-digestion of pancreas. WMSO as antioxidant neutralize an impact of reactive oxygen species (ROS) and inhibit numerous disorders of pancreas, heart, liver, etc. WMSO containing phytochemicals such as Cucurbitacin-E and Vitamin-E reduce cell-damages while tannins, Lycopene, flavonoids, terpenoids, and alkaloids reduce oxidative stress because of its strong antioxidant potency.[9]

CONCLUSION

WMSO has anti-diabetic potential as indicated by its opposing effects on hyperglycaemia, insulin deficiency and ROS generation created by alloxan in Wistar rats. Further WMSO has also protective effects on renal and hepatic functions endorsing its importance for safe consumption and healthy outcomes. Therefore the study concludes that WMSO as a dietary-supplement is beneficial because of its phytochemical constituents that show anti-hyperglycaemic, antioxidants, anti-inflammatory and hepatorenal protective effects.

Conflicts Of Interest

The author declares no conflicts of interest

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Author's Contribution

IN and LN contributed to the conception and design of the study. Data collection was carried out by IN. Data analysis, and interpretation was performed by IN and LN. Manuscript drafting and critical revision were undertaken by all authors (IN, LN, MAM, and MN). All authors have read and approved the final manuscript.

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